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International filing date: 06 August 2021 (06.08.2021)
Document type: Certified copy of priority document
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Number: 63/143,435
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Date of receipt at the International Bureau: 07 August 2021 (07.08.2021)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-bis)
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Filing date: **29 Jan 2021 (29.01.2021)**  
Application number: **63143435**

Date of availability of document: **09 Feb 2021 (09.02.2021)**

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Date of issue of this certificate: **09 Aug 2021 (09.08.2021)**
August 09, 2021

THIS IS TO CERTIFY THAT ANNEXED HEREETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 63/143,435
FILING DATE: January 29, 2021

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS US63/143,435

Certified by

Performing the Functions and Duties of the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office
**Application Data Sheet 37 CFR 1.76**

| Title of Invention        | Nitrile-Containing Antiviral Compounds |

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

**Secrecy Order 37 CFR 5.2:**

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

**Inventor Information:**

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**Mailing Address of Inventor:**

| Address 1 | No Pfizer Inc. |
| Address 2 | 610 Main Street |
| City      | Cambridge       | State/Province | MA |
| Postal Code | 02139 | Country | US |

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**Mailing Address of Inventor:**

| Address 1 | 3 Gilson Road |
| Address 2 |               |
| City      | Littleton     | State/Province | MA |
| Postal Code | 01460 | Country | US |

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**Mailing Address of Inventor:**

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**Application Data Sheet 37 CFR 1.76**

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**Correspondence Information:**

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

- An Address is being provided for the correspondence Information of this application.

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<tbody>
<tr>
<td>Email Address</td>
<td><a href="mailto:PfizerPatentDocketing@pfizer.com">PfizerPatentDocketing@pfizer.com</a></td>
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Application Data Sheet 37 CFR 1.76

Title of Invention: Nitrile-Containing Antiviral Compounds

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

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Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer number will be used for the Representative Information during processing.

Please Select One:
- Customer Number
- US Patent Practitioner
- Limited Recognition (37 CFR 11.9)

Customer Number: 26523

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78. When referring to the current application, please leave the "Application Number" field blank.

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Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.
Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Additional Foreign Priority Data may be generated within this form by selecting the Add button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.
Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant must opt-out of the authorization by checking the corresponding box A or B or both in subsection 2 below.

**NOTE:** This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

   A. **Priority Document Exchange (PDX)** - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People’s Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

   B. **Search Results from U.S. Application to EPO** - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby grants the USPTO authority to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

   The applicant is reminded that the EPO’s Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

   A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

   B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

   **NOTE:** Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.
Application Data Sheet 37 CFR 1.76

Attorney Docket Number
PC072660-Prov2

Application Number

Title of Invention
Nitrile-Containing Antiviral Compounds

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43, or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an assignee under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or assignee who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Assignee

Legal Representative under 35 U.S.C. 117

Joint Inventor

- Person to whom the inventor is obligated to assign.
- Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name
Pfizer Inc.

Mailing Address Information For Applicant:

Address 1
235 East 42nd Street

Address 2
Attn: Legal Patent Department, Chief IP Counsel

City
New York

State/Province
NY

Country
US

Postal Code
10017

Phone Number
Fax Number

Email Address
PfizerPatentDocketing@pfizer.com

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.
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**Assignee**

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Assignee Information" section will appear on the patent application publication as an assignee. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee is an Organization check here. ☒

**Organization Name** Pfizer Inc.

| Mailing Address Information For Assignee including Non-Applicant Assignee: |
|-----------------------------------|-------------------|-------------------|
| Address 1                         | 235 East 42nd Street |
| Address 2                         | Attn: Legal Patent Department, Chief IP Counsel |
| City                              | New York          |
| State/Province                    | NY                |
| Country                          | US                |
| Phone Number                      |                   |
| Email Address                     | PfizerPatentDocketing@pfizer.com |

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

**Signature:**

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the “Authorization or Opt-Out of Authorization to Permit Access” section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet must be signed by a patent practitioner if one or more of the applicants is a juristic entity (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, all joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of all joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

**Signature** / John A. Wichtowski /

**Date (YYYY-MM-DD)** 2021-01-29

**First Name** John A. **Last Name** Wichtowski **Registration Number** 48032

Additional Signature may be generated within this form by selecting the Add button.
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This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.
Privacy Act Statement

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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# Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

## Inventor(s)

<table>
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<tr>
<th>Inventor 1</th>
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All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add** button.
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<th>Title of Invention</th>
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<td>Attorney Docket Number (if applicable)</td>
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Entity Status
Applicant asserts small entity status under 37 CFR 1.27 or applicant certifies micro entity status under 37 CFR 1.29

☐ Applicant asserts small entity status under 37 CFR 1.27
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<tr>
<td>John A. Wichtowski /</td>
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<tr>
<th>First Name</th>
<th>Last Name</th>
<th>Registration Number (If appropriate)</th>
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<tr>
<td>John A.</td>
<td>Wichtowski</td>
<td>48032</td>
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Nitrile-Containing Antiviral Compounds

Background of the Invention

The invention relates to compounds and methods of inhibiting viral replication activity comprising contacting a SARS-CoV-2-related 3C-like ("3CL") proteinase with a therapeutically effective amount of a SARS-CoV-2-related 3C-like protease inhibitor. The invention also relates to methods of treating Coronavirus Disease 2019 ("COVID-19") in a patient by administering a therapeutically effective amount of a SARS-CoV-2-related 3C-like protease inhibitor to a patient in need thereof. The invention further relates to methods of treating COVID-19 in a patient, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of the SARS-CoV-2-related 3C-like protease inhibitor to a patient in need thereof.

A worldwide outbreak of Coronavirus Disease 2019 ("COVID-19") has been associated with exposures originating in late 2019 in Wuhan, Hubei Province, China. By mid-2020 the outbreak of COVID-19 has evolved into a global pandemic with millions of people having been confirmed as infected and resulting in hundreds of thousands of deaths. The causative agent for COVID-19 has been identified as a novel coronavirus which has been named Severe Acute Respiratory Syndrome Corona Virus 2 ("SARS-CoV-2"). The genome sequence of SARS-CoV-2 has been sequenced from isolates obtained from nine patients in Wuhan, China and has been found to be of the subgenus Sarbecovirus of the genus Betacoronavirus. Lu, R. et al. The Lancet, 395, 10224, 565-574; online January 29, 2020. The sequence of SARS-CoV-2 was found to have 88% homology with two bat-derived SARS-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, which were collected in 2018 in Zhoushan, eastern China. SARS-CoV-2 was also found to share about 79% homology with Severe Acute Respiratory Syndrome Corona Virus ("SARS-CoV"), the causative agent of the SARS outbreak in 2002-2003, and about 50% homology with Middle East Respiratory Syndrome Coronavirus ("MERS-CoV"), the causative agent of a respiratory viral outbreak originating in the Middle East in 2012. Based on a recent analysis of 103 sequenced genomes of SARS-CoV-2 it has been proposed that SARS-CoV-2 can be divided into two major types (L and S types) with the S type being ancestral and the L type having evolved from the S-type. Lu, J.; Cui, J. et al. On the origin and continuing evolution of SARS-CoV-2; http://doi.org/10.1093/nsr/nwa036. The S and L types can
be clearly defined by just two tightly linked SNPs at positions 8,782 (orf1ab:T8517C, synonymous) and 28,144 (ORF8: C251T, S64L). In the 103 genomes analyzed approximately 70% were of the L-type and approximately 30% were of the S-type. It is unclear if the evolution of the L-type from the S-type occurred in humans or through a zoonotic intermediate but it appears that the L-type is more aggressive than the S-type and human interference in attempting to contain the outbreak may have shifted the relative abundance of the L and S types soon after the SARS-CoV-2 outbreak began. The discovery of the proposed S- and L- subtypes of SARS-CoV-2 raises the possibility that an individual could potentially be infected sequentially with the individual subtypes or be infected with both subtypes at the same time. In view of this evolving threat there is an acute need in the art for an effective treatment for COVID-19 and for methods of inhibiting replication of the SARS-CoV-2 coronavirus.

Recent evidence clearly shows that the newly emerged coronavirus SARS-CoV-2, the causative agent of COVID-19 (Centers for Disease Control, CDC) has acquired the ability of human-to-human transmission leading to community spread of the virus. The sequence of the SARS-CoV-2 spike protein receptor-binding domain (“RBD”), including its receptor-binding motif (RBM) that directly contacts the angiotensin-converting enzyme 2 receptor, ACE2, is similar to the RBD and RBM of SARS-CoV, strongly suggesting that SARS-CoV-2 uses ACE2 as its receptor. Wan, Y.; Shang, J.; Graham, R.; Baric, R.S.; Li, F.; Receptor recognition by the novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS coronavirus; J. Virol. 2020; doi:10.1128/JVI.00127-20. Several critical residues in SARS-CoV-2 RBM (particularly Gln493) provide favorable interactions with human ACE2, consistent with SARS-CoV-2’s capacity for human cell infection. Several other critical residues in SARS-CoV-2’s RBM (particularly Asn501) are compatible with, but not ideal for, binding human ACE2, suggesting that SARS-CoV-2 uses ACE2 binding in some capacity for human-to-human transmission.

Coronavirus replication and transcription function is encoded by the so-called “replicase” gene (Ziebuhr, J., Snijder, E.J., and Gorbalyova, A.E.; Virus-encoded proteinases and proteolytic processing in the Nidovirales. J. Gen. Virol. 2000, 81, 853-879; and Fehr, A.R.; Perlman, S.; Coronaviruses: An Overview of Their Replication and Pathogenesis, Methods Mol. Biol. 2015; 1282: 1–23. doi:10.1007/978-1-4939-2438-7_1), which consists of two overlapping polyproteins that are extensively processed by viral proteases. The C-proximal region is processed at eleven conserved interdomain junctions by the coronavirus main or “3C-like” protease (Ziebuhr, Snijder, Gorbalyova,
2000 and Fehr, Perlman et al., 2015). The name “3C-like” protease derives from certain similarities between the coronavirus enzyme and the well-known picornavirus 3C proteases. These include substrate preferences, use of cysteine as an active site nucleophile in catalysis, and similarities in their putative overall polypeptide folds. The SARS-CoV-2 3CL protease sequence (Accession No. YP_009725301.1) has been found to share 96.08% homology when compared with the SARS-CoV 3CL protease (Accession No. YP_009725301.1) Xu, J.; Zhao, S.; Teng, T.; Abdalla, A.E.; Zhu, W.; Xie, L.; Wang, Y.; Guo, X.; Systematic Comparison of Two Animal-to-Human Transmitted Human Coronaviruses: SARS-CoV-2 and SARS-CoV; Viruses 2020, 12, 244; doi:10.3390/v12020244. Very recently, Hilgenfeld and colleagues published a high-resolution X-ray structure of the SARS-CoV-2 coronavirus main protease (3CL) Zhang, L.; Lin, D.; Sun, X.; Rox, K.; Hilgenfeld, R.; X-ray Structure of Main Protease of the Novel Coronavirus SARS-CoV-2 Enables Design of α-Ketoamide Inhibitors; bioRxiv preprint doi: https://doi.org/10.1101/2020.02.17.952879. The structure indicates that there are differences when comparing the 3CL proteases of SARS-CoV-2 and SARS-CoV. In the SARS-CoV but not in the SARS-CoV-2 3CL protease dimer, there is a polar interaction between the two domains III involving a 2.60-Å hydrogen bond between the side-chain hydroxyl groups of residue Thr285 of each protomer, and supported by a hydrophobic contact between the side-chain of Ile286 and Thr285 Cγ2. In the SARS-CoV-2 3CL, the threonine is replaced by alanine, and the isoleucine by leucine when compared with the same residues in the SARS-CoV 3CL. The Thr285Ala replacement observed in the SARS-CoV-2 3CL protease allows the two domains III to approach each other somewhat closer (the distance between the Cα atoms of residues 285 in molecules A and B is 6.77 Å in SARS-CoV 3CL protease and 5.21 Å in SARS-CoV-2 3CL protease and the distance between the centers of mass of the two domains III shrinks from 33.4 Å to 32.1 Å). In the active site of SARS-CoV-2 3CL, Cys145 and His41 form a catalytic dyad, which when taken together with a with a buried water molecule that is hydrogen-bonded to His41 can be considered to constitute a catalytic triad of the SARS-CoV-2 3CL protease. In view of the ongoing SARS-CoV-2 spread that has caused the current worldwide COVID-19 outbreak, it is desirable to have new methods of inhibiting SARS-CoV-2 viral replication and of treating COVID-19 in patients.
Summary of The Invention

The present invention provides novel compounds which act in inhibiting or preventing SARS-CoV-2 viral replication and thus are useful in the treatment of COVID-19. The present invention also provides pharmaceutical compositions comprising the compounds and methods of treating COVID-19 and inhibiting SARS-CoV-2 viral replication by administering the compounds of the invention or pharmaceutical compositions comprising the compounds of the invention.

A first embodiment of a first aspect of the present invention is a compound of

Formula I

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{R}^2
\end{align*}
\]

or a pharmaceutically acceptable salt thereof; wherein \( \text{R}^1 \) is selected from the group consisting of \( \text{C}_1-\text{C}_6 \) alkyl which is optionally substituted with a cyano or with one to five fluoro; \( \text{C}_2-\text{C}_6 \) alkynyl; and \( (\text{C}_3-\text{C}_6 \text{ cycloalkyl})-\text{C}_1-\text{C}_3 \) alkyl which is optionally substituted with one to two substituents selected from trifluoromethyl and \( \text{C}_1-\text{C}_3 \) alkyl or with one to five fluoro; \( \text{R}^2 \) is hydrogen or \( \text{R}^2 \) and \( \text{R}^1 \) taken together with the nitrogen and carbon atoms to which they are attached are a pyrrolidine or piperidine ring which is optionally substituted with one to four \( \text{R}^{2\alpha} \); \( \text{R}^{2\alpha} \) at each occurrence is independently selected from the group consisting of fluoro, \( \text{C}_1-\text{C}_6 \) alkyl optionally substituted with one to three fluoro and \( \text{C}_1-\text{C}_6 \) alkoxy optionally substituted with one to three fluoro; or two \( \text{R}^{2\alpha} \) groups when attached to adjacent carbons and taken together with the carbons to which they are attached are a fused \( \text{C}_3-\text{C}_6 \) cycloalkyl which is optionally substituted with one to four \( \text{R}^{2\beta} \); or two \( \text{R}^{2\alpha} \) groups when attached to the same carbon and taken together with the carbon to which they are attached are a spiro \( \text{C}_3-\text{C}_6 \) cycloalkyl which is optionally substituted with one to four \( \text{R}^{2\beta} \); \( \text{R}^{2\beta} \) at each occurrence is independently selected from fluoro, \( \text{C}_1-\text{C}_3 \) alkyl optionally substituted with one to three fluoro, and \( \text{C}_1-\text{C}_3 \) alkoxy optionally substituted with one to three fluoro; \( \text{R}^3 \) is selected from the group consisting
of C₁-C₆ alkyl, C₁-C₆ alkoxy, (C₁-C₆ alkoxy)-C₁-C₆ alkyl, C₂-C₆ alkynyl, C₂-C₆ alkynoxy, C₃-C₁₂ cycloalkyl optionally fused with a 5- to 6-membered heteroaryl or phenyl, (C₃-C₁₂ cycloalkyl)-C₁-C₆ alkyl, C₃-C₁₂ cycloalkoxy, (C₃-C₁₂ cycloalkoxy)-C₁-C₆ alkyl, 4- to 12-membered heterocycloalkyl which is optionally fused with a 5- to 6-membered heteroaryl or phenyl and wherein said heterocycloalkyl comprises one to four heteroatoms independently selected from N, O and S(O)ₙ, (4- to 12-membered heterocycloalkyl)-C₁-C₆ alkyl wherein said heterocycloalkyl moiety comprises one to four heteroatoms independently selected from N, O and S(O)ₙ, C₆-C₁₀ aryl optionally fused with a C₄-C₆ cycloalkyl or a 4- to 7-membered heterocycloalkyl, (C₆-C₁₀ aryl)-C₁-C₆ alkyl, 5- to 10-membered heteroaryl comprising one to five heteroatoms independently selected from N, O and S, which is optionally fused with a C₅-C₆ cycloalkyl; (5- to 10-membered heteroaryl)-C₁-C₆ alkyl wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S; (C₆-C₁₀ aryl)-(5- to 10-membered heteroaryl)- wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S, (5- to 10-membered heteroaryloxy)-C₁-C₆ alkyl wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S; (5- to 6-membered heteroaryl)-(5- to 6-membered heteroaryl)- wherein each heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S; (4- to 7-membered heterocycloalkyl)-(5- to 6-membered heteroaryl)- wherein the heterocycloalkyl moiety comprises one to three heteroatoms independently selected from N, O and S(O)ₙ and the heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S; wherein each R³ group is optionally substituted with one to five R⁴; R⁴ at each occurrence is independently selected from the group consisting of oxo, halo, hydroxy, cyano, phenyl, benzyl, amino, (C₁-C₆ alkyl)amino optionally substituted with one to five fluoro, di(C₁-C₆ alkyl)amino optionally substituted with one to ten fluoro, C₁-C₆ alkyl optionally substituted with one to five fluoro, C₁-C₆ alkoxy optionally substituted with one to five fluoro, C₁-C₃ alkoxy-C₁-C₃ alkyl optionally substituted with one to five fluoro, C₂-C₆ cycloalkyl optionally substituted with one to three fluoro or C₁-C₃ alkyl, C₁-C₆ alkyl-C(O)NH optionally substituted with one to five fluoro, C₁-C₆ alkyl-S(O)₂NH optionally substituted with one to five fluoro, C₁-C₆ alkoxy optionally substituted with one to five fluoro, C₁-C₆ alkoxy-C₁-C₆ alkoxy optionally substituted with one to five fluoro, C₁-C₆ alkoxy-C₁-C₆ alkoxy optionally substituted with one to five fluoro, C₂-C₆ cycloalkyl optionally substituted with one to three fluoro or C₁-C₃ alkyl, C₁-C₆ alkyl-C(O)NH optionally substituted with one to five fluoro, C₁-C₆ alkoxy optionally substituted with one to five fluoro, C₁-C₆ alkoxy optionally substituted with one to five fluoro, C₁-C₆ alkoxy optionally substituted with one to five fluoro, C₁-C₆ alkoxy optionally substituted with one to five fluoro, C₁-C₆ alkoxy optionally substituted with one to five fluoro, C₁-C₆ alkoxy optionally substituted with one to five fluoro.
C₆ alkyl-C(O)- optionally substituted with one to five fluoro, C₁-C₆ alkyl-S(O)ₙ- optionally substituted with one to five fluoro; and

n at each occurrence is independently selected from 0, 1 and 2.

A second embodiment of a first aspect of the invention is the compound of the
first embodiment of the first aspect wherein R¹ is selected from the group consisting of
(CH₃)₂CHCH₂-, (CH₃)₂CCH₂-, cyanomethyl, 2-cyanoethyl, 2,2-difluoroethyl, 2,2,2-
trifluoroethyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 3,3,3-trifluoro-2-methylpropyl,
cyclopropymethyl, (2,2-difluorocyclopropyl)methyl, [1-
(trifluoromethyl)cyclopropyl]methyl, (2-methylcyclopropyl)methyl, (3,3-
difluorocyclobutyl)methyl, cyclopentylmethyl and propynyl; and R² is hydrogen; or a
pharmaceutically acceptable salt thereof.

A third embodiment of a first aspect of the invention is the compound of the first
embodiment of the first aspect of the invention wherein R² and R¹ taken together with
the nitrogen and carbon atoms to which they are attached are a pyrrolidine or piperidine
ring which is optionally substituted with one to four R²ᵃ; or a pharmaceutically
acceptable salt thereof.

A fourth embodiment of a first aspect of the invention is the compound of the
third embodiment of the first aspect of the invention wherein R²ᵃ at each occurrence is
independently selected from the group consisting of fluoro, methyl, isopropyl,
trifluoromethyl and tert-butoxy; or two R²ᵃ groups when attached to adjacent carbons
and taken together with the carbons to which they are attached are a fused
cyclopentane or cyclopropane which is optionally substituted with one to four R²ᵇ; or two
R²ᵃ groups when attached to the same carbon and taken together with the carbon to
which they are attached are a spirocyclopropane ring which is optionally substituted with
one to four R²ᵇ; or a pharmaceutically acceptable salt thereof.

A fifth embodiment of a first aspect of the invention is the compound of the fourth
embodiment of the first aspect wherein R²ᵇ at each occurrence is independently
selected from the group consisting of fluoro, methyl and methoxy; or a pharmaceutically
acceptable salt thereof.

A sixth embodiment of a first aspect of the invention is the compound of the first
embodiment of the first aspect selected from the group consisting of formulae la through
lg
A seventh embodiment of a first aspect of the invention is the compound of the first embodiment of the first aspect selected from the group consisting of formulae \( \text{Ih} \) through \( \text{Ik} \).
or a pharmaceutically acceptable salt thereof.

An eighth embodiment of the first aspect of the invention is the compound of the seventh embodiment of the first aspect of the invention selected from the group consisting of
A ninth embodiment of a first aspect of the invention is the compound of the eighth embodiment of the first aspect of the invention wherein \( R^3 \) is selected from the group consisting of \( C_1-C_6 \) alkyl and \( (C_3-C_8 \text{ cycloalkyl})-C_1-C_2 \) alkyl; each of which is substituted with one to four \( R^4 \); or a pharmaceutically acceptable salt thereof.

A tenth embodiment of a first aspect of the invention is the compound of the ninth embodiment of the first aspect of the invention wherein \( R^3 \) is selected from the group consisting of \( (\text{CH}_3)_2\text{CHCH}(R^4^-) , (\text{CH}_3)_3\text{CCH}(R^4^-) \) and \( (\text{cyclohexyl})\text{CH}(R^4^-) \); or a pharmaceutically acceptable salt thereof.

An eleventh embodiment of a first aspect of the invention is the compound of the tenth embodiment of the first aspect of the invention selected from the group consisting of
or a pharmaceutically acceptable salt thereof.

A twelfth embodiment of a first aspect of the invention is the compound of the

eleventh embodiment of the first aspect of the invention wherein $R^4$ is selected from the

group consisting of ($C_1$-$C_6$ alkyl)amino optionally substituted with one to five fluoro, $C_1$-$C_6$ alkyl-C(O)NH- optionally substituted with one to five fluoro, and $C_1$-$C_6$ alkyl-S(O)₂NH- optionally substituted with one to five fluoro; or a pharmaceutically acceptable salt thereof.

A thirteenth embodiment of a first aspect of the invention is the compound of the
twelfth embodiment of the first aspect of the invention wherein $R^4$ is selected from the
group consisting of CF₃C(O)NH-, CF₃S(O)₂NH-, CH₃C(O)NH-, CH₃CH₂C(O)NH- and CF₃CH₂NH--; or a pharmaceutically acceptable salt thereof.
A fourteenth embodiment of a first aspect of the invention is the compound of the thirteenth embodiment of the first aspect of the invention wherein \( R^4 \) is \( \text{CF}_3\text{C(O)NH-} \) or \( \text{CF}_3\text{S(O)NH-} \); or a pharmaceutically acceptable salt thereof.

A fifteenth embodiment of a first aspect of the invention is the compound of any one of the first through eighth embodiments of the first aspect of the invention wherein \( R^3 \) is a 4- to 12-membered heterocycloalkyl which is optionally fused with a 5- to 6-membered heteroaryl or phenyl and wherein said heterocycloalkyl comprises one to four heteroatoms independently selected from N, O and S(O)\( \_n \), or is a (4- to 12-membered heterocycloalkyl)-C\(_1\)-C\(_8\) alkyl wherein said heterocycloalkyl moiety comprises one to four heteroatoms independently selected from N, O and S(O)\( \_n \), each of which is optionally substituted with one to five R\(^4\), or a pharmaceutically acceptable salt thereof.

A sixteenth embodiment of a first aspect of the invention is the compound of the fifteenth embodiment of the invention wherein the 4- to 12-membered heterocycloalkyl moiety in \( R^3 \) is selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, oxetanyl, tetrahydrofuranyl, pyranyl, 2-oxo-1,3-oxazolidinyl, oxabicyclo[2.2.1]heptyl, 1-oxa-8-azaspiro[4.5]decy1, 1,1-dioxido-1,2-thiazolidinyl and 1,1-dioxido-1,2-thiazinanyl; each of which is optionally substituted with one to three R\(^4\); or a pharmaceutically acceptable salt thereof.

A seventeenth embodiment of a first aspect of the invention is the compound of any one of the first through eighth embodiments of the first aspect of the invention wherein \( R^3 \) is selected from the group consisting of phenyl, benzyl, phenethyl, a 5- to 10-membered heteroaryl comprising one to five heteroatoms independently selected from N, O and S; (5- to 10-membered heteroaryl)-C\(_1\)-C\(_8\) alkyl wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S; and a (5- to 10-membered heteroaryloxy)-C\(_1\)-C\(_8\) alkyl wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S; each of which is optionally substituted with one to five R\(^4\); or a pharmaceutically acceptable salt thereof.

An eighteenth embodiment of a first aspect of the invention is the compound of the seventeenth embodiment of a first aspect of the invention wherein the 5- to 10-membered heteroaryl moiety in \( R^3 \) is selected from the group consisting of imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, benzimidazolyl, pyridinopyrrolyl, quinolinyl,
quinoxalinyl, benzotriazolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, 4H-furo[3,2-b]pyrrolyl, 4H-thieno[3,2-b]pyrrolyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,3]triazolo[1,5-a]pyridinyl and naphthyridinyl; each of which is optionally substituted with one to four R⁴; or a pharmaceutically acceptable salt thereof.

A nineteenth embodiment of a first aspect of the invention is the compound of the eighteenth embodiment of the first aspect of the invention wherein R⁵ is indolyl; which is optionally substituted with one to four R⁴; or a pharmaceutically acceptable salt thereof.

A twentieth embodiment of a first aspect of the invention is the compound of the nineteenth embodiment of the first aspect of the invention wherein R⁵ is indol-2-yl; which is optionally substituted with one to four R⁴; and R⁴ at each occurrence is independently selected from the group consisting of fluoro, chloro, bromo, hydroxy, methyl, ethyl, propyl, isopropyl, 1-methylpropyl, butyl, tert-butyl, acetyl, methoxy, ethoxy, propoxy, butoxy, trifluoromethyl, trifluoromethoxy, cyclohexyl and diethylamino; or a pharmaceutically acceptable salt thereof.

A twenty-first embodiment of a first aspect of the invention is the compound of the twentieth embodiment of the first aspect of the invention of the formula

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof.

A twenty-second embodiment of a first aspect of the invention is the compound of the twenty-first embodiment of the first aspect of the invention wherein R⁵ is selected from the group consisting of 1H-indol-2-yl, 7-fluoro-4-methoxy-1H-indol-2-yl, 4-methoxy-7-(trifluoromethyl)-1H-indol-2-yl, 4-methoxy-1H-indol-2-yl, 4-(trifluoromethoxy)-1H-indol-2-yl, 6-(trifluoromethyl)-1H-indol-2-yl, 4-methoxy-3,6,7-tris(trifluoromethyl)-1H-indol-2-yl, 3-fluoro-4-methoxy-1H-indol-2-yl and 3,5-difluoro-4-methoxy-1H-indol-2-yl; or a pharmaceutically acceptable salt thereof.
A twenty-third embodiment of a first aspect of the invention is the compound of the first embodiment of the first aspect of the invention wherein $R^3$ is $C_1$-$C_6$ alkoxy; or a pharmaceutically acceptable salt thereof.

A twenty-fourth embodiment of a first aspect of the invention is the compound of the twenty-third embodiment of the first aspect of the invention wherein $R^3$ is selected from the group consisting of methoxy, ethoxy and prop-2-oxy; or a pharmaceutically acceptable salt thereof.

A twenty-fifth embodiment of a first aspect of the invention is the compound of the first embodiment of the first aspect of the invention wherein $R^3$ is selected from the group consisting of $C_3$-$C_{12}$ cycloalkyl optionally fused with a 5- to 6-membered heteroaryl or phenyl, $(C_3$-$C_{12}$ cycloalkyl)$-C_1$-$C_6$ alkyl, $C_3$-$C_{12}$ cycloalkoxy and $(C_3$-$C_{12}$ cycloalkoxy)$-C_1$-$C_6$ alkyl; each of which is optionally substituted with one to three $R^4$; or a pharmaceutically acceptable salt thereof.

A twenty-sixth embodiment of a first aspect of the invention is the compound of the twenty-fifth embodiment of a first aspect of the invention wherein $R^3$ is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-(cyclohexylxoxymethyl), cyclopropylethyl, cyclopropylmethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl and cyclohexymethyl; each of which is optionally substituted with one to three $R^4$; or a pharmaceutically acceptable salt thereof.

A twenty-seventh embodiment of a first aspect of the invention is the compound of the seventeenth embodiment of the first aspect of the invention wherein $R^3$ is selected from the group consisting of phenyl, benzyl and phenethyl, each of which is optionally substituted with one to three $R^4$; or a pharmaceutically acceptable salt thereof.

A twenty-eighth embodiment of a first aspect of the invention is the compound of the twenty-seventh embodiment of the first aspect of the invention wherein $R^4$ is selected from the group consisting of fluoro, chloro, dimethylamino, trifluoromethyl, $CF_3C(O)NH$- and $CF_3S(O)_2NH$-; or a pharmaceutically acceptable salt thereof.

A twenty-ninth embodiment of a first aspect of the invention is a compound selected from the group consisting of
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N²-{(2R)-2-(dimethylamino)-2-[4-(trifluoromethyl)phenyl]acetyl}-4-methyl-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N²-{(2R)-2-(dimethylamino)-2-[3-(trifluoromethyl)phenyl]acetyl}-4-methyl-L-leucinamide;

N-[(2S)-1-{{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4,4-dimethyl-1-oxopentan-2-yl]-6-(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(2S)-1-{{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4-methyl-1-oxopentan-2-yl]-6-(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(2S)-1-{{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4-methyl-1-oxopentan-2-yl]-4-methoxy-3,6,7-tris(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(2S)-1-{{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4,4-dimethyl-1-oxopentan-2-yl]-4-(trifluoromethoxy)-1H-indole-2-carboxamide;

N-[(2S)-1-{{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4-methyl-1-oxopentan-2-yl]-4-(trifluoromethoxy)-1H-indole-2-carboxamide;

N-[(2S)-1-{{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4-methyl-1-oxopentan-2-yl]-3-fluoro-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-{{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4-methyl-1-oxopentan-2-yl]-3,5-difluoro-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-{{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4-methyl-1-oxopentan-2-yl]-5,7-difluoro-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-{{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4-methyl-1-oxopentan-2-yl]-5-fluoro-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-{{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4-methyl-1-oxopentan-2-yl]-4-methoxy-3,5,7-tris(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(2S)-1-{{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4-methyl-1-oxopentan-2-yl]-4-methoxy-3,7-bis(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(2S)-1-{{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4,4-dimethyl-1-oxopentan-2-yl]-5-(trifluoromethyl)-1H-indole-2-carboxamide;
7-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-7-methyl-1H-indole-2-carboxamide;

6-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

4-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

5-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-7-(trifluoromethyl)-1H-indole-2-carboxamide;

4,6-dichloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-4-(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-5-(trifluoromethyl)-1H-indole-2-carboxamide;

7-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-7-methyl-1H-indole-2-carboxamide;

6-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

4-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

5,7-dichloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;
5-chloro-N-\{(2S)-1-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino\}-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-\{(2S)-1-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino\}-4-methyl-1-oxopentan-2-yl]-7-(trifluoromethyl)-1H-indole-2-carboxamide;

4,6-dichloro-N-\{(2S)-1-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino\}-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-\{(2S)-1-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino\}-4-methyl-1-oxopentan-2-yl]-4-(trifluoromethyl)-1H-indole-2-carboxamide;

N-\{(2S)-1-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino\}-4,4-dimethyl-1-oxopentan-2-yl]-3-methyl-5-(trifluoromethyl)imidazo[2,1-b][1,3]thiazole-2-carboxamide;

N-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}-4-methyl-N^2-\{(4-methyl-2-(trifluoromethyl)-1,3-thiazol-5-yl)carbonyl\}-L-leucinamide;

N-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}-4-methyl-N^2-\{(5-methyl-2-(trifluoromethyl)-1,3-thiazol-4-yl)carbonyl\}-L-leucinamide;

N^2-\{(4-bromo-1-ethyl-3-methyl-1H-pyrazol-5-yl)carbonyl\}-N-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}-L-leucinamide;

N^2-\{(4-chloro-1,3-dimethyl-1H-pyrazol-5-yl)carbonyl\}-N-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}-L-leucinamide;

3-acetyl-N-\{(2S)-1-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino\}-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-\{(2S)-1-\{(1S)-1-cyano-2-\{(3R)-2,5-dioxopyrrolidin-3-yl\}ethyl\}amino\}-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-\{(2S)-1-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino\}-4-methyl-1-oxopentan-2-yl]-4-hydroxy-1H-indole-2-carboxamide;

N-\{(2S)-1-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino\}-4-methyl-1-oxopentan-2-yl]-5-hydroxy-4-methoxy-1H-indole-2-carboxamide;

N-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}-N^2-\{(3,3-difluorocyclobutyl)acetyl\}-4-methyl-L-leucinamide;
N²-[[trans-4-cyanocyclohexyl]carbonyl]-N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-4-methyl-L-leucinamide;

N²-[[trans-4-cyanocyclohexyl]carbonyl]-N-{{(1R)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-4-methyl-L-leucinamide;

N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N²-2-(cyclohexyloxy)propanoyl]-4-methyl-L-leucinamide;

N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N²-[cyclohexyl(methoxy)acetyl]-4-methyl-L-leucinamide;

N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N²-[cyclohexyl(methoxy)acetyl]-4-methyl-L-leucinamide;

N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N²-[(2S)-2-(dimethylamino)-2-phenylacetyl]-4-methyl-L-leucinamide;

N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-4-methyl-N²-(pyrrolidin-1-ylacetyl)-L-leucinamide;

N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N²-[(2R)-2-(dimethylamino)-2-phenylacetyl]-4-methyl-L-leucinamide;

N²-[[4-chloro-1,3-dimethyl-1H-pyrazol-5-yl]carbonyl]-N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-4-methyl-L-leucinamide;

N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-3-(trifluoromethyl)-1H-indole-2-carboxamide;

N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-7-(trifluoromethyl)-1H-indole-2-carboxamide;

N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-3,7-bis(trifluoromethyl)-1H-indole-2-carboxamide;

N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-3,5-bis(trifluoromethyl)-1H-indole-2-carboxamide;

N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-3,6-bis(trifluoromethyl)-1H-indole-2-carboxamide;
N-[(2S)-1-[[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-4-methoxy-3-(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N2-(cyclohexylcarbonyl)-4-methyl-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N2-(cyclohexylcarbonyl)-4-methyl-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N2-[[2-(trifluoromethyl)-1,3-thiazol-4-yl]carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N2-[(propan-2-yl)oxy]acetyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N2-[(cyclohexyloxy)acetyl]-4-methyl-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N2-(4,4,4-trifluoro-3-methylbutanoyl)-L-leucinamide;

N-[(2S)-1-[[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-3-methylimidazo[2,1-b][1,3]thiazole-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

N-[(2S)-1-[[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-5,5,5-trifluoro-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-[[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-7-fluoro-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-[[[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

N2-[(4-bromo-1-ethyl-3-methyl-1H-pyrazol-5-yl)carbonyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;
N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-4-methoxy-7-(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-(2,6-dichlorobenzoyl)-4-methyl-L-leucinamide;

(2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4,4-dimethyl-1-[[3-methyl-N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

3-methyl-N-(trifluoroacetyl)-L-valyl-(4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-4-(trifluoromethyl)-L-prolinamide;

(2S,4S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[[3-methyl-N-(trifluoromethyl)sulfonyl]-L-valyl]piperidine-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[[2-(trifluoromethyl)-1,3-thiazol-5-y]carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(2S)-2-(dimethylamino)-2-phenylacetyl]-4-methyl-L-leucinamide;

N^2-[[trans-4-cyanocyclohexyl]carbonyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;

N^2-[[trans-4-cyanocyclohexyl]carbonyl]-N-[(1R)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;

N-[(1R)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[[2-(cyclohexyloxy)propanoyl]-4-methyl-L-leucinamide;

(2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

5-(butan-2-yl)-N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[[4,5-dichloro-1H-imidazol-2-yl]carbonyl]-4-methyl-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(4,5-dichloro-1H-pyrazol-3-yl)carbonyl]-4-methyl-L-leucinamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-2,3-dimethyl-4H-furo[3,2-b]pyrrole-5-carboxamide;

5-chloro-N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-(trifluoromethyl)-1H-benimidazole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-methoxy-1H-pyrrolo[3,2-b]pyridine-2-carboxamide;

5-chloro-N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-pyrrolo[3,2-b]pyridine-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-fluoro-1H-benimidazole-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[(3-(propan-2-yl)-1H-pyrazol-5-yl)carbonyl]-L-leucinamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-fluoro-1H-benimidazole-2-carboxamide;

5-chloro-N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-benimidazole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-5,6-difluoro-1H-benimidazole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-4H-thieno[3,2-b]pyrrole-5-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[(3-(2-methylpropyl)-1H-pyrazol-5-yl)carbonyl]-L-leucinamide;

N^2-[(4-(3-chlorophenyl)-1H-imidazol-2-yl)carbonyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;
N²-[(3-tert-butyl-1H-pyrazol-5-yl)carbonyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;

6-bromo-N-[(2S)-1-[[{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-benzimidazole-2-carboxamide;

N-[(2S)-1-[[{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-methyl-1H-benzimidazole-2-carboxamide;

N-[(2S)-1-[[{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;

4,6-dichloro-N-[(2S)-1-[[{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-benzimidazole-2-carboxamide;

N-[(2S)-1-[[{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-6-(1-methylcyclopropyl)-4-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

N²-[[5-(2-chlorophenyl)-4-fluoro-1H-pyrazol-3-yl]carbonyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;

N-[(2S)-1-[[{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-2-methyl-4H-thieno[3,2-b]pyrrole-5-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N²-[[3-(4-methoxyphenyl)-1H-pyrazol-5-yl]carbonyl]-4-methyl-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N²-[[3-(2-methoxyphenyl)-1H-pyrazol-5-yl]carbonyl]-4-methyl-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N²-[[4-(4-methoxyphenyl)-1H-imidazol-2-yl]carbonyl]-4-methyl-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N²-[[3-(4-methylphenyl)-1H-pyrazol-5-yl]carbonyl]-L-leucinamide;

7-bromo-N-[(2S)-1-[[{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-methyl-1H-indole-2-carboxamide;

7-bromo-N-[(2S)-1-[[{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;
(2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[3-methyl-N-(methylsulfanyl)-L-valyl]piperidine-2-carboxamide;

(2S,4S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

(2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[3-methyl-N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

(2S,4S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

5-(2S)-butan-2-yl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3',3',3'-trifluoro-N-(trifluoroacetyl)-L-isoleucyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-{(2S)-2-cyclohexyl-2-[(trifluoroacetyl)amino]acetyl}-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-{(2S)-2-cyclopentyl-2-[(trifluoroacetyl)amino]acetyl}-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[4-methyl-N-(trifluoroacetyl)-L-leucyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-{(2S)-2-(4,4-difluorocyclohexyl)-2-[(trifluoroacetyl)amino]acetyl}-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[3-cyclopentyl-N-(trifluoroacetyl)-L-alanyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[3-cyclohexyl-N-(trifluoroacetyl)-L-alanyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(trifluoroacetyl)-L-leucyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[6,6-difluoro-N-(trifluoroacetyl)-L-norleucyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,2S,5S)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-6,6-dimethyl-3-[(2S)-4,4,4-trifluoro-2-[(trifluoroacetyl)amino]butanoyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-3-[3-fluoro-N-(trifluoroacetyl)-L-valyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-3-[(2S)-2-cyclopropyl-2-[(trifluoroacetyl)amino]acetyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-3-[3-(3,3-difluorocyclobutyl)-N-(trifluoroacetyl)-L-alanyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-6,6-dimethyl-3-[N-(trifluoroacetyl)-O-(trifluoromethyl)-L-seryl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-6,6-dimethyl-3-[(2S)-2-phenyl-2-[(trifluoroacetyl)amino]acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-6,6-dimethyl-3-[N-(trifluoroacetyl)-L-phenylalanyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-3-[3,5-difluoro-N-(trifluoroacetyl)-L-phenylalanyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-6,6-dimethyl-3-[N-(trifluoroacetyl)-3-(trifluoromethyl)-L-phenylalanyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-6,6-dimethyl-3-[N-(2,2,2-trifluoroethyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(2S,4R)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-4-methyl-1-[(2S)-3-methyl-2-[(trifluoroacetyl)amino]butyl]piperidine-2-carboxamide;

(2S,4R)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-4-methyl-1-[(2S)-3-methyl-2-[(2,2,2-trifluoroethyl)amino]butyl]piperidine-2-carboxamide;

(1R,2S,5S)-N-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-y]ethyl)-6,6-dimethyl-3-[N-(3,3,3-trifluoropropanoyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-(N-propanoyl-L-valyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[N-(2,2,2-trifluoroethyl)-L-valyl]piperidine-2-carboxamide;

N^2-[(4-chloro-1-ethyl-3-methyl-1H-pyrazol-5-yl)carbonyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-L-leucinamide;

5-chloro-N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-3-ethyl-1H-indole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-5-cyclohexyl-1H-indole-2-carboxamide;

5-chloro-N-[(2S)-1-([(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino)-4-methyl-1-oxopentan-2-yl]-3-methyl-1H-indole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-3,5-dimethyl-1H-indole-2-carboxamide;

5-tert-butyl-N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-5-(propan-2-yl)-1H-indole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-3-ethyl-1H-indole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-6-ethyl-1H-indole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-5-ethyl-1H-indole-2-carboxamide;

4-butoxy-N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-5-(trifluoromethoxy)-1H-indole-2-carboxamide;
N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-6-(diethylamino)-1H-indole-2-carboxamide;

4-bromo-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

5-bromo-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

6-bromo-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-3-methyl-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-6-propoxy-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-7-fluoro-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-7-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-6-fluoro-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-5-fluoro-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-5-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-4,5-dimethoxy-1H-indole-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopurroldin-3-yl]ethyl]-4-methyl-\text{N}^2-[(4-methyl-1,3-thiazol-5-\text{yl})carbonyl]-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-(ethoxycarbonyl)-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-(ethoxycarbonyl)-4-methyl-L-leucinamide;
N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-5,5,5-trifluoro-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[[2-(trifluoromethyl)]-1,3-oxazol-4-yl]carbonyl]-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[[3-(trifluoromethyl)]-1,2-thiazol-4-yl]carbonyl]-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[[3-(trifluoromethyl)]-1,2-oxazol-4-yl]carbonyl]-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[[2-(trifluoromethyl)]-1,3-thiazol-4-yl]carbonyl]-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-5,5,5-trifluoro-N^2-[[2-(trifluoromethyl)]-1,3-thiazol-4-yl]carbonyl]-L-norvalinamide;
(4S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-5,5,5-trifluoro-N^2-[[2-(trifluoromethyl)]-1,3-thiazol-4-yl]carbonyl]-L-leucinamide;
(4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-5,5,5-trifluoro-N^2-[[2-(trifluoromethyl)]-1,3-thiazol-4-yl]carbonyl]-L-leucinamide;
N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-3-cyclopentyl-1-oxopropan-2-yl]-2-(trifluoromethyl)-1,3-thiazole-4-carboxamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[[5-(trifluoromethyl)]-1,2-thiazol-4-yl]carbonyl]-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[[5-(trifluoromethyl)]-1,2-oxazol-4-yl]carbonyl]-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[[2-(trifluoromethyl)]-1,3-oxazol-5-yl]carbonyl]-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N2-[(2-(trifluoromethyl)-1,3-thiazol-5-yl)carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-5,5-trifluoro-4-methyl-N2-[(2-(trifluoromethyl)-1,3-thiazol-4-yl)carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N2-[(2S)-2-methyltetrahydrofuran-2-yl]carbonyl]-L-leucinamide;

N-[(2S,4R)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-5,5-trifluoro-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-[(2S,4S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-5,5-trifluoro-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-5,5-trifluoro-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-3-cyclopentyl-1-oxopropan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

5,7-dichloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

5-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-3-ethyl-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-5-cyclohexyl-1H-indole-2-carboxamide;

5-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-3-methyl-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-3,5-dimethyl-1H-indole-2-carboxamide;

5-tert-butyl-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-5-(propan-2-yl)-1H-indole-2-carboxamide;
N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-7-(propan-2-yl)-1H-indole-2-carboxamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-3-ethyl-1H-indole-2-carboxamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-6-ethyl-1H-indole-2-carboxamide;

4-butoxy-N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-5-(trifluoromethoxy)-1H-indole-2-carboxamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-6-(diethylamino)-1H-indole-2-carboxamide;

4-bromo-N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

5-bromo-N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

6-bromo-N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-3-methyl-1H-indole-2-carboxamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-6-propoxy-1H-indole-2-carboxamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-4-methyl-1H-indole-2-carboxamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-5-methyl-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-6-methyl-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-7-fluoro-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-7-methoxy-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-6-fluoro-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-fluoro-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-6-methoxy-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-methoxy-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-4,5-dimethoxy-1H-indole-2-carboxamide;
5-(butan-2-yl)-N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-7-(propan-2-yl)-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-4-methyl-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-5-methyl-1H-indole-2-carboxamide;
N-[(2S)-1-[[1(S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-6-methyl-1H-indole-2-carboxamide;
N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4-methyl-1-oxopentan-2-yl]-6-methoxy-1H-indole-2-carboxamide;

5-(butan-2-yl)-N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(2R)-2-cyclohexyl-2-methoxyacetyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(2R)-2-(cyclohexyloxy)propanoyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-(4,4,4-trifluoro-3-methylbutanoyl)-L-leucinamide;

N^2-[(trans-4-cyanocyclohexyl)carbonyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(1-ethyl-4-methyl-1H-pyrazol-5-yl)carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-(cyclohexylcarbonyl)-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-(cyclohexyloxy)acetyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[3,3-difluorocyclobutyl]acetyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(propan-2-yloxy)acetyl]-L-leucinamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4-methyl-1-oxopentan-2-yl]-3-methylimidazo[2,1-b][1,3]thiazole-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(2R)-2-cyclohexyl-2-methoxyacetyl]-4-methyl-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(1-ethyl-4-methyl-1H-pyrazol-5-yl)carbonyl]-4-methyl-L-leucinamide;
N²-[2-chloro-4-(methylsulfonyl)benzoyl]-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-L-leucinamide;

N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N²-(2,6-dichlorobenzoyl)-L-leucinamide;

(1R,2S,5S)-3-[N-(tert-butylsulfonyl)-3-methyl-L-valyl]-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-3-[[3R]-1-benzyl-5-oxopyrrolidin-3-yl]carbonyl]-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-[[3R]-5-oxo-1-phenylpyrrolidin-3-yl]carbonyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-3-[[3R]-1-tert-butyl-5-oxopyrrolidin-3-yl]carbonyl]-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-[[3-methylimidazo[2,1-b][1,3]thiazol-2-yl]carbonyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-[[2-(trifluoromethyl)-1,3-thiazol-4-yl]carbonyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

N-{(2S)-1-[[{1S}-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-3-cyclopropyl-1-oxopropan-2-yl]-4-methoxy-1H-indole-2-carboxamide; and

N-{(2S)-1-[[{1S}-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-3-cyclopropyl-1-oxopropan-2-yl]-1H-indole-2-carboxamide;

or a pharmaceutically acceptable salt thereof.

A thirtieth embodiment of a first aspect of the invention is a compound of the first embodiment of the first aspect of the invention selected from the group consisting of

N-{(2S)-1-[[{1S}-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-7-fluoro-4-methoxy-1H-indole-2-carboxamide;

N-{(2S)-1-[[{1S}-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-4-methoxy-7-(trifluoromethyl)-1H-indole-2-carboxamide;
(1R,2S,5S)-N-[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-7-fluoro-4-methoxy-1H-indole-2-carboxamide;

(2S,4S)-N-[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

(2S,4S)-N-[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[3-methyl-N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]-3-[(2S)-2-cyclohexyl-2-[(trifluoroacetyl)amino]acetyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(2S,4S)-N-[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-{3-methyl-N-[(trifluoromethyl)sulfonyl]-L-valyl}piperidine-2-carboxamide;

3-methyl-N-(trifluoroacetyl)-L-valyl-(4R)-N-[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-4-(trifluoromethyl)-L-prolinamide; and

(2S)-N-[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]-4,4-dimethyl-1-[3-methyl-N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

or a pharmaceutically acceptable salt thereof.

A first embodiment of a second aspect of the invention is a pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of the first through thirtieth embodiments of the first aspect of the invention or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

A second embodiment of a second aspect of the invention is the pharmaceutical composition of the first embodiment of the second aspect of the invention wherein the composition is in the form of an intravenous, subcutaneous, inhaled or oral dosage form.
A third embodiment of a second aspect of the invention is the pharmaceutical composition of a second embodiment of the second aspect of the invention wherein the composition is in an oral dosage form.

A fourth embodiment of a second aspect of the invention is the pharmaceutical composition of the first embodiment of the second aspect of the invention further comprising an additional therapeutic agent.

A fifth embodiment of a second aspect of the invention is the pharmaceutical composition of the fourth embodiment of the second aspect of the invention wherein the pharmaceutical composition further comprises one or more of dexamethasone, azithromycin, and remdesivir.

A first embodiment of a third aspect of the invention is a method of treating a coronavirus infection in a patient, the method comprising administering a therapeutically effective amount of a compound of any one of the first through thirtieth embodiments of the first aspect of the invention or a pharmaceutically acceptable salt thereof to a patient in need thereof.

A second embodiment of a third aspect of the invention is the method of the first embodiment of the third aspect of the invention wherein the coronavirus infection is COVID-19.

A first embodiment of a fourth aspect of the invention is a method of treating a coronavirus infection in a patient, the method comprising administering a pharmaceutical composition of any one of the first through fifth embodiments of the second aspect of the invention to a patient in need thereof.

A second embodiment of a fourth aspect of the invention is the method of the first embodiment of the fourth aspect of the invention wherein the coronavirus infection is COVID-19.

Another embodiment of the invention is a method of inhibiting or preventing SARS-CoV-2 viral replication comprising contacting the SARS-CoV-2 coronavirus 3CL protease with a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of the first through thirtieth embodiments of the first aspect of the invention.
Another embodiment of the invention is a method of inhibiting or preventing SARS-CoV-2 viral replication in a patient comprising administering to the patient in need of inhibition of or prevention of SARS-CoV-2 viral replication a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof of any one of the first through thirtieth embodiments of the first aspect of the invention.

Another embodiment of the invention is the use of a compound or a pharmaceutically acceptable salt thereof of any one of the first through thirtieth embodiments of the first aspect of the invention for the treatment of a coronavirus infection. Another embodiment of the invention is the use of the immediately preceding embodiment wherein the coronavirus infection is COVID-19.

Another embodiment of the invention is the use of a compound or a pharmaceutically acceptable salt thereof of any one of the first through thirtieth embodiments of the first aspect of the invention for the preparation of a medicament that is useful for the treatment of a coronavirus infection. The use of the immediately preceding embodiment wherein the coronavirus infection is COVID-19.

Another embodiment of the present invention is a compound of Formula I'

\[ \text{Diagram of molecular structure} \]

or a pharmaceutically acceptable salt thereof; wherein \( R \) at each occurrence is independently hydroxy or oxo; \( p \) is 0, 1 or 2; \( R^1 \) is selected from the group consisting of C\(_1\)-C\(_6\) alkyl which is optionally substituted with a cyano or with one to five fluoro; C\(_2\)-C\(_6\) alkynyl; and (C\(_3\)-C\(_8\) cycloalkyl)-C\(_1\)-C\(_3\) alkyl which is optionally substituted with one to two substituents selected from trifluoromethyl and C\(_1\)-C\(_3\) alkyl or with one to five fluoro; \( R^2 \) is hydrogen or R\(^2\) and R\(^1\) taken together with the nitrogen and carbon atoms to which they are attached are a pyrrolidine or piperidine ring which is optionally substituted with one to four R\(^2\); R\(^2\) at each occurrence is independently selected from the group consisting of fluoro, hydroxy, C\(_1\)-C\(_6\) alkyl optionally substituted with one to three fluoro and C\(_1\)-C\(_6\)
alkoxy optionally substituted with one to three fluoro; or two R\textsuperscript{2a} groups when attached to adjacent carbons and taken together with the carbons to which they are attached are a fused C\textsubscript{3}-C\textsubscript{5} cycloalkyl which is optionally substituted with one to four R\textsuperscript{2b}; or two R\textsuperscript{2a} groups when attached to the same carbon and taken together with the carbon to which they are attached are a spiro C\textsubscript{3}-C\textsubscript{6} cycloalkyl which is optionally substituted with one to four R\textsuperscript{2b}; R\textsuperscript{2a} at each occurrence is independently selected from fluoro, hydroxy, C\textsubscript{1}-C\textsubscript{3} alkyl optionally independently substituted with one to three fluoro or hydroxy and C\textsubscript{1}-C\textsubscript{3} alkoxy optionally independently substituted with one to three fluoro or hydroxy; R\textsuperscript{3} is selected from the group consisting of C\textsubscript{1}-C\textsubscript{8} alkyl, C\textsubscript{2}-C\textsubscript{8} alkoxy, C\textsubscript{2}-C\textsubscript{8} alkynyl, C\textsubscript{3}-C\textsubscript{12} cycloalkyl optionally fused with a 5- to 6-membered heteroaryl or phenyl, (C\textsubscript{3}-C\textsubscript{12} cycloalkyl)-C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{12} cycloalkoxy, (C\textsubscript{3}-C\textsubscript{12} cycloalkoxy)-C\textsubscript{1}-C\textsubscript{6} alkyl, 4- to 12-membered heterocycloalkyl which is optionally fused with a 5- to 6-membered heteroaryl or phenyl and wherein said heterocycloalkyl comprises one to four heteroatoms independently selected from N, O and S(O)\textsubscript{n}, (4- to 12-membered heterocycloalkyl)-C\textsubscript{1}-C\textsubscript{6} alkyl wherein said heterocycloalkyl moiety comprises one to four heteroatoms independently selected from N, O and S(O)\textsubscript{n}, C\textsubscript{6}-C\textsubscript{10} aryl optionally fused with a C\textsubscript{4}-C\textsubscript{6} cycloalkyl or a 4- to 7-membered heterocycloalkyl, (C\textsubscript{6}-C\textsubscript{10} aryl)-C\textsubscript{1}-C\textsubscript{6} alkyl, 5- to 10-membered heteroaryl comprising one to five heteroatoms independently selected from N, O and S, (4- to 10-membered heterocycloalkyl)-C\textsubscript{1}-C\textsubscript{6} alkyl wherein the heterocycloalkyl moiety comprises one to five heteroatoms independently selected from N, O and S, (5- to 10-membered heteroaryl)-C\textsubscript{1}-C\textsubscript{6} alkyl wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S, (5- to 10-membered heterocycloalkyl)-C\textsubscript{1}-C\textsubscript{6} alkyl wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S, (5- to 6-membered heteroaryl)-C\textsubscript{1}-C\textsubscript{6} alkyl wherein each heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S, (5- to 6-membered heteroaryl)-C\textsubscript{1}-C\textsubscript{6} alkyl wherein each heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S, (4- to 7-membered heterocycloalkyl)-C\textsubscript{1}-C\textsubscript{6} alkyl wherein the heterocycloalkyl moiety comprises one to three heteroatoms independently selected from N, O and S(O)\textsubscript{n}, and the heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S, (4- to 7-membered heterocycloalkyl)-C\textsubscript{1}-C\textsubscript{6} alkyl wherein the heterocycloalkyl moiety comprises one to three heteroatoms independently selected from N, O and S(O)\textsubscript{n}, and the heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S, wherein each R\textsuperscript{3} group is optionally substituted with one to five R\textsuperscript{4}; R\textsuperscript{4} at each occurrence is independently
selected from the group consisting of oxo, halo, hydroxy, cyano, phenyl, benzyl, amino, (C1-C6 alkyl)amino optionally substituted with one to five fluoro, di(C1-C6 alkyl)amino optionally substituted with one to ten fluoro, C1-C6 alkyl optionally substituted with one to five fluoro, C1-C6 alkoxy optionally substituted with one to five fluoro, C1-C3 alkoxy-C1-C3 alkyl optionally substituted with one to five fluoro, C3-C8 cycloalkyl optionally substituted with one to three fluoro or C1-C3 alkyl, C1-C8 alkyl-C(O)NH- optionally substituted with one to five fluoro, C1-C8 alkyl-OC(O)NH- optionally substituted with one to five fluoro or with one R5, C1-C8 alkyl-NHC(O)NH- optionally substituted with one to five fluoro or with one R5, C1-C8 alkyl-S(O)2NH- optionally substituted with one to five fluoro or with one R5, C1-C8 alkyl-C(O)- optionally substituted with one to five fluoro or with one R5, C1-C8 alkyl-S(O)n- optionally substituted with one to five fluoro or with one R5; R5 is selected from phenyl, phenoxy, C3-C8 cycloalkyl, C3-C8 cycloalkoxy, 4- to 7-membered heterocycloalkyl- wherein the heterocycloalkyl moiety comprises one to three heteroatoms independently selected from N, O and S(O)n and 5- to 6-membered heteroaryl- wherein the heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S; wherein each R5 is optionally independently substituted with one to three halo, C1-C3 alkyl and C1-C3 alkoxy; and n at each occurrence is independently selected from 0, 1 and 2.

Another embodiment of the present invention is a compound of selected from the group consisting of (2S,4R)-4-tert-butyl-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-1-(N-[[trifluoromethyl]sulfonyl]-L-valyl)piperidine-2-carboxamide; (2R,4S)-4-tert-butyl-N-{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-(N-[[trifluoromethyl]sulfonyl]-L-valyl)piperidine-2-carboxamide; 3-methyl-N-(trifluoroadetyl)-L-valyl-(4R)-N-{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-4-(trifluoromethyl)-L-prolinamide; (1R,2S,5S)-N-{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-[3-methyl-N-(methylcarbamoyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; methyl ((2S)-1-[(1R,2S,5S)-2-{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl}-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl]-3,3-dimethyl-1-oxobutan-2-yl)carbamate; and N-(trifluoroadetyl)-L-valyl-(4R)-N-{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-4-(trifluoromethyl)-L-prolinamide; or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is a method of treating a coronavirus infection in a patient, the method comprising administering a therapeutically effective amount of a compound of any one of the immediately preceding two embodiments or a pharmaceutically acceptable salt thereof to a patient in need thereof.
Another embodiment of the present invention is the method of the immediately preceding embodiment wherein the coronavirus infection is COVID-19.

Another embodiment of the present invention is a method of treating a coronavirus infection in a patient, the method comprising administering a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof wherein an additional therapeutic agent is administered and the additional therapeutic agent is selected from the group consisting of remdesivir, galidesivir, favlavitavir, favipiravir, mulnupiravir, AT-527, AT-301, BLD-2660, favipiravir, camostat, SLV213, emtricitabine/tenofovir, clevudine, dalcetrapib, boceprevir, ABX464, dexamethasone, hydrocortisone, convalescent plasma, gelsolin (Rhu-p65N), regdanvimab (Regkriova), ravulizumab (Ultomiris), VIR-7831/VIR-7832, BRII-196/BRII-198, COVI-AMG/COVI DROPS (ST-2020), bamlanivimab (LY-CoV555), mavrilimab, leronlimab (PRO140), AZD7442, lenzilumab, infliximab, adalimumab, JS 016, STI-1499 (COVIGUARD), lanadelumab (Takhzyro), canakinumab (Ilaris), gimsilumab, otilimab, casivimab/imdevimab (REGN-Cov2), MK-7110 (CD24Fc/SACCOVID), heparin, apixaban, tocilizumab (Actemra), sarilumab (Kevzara), apilimod dimesylate, DNL758, PB1046, dapaglifozin, abivertinib, ATR-002, bemcentinib, acalabrutinib, losmapimod, famotidine, ritonavir, nicosamide and diminazene.

Another embodiment of the present invention is the compound (1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is a pharmaceutical composition comprising a therapeutically effective amount of (1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

Another embodiment of the present invention is a method of treating a coronavirus infection in a patient, the method comprising administering a therapeutically effective amount of (1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof.
Another embodiment of the present invention is the method of the immediately preceding embodiment wherein the coronavirus infection is COVID-19.

Another embodiment of the present invention is the method of either of the two immediately preceding embodiments wherein (1R,2S,5S)-N-{(1S)-1-Cyano-2-[(3S)-2-oxopyrroloidin-3-yl]ethyl}-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof is administered orally.

Another embodiment of the present invention is the method of the immediately preceding embodiment wherein 50 mg to 1500 mg of (1R,2S,5S)-N-{(1S)-1-Cyano-2-[(3S)-2-oxopyrroloidin-3-yl]ethyl}-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof is administered each day.

Another embodiment of the present invention is the method of the immediately preceding embodiment wherein 380 mg of (1R,2S,5S)-N-{(1S)-1-Cyano-2-[(3S)-2-oxopyrroloidin-3-yl]ethyl}-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof is administered three times a day.

Another embodiment of the present invention is the method wherein 50 mg to 1500 mg of (1R,2S,5S)-N-{(1S)-1-Cyano-2-[(3S)-2-oxopyrroloidin-3-yl]ethyl}-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof is administered each day as an oral suspension, capsule or tablet.

Another embodiment of the present invention is the method of the immediately preceding embodiment wherein a tablet is administered.

The present invention also provides a method of targeting SARS-CoV-2 inhibition as a means of treating indications caused by SARS-CoV-2-related viral infections.

The present invention also provides a method of identifying cellular or viral pathways interfering with the functioning of the members of which could be used for treating indications caused by SARS-CoV-2 infections by administering a SARS-CoV-2 protease inhibitor as described herein.
The present invention also provides a method of using SARS-CoV-2 protease inhibitors as described herein as tools for understanding mechanism of action of other SARS-CoV-2 inhibitors.

The present invention also provides a method of using SARS-CoV-2 3C-like protease inhibitors for carrying out gene-profiling experiments for monitoring the up- or down-regulation of genes for the purpose of identifying inhibitors for treating indications caused by SARS-CoV-2 infections such as COVID-19.

The present invention further provides a pharmaceutical composition for the treatment of COVID-19 in a mammal containing an amount of a SARS-CoV-2 3C-like protease inhibitor that is effective in treating COVID-19 and a pharmaceutically acceptable carrier.

Another embodiment of the present invention is a method of treating MERS in a patient, the method comprising administering a therapeutically effective amount of a compound of any one of the first through thirtieth embodiments of the first aspect of the invention or a pharmaceutically acceptable salt thereof to a patient in need thereof.

Another embodiment of the invention is a method of treating MERS in a patient, the method comprising administering a pharmaceutical composition of any one of the first through fifth embodiments of the second aspect of the invention to a patient in need thereof.

Another embodiment of the invention is a method of inhibiting or preventing MERS viral replication comprising contacting the SARS-CoV-2 coronavirus 3CL protease with a therapeutically effective amount of a compound of any one of the first through thirtieth embodiments of the first aspect of the present invention or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is a method of inhibiting or preventing MERS viral replication in a patient comprising administering to the patient in need of inhibition of or prevention of MERS viral replication a therapeutically effective amount of a compound of any one of the first through thirtieth embodiments of the first aspect of the invention or a pharmaceutically acceptable salt thereof.

**Detailed Description of The Invention**
For the purposes of the present invention, as described and claimed herein, the following terms are defined as follows:

As used herein, the terms “comprising” and “including” are used in their open, non-limiting sense. The term “treating”, as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term “treatment”, as used herein, unless otherwise indicated, refers to the act of treating as “treating” is defined immediately above.

The term "alkyl" as used herein refers to a linear or branched-chain saturated hydrocarbyl substituent (i.e., a substituent obtained from a hydrocarbon by removal of a hydrogen); in one embodiment containing from one to eight carbon atoms, in another one to six carbon atoms and in yet another one to three carbon atoms. Non-limiting examples of such substituents include methyl, ethyl, propyl (including \( n \)-propyl and isopropyl), butyl (including \( n \)-butyl, isobutyl, sec-butyl and \( \text{tert} \)-butyl), pentyl, isoamyl, hexyl, heptyl, octyl and the like. In another embodiment containing one to three carbons and consisting of methyl, ethyl, \( n \)-propyl and isopropyl.

The term "alkynyl" as used herein refers to a linear or branched-chain saturated hydrocarbyl substituent that contains a carbon-carbon triple bond (i.e., a substituent obtained from a triple bond-containing hydrocarbon by removal of a hydrogen); in one embodiment containing from two to six carbon atoms. Non-limiting examples of such substituents include prop-2-yn-1-yl, but-3-yn-1-yl, pent-4-yn-1-yl and hex-5-yn-1-yl.

The term "alkoxy" refers to a linear or branched-chain saturated hydrocarbyl substituent attached to an oxygen radical (i.e., a substituent obtained from a hydrocarbon alcohol by removal of the hydrogen from the \( \text{OH} \)); in one embodiment containing from one to six carbon atoms. Non-limiting examples of such substituents include methoxy, ethoxy, propoxy (including \( n \)-propoxy and isopropoxy), butoxy (including \( n \)-butoxy, isobutoxy, sec-butoxy and \( \text{tert} \)-butoxy), pentoxy, hexoxy and the like. In another embodiment having one to three carbons and consisting of methoxy, ethoxy, \( n \)-propoxy and isopropoxy. An alkoxy group which is attached to an alkyl group is referred to as an alkoxyalkyl. An example of an alkoxyalkyl group is methoxymethyl.

The term "alkynylxyloxy" refers to a linear or branched-chain saturated hydrocarbyl substituent containing a carbon-carbon triple bond attached to an oxygen radical (i.e., a substituent obtained from a triple bond-containing hydrocarbon alcohol by removal of
the hydrogen from the OH); in one embodiment containing from three to six carbon atoms. Non-limiting examples of such substituents include propynloxy, butynloxy and pentynloxy and the like.

In some instances, the number of carbon atoms in a hydrocarbyl substituent (i.e., alkyl, cycloalkyl, etc.) is indicated by the prefix "C\textsubscript{x}-C\textsubscript{y}" or "C\textsubscript{x:y}", wherein \(x\) is the minimum and \(y\) is the maximum number of carbon atoms in the substituent. Thus, for example, "C\textsubscript{1}-C\textsubscript{8} alkyl" or "C\textsubscript{1:8} alkyl" refers to an alkyl substituent containing from 1 to 8 carbon atoms, "C\textsubscript{1}-C\textsubscript{8} alkyl" or "C\textsubscript{1:8} alkyl" refers to an alkyl substituent containing from 1 to 6 carbon atoms, "C\textsubscript{1}-C\textsubscript{3} alkyl" or "C\textsubscript{1:3} alkyl" refers to an alkyl substituent containing from 1 to 3 carbon atoms. Illustrating further, C\textsubscript{3}-C\textsubscript{6} cycloalkyl or C\textsubscript{3:6}-cycloalkyl refers to a saturated cycloalkyl group containing from 3 to 6 carbon ring atoms.

The term "cycloalkyl" refers to a carbocyclic substituent obtained by removing a hydrogen from a saturated carbocyclic molecule, for example one having three to seven carbon atoms. The term "cycloalkyl" includes monocyclic saturated carbocycles. The term "C\textsubscript{3}-C\textsubscript{7} cycloalkyl" means a radical of a three- to seven-membered ring system which includes the groups cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "C\textsubscript{3}-C\textsubscript{6} cycloalkyl" means a radical of a three- to six-membered ring system which includes the groups cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The cycloalkyl groups can also be bicyclic or spirocyclic carbocycles. For example, the term "C\textsubscript{3}-C\textsubscript{12} cycloalkyl" includes monocyclic carbocycles and bicyclic and spirocyclic cycloalkyl moieties such as bicyclopentyl, bicyclohexyl, bicycloheptyl, bicyclooctyl, bicyclononyl, spiropentyl, spirohexyl, spiroheptyl, spirooctyl and spirononyl.

The term "C\textsubscript{3}-C\textsubscript{6} cycloalkoxy" refers to a three- to six-membered cycloalkyl group attached to an oxygen radical. Examples include cyclopropoxy, cyclobutoxy, cyclopentoxy and cyclohexoxy.

The term "aryl" refers to a carbocyclic aromatic system. The term "C\textsubscript{6}-C\textsubscript{10} aryl" refers to carbocyclic aromatic systems with 3 to 10 atoms and includes phenyl and naphthyl.

In some instances, the number of atoms in a cyclic substituent containing one or more heteroatoms (i.e., heteroaryl or heterocycloalkyl) is indicated by the prefix "x- to y-membered", wherein \(x\) is the minimum and \(y\) is the maximum number of atoms forming the cyclic moiety of the substituent. Thus, for example, "4- to 6-membered heterocycloalkyl" refers to a heterocycloalkyl containing from 4 to 6 atoms, including one
to three heteroatoms, in the cyclic moiety of the heterocycloalkyl. Likewise, the phrase “5- to 6-membered heteroaryl” refers to a heteroaryl containing from 5 to 6 atoms, and “5- to 10-membered heteroaryl” refers to a heteroaryl containing from 5 to 10 atoms, each including one or more heteroatoms, in the cyclic moiety of the heteroaryl.

Furthermore, the phrases “5-membered heteroaryl” and “6-membered heteroaryl” refer to a five-membered heteroaromatic ring system and a six-membered heteroaromatic ring system, respectively. The heteroatoms present in these ring systems are selected from N, O and S.

The term “hydroxy” or “hydroxyl” refers to –OH. When used in combination with another term(s), the prefix “hydroxy” indicates that the substituent to which the prefix is attached is substituted with one or more hydroxy substituents. Compounds bearing a carbon to which one or more hydroxy substituents include, for example, alcohols, enols and phenol. The terms cyano and nitrile refer to a -CN group. The term “oxo” means an oxygen which is attached to a carbon by a double bond (i.e., when R^4 is oxo then R^4 together with the carbon to which it is attached are a C=O moiety).

The term “halo” or “halogen” refers to fluorine (which may be depicted as -F), chlorine (which may be depicted as -Cl), bromine (which may be depicted as -Br), or iodine (which may be depicted as -I).

The term “heterocycloalkyl” refers to a substituent obtained by removing a hydrogen from a saturated or partially saturated ring structure containing a total of the specified number of atoms, such as 4 to 6 ring atoms or 4 to 12 atoms, wherein at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. The sulfur may be oxidized [i.e., S(O) or S(O)_2] or not. In a group that has a heterocycloalkyl substituent, the ring atom of the heterocycloalkyl substituent that is bound to the group may be a nitrogen heteroatom, or it may be a ring carbon atom. Similarly, if the heterocycloalkyl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to a nitrogen heteroatom, or it may be bound to a ring carbon atom. It is to be understood that a heterocyclic group may be monocyclic, bicyclic, polycyclic or spirocyclic.

The term “heteroaryl” refers to an aromatic ring structure containing the specified number of ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the
group consisting of carbon, oxygen, nitrogen, and sulfur. Examples of heteroaryl substituents include 6-membered heteroaryl substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; and 5-membered heteroaryl substituents such as triazolyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl. The heteroaryl group can also be a bicyclic heteroaromatic group such as indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzoazolyl, benzoisoxazolyl, oxazolopyridinyl, imidazopyridinyl, imidazopyrimidinyl and the like. In a group that has a heteroaryl substituent, the ring atom of the heteroaryl substituent that is bound to the group may be one of the heteroatoms, or it may be a ring carbon atom. Similarly, if the heteroaryl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to one of the heteroatoms, or it may be bound to a ring carbon atom. The term “heteroaryl” also includes pyridyl N-oxides and groups containing a pyridine N-oxide ring. In addition, the heteroaryl group may contain an oxo group such as the one present in a pyridone group. Further examples include furyl, thieryl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyridin-2(1H)-onyl, pyridazin-2(1H)-onyl, pyrimidin-2(1H)-onyl, pyrazin-2(1H)-onyl, imidazo[1,2-a]pyridinyl, and pyrazolo[1,5-a]pyridinyl. The heteroaryl can be further substituted as defined herein.

Examples of single-ring heteroaryl and heterocycloalkyls include furanyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isomimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathioliol, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, 1,2,4-oxadiazolyl, or 1,3,4-oxadiazolyl, pyranyl (including 1,2-pyranyl or 1,4-pyranyl), dihydropyranyl, pyridinyl, piperidinyl, diazinnyl (including pyridazinyl, pyrimidinyl, piperazinyl, triazinyl (including s-triazinyl, as-triazinyl and v-triazinyl), oxazinyl (including 2H-1,2-oxazinyl, 6H-1,3-oxazinyl, or 2H-1,4-oxazinyl), isoxazinyl (including α-isoxazinyl or β-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 2H-1,2,4-oxadiazinyl or 2H-1,2,5-oxadiazinyl), and morpholinyl.

The term “heteroaryl” can also include, when specified as such, ring systems having two rings wherein such rings may be fused and wherein one ring is aromatic and the other ring is not fully part of the conjugated aromatic system (i.e., the heteroaromatic
ring can be fused to a cycloalkyl or heterocycloalkyl ring. Non-limiting examples of such ring systems include 5,6,7,8-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydroquinolinyl, 6,7-dihydro-5H-cyclopenta[b]pyridinyl, 6,7-dihydro-5H-cyclopenta[c]pyridinyl, 1,4,5,6-tetrahydrocyclopenta[c]pyrazolyl, 2,4,5,6-tetrahydrocyclopenta[c]pyrazolyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, 6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazolyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridinyl, 4,5,6,7-tetrahydro-1H-indazolyl and 4,5,6,7-tetrahydro-2H-indazolyl. It is to be understood that if a carbocyclic or heterocyclic moiety may be bonded or otherwise attached to a designated substrate through differing ring atoms without denoting a specific point of attachment, then all possible points are intended, whether through a carbon atom or, for example, a trivalent nitrogen atom. For example, the term "pyridyl" means 2-, 3- or 4-pyridyl, the term "thienyl" means 2- or 3-thienyl, and so forth.

If substituents are described as "independently" having more than one variable, each instance of a substituent is selected independent of the other(s) from the list of variables available. Each substituent therefore may be identical to or different from the other substituent(s).

If substituents are described as being "independently selected" from a group, each instance of a substituent is selected independent of the other(s). Each substituent therefore may be identical to or different from the other substituent(s).

As used herein, the term "Formula I" may be hereinafter referred to as a "compound(s) of the invention," "the present invention," and "compound of Formula I." Such terms are also defined to include all forms of the compound of Formula I, including hydrates, solvates, isomers, crystalline and non-crystalline forms, isomorphs, polymorphs, and metabolites thereof. For example, the compounds of the invention, or pharmaceutically acceptable salts thereof, may exist in unsolvated and solvated forms. When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

The compounds of the invention may exist as clathrates or other complexes. Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein the drug and host are present in stoichiometric or non-
stoichiometric amounts. Also included are complexes of the compounds of the invention containing two or more organic and/or inorganic components, which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J. Pharm. Sci., 64 (8), 1269-1288 by Haleblian (August 1975).

The compounds of the invention have asymmetric carbon atoms. The carbon-carbon bonds of the compounds of the invention may be depicted herein using a solid line (---), a solid wedge (\[\text{\textbullet}\]), or a dotted wedge (\[\text{\textbullet\textbullet\textbullet\textbullet}\]). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers (e.g., specific enantiomers, racemic mixtures, etc.) at that carbon atom are included. The use of either a solid or dotted wedge to depict bonds to asymmetric carbon atoms is meant to indicate that only the stereoisomer shown is meant to be included. It is possible that compounds of Formula I may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included. For example, unless stated otherwise, it is intended that the compounds of Formula I can exist as enantiomers and diastereomers or as racemates and mixtures thereof. The use of a solid line to depict bonds to one or more asymmetric carbon atoms in a compound of Formula I and the use of a solid or dotted wedge to depict bonds to other asymmetric carbon atoms in the same compound is meant to indicate that a mixture of diastereomers is present.

Stereoisomers of Formula I include cis and trans isomers, optical isomers such as R and S enantiomers, diastereomers, geometric isomers, rotational isomers, conformational isomers, and tautomers of the compounds of the invention, including compounds exhibiting more than one type of isomerism; and mixtures thereof (such as racemates and diastereomeric pairs). Also included are acid addition or base addition salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.
The compounds of Formula I may exhibit the phenomenon of tautomerism; such tautomers are also regarded as compounds of the invention. All such tautomeric forms, and mixtures thereof, are included within the scope of compounds of Formula I. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the compounds of Formula I and salts thereof.

The phrase "pharmacologically acceptable salts(s)" as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds described herein. The compounds used in the methods of the invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, ethylsuccinate, fumarate, gluceptate, gluconate, glutamate, hexylresorcinol, hydrabamine, hydrobromide, hydrochloride, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, olate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

With respect to the compounds of the invention used in the methods of the invention, if the compounds also exist as tautomeric forms then this invention relates to those tautomers and the use of all such tautomers and mixtures thereof.

The subject invention also includes compounds and methods of treatment of coronavirus infections such as COVID-19 and methods of inhibiting SARS-CoV-2 with isotopically labelled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as \(^2\)H, \(^3\)H, \(^13\)C, \(^14\)C, \(^15\)N, \(^18\)O, \(^17\)O, \(^31\)P, \(^32\)P, \(^35\)S, \(^18\)F, and \(^36\)Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically
acceptable salts of said compounds or of said prodrugs which contain
the aforementioned isotopes and/or isotopes of other atoms are with the scope of this
invention. Certain isotopically labelled compounds of the present invention, for example
those into which radioactive isotopes such as $^3$H and $^{14}$C are incorporated, are useful in
drug and/or substrate tissue distribution assays. Tritiated, i.e., $^3$H, and carbon-14, i.e.,
$^{14}$C, isotopes are particularly preferred for their ease of preparation and detectability.
Further, substitution with heavier isotopes such as deuterium, i.e., $^2$H, can afford certain
therapeutic advantages resulting from greater metabolic stability, for example increased
in vivo half-life or reduced dosage requirements and, hence, may be preferred in some
circumstances. Isotopically labelled compounds used in the methods of this invention
and prodrugs thereof can generally be prepared by carrying out the procedures for
preparing the compounds disclosed in the art by substituting a readily available
isotopically labelled reagent for a non-isotopically labelled reagent.

This invention also encompasses methods using pharmaceutical compositions
and methods of treating coronavirus infections such as COVID-19 infections through
administering prodrugs of compounds of the invention. Compounds having free amino,
amido or hydroxy groups can be converted into prodrugs. Prodrugs include compounds
wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or
four) amino acid residues is covalently joined through an ester bond to a hydroxy of
compounds used in the methods of this invention. The amino acid residues include but
are not limited to the 20 naturally occurring amino acids commonly designated by three
letter symbols and also include 4-hydroxyproline, hydroxylysine, desmosine,
isodesmosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid,
citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Additional
types of prodrugs are also encompassed. For instance, free hydroxy groups may be
derivatized using groups including but not limited to hemisuccinates, phosphate esters,
dimethylaminoacetates, and phosphoryloxymethylxycarbonyls, as outlined in
Advanced Drug Delivery Reviews, 1996, 19, 115. Carbamate prodrugs of hydroxy and
amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate
esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and
(acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally
substituted with groups including but not limited to ether, amine and carboxylic acid
functionalities, or where the acyl group is an amino acid ester as described above, are
also encompassed. Prodrugs of this type are described in J. Med. Chem., 1996, 29, 10.
Free amines can also be derivatized as amides, sulfonamides or phosphoramides. All
of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

The compounds of the present invention can be used in the methods of the invention in combination with other drugs. For example, dosing a SARS-CoV-2 coronavirus-infected patient (i.e., a patient with COVID-19) with the SARS-CoV-2 coronavirus 3CL protease inhibitor of the invention and an interferon, such as interferon alpha, or a pegylated interferon, such as PEG-Intron or Pegasys, may provide a greater clinical benefit than dosing either the interferon, pegylated interferon or the SARS-CoV-2 coronavirus inhibitor alone. Other additional agents that can be used in the methods of the present invention include dexamethasone, azithromycin and remdesivir. Examples of greater clinical benefits could include a larger reduction in COVID-19 symptoms, a faster time to alleviation of symptoms, reduced lung pathology, a larger reduction in the amount of SARS-CoV-2 coronavirus in the patient (viral load), and decreased mortality.

The SARS-CoV-2 coronavirus infects cells which express P-glycoprotein. Some of the SARS-CoV-2 coronavirus 3CL protease inhibitors of the invention are P-glycoprotein substrates. Compounds which inhibit the SARS-CoV-2 coronavirus which are also P-glycoprotein substrates may be dosed with a P-glycoprotein inhibitor. Examples of P-glycoprotein inhibitors are verapamil, vinblastine, ketoconazole, nelfinavir, ritonavir or cyclosporine. The P-glycoprotein inhibitors act by inhibiting the efflux of the SARS-CoV-2 coronavirus inhibitors of the invention out of the cell. The inhibition of the P-glycoprotein-based efflux will prevent reduction of intracellular concentrations of the SARS-CoV-2 coronavirus inhibitor due to P-glycoprotein efflux. Inhibition of the P-glycoprotein efflux will result in larger intracellular concentrations of the SARS-CoV-2 coronavirus inhibitors. Dosing a SARS-CoV-2 coronavirus-infected patient with the SARS-CoV-2 coronavirus 3CL protease inhibitors of the invention and a P-glycoprotein inhibitor may lower the amount of SARS-CoV-2 coronavirus 3CL protease inhibitor required to achieve an efficacious dose by increasing the intracellular concentration of the SARS-CoV-2 coronavirus 3CL protease inhibitor.

Among the agents that may be used to increase the exposure of a mammal to a compound of the present invention are those that can act as inhibitors of at least one isoform of the cytochrome P450 (CYP450) enzymes. The isoforms of CYP450 that may be beneficially inhibited include, but are not limited to CYP1A2, CYP2D6, CYP2C9, CYP2C19 and CYP3A4. The compounds used in the methods of the invention include
compounds that may be CYP3A4 substrates and are metabolized by CYP3A4. Dosing a SARS-CoV-2 coronavirus-infected patient with a SARS-CoV-2 coronavirus inhibitor which is a CYP3A4 substrate, such as SARS-CoV-2 coronavirus 3CL protease inhibitor, and a CYP3A4 inhibitor, such as ritonavir, nelfinavir or delavirdine, will reduce the metabolism of the SARS-CoV-2 coronavirus inhibitor by CYP3A4. This will result in reduced clearance of the SARS-CoV-2 coronavirus inhibitor and increased SARS-CoV-2 coronavirus inhibitor plasma concentrations. The reduced clearance and higher plasma concentrations may result in a lower efficacious dose of the SARS-CoV-2 coronavirus inhibitor.

Additional therapeutic agents that can be used in combination with the SARS-CoV-2 inhibitors in the methods of the present invention include the following:

PLpro inhibitors, Apilomod, EIDD-2801, Ribavirin, Valganciclovir, β-Thymidine, Aspartame, Oxrenolol, Doxycline, Acetophenazine, Iopromide, Riboflavin, Reproterol, 2,2'-Cycloctydine, Chloramphenicol, Chlorhenesin carbamate, Levodropropizine, Cefamandole, Fluoxuridine, Tigecycline, Pemetrexed, L(+)-Ascorbic acid, Glutathione, Hesperitine, Ademetionine, Masoprocol, Isoretinoin, Dantrolene, Sulfasalazine Anti-bacterial, Silybin, Nicardipine, Sildenafil, Platycodin, Chrysin, Neohesperidin, Baicalin, Sugetriol-3,9-diacetate, (++)-Epigallocatechin gallate, Phaitanthrin D, 2-(3,4-Dihydroxyphenyl)-2-[(2-(3,4-dihydroxyphenyl)-3,4-dihydro-5,7-dihydroxy-2H-1-benzopyran-3-yl)[oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol, 2,2-di(3-indolyl)-3-indolone, (S)-(1S,2R,4aS,5R,8aS)-1-Formamido-1,4a-dimethyl-6-methylene-5-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)ethenyl)decahydronaphthalene-2-yl-2-amino-3-phenylpropanoate, Piceatannol, Rosmarinic acid, and Magnolol.

3CLpro inhibitors, Lymecycline, Chlorhexidine, Alfuzosin, Cilastatin, Famotidine, Almitrine, Pregabide, Nepafenac, Carvedilol, Amprenavir, Tigecycline, Montelukast, Carminic acid, Mimosine, Flavin, Lutein, Cefpiramide, Phenethicilllin, Candoxatril, Nicardipine, Estradiol valerate, Pioglitazone, Conivaptan, Telmisartan, Doxycycline, Oxytetracycline, (1S,2R,4aS,5R,8aS)-1-Formamido-1,4a-dimethyl-6-methylene-5-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)ethenyl)decahydronaphthalene-2-yl5-((R)-1,2-dithiolan-3-yl) pentanoate, Betulonal, Chrysin-7-O-β-glucuronide, Andrographiside, (1S,2R,4aS,5R,8aS)-1-Formamido-1,4a-dimethyl-6-methylene-5-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)ethenyl)decahydronaphthalene-2-yl 2-nitrobenzoate, 2β-Hydroxy-3,4-seco-friedelolactone-27-oic acid (S)-(1S,2R,4aS,5R,8aS)-1-Formamido-1,4a-dimethyl-6-methylene-5-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)ethenyl) decahydronaphthalene-2-yl-2-
amino-3-phenylpropanoate, Isodecortinol, Cerevisterol, Hesperidin, Neohesperidin, Andrograpanin, 2-((1R,5R,6R,8aS)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylenedecahydropyran-1-yl)ethyl benzoate, Cosmosiin, Cleistocaltone A, 2,2-Di(3-indolyl)-3-indolone, Biorobin, Gnidicin, Phyllaemblinol, Theaflavin 3,3′-di-O-gallate, Rosmarinic acid, Kouichenside I, Oleanolic acid, Stigmast-5-en-3-ol, Deacetyldentapicrin, and Berchemol.

**RdRp inhibitors, Valganciclovir, Chlorhexidine, Ceftibuten, Fenoterol, Fludarabine, Itraconazole, Cefuroxime, Atovaquone, Chenodeoxycholic acid, Cromolyn, Pencurion bromide, Cortisone, Tibolone, Novobiocin, Silybin, Idarubicin Bromocriptine, Diphenoxylate, Benzylpenicilloyl G, Dabigatran etexilate, Betulonal, Gnidicin, 2β,3β-Dihydroxy-3,4-seco-friedelolactone-27-lactone, 14-Deoxy-11,12-didehydroandrographolide, Gniditrin, Theaflavin 3,3′-di-O-gallate, (R)-((1R,5aS,6R,9aS)-1,5a-Dimethyl-7-methylene-3-oxo-6-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)ethenyl)decahydro-1H-benzo[c]azepin-1-yl)methyl2-amino-3-phenylpropanoate, 2β-Hydroxy-3,4-seco-friedelolactone-27-oic acid, 2-(3,4-Dihydroxyphenyl)-2-[2-(3,4-dihydroxyphenyl)-3,4-dihydro-5,7-dihydroxy-2H-1-benzopyran-3-yl]oxy]-3,4-dihydro-2H-1-benzopyran-3,4,5,7-tetrol, Phyllaemblinol B, 14-hydroxycurcumin, Andrographside, 2-((1R,5R,6R,8aS)-6-Hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylenedecahydro naphthalen-1-yl)ethyl benzoate, Andrographolide, Sugetriol-3,9-diacetate, Baicalin, (1S,2R,4aS,5R,8aS)-1-Formamido-1,4a-dimethyl-6-methylene-5-((E)-2-(2-oxo-2,5-dihydrofuran-3-yl)ethenyl)decahydropyran-2-yl 5-((R)-1,2-dithiolan-3-yl)pentanoate, 1,7-Dihydroxy-3-methoxyxanthone, 1,2,6-Trimethoxy-8-[6-(O-β-D-xylopyranosyl-β-D-glucopyranosyl)oxy]-9H-xanthen-9-one, and 1,8-Dihydroxy-6-methoxy-2-[6-(O-β-D-xylopyranosyl-β-D-glucopyranosyl)oxy]-9H-xanthen-9-one, 8-(β-D-Glucopyranosyloxy)-1,3,5-trihydroxy-9H-xanthen-9-one.

Additional therapeutic agents that can be used in the methods of the invention include Diosmin, Hesperidin, MK-3207, Venetoclax, Dihydroergocristine, Bolazine, R428, Ditercalinium, Etospose, Teniposide, UK-432097, Iriotanecan, Lumacaftor, Velpatavir, Eluxadoline, Ledipasvir, Lopinavir / Ritonavir + Ribavirin, Alferon, and prednisone. Other additional agents useful in the methods of the present invention include dexamethasone, azithromycin and remdesivir as well as boceprevir, umifenovir and favipiravir.
Other additional agents that can be used in the methods of the present invention include \(\alpha\)-ketoamides compounds designated as 11r, 13a and 13b, shown below, as described in Zhang, L.; Lin, D.; Sun, X.; Rox, K.; Hilgenfeld, R.; X-ray Structure of Main Protease of the Novel Coronavirus SARS-CoV-2 Enables Design of \(\alpha\)-Ketoamide Inhibitors; bioRxiv preprint doi: https://doi.org/10.1101/2020.02.17.952879

![Chemical structures](image)

Additional agents that can be used in the methods of the present invention include RIG 1 pathway activators such as those described in US Patent No. 9,884,876.

Another embodiment of the present invention is a method of treating COVID-19 in a patient wherein in addition to administering a compound of the present invention (i.e. a compound of Formula I or a pharmaceutically acceptable salt thereof) an additional agent is administered and the additional agent is selected from antivirals such as remdesivir, galidesivir, favilavir/avifavir, mulnupiravir (MK-4482/EIDD 2801), AT-527, AT-301, BLD-2660, favipiravir, camostat, SLV213 emtricitabine/tenofovir, clevudine, dalcetrapib, boceprevir and ABX464, glucocorticoids such as dexamethasone and hydrocortisone, convalescent plasma, a recombinant human plasma such as gelsolin (Rhu-p65N), monoclonal antibodies such as regdanvimab (Regkirova), ravalizumab (Ultomiris), VIR-7831/VIR-7832, BRILI-196/BRILI-198, COVI-AMG/COVI DROPS (STI-2020), bamlanivimab (LY-CoV555), mavrilimab, lerionlimab (PRO140), AZD7442, lenzilumab, infliximab, adalimumab, JS 016, STI-1499 (COVIGUARD), lanadelumab (Takhzyro), canakinumab (Ilaris), gimsilumab and otilimab, antibody cocktails such as casirivimab/imdevimab (REGN-Cov2), recombinant fusion protein such as MK-7110 (CD24Fc/SACCovid), anticoagulants such as heparin and apixaban, IL-6 receptor agonists such as tocilizumab (Actemra) and sarilumab (Kevzara), PIKfyve inhibitors such as apilimod mimesylate, RIPK1 inhibitors such as DNL758, VIP receptor agonists such as PB1046, SGLT2 inhibitors such as dapagliflozin, TYK inhibitors such as abivotinib, kinase inhibitors such as ATR-002, bemcentinib, acalabrutinib and...
losmapimod, H2 blockers such as famotidine, anthelmintics such as niclosamide, furin inhibitors such as dimazene.

The term “SARS-CoV-2 inhibiting agent” means any SARS-CoV-2-related coronavirus 3C-like protease inhibitor compound described herein or a pharmaceutically acceptable salt, hydrate, prodrug, active metabolite or solvate thereof or a compound which inhibits replication of SARS-CoV-2 in any manner.

The term "interfering with or preventing" SARS-CoV-2-related coronavirus ("SARS-CoV-2") viral replication in a cell means to reduce SARS-CoV-2 replication or production of SARS-CoV-2 components necessary for progeny virus in a cell treated with a compound of this invention as compared to a cell not being treated with a compound of this invention. Simple and convenient assays to determine if SARS-CoV-2 viral replication has been reduced include an ELISA assay for the presence, absence, or reduced presence of anti-SARS-CoV-2 antibodies in the blood of the subject (Nasoff, et al., PNAS 88:5462-5466, 1991), RT-PCR (Yu, et al., in Viral Hepatitis and Liver Disease 574-577, Nishioka, Suzuki and Mishiro (Eds.); Springer-Verlag, Tokyo, 1994). Such methods are well known to those of ordinary skill in the art. Alternatively, total RNA from transduced and infected "control" cells can be isolated and subjected to analysis by dot blot or northern blot and probed with SARS-CoV-2-specific DNA to determine if SARS-CoV-2 replication is reduced. Alternatively, reduction of SARS-CoV-2 protein expression can also be used as an indicator of inhibition of SARS-CoV-2 replication. A greater than fifty percent reduction in SARS-CoV-2 replication as compared to control cells typically quantitates a prevention of SARS-CoV-2 replication.

If a SARS-CoV-2 inhibitor compound used in the method of the invention is a base, a desired salt may be prepared by any suitable method known to the art, including treatment of the free base with an inorganic acid (such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like), or with an organic acid (such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acid (such as glucuronic acid or galacturonic acid), alpha-hydroxy acid (such as citric acid or tartaric acid), amino acid (such as aspartic acid or glutamic acid), aromatic acid (such as benzoic acid or cinnamic acid), sulfonic acid (such as p-toluenesulfonic acid or ethanesulfonic acid), and the like.
If a SARS-CoV-2 inhibitor compound used in the method of the invention is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base [such as an amine (primary, secondary, or tertiary)], an alkali metal hydroxide, or alkaline earth metal hydroxide. Illustrative examples of suitable salts include organic salts derived from amino acids (such as glycine and arginine), ammonia, primary amines, secondary amines, tertiary amines, and cyclic amines (such as piperidine, morpholine, and piperazine), as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

In the case of SARS-CoV-2 inhibitor compounds, prodrugs, salts, or solvates that are solids, it is understood by those skilled in the art that the compound, prodrugs, salts, and solvates used in the method of the invention, may exist in different polymorph or crystal forms, all of which are intended to be within the scope of the present invention and specified formulas. In addition, the compound, salts, prodrugs and solvates used in the method of the invention may exist as tautomers, all of which are intended to be within the broad scope of the present invention.

Solubilizing agents may also be used with the compounds of the invention to increase the compounds’ solubility in water of physiologically acceptable solutions. These solubilizing agents include cyclodextrins, propylene glycol, diethylacetamide, polyethylene glycol, Tween, ethanol and micelle-forming agents. Offered solubilizing agents are cyclodextrins, particularly beta-cyclodextrins and in particular hydroxypropyl beta-cyclodextrin and sulfobutylether beta-cyclodextrin.

In some cases, the SARS-CoV-2 inhibitor compounds, salts, prodrugs and solvates used in the method of the invention may have chiral centers. When chiral centers are present, the compound, salts, prodrugs and solvates may exist as single stereoisomers, racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates, and mixtures thereof are intended to be within the broad scope of the present invention.

As generally understood by those skilled in the art, an optically pure compound is one that is enantiomerically pure. As used herein, the term “optically pure” is intended to mean a compound comprising at least a sufficient activity. Preferably, an optically pure amount of a single enantiomer to yield a compound having the desired pharmacologically pure compound of the invention comprises at least 90% of a single
isomer (80% enantiomeric excess), more preferably at least 95% (90% e.e.), even more preferably at least 97.5% (95% e.e.), and most preferably at least 99% (98% e.e.).

The term “treating”, as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term “treatment”, as used herein, unless otherwise indicated, refers to the act of treating as “treating” is defined immediately above. In a preferred embodiment of the present invention, “treating” or “treatment” means at least the mitigation of a disease condition in a human, that is alleviated by the inhibition of the activity of the SARS-CoV-2 3C-like protease which is the main protease of SARS-CoV-2, the causative agent for COVID-19. For patients suffering from COVID-19, fever, fatigue, and dry cough are the main manifestations of the disease, while nasal congestion, runny nose, and other symptoms of the upper respiratory tract are rare. Beijing Centers for Diseases Control and Prevention indicated that the typical case of COVID-19 has a progressive aggravation process. COVID-19 can be classified into light, normal, severe, and critical types based on the severity of the disease. National Health Commission of the People’s Republic of China. Diagnosis and Treatment of Pneumonia Caused by 2019-nCoV (Trial Version 4). Available online: http://www.nhc.gov.cn/jkj/s3577/202002/573340613ab243b3a7f61df260551dd4/files/c791e5a7ea5149f680fdbc34dac0f54e.pdf: (1) Mild cases—the clinical symptoms were mild, and no pneumonia was found on the chest computed tomography (CT); (2) normal cases—fever, respiratory symptoms, and patients found to have imaging manifestations of pneumonia; (3) severe cases—one of the following three conditions: Respiratory distress, respiratory rate ≥ 30 times / min (in resting state, refers to oxygen saturation ≤ 93%), partial arterial oxygen pressure (PaO2)/oxygen absorption concentration (FiO2) ≤300 mmHg (1 mm Hg = 0.133 kPa); (4) critical cases—one of the following three conditions: Respiratory failure and the need for mechanical ventilation, shock, or the associated failure of other organs requiring the intensive care unit. The current clinical data shows that the majority of deaths occurred in the older patients. However, severe cases have been documented in young adults who have unique factors, particularly those with chronic diseases, such as diabetes or hepatitis B. Those with a long-term use of hormones or immunosuppressants, and decreased immune function, are likely to get severely infected.

Methods of treatment for mitigation of a coronavirus disease condition such as COVID-19 include the use of one or more of the compounds of the invention in any
conventionally acceptable manner. According to certain preferred embodiments of the invention, the compound or compounds used in the methods of the present invention are administered to a mammal, such as a human, in need thereof. Preferably, the mammal in need thereof is infected with a coronavirus such as the causative agent of COVID-19, namely SARS-CoV-2.

The present invention also includes prophylactic methods, comprising administering an effective amount of a SARS-CoV-2 inhibitor of the invention, or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof to a mammal, such as a human at risk for infection by SARS-CoV-2.

According to certain preferred embodiments, an effective amount of one or more compounds of the invention, or a pharmaceutically acceptable salt, prodrug, pharmaceutically active metabolite, or solvate thereof is administered to a human at risk for infection by SARS-CoV-2, the causative agent for COVID-19. The prophylactic methods of the invention include the use of one or more of the compounds in the invention in any conventionally acceptable manner.

Certain of the compounds used in the methods of the invention, for example dexamethasone, azithromycin and remdesivir are known and can be made by methods known in the art.

Recent evidence indicates that a new coronavirus SARS-CoV-2 is the causative agent of COVID-19. The nucleotide sequence of the SARS-CoV-2 coronavirus as well as the recently determined L- and S- subtypes have recently been determined and made publicly available.

The activity of the inhibitor compounds as inhibitors of SARS-CoV-2 viral activity may be measured by any of the suitable methods available in the art, including in vivo and in vitro assays. The activity of the compounds of the present invention as inhibitors of coronavirus 3C-like protease activity (such as the 3C-like protease of the SARS-CoV-2 coronavirus) may be measured by any of the suitable methods known to those skilled in the art, including in vivo and in vitro assays. Examples of suitable assays for activity measurements include the antiviral cell culture assays described herein as well as the antiprotease assays described herein, such as the assays described in the Experimental section.

Administration of the SARS-CoV-2 inhibitor compounds and their pharmaceutically acceptable prodrugs, salts, active metabolites, and solvates may be
performed according to any of the accepted modes of administration available to those skilled in the art. Illustrative examples of suitable modes of administration include oral, nasal, pulmonary, parenteral, topical, intravenous, injected, transdermal, and rectal. Oral, intravenous, subcutaneous and nasal deliveries are preferred.

A SARS-CoV-2-inhibiting agent may be administered as a pharmaceutical composition in any suitable pharmaceutical form. Suitable pharmaceutical forms include solid, semisolid, liquid, or lyophilized formulations, such as tablets, powders, capsules, suppositories, suspensions, liposomes, and aerosols. The SARS-CoV-2-inhibiting agent may be prepared as a solution using any of a variety of methodologies. For example, SARS-CoV-2-inhibiting agent can be dissolved with acid (e.g., 1 M HCl) and diluted with a sufficient volume of a solution of 5% dextrose in water (D5W) to yield the desired final concentration of SARS-CoV-2-inhibiting agent (e.g., about 15 mM). Alternatively, a solution of D5W containing about 15 mM HCl can be used to provide a solution of the SARS-CoV-2-inhibiting agent at the appropriate concentration. Further, the SARS-CoV-2-inhibiting agent can be prepared as a suspension using, for example, a 1% solution of carboxymethylcellulose (CMC).

Acceptable methods of preparing suitable pharmaceutical forms of the pharmaceutical compositions are known or may be routinely determined by those skilled in the art. For example, pharmaceutical preparations may be prepared following conventional techniques of the pharmaceutical chemist involving steps such as mixing, granulating, and compressing when necessary for tablet forms, or mixing, filling and dissolving the ingredients as appropriate, to give the desired products for intravenous, oral, parenteral, topical, intravaginal, intranasal, intrabronchial, intraocular, intraaural, and/or rectal administration.

Pharmaceutical compositions of the invention may also include suitable excipients, diluents, vehicles, and carriers, as well as other pharmaceutically active agents, depending upon the intended use. Solid or liquid pharmaceutically acceptable carriers, diluents, vehicles, or excipients may be employed in the pharmaceutical compositions. Illustrative solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, pectin, acacia, magnesium stearate, and stearic acid. Illustrative liquid carriers include syrup, peanut oil, olive oil, saline solution, and water. The carrier or diluent may include a suitable prolonged-release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. When a liquid carrier is used, the preparation may be in the form of a syrup, elixir, emulsion, soft
gelatin capsule, sterile injectable liquid (e.g., solution), or a nonaqueous or aqueous liquid suspension.

A dose of the pharmaceutical composition may contain at least a therapeutically effective amount of a SARS-CoV-2-inhibiting agent and preferably is made up of one or more pharmaceutical dosage units. The selected dose may be administered to a mammal, for example, a human patient, in need of treatment mediated by inhibition of SARS-CoV-2 related coronavirus activity, by any known or suitable method of administering the dose, including topically, for example, as an ointment or cream; orally; rectally, for example, as a suppository; parenterally by injection; intravenously; or continuously by intravaginal, intranasal, intrabronchial, intraural, or intraocular infusion.

The phrases “therapeutically effective amount” and “effective amount” are intended to mean the amount of an inventive agent that, when administered to a mammal in need of treatment, is sufficient to effect treatment for injury or disease conditions alleviated by the inhibition of SARS-CoV-2 viral replication. The amount of a given SARS-CoV-2-inhibiting agent used in the method of the invention that will be therapeutically effective will vary depending upon factors such as the particular SARS-CoV-2-inhibiting agent, the disease condition and the severity thereof, the identity and characteristics of the mammal in need thereof, which amount may be routinely determined by those skilled in the art.

It will be appreciated that the actual dosages of the SARS-CoV-2-inhibiting agents used in the pharmaceutical compositions of this invention will be selected according to the properties of the particular agent being used, the particular composition formulated, the mode of administration and the particular site, and the host and condition being treated. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage-determination tests. For oral administration, e.g., a dose that may be employed is from about 0.01 to about 1000 mg/kg body weight, preferably from about 0.1 to about 500 mg/kg body weight, and even more preferably from about 1 to about 500 mg/kg body weight, with courses of treatment repeated at appropriate intervals. For intravenous dosing a dose of up to 5 grams per day may be employed. Intravenous administration can occur for intermittent periods during a day or continuously over a 24-hour period.

The terms “cytochrome P450-inhibiting amount” and “cytochrome P450 enzyme activity-inhibiting amount”, as used herein, refer to an amount of a compound required
to decrease the activity of cytochrome P450 enzymes or a particular cytochrome P450 enzyme isoform in the presence of such compound. Whether a particular compound decreases cytochrome P450 enzyme activity, and the amount of such a compound required to do so, can be determined by methods known to those of ordinary skill in the art and the methods described herein.

Protein functions required for coronavirus replication and transcription are encoded by the so-called "replicase" gene. Two overlapping polyproteins are translated from this gene and extensively processed by viral proteases. The C-proximal region is processed at eleven conserved interdomain junctions by the coronavirus main or "3C-like" protease. The name "3C-like" protease derives from certain similarities between the coronavirus enzyme and the well-known picornavirus 3C proteases. These include substrate preferences, use of cysteine as an active site nucleophile in catalysis, and similarities in their putative overall polypeptide folds. A comparison of the amino acid sequence of the SARS-CoV-2-associated coronavirus 3C-like protease to that of other known coronaviruses such as SARS-CoV shows the amino acid sequences have approximately 96% shared homology.

Amino acids of the substrate in the protease cleavage site are numbered from the N to the C terminus as follows: -P3-P2-P1-P1'-P2'-P3', with cleavage occurring between the P1 and P1' residues (Schechter & Berger, 1967). Substrate specificity is largely determined by the P2, P1 and P1' positions. Coronavirus main protease cleavage site specificities are highly conserved with a requirement for glutamine at P1 and a small amino acid at P1' [Journal of General Virology, 83, pp. 595-599 (2002)].

The compounds of the present invention can be prepared according to the methods set forth in Reaction Schemes 1 to 3 below.

The schemes provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center may exist as a single enantiomer or a racemic mixture. Those molecules with two or more chiral centers may exist as a single enantiomer, a racemic or otherwise mixture of two enantiomers, or as various mixtures of diastereomers. Such enantiomers, racemates, and diastereomers may be obtained and / or separated by methods known to those skilled in the art. It will be appreciated by one skilled in the art
that certain synthetic manipulations may epimerize or racemize a stereocenter, and synthetic conditions may be selected to either promote or discourage such epimerization or racemization.

Scheme 1 illustrates a synthetic sequence for the preparation of compounds of Formula 1 as shown, wherein the N-BOC methyl ester of Formula 1 (WO 2005/113580) is converted to a primary amide of Formula 3 (N-BOC being N-tert-butoxycarbonyl). This may be accomplished directly, for example, by treatment with ammonia (NH₃) in a sealed vessel in a solvent such as methanol or ethanol, for example, optionally in the presence of additives such as calcium chloride (CaCl₂) or magnesium dimethoxide, Mg(OMe)₂.

The transformation of the compound of Formula 1 to the compound of Formula 3 may also be carried out by prior conversion to the carboxylic acid of Formula 2 (WO 2005/113580). In this case the compound of Formula 2 may be converted to the compound of Formula 3 using methods well known to those skilled in the art. For example, the compound of Formula 2 may be treated with a reagent such as O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU),
isobutyl chloroformate, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and hydroxybenzotriazole (HOBt), or 1,1'-carbonyldiimidazole (CDI), optionally in the presence of a base such as N,N-diisopropylethylamine (DIEA), 4-methylmorpholine (NMM), or triethylamine (TEA), followed by treatment with NH₃ administered as a gas or a solution in a reaction compatible solvent, or with a salt of NH₃ such as ammonium acetate or ammonium chloride in the presence of a base such as N,N-diisopropylethylamine, 4-methylmorpholine, or triethylamine. Suitable solvents include, but are not limited to, dichloromethane (CH₂Cl₂), N,N-dimethylformamide (DMF), tetrahydrofuran (THF), or acetonitrile (CH₃CN).

The compound of Formula 3 may be N-deprotected to provide an amine of Formula 4 using methods well known to those skilled in the art for effecting such deprotections. Frequently acidic reagents such as hydrogen chloride, methanesulfonic acid, or trifluoroacetic acid are used, typically in a reaction compatible solvent such as CH₂Cl₂, 1,4-dioxane, 1,2-dichloroethane, or CH₃CN. One skilled in the art will appreciate that the compound of Formula 4 will frequently be obtained as an acid addition salt. The compound of Formula 4 may then be transformed into a compound of Formula 6 by treatment with an N-protected amino acid compound of Formula 5 under appropriate conditions. Such methods are well known to those skilled in the art, and in general standard peptide coupling conditions may be selected.

The compound of Formula 6 may be N-deprotected to provide an amine of Formula 7 using methods well known to those skilled in the art for effecting such deprotections. Frequently acidic reagents such as hydrogen chloride, methanesulfonic acid, or trifluoroacetic acid are used, typically in a reaction compatible solvent such as CH₂Cl₂, 1,4-dioxane, 1,2-dichloroethane, or CH₃CN. One skilled in the art will appreciate that the compound of Formula 7 will frequently be obtained as an acid addition salt. The compound of Formula 7 may then be transformed into a compound of Formula 9 by treatment with a carboxylic acid compound of Formula 8 under appropriate conditions. Such methods are well known to those skilled in the art. For example, when X = a chlorine atom, the carboxylic acid compound is known as an acid chloride and the reaction is conducted in the presence of a base to consume the hydrogen halide HX produced as a by-product of the reaction. Examples of suitable bases include, but are not limited to, tertiary amines such as 4-methylmorpholine, 2,6-dimethylpyridine, or N,N-diisopropylethylamine, or inorganic bases such as magnesium oxide (MgO), sodium carbonate (Na₂CO₃), or potassium bicarbonate (KHCO₃). Suitable solvents include, but
are not limited to, CH₂Cl₂, DMF, THF, or CH₃CN. When X = OH, it is customary to use a reagent or combination of reagents to facilitate the reaction of the carboxylic acid compound of Formula 8. One skilled in the art may choose to use, for example, a carbodiimide reagent such as 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) or N,N'-dicyclohexyl carbodiimide (DCC), optionally in the presence of an auxiliary nucleophile such as hydroxybenzotriazole (HOBT) or 2-hydroxypyridine-N-oxide (HOPO). Further, when X = OH, one skilled in the art may choose to use reagents that are suitable for the formation of mixed carboxyl / carbonic anhydrides, such as CDI, isobutyl or ethyl chloroformate, frequently in the presence of a base such as described above. Suitable solvents include, but are not limited to, CH₂Cl₂, THF, or CH₃CN. Another approach commonly used by those skilled in the art when X = OH is to treat the carboxylic acid compound of Formula 8 with a carboxylic acid chloride, for example such as Me₃CCOCl, in the presence of a base such as described above to generate a mixed carboxylic anhydride of the Formula R₃C(O)(O)CCMe₃. Suitable solvents include, but are not limited to, CH₂Cl₂, THF, or CH₃CN. In many cases it is possible to use a symmetric anhydride of the desired carboxylic acid compound of Formula 8 to effect the reaction, optionally in the presence of a base such as described above, in which case X = O(O)CR₃ and the carboxylic acid compound of Formula 8 is therefore R₃C(O)(O)CR₃. Suitable solvents include, but are not limited to, CH₂Cl₂, THF, or CH₃CN.

The compound of Formula 9 may be transformed into the compound of Formula 1 by treatment under dehydrating conditions well known to those skilled in the art. Frequently this dehydration step may be accomplished using an excess of trifluoroacetic anhydride or phosphorus oxychloride, generally in the presence of a base such as pyridine, N,N-diisopropylethylamine, 4-methylmorpholine, or triethylamine.

One skilled in the art will know that the N-BOC protected amino acids of Formula 5 are known in the chemical literature, are commercially available, and may be prepared from the corresponding known and commercially available amino acids by one skilled in the art using well established procedures for the synthesis of N-protected amino acids. Likewise, one skilled in the art will understand that the carboxylic acid compounds of Formula 8 may be known in the chemical literature, and / or are commercially available, and / or may be prepared by published methods or by analogy to published methods.

One skilled in the art will appreciate that the bond-forming steps in Scheme 1 may be conducted in a different order with appropriate considerations, for example as shown in Scheme 2.
In Scheme 2, the compound of Formula 3 is converted into the compound of Formula 10 by treatment under dehydrating conditions well known to those skilled in the art. Frequently this dehydration step may be accomplished using an excess of trifluoroacetic anhydride or phosphorus oxychloride, generally in the presence of a base such as pyridine, N,N-diisopropylethylamine, 4-methylmorpholine, or triethylamine. The compound of Formula 10 is N-deprotected to provide an amine of Formula 11 using methods well known to those skilled in the art for effecting such deprotections. Frequently, acidic reagents such as hydrogen chloride, methanesulfonic acid, or trifluoroacetic acid are used, typically in a reaction-compatible solvent such as CH₂Cl₂, 1,4-dioxane, 1,2-dichloroethane, or CH₃CN. One skilled in the art will appreciate that the compound of Formula 11 will frequently be obtained as an acid addition salt. The compound of Formula 11 may then be transformed into a compound of Formula 1 by treatment with a compound of Formula 12 under appropriate conditions. Such methods are well known to those skilled in the art, and in general standard peptide coupling conditions may be selected. Compounds of Formula 12 are exceptionally well known in the chemical literature, and one skilled in the art may choose to prepare any given compound of Formula 12 using methods analogous to those described in the chemical literature.

One skilled in the art will appreciate that the bond-forming steps in Schemes 1 and 2 may be conducted in still further different orders with appropriate considerations, for example as shown in Scheme 3.
In Scheme 3, the compound of Formula 4 may then be transformed into a compound of Formula 9 by treatment with a compound of Formula 12 under appropriate conditions. Such methods are well known to those skilled in the art, and in general standard peptide coupling conditions may be selected. Compounds of Formula 12 are exceptionally well known in the chemical literature, and one skilled in the art may choose to prepare any given compound of Formula 12 using methods analogous to those described in the chemical literature. The compound of Formula 9 is then converted into the compound of Formula 1 by treatment under dehydrating conditions well known to those skilled in the art. Frequently this dehydration step may be accomplished using an excess of trifluoroacetic anhydride or phosphorus oxychloride, generally in the presence of a base such as pyridine, N,N-diisopropylethylamine, 4-methylmorpholine, or triethylamine.

One skilled in the art will recognize that still further permutations of the bond-forming steps and functional group manipulations in Schemes 1, 2 and 3 may be applied with appropriate considerations. Such permutations in the selection of step order are well known in the chemical literature and one skilled in the art may consult the chemical literature for further guidance if desired. One skilled in the art will recognize that other selections of protecting groups and reagents for effecting the various transformations may be made.
EXAMPLES

Experimental Procedures

The following illustrate the synthesis of various compounds of the present invention. Additional compounds within the scope of this invention may be prepared using the methods illustrated in these Examples, either alone or in combination with techniques generally known in the art. All starting materials in these Preparations and Examples are either commercially available or can be prepared by methods known in the art or as described herein.

All reactions were carried out using continuous stirring under an atmosphere of nitrogen or argon gas unless otherwise noted. When appropriate, reaction apparatuses were dried under dynamic vacuum using a heat gun, and anhydrous solvents (Sure-Seal™ products from Aldrich Chemical Company, Milwaukee, Wisconsin or DriSolv™ products from EMD Chemicals, Gibbstown, NJ) were employed. In some cases, commercial solvents were passed through columns packed with 4Å molecular sieves, until the following QC standards for water were attained: a) <100 ppm for dichloromethane, toluene, N,N-dimethylformamide, and tetrahydrofuran; b) <180 ppm for methanol, ethanol, 1,4-dioxane, and diisopropylamine. For very sensitive reactions, solvents were further treated with metallic sodium, calcium hydride, or molecular sieves, and distilled just prior to use. Other commercial solvents and reagents were used without further purification. For syntheses referencing procedures in other Examples or Methods, reaction conditions (reaction time and temperature) may vary. Products were generally dried under vacuum before being carried on to further reactions or submitted for biological testing.

When indicated, reactions were heated by microwave irradiation using Biotage Initiator or Personal Chemistry Emrys Optimizer microwaves. Reaction progress was monitored using thin-layer chromatography (TLC), liquid chromatography-mass spectrometry (LCMS), high-performance liquid chromatography (HPLC), and/or gas chromatography-mass spectrometry (GCMS) analyses. TLC was performed on pre-coated silica gel plates with a fluorescence indicator (254 nm excitation wavelength) and visualized under UV light and/or with I₂, KMnO₄, CoCl₂, phosphomolybdic acid, and/or ceric ammonium molybdate stains. LCMS data were acquired on an Agilent 1100 Series instrument with a Leap Technologies autosampler, Gemini C18 columns, acetonitrile/water gradients, and either trifluoroacetic acid, formic acid, or ammonium
hydroxide modifiers. The column eluate was analyzed using a Waters ZQ mass
spectrometer scanning in both positive and negative ion modes from 100 to 1200 Da.
Other similar instruments were also used. HPLC data were generally acquired on an
Agilent 1100 Series instrument, using the columns indicated, acetonitrile/water
gradients, and either trifluoroacetic acid or ammonium hydroxide modifiers. GCMS data
were acquired using a Hewlett Packard 6890 oven with an HP 6890 injector, HP-1
column (12 m x 0.2 mm x 0.33 μm), and helium carrier gas. The sample was analyzed
on an HP 5973 mass selective detector scanning from 50 to 550 Da using electron
ionization. Purifications were performed by medium performance liquid chromatography
(MPLC) using Isco CombiFlash Companion, AnaLogix IntelliFlash 280, Biotage SP1, or
Biotage Isolera One instruments and pre-packed Isco RediSep or Biotage Snap silica
cartridges. Chiral purifications were performed by chiral supercritical fluid
chromatography (SFC), generally using Berger or Thar instruments; columns such as
ChiralPAK-AD, -AS, -IC, Chiralcel-OD, or -OJ columns; and CO₂ mixtures with
methanol, ethanol, 2-propanol, or acetonitrile, alone or modified using trifluoroacetic
acid or propan-2-amine. UV detection was used to trigger fraction collection. For
syntheses referencing procedures in other Examples or Methods, purifications may
vary: in general, solvents and the solvent ratios used for eluents/gradients were chosen
to provide appropriate RIs or retention times.

Mass spectrometry data are reported from LCMS analyses. Mass spectrometry
(MS) was performed via atmospheric pressure chemical ionization (APCI), electrospray
ionization (ESI), electron impact ionization (EI) or electron scatter ionization (ES)
sources. Proton nuclear magnetic spectroscopy ('H NMR) chemical shifts are given in
parts per million downfield from tetramethylsilane and were recorded on 300, 400, 500,
or 600 MHz Varian, Bruker, or Jeol spectrometers. Chemical shifts are expressed in
parts per million (ppm, δ) referenced to the deuterated solvent residual peaks
(chloroform, 7.26 ppm; CD₃HOD, 3.31 ppm; acetonitrile-d₂, 1.94 ppm; dimethyl
sulfoxide-d₅, 2.50 ppm; DHO, 4.79 ppm). The peak shapes are described as follows: s,
singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br s, broad singlet;
app, apparent. Analytical SFC data were generally acquired on a Berger analytical
instrument as described above. Optical rotation data were acquired on a PerkinElmer
model 343 polarimeter using a 1 dm cell. Microanalyses were performed by Quantitative
Technologies Inc. and were within 0.4% of the calculated values.
Unless otherwise noted, chemical reactions were performed at room temperature (about 23 degrees Celsius).

Unless noted otherwise, all reactants were obtained commercially and used without further purification, or were prepared using methods known in the literature.

The terms “concentrated”, “evaporated”, and “concentrated in vacuo” refer to the removal of solvent at reduced pressure on a rotary evaporator with a bath temperature less than 60 °C. The abbreviations "min" and "h" stand for “minutes” and “hours,” respectively. The term “TLC” refers to thin-layer chromatography, “room temperature or ambient temperature” means a temperature between 18 to 25 °C, “GCMS” refers to gas chromatography–mass spectrometry, “LCMS” refers to liquid chromatography–mass spectrometry, “UPLC” refers to ultra-performance liquid chromatography, “HPLC” refers to high-performance liquid chromatography, and “SFC” refers to supercritical fluid chromatography.

Hydrogenation may be performed in a Parr shaker under pressurized hydrogen gas, or in a Thales-nano H-Cube flow hydrogenation apparatus at full hydrogen and a flow rate between 1–2 mL/min at specified temperature.

HPLC, UPLC, LCMS, GCMS, and SFC retention times were measured using the methods noted in the procedures.

In some examples, chiral separations were carried out to separate enantiomers or diastereomers of certain compounds of the invention (in some examples, the separated enantiomers are designated as ENT-1 and ENT-2, according to their order of elution; similarly, separated diastereomers are designated as DIAST-1 and DIAST-2, according to their order of elution). In some examples, the optical rotation of an enantiomer was measured using a polarimeter. According to its observed rotation data (or its specific rotation data), an enantiomer with a clockwise rotation was designated as the (+)-enantiomer and an enantiomer with a counter-clockwise rotation was designated as the (−)-enantiomer. Racemic compounds are indicated either by the absence of drawn or described stereochemistry, or by the presence of (+/-) adjacent to the structure; in this latter case, the indicated stereochemistry represents just one of the two enantiomers that make up the racemic mixture.

The compounds and intermediates described below were named using the naming convention provided with ACD/ChemSketch 2019.1.1, File Version C05H41,
Build 110712 (Advanced Chemistry Development, Inc., Toronto, Ontario, Canada). The naming convention provided with ACD/ChemSketch 2019.1.1 is well known by those skilled in the art and it is believed that the naming convention provided with ACD/ChemSketch 2019.1.1 generally comports with the IUPAC (International Union for Pure and Applied Chemistry) recommendations on Nomenclature of Organic Chemistry and the CAS Index rules.

Example 1

\[(1R,2S,5S)-N-\{[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide (1)\]

\[\text{C1}\]

\[\text{C2}\]

\[\text{C3}\]

\[\text{C4}\]

\[\text{C5}\]
Step 1. Synthesis of methyl (1R,2S,5S)-3-[(N-tert-butoxycarbonyl)-L-valyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate (C1).

A 0 °C solution of N-(tert-butoxycarbonyl)-L-valine (69.7 g, 321 mmol) in a mixture of acetonitrile and N,N-dimethylformamide (10:1, 1.10 L) was treated with O-(7-azabenzotriazol-1-yl)-N,N',N'-tetramethyluronium hexafluorophosphate (HATU; 122 g, 321 mmol), followed by N,N-diisopropylethylamine (127 mL, 729 mmol). After the reaction mixture had been stirred for 5 minutes, methyl (1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate, hydrochloride salt (60.0 g, 292 mmol) was added, and stirring was continued at 0 °C for 1 hour. The reaction mixture was then diluted with aqueous citric acid solution (1 N; 50 mL) and water (100 mL), stirred for 2 minutes, and concentrated in vacuo to approximately one-half of the initial volume. The resulting mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were then washed three times with water and once with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was stirred in a minimal amount of ethyl acetate, and then filtered; the insoluble material was washed with ethyl acetate until it was white. The combined filtrates were concentrated under reduced pressure and then subjected to silica gel chromatography (Eluent: 1:1 ethyl acetate / heptane), affording C1 as a yellow oil. Yield: 109 g, quantitative. LCMS m/z 369.3 [M+H]^+. 1H NMR (400 MHz, chloroform-d) δ 5.08 (d, J = 9.6 Hz, 1H), 4.45 (s,
1H), 4.11 (dd, J = 9.7, 7.8 Hz, 1H), 3.95 (d, half of AB quartet, J = 10.1 Hz, 1H), 3.86 (dd, component of ABX system, J = 10.2, 4.8 Hz, 1H), 3.74 (s, 3H), 2.04 – 1.93 (m, 1H), 1.50 – 1.41 (m, 2H), 1.40 (s, 9H), 1.04 (s, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.93 (s, 3H).

Step 2. Synthesis of methyl (1R,2S,5S)-6,6-dimethyl-3-L-valyl-3-azabicyclo[3.1.0]hexane-2-carboxylate, hydrochloride salt (C2).

A solution of hydrogen chloride in 1,4-dioxane (4 M; 15 mL, 60 mmol) was added to a 0 °C solution of C1 (1.00 g, 2.71 mmol) in ethyl acetate (50 mL). The reaction mixture was stirred at 0 °C for 2 hours, whereupon additional hydrogen chloride in 1,4-dioxane solution (4 M; 10 mL, 40 mmol) was added, and stirring was continued at 0 °C for 3 hours, then at room temperature for 1 hour. The reaction mixture was then treated with a solution of hydrogen chloride in 1,4-dioxane (4 M; 10 mL, 40 mmol) and methanol (15 mL) and allowed to stir overnight at room temperature. Concentration in vacuo afforded C2 as a gum; this material was used in further chemistry without additional purification, and the reaction was assumed to be quantitative. LCMS m/z 269.3 [M+H]^+.

1H NMR (400 MHz, DMSO-d6) δ 8.24 (br s, 3H), 4.27 (s, 1H), 3.81 – 3.61 (m, 3H), 3.67 (s, 3H), 2.21 – 2.06 (m, 1H), 1.63 – 1.55 (m, 1H), 1.49 (d, component of AB quartet, J = 7.6 Hz, 1H), 1.09 – 0.88 (m, 12H).


Triethylamine (1.55 mL, 11.1 mmol) was added to a 0 °C solution of C2 (1.0 g, 3.3 mmol) in dichloromethane (37 mL), followed by drop-wise addition of trifluoroacetic anhydride (0.57 mL, 4.0 mmol) over 30 minutes. The reaction mixture was stirred at 0 °C for 30 minutes, whereupon it was diluted with dichloromethane (100 mL), washed sequentially with 10% aqueous potassium bisulfate solution (50 mL) and saturated aqueous sodium chloride solution (30 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to provide C3 as a light-yellow oil. Yield: 1.2 g, 3.3 mmol, quantitative. LCMS m/z 365.2 [M+H]^+. 1H NMR (400 MHz, chloroform-d) δ 7.04 (br d, J = 8.8 Hz, 1H), 4.54 (dd, J = 8.9, 6.3 Hz, 1H), 4.46 (s, 1H), 3.91 (dd, J = 10.1, 5.0 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.76 (s, 3H), 2.25 – 2.13 (m, 1H), 1.55 – 1.47 (m, 2H), 1.09 – 1.03 (m, 6H), 0.94 (d, J = 6.8 Hz, 3H), 0.92 (s, 3H).

Concentrated hydrochloric acid (0.57 mL, 6.6 mmol) was added to a solution of C3 (1.25 g, 3.43 mmol) in a mixture of acetic acid (40.8 mL) and water (8.2 mL). The reaction mixture was heated at 55 °C for 3 days, whereupon it was partitioned between water (50 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to afford C4 as a white foam. Yield: 1.00 g, 2.85 mmol, 83%.

LCMS m/z 351.2 [M+H]+. 1H NMR (400 MHz, chloroform-d), characteristic peaks: δ 4.56 – 4.44 (m, 2H), 2.24 – 2.12 (m, 1H), [1.66 (d, component of AB quartet, J = 7.5 Hz) and 1.59 – 1.47 (m, total 2H)], 1.10 – 1.01 (m, 6H), 0.96 – 0.91 (m, 6H).

Step 5. Synthesis of tert-butyl (2S)-1-amino-1-oxo-3-[(3S)-2-oxopyrrolidin-3-yl]propan-2-yl)carbamate (C5).

A solution of ammonia in methanol (7.0 M; 150 mL, 1.0 mol) was added to a 0 °C solution of methyl N-(tert-butoxycarbonyl)-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninate (5.00 g, 17.5 mmol) in methanol (25 mL). After the reaction mixture had been stirred at room temperature for 3 days, it was concentrated in vacuo; the residue was diluted and reconcentrated sequentially with a mixture of ethyl acetate and heptane (1:1, 4 x 50 mL) followed by heptane (50 mL) to provide C5 as a solid (5.27 g, assumed quantitative) that contained residual solvent. A portion of this material was used in the following step. LCMS m/z 216.2 [(M – 2-methylprop-1-ene)+H]+. 1H NMR (400 MHz, methanol-d4) δ 4.16 – 3.96 (m, 1H), 3.40 – 3.27 (m, 2H, assumed; partially obscured by solvent peak), 2.55 – 2.42 (m, 1H), 2.35 (dddd, J = 12.2, 8.6, 6.8, 3.3 Hz, 1H), 2.03 (ddd, J = 14.0, 11.0, 4.4 Hz, 1H), 1.93 – 1.81 (m, 1H), 1.74 (ddd, J = 14.2, 10.1, 4.3 Hz, 1H), 1.45 (s, 9H).


2.6-Dimethylpyridine (2 mL, 17 mmol) and trifluoroacetic anhydride (0.94 mL, 6.6 mmol) were added to a 0 °C solution of C5 (from the previous step; 1.0 g, ≤3.3 mmol) in dichloromethane (12 mL). The reaction mixture was stirred at room temperature for 1.5 hours, whereupon it was treated with hydrochloric acid (1 M; 30 mL) and
dichloromethane (60 mL). The organic layer was washed sequentially with saturated aqueous sodium chloride solution (30 mL) and saturated aqueous sodium bicarbonate solution (30 mL), dried over sodium sulfate, and concentrated in vacuo; chromatography on silica gel (Gradient: 40% to 100% ethyl acetate in heptane) afforded C6 as a solid.

Yield: 737 mg, 2.91 mmol, 88% over 2 steps. LCMS m/z 254.3 [M+H]^+. 1H NMR (400 MHz, methanol-d4) δ 4.72 (dd, J = 9.3, 6.8 Hz, 1H), 3.39 – 3.27 (m, 2H, assumed; partially obscured by solvent peak), 2.57 – 2.46 (m, 1H), 2.36 (dddd, J = 12.2, 8.6, 6.3, 3.4 Hz, 1H), 2.21 (dddd, J = 13.8, 9.3, 5.6 Hz, 1H), 1.92 – 1.79 (m, 2H), 1.47 (s, 9H).

Step 7. Synthesis of (2S)-2-amino-3-[(3S)-2-oxopyrrolidin-3-yl]propanenitrile, methanesulfonate salt (C7).

To a solution of C6 (317 mg, 1.25 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (3 mL) was added methanesulfonic acid (81.2 μL, 1.25 mmol). After the reaction mixture had been stirred at room temperature for 45 minutes, it was concentrated in vacuo, then repeatedly taken up in a mixture of solvents and reconcentrated: acetonitrile and ethyl acetate (1:1, 2 x 10 mL) followed by ethyl acetate and heptane (1:1, 2 x 10 mL). The resulting C7 was obtained as a glass (423 mg), which was free of the nitrile epimer via 1H and 13C NMR analysis. A portion of this material was used in further reactions without additional purification. LCMS m/z 154.2 [M+H]^+. 1H NMR (400 MHz, methanol-d4) δ 4.78 (t, J = 7.3 Hz, 1H), 3.42 – 3.36 (m, 2H), 2.82 – 2.68 (m, 1H), 2.70 (s, 3H), 2.50 – 2.39 (m, 1H), 2.20 (t, J = 7.3 Hz, 1H), 2.07 – 1.80 (m, 2H).


A mixture of C7 (from the previous step; 98.8 mg, ≤0.292 mmol) and C4 (100 mg, 0.285 mmol) in acetonitrile (1.5 mL) was cooled to 0 °C. O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU, 97%; 112 mg, 0.286 mmol) was added, followed by a solution of 4-methylmorpholine (94.0 μL, 0.855 mmol) in acetonitrile (0.5 mL), and the reaction mixture was stirred at 0 °C for approximately 2 hours. Saturated aqueous sodium bicarbonate solution (30 mL) was then added to the 0 °C reaction mixture, followed by dichloromethane (50 mL), and the organic layer was washed with hydrochloric acid (1 M; 30 mL). The combined aqueous layers were extracted with dichloromethane (60 mL), whereupon the combined organic layers were dried over sodium sulfate, concentrated in vacuo, and subjected to silica gel chromatography (Gradient: 0% to 20% methanol in ethyl acetate). As the resulting
material was judged by NMR and LCMS to be contaminated with an epimer of the product, it was then purified via reversed-phase HPLC (Column: Waters Sunfire C18, 19 x 100 mm, 5 μm; Mobile phase A: water containing 0.05% trifluoroacetic acid (v/v); Mobile phase B: acetonitrile containing 0.05% trifluoroacetic acid (v/v); Gradient: 5% to 95% B over 8.54 minutes, then 95% B for 1.46 minutes; Flow rate: 25 mL/minute) to afford (1R,2S,5S)-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-[N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide (1). Yield: 14.6 mg, 30.1 μmol, 11%. LCMS m/z 486.5 [M+H]^+. Retention time: 2.33 minutes (Analytical conditions. Column: Waters Atlantis C18, 4.6 x 50 mm, 5 μm; Mobile phase A: water containing 0.05% trifluoroacetic acid (v/v); Mobile phase B: acetonitrile containing 0.05% trifluoroacetic acid (v/v). Gradient: 5% to 95% B over 4.0 minutes, then 95% B for 1.0 minute. Flow rate: 2 mL/minute).

Alternate Synthesis of C4

(1R,2S,5S)-6,6-Dimethyl-3-[N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (C4)

![Chemical structures](image)

Step 1. Synthesis of (1R,2S,5S)-3-[N-(tert-butoxycarbonyl)-L-valyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (C8).
An aqueous solution of lithium hydroxide (2.0 M; 436 mL, 872 mmol) was added to a solution of C1 (107 g, 290 mmol) in tetrahydrofuran (730 mL). After the resulting mixture had been stirred at room temperature for approximately 2 hours, it was diluted with water and ethyl acetate, then treated with 1 M aqueous sodium hydroxide solution. The aqueous layer was washed with ethyl acetate, and the combined organic layers were extracted three times with 1 M aqueous sodium hydroxide solution, until LCMS analysis indicated that C8 had been completely removed from the organic layer. Acidification of the combined aqueous layers to pH 2 was carried out by addition of concentrated hydrochloric acid, whereupon the mixture was extracted three times with ethyl acetate.

The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated; trituration of the residue with heptane afforded C8 as a white solid. Yield: 92.8 g, 262 mmol, 90%. LCMS m/z 355.3 [M+H]⁺. ¹H NMR (400 MHz, methanol-d₄) δ 4.32 (s, 1H), 4.05 (d, half of AB quartet, J = 10.5 Hz, 1H), 3.88 (dd, component of ABX system, J = 10.4, 5.3 Hz, 1H), 2.03 – 1.91 (m, 1H), 1.57 (dd, component of ABX system, J = 7.5, 5.2 Hz, 1H), 1.50 (d, half of AB quartet, J = 7.5 Hz, 1H), 1.41 (s, 9H), 1.08 (s, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.97 – 0.94 (m, 6H).

Step 2. Synthesis of (1R,2S,5S)-6,6-dimethyl-3-L-valyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid, hydrochloride salt (C9).

To a solution of C8 (82.8 g, 234 mmol) in dichloromethane (230 mL) was added a solution of hydrogen chloride in 1,4-dioxane (4.0 M; 409 mL, 1.64 mol). The reaction mixture was stirred overnight at room temperature, whereupon it was concentrated in vacuo, providing C9 as a white foam. This material was used directly in the following step. LCMS m/z 255.3 [M+H]⁺. ¹H NMR (400 MHz, methanol-d₄) δ 4.42 (s, 1H), 3.89 (dd, component of ABX system, J = 10.5, 5.2 Hz, 1H), 3.74 (d, half of AB quartet, J = 10.5 Hz, 1H), 2.36 – 2.25 (m, 1H), 1.62 (dd, component of ABX system, J = 7.5, 5.1 Hz, 1H), 1.57 (d, half of AB quartet, J = 7.6 Hz, 1H), 1.16 (d, J = 7.0 Hz, 3H), 1.10 (s, 3H), 1.04 (d, J = 6.9 Hz, 3H), 1.01 (s, 3H).

A solution of C9 (from the previous step; ≤234 mmol) in methanol (230 mL) was cooled to 0 °C, treated with triethylamine (66.7 mL, 479 mmol), and stirred for 5 minutes, whereupon ethyl trifluoroacetate (36.1 mL, 303 mmol) was slowly added. After the reaction mixture had been allowed to stir at room temperature for 90 minutes, it was concentrated in vacuo. The residue was diluted with water, 1 M aqueous sodium hydroxide solution, and ethyl acetate, and the resulting organic layer was extracted twice with 1 M aqueous sodium hydroxide solution. The combined aqueous layers were acidified to pH 2 by addition of 1 M hydrochloric acid, then extracted three times with ethyl acetate. The combined organic layers were washed with water and with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo, affording C4 as a white foam. Yield: 73.4 g, 210 mmol, 90% over 2 steps.

LCMS m/z 351.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 12.65 (v br s, 1H), 9.82 (d, J = 7.7 Hz, 1H), 4.16 (dd, J = 9.9, 7.9 Hz, 1H), 4.12 (s, 1H), 3.86 (d, half of AB quartet, J = 10.4 Hz, 1H), 3.81 (dd, component of ABX system, J = 10.5, 5.0 Hz, 1H), 2.18 – 2.05 (m, 1H), 1.54 (dd, component of ABX system, J = 7.7, 4.6 Hz, 1H), 1.42 (d, half of AB quartet, J = 7.5 Hz, 1H), 1.02 (s, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.84 (s, 3H).

Alternate Synthesis of Example 1

(1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide (1)
Step 1. Synthesis of methyl 3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninate, methanesulfonate salt (C10).

To a solution of methyl N-(tert-butoxycarbonyl)-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninate (10.1 g, 35.3 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (70 mL) was added methanesulfonic acid (2.30 mL, 35.4 mmol). After the reaction mixture had been stirred at room temperature for 70 minutes, LCMS analysis indicated that the starting material had been converted to C10: LCMS m/z 187.2 [M+H]^+. The reaction mixture was concentrated in vacuo, and the residue was redissolved twice, followed by concentration under reduced pressure, in a mixture of acetonitrile and ethyl acetate (1:1, 2 x 20 mL). The resulting material was taken up in a mixture of acetonitrile and ethyl acetate (1:1, 30 mL), concentrated, then twice redissolved in ethyl acetate (2 x 40 mL) and concentrated. The residue was triturated with ethyl acetate (60 mL) to afford C10. Yield: 9.87 g, 35.0 mmol, 99%. 1H NMR (400 MHz, methanol-d4) δ 4.22 (dd, J = 9.7, 3.6 Hz, 1H), 3.86 (s, 3H), 3.41 – 3.36 (m, 2H), 2.84 – 2.74 (m, 1H), 2.70 (s, 3H),
2.41 (ddddd, J = 12.3, 8.6, 5.1, 3.6 Hz, 1H), 2.25 (dd, J = 15.1, 4.5, 3.6 Hz, 1H), 1.98 (dd, J = 15.1, 9.6, 9.6 Hz, 1H), 1.87 (ddddd, J = 12.6, 10.9, 9.2, 9.2 Hz, 1H).


To a 0 °C solution of C10 (2.76 g, 9.78 mmol) and C4 (3.43 g, 9.79 mmol) in acetonitrile (40 mL) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.88 g, 9.81 mmol), followed by drop-wise addition of pyridine (2.37 mL, 29.3 mmol). The reaction mixture was stirred at 0 °C for 2.25 hours, whereupon it was treated with hydrochloric acid (1 M; 50 mL) and extracted with ethyl acetate (150 mL). The organic layer was washed sequentially with saturated aqueous sodium chloride solution (50 mL), saturated aqueous sodium bicarbonate solution (50 mL), and saturated aqueous sodium chloride solution (50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was taken up in tert-butyl methyl ether (30 mL) and concentrated under reduced pressure, and the resulting glass was stirred with tert-butyl methyl ether (50 mL) at room temperature overnight. After filtration, the filter cake was washed with tert-butyl methyl ether (3 x 6 mL) to afford C11 as a solid, which by 1H NMR analysis contained substantial residual tert-butyl methyl ether. A portion of this material was used in the following step. Yield: 3.74 g; corrected for residual tert-butyl methyl ether: 2.94 g, 5.67 mmol, 58%. LCMS m/z 519.5 [M+H]+. 1H NMR (400 MHz, methanol-d4) δ 4.55 (dd, J = 12.0, 3.8 Hz, 1H), 4.34 (s, 1H), 4.29 (d, J = 9.6 Hz, 1H), 3.97 (d, J = 3.1 Hz, 2H), 3.74 (s, 3H), 3.37 – 3.23 (m, 2H, assumed; partially obscured by solvent peak), 2.73 – 2.62 (m, 1H), 2.32 (dddd, J = 12.4, 8.8, 6.7, 2.4 Hz, 1H), 2.21 – 2.10 (m, 2H), 1.86 – 1.74 (m, 2H), 1.60 (dt, component of ABX2 system, J = 7.7, 3.1 Hz, 1H), 1.49 (d, half of AB quartet, J = 7.6 Hz, 1H), 1.09 (s, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.99 – 0.95 (m, 6H).


A solution of ammonia in methanol (7.0 M; 5 mL, 40 mmol) was added to a solution of C11 (from the previous step: 205 mg, 0.311 mmol) in methanol (1 mL). The resulting solution was stirred at room temperature for 1.5 hours, whereupon a solution of ammonia in methanol (7.0 M; 5 mL, 40 mmol) was again added, and stirring was continued overnight. The reaction mixture was then treated for a third time with the
same quantity of ammonia in methanol; after a further 8 hours of reaction, it was concentrated in vacuo. The residue was diluted and re-concentrated sequentially with ethyl acetate (2 x 20 mL) and a mixture of ethyl acetate and heptane (1:1, 2 x 20 mL). The resulting material was dissolved in dichloromethane (50 mL), washed with hydrochloric acid (1 M; 30 mL) and with saturated aqueous sodium chloride solution (30 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to provide C12 as a solid. Yield: 87 mg, 0.17 mmol, 55%. LCMS m/z 504.5 [M+H]+. 1H NMR (400 MHz, methanol-d4) δ 8.68 (d, J = 7.9 Hz, <1H, incompletely exchanged with solvent), 4.44 (ddd, J = 11.9, 7.9, 4.0 Hz, 1H), 4.37 – 4.26 (m, 2H), 4.01 (dd, component of ABX system, J = 10.3, 5.1 Hz, 1H), 3.94 (d, half of AB quartet, J = 10.2 Hz, 1H), 3.39 – 3.24 (m, 2H, assumed; largely obscured by solvent peak), 2.72 – 2.62 (m, 1H), 2.38 – 2.28 (m, 1H), 2.21 – 2.08 (m, 2H), 1.90 – 1.72 (m, 2H), 1.58 (dd, component of ABX system, J = 7.5, 5 Hz, 1H), 1.54 (d, half of AB quartet, J = 7.7 Hz, 1H), 1.08 (s, 3H), 1.02 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.96 (s, 3H).


Methyl N-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 88.4 mg, 0.371 mmol) was added to a solution of C12 (85.0 mg, 0.17 mmol) in dichloromethane (4.0 mL), and the reaction mixture was stirred at room temperature. After 3 hours, methyl N-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 20 mg, 84 μmol) was again added; 30 minutes later, the reaction mixture was diluted with ethyl acetate (60 mL), washed sequentially with hydrochloric acid (1 M; 30 mL), saturated aqueous sodium bicarbonate solution (30 mL), and saturated aqueous sodium chloride solution (30 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was taken up in heptane and re-concentrated before being purified via silica gel chromatography (Gradient: 0% to 5% methanol in ethyl acetate). (1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrroloidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide (1) was isolated as a solid. Yield: 35 mg, 72 μmol, 42%. LCMS m/z 486.5 [M+H]+. 1H NMR (400 MHz, methanol-d4) δ 5.04 (dd, J = 10.7, 5.4 Hz, 1H), 4.28 (d, J = 9.6 Hz, 1H), 4.25 (s, 1H), 4.03 – 3.94 (m, 2H), 3.35 – 3.23 (m, 2H, assumed; largely obscured by solvent peak), 2.72 – 2.62 (m, 1H), 2.37 – 2.26 (m, 2H), 2.19 – 2.08 (m, 1H), 1.93 – 1.75 (m, 2H), 1.64 (ddd, J = 7.6, 4.2, 2.1 Hz, 1H), 1.41 (d, J = 7.6 Hz, 1H), 1.09 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H), 1.00 – 0.95 (m, 6H).
Example 2

$N$-{(1$S$)-1-Cyano-2-[(3$S$)-2-oxopyrrolidin-3-yl]ethyl}-4-methyl-$N^2$-(pyrrolidin-1-ylacetyl)-L-leucinamide, trifluoroacetate salt (2)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{H}_2\text{N} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

C13

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{H}_2\text{N} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

C14

Step 1. Synthesis of benzyl 4-methyl-L-leucinate, $p$-toluenesulfonic acid salt (C13).

A suspension of 4-methyl-L-leucine (9.5 g, 65 mmol), benzyl alcohol (28.3 g, 262 mmol), and $p$-toluenesulfonic acid monohydrate (14.9 g, 78.3 mmol) in toluene (200 mL) was heated at reflux overnight; a Dean-Stark trap was employed to azeotropically remove the resulting water. The reaction mixture was then concentrated in vacuo, whereupon the residue was diluted with diethyl ether (200 mL) and ethyl acetate (100 mL). The resulting suspension was stirred for 1.5 hours and filtered; the filter cake was washed with diethyl ether to provide C13 as a white solid. Yield: 24.9 g, 61.1 mmol, 94%. LCMS m/z 236.3 [M+H]^+. 1H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.30 (br s, 3H), 7.47 (d, $J = 8.1$ Hz, 2H), 7.44 – 7.36 (m, 5H), 7.11 (d, $J = 7.8$ Hz, 2H), 5.23 (AB quartet, $J_{AB} = 12.3$ Hz, $\Delta V_{AB} = 13.7$ Hz, 2H), 4.02 (dd, $J = 7.3$, 4.5 Hz, 1H), 2.29 (s, 3H), 1.81 (dd, $J = 14.5$, 7.3 Hz, 1H), 1.57 (dd, $J = 14.5$, 4.6 Hz, 1H), 0.90 (s, 9H).
Step 2. Synthesis of benzyl 4-methyl-N-(pyrrolidin-1-ylacetyl)-L-leucinate (C14).

A 0 °C mixture of C13 (800 mg, 1.96 mmol) and pyrrolidin-1-ylacetic acid (254 mg, 1.97 mmol) in N,N-dimethylformamide (4 mL) was treated with O-(7-azabenzotriazol-1-yl)-N,N',N'-tetramethyluronium hexafluorophosphate (HATU; 746 mg, 1.96 mmol), followed by a solution of 4-methylmorpholine (0.496 mL, 4.51 mmol) in dichloromethane (1 mL). After the reaction mixture had been stirred at 0 °C for 2 hours, saturated aqueous sodium bicarbonate solution (30 mL) was added at 0 °C; the resulting mixture was extracted with ethyl acetate (2 x 60 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo.

Purification via silica gel chromatography was carried out twice (Gradient: 0% to 20% ethyl acetate in heptane, followed by a second chromatographic purification using 0% to 10% ethyl acetate in heptane), to afford C14 as a gum (761 mg). This material was used directly in the following step. LCMS *m/z* 347.4 [M+H]+. 1H NMR (400 MHz, methanol-d4) δ 7.40 – 7.29 (m, 5H), 5.16 (AB quartet, JAB = 12.2 Hz, ΔνAB = 11.1 Hz, 2H), 4.56 (dd, J = 9.0, 3.1 Hz, 1H), 3.76 (AB quartet, JAB = 15.6 Hz, ΔνAB = 13.6 Hz, 2H), 3.17 – 3.06 (m, 4H), 2.03 – 1.93 (m, 4H), 1.81 (dd, J = 14.5, 3.1 Hz, 1H), 1.60 (dd, J = 14.5, 9.0 Hz, 1H), 0.95 (s, 9H).


To a solution of C14 (from the previous step; 760 mg, ≤1.96 mmol) in methanol (5 mL) was added palladium on carbon (76.0 mg). The reaction mixture was stirred at room temperature under hydrogen (50 psi) overnight, whereupon LCMS analysis indicated conversion to C15: LCMS *m/z* 257.4 [M+H]+. The reaction mixture was filtered twice through a 0.15 μm filter, and the filtrate was concentrated in vacuo. The residue was twice dissolved in a mixture of ethyl acetate and heptane (1:1, 2 x 20 mL), followed by concentration under reduced pressure; this provided C15 as a solid (646 mg).

Portions of this material were used in subsequent chemistry without further purification. 1H NMR (400 MHz, DMSO-d6) δ 8.46 (d, J = 8.3 Hz, 1H), 4.31 (ddd, J = 8.9, 8.6, 3.0 Hz, 1H), 3.74 – 3.60 (m, 2H), 3.00 br (s, 4H), 1.90 – 1.79 (m, 4H), 1.70 (dd, component of ABX system, J = 14.3, 3.0 Hz, 1H), 1.56 (dd, component of ABX system, J = 14.3, 9.2 Hz, 1H), 0.90 (s, 9H).

Step 4. Synthesis of N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-4-methyl-N^2-(pyrrolidin-1-ylacetyl)-L-leucinamide, trifluoroacetate salt (2).
A mixture of C15 (from the previous step; 30 mg, ≤91 μmol) and C7 (from Step 7 of Example 1; 35.3 mg, ≤0.104 mmol) in N,N-dimethylformamide (1 mL) was cooled to 0 °C and treated with O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethylyluronium hexafluorophosphate (HATU, 97%; 39.9 mg, 0.102 mmol), followed by a solution of 4-methylmorpholine (28.0 μL, 0.255 mmol) in dichloromethane (0.25 mL). After the reaction mixture had been stirred at 0 °C for about 1.5 hours, it was diluted with saturated aqueous sodium bicarbonate solution (3 mL) at 0 °C and extracted with dichloromethane (4 x 4 mL). The combined organic layers were concentrated in vacuo and purified via reversed-phase HPLC (Column: Waters Sunfire C18, 19 x 100 mm, 5 μm; Mobile phase A: water containing 0.05% trifluoroacetic acid (v/v); Mobile phase B: acetonitrile containing 0.05% trifluoroacetic acid (v/v); Gradient: 5% to 25% B over 8.5 minutes, then 25% to 95% acetonitrile over 0.5 minutes, then 95% B for 1.0 minute; Flow rate: 25 mL/minute) to afford N-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-4-methyl-N²-(pyrrolidin-1-ylacetyl)-L-leucinamide, trifluoroacetate salt (2) as a gum. Yield: 8.1 mg, 16 μmol, 18% over 3 steps. LCMS m/z 392.6 [M+H]⁺. Retention time: 1.47 minutes (Analytical conditions. Column: Waters Atlantis C18, 4.6 x 50 mm, 5 μm; Mobile phase A: water containing 0.05% trifluoroacetic acid (v/v); Mobile phase B: acetonitrile containing 0.05% trifluoroacetic acid (v/v). Gradient: 5% to 95% B over 4.0 minutes, then 95% B for 1.0 minute. Flow rate: 2 mL/minute).

Example 3

N-{{(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N²-(2,6-dichlorobenzoyl)-4-methyl-L-leucinamide (3)
Step 1. Synthesis of 3-[(3S)-2-oxypyrrolidin-3-yl]-L-alaninamide, methanesulfonate salt, (C16).

To a solution of C5 (6.13 g, ≤19 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (40 mL) was added methanesulfonic acid (1.83 g, 19 mmol). The reaction mixture was stirred at room temperature for 1 hour, whereupon it was concentrated in vacuo, resuspended in a mixture of toluene and heptane, and concentrated once more, providing a hygroscopic glass (7.47 g). A portion of this material (6.47 g) was diluted and reconcentrated sequentially with the following: a mixture of dichloromethane and ethanol (2:3, 2 x 50 mL); ethyl acetate and ethanol (2:3, 50 mL); ethyl acetate, heptane, and dichloromethane (4:4:1, 2 x 50 mL). The resulting material was dissolved in a mixture of acetonitrile and water (1:1, 22 mL) and lyophilized for 2 days to afford C16 as a glass. Yield: 3.23 g, 12.1 mmol, 73% over 2 steps. LCMS m/z 172.2 [M+H]+. 1H NMR (400 MHz, methanol-d4) δ 4.03 (dd, J = 9.1, 4.6 Hz, 1H), 3.43 – 3.35 (m, 2H), 2.82 – 2.72 (m, 1H), 2.71 (s, 3H), 2.49 – 2.38 (m, 1H), 2.12 – 1.96 (m, 2H), 1.94 – 1.81 (m, 1H).

Step 2. Synthesis of N-[(tert-butoxycarbonyl)-4-methyl-L-leucyl-3-[(3S)-2-oxypyrrolidin-3-yl]-L-alaninamide (C17).

A 0 ºC solution of C16 (1.34 g, 5.02 mmol) and N-[(tert-butoxycarbonyl)-4-methyl-L-leucine (1.28 g, 5.22 mmol) in N,N-dimethylformamide (7.0 mL) was treated with O-(7-
azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU, 97%; 2.04 g, 5.20 mmol), followed by a solution of 4-methylmorpholine (1.43 mL, 13.0 mmol) in dichloromethane (3 mL). After the reaction mixture had been stirred at 0 °C for 2.25 hours, it was quenched at 0 °C by addition of hydrochloric acid (1 M; 30 mL) and then diluted with dichloromethane (50 mL). The organic layer was washed with saturated aqueous sodium bicarbonate solution (30 mL), and the combined aqueous layers were extracted with dichloromethane (60 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated in vacuo, and suspended / concentrated with heptane (3 x 10 mL). Purification of the residue via silica gel chromatography (Gradient: 0% to 20% methanol in ethyl acetate) afforded C17 as a solid. Yield: 1.42 g, 3.56 mmol, 71%. LCMS m/z 399.4 [M+H]+. 1H NMR (400 MHz, methanol-d4) δ 6.83 (d, J = 7.4 Hz, <1H, incompletely exchanged with solvent), 4.43 (dd, J = 11.2, 4.2 Hz, 1H), 4.11 – 4.05 (m, 1H), 3.38 – 3.24 (m, 2H, assumed; partially obscured by solvent peak), 2.52 – 2.41 (m, 1H), 2.40 – 2.30 (m, 1H), 2.13 (ddd, J = 14.0, 11.2, 4.5 Hz, 1H), 1.91 – 1.75 (m, 2H), 1.71 (dd, component of ABX system, J = 14.4, 3.2 Hz, 1H). 1.51 (dd, component of ABX system, J = 14.4, 9.3 Hz, 1H), 1.45 (s, 9H), 0.97 (s, 9H).

Step 3. Synthesis of 4-methyl-L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninamide, methanesulfonate salt (C18).

Methanesulfonic acid (32.6 µL, 0.502 mmol) was added to a solution of C17 (200 mg, 0.502 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (1.5 mL). The reaction mixture was stirred at room temperature for 40 minutes, whereupon it was concentrated in vacuo, dissolved in ethyl acetate and concentrated once more, providing C18 as a solid (238 mg). Most of this material was used in the following step. LCMS m/z 299.4 [M+H]+. 1H NMR (400 MHz, methanol-d4) δ 4.53 (dd, J = 10.3, 5.0 Hz, 1H), 3.91 (dd, J = 7.6, 5.5 Hz, 1H), 3.41 – 3.27 (m, 2H, assumed; partially obscured by solvent peak), 2.70 (s, 3H), 2.57 – 2.47 (m, 1H), 2.41 (ddd, J = 12.0, 8.6, 7.0, 3.2 Hz, 1H), 2.15 (ddd, J = 14.0, 10.3, 5.0 Hz, 1H), 2.01 (dd, J = 14.4, 7.5 Hz, 1H), 1.96 – 1.85 (m, 1H), 1.78 (ddd, J = 14.1, 9.1, 5.0 Hz, 1H), 1.59 (dd, J = 14.3, 5.5 Hz, 1H), 1.01 (s, 9H).

Step 4. Synthesis of N-(2,6-dichlorobenzoyl)-4-methyl-L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninamide (C19).

A 0 °C suspension of C18 (from the previous step: 234 mg, ≤0.49 mmol) in dichloromethane (2 mL) was treated with triethylamine (170 µL, 1.2 mmol) followed by drop-wise addition of a solution of 2,6-dichlorobenzoyl chloride (130 mg, 0.621 mmol) in
dichloromethane (0.2 mL). The reaction mixture was stirred at room temperature for 1 hour, whereupon it was diluted with dichloromethane (60 mL), then washed with hydrochloric acid (1 M; 30 mL) followed by saturated aqueous sodium bicarbonate solution (30 mL). The organic layer was dried over sodium sulfate, filtered, concentrated \textit{in vacuo}, and subjected to chromatography on silica gel (Gradient: 0% to 30% methanol in ethyl acetate) to afford \textbf{C19}. Yield: 120 mg, 0.255 mmol, 52% over 2 steps. LCMS \textit{m/z} 471.4 (dichloro isotope pattern observed) [M+H]+. \textsuperscript{1}H NMR (400 MHz, methanol-\textit{d}4) \(\delta\) 8.45 (d, \(J = 7.9\) Hz, <1H, incompletely exchanged with solvent), 7.45 – 7.35 (m, 3H), 4.59 (dd, \(J = 7.8, 4.5\) Hz, 1H), 4.52 – 4.44 (m, 1H), 3.37 – 3.24 (m, 2H, assumed; partially obscured by solvent peak), 2.65 – 2.55 (m, 1H), 2.37 (dddd, \(J = 12.5, 8.8, 6.6, 2.8\) Hz, 1H), 2.19 (dddd, \(J = 13.9, 11.3, 4.5\) Hz, 1H), 1.91 – 1.72 (m, 3H), 1.66 (dd, component of ABX system, \(J = 14.4, 7.8\) Hz, 1H), 1.03 (s, 9H).

Step 5. Synthesis of \(\text{N-\{1(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}-N^2\{2,6-dichlorobenzoyl\}-4-methyl-L-leucinamide (3).}

A solution of \textbf{C19} (90 mg, 0.19 mmol) and 1H-imidazole (33.8 mg, 0.496 mmol) in pyridine (1 mL) was cooled in an acetonitrile / dry ice bath (–35 °C). To this was added phosphorus oxychloride (0.100 mL, 1.07 mmol), and the reaction mixture was stirred at –30 °C to –20 °C. After 30 minutes, pyridine (2 mL) was added to facilitate stirring; after 1 hour, dichloromethane (2 mL) was added for the same reason. At 2 hours of reaction, phosphorus oxychloride (0.100 mL, 1.07 mmol) was again added, and stirring was continued for 30 minutes at –30 °C, whereupon the reaction mixture was warmed to 0 °C and stirred for an additional 40 minutes. It was then treated with hydrochloric acid (1 M; 30 mL) and extracted with dichloromethane (2 x 60 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated \textit{in vacuo}, and subjected to silica gel chromatography (Gradient: 0% to 15% methanol in ethyl acetate) to provide a solid (67 mg). This material was combined with the product (12 mg) from a similar reaction carried out using \textbf{C19} (30 mg, 64 \textmu mol) and twice taken up in ethyl acetate (2 x 3 mL) followed by concentration under reduced pressure. The residue was stirred with a mixture of ethyl acetate and heptane (1:3, 4 mL) at room temperature for 40 minutes and filtered; the filter cake was washed with a mixture of ethyl acetate and heptane (1:3, 5 x 2 mL), to provide \(\text{N-\{1(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}-N^2\{2,6-dichlorobenzoyl\}-4-methyl-L-leucinamide (3)} as a solid. Combined yield: 70 mg, 0.15 mmol, 59%. LCMS \textit{m/z} 453.3 (dichloro isotope pattern observed) [M+H]+. \textsuperscript{1}H NMR (400 MHz, methanol-\textit{d}4) \(\delta\) 7.45 – 7.34 (m, 3H), 5.05 (dd, \(J =
10.7, 5.4 Hz, 1H), 4.56 (dd, J = 7.0, 5.7 Hz, 1H), 3.37 – 3.23 (m, 2H, assumed; partially obscured by solvent peak), 2.70 – 2.59 (m, 1H), 2.42 – 2.29 (m, 2H), 1.95 – 1.77 (m, 3H), 1.67 (dd, component of ABX system, J = 14.4, 7.0 Hz, 1H), 1.04 (s, 9H).

Example 4

N-[(2S)-1-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide (4)

Step 1. Synthesis of methyl L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninate, hydrochloride salt (C20).
A solution of methyl N-(tert-butoxycarbonyl)-L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninate (see Prior, A.M., et al., Bioorg. Med. Chem. Lett. 2013, 23, 6317–6320; 2.0 g, 5.0 mmol) in a mixture of methanol (2 mL) and a solution of hydrogen chloride in ethyl acetate (4 M; 20 mL) was stirred at 25 °C for 1 hour. Concentration in vacuo afforded C20 as a white solid (1.92 g, assumed quantitative). \(^1\)H NMR (400 MHz, DMSO-d6), characteristic peaks: δ 9.09 – 8.98 (m, 1H), 8.39 (br s, 3H), 7.69 (s, 1H), 4.44 – 4.31 (m, 1H), 3.22 – 3.07 (m, 2H), 2.5 – 2.38 (m, 1H, assumed; partially obscured by solvent peak), 2.24 – 2.11 (m, 1H), 2.11 – 1.99 (m, 1H), 1.78 – 1.48 (m, 5H), 0.92 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H).

Step 2. Synthesis of methyl N-(4-methoxy-1H-indole-2-carbonyl)-L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninate (C21).

O-(7-Azabenzotriazol-1-yil)-N,N,N’,N’-tetramethyluronium hexafluorophosphate (HATU; 494 mg, 1.30 mmol) and N,N-diisopropylethylamine (388 mg, 3.00 mmol) were added to a 0 °C solution of C20 (from a smaller-scale experiment similar to Step 1; 336 mg, ≤0.840 mmol) and 4-methoxy-1H-indole-2-carboxylic acid (159 mg, 0.832 mmol) in N,N-dimethylformamide (6 mL). The solution was stirred at 0 °C for 1.5 hours, whereupon it was poured into water / ice (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Eluent: 10:1 dichloromethane / methanol) provided C21 as a yellow oil. Yield: 380 mg, 0.804 mmol, 97%. LCMS m/z 473.2 [M+H]⁺. \(^1\)H NMR (400 MHz, DMSO-d6) δ 11.59 – 11.53 (m, 1H), 8.53 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.37 – 7.33 (m, 1H), 7.09 (dd, J = 8, 8 Hz, 1H), 7.00 (d, component of AB quartet, J = 8.2 Hz, 1H), 6.50 (d, J = 7.6 Hz, 1H), 4.56 – 4.47 (m, 1H), 4.40 – 4.31 (m, 1H), 3.88 (s, 3H), 3.62 (s, 3H), 3.18 – 3.05 (m, 2H), 2.41 – 2.29 (m, 1H), 2.15 – 2.03 (m, 2H), 1.78 – 1.49 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H).

Step 3. Synthesis of N-(4-methoxy-1H-indole-2-carbonyl)-L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alanine (C22).

To a stirring mixture of calcium chloride (0.887 g, 7.99 mmol) and sodium hydroxide (0.168 g, 4.20 mmol) in 2-propanol (7 mL) and water (3 mL) was added C21 (1.8 g, 3.8 mmol). The reaction mixture was stirred at 20 °C for 6 hours, whereupon it was concentrated in vacuo, diluted with water (4 mL), adjusted to pH 4 by addition of 1 M hydrochloric acid, and extracted with ethyl acetate (3 x 10 mL). The combined
organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Eluent: 10:1 dichloromethane / methanol / acetic acid) afforded C22 as a yellow solid. Yield: 1.76 g, 3.84 mmol, 100%. LCMS m/z 459.2 [M+H]^+. 1H NMR (400 MHz, chloroform-d), characteristic peaks: δ 6.51 – 6.43 (m, 1H), 4.80 – 4.66 (m, 1H), 4.60 – 4.45 (m, 1H), 3.92 (s, 3H), 3.36 – 3.18 (m, 2H), 2.59 – 2.44 (m, 1H).

Alternate Step 3. Synthesis of N-(4-methoxy-1H-indole-2-carbonyl)-L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alanine (C22).

A solution of C21 (20 mg, 42 μmol) in tetrahydrofuran (0.4 mL) was treated with an aqueous solution containing lithium hydroxide (14.2 mg, 0.593 mmol). After the reaction mixture had been stirred at room temperature for 2.5 hours, it was diluted with ethyl acetate and washed with 10% aqueous potassium bisulfate solution. The organic layer was then dried over sodium sulfate, filtered, and concentrated in vacuo, providing C22 as a white solid. Yield: 20 mg, quantitative. LCMS m/z 459.2 [M+H]^+. 1H NMR (400 MHz, methanol-d4) δ 7.27 (s, 1H), 7.14 (dd, component of ABX system, J = 8, 8 Hz, 1H), 7.02 (d, component of AB quartet, J = 8.3 Hz, 1H), 6.50 (d, J = 7.7 Hz, 1H), 4.66 (dd, J = 9.0, 5.9 Hz, 1H), 4.52 (dd, J = 11.7, 3.9 Hz, 1H), 3.92 (s, 3H), 3.30 – 3.18 (m, 2H), 2.65 – 2.52 (m, 1H), 2.38 – 2.26 (m, 1H), 2.21 (ddd, J = 14.0, 11.7, 4.1 Hz, 1H), 1.90 – 1.70 (m, 5H), 1.02 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 6.3 Hz, 3H).

Step 4. Synthesis of N-(4-methoxy-1H-indole-2-carbonyl)-L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninamide (C23).

To a 0 °C solution of C22 (1.76 g, 3.84 mmol) and ammonium chloride (0.246 g, 4.60 mmol) in N,N-dimethylformamide (15 mL) were added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU; 1.90 g, 5.00 mmol) and N,N-diisopropylethylamine (1.49 g, 11.5 mmol). After the reaction mixture had been stirred at 0 °C for 1.5 hours, N,N-diisopropylethylamine (2.3 g, 18 mmol) was used to adjust the pH to 8. The reaction mixture was stirred for an additional 30 minutes, whereupon it was poured into a mixture of hydrochloric acid (1 M; 20 mL, 20 mmol) and ice. The resulting mixture was extracted with ethyl acetate (3 x 10 mL); the combined organic layers were washed sequentially with hydrochloric acid (1 M; 10 mL) and saturated aqueous sodium chloride solution (10 mL), dried over sodium sulfate, filtered, concentrated in vacuo, and purified via silica gel chromatography (Eluent: 10:1 dichloromethane / methanol), affording C23 as a yellow solid. Yield: 1.09 g, 2.38 mmol.
62%. LCMS m/z 458.0 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.62 – 11.55 (m, 1H), 8.42 (d, J = 7.9 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.60 (br s, 1H), 7.38 – 7.26 (m, 2H), 7.10 (dd, component of ABX system, J = 8, 8 Hz, 1H), 7.06 (br s, 1H), 7.00 (d, component of AB quartet, J = 8.2 Hz, 1H), 6.51 (d, J = 7.7 Hz, 1H), 4.54 – 4.41 (m, 1H), 4.34 – 4.22 (m, 1H), 3.88 (s, 3H), 3.17 – 3.01 (m, 2H), 2.31 – 1.95 (m, 3H), 1.76 – 1.45 (m, 5H), 0.92 (d, J = 6.1 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H).


To a 0 °C mixture of C23 (500 mg, 1.09 mmol) and N,N-diisopropylethylamine (565 mg, 4.37 mmol) in tetrahydrofuran (8 mL) was added 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinanate 2,4,6-trioxide (50% solution by weight in ethyl acetate; 2.78 g, 4.37 mmol). After the reaction mixture had been stirred at 50 °C for 3 hours, it was concentrated in vacuo, diluted with water (5 mL), and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo; silica gel chromatography (Eluent: 10:1 dichloromethane / methanol) followed by reversed-phase HPLC purification (Column: YMC-Actus Triart C18, 50 x 250 mm, 7 μm; Mobile phase A: water containing 0.225% formic acid; Mobile phase B: acetonitrile; Gradient: 18% to 58% B; Flow rate: 25 mL/minute) afforded N-[(2S)-1-((((1S)-1-cyano-2-[(3S)-2-oxypyrrolidin-3-yl]ethyl]amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide (4) as a yellow solid. Yield: 130 mg, 0.296 mmol, 27%. LCMS m/z 440.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.58 (br s, 1H), 8.90 (d, J = 8.0 Hz, 1H), 8.47 (d, J = 7.7 Hz, 1H), 7.71 (br s, 1H), 7.38 – 7.35 (m, 1H), 7.09 (dd, component of ABX system, J = 8, 8 Hz, 1H), 7.00 (d, component of AB quartet, J = 8.2 Hz, 1H), 6.51 (d, J = 7.7 Hz, 1H), 5.02 – 4.93 (m, 1H), 4.49 – 4.40 (m, 1H), 3.88 (s, 3H), 3.19 – 3.05 (m, 2H), 2.41 – 2.29 (m, 1H), 2.20 – 2.06 (m, 2H), 1.85 – 1.62 (m, 4H), 1.58 – 1.47 (m, 1H), 0.94 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H).

Alternate Synthesis of Example 4

N-[(2S)-1-((((1S)-1-Cyano-2-[(3S)-2-oxypyrrolidin-3-yl]ethyl]amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide (4)
Step 1. Synthesis of N-[(4-methoxy-1H-indol-2-yl)carbonyl]-L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninamide (C23).

A solution of ammonia in methanol (7.0 M; 21 mL, 150 mmol) was added to a solution of C21 (500 mg, 1.06 mmol) in methanol (2.0 mL). After the reaction mixture had been stirred at room temperature for 6 hours, a solution of ammonia in methanol (7.0 M; 7.0 mL, 49 mmol) was again added, and stirring was continued overnight. A solution of ammonia in methanol (7.0 M; 7.0 mL, 49 mmol) was again added, and stirring was continued for 24 hours, whereupon a final treatment with a solution of ammonia in methanol (7.0 M; 7.0 mL, 49 mmol) was carried out. The reaction mixture was stirred for one more day, at which point it was concentrated in vacuo. The residue was combined with the product of a similar reaction (350 mg of the 512 mg isolated) carried out using C21 (500 mg, 1.06 mmol), and the mixture was repeatedly dissolved in ethyl acetate (5 x 10 mL) and concentrated under reduced pressure, providing C23 (835 mg). This material was used directly in the following step. LCMS m/z 458.4 [M+H]+. 1H NMR (400 MHz, methanol-d4) δ 7.29 (d, J = 0.9 Hz, 1H), 7.15 (dd, component of ABX system, J = 8, 8 Hz, 1H), 7.03 (br d, component of AB quartet, J = 8.3 Hz, 1H), 6.51 (d, J = 7.7 Hz, 1H), 4.59 (dd, J = 9.7, 5.0 Hz, 1H), 4.45 (dd, J = 11.3, 4.2 Hz, 1H), 3.93 (s, 3H), 3.34 – 3.19 (m, 2H, assumed; partially obscured by solvent peak), 2.57 – 2.47 (m, 1H), 2.31 (dddd, J = 12.6, 8.5, 6.8, 2.8 Hz, 1H), 2.15 (ddd, J = 14.0, 11.4, 4.6 Hz, 1H), 1.88 – 1.67 (m, 5H), 1.02 (d, J = 6.1 Hz, 3H), 0.98 (d, J = 6.1 Hz, 3H).
Step 2. Synthesis of \( N-[(2S)-1-\text{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}l]amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide \((4)\).

A solution of \( \text{C23} \) (from the previous step: 835 mg, \( \leq 1.78 \text{ mmol} \)) and 1\( \text{H} \)-imidazole (323 mg, 4.74 mmol) in a mixture of pyridine (4 mL) and dichloromethane (4 mL) was cooled to \(-35 \text{ °C} \) using an acetonitrile / dry ice bath, whereupon phosphorus oxychloride (0.956 mL, 10.2 mmol) was added in a drop-wise manner over 5 minutes. The reaction was stirred at a temperature between \(-30 \text{ °C} \) and \(-20 \text{ °C} \) for about 1.5 hours, then treated with hydrochloric acid (1 M; 50 mL) and stirred for 1 hour. After extraction with dichloromethane (3 x 60 mL), the resulting organic layers were combined, dried over sodium sulfate, filtered, and concentrated \textit{in vacuo}. The residue was combined with purified \( \text{C4} \) from a different batch (75 mg, 0.17 mmol) and subjected to silica gel chromatography (Gradient: 0% to 5% methanol in ethyl acetate) to provide \( \text{C4} \) as a solid (600 mg). This material was combined with the product (80 mg) from a similar reaction carried out using \( \text{C23} \) (161 mg, 0.352 mmol); the resulting material was stirred in diethyl ether (25 mL) for 3 days, whereupon it was filtered. The filter cake was washed with a mixture of diethyl ether and heptane (1:1, 4 \times 2 mL) to afford \( N-[(2S)-1-\text{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}l]amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide \((4)\) as a solid. Combined yield: 519 mg, 1.18 mmol, approximately 50% over 2 steps. LCMS \textit{m/z} 440.5 [M+H]+. \textit{1H} NMR (400 MHz, DMSO-\( \text{d6} \)) \( \delta \) 11.57 (d, \( J = 2.3 \text{ Hz} \), 1H), 8.90 (d, \( J = 8.1 \text{ Hz} \), 1H), 8.46 (d, \( J = 7.7 \text{ Hz} \), 1H), 7.70 (s, 1H), 7.37 (d, \( J = 2.3 \text{ Hz} \), 1H), 7.10 (dd, component of ABX system, \( J = 8, 8 \text{ Hz} \), 1H), 7.00 (d, component of AB quartet, \( J = 8.2 \text{ Hz} \), 1H), 6.51 (d, \( J = 7.7 \text{ Hz} \), 1H), 5.03 – 4.92 (m, 1H), 4.51 – 4.39 (m, 1H), 3.88 (s, 3H), 3.19 – 3.05 (m, 2H), 2.42 – 2.30 (m, 1H), 2.20 – 2.06 (m, 2H), 1.80 (ddd, \( J = 13.2, 9.3, 6.7 \text{ Hz} \), 1H), 1.75 – 1.63 (m, 3H), 1.58 – 1.47 (m, 1H), 0.94 (d, \( J = 6.2 \text{ Hz} \), 3H), 0.89 (d, \( J = 6.2 \text{ Hz} \), 3H).

Examples 5 and 6

\( N-[(2S)-1-\text{[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}l]amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-3-(trifluoromethyl)-1H-indole-2-carboxamide \((5)\) and \( N-[(2S)-1-\text{[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}l]amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-7-(trifluoromethyl)-1H-indole-2-carboxamide \((6)\)
To a pressure release vial containing zinc(II) trifluoromethanesulfinate (98%, 2.44 mg, 7.21 μmol) were sequentially added a solution of 4 (0.79 mg, 1.8 μmol) in dimethyl sulfoxide (60 μL), trifluoroacetic acid (0.56 μL, 7.3 μmol), and tert-butyl hydroperoxide (70% in water; 1.25 μL, 9.03 μmol). The vial was capped and heated to 50 °C overnight, whereupon the reaction mixture was cooled and diluted with acetonitrile and a 1% solution of formic acid in water, to a volume of approximately 2 to 3 mL. The final solvent composition was such that the resulting mixture appeared clear, generally about 20% to 30% acetonitrile. The entire mixture was subjected to reversed-phase HPLC (Column: Phenomenex Luna C18, 10 x 250 mm, 10 μm; Mobile phase A: 0.5% acetic acid in water; Mobile phase B: 9:1 acetonitrile / methanol; Gradient: 15% B for 5 minutes, then 15% to 70% B linear gradient over 84 minutes, then 70% to 95% B over 1 minute, then 95% B for 9 minutes; Flow rate: 2 mL/min). The eluate was passed through a UV/VIS detector and then was split at approximately 15:1 between a fraction collector and an ion trap mass spectrometer. Fractions were collected every 20 seconds and those potentially containing products of interest were evaluated by UHPLC-UV-HRMS before pooling. The two products eluted at approximately 71 and 75 minutes. The first-eluting product was 5 \(N\-\{(2S)-1-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}\}ethyl\}amino\}-4-methyl-1-oxopentan-2-yl\}-4-methoxy-3-(trifluoromethyl)-1H-indole-2-carboxamide}, and the second-eluting was 6 \(N\-\{(2S)-1-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}\}ethyl\}amino\}-4-methyl-1-oxopentan-2-yl\}-4-methoxy-7-(trifluoromethyl)-1H-indole-2-carboxamide}. 

5 – Yield: 0.101 mg, 0.199 μmol, 11%. High-resolution MS \(m/z\ 508.2171 \[M+H]^+\}; calculated for \(C_{24}H_{29}F_3N_3O_4\), 508.2172. \(^1H\ NMR (600 MHz, DMSO-\text{d}_6) \delta 12.22 \) (br s,
1H), 9.01 (d, J = 7.6 Hz, 1H), 8.96 (d, J = 7.9 Hz, 1H), 7.73 (s, 1H), 7.21 (dd, J = 8, 8 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 5.03 – 4.95 (m, 1H), 4.49 – 4.40 (m, 1H), 3.87 (s, 3H), 3.22 – 3.08 (m, 2H), 2.43 – 2.34 (m, 1H), 2.23 – 2.10 (m, 2H), 1.82 (ddd, J = 13.7, 9.3, 6.8 Hz, 1H), 1.78 – 1.66 (m, 2H), 1.62 (ddd, J = 14.6, 9.7, 5.2 Hz, 1H), 1.49 (ddd, J = 13.8, 8.8, 5.5 Hz, 1H), 0.97 – 0.88 (m, 6H). Retention time: 8.43 minutes (Analytical conditions. Column: Phenomenex Kinetex XB-C18, 2.1 x 100 mm, 2.6 μm; Mobile phase A: water containing 0.1% formic acid; Mobile phase B: acetonitrile; Gradient: 5% B for 0.5 minutes, then 5% to 70% B over 10.5 minutes, then 70% to 95% B over 2 minutes; Flow rate: 0.4 mL/min).

6 – Yield: 14.7 μg, 0.029 μmol, 1.6%. High-resolution MS m/z 508.2178 [M+H]^+; calculated for C24H29F3N5O4, 508.2172. 1H NMR (600 MHz, DMSO-d6) δ 11.47 (br s, 1H), 9.00 (d, J = 7.9 Hz, 1H), 8.79 (d, J = 7.8 Hz, 1H), 7.70 (s, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.35 (s, 1H), 6.72 (d, J = 8.3 Hz, 1H), 5.02 – 4.94 (m, 1H), 4.56 – 4.48 (m, 1H), 3.97 (s, 3H), 3.18 – 3.05 (m, 2H), 2.39 – 2.30 (m, 1H), 2.18 – 2.08 (m, 2H), 1.86 – 1.77 (m, 1H), 1.75 – 1.64 (m, 3H), 1.61 – 1.52 (m, 1H), 0.95 (d, J = 6.1 Hz, 3H), 0.90 (d, J = 6.1 Hz, 3H). Retention time: 8.92 minutes (Analytical conditions identical to those used for 5).

Alternate Synthesis of Example 6

\[ N-\{(2S)\}-1-\{(1S)\}-Cyano-2-\{(3S)\}-2-oxopyrrolidin-3-yl\}ethyl\}amino\}-4-methyl-1-oxopentan-2-yl\}4-methoxy-7-(trifluoromethyl)-1H-indole-2-carboxamide (6) \]
Step 1. Synthesis of trifluoromethylated 4-methoxy-1H-indole-2-carboxylic acid (C24).

A mixture of 4-methoxy-1H-indole-2-carboxylic acid (100 mg, 0.523 mmol) and zinc(II) trifluoromethanesulfinate (120 mg, 0.362 mmol) was treated with dimethyl sulfoxide (1.5 mL) followed by trifluoroacetic acid (56 μL, 0.727 mmol). After the reaction mixture had been cooled to 0 °C, tert-butyl hydroperoxide (70% in water; 143 μL, 1.03 mmol) was added, and stirring was continued at 0 °C for 20 minutes, then at room temperature for 25 minutes. The reaction mixture was subsequently heated at 52 °C for 2 hours, whereupon it was cooled to room temperature and treated in a drop-wise manner with aqueous sodium bicarbonate solution until bubbling had ceased. After the resulting mixture had been partitioned between aqueous sodium bicarbonate solution and ethyl acetate, the aqueous layer was extracted once with ethyl acetate and the organic layers were discarded. The aqueous layer was then acidified to pH 7 with 1 M hydrochloric acid; ethyl acetate was added, and the mixture was stirred while the pH was adjusted to 1 by addition of 1 M hydrochloric acid. After the biphasic mixture had been stirred for 10 minutes, the organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated in
vacuo. By LCMS analysis, the residue (115 mg) contained a mixture of starting material and mono-trifluoromethylated products, as well as a small amount of di-trifluoromethylated material. The bulk of this mixture was used in Step 4. Yield: 115 mg, <0.4 mmol. LCMS m/z 189.8, 257.8, 325.8 (minor) [M−H]⁺. ¹H NMR (400 MHz, methanol-δ₄), characteristic peaks from the three major components: δ 7.07 (br d, J = 8.4 Hz), 7.02 (br d, J = 8.4 Hz), 6.81 (d, J = 7.8 Hz), 6.66 (d, J = 7.8 Hz), 6.51 (d, J = 7.7 Hz), 4.06 (s, -OMe), 3.93 (s, -OMe), 3.92 (s, -OMe).  

Step 2. Synthesis of N-(tert-butoxycarbonyl)-L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninamide (C25).  

To a 0 ºC solution of methyl N-(tert-butoxycarbonyl)-L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninate (see Prior, A.M., et al., Bioorg. Med. Chem. Lett. 2013, 23, 6317–6320; 1.5 g, 3.8 mmol) in methanol (5 mL) was added a solution of ammonia in methanol (7 M; 43 mL, 300 mmol). After the reaction vessel had been capped, the reaction mixture was stirred overnight at room temperature. A solution of ammonia in methanol (7 M; 10.7 mL, 74.9 mmol) was again added, and the reaction was allowed to continue at room temperature for 3 days, whereupon it was concentrated in vacuo. The residue was taken up twice in diethyl ether (40 mL) and concentrated under reduced pressure, affording C25 as a white solid. Yield: 1.46 g, 3.80 mmol, quantitative. LCMS m/z 385.4 [M+H]⁺. ¹H NMR (400 MHz, chloroform-d) δ 8.29 – 8.17 (m, 1H), 7.23 (br s, 1H), 5.64 (br s, 1H), 5.32 (br s, 1H), 5.02 (d, J = 6.1 Hz, 1H), 4.50 – 4.38 (m, 1H), 4.05 (ddd, J = 10.3, 6.3, 4.5 Hz, 1H), 3.44 – 3.32 (m, 2H), 2.51 – 2.35 (m, 2H), 2.16 – 1.98 (m, 2H), 1.97 – 1.83 (m, 1H), 1.76 – 1.6 (m, 2H, assumed; partially obscured by water peak), 1.49 – 1.39 (m, 1H), 1.45 (s, 9H), 0.94 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H).  

Step 3. Synthesis of L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninamide, methanesulfonate salt (C26).  

A solution of methanesulfonic acid (0.061 mL, 13.3 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (5 mL) was slowly added to a solution of C25 (5.1 g, 13 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (43 mL). After 30 minutes, LCMS analysis indicated conversion to C26: LCMS m/z 285.3 [M+H]⁺. The reaction mixture was concentrated in vacuo, then taken up in the following solvent mixtures and reconcentrated: a mixture of acetonitrile and ethyl acetate (1:1, 2 x 20 mL), then a mixture of ethyl acetate and heptane, (1:1, 2 x 20 mL). The resulting solid was azeotroped twice with a mixture of
acetonitrile and ethyl acetate, then twice with a mixture of ethyl acetate and heptane, affording C26 as a white solid (6.05 g) that retained solvents by ¹H NMR analysis. Yield: assumed quantitative. ¹H NMR (600 MHz, methanol-d₄) δ 4.50 (dd, J = 10.7, 4.9 Hz, 1H), 3.91 (dd, J = 8.6, 5.5 Hz, 1H), 3.39 – 3.28 (m, 2H, assumed; partially obscured by solvent peak), 2.70 (s, 3H), 2.53 – 2.46 (m, 1H), 2.43 – 2.36 (m, 1H), 2.14 (ddd, J = 14.0, 10.7, 5.0 Hz, 1H), 1.95 – 1.86 (m, 1H), 1.82 – 1.71 (m, 3H), 1.70 – 1.64 (m, 1H), 1.02 (d, J = 6.3 Hz, 3H), 1.01 (d, J = 6.1 Hz, 3H).

Step 4. Synthesis of N-[(4-methoxy-7-(trifluoromethyl)-1H-indol-2-yl)carbonyl]-L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninamide (C27).

A solution of C24 (from Step 1; 101 mg, <0.35 mmol) and C26 (from the previous step; 204 mg, <0.438 mmol) in acetonitrile (1.7 mL) and N,N-dimethylformamide (1 mL) was cooled to 0 °C and treated with O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU; 163 mg, 0.429 mmol) followed by 4-methylmorpholine (0.129 mL, 1.17 mmol). The reaction mixture was stirred at 0 °C for 40 minutes, whereupon a 1:1 mixture of aqueous sodium bicarbonate solution and ice was slowly added until a cloudy precipitate formed. Ethyl acetate was then added, and the biphasic mixture was stirred for 5 minutes. The aqueous layer was extracted once with ethyl acetate, and the combined organic layers were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification via silica gel chromatography was carried out twice (Gradient #1: 0% to 10% methanol in dichloromethane; Gradient #2: 5% to 10% methanol in dichloromethane) to afford C27. The regiochemistry of this material was confirmed by 2D NMR experiments. Yield: 19 mg, 36 μmol, approximately 10%. LCMS m/z 526.5 [M+H]+. ¹H NMR (400 MHz, methanol-d₄) δ 7.53 (br d, J = 8.2 Hz, 1H), 7.41 (s, 1H), 6.68 (d, J = 8.3 Hz, 1H), 4.60 (dd, J = 9.5, 5.1 Hz, 1H), 4.45 (dd, J = 11.4, 4.2 Hz, 1H), 4.01 (s, 3H), 3.3 – 3.21 (m, 2H, assumed; partially obscured by solvent peak), 2.60 – 2.49 (m, 1H), 2.36 – 2.26 (m, 1H), 2.15 (ddd, J = 14.1, 11.5, 4.6 Hz, 1H), 1.89 – 1.68 (m, 5H), 1.03 (d, J = 6.1 Hz, 3H), 0.99 (d, J = 6.2 Hz, 3H).

Step 5. Synthesis of N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-4-methoxy-7-(trifluoromethyl)-1H-indole-2-carboxamide (6).

Methyl N-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 17.2 mg, 72.2 μmol) was added to a solution of C27 (19 mg, 36 μmol) in a mixture of dichloromethane (0.5 mL) and acetonitrile (0.2 mL). After the reaction mixture had been
stirred at room temperature for 1 hour, it was diluted with ethyl acetate and washed with a 1:1 mixture of aqueous sodium bicarbonate solution and ice. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with saturated aqueous sodium chloride solution, and passed through a solid-phase extraction cartridge packed with magnesium sulfate. Concentration of the filtrate in vacuo provided a residue, which was purified via reversed-phase HPLC (Column: Waters Sunfire C18, 19 x 100 mm, 5 µm; Mobile phase A: water containing 0.05% trifluoroacetic acid (v/v); Mobile phase B: acetonitrile containing 0.05% trifluoroacetic acid (v/v); Gradient: 25% to 65% B over 8.5 minutes, then 65% to 95% B over 0.5 minutes, then 95% B for 1.0 minute; Flow rate: 25 mL/minute) to afford N-[(2S)-1-((1S)-1-cyano-2-[(3S)-2-oxypyrrrolidin-3-yl]ethyl]amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-7-(trifluoromethyl)-1H-indole-2-carboxamide (6). Yield: 4.3 mg, 8.5 µmol, 24%. LCMS m/z 508.6 [M+H]+. Retention time: 2.83 minutes (Column: Waters Atlantis C18, 4.6 x 50 mm, 5 µm; Mobile phase A: water containing 0.05% trifluoroacetic acid (v/v); Mobile phase B: acetonitrile containing 0.05% trifluoroacetic acid (v/v); Gradient: 5% to 95% B over 4.0 minutes, then 95% B for 1.0 minute; Flow rate: 2 mL/minute).

Example 7

N-[(2S)-1-((1S)-1-Cyano-2-[(3S)-2-oxypyrrrolidin-3-yl]ethyl]amino)-4,4-dimethyl-1-oxopentan-2-yl]-3-methylimidazo[2,1-b][1,3]thiazole-2-carboxamide (7)
Step 1. Synthesis of \( N^2-\text{(tert-butoxycarbonyl)}-N-\{(1S)-1-cyano-2-\{[3S]-2-oxopyrrolidin-3-yl\}ethyl\}-4\text{-methyl}-L\text{-leucinamide} (C28) \).

A solution of C17 (560 mg, 1.41 mmol) and 1\( H \)-imidazole (249 mg, 3.65 mmol) in a mixture of pyridine (3 mL) and dichloromethane (3 mL) was cooled to \(-35^\circ\text{C}\) using an acetonitrile / dry ice bath. Phosphorus oxychloride (0.74 mL, 7.94 mmol) was added in a drop-wise manner, over 4 minutes, followed by additional dichloromethane (2 mL), and stirring was continued at \(-30^\circ\text{C}\) to \(-20^\circ\text{C}\). After 1 hour, the reaction mixture was diluted with dichloromethane (2 mL). After approximately 1.5 hours, hydrochloric acid (1 M; 30 mL) was added; the resulting mixture was stirred for 30 minutes, and then extracted with dichloromethane (2 x 60 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated \textit{in vacuo}, affording C28 as a solid. Yield: 492 mg, 1.29 mmol, 91%. LCMS \( m/z \) 381.4 [M+H]*. \( ^1\text{H} \) NMR (400 MHz, methanol-d4) \( \delta \) 5.03 (dd, \( J = 10.4, 5.7 \text{ Hz} \), 1H), 4.09 (dd, \( J = 8.7, 4.2 \text{ Hz} \), 1H), 3.39 – 3.25 (m, 2H, assumed; partially obscured by solvent peak), 2.64 – 2.52 (m, 1H), 2.40 – 2.27 (m, 2H), 1.97 – 1.78 (m, 2H), 1.70 (dd, component of ABX system, \( J = 14.3, 4.1 \text{ Hz} \), 1H), 1.54 (dd, component of ABX system, \( J = 14.3, 8.7 \text{ Hz} \), 1H), 1.45 (s, 9H), 1.00 (s, 9H).

Step 2. Synthesis of \( N-\{(2S)-1-\{(1S)-1-cyano-2-\{[(3S)-2-oxopyrrolidin-3-yl]ethyl\}amino\}-4,4\text{-dimethyl-1-oxopentan-2-yl}\} \text{-3-methylimidazo[2,1-b][1,3]thiazole-2-carboxamide (7)} \).

A solution of hydrogen chloride in 1,4-dioxane (4.0 M; 0.3 mL, 1.2 mmol) was added to a solution of C28 (100 mg, 0.263 mmol) in a mixture of acetonitrile (1.5 mL) and methanol (1.0 mL). The reaction mixture was stirred at room temperature for 30 minutes, whereupon it was treated with 4-methylmorpholine (0.144 mL, 1.31 mmol). After solvents had been removed \textit{in vacuo}, the residue was twice resuspended in a mixture of dichloromethane and heptane (1:1, 2 x 10 mL) and concentrated under reduced pressure. The residue was combined with 3-methylimidazo[2,1-b][1,3]thiazole-2-carboxylic acid (47.9 mg, 0.263 mmol) in \( N,N \)-dimethylformamide (3.3 mL), cooled to 0 \( ^\circ\text{C} \), and treated with O-(7-azabenzotriazol-1-yl)-\( N,N,N',N' \)-tetramethyluronium hexafluorophosphate (HATU; 99.9 mg, 0.263 mmol) followed by a solution of 4-methylmorpholine (72 \( \mu\text{L} \), 0.655 mmol) in dichloromethane (0.2 mL). After the reaction mixture had been stirred at 0 \( ^\circ\text{C} \) for approximately 2 hours, it was treated at 0 \( ^\circ\text{C} \) with hydrochloric acid (1 M; 30 mL), and the resulting mixture was extracted with dichloromethane (2 x 60 mL). The aqueous layer was then basified to pH 9 by addition of saturated aqueous sodium bicarbonate solution, whereupon it was extracted with
dichloromethane (3 x 60 mL). The combined organic layers were washed with saturated aqueous ammonium chloride solution (50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. $^1$H NMR analysis of this material indicated the presence of a minor epimer, presumed to arise from partial racemization at the center bearing the nitrile. The major product was isolated using silica gel chromatography (Gradient: 0% to 20% methanol in ethyl acetate), providing N-{(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-3-methylimidazo[2,1-b][1,3]thiazole-2-carboxamide (7) as a solid. Yield: 56 mg, 0.13 mmol, 49%. LCMS m/z 445.4 [M+H]⁺. $^1$H NMR (400 MHz, methanol-d₄) δ 7.73 (d, J = 1.6 Hz, 1H), 7.37 (d, J = 1.6 Hz, 1H), 5.04 (dd, J = 10.3, 5.9 Hz, 1H), 4.53 (dd, J = 7.8, 5.0 Hz, 1H), 3.36 – 3.24 (m, 2H; assumed; partially obscured by solvent peak), 2.70 (s, 3H), 2.67 – 2.57 (m, 1H), 2.38 – 2.27 (m, 2H), 1.93 (ddd, J = 14.0, 9.4, 6.0 Hz, 1H), 1.88 – 1.78 (m, 3H), 1.03 (s, 9H).

Examples 8 and 9

N-{1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N²-[cyclohexyl(methoxy)acetyl]-4-methyl-L-leucinamide, DIAST-1 (8) and N-{1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N²-[cyclohexyl(methoxy)acetyl]-4-methyl-L-leucinamide, DIAST-2 (9)
Step 1. Synthesis of N-{1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-4-methyl-L-leucinamide (C29).

To a solution of C28 (114 mg, 0.300 mmol) in a mixture of acetonitrile (1 mL) and methanol (1 mL) was added a solution of hydrogen chloride in 1,4-dioxane (4 M; 0.4 mL, 1.6 mmol). The reaction mixture was stirred at room temperature for 30 minutes, whereupon 4-methylmorpholine (0.165 mL, 1.50 mmol) was added, bringing the pH to 7 to 8. After solvents were removed in vacuo, the residue was twice taken up in a mixture of ethyl acetate and heptane (1:1, 2 x 10 mL) and concentrated under reduced pressure to provide C29 as a solid (269 mg); by 1H NMR analysis, this consisted of a mixture of epimers, presumed to be at the center bearing the nitrile, in a ratio of 2–3 to 1. A portion of this material was used in the following step. LCMS m/z 281.3 [M+H]+. 1H NMR (400 MHz, methanol-d4), characteristic peaks: δ [5.11 (dd, J = 8.8, 7.3 Hz, major) and 5.01 (dd, J = 6.5, 6.5 Hz, minor), total 1H], [2.75 – 2.65 (m, minor) and 2.64 – 2.54 (m, major), total 1H], 2.48 – 2.38 (m, 1H), 2.30 – 2.20 (m, 1H), 2.06 – 1.83 (m, 3H), 1.64 (dd, J = 14.1, 4.8 Hz, 1H), [1.04 (s, major), 1.01 (s, minor), total 9H].

Step 2. Synthesis of N-{1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N²-cyclohexyl(methoxy)acetyl]-4-methyl-L-leucinamide, DIAST-1 (8) and N-{1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N²-cyclohexyl(methoxy)acetyl]-4-methyl-L-leucinamide, DIAST-2 (9).

To a 0 °C solution of C29 (from the previous step; 83.4 mg, 0.093 μmol) and cyclohexyl(methoxy)acetic acid (17.2 mg, 99.9 μmol) in N,N-dimethylformamide (1 mL) was added O-(7-azabenztiazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU; 38.0 mg, 0.100 mmol), followed by a solution of 4-methylmorpholine (30.8 μL, 0.280 mmol) in dichloromethane (0.2 mL). After the reaction mixture had been stirred at 0 °C for about 2 hours, it was diluted with saturated aqueous sodium bicarbonate solution (3 mL) at 0 °C, and extracted with dichloromethane (4 x 4 mL). The combined organic layers were concentrated in vacuo; by LCMS analysis, the residue consisted of two components, assumed to correspond to the two epimers at the center bearing the nitrile. These diastereomers were separated via reversed-phase HPLC (Column: Waters XBridge C18, 19 x 100 mm, 5 μm; Mobile phase A: water; Mobile phase B: acetonitrile; Gradient: 5% to 95% B over 8.54 minutes, then 95% B for 1.46 minutes; Flow rate: 25 mL/minute). The first-eluting diastereomer was designated as 8 (N-{1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N²-cyclohexyl(methoxy)acetyl]-4-
methyl-L-leucinamide, DIAST-1), and the second-eluting diastereomer as 9 (N-[1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N²-cyclohexyl(methoxy)acetyl]-4-methyl-L-leucinamide, DIAST-2).

8 – Yield: 12.8 mg, 29.4 μmol, 32% over 2 steps. LCMS m/z 435.6 [M+H]+. Retention time: 2.63 minutes (Analytical conditions. Column: Waters Atlantis C18, 4.6 x 50 mm, 5 μm; Mobile phase A: water containing 0.05% trifluoroacetic acid (v/v); Mobile phase B: acetonitrile containing 0.05% trifluoroacetic acid (v/v). Gradient: 5% to 95% B over 4.0 minutes, then 95% B for 1.0 minute. Flow rate: 2 mL/minute).

9 – Yield: 10 mg, 23.0 μmol, 25% over 2 steps. LCMS m/z 435.6 [M+H]+. Retention time: 2.72 minutes (Analytical conditions identical to those used for 8).

Example 10

N-[(2S)-1-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide (10)

Step 1. Synthesis of N-[(4-methoxy-1H-indol-2-yl)carbonyl]-4-methyl-L-leucyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninamide (C30).

To a 0 °C solution of C18 (200 mg, ≤0.46 mmol) and 4-methoxy-1H-indole-2-carboxylic acid (88.2 mg, 0.460 mmol) in acetonitrile (2 mL) was added O-(7-
azabenzo triazol-1-yl)-N,N,N’,N’-tetramethyluronium hexafluorophosphate (HATU; 175 mg, 0.460 mmol), followed by a solution of 4-methylmorpholine (0.127 mL, 1.16 mmol) in acetonitrile (0.2 mL). The reaction mixture was stirred at 0 °C for 2.5 hours, whereupon it was diluted with saturated aqueous sodium bicarbonate solution (30 mL) at 0 °C, then extracted with dichloromethane (50 mL). The organic layer was washed with hydrochloric acid (1 M; 30 mL), and the aqueous layers were extracted with dichloromethane (60 mL). After the combined organic layers had been dried over sodium sulfate, filtered, and concentrated in vacuo, the residue was purified via silica gel chromatography (Gradient: 0% to 30% methanol in ethyl acetate) to provide **C30** as a solid. Yield: 148 mg, 0.314 mmol, 68% over 2 steps. LCMS *m/z* 472.4 [M+H]+. 1H NMR (400 MHz, methanol-d4) δ 7.25 (d, *J* = 0.9 Hz, 1H), 7.15 (dd, *J* = 8, 8 Hz, 1H), 7.03 (br d, component of AB quartet, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 7.7 Hz, 1H), 4.65 (dd, *J* = 9.2, 3.4 Hz, 1H), 4.44 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.93 (s, 3H), 3.29 – 3.15 (m, 2H), 2.54 – 2.44 (m, 1H), 2.29 (dddd, *J* = 12.6, 8.6, 7.0, 2.7 Hz, 1H), 2.14 (dddd, *J* = 14.0, 11.2, 4.6 Hz, 1H), 1.89 (dd, component of ABX system, *J* = 14.5, 3.4 Hz, 1H), 1.85 – 1.74 (m, 3H), 1.02 (s, 9H).

Step 2. Synthesis of N-[(2S)-1-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide (10).

A solution of **C30** (143 mg, 0.303 mmol) and 1H-imidazole (53.7 mg, 0.789 mmol) in a mixture of pyridine (1 mL) and dichloromethane (1 mL) was cooled in an acetonitrile / dry ice bath (−35 °C). Phosphorus oxychloride (0.159 mL, 1.71 mmol) was added in a drop-wise manner over 5 minutes, and the reaction mixture was stirred at −30 °C to −20 °C for 2 hours, whereupon it was treated with hydrochloric acid (1 M; 30 mL), stirred for 20 minutes, and extracted with dichloromethane (2 x 60 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel (Gradient: 0% to 10% methanol in ethyl acetate) provided N-[(2S)-1-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide (10) as a solid. Yield: 68 mg, 0.15 mmol, 50%. LCMS *m/z* 454.5 [M+H]+. 1H NMR (400 MHz, methanol-d4) δ 7.24 (d, *J* = 0.9 Hz, 1H), 7.14 (dd, *J* = 8, 8 Hz, 1H), 7.02 (br d, component of AB quartet, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 7.7 Hz, 1H), 5.03 (dd, *J* = 10.1, 6.0 Hz, 1H), 4.64 (dd, *J* = 8.6, 4.3 Hz, 1H), 3.93 (s, 3H), 3.30 – 3.17 (m, 2H), 2.63 – 2.52 (m, 1H), 2.37 – 2.21 (m, 2H), 1.95 – 1.74 (m, 4H), 1.03 (s, 9H).
Example 11

$N\textsuperscript{2}$-[(4-Bromo-1-ethyl-3-methyl-1$H$-pyrazol-5-yl)carbonyl]-$N\textsuperscript{1}$-((1$S$)-1-cyano-2-[(3$S$)-2-oxopyrrolidin-3-yl]ethyl)-4-methyl-L-leucinamide (11)

![Chemical Structures]

To a 0 °C slurry of C18 (43.4 mg, ≤0.10 mmol) and 4-bromo-1-ethyl-3-methyl-1$H$-pyrazole-5-carboxylic acid (23.3 mg, 0.100 mmol) in acetonitrile (1.0 mL) was added O-(7-azabenzotriazol-1-yl)-$N\textsubscript{2},N\textsubscript{3},N\textsubscript{3}$-tetramethyluronium hexafluorophosphate (HATU; 38.0 mg, 0.100 mmol), followed by a solution of 4-methylmorpholine (30 μL, 0.27 mmol) in acetonitrile (0.2 mL). After the reaction mixture had been stirred at 0 °C for approximately 80 minutes, methyl $N$-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 71.5 mg, 0.300 mmol) was added, and stirring was continued. After approximately 2.75 hours, methyl $N$-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 71.5 mg, 0.300 mmol) was again added, and the reaction was allowed to proceed for 1.5 hours, whereupon it was treated with saturated aqueous sodium bicarbonate solution (3 mL) at 0 °C, and extracted with dichloromethane (2 x 8 mL). The combined organic layers were concentrated in vacuo, then dissolved in acetonitrile (4 mL) and concentrated again using a Genevac evaporator to provide the crude product (138 mg). A portion of this material (80 mg) was purified via reversed-phase HPLC (Column: Waters Sunfire C18, 19 x 100 mm, 5 μm; Mobile phase A: water containing 0.05% trifluoroacetic acid (v/v); Mobile phase B: acetonitrile containing 0.05% trifluoroacetic acid (v/v); Gradient: 5% to 95% B over 8.54 minutes, then 95% B for 1.46 minutes; Flow rate: 25 mL/minute) to afford $N\textsuperscript{2}$-[(4-bromo-1-ethyl-3-methyl-1$H$-pyrazol-5-yl)carbonyl]-$N\textsuperscript{1}$-((1$S$)-1-cyano-2-[(3$S$)-2-oxopyrrolidin-3-yl]ethyl)-4-methyl-L-leucinamide (11). Yield: 24.7 mg, 49.8 μmol, 86% over 2 steps. LCMS m/z 495.5
(bromine isotope pattern observed) [M+H]⁺. Retention time: 2.48 minutes (Analytical conditions. Column: Waters Atlantis C18, 4.6 x 50 mm, 5 μm; Mobile phase A: water containing 0.05% trifluoroacetic acid (v/v); Mobile phase B: acetonitrile containing 0.05% trifluoroacetic acid (v/v). Gradient: 5% to 95% B over 4.0 minutes, then 95% B for 1.0 minute. Flow rate: 2 mL/minute).

Example 12

\[ N-\{(1S)-1-Cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}-N^\{\}\{\}(3,3-difluorocyclobutyl)acetyl\}-4-methyl-L-leucinamide (12) \]

\[ C17 \] \[ \text{HCl} \] \[ \rightarrow \]

\[ C18, \text{HCl salt} \]

\[ \]

\[ \]

10

Step 1. Synthesis of 4-methyl-L-leucyl-3-\{(3S)-2-oxopyrrolidin-3-yl\}-L-alaninamide, hydrochloride salt (C18, HCl salt).

A solution of hydrogen chloride in 1,4-dioxane (4 M; 1.7 mL, 6.8 mmol) was added to a solution of C17 (260 mg, 0.652 mmol) in acetonitrile (3 mL). The reaction mixture was stirred at room temperature for 1.5 hours, whereupon it was concentrated \textit{in vacuo}, then repeatedly dissolved in a mixture of dichloromethane and heptane (1:1, 3 x 10 mL) and re-concentrated, affording C18, HCl salt (242 mg) as a glass. A portion of this material was used in the following step. LCMS m/z 299.3 [M+H]⁺. ¹H NMR (400 MHz, methanol-d₄) ð 4.53 (dd, J = 10.3, 5.0 Hz, 1H), 3.91 (dd, J = 7.5, 5.4 Hz, 1H), 3.41
- 3.26 (m, 2H, assumed; partially obscured by solvent peak), 2.57 – 2.47 (m, 1H), 2.41 (ddddd, J = 12.0, 8.7, 7.0, 3.1 Hz, 1H), 2.15 (ddddd, J = 13.9, 10.3, 4.9 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.97 – 1.85 (m, 1H), 1.78 (ddddd, J = 14.1, 9.1, 5.0 Hz, 1H), 1.60 (dd, J = 14.3, 5.4 Hz, 1H), 1.01 (s, 9H).


A slurry of C18, HCl salt (from the previous step; 37.2 mg, ≤0.100 mmol) and (3,3-difluorocyclobutyl)acetic acid (15.8 mg, 0.105 mmol) in tetrahydrofuran (1.0 mL) was treated with 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide trioxide (50% solution by weight in ethyl acetate; 65.5 µL, 0.110 mmol) and 4-methylmorpholine (27.5 µL, 0.250 mmol). After the reaction mixture had been stirred at room temperature overnight, it was heated at 50 °C for 4.5 hours, whereupon 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide trioxide (50% solution by weight in ethyl acetate; 2.2 equivalents) and 4-methylmorpholine (5 equivalents) were again added. After the reaction mixture had been stirred at 50 °C for 3 additional days, it was treated with saturated aqueous sodium bicarbonate solution (3 mL) and extracted with dichloromethane (4 x 4 mL). The combined organic layers were concentrated in vacuo and purified via reversed-phase HPLC (Column: Waters XBridge C18, 19 x 100 mm, 5 µm; Mobile phase A: water; Mobile phase B: acetonitrile; Gradient: 20% to 40% B over 8.5 minutes, then 40% to 95% B over 0.5 minutes, then 95% B for 1.0 minute; Flow rate: 25 mL/minute) to afford N-{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-N'{-[(3,3-difluorocyclobutyl)acetyl]}-4-methyl-L-leucinamide (12). Yield: 10.1 mg, 24.5 µmol, 24% over 2 steps. LCMS m/z 413.5 [M+H]+. Retention time: 1.96 minutes (Analytical conditions. Column: Waters Atlantis C18, 4.6 x 50 mm, 5 µm; Mobile phase A: water containing 0.05% trifluoroacetic acid (v/v); Mobile phase B: acetonitrile containing 0.05% trifluoroacetic acid (v/v). Gradient: 5% to 95% B over 4.0 minutes, then 95% B for 1.0 minute. Flow rate: 2 mL/minute).

Example 13

(1R,2S,5S)-N-{[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide (13)
Step 1. Synthesis of methyl (1R,2S,5S)-3-[N-(tert-butoxycarbonyl)-3-methyl-L-valyl]-6,6-
dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate (C31).

O-(7-Azabenzotriazol-1-yl)-N,N',N'-tetramethyluronium hexafluorophosphate
(HATU; 7.92 g, 20.8 mmol) was added to a 0 °C mixture of N-(tert-butoxycarbonyl)-3-
methyl-L-valine (4.38 g, 18.9 mmol) and methyl (1R,2S,5S)-6,6-dimethyl-3-
azabicyclo[3.1.0]hexane-2-carboxylate, hydrochloride salt (3.9 g, 19 mmol) in N,N-
dimethylformamide (95 mL). After the reaction mixture had been stirred for 5 minutes,
N,N-diisopropylethylamine (8.25 mL, 47.4 mmol) was added; stirring was continued at 0
°C for 2 hours, whereupon aqueous citric acid solution (1 N, 20 mL) and water (40 mL) were added. The resulting mixture was stirred for 2 minutes, and then diluted with ethyl acetate (250 mL). The organic layer was washed with water (3 x 150 mL) and with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. Purification via silica gel chromatography (Gradient: 0% to 100% ethyl acetate in heptane) afforded C31 as an oil. Yield: 3.60 g, 9.41 mmol, 50%. 1H NMR (400 MHz, methanol-d4) δ 6.42 (d, J = 9.7 Hz, <1H; incompletely exchanged with solvent), 4.35 (s, 1H), 4.21 (d, J = 9.7 Hz, 1H), 4.02 (d, half of AB quartet, J = 10.4 Hz, 1H), 3.91 (dd, component of ABX system, J = 10.3, 5.3 Hz, 1H), 3.73 (s, 3H), 1.57 (dd, component of ABX system, J = 7.5, 5.1 Hz, 1H), 1.47 (d, half of AB quartet, J = 7.5 Hz, 1H), 1.41 (s, 9H), 1.07 (s, 3H), 1.02 (s, 9H), 0.93 (s, 3H).


Aqueous lithium hydroxide solution (1.0 M; 14.7 mmol, 14.7 mL) was added in a drop-wise manner to a 0 °C solution of C31 (3.60 g, 9.41 mmol) in a mixture of tetrahydrofuran and methanol (1:1, 30 mL). After the reaction mixture had been stirred at 0 °C for 1 hour, it was allowed to warm to room temperature and stirred for 1 hour, whereupon LCMS analysis indicated conversion to C32: LCMS m/z 367.3 [M-H]^{-}. Adjustment to pH 3 was carried out via addition of 1 M hydrochloric acid, after which the mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (2 x 75 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide C32 as an off-white solid. Yield: 3.10 g, 8.41 mmol, 89%. 1H NMR (400 MHz, methanol-d4) δ 6.39 (d, J = 9.7 Hz, approximately 0.5H; incompletely exchanged with solvent), 4.33 (s, 1H), [4.21 (d, J = 9.6 Hz) and 4.21 (s), total 1H], 4.01 (d, half of AB quartet, J = 10.5 Hz, 1H), 3.91 (dd, component of ABX system, J = 10.4, 5.2 Hz, 1H), 1.56 (dd, component of ABX system, J = 7.5, 5.0 Hz, 1H), 1.50 (d, half of AB quartet, J = 7.6 Hz, 1H), 1.42 (s, 9H), 1.07 (s, 3H), 1.02 (s, 9H), 0.93 (s, 3H).


A 0 °C mixture of C7 (31.9 mg, ≤94 μmol) and C32 (34 mg, 92 μmol) in acetonitrile (1 mL) was treated with O-(7-azabenzotriazol-1-yl)-N,N,N',N'-
tetramethyluronium hexafluorophosphate (HATU, 97%; 36.2 mg, 92.3 μmol) followed by a solution of 4-methylmorpholine (25 μL, 0.23 mmol) in acetonitrile (0.25 mL). After the reaction mixture had been stirred at 0 °C for approximately 1 hour, it was diluted with saturated aqueous sodium bicarbonate solution (3 mL) at 0 °C, and extracted with dichloromethane (4 x 4 mL). The combined organic layers were concentrated *in vacuo* to provide C33 as a gum (48 mg). Most of this material was used in the following step. LCMS *m/z* 504.6 [M+H]+.


A stock solution of methanesulfonic acid (60 μL) in 1,1,1,3,3,3-hexafluoropropan-2-ol (940 μL) was prepared. To a solution of C33 (from the previous step; 47 mg, ≤90 μmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (1 mL) was added a portion of the methanesulfonic acid stock solution (0.1 mL; 100 μmol). After the reaction mixture had been stirred at room temperature for 1 hour, it was concentrated *in vacuo*, then taken up in the following solvent mixtures and reconcentrated: a mixture of acetonitrile and ethyl acetate (1:1, 2 x 10 mL), and then a mixture of ethyl acetate and heptane (1:1, 2 x 10 mL). The residue was dissolved in dichloromethane (1 mL) and treated with 4-methylmorpholine (30.8 μL, 0.280 mmol), followed by trifluoroacetic anhydride (0.143 mL, 1.01 mmol). The reaction mixture was stirred at room temperature for 40 minutes, whereupon it was treated with 4-methylmorpholine (30.8 μL, 0.280 mmol) followed by trifluoroacetic anhydride (0.143 mL, 1.01 mmol); after 30 minutes, 4-methylmorpholine (30.8 μL, 0.280 mmol) was again added, followed by trifluoroacetic anhydride (0.143 mL, 1.01 mmol). After an additional 15 minutes of stirring, the reaction mixture was treated with hydrochloric acid (1 M; 3 mL), and the resulting mixture was extracted with dichloromethane (3 x 4 mL); the combined organic layers were concentrated *in vacuo* and purified using reversed-phase HPLC (Waters Sunfire C18, 19 x 100 mm, 5 μm; Mobile phase A: water containing 0.05% trifluoroacetic acid (v/v); Mobile phase B: acetonitrile containing 0.05% trifluoroacetic acid (v/v). Gradient: 20% to 60% B over 8.5 minutes, then 60% to 95% B over 0.5 minutes, then 95% B for 1 minute; Flow rate: 25 mL/minute) to afford (1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide (13). Yield: 7.5 mg, 15 μmol, 17% over 2 steps. LCMS *m/z* 500.5 [M+H]+.

Retention time: 2.66 minutes (Analytical conditions. Column: Waters Atlantis dC18, 4.6
x 50 mm, 5 μm; Mobile phase A: 0.05% trifluoroacetic acid in water (v/v); Mobile phase B: 0.05% trifluoroacetic acid in acetonitrile (v/v); Gradient: 5.0% to 95% B over 4.0 minutes, then 95% B for 1.0 minute; Flow rate: 2 mL/minute.

Alternate Synthesis of Example 13

$\text{(1R,2S,5S)-N-\{1-(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl\}-6,6$-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide (13)}$

(C5) $\xrightarrow{\text{NH}_3} \text{C16, HCl salt}$

(C31) $\xrightarrow{\text{LiOH}}$

(C32) $\xrightarrow{\text{HCl}} \text{C41}$

This experiment was carried out in 2 parallel batches. A solution of ammonia in methanol (7 M; 2.4 L, 17 mol) was added to methyl N-(tert-butoxycarbonyl)-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninate (600 g, 2.10 mol) and the reaction mixture was stirred at 25 °C for 40 hours. Concentration in vacuo and combination of the 2 batches provided C5 as a yellow solid. Combined yield: 1.10 kg, 4.05 mol, 96%. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.63 (br s, 1H), 7.29 (br s, 1H), 7.01 (br s, 1H), 6.89 (d, $J = 8.5$ Hz, 1H), 3.96 – 3.85 (m, 1H), 3.22 – 3.06 (m, 2H, assumed; partially obscured by water peak), 2.28 – 2.08 (m, 2H), 1.89 (ddd, $J = 14.6$, 10.8, 4.0 Hz, 1H), 1.74 – 1.60 (m, 1H), 1.56 – 1.43 (m, 1H), 1.36 (s, 9H).

Step 2. Synthesis of 3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninamide, hydrochloride salt (C16, HCl salt).
This experiment was carried out in 3 parallel batches. To a 0 °C solution of C5 (840 g, 3.10 mol) in dichloromethane (2.0 L) was added a solution of hydrogen chloride in 1,4-dioxane (4 M; 2 L, 8 mol). The reaction mixture was stirred at 25 °C for 2 hours, whereupon it was concentrated in vacuo; combination of the 3 batches afforded C16, HCl salt as a white solid. Combined yield: 1.20 kg, 5.78 mol, 62%. MS m/z 172.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-­d₆) δ 8.52 – 8.35 (br s, 3H), 8.12 (s, 1H), 7.95 (s, 1H), 7.57 (s, 1H), 3.86 – 3.76 (m, 1H), 3.24 – 3.10 (m, 2H), 2.59 – 2.5 (m, 1H, assumed; partially obscured by solvent peak), 2.35 – 2.24 (m, 1H), 2.01 (ddd, J = 14.9, 9.2, 6.1 Hz, 1H), 1.80 – 1.68 (m, 2H).


This experiment was carried out in 3 parallel batches. To a 0 °C solution of methyl (1R,2S,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate, hydrochloride salt (237 g, 1.15 mol) and N-(tert-butoxycarbonyl)-3-methyl-L-valine (293 g, 1.27 mol) in a mixture of N,N-dimethylformamide (400 mL) and acetonitrile (3.6 L) was added O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU; 481 g, 1.26 mol), followed by drop-wise addition of N,N-diisopropylethylamine (601 mL, 3.45 mol). The reaction mixture was then allowed to warm to 25 °C and was stirred for 16 hours, whereupon it was poured into a mixture of ice water (1 L) and hydrochloric acid (0.5 M; 1 L), of pH approximately 5, and stirred for 6 minutes. The resulting mixture was extracted with ethyl acetate (2 L), and the organic layer was washed with water (2 L), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified using silica gel chromatography (Gradient: 0% to 50% ethyl acetate in petroleum ether), affording, after combination of the 3 batches, C31 as a colorless oil. Combined yield: 1.17 kg, 3.06 mol, 89%. LCMS m/z 383.3 [M+H]⁺. ¹H NMR (400 MHz, chloroform-d) δ 5.10 (d, J = 10.2 Hz, 1H), 4.46 (s, 1H), 4.20 (d, J = 10.3 Hz, 1H), 3.98 (d, half of AB quartet, J = 10.2 Hz, 1H), 3.89 – 3.82 (m, 1H), 3.74 (s, 3H), 1.48 – 1.41 (m, 2H), 1.38 (s, 9H), 1.03 (s, 3H), 1.01 (s, 9H), 0.89 (s, 3H).


This experiment was carried out in 3 parallel batches. To a solution of C31 (668 g, 1.75 mol) in tetrahydrofuran (2.5 L) was added lithium hydroxide monohydrate (220 g, 5.24 mol) and water (500 mL). After the reaction mixture had been stirred at 25 °C for 2
hours, it was concentrated in vacuo to remove most of the tetrahydrofuran; the residue was then adjusted to pH 2 by addition of 1 M hydrochloric acid. The resulting mixture was extracted with ethyl acetate (2 x 500 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (500 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to provide C32 as a white solid (2.0 kg) after combination of the 3 batches. This material was used directly in the following step.

LCMS m/z 313.2 [(M - 2-methylprop-1-ene)+H]+. \(^1\)H NMR (400 MHz, chloroform-d) \(\delta\) 5.14 (d, \(J = 10.2\ Hz, 1H\)), 4.46 (s, 1H), 4.24 (d, \(J = 10.2\ Hz, 1H\)), 4.06 (d, half of AB quartet, \(J = 10.5, 5.5\ Hz, 1H\)), 3.82 (dd, component of ABX system, \(J = 10.5, 5.5\ Hz, 1H\)), 1.75 (d, \(J = 7.7\ Hz, 1H\)), 1.49 (dd, \(J = 7.7, 5.4\ Hz, 1H\)), 1.40 (s, 9H), 1.06 (s, 3H), 1.00 (s, 9H), 0.89 (s, 3H).

Step 5. Synthesis of \((1R,2S,5S)-6,6\text{-dimethyl-3-(3-methyl-L-valyl)}\text{-3-azabicyclo[3.1.0]hexane-2-carboxylic acid, hydrochloride salt (C41)}\).

This experiment was carried out in 2 parallel batches. A solution of hydrogen chloride in 1,4-dioxane (4 M; 4.0 L, 16 mol) was added to a solution of C32 (from the previous step; 1.00 kg, \(\leq 2.62\) mol) in dichloromethane (1.0 L), and the reaction mixture was stirred at 25 °C for 16 hours. Removal of solvents in vacuo at 50 °C afforded C41 as a white solid (1.8 kg) after combination of the 2 batches. This material was used directly in the following step. \(^1\)H NMR (400 MHz, methanol-d\(_4\)) \(\delta\) 4.42 (s, 1H), 4.00 (s, 1H), 3.94 (dd, component of ABX system, \(J = 10.7, 5.4\ Hz, 1H\)), 3.80 (d, half of AB quartet, \(J = 10.7\ Hz, 1H\)), 1.62 (dd, component of ABX system, \(J = 7.7, 5.2\ Hz, 1H\)), 1.56 (d, half of AB quartet, \(J = 7.6\ Hz, 1H\)), 1.15 (s, 9H), 1.09 (s, 3H), 1.03 (s, 3H).

Step 6. Synthesis of \((1R,2S,5S)-6,6\text{-dimethyl-3-[3-methyl-N-(trifluoroacetyl)]-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (C42)}\).

This experiment was carried out in 3 parallel batches. To a 0 °C solution of C41 (from the previous step; 600 g, \(\leq 1.75\) mol) in methanol (2 L) was added triethylamine (1.64 L, 11.8 mol), followed by ethyl trifluoroacetate (699 g, 4.92 mol), whereupon the reaction mixture was allowed to warm to 25 °C, and was stirred for 16 hours. It was then concentrated in vacuo at 50 °C, and the residue was diluted with ethyl acetate (3 L) and adjusted to a pH of 3 to 4 by addition of 2 M hydrochloric acid. After extraction of the aqueous layer with ethyl acetate (1 L), the combined organic layers were washed with saturated aqueous sodium chloride solution (3 L), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The 3 batches were combined at this point,
treated with a mixture of petroleum ether and ethyl acetate (5:1, 3 L), and stirred at 25 °C for 2 hours. Filtration afforded C42 as a white solid. Combined yield: 1.90 kg, 5.21 mol, 99% over 3 steps. LCMS m/z 365.1 [M+H]+. 1H NMR (400 MHz, methanol-d4) δ 8.88 (d, J = 8.8 Hz, <1H; incompletely exchanged), 4.60 (d, J = 8.9 Hz) and 4.59 (s, total 1H), 4.35 (s, 1H), 3.96 (dd, component of ABX system, J = 10.5, 5.1 Hz, 1H), 3.90 (d, half of AB quartet, J = 10.4 Hz, 1H), 1.58 (dd, component of ABX system, J = 7.6, 4.9 Hz, 1H), 1.52 (d, half of AB quartet, J = 7.6 Hz, 1H), 1.08 (s, 12H), 0.92 (s, 3H).


This experiment was carried out in 4 parallel batches. 2-Hydroxypyridine 1-oxide (33.9 g, 305 mmol) was added to a solution of C42 (445 g, 1.22 mol) and C16, HCl salt (256 g, 1.23 mol) in butan-2-one (2.5 L), and the mixture was cooled to 0 °C. N,N-Diisopropylethylamine (638 mL, 3.66 mol) was then added, followed by drop-wise addition of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (351 g, 1.83 mol). The reaction mixture was stirred at 25 °C for 16 hours, whereupon it was diluted with ethyl acetate (1 L) and treated with a mixture of hydrochloric acid (1 M; 1.5 L, 1.5 mol) and saturated aqueous sodium chloride solution (1 L). The organic layer was washed with a mixture of aqueous sodium hydroxide solution (1 M; 1.5 L, 1.5 mol) and saturated aqueous sodium chloride solution (1 L), dried over sodium sulfate, filtered, and concentrated in vacuo. Combination of the 4 batches provided C43 as a white solid (2.3 kg). Combined yield: 2.1 kg (corrected for residual ethyl acetate), 4.1 mol, 84%. LCMS m/z 518.3 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 9.41 (br d, J = 7.7 Hz, 1H), 8.30 (d, J = 8.8 Hz, 1H), 7.56 (s, 1H), 7.32 (br s, 1H), 7.04 (br s, 1H), 4.43 (br d, J = 7.3 Hz, 1H), 4.35 – 4.25 (m, 1H), 4.28 (s, 1H), 3.89 (dd, J = 10.3, 5.5 Hz, 1H), 3.67 (d, J = 10.4 Hz, 1H), 3.17 – 3.09 (m, 1H), 3.07 – 2.98 (m, 1H), 2.46 – 2.35 (m, 1H), 2.19 – 2.10 (m, 1H), 1.99 – 1.89 (m, 1H), 1.70 – 1.58 (m, 1H), 1.55 – 1.44 (m, 2H), 1.38 (d, half of AB quartet, J = 7.6 Hz, 1H), 1.01 (s, 3H), 0.98 (s, 9H), 0.84 (s, 3H).


This experiment was carried out in 3 parallel batches. Methyl N-(triethylammoniosulfonil)carbamate, inner salt (Burgess reagent; 552 g, 2.32 mol) was
added to a solution of \textbf{C43} (600 g, 1.16 mol) in ethyl acetate (3 L). After the reaction mixture had been stirred at 25 °C for 3 hours, it was treated with additional methyl N-(triethylammoniosulfonfonyl)carbamate, inner salt (Burgess reagent; 27.6 g, 116 mmol) and the reaction mixture was stirred for 1 hour. It was then filtered; the filter cake was washed with ethyl acetate (2 × 500 mL), and the combined filtrates were washed sequentially with aqueous sodium bicarbonate solution (1 M; 2 L), saturated aqueous sodium chloride solution (2 L), hydrochloric acid (1 M; 2 L), and saturated aqueous sodium chloride solution (2 L). The organic layer was then dried over sodium sulfate, filtered, and concentrated \textit{in vacuo}. The residue was treated with a mixture of ethyl acetate and tert-butyl methyl ether (1:10, 2.5 L) and heated to 50 °C; after stirring for 1 hour at 50 °C, it was cooled to 25 °C and stirred for 2 hours. The solid was collected via filtration, and the 3 batches were combined in ethyl acetate (8 L) and filtered through silica gel (3.0 kg); the silica gel was then washed with ethyl acetate (2 × 2 L). After the combined eluates had been concentrated \textit{in vacuo}, the residue was taken up in ethyl acetate (900 mL) and tert-butyl methyl ether (9 L). This mixture was heated to 50 °C for 1 hour, cooled to 25 °C, and stirred for 2 hours. Filtration afforded (1R,2S,5S)-N-\{(1S)-1-cyano-2-(3S)-2-oxopyrrolidin-3-yl\}ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide (13) as a white solid. Combined yield: 1.41 kg, 2.82 mol, 81%. LCMS \textit{m/z} 500.3 [M+H]+= 1H NMR (400 MHz, DMSO-\textit{d}_6) \delta 9.42 (d, \textit{J} = 8.4 Hz, 1H), 9.03 (d, \textit{J} = 8.6 Hz, 1H), 7.68 (s, 1H), 4.97 (ddd, \textit{J} = 10.9, 8.5, 5.1 Hz, 1H), 4.41 (d, \textit{J} = 8.5 Hz, 1H), 4.16 (s, 1H), 3.91 (dd, \textit{J} = 10.4, 5.5 Hz, 1H), 3.69 (d, \textit{J} = 10.4 Hz, 1H), 3.18 – 3.10 (m, 1H), 3.08 – 2.99 (m, 1H), 2.46 – 2.34 (m, 1H), 2.20 – 2.03 (m, 2H), 1.78 – 1.65 (m, 2H), 1.57 (dd, \textit{J} = 7.6, 5.4 Hz, 1H), 1.32 (d, \textit{J} = 7.6 Hz, 1H), 1.03 (s, 3H), 0.98 (s, 9H), 0.85 (s, 3H).

\textbf{Example 14}

\textit{N-\{(2S)-1-\{(1S)-1-Cyano-2-(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino}-5,5,5-trifluoro-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide (14)

Sodium bicarbonate (4.8 g, 57 mmol) was added to a solution of 5,5,5-trifluoro-L-norvalinamide, hydrochloride salt (this was synthesized using the method described for its enantiomer, in J. E. Starrett, PCT Int. Appl., 2010107997, September 23, 2010; 4.0 g, 19 mmol) and 9H-fluoren-9-ylmethyl carbonochloridate (Fmoc chloride; 10.2 g, 39.4 mmol) in water (80 mL). The resulting slurry was stirred at 15 °C to 25 °C for 24 hours, whereupon it was partitioned between water and dichloromethane. The organic layer was washed sequentially with water and saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo, providing C34 as a solid. Yield: 6.2 g, 16 mmol, 83%. LCMS m/z 393.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 7.9 (d, 2H), 7.7 (m, 2H), 7.5 (d, 1H), 7.4 (m, 5H), 7.1 (br s, 1H), 4.3 (m, 3H), 4.0 (m, 1H), 2.2 (m, 2H), 1.9 (m, 1H), 1.7 (m, 1H).


To a solution of C34 (6.2 g, 16 mmol) in 1,4-dioxane (60 mL) was added hydrochloric acid (3 M; 10 mL, 30 mmol), and the reaction mixture was stirred at 80 °C for 16 hours. It was then partitioned between water and dichloromethane, and the organic layer was washed with water and with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was triturated with petroleum ether to afford C35 as a solid. Yield: 5.5 g, 14 mmol, 88%. LCMS m/z 392.1 [M-H]-. 1H NMR (400 MHz, DMSO-d6) δ 12.83 (br s, 1H), 7.89 (d, J = 7.4 Hz, 2H), 7.77 – 7.67 (m, 3H), 7.46 – 7.38 (m, 2H), 7.36 – 7.28 (m, 2H), 4.38 – 4.28 (m, 2H), 4.26 – 4.19 (m, 1H), 4.06 (ddd, J = 9, 9, 4.9 Hz, 1H), 2.43 – 2.15 (m, 2H), 2.01 – 1.89 (m, 1H), 1.89 – 1.75 (m, 1H).

A mixture of C35 (435 mg, 1.11 mmol), benzyl bromide (0.263 mL, 2.21 mmol), and sodium bicarbonate (464 mg, 5.52 mmol) in N,N-dimethylformamide (20 mL) was stirred for 15 hours at 25 °C. After the reaction mixture had been diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL), the combined organic layers were washed sequentially with saturated aqueous sodium chloride solution and 5% aqueous lithium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 100% ethyl acetate in petroleum ether) provided C36 as a white solid. Yield: 510 mg, 1.05 mmol, 95%. LCMS m/z 506.1 [M+Na*].


Diethylamine (10 mL) was added to a 0 °C mixture of C36 (510 mg, 1.05 mmol) in acetonitrile (25 mL). After the reaction mixture had been stirred at 20 °C for 2 hours, it was concentrated under reduced pressure; chromatography on silica gel (Gradient: 0% to 10% methanol in dichloromethane) then afforded C37 as a colorless oil. Yield: 250 mg, 0.957 mmol, 91%. LCMS m/z 302.9 [M + CH₃CN + H]*. ¹H NMR (400 MHz, chloroform-d) δ 7.42 – 7.32 (m, 5H), 5.17 (s, 2H), 3.50 (dd, J = 8.4, 5.0 Hz, 1H), 2.32 – 2.13 (m, 2H), 2.01 (dddd, J = 13.7, 10.8, 5.2, 5.2 Hz, 1H), 1.76 (dddd, J = 13.6, 10.8, 8.4, 5.3 Hz, 1H).

Step 5. Synthesis of benzyl 5,5,5-trifluoro-N-[(4-methoxy-1H-indol-2-yl)carbonyl]-L-norvalinate (C38).

To a 0 °C solution of C37 (250 mg, 0.957 mmol) and 4-methoxy-1H-indole-2-carboxylic acid (220 mg, 1.15 mmol) in N,N-dimethylformamide (10 mL) was added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU; 437 mg, 1.15 mmol), followed by drop-wise addition of 4-methylmorpholine (194 mg, 1.92 mmol). Stirring was continued at 0 °C to 10 °C for 1 hour, whereupon the reaction mixture was diluted with water (20 mL) and aqueous citric acid solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed sequentially with saturated aqueous sodium bicarbonate solution (30 mL), saturated aqueous sodium chloride solution, and aqueous lithium chloride solution (5%, 20 mL),
then dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified using silica gel chromatography (Gradient: 0% to 100% ethyl acetate in petroleum ether) to provide C38 as a white solid. Yield: 350 mg, 0.806 mmol, 84%.

LCMS m/z 435.1 [M+H]^+. 1H NMR (400 MHz, chloroform-d) δ 9.09 (br s, 1H), 7.42 – 7.33 (m, 3H), 7.23 (dd, J = 8, 8 Hz, 1H), 7.09 (d, J = 2.3 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 6.76 (br d, J = 7.6 Hz, 1H), 6.53 (d, J = 7.8 Hz, 1H), 5.25 (AB quartet, J_AB = 12.1 Hz, 1H), 4.94 – 4.87 (m, 1H), 3.96 (s, 3H), 2.35 – 2.14 (m, 2H), 2.14 – 1.96 (m, 2H).


A mixture of C38 (350 mg, 0.806 mmol) and palladium on carbon (10%, 85.7 mg, 80.5 µmol) in methanol (10 mL) was hydrogenated for 16 hours at 20 °C and 15 psi. The reaction mixture was then filtered, and the filter cake was washed with methanol (10 mL); the combined filtrates were concentrated in vacuo and subjected to silica gel chromatography (Eluent: ethyl acetate) to afford C39 as a white solid. Yield: 270 mg, 0.784 mmol, 97%. LCMS m/z 345.0 [M+H]^+. 1H NMR (400 MHz, DMSO-d6) δ 11.62 (br s, 1H), 8.61 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.11 (dd, J = 8, 8 Hz, 1H), 7.01 (d, half of AB quartet, J = 8.2 Hz, 1H), 6.51 (d, J = 7.6 Hz, 1H), 4.47 (ddd, J = 8.5, 8.5, 4.8 Hz, 1H), 3.89 (s, 3H), 2.5 – 2.27 (m, 2H, assumed; partially obscured by solvent peak), 2.12 – 1.92 (m, 2H).

Step 7. Synthesis of 5,5,5-trifluoro-N-[(4-methoxy-1H-indol-2-yl)carbonyl]-L-norvalyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninamide (C40).

A 0 °C mixture of C16 (58.2 mg, 0.218 mmol) and C39 (75.0 mg, 0.218 mmol) in N,N-dimethylformamide (4 mL) was treated with O-(7-azabenzotriazol-1-yl)-N,N',N'-tetramethyluronium hexafluorophosphate (HATU; 99.4 mg, 0.261 mmol) and 4-methylmorpholine (44.1 mg, 0.436 mmol). After the reaction mixture had been stirred at 0 °C for 1 hour, it was diluted with water (20 mL) and aqueous citric acid solution (1 M; 20 mL), and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (20 mL) and with saturated aqueous sodium chloride solution (3 x 20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel (Eluent: 10:1 ethyl acetate /
methanol) provided C40 as a white solid. Yield: 72 mg, 0.145 mmol, 66%. LCMS m/z 498.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.60 (br s, 1H), 8.52 (d, J = 7.7 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.61 (s, 1H), 7.42 – 7.33 (m, 2H), 7.14 – 7.05 (m, 2H), 7.00 (d, half of AB quartet, J = 8.2 Hz, 1H), 6.51 (d, J = 7.7 Hz, 1H), 4.58 – 4.46 (m, 1H), 4.32 – 4.22 (m, 1H), 3.89 (s, 3H), 3.18 – 3.02 (m, 2H), 2.45 – 2.21 (m, 3H), 2.18 – 2.07 (m, 1H), 2.06 – 1.88 (m, 3H), 1.73 – 1.59 (m, 1H), 1.59 – 1.48 (m, 1H).


To a mixture of C40 (52 mg, 0.10 mmol) in dichloromethane (13 mL) was added methyl N-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 37 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 1.5 hours, whereupon methyl N-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 37 mg, 0.16 mmol) was again added, and stirring was continued for 16 hours. A final addition of methyl N-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 24.9 mg, 0.105 mmol) was followed by stirring for 2 hours, whereupon the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 x 20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo; preparative thin-layer chromatography (Eluent: 20:1 ethyl acetate / methanol) afforded N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxypyrrolidin-3-yl]ethyl}amino}-5,5,5-trifluoro-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide (14) as a white solid. Yield: 17.4 mg, 36.3 µmol, 36%. This material was combined with the purified products from two other syntheses of 14 (3 mg and 4 mg) and subjected to supercritical fluid chromatography [Column: Chiral Technologies ChiralCel OD-H, 30 x 250 mm, 5 µm; Mobile phase: 7:3 carbon dioxide / (ethanol containing 0.1% ammonium hydroxide); Flow rate: 60 mL/minute] to provide N-[(2S)-1-{{(1S)-1-cyano-2-[(3S)-2-oxypyrrolidin-3-yl]ethyl}amino}-5,5,5-trifluoro-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide (14) as a solid. Yield: 11.3 mg, 23.6 µmol, 46% for the supercritical fluid chromatography. LCMS m/z 480.2 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 11.61 (br s, 1H), 8.96 (d, J = 8.0 Hz, 1H), 8.61 (d, J = 7.7 Hz, 1H), 7.71 (s, 1H), 7.37 (d, J = 2.2 Hz, 1H), 7.11 (dd, J = 8, 8 Hz, 1H), 7.01 (d, half of AB quartet, J = 8.2 Hz, 1H), 6.51 (d, J = 7.7 Hz, 1H), 5.03 – 4.94 (m, 1H), 4.51 – 4.43 (m, 1H), 3.89 (s, 3H), 3.19 – 3.07 (m, 2H), 2.43 – 2.28 (m, 3H), 2.20 – 2.08 (m, 2H), 2.06 – 1.92 (m, 2H), 1.86 – 1.76 (m, 1H), 1.76 – 1.64 (m, 1H).
Examples 15, 16, 17, 18, and 19

\[ N-[(2S)-1-\{(1S)-1-Cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino]-4-methyl-1-oxopentan-2-yl]-7-fluoro-4-methoxy-1H-indole-2-carboxamide (15), N-[(2S)-1-\{(1S)-1-Cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino]-4-methyl-1-oxopentan-2-yl]-5-fluoro-4-methoxy-1H-indole-2-carboxamide (16), N-[(2S)-1-\{(1S)-1-Cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino]-4-methyl-1-oxopentan-2-yl]-3-fluoro-4-methoxy-1H-indole-2-carboxamide (17), N-[(2S)-1-\{(1S)-1-Cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino]-4-methyl-1-oxopentan-2-yl]-5,7-difluoro-4-methoxy-1H-indole-2-carboxamide (18), and N-[(2S)-1-\{(1S)-1-Cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}amino]-4-methyl-1-oxopentan-2-yl]-3,5-difluoro-4-methoxy-1H-indole-2-carboxamide (19) \]

![Chemical structures]
A mixture of 4 (10.0 mg, 22.8 μmol), tetra-n-butylammonium decatungstate (TBADT; 3.78 mg, 1.14 μmol), and N-fluoro-N-(phenylsulfonyl)benzenesulfonamide (8.61 mg, 27.3 μmol) was treated with acetonitrile (0.75 mL), water (0.5 mL), and trifluoroacetic acid (1.74 uL, 22.6 μmol) under argon. The reaction vial was then sealed, placed in an EvoluChem™ PhotoRedOx Box equipped with a fan, and irradiated with black light (PAR20-18W LG 365 nm, 100-240 VAC) at 25 °C for 16 hours. To the reaction mixture was added aqueous potassium phosphate solution (1 M, pH 7.45; 1 mL), followed by alternating aliquots of water and acetonitrile to maintain a clarified solution at a final volume of 18 mL. Aliquots (3 mL) of this mixture were applied to Biotage Isolute C18 solid phase extraction cartridges that had been preconditioned with methanol (3 mL) followed by water (3 mL). The cartridges were washed with water (3 mL) and with 20% acetonitrile in 20 mM aqueous ammonium acetate solution (3 mL), then eluted with acetonitrile (3 mL). After the eluates had been evaporated in a vacuum centrifuge, the residues were reconstituted in a mixture of 1% aqueous formic acid and acetonitrile, and combined to a total of 6 mL. This solution was divided in half, and each half was subjected to reversed-phase HPLC (Column: Phenomenex Luna C18, 10 x 250 mm, 10 μm; Mobile phase A: water containing 0.1% formic acid; Mobile phase B: acetonitrile; Gradient: 15% B for 5 minutes, then 15% to 70% B over 70 minutes, then 70% to 95% B over 15 minutes; Flow rate: 2 mL/min). Fractions were collected every 20 seconds, and like fractions of interest from the two separations were pooled and concentrated. These fractions were further purified via reversed-phase HPLC (Column: Agilent Polaris C18, 4.6 x 250 mm, 5 μm; Mobile phase A: water containing 10 mM ammonium acetate; Mobile phase B: acetonitrile; Gradient: 10% B for 5 minutes, then 10% to 35% B over 35 minutes, then 35% to 60% B over 15 minutes, then 60% to 95% B over 9 minutes; Flow rate: 0.8 mL/min). Fractions were collected every 20 seconds, affording N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-7-fluoro-4-methoxy-1H-indole-2-carboxamide (15), N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-5-fluoro-4-methoxy-1H-indole-2-carboxamide (16), N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-7-fluoro-4-methoxy-1H-indole-2-carboxamide (15), N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-5-fluoro-4-methoxy-1H-indole-2-carboxamide (16), N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)
oxopyrrolidin-3-yl[ethyl]amino)-4-methyl-1-oxopentan-2-yl]-3-fluoro-4-methoxy-1H-indole-2-carboxamide (17), N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-5,7-difluoro-4-methoxy-1H-indole-2-carboxamide (18), and N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-3,5-difluoro-4-methoxy-1H-indole-2-carboxamide (19).

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15 – First separation, fraction numbers 172–174; Second separation, fraction numbers 136–137. Yield: 58 μg, 0.13 μmol, 0.6%. High-resolution MS m/z 458.2201 [M+H]^+; calculated for C_{23}H_{20}FN_{2}O_{4}, 458.2204. ^1H NMR (600 MHz, DMSO-d₆) δ 12.05 (br s, 1H), 8.93 (d, J = 7.9 Hz, 1H), 8.51 (d, J = 7.6 Hz, 1H), 7.70 (s, 1H), 7.37 (d, J = 2.3 Hz, 1H), 6.92 (dd, J = 10.8, 8.6 Hz, 1H), 6.42 (dd, J = 8.4, 2.5 Hz, 1H), 5.01 – 4.94 (m, 1H), 4.50 – 4.43 (m, 1H), 3.87 (s, 3H), 3.18 – 3.07 (m, 2H), 2.40 – 2.31 (m, 1H), 2.19 – 2.08 (m, 2H), 1.85 – 1.76 (m, 1H), 1.76 – 1.64 (m, 3H), 1.58 – 1.49 (m, 1H), 0.94 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H). Retention time: 7.90 minutes (Analytical conditions. Column: Phenomenex Kinetex XB-C18, 2.1 x 100 mm, 2.6 μm; Mobile phase A: water containing 0.1% formic acid; Mobile phase B: acetonitrile; Gradient: 5% B for 0.5 minutes, then 5% to 70% B over 10.5 minutes, then 70% to 95% B over 2 minutes; Flow rate: 0.4 mL/min).

16 – First separation, fraction numbers 172–174; Second separation, fraction numbers 138–139. Yield: 153 μg, 0.33 μmol, 1.4%. High-resolution MS m/z 458.2201 [M+H]^+;
calculated for C_{23}H_{20}F_{5}N_{4}O_{4}, 458.2204. \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) 11.73 (br s, 1H), 8.95 (d, \(J = 8.0\) Hz, 1H), 8.61 (d, \(J = 7.7\) Hz, 1H), 7.70 (s, 1H), 7.49 (s, 1H), 7.09 – 7.03 (m, 2H), 5.01 – 4.94 (m, 1H), 4.51 – 4.43 (m, 1H), 4.06 (s, 3H), 3.18 – 3.07 (m, 2H), 2.40 – 2.31 (m, 1H), 2.19 – 2.08 (m, 2H), 1.80 (dd, \(J = 13.6, 9.2, 7.2\) Hz, 1H), 1.76 – 1.65 (m, 3H), 1.58 – 1.50 (m, 1H), 0.94 (d, \(J = 6.3\) Hz, 3H), 0.89 (d, \(J = 6.3\) Hz, 3H).

Retention time: 7.94 minutes (Analytical conditions identical to those used for 15).

17 – First separation, fraction numbers 176–177; Second separation, fraction numbers 141–142. Yield: 22 \(\mu\)g, 0.048 \(\mu\)mol, 0.21%. High-resolution MS m/z 458.2199 [M+H]*; calculated for C_{23}H_{20}F_{5}N_{4}O_{4}, 458.2204. \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) 11.45 (s, 1H), 8.94 (d, \(J = 7.8\) Hz, 1H), 7.71 (s, 1H), 7.62 (br d, \(J = 7.5\) Hz, 1H), 7.16 (dd, \(J = 8, 8\) Hz, 1H), 6.95 (br d, \(J = 8.3\) Hz, 1H), 6.54 (d, \(J = 7.8\) Hz, 1H), 5.02 – 4.94 (m, 1H), 4.54 – 4.46 (m, 1H), 3.88 (s, 3H), 3.19 – 3.07 (m, 2H), 2.41 – 2.31 (m, 1H), 2.20 – 2.08 (m, 2H), 1.85 – 1.77 (m, 1H), 1.76 – 1.63 (m, 3H), 1.61 – 1.53 (m, 1H), 0.94 (d, \(J = 6.3\) Hz, 3H), 0.91 (d, \(J = 6.3\) Hz, 3H). Retention time: 8.06 minutes (Analytical conditions identical to those used for 15).

18 – First separation, fraction numbers 180–181; Second separation, fraction number 145. Yield: 17 \(\mu\)g, 0.036 \(\mu\)mol, 0.16%. High-resolution MS m/z 476.2100 [M+H]*; calculated for C_{23}H_{20}F_{5}N_{4}O_{4}, 476.2109. \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) 12.23 (s, 1H), 8.96 (d, \(J = 8.0\) Hz, 1H), 8.62 (d, \(J = 7.6\) Hz, 1H), 7.70 (s, 1H), 7.52 – 7.48 (m, 1H), 7.13 (dd, \(J = 11, 11\) Hz, 1H), 5.02 – 4.94 (m, 1H), 4.53 – 4.44 (m, 1H), 4.01 (s, 3H), 3.18 – 3.07 (m, 2H), 2.38 – 2.30 (m, 1H), 2.19 – 2.08 (m, 2H), 1.81 (dd, \(J = 13.6, 9.1, 7.0\) Hz, 1H), 1.76 – 1.65 (m, 3H), 1.59 – 1.51 (m, 1H), 0.95 (d, \(J = 6.2\) Hz, 3H), 0.90 (d, \(J = 6.3\) Hz, 3H). Retention time: 8.20 minutes (Analytical conditions identical to those used for 15).

19 – First separation, fraction numbers 185–187; Second separation, fraction numbers 150–151. Yield: 35 \(\mu\)g, 0.074 \(\mu\)mol, 0.32%. High-resolution MS m/z 476.2107 [M+H]*; calculated for C_{23}H_{20}F_{5}N_{4}O_{4}, 476.2109. \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) 11.64 (s, 1H), 8.94 (d, \(J = 7.9\) Hz, 1H), 7.80 (br d, \(J = 7\) Hz, 1H), 7.71 (s, 1H), 7.16 (dd, component of ABX system, \(J = 11.9, 9.1\) Hz, 1H), 7.08 (br d, half of AB quartet, \(J = 8.5\) Hz, 1H), 5.02 – 4.94 (m, 1H), 4.55 – 4.47 (m, 1H), 3.99 (s, 3H), 3.19 – 3.08 (m, 2H), 2.41 – 2.32 (m, 1H), 2.19 – 2.10 (m, 2H), 1.81 (dd, \(J = 13.7, 9.0, 7.2\) Hz, 1H), 1.77 – 1.63 (m, 3H), 1.57 (dd, \(J = 12.9, 8.4, 4.8\) Hz, 1H), 0.94 (d, \(J = 6.4\) Hz, 3H), 0.91 (d, \(J = 6.4\) Hz, 3H). Retention time: 8.44 minutes (Analytical conditions identical to those used for 15).
Examples 20, 21, 22, and 23

\[ N-[(2S)-1-\{(1S)-1-Cyano-2-\{(3S)-2-oxopyrroolidin-3-yl\}ethyl\}amino]-4,4-dimethyl-1-oxopentan-2-yl]-7-fluoro-4-methoxy-1H-indole-2-carboxamide (20), N-[(2S)-1-\{(1S)-1-Cyano-2-\{(3S)-2-oxopyrroolidin-3-yl\}ethyl\}amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-fluoro-4-methoxy-1H-indole-2-carboxamide (21), N-[(2S)-1-\{(1S)-1-Cyano-2-\{(3S)-2-oxopyrroolidin-3-yl\}ethyl\}amino]-4,4-dimethyl-1-oxopentan-2-yl]-3-fluoro-4-methoxy-1H-indole-2-carboxamide (22), and N-[(2S)-1-\{(1S)-1-Cyano-2-\{(3S)-2-oxopyrroolidin-3-yl\}ethyl\}amino]-4,4-dimethyl-1-oxopentan-2-yl]-5,7-difluoro-4-methoxy-1H-indole-2-carboxamide (23) \]

A mixture of 10 (10.0 mg, 22.0 µmol), tetra-\(n\)-butylammonium decatungstate (TBADT; 3.66 mg, 1.10 µmol), and N-fluoro-N-(phenylsulfonyl)benzenesulfonamide (8.34 mg, 26.4 µmol) was treated with acetonitrile (0.75 mL), water (0.5 mL), and trifluoroacetic acid (1.69 µL, 21.9 µmol) under argon. The reaction vial was then sealed, placed in an EvoluChem™ PhotoRedOx Box equipped with a fan, and irradiated with
black light (PAR20-18W LG 365 nm, 100-240 VAC) at 25 °C for 16 hours. To the reaction mixture was added aqueous potassium phosphate solution (1 M, pH 7.45; 1 mL), followed by alternating aliquots of water and acetonitrile to maintain a clarified solution at a final volume of 18 mL. Aliquots (3 mL) of this mixture were applied to Biotage Isolute C18 solid phase extraction cartridges that had been preconditioned with methanol (3 mL) followed by aqueous ammonium acetate solution (10 mM; 3 mL). The cartridges were washed with aqueous ammonium acetate solution (10 mM; 3 mL) and with 20% acetonitrile in 20 mM ammonium acetate (3 mL), then eluted with acetonitrile (3 mL). After the eluates had been evaporated in a vacuum centrifuge, the residues were reconstituted in a mixture of 1% aqueous formic acid and acetonitrile, and combined to a total of 6 mL. This solution was divided in half, and each half was subjected to reversed-phase HPLC (Column: Phenomenex Luna C18, 10 x 250 mm, 10 μm; Mobile phase A: water containing 0.1% formic acid; Mobile phase B: acetonitrile; Gradient: 15% B for 5 minutes, then 15% to 70% B over 70 minutes, then 70% to 95% B over 15 minutes; Flow rate: 2 mL/min). Fractions were collected every 20 seconds, and like fractions of interest from the two separations were pooled and concentrated. These fractions were further purified via reversed-phase HPLC (Column: Agilent Polaris C18, 4.6 x 250 mm, 5 μm; Mobile phase A: water containing 10 mM ammonium acetate; Mobile phase B: acetonitrile; Gradient: 10% B for 5 minutes, then an immediate increase to 20% B, then 20% to 40% B over 35 minutes, then 40% to 60% B over 15 minutes, then 60% to 95% B over 9 minutes; Flow rate: 0.8 mL/min). Fractions were collected every 20 seconds, affording N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-7-fluoro-4-methoxy-1H-indole-2-carboxamide (20), N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-5-fluoro-4-methoxy-1H-indole-2-carboxamide (21), N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-3-fluoro-4-methoxy-1H-indole-2-carboxamide (22), and N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-5,7-difluoro-4-methoxy-1H-indole-2-carboxamide (23).

<table>
<thead>
<tr>
<th>Example Number</th>
<th>Retention time, first HPLC purification (minutes)</th>
<th>Retention time, second HPLC purification (minutes)</th>
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124
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<th>20</th>
<th>49.8</th>
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<td>22</td>
<td>50.8</td>
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<tr>
<td></td>
<td>23</td>
<td>51.9</td>
</tr>
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</table>

20 – First separation, fraction numbers 183–185; Second separation, fraction numbers 150–151. Yield: 24 µg, 0.051 µmol, 0.23%. High-resolution MS m/z 472.2342 [M+H]^+; calculated for C_{24}H_{31}FN_3O_4, 472.2360. ¹H NMR (600 MHz, DMSO- d6) δ 12.05 (br s, 1H), 8.91 (d, J = 8.0 Hz, 1H), 8.52 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.37 – 7.32 (m, 1H), 6.92 (dd, J = 10.9, 8.4 Hz, 1H), 6.41 (dd, J = 8.5, 2.7 Hz, 1H), 5.00 – 4.93 (m, 1H), 4.52 (ddd, J = 8.5, 8.2, 3.7 Hz, 1H), 3.87 (s, 3H), 3.17 – 3.05 (m, 2H), 2.38 – 2.30 (m, 1H), 2.18 – 2.06 (m, 2H), 1.85 – 1.64 (m, 4H), 0.94 (s, 9H). Retention time: 8.32 minutes (Analytical conditions. Column: Phenomenex Kinetex XB-C18, 2.1 x 100 mm, 2.6 µm; Mobile phase A: water containing 0.1% formic acid; Mobile phase B: acetonitrile; Gradient: 5% B for 0.5 minutes, then 5% to 70% B over 10.5 minutes, then 70% to 95% B over 2 minutes; Flow rate: 0.4 mL/minute).

21 – First separation, fraction numbers 183–185; Second separation, fraction numbers 152–153. Yield: 68 µg, 0.14 µmol, 0.64%. High-resolution MS m/z 472.2344 [M+H]^+; calculated for C_{24}H_{31}FN_3O_4, 472.2360. ¹H NMR (600 MHz, DMSO- d6) δ 11.72 (br s, 1H), 8.91 (d, J = 8.1 Hz, 1H), 8.59 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.47 (d, J = 2.2 Hz, 1H), 7.09 – 7.04 (m, 2H), 5.00 – 4.93 (m, 1H), 4.52 (ddd, J = 8.5, 8.5, 3.8 Hz, 1H), 4.06 (br s, 3H), 3.17 – 3.05 (m, 2H), 2.39 – 2.31 (m, 1H), 2.18 – 2.06 (m, 2H), 1.84 – 1.77 (m, 1H), 1.78 (dd, J = 13.9, 9.0 Hz, 1H), 1.74 – 1.64 (m, 2H), 0.94 (s, 9H). Retention time: 8.34 minutes (Analytical conditions identical to those used for 20).

22 – First separation, fraction numbers 187–188; Second separation, fraction number 154. Yield: 5 µg, 0.011 µmol, 0.05%. High-resolution MS m/z 472.2354 [M+H]^+; calculated for C_{24}H_{31}FN_3O_4, 472.2360. ¹H NMR (600 MHz, DMSO- d6) δ 11.45 (s, 1H), 8.91 (d, J = 7.9 Hz, 1H), 7.70 (s, 1H), 7.57 (dd, J = 8.2, 3.6 Hz, 1H), 7.15 (dd, J = 8.8 Hz, 1H), 6.95 (br d, J = 8.3 Hz, 1H), 6.54 (d, J = 7.8 Hz, 1H), 5.00 – 4.94 (m, 1H), 4.56 – 4.49 (m, 1H), 3.88 (s, 3H), 3.18 – 3.07 (m, 2H), 2.40 – 2.32 (m, 1H), 2.17 – 2.09 (m,
2H), 1.84 – 1.77 (m, 1H), 1.76 – 1.65 (m, 3H), 0.95 (s, 9H). Retention time: 8.51 minutes (Analytical conditions identical to those used for 20).

23 – First separation, fraction numbers 190–192; Second separation, fraction numbers 156-157. Yield: 21 µg, 0.043 µmol, 0.19%. High-resolution MS m/z 490.2258 [M+H]^+; calculated for C_{24}H_{30}F_{2}N_{5}O_{4}, 490.2266. ¹H NMR (600 MHz, DMSO-d$_6$) δ 12.24 (s, 1H), 8.95 (d, J = 8.0 Hz, 1H), 8.64 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.49 – 7.47 (m, 1H), 7.13 (dd, J = 11.1, 11.1 Hz, 1H), 5.00 – 4.93 (m, 1H), 4.54 (ddd, J = 8, 8, 4.1 Hz, 1H), 4.00 (s, 3H), 3.17 – 3.06 (m, 2H), 2.38 – 2.30 (m, 1H), 2.18 – 2.07 (m, 2H), 1.85 – 1.65 (m, 4H), 0.95 (s, 9H). Retention time: 8.65 minutes (Analytical conditions identical to those used for 20).

Table 1. Method of synthesis, structure, and physicochemical data for Examples 24 – 74.

<table>
<thead>
<tr>
<th>Ex. #</th>
<th>Method of synthesis ; Non-commercial starting materials</th>
<th>Structure</th>
<th>¹H NMR (600 MHz, DMSO-d$_6$) δ; Mass spectrum, observed ion m/z [M+H]^+ or HPLC retention time; Mass spectrum m/z [M+H]^+ (unless otherwise indicated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>Example 10; C18</td>
<td>![Structure Image]</td>
<td>¹H NMR (400 MHz, methanol-d$_4$) δ 8.58 (s, 1H), 5.04 (dd, J = 9.9, 6.1 Hz, 1H), 4.64 (dd, J = 8.7, 4.1 Hz, 1H), 3.34 – 3.23 (m, 2H; assumed; partially obscured by solvent peak), 2.61 – 2.50 (m, 1H), 2.35 – 2.24 (m, 2H), 1.96 – 1.76 (m, 4H), 1.01 (s, 9H); 460.4</td>
</tr>
<tr>
<td>25</td>
<td>Example 8 and 9&lt;sup&gt;1,2&lt;/sup&gt;; <strong>C28</strong></td>
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<tr>
<td></td>
<td><img src="image1.png" alt="Chemical Structure 1" /> or <img src="image2.png" alt="Chemical Structure 2" /></td>
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<tr>
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<td>DIAST-1</td>
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</tr>
<tr>
<td></td>
<td>2.29 minutes&lt;sup&gt;3&lt;/sup&gt;; 391.4</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>26</th>
<th>Example 8 and 9&lt;sup&gt;1,2&lt;/sup&gt;; <strong>C28</strong></th>
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<tr>
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<td>DIAST-2</td>
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<tr>
<td></td>
<td>2.69 minutes&lt;sup&gt;3&lt;/sup&gt;; 391.4</td>
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<tr>
<th>27</th>
<th>Example 7; <strong>C28</strong></th>
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<tbody>
<tr>
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<td><img src="image5.png" alt="Chemical Structure" /></td>
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<td>2.18 minutes&lt;sup&gt;4&lt;/sup&gt;; 381.4</td>
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<td>Example</td>
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<tr>
<td>28</td>
<td>7; C28</td>
</tr>
<tr>
<td>29</td>
<td>7; C28</td>
</tr>
<tr>
<td>30</td>
<td>71; C28</td>
</tr>
<tr>
<td>31</td>
<td>C29</td>
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<td><strong>C29</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| 33 | **Example** 4<sup>7</sup> | \[\begin{align*}
11.40 \ (s, \ 1H), \ 9.60 \ (br \ s, \ 1H), \\
8.90 \ (d, \ J = 8.1 \ Hz, \ 1H), \ 8.44 \\
(d, \ J = 7.9 \ Hz, \ 1H), \ 7.70 \ (s, \ 1H), \\
7.31 \ (s, \ 1H), \ 6.95 \ (dd, \ J = 8, 8 \ Hz, \ 1H), \\
6.85 \ (d, \ J = 8.2 \ Hz, \ 1H), \ 6.36 \ (d, \ J = 7.5 \ Hz, \ 1H), \\
5.02 - 4.93 \ (m, \ 1H), \\
4.50 - 4.41 \ (m, \ 1H), \ 3.17 - \\
3.07 \ (m, \ 2H), \ 2.41 - 2.31 \ (m, \ 1H), \\
2.19 - 2.08 \ (m, \ 2H), \ 1.80 \\
(ddd, \ J = 13.6, 9.4, 6.8 \ Hz, \ 1H), \ 1.76 - 1.65 \ (m, \ 3H), \\
1.57 - 1.48 \ (m, \ 1H), \ 0.94 \ (d, \ J = 6.3 \ Hz, \ 3H), \\
0.89 \ (d, \ J = 6.3 \ Hz, \ 3H); \text{high-resolution MS} \\
m/z \ 426.2139 [M+H]<sup>+</sup>; \\
calculated for C22H26Ni2O4, \\
426.2141\end{align*}\] |
| 34 | Example 4<sup>7</sup> | 11.34 (s, 1H), 8.91 (d, J = 8.1 Hz, 1H), 8.46 (d, J = 7.9 Hz, 1H), 7.69 (s, 1H), 7.29 (s, 1H), 6.95 (d, J = 8.6 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 5.02 – 4.93 (m, 1H), 4.50 – 4.41 (m, 1H), 3.91 (s, 3H), 3.18 – 3.06 (m, 2H, assumed; partially obscured by solvent peak), 2.39 – 2.31 (m, 1H), 2.20 – 2.07 (m, 2H), 1.84 – 1.65 (m, 4H), 1.58 – 1.49 (m, 1H), 0.94 (d, J = 6.2 Hz, 3H), 0.89 (d, J = 6.2 Hz, 3H); high-resolution MS m/z 456.2238 [M+H]<sup>+</sup>; calculated for C<sub>23</sub>H<sub>30</sub>N<sub>5</sub>O<sub>5</sub>, 456.2247 |
| 35 | Example 11<sup>8</sup>; C<sub>18</sub> | 2.39 minutes<sup>4</sup>; 437.4 (chlorine isotope pattern observed) |
| 36 | Example 11; C18 | $^{1}$H NMR (600 MHz, methanol-$d_{4}$) $\delta$ 7.45 – 7.40 (m, 2H), 7.34 – 7.27 (m, 3H), 4.98 (dd, $J = 10.5$, 5.6 Hz, 1H), 4.27 (dd, $J = 8.4$, 4.3 Hz, 1H), 3.70 (s, 1H), 3.28 – 3.23 (m, 1H), 3.20 (ddd, $J = 9.5$, 9.3, 7.1 Hz, 1H), 2.57 – 2.49 (m, 1H), 2.27 (ddd, $J = 13.8$, 10.5, 5.2 Hz, 1H), 2.21 – 2.13 (m, 1H), 2.17 (s, 6H), 1.85 (ddd, $J = 13.8$, 9.7, 5.7 Hz, 1H), 1.79 – 1.70 (m, 1H), 1.67 (dd, component of ABX system, $J = 14.4$, 4.3 Hz, 1H), 1.59 (dd, component of ABX system, $J = 14.4$, 8.4 Hz, 1H), 0.84 (s, 9H); 442.5 |
| 37 | Example s 5 and 6$^{a}$; Example 10 | 12.13 (s, 1H), 8.96 (br d, $J = 7.6$ Hz, 2H), 7.69 (s, 1H), 7.21 (dd, $J = 8$, 8 Hz, 1H), 7.08 (d, $J = 8.2$ Hz, 1H), 6.68 (d, $J = 7.8$ Hz, 1H), 5.00 – 4.92 (m, 1H), 4.52 – 4.45 (m, 1H), 3.86 (s, 3H), 3.20 – 3.15 (m, 1H), 3.14 – 3.08 (m, 1H), 2.43 – 2.34 (m, 1H), 2.23 – 2.13 (m, 2H), 1.85 – 1.78 (m, 1H), 1.78 – 1.68 (m, 2H), 1.59 (dd, $J = 14.1$, 6.6 Hz, 1H), 0.95 (s, 9H); high-resolution MS $m/z$ 522.2321 [M+H]$^{+}$; calculated for C$_{26}$H$_{31}$F$_{3}$N$_{5}$O$_{4}$, 522.2328; retention time 7.18 minutes$^{10}$ |
Example 5 and 6a; Example 10

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11.41 (s, 1H), 8.96 (d, J = 7.7 Hz, 1H), 8.79 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.34 (s, 1H), 6.72 (d, J = 8.3 Hz, 1H), 5.01 – 4.94 (m, 1H), 4.62 – 4.55 (m, 1H), 3.97 (s, 3H), 3.17 – 3.11 (m, 1H), 3.11 – 3.04 (m, 1H), 2.38 – 2.30 (m, 1H), 2.18 – 2.07 (m, 2H), 1.86 – 1.78 (m, 1H), 1.77 – 1.64 (m, 3H), 0.95 (s, 9H); high-resolution MS m/z 522.2316 [M+H]*; calculated for calculated for C_{25}H_{31}F_{3}N_{5}O_{4}, 522.2328; retention time 7.45 minutes^{10}

Example 5 and 6a; Example 10

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9.08 (br s, 1H), 9.03 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.60 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 4.98 – 4.91 (m, 1H), 4.53 – 4.47 (m, 1H), 3.95 (s, 3H), 3.20 – 3.14 (m, 1H), 3.13 – 3.06 (m, 1H), 2.44 – 2.36 (m, 1H), 2.23 – 2.12 (m, 2H), 1.85 (ddd, J = 13.9, 7.8 Hz, 1H), 1.60 (ddd, J = 13.6, 9.6, 6.5 Hz, 1H), 1.76 – 1.68 (m, 1H), 1.54 (ddd, J = 13.9, 5.1 Hz, 1H), 0.95 (s, 9H); high-resolution MS m/z 590.2177 [M+H]*; calculated for C_{26}H_{30}FeN_{5}O_{4}, 590.2202; retention time 7.70 minutes^{10}
| 40 | Example s 5 and 69; Example 10 | ![Chemical Structure Image] | 12.76 (br s, 1H), 9.19 – 9.10 (m, 1H), 9.06 – 9.00 (m, 1H), 7.69 (s, 1H), 7.49 (AB quartet, $J_{AB} = 8.6$ Hz, $\Delta

\nu_{AB} = 48.9$ Hz, 2H), 5.01 – 4.93 (m, 1H), 4.54 – 4.47 (m, 1H), 3.85 (s, 3H), 3.21 – 3.15 (m, 1H), 3.15 – 3.07 (m, 1H), 2.43 – 2.35 (m, 1H), 2.22 – 2.13 (m, 2H), 1.86 – 1.78 (m, 1H), 1.78 – 1.70 (m, 2H), 1.59 (dd, component of ABX system, $J = 14.1$, 6.5 Hz, 1H), 0.96 (s, 9H); high-resolution MS $m/z$ 590.2181 [$M+H]^+$; calculated for $C_{20}H_{36}F_{10}N_5O_4$, 590.2202; retention time 7.79 minutes$^{10}$ |

<p>| 41 | Example s 5 and 69,11; Example 10 | ![Chemical Structure Image] | 12.62 (s, 1H), 9.14 (d, $J = 7.5$ Hz, 1H), 9.03 (d, $J = 7.8$ Hz, 1H), 7.70 (s, 1H), 7.42 (s, 1H), 6.92 (s, 1H), 5.00 – 4.93 (m, 1H), 4.54 – 4.47 (m, 1H), 3.96 (s, 3H), 3.21 – 3.15 (m, 1H), 3.15 – 3.08 (m, 1H), 2.43 – 2.35 (m, 1H), 2.22 – 2.13 (m, 2H), 1.86 – 1.79 (m, 1H), 1.78 – 1.69 (m, 2H), 1.59 (dd, component of ABX system, $J = 14.0$, 6.4 Hz, 1H), 0.96 (s, 9H); high-resolution MS $m/z$ 590.2175 [$M+H]^+$; calculated for $C_{20}H_{36}F_{10}N_5O_4$, 590.2202; retention time 7.84 minutes$^{10}$ |</p>
<table>
<thead>
<tr>
<th></th>
<th>Example s 5 and 6\textsuperscript{12}; Example 36</th>
<th>Example s 5 and 6\textsuperscript{12}; Example 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>8.92 (d, ( J = 8.0 ) Hz, 1H), 8.45 (d, ( J = 7.9 ) Hz, 1H), 7.71 (s, 2H), 7.67 (d, ( J = 7.6 ) Hz, 1H), 7.64 – 7.60 (m, 1H), 7.58 – 7.52 (m, 1H), 4.99 – 4.87 (m, 1H), 4.24 – 4.17 (m, 1H), 3.92 (s, 1H), 3.20 – 3.10 (m, 1H), 3.09 – 3.00 (m, 1H), 2.36 – 2.27 (m, 1H), 2.19 – 2.00 (m, 2H), 2.08 (s, 6H), 1.81 – 1.64 (m, 2H), 1.49 (d, ( J = 6.5 ) Hz, 2H), 0.74 (s, 9H); high-resolution MS ( m/z ) 510.2679 [M+H]\textsuperscript{+}; calculated for C\textsubscript{25}H\textsubscript{35}F\textsubscript{3}N\textsubscript{5}O\textsubscript{3}, 510.2692; retention time 5.83 minutes\textsuperscript{10}</td>
</tr>
<tr>
<td>43</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>8.93 (d, ( J = 8.1 ) Hz, 1H), 8.42 (d, ( J = 8.1 ) Hz, 1H), 7.71 (s, 1H), 7.63 (AB quartet, ( J_{AB} = 7.6 ) Hz, ( \Delta \nu_{AB} = 48.8 ) Hz, 4H), 4.97 – 4.88 (m, 1H), 4.26 – 4.19 (m, 1H), 3.91 (s, 1H), 3.19 – 3.11 (m, 1H), 3.07 – 3.00 (m, 1H), 2.35 – 2.26 (m, 1H), 2.18 – 1.99 (m, 2H), 2.08 (s, 6H), 1.80 – 1.64 (m, 2H), 1.56 – 1.44 (m, 2H), 0.77 (s, 9H); high-resolution MS ( m/z ) 510.2676 [M+H]\textsuperscript{+}; calculated for C\textsubscript{26}H\textsubscript{35}F\textsubscript{3}N\textsubscript{5}O\textsubscript{3}, 510.2692; retention time 5.92 minutes\textsuperscript{10}</td>
</tr>
<tr>
<td></td>
<td>Alternate Synthesis of Example 6; <strong>C26</strong></td>
<td>2.85 minutes(^4), 478.6</td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>44</td>
<td><img src="image1.png" alt="Chemical Structure 1" /></td>
<td><img src="image2.png" alt="Chemical Structure 2" /></td>
</tr>
<tr>
<td></td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td>2.95 minutes(^4), 492.6</td>
</tr>
<tr>
<td>45</td>
<td><img src="image3.png" alt="Chemical Structure 3" /></td>
<td><img src="image4.png" alt="Chemical Structure 4" /></td>
</tr>
<tr>
<td></td>
<td>Example s 5 and 6(^{13}); <strong>4</strong></td>
<td>12.48 (s, 1H), 9.13 (d, (J = 7.4) Hz, 1H), 8.97 (d, (J = 7.7) Hz, 1H), 7.70 (s, 1H), 7.62 (d, (J = 8.3) Hz, 1H), 6.86 (d, (J = 8.3) Hz, 1H), 5.04 – 4.95 (m, 1H), 4.53 – 4.44 (m, 1H), 3.96 (s, 3H), 3.22 – 3.14 (m, 1H), 3.14 – 3.06 (m, 1H), 2.44 – 2.34 (m, 1H), 2.24 – 2.10 (m, 2H), 1.87 – 1.77 (m, 1H), 1.77 – 1.61 (m, 2H), 1.61 – 1.50 (m, 2H), 0.98 – 0.89 (m, 6H); high-resolution MS (m/z) 576.2055 [M+H](^{+}); calculated for C(<em>26)H(</em>{28})FeN(_2)O(_4), 576.2045; retention time 6.70 minutes(^{14})</td>
</tr>
<tr>
<td></td>
<td><img src="image5.png" alt="Chemical Structure 5" /></td>
<td><img src="image6.png" alt="Chemical Structure 6" /></td>
</tr>
</tbody>
</table>
47  Example 5 and 613; 4

12.61 (s, 1H), 9.23 (d, J = 7.6 Hz, 1H), 9.01 (d, J = 7.9 Hz, 1H), 7.71 (s, 1H), 7.20 (s, 1H), 5.04 – 4.95 (m, 1H), 4.54 – 4.45 (m, 1H), 4.07 (s, 3H), 3.22 – 3.14 (m, 1H), 3.14 – 3.06 (m, 1H), 2.43 – 2.34 (m, 1H), 2.23 – 2.11 (m, 2H), 1.82 (ddd, J = 13.5, 9.0, 7.0 Hz, 1H), 1.78 – 1.61 (m, 2H), 1.61 – 1.49 (m, 2H), 0.99 – 0.89 (m, 6H); high-resolution MS m/z 644.1914 [M+H]^+; calculated for C26H27F5N5O4, 644.1919; retention time 7.43 minutes14

48  Example 5 and 613; 4

13.21 (s, 1H), 9.28 (d, J = 7.5 Hz, 1H), 9.05 (d, J = 7.8 Hz, 1H), 7.86 (s, 1H), 7.72 (s, 1H), 5.04 – 4.96 (m, 1H), 4.54 – 4.47 (m, 1H), 3.93 (s, 3H), 3.22 – 3.15 (m, 1H), 3.15 – 3.07 (m, 1H), 2.43 – 2.35 (m, 1H), 2.23 – 2.11 (m, 2H), 1.82 (ddd, J = 13.7, 9.0, 6.9 Hz, 1H), 1.78 – 1.63 (m, 2H), 1.61 – 1.51 (m, 2H), 0.98 – 0.91 (m, 6H); high-resolution MS m/z 644.1901 [M+H]^+; calculated for C26H27F5N5O4, 644.1919; retention time 7.51 minutes14
<table>
<thead>
<tr>
<th>Page</th>
<th>Alternate Synthesis of Example 6; <strong>C26</strong></th>
<th>2.95 minutes(^4); 494.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td>3.04 minutes(^4); 508.4</td>
</tr>
<tr>
<td>51</td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td>3.00 minutes(^4); 492.4</td>
</tr>
<tr>
<td>52</td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td>2.84 minutes(^4); 458.4 (chlorine isotope pattern observed)</td>
</tr>
<tr>
<td>53</td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td>2.80 minutes(^4); 468.5</td>
</tr>
<tr>
<td>54</td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td>2.89 minutes(^4); 458.4 (chlorine isotope pattern observed)</td>
</tr>
<tr>
<td>Page</td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td>2.90 minutes(^4); 458.4 (chlorine isotope pattern observed)</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>56</td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td>2.89 minutes(^4); 458.4 (chlorine isotope pattern observed)</td>
</tr>
<tr>
<td>57</td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td>2.95 minutes(^4); 492.4</td>
</tr>
<tr>
<td>58</td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td>3.16 minutes(^4); 492.3 (dichloro isotope pattern observed)</td>
</tr>
<tr>
<td>59</td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td>2.99 minutes(^4); 492.4</td>
</tr>
<tr>
<td>60</td>
<td>Alternate Synthesis of Example 6; <strong>C26</strong></td>
<td>2.91 minutes(^4); 478.4</td>
</tr>
<tr>
<td></td>
<td>Alternate Synthesis of Example 6; <strong>C26</strong></td>
<td></td>
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</tr>
<tr>
<td>61</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>2.74 minutes$^4$; 444.4 (chlorine isotope pattern observed)</td>
</tr>
<tr>
<td>62</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>2.70 minutes$^4$; 454.4</td>
</tr>
<tr>
<td>63</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>2.80 minutes$^4$; 444.4 (chlorine isotope pattern observed)</td>
</tr>
<tr>
<td>64</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>2.81 minutes$^4$; 444.4 (chlorine isotope pattern observed)</td>
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<td>65</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>2.80 minutes$^4$; 444.4 (chlorine isotope pattern observed)</td>
</tr>
<tr>
<td>66</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>2.86 minutes$^4$; 478.4</td>
</tr>
<tr>
<td>Page</td>
<td>Alternate Synthesis of Example 6; <strong>C26</strong></td>
<td><strong>C26</strong></td>
</tr>
<tr>
<td>------</td>
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</tr>
<tr>
<td>68</td>
<td>Alternate Synthesis of Example 6; <strong>C26</strong></td>
<td><strong>C26</strong></td>
</tr>
<tr>
<td>69</td>
<td>Example 5 and 6$^{15}$; <strong>7</strong></td>
<td><strong>C26</strong></td>
</tr>
<tr>
<td>70</td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td><strong>C18</strong></td>
</tr>
<tr>
<td>Page</td>
<td>Alternate Synthesis of Example 6; <strong>C18</strong></td>
<td>2.70 minutes⁴; 474.5</td>
</tr>
<tr>
<td>------</td>
<td>------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>71</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Page</th>
<th>Alternate Synthesis of Example 6; <strong>C26</strong></th>
<th>2.41 minutes⁴; 481.5 (bromine isotope pattern observed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Page</th>
<th>Alternate Synthesis of Example 6; <strong>C26</strong></th>
<th>2.30 minutes⁴; 423.5 (chlorine isotope pattern observed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td></td>
</tr>
</tbody>
</table>
1. In this case, C28 was deprotected using methanesulfonic acid, rather than hydrogen chloride.

2. Epimers Example 25 and Example 26 were separated via supercritical fluid chromatography (Column: Chiral Technologies Chiralpak IB, 21 x 250 mm, 5 μm; Mobile phase: 9:1 carbon dioxide / methanol; Back pressure: 120 bar, Flow rate: 75 mL/minute). The first-eluting diastereomer was designated as Example 25, and the second-eluting diastereomer as Example 26.

3. Conditions for analytical HPLC. Column: Chiral Technologies Chiralpak IB, 4.6 x 100 mm, 5 μm; Mobile phase: 85:15 carbon dioxide / methanol; Back pressure: 120 bar; Flow rate: 1.5 mL/minute.

4. Conditions for analytical HPLC. Column: Waters Atlantis dC18, 4.6 x 50 mm, 5 μm; Mobile phase A: water containing 0.05% trifluoroacetic acid (v/v); Mobile phase B:
acetonitrile containing 0.05% trifluoroacetic acid (v/v); Gradient: 5.0% to 95% B, linear over 4.0 minutes, then 95% B for 1.0 minute; Flow rate: 2 mL/minute.

5. $^1$H NMR of Example 30 before final purification: $^1$H NMR (400 MHz, methanol-d$_4$) $\delta$ 7.48 – 7.42 (m, 2H), 7.36 – 7.26 (m, 3H), 4.90 (dd, $J = 10.5$, 5.7 Hz, 1H), 4.37 (dd, $J = 7.7$, 4.9 Hz, 1H), 3.69 (s, 1H), 3.25 (ddd, $J = 9.9$, 8.9, 2.5 Hz, 1H), 3.18 (ddd, $J = 9.6$, 9.0, 7.1 Hz, 1H), 2.40 – 2.29 (m, 1H), 2.20 (s, 6H), 2.2 – 2.10 (m, 1H), 2.09 – 1.99 (m, 1H), 1.80 – 1.61 (m, 2H), 1.73 (dd, $J = 14.5$, 5.0 Hz, 1H), 1.61 (dd, $J = 14.4$, 7.8 Hz, 1H), 0.95 (s, 9H).

6. Amide coupling with the appropriate carboxylic acid was carried out using 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinan e 2,4,6-trioxide trioxide.

7. Example 4 (25 μM) was incubated with human cytochrome P450 3A5 (4 nmol) in potassium phosphate buffer (100 mM, pH 7.4; 40 mL) containing magnesium chloride (3.3 mM), and NADPH (1.3 mM). The incubation was carried out for 0.75 hours in a shaking water bath maintained at 37 °C. The incubation was terminated by addition of an equal volume of acetonitrile, whereupon the mixture was spun in a centrifuge at 1700 x g for 5 minutes, and the supernatant was subjected to vacuum centrifugation for approximately 1.5 hours. To this mixture was added formic acid (0.5 mL), acetonitrile (0.5 mL), and water to a final volume of 50 mL, and the resulting mixture was spun in a centrifuge at 40000 x g for 30 minutes. The supernatant was subjected to reversed-phase HPLC (Column: Polaris C18, 4.6 x 250 mm; 5 μm; Mobile phase A: water containing 0.1% formic acid; Mobile phase B: methanol; Gradient: 15% B for 5 minutes, then 15% to 35% B over 75 minutes, then 35% to 95% B over 10 minutes; Flow rate: 0.8 mL/minute). Fractions were collected every 20 seconds. The first-eluting material, impure Example 33, eluted at 54.7 minutes, and Example 34 eluted at 55.3 minutes.

The impure Example 33 was repurified using reversed-phase HPLC (Column: Phenomenex Kinetex XB-C18, 2.1 x 100 mm, 2.6 μm; Mobile phase A: water containing 0.5% acetic acid; Mobile phase B: 9:1 acetonitrile / methanol; Gradient: 10% B for 0.5 minutes, then 10% to 35% over 26.5 minutes, then 35% to 60% B over 3 minutes; Flow rate 0.5 mL/minute); fractions were collected every 15 seconds. In this system, Example 33 had a retention time of 12.7 minutes; additional Example 34 eluted at 13.5 minutes.

8. The requisite 4-chloro-1,3-dimethyl-1H-pyrazole-5-carboxylic acid may be prepared by hydrolysis of the commercially available ethyl ester.
9. The reaction mixture was diluted with acetonitrile and 1% aqueous formic acid, to a volume of approximately 2 mL; the final solvent composition was such that mixture appeared clear, with approximately 20% to 30% acetonitrile content. The components of this mixture were separated via reversed-phase HPLC (Column: Phenomenex Luna C18, 10 x 250 mm, 10 µm; Mobile phase A: water containing 0.1% formic acid; Mobile phase B: acetonitrile; Gradient: 15% B for 5 minutes, then 15% to 70% B over 70 minutes, then 70% to 95% B over 15 minutes; Flow rate: 2 mL/minute); fractions were collected every 20 seconds. Examples 37, 38, 39, 40, and 41 eluted at the retention times given below.

<table>
<thead>
<tr>
<th>Example</th>
<th>Retention time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>64.9</td>
</tr>
<tr>
<td>38</td>
<td>68.4</td>
</tr>
<tr>
<td>39</td>
<td>72.1</td>
</tr>
<tr>
<td>40</td>
<td>73.5</td>
</tr>
<tr>
<td>41</td>
<td>74.2</td>
</tr>
</tbody>
</table>

10. Conditions for analytical HPLC. Column: Phenomenex Kinetex XB-C18, 2.1 x 100 mm, 2.6 µm; Mobile phase A: water containing 0.1% formic acid; Mobile phase B: acetonitrile; Gradient: 5% B for 0.5 minutes, then 5% to 70% B over 10.5 minutes, then 70% to 95% B over 2 minutes; Flow rate: 0.4 mL/min.

11. The regiochemistry of Example 41 was not rigorously determined; other possible structures for this example are N-[(2S)-1-{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-5,6-bis(trifluoromethyl)-1H-indole-2-carboxamide and N-[(2S)-1-{[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-6,7-bis(trifluoromethyl)-1H-indole-2-carboxamide.

12. The reaction mixture was purified using the conditions described in footnote 9. Example 42 eluted at 58.1 minutes and Example 43 eluted at 59.2 minutes.
13. The reaction mixture was diluted with a mixture of acetonitrile (0.3 mL) and 1% aqueous formic acid (0.7 mL). The resulting mixture was centrifuged, and the supernatant was subjected to reversed-phase HPLC (Column: Phenomenex Luna C18, 10 x 250 mm, 10 μm; Mobile phase A: water containing 0.1% formic acid; Mobile phase B: acetonitrile; Gradient: 2% to 10% B over 5.0 minutes, then 10% to 95% B over 95 minutes; Flow rate: 2 mL/minute); fractions were collected every 20 seconds. Examples 46, 47, and 48 eluted at the retention times given below. Example 5 was also isolated from this reaction, in fractions 189–190.

<table>
<thead>
<tr>
<th>Example</th>
<th>Fraction number</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td>207</td>
</tr>
<tr>
<td>47</td>
<td>225–226</td>
</tr>
<tr>
<td>48</td>
<td>231–232</td>
</tr>
</tbody>
</table>

14. Conditions for analytical HPLC. Column: Phenomenex Kinetex C18, 2.1 x 50 mm, 1.7 μm; Mobile phase A: water containing 0.1% formic acid; Mobile phase B: acetonitrile containing 0.1% formic acid; Gradient: 5% B for 0.5 minutes, then 5% to 50% B over 6.0 minutes, then 50% to 80% B over 1.5 minutes, then 80% to 95% B over 1.0 minute; Flow rate: 0.4 mL/min.

15. Only the indicated product was observed from this reaction.

16. A stock solution of Example 4 (5.56 mg, 12.7 μmol) and trifluoroacetic acid (4 μL, 50 μL) in dimethyl sulfoxide (420 μL) was prepared. One-sixth of this solution was treated with sodium 1,1-difluoroethanesulfinate 1.3 mg, 8.5 μmol), followed by tert-butyl hydroperoxide (70% in water; 1.4 μL, 10 μmol), and heated at 50 °C overnight. The reaction mixture was diluted with acetonitrile and 1% aqueous formic acid, to a volume of approximately 2–3 mL; the final solvent composition was such that mixture appeared clear, with approximately 20% to 30% acetonitrile content. The components of this mixture were separated via reversed-phase HPLC (Column: Phenomenex Luna C18, 10 x 250 mm, 10 μm; Mobile phase A: water containing 0.1% formic acid; Mobile phase B: acetonitrile; Gradient: 15% B for 5 minutes, then 15% to 40% B over 70 minutes, then
40% to 95% B over 15 minutes; Flow rate: 2 mL/minute; fractions were collected every 20 seconds. Example 74 eluted at 68.6 minutes.

Examples 75 and 76

\[(2S,4R)-4\text{-tert-Butyl}-N-\{(1S)-1\text{-cyano-2-\{(3S)-2\text{-oxopyrrolidin-3-yl}ethyl\}-1\{-[N-}\{(\text{trifluoromethyl)sulfonyl}\}-L\text{-valyl}\}\text{piperidine-2-carboxamide\} and (2R,4S)-4\text{-tert-Butyl}-N-\{(1S)-1\text{-cyano-2-\{(3S)-2\text{-oxopyrrolidin-3-yl}ethyl\}-1\{-[N-}\{(\text{trifluoromethyl)sulfonyl}\}-L\text{-valyl}\}\text{piperidine-2-carboxamide\} \} [75 \textbf{(DIAST-1)} \text{ and } 76 \textbf{(DIAST-2)}] \]
Step 1. Synthesis of tert-butyl N-[(trifluoromethyl)sulfonyl]-L-valinate (C44).

A solution of trifluoromethanesulfonic anhydride (8.88 mL, 52.8 mmol) in dichloromethane (10 mL) was added to a −78 °C solution of tert-butyl L-valinate, hydrochloride salt (10.0 g, 47.7 mmol) and triethylamine (18.7 mL, 134 mmol) in dichloromethane (90 mL). The reaction mixture was stirred at −78 °C for 2 hours, whereupon it was poured into water and acidified to a pH of approximately 4 by addition of 1 M hydrochloric acid. The resulting mixture was extracted with dichloromethane, and the organic layer was washed with aqueous sodium bicarbonate solution and with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was combined with the products of two similar reactions carried out using tert-butyl L-valinate, hydrochloride salt (1.00 g, 4.77 mmol;
1.00 g, 4.77 mmol) and purified via chromatography on silica gel (Gradient: 0% to 20% ethyl acetate in petroleum ether), affording C44 as a white solid. Combined yield: 14.0 g, 45.9 mmol, 80%. 1H NMR (400 MHz, DMSO-<em>d</em><sub>6</sub>) δ 9.92 (d, J = 8.8 Hz, 1H), 3.68 (dd, J = 8.8, 6.2 Hz, 1H), 2.16 – 2.02 (m, 1H), 1.43 (s, 9H), 0.92 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H).

Step 2. Synthesis of N-[(trifluoromethyl)sulfonyl]-L-valine (C45).

To a solution of C44 (14.0 g, 45.9 mmol) in dichloromethane (85 mL) was added trifluoroacetic acid (85 mL). The reaction mixture was stirred at room temperature for 3 hours, whereupon it was concentrated in vacuo; the residue was washed with petroleum ether to provide C45 as a white solid. Yield: 10.9 g, 43.7 mmol, 95%. MS m/z 248.0 [M–H]–. 1H NMR (400 MHz, DMSO-<em>d</em><sub>6</sub>) δ 9.86 (br d, J = 8.3 Hz, 1H), 3.79 – 3.71 (m, 1H), 2.19 – 2.05 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H).

Step 3. Synthesis of methyl cis-4-<em>t</em>ert-butylpiperidine-2-carboxylate, hydrochloride salt (C46).

To a 0 ºC solution of cis-4-<em>t</em>ert-butylpiperidine-2-carboxylic acid, hydrochloride salt (See R. T. Shuman et al., J. Org. Chem. 1990, 55, 738–741; 4.00 g, 18.0 mmol) in methanol (40 mL) was added thionyl chloride (6.44 g, 54.1 mmol). After the reaction mixture had been stirred at 25 ºC for 16 hours, it was concentrated in vacuo to afford C46 as an off-white solid (4.50 g). A portion of this material was used in the following step. LCMS m/z 200.0 [M+H]+. 1H NMR (400 MHz, DMSO-<em>d</em><sub>6</sub>) δ 9.46 (br s, 1H), 9.09 (br s, 1H), 4.11 – 3.96 (m, 1H), 3.76 (s, 3H), 3.04 – 3.22 (m, 1H, assumed; largely obscured by water peak), 2.93 – 2.77 (m, 1H), 2.07 (br d, J = 10.8 Hz, 1H), 1.75 (br d, J = 10.6 Hz, 1H), 1.51 – 1.32 (m, 3H), 0.84 (s, 9H).

Step 4. Synthesis of methyl (2S,4R)-4-<em>t</em>ert-butyl-1-[(N-[(trifluoromethyl)sulfonyl]-L-valyl)piperidine-2-carboxylate and methyl (2R,4S)-4-<em>t</em>ert-butyl-1-[(N-[(trifluoromethyl)sulfonyl]-L-valyl)piperidine-2-carboxylate (C47).

To a 25 ºC mixture of C45 (300 mg, 1.20 mmol) and C46 (from the previous step; 341 mg, ≤1.36 mmol) in N,N-dimethylformamide (3 mL) was added 4-methylmorpholine (365 mg, 3.61 mmol). The resulting mixture was cooled to 0 ºC and treated with O-(7-azabenzotriazol-1-yl)-N,N',N,N'-tetramethyluronium hexafluorophosphate (HATU; 549 mg, 1.44 mmol). After the reaction mixture had been sparged with nitrogen for 1 minute, it was stirred at 25 ºC for 12 hours. LCMS analysis at this point indicated the presence
of C47: LCMS m/z 431.1 [M+H]+. The reaction mixture was partitioned between ethyl acetate (20 mL) and water (20 mL), and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (4 x 20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 20% ethyl acetate in petroleum ether) provided C47 as a yellow gum. 1H NMR analysis confirmed that this comprised a mixture of diastereomers. Yield: 320 mg, 0.743 mmol, 62%. 1H NMR (400 MHz, chloroform-d) δ 6.12 – 5.94 (m, 1H), [4.51 (dd, J = 11.7, 6.3 Hz) and 4.32 – 4.18 (m), total 2H], [3.73 (s) and 3.71 (s), total 3H], [3.63 – 3.49 (m) and 3.48 – 3.39 (m), total 2H], 2.18 – 1.93 (m, 2H), 1.91 – 1.77 (m, 1H), 1.63 – 1.37 (m, 2H), 1.37 – 1.22 (m, 1H), 1.13 – 1.04 (m, 3H), [0.94 (d, J = 6.8 Hz) and 0.91 (d, J = 6.8 Hz), total 3H], 0.87 (s, 9H).

Step 5. Synthesis of (2S,4R)-4-tert-butyl-1-{N-[(trifluoromethyl)sulfonyl]-L-valyl}piperidine-2-carboxylic acid and (2R,4S)-4-tert-butyl-1-{N-[(trifluoromethyl)sulfonyl]-L-valyl}piperidine-2-carboxylic acid (C48).

A solution of C47 (314 mg, 0.729 mmol) in a mixture of methanol (2 mL) and tetrahydrofuran (2 mL) was treated with a solution of lithium hydroxide monohydrate (91.8 mg, 2.19 mmol) in water (1.4 mL), and the reaction mixture was stirred at 25 °C for 3 hours. After removal of solvent in vacuo, the residue was diluted with water (10 mL) and acidified to a pH of approximately 1 by addition of 1 M hydrochloric acid. The resulting mixture was extracted with ethyl acetate (2 x 20 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL), dried over sodium sulfate, filtered, and concentrated in vacuo, affording C48 as a yellow glass. 1H NMR analysis confirmed that this comprised a mixture of diastereomers. Yield: 304 mg, quantitative. 1H NMR (400 MHz, DMSO-d6) δ [9.82 (d, J = 8.7 Hz) and 9.69 (br d, J = 8.8 Hz), total 1H], [4.28 (dd, J = 11.5, 6.4 Hz), 4.24 – 4.14 (m), and 4.05 – 3.96 (m), total 2H], [3.80 – 3.69 (m) and 3.6 – 3.2 (m, assumed; substantially obscured by water peak), total 2H], 2.06 – 1.90 (m, 2H), 1.80 – 1.65 (m, 1H), 1.41 – 1.17 (m, 3H), [0.96 (d, J = 6.8 Hz) and 0.93 (d, J = 6.5 Hz), total 3H], [0.89 (d, J = 6.9 Hz) and 0.86 – 0.80 (m), total 12H].

Step 6. Synthesis of (2S,4R)-N-((2S)-1-amino-1-oxo-3-[(3S)-2-oxopyrrolidin-3-yl]propan-2-yl)-4-tert-butyl-1-{N-[(trifluoromethyl)sulfonyl]-L-valyl}piperidine-2-carboxamide and
(2R,4S)-N-\{(2R)-1-amino-1-oxo-3-\{(3S)-2-oxopyrrolidin-3-yl\}propan-2-yl\}-4-\text{tert}-butyl-1-\{N-\{(trifluoromethyl)sulfonyl\}-L-valyl\}piperidine-2-carboxamide (C49).

To a 25 °C mixture of C16 (120 mg, 0.449 mmol) and C48 (144 mg, 0.346 mmol) in N,N-dimethylformamide (3 mL) was added 4-methylmorpholine (100 mg, 0.989 mmol), whereupon the mixture was cooled to 0 °C and treated with O-(7-azabenzotriazol-1-yl)-N,N',N'-tetramethyluronium hexafluorophosphate (HATU; 151 mg, 0.397 mmol). The reaction mixture was sparged with nitrogen for 1 minute and then stirred at 25 °C for 12 hours. LCMS analysis indicated the presence of C49: LCMS m/z 570.3 [M+H]^+*. The reaction mixture was then partitioned between ethyl acetate (20 mL) and water (20 mL), and the aqueous layer was saturated with solid sodium chloride and extracted with ethyl acetate (5 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated in vacuo, and subjected to silica gel chromatography (Gradient: 0% to 15% methanol in dichloromethane), providing C49 as a white solid. This material contained a mixture of diastereomers, by 1H NMR analysis.

Yield: 190 mg, 0.334 mmol, 96%. 1H NMR (400 MHz, DMSO-\text{d6}), characteristic peaks, integrations are approximate: δ [9.88 (d, J = 8.6 Hz) and 9.82 – 9.68 (m, total 1H), [8.12 (d, J = 8.8 Hz) and 8.09 – 7.98 (m, total 1H), [7.63 (s) and 7.57 (s), total 1H], [7.30 (br s) and 7.18 (br s), total 1H], [7.06 (br s) and 7.03 (br s), total 1H], [4.36 (dd, J = 12.0, 6.1 Hz) and 4.32 – 4.08 (m), total 2H], 2.26 – 2.05 (m, 2H), 1.81 – 1.54 (m, 2H), 1.53 – 1.30 (m, 2H), 0.98 – 0.87 (m, 6H), 0.86 – 0.76 (m, 9H).

Step 7. Synthesis of (2S,4R)-4-\text{tert}-butyl-N-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}-1-\{N-\{(trifluoromethyl)sulfonyl\}-L-valyl\}piperidine-2-carboxamide and (2R,4S)-4-\text{tert}-butyl-N-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}ethyl\}-1-\{N-\{(trifluoromethyl)sulfonyl\}-L-valyl\}piperidine-2-carboxamide [75 (DIAST-1) and 76 (DIAST-2)].

A mixture of C49 (190.0 mg, 0.334 mmol) and methyl N-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 238 mg, 1.00 mmol) in dichloromethane (10 mL) was stirred at 25 °C for 2 days, whereupon the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel (Gradient: 0% to 8% methanol in dichloromethane) provided a white solid, which by LCMS analysis contained a roughly 3:1 mixture of products: LCMS m/z 552.2 [M+H]^+ and LCMS m/z 552.2 [M+H]^+*. These diastereomers
were separated via supercritical fluid chromatography [Column: Chiral Technologies Chiralpak IG, 30 x 250 mm, 10 µm; Mobile phase: 3:1 carbon dioxide / (ethanol containing 0.1% ammonium hydroxide); Flow rate: 70 mL/minute]. The first-eluting diastereomer, isolated as a white solid, was designated as 75, and the second-eluting diastereomer, also a white solid, was designated as 76 [(2S,4R)-4-tert-butyl-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-[(N-[(trifluoromethyl)sulfonyl]-L-valyl)piperidine-2-carboxamide and (2R,4S)-4-tert-butyl-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-[(N-[(trifluoromethyl)sulfonyl]-L-valyl)piperidine-2-carboxamide].

75 – Yield: 26.2 mg, 47.5 µmol, 14%. 1H NMR (400 MHz, DMSO-d6) δ 9.87 (d, J = 8.8 Hz, 1H), 8.87 (d, J = 8.4 Hz, 1H), 7.70 (s, 1H), 4.99 – 4.91 (m, 1H), 4.24 (dd, J = 12.3, 6.0 Hz, 1H), 4.18 (dd, J = 8.3, 8.3 Hz, 1H), 3.88 – 3.78 (m, 1H), 3.19 – 3.00 (m, 2H), 2.46 – 2.35 (m, 1H), 2.17 – 2.02 (m, 2H), 1.99 – 1.85 (m, 2H), 1.79 – 1.62 (m, 3H), 1.50 – 1.36 (m, 2H), 1.26 – 1.12 (m, 2H), 0.97 – 0.87 (m, 6H), 0.84 (s, 9H). Retention time: 1.30 minutes (Analytical conditions. Column: Chiral Technologies Chiralpak IG-3, 4.6 x 50 mm, 3 µm; Mobile phase A: carbon dioxide; Mobile phase B: ethanol containing 0.05% diethylamine; Gradient: 5% to 40% B over 2 minutes, then 40% B for 1.2 minutes; Flow rate: 4 mL/minute; Back pressure: 1500 psi).

76 – Yield: 8.8 mg, 16 µmol, 5%. LCMS m/z 552.3 [M+H]+. By 1H NMR analysis, this sample of 76 contained impurities. 1H NMR (400 MHz, DMSO-d6), characteristic peaks, integrations are approximate: δ 9.76 (d, J = 8.8 Hz, 1H), 8.59 (d, J = 8.1 Hz, 1H), 7.72 (s, 1H), 5.02 – 4.90 (m, 1H), 0.94 – 0.86 (m, 6H), 0.82 (s, 9H). Retention time: 1.61 minutes (Analytical conditions identical to those used for 75).

Example 77

3-Methyl-N-(trifluoracetyl)-L-valyl-(4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl] ethyl]-4-(trifluoromethyl)-L-prolinamide (77)
Step 1. Synthesis of (4R)-1-(tert-butoxycarbonyl)-4-(trifluoromethyl)-L-prolyl-3-[[3S]-2-oxopyrrolidin-3-yl]-L-alaninamide (C50).

To a \(-30^\circ\) C mixture of (4R)-1-(tert-butoxycarbonyl)-4-(trifluoromethyl)-L-proline (429 mg, 1.51 mmol) and C16, HCl salt (346 mg, 1.67 mmol) in N,N-dimethylformamide (7.8 mL) was added N,N-diisopropylethylamine (0.791 mL, 4.54 mmol), followed by O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU; 633 mg, 1.66 mmol). The reaction mixture was allowed to warm to 0 °C over 1 hour,
whereupon it was diluted with aqueous sodium bicarbonate solution (30 mL) and extracted with a mixture of 2-butanol and dichloromethane (9:1, 3 x 7 mL). The combined organic layers were concentrated \textit{in vacuo} and purified via silica gel chromatography (Gradient: 0% to 100% methanol in dichloromethane), affording \textbf{C50} as an off-white foam. By \textsuperscript{1}H NMR analysis, this material existed as a mixture of rotamers, and contained impurities derived from the reagents employed; a portion of this sample was progressed to the following step. Yield: 613 mg, 1.40 mmol, 93%. LCMS \textit{m/z} 459.3 [M+Na\textsuperscript{+}]. \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}), characteristic product peaks only: δ 8.33 – 8.18 (m, 1H), [7.65 (br s) and 7.59 (br s), total 1H], [7.39 (br s) and 7.27 br (s), total 1H], 7.05 (br s, 1H), 4.38 – 4.28 (m, 1H), 4.28 – 4.17 (m, 1H), 3.46 – 3.36 (m, 1H), 2.02 – 1.89 (m, 1H), 1.80 – 1.45 (m, 2H), [1.39 (s) and 1.32 (s), total 9H].

Step 2. Synthesis of \textit{N-\textit{(tert-butoxycarbonyl)-3-methyl-L-valyl-(4R)-4-(trifluoromethyl)-L-prolyl-3-[(3S)-2-oxopyrrolidin-3-yl]-L-alaninamide (C51).}

A mixture of \textbf{C50} (242 mg, 0.554 mmol) and a solution of hydrogen chloride in 1,4-dioxane (4 M; 2 mL, 8 mmol) was stirred at room temperature for 5 minutes, whereupon the reaction mixture was concentrated \textit{in vacuo} to remove solvent and residual hydrogen chloride. The resulting deprotected material was combined with \textit{N-\textit{(tert-butoxycarbonyl)-3-methyl-L-valine (128 mg, 0.553 mmol) and O-(7-azabenzotriazol-1-yl)-N,N',N''-tetramethyluronium hexafluorophosphate (HATU: 232 mg, 0.610 mmol) in N,N-dimethylformamide (2 mL), and then cooled to −30 °C. \textit{N,N'-Diisopropylethylamine (0.290 mL, 1.66 mmol) was added, and the reaction mixture was warmed to 0 °C over 1 hour. After addition of aqueous sodium bicarbonate solution, the resulting mixture was extracted three times with ethyl acetate; the combined organic layers were concentrated \textit{in vacuo} and purified via silica gel chromatography (Gradient: 0% to 30% methanol in dichloromethane), affording \textbf{C51} as a solid. Yield: 230 mg, 0.418 mmol, 75%. LCMS \textit{m/z} 550.3 [M+H]\textsuperscript{+}.

Step 3. Synthesis of 3-methyl-\textit{N-(trifluoroacetyl)-L-valyl-(4R)-N-\{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethy\}-4-(trifluoromethyl)-L-prolinamide (77).}

A mixture of \textbf{C51} (230 mg, 0.418 mmol) and a solution of hydrogen chloride in 1,4-dioxane (4 M; 2 mL, 8 mmol) was stirred at room temperature for 5 minutes, whereupon the reaction mixture was concentrated \textit{in vacuo} to remove solvent and residual hydrogen chloride. The resulting deprotected material was combined with ethyl trifluoroacetate (595 mg, 4.19 mmol) and \textit{N,N'-diisopropylethylamine (0.219 mL, 1.26
mmol) in methanol (1.0 mL). After the reaction mixture had been stirred at room temperature for 30 minutes, ethyl trifluoroacetate (60 mg, 0.422 mmol) was again added, and stirring was continued for 30 minutes. Aqueous sodium bicarbonate solution was then added, and the resulting mixture was extracted three times with ethyl acetate.

The combined organic layers were dried over magnesium sulfate, filtered, concentrated in vacuo, and dissolved in dichloromethane (3 mL). To this was added ethyl N-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 299 mg, 1.25 mmol), and the reaction mixture was stirred at room temperature for 2 hours, whereupon it was treated with additional methyl N-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 100 mg, 0.420 mmol) and allowed to stir for a further 30 minutes. Dilute aqueous sodium carbonate solution was then added, and the mixture was extracted twice with ethyl acetate; the combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification via supercritical fluid chromatography (Column: Princeton Dinitrophenyl, 10 x 250 mm, 5 μm; Mobile phase: 9:1 carbon dioxide / methanol; Back pressure: 120 bar; Flow rate: 80 mL/minute) afforded material that was then slurried in heptane (2.0 mL) at 50 °C for 2 hours, cooled to room temperature, and collected via filtration, providing 3-methyl-N-(trifluoroacetyl)-L-valyl-(4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-(trifluoromethyl)-L-prolinamide (77) as a solid. Yield: 64 mg, 0.121 mmol, 29%. LCMS m/z 528.2 [M+H]+.

1H NMR (400 MHz, DMSO-d6) δ 9.46 (d, J = 8.4 Hz, 1H), 9.05 (d, J = 8.6 Hz, 1H), 7.67 (s, 1H), 4.96 (ddd, J = 11.0, 8.5, 5.0 Hz, 1H), 4.56 (d, J = 8.5 Hz, 1H), 4.37 (dd, J = 7.5, 7.5 Hz, 1H), 3.98 (dd, component of ABX system, J = 11.2, 7.5 Hz, 1H), 3.92 (dd, component of ABX system, J = 11.3, 4.8 Hz, 1H), 3.46 – 3.35 (m, 1H), 3.19 – 3.10 (m, 1H), 3.09 – 3.00 (m, 1H), 2.5 – 2.38 (m, 1H, assumed; partially obscured by solvent peak), 2.38 – 2.28 (m, 1H), 2.21 – 2.04 (m, 3H), 1.78 – 1.65 (m, 2H), 0.99 (s, 9H).

Example 78

(1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(methylcarbamoyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide (78)
Step 1. Synthesis of methyl (1R,2S,5S)-6,6-dimethyl-3-(3-methyl-L-valyl)-3-azabicyclo[3.1.0]hexane-2-carboxylate, hydrochloride salt (C52).

To a 0 °C solution of C31 (1.00 g, 2.61 mmol) in dichloromethane (20 mL) was added, in a drop-wise manner, a solution of hydrogen chloride in ethyl acetate (4 M; 20 mL, 80 mmol). After the reaction mixture had been stirred at 25 °C overnight, it was concentrated in vacuo to afford C52 as a white gum. Yield: 700 mg, 2.20 mmol, 84%.

LCMS m/z 283.1 [M+H]+. 1H NMR (400 MHz, DMSO-d6) δ 8.22 (br s, 3H), 4.25 (s, 1H), 3.87 – 3.77 (m, 2H), 3.72 (d, half of AB quartet, J = 10.8 Hz, 1H), 3.67 (s, 3H), 1.59 (dd, component of ABX system, J = 7.7, 5.3 Hz, 1H), 1.49 (d, half of AB quartet, J = 7.7 Hz, 1H), 1.03 (s, 9H), 1.02 (s, 3H), 0.96 (s, 3H).
Step 2. Synthesis of methyl \( (R,2S,5S)-6,6\text{-dimethyl-3-[3-methyl-N-(methylcarbamoyl)-L-valyl]}-3\text{-azabicyclo[3.1.0]hexane-2-carboxylate (C53).} \)

To a 0 °C solution of C52 (320 mg, 1.00 mmol) in dichloromethane (6 mL) were slowly added triethylamine (0.769 mL, 5.52 mmol) and methylcarbamyl chloride (188 mg, 2.01 mmol). The reaction mixture was allowed to warm to 20 °C and stir for 18 hours, whereupon it was treated in a drop-wise manner with saturated aqueous sodium carbonate solution (5 mL) and extracted with dichloromethane (2 x 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 x 20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 10% methanol in dichloromethane) provided C53 as a light-yellow gum. Yield: 190 mg, 0.560 mmol, 56%. LCMS m/z 339.9 [M+H]^+. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 6.03 (d, \(J = 9.4\) Hz, 1H), 5.89 (br q, \(J = 5\) Hz, 1H), 4.20 – 4.14 (m, 2H), 3.91 (d, half of AB quartet, \(J = 10.3\) Hz, 1H), 3.79 (dd, component of ABX system, \(J = 10.3, 5.3\) Hz, 1H), 3.65 (s, 3H), 3.17 (d, \(J = 5.3\) Hz, 3H), 1.55 – 1.49 (m, 1H), 1.40 (d, half of AB quartet, \(J = 7.4\) Hz, 1H), 1.00 (s, 3H), 0.92 (s, 9H), 0.83 (s, 3H).

Step 3. Synthesis of \((R,2S,5S)-6,6\text{-dimethyl-3-[3-methyl-N-(methylcarbamoyl)-L-valyl]}-3\text{-azabicyclo[3.1.0]hexane-2-carboxylic acid (C54).} \)

To a 0 °C solution of C53 (190 mg, 0.560 mmol) in a mixture of tetrahydrofuran (2 mL), water (4 mL), and methanol (1 mL) was added lithium hydroxide monohydrate (82.0 mg, 1.95 mmol). After the reaction mixture had been stirred at 20 °C for 2 hours, it was diluted with ethyl acetate (10 mL); the aqueous layer was then cooled to 0 °C to 5 °C and acidified to pH 2 to 3 by addition of 1 M hydrochloric acid. The aqueous mixture was extracted with ethyl acetate (3 x 15 mL), and these combined ethyl acetate layers were dried over sodium sulfate, filtered, and concentrated in vacuo to provide C54 as a white solid. Yield: 120 mg, 0.369 mmol, 66%. LCMS m/z 348.3 [M+Na\(^+\)]. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)), characteristic peaks: \(\delta\) 6.04 (d, \(J = 9.6\) Hz, 1H), 5.89 (d, \(J = 4.7\) Hz, 1H), 4.17 (d, \(J = 9.6\) Hz, 1H), 4.09 (s, 1H), 3.87 (d, half of AB quartet, \(J = 10.4\) Hz, 1H), 3.77 (dd, component of ABX system, \(J = 10.3, 5.4\) Hz, 1H), 1.49 (dd, component of ABX system, \(J = 7.6, 5.1\) Hz, 1H), 1.38 (d, half of AB quartet, \(J = 7.5\) Hz, 1H), 1.00 (s, 3H), 0.92 (s, 9H), 0.82 (s, 3H).

Step 4. Synthesis of \((R,2S,5S)-N\{((2S)-1-amino-1-oxo-3-[(3S)-2-oxopyrrolidin-3-yl]propan-2-yl]-6,6\text{-dimethyl-3-[3-methyl-N-(methylcarbamoyl)-L-valyl]}-3\text{-azabicyclo[3.1.0]hexane-2-carboxamide (C55).} \)
To a 0 °C to 5 °C solution of C54 (120 mg, 0.369 mmol) and C16, HCl salt (75%, 107 mg, 0.387 mmol) in N,N-dimethylformamide (3.0 mL) were added O-(7-azabenzotriazol-1-yl)-N,N',N',N''-tetramethyluronium hexafluorophosphate (HATU; 154 mg, 0.405 mmol) and 4-methylmorpholine (0.144 mL, 1.31 mmol). After the reaction mixture had been allowed to warm from 0 °C to 20 °C over 1.5 hours, it was allowed to stir at 20 °C for 18 hours, whereupon it was diluted with water and treated with solid sodium sulfate to saturation. The resulting mixture was extracted with a mixture of 2-propanol and chloroform (1:4, 3 x 20 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 20% methanol in dichloromethane) provided C55 (240 mg) as a colorless glass. A portion of this material was used in the following step. LCMS m/z 479.2 [M+H]⁺. By ¹H NMR analysis, this material was contaminated with a byproduct derived from the HATU reagent. ¹H NMR (400 MHz, DMSO-d₆), characteristic product peaks only: δ 8.21 (d, J = 8.7 Hz, 1H), 7.53 (br s, 1H), 7.29 (br s, 1H), 7.03 (br s, 1H), 6.02 (d, J = 9.6 Hz, 1H), 5.86 (q, J = 4.6 Hz, 1H), 4.31 – 4.23 (m, 1H), 4.21 (s, 1H), 4.15 (d, J = 9.6 Hz, 1H), 2.18 – 2.08 (m, 1H), 1.98 – 1.88 (m, 1H), 1.68 – 1.55 (m, 1H), 1.54 – 1.42 (m, 2H), 1.34 (d, half of AB quartet, J = 7.6 Hz, 1H), 1.01 (s, 3H), 0.90 (s, 9H), 0.84 (s, 3H).


To a solution of C55 (from the previous step; 190 mg, ≤0.292 mmol) in acetonitrile (12 mL) was added methyl N-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 303 mg, 1.26 mmol). The reaction mixture was stirred at 20 °C for 22 hours, whereupon it was combined with a similar reaction carried out using C55 (from the previous step; 50 mg, ≤77 μmol). The resulting solution was concentrated in vacuo, diluted with water (10 mL), and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo; purification via reversed-phase HPLC (Column: Boston Prime C18, 30 x 150 mm, 5 μm; Mobile phase A: 0.225% formic acid in water; Mobile phase B: acetonitrile; Gradient: 23% to 46% B; Flow rate: 25 mL/minute) afforded (1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(methylcarbamoyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide (78) as a white solid. Combined yield: 25 mg, 54 μmol, 15% over 2 steps. LCMS m/z 461.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆),
characteristic peaks: δ 8.96 (d, J = 8.6 Hz, 1H), 7.65 (s, 1H), 6.02 (d, J = 9.5 Hz, 1H), 5.85 (q, J = 4.5 Hz, 1H), 4.95 (ddd, J = 10.8, 8.4, 5.1 Hz, 1H), 4.13 (d, J = 9.6 Hz, 1H), 4.11 (s, 1H), 3.88 – 3.79 (m, 2H), 3.18 – 3.09 (m, 1H), 3.07 – 2.98 (m, 1H), 2.48 – 2.37 (m, 1H), 2.20 – 2.02 (m, 2H), 1.77 – 1.62 (m, 2H), 1.56 – 1.50 (m, 1H), 1.27 (d, half of AB quartet, J = 7.6 Hz, 1H), 1.02 (s, 3H), 0.89 (s, 9H), 0.85 (s, 3H). 1H NMR (400 MHz, chloroform-d), characteristic peaks: δ 8.12 (d, J = 7.6 Hz, 1H), 5.78 (br s, 1H), 5.04 (br d, J = 9.4 Hz, 1H), 4.99 – 4.90 (m, 1H), 4.57 – 4.49 (m, 1H), 4.39 (d, J = 9.7 Hz, 1H), 4.25 (s, 1H), 4.01 (d, half of AB quartet, J = 10.2 Hz, 1H), 3.93 (br dd, component of ABX system, J = 10.6, 4.9 Hz, 1H), 3.43 – 3.25 (m, 2H), 2.71 (d, J = 4.8 Hz, 3H), 2.61 – 2.50 (m, 1H), 2.45 – 2.30 (m, 2H), 2.03 – 1.93 (m, 1H), 1.91 – 1.78 (m, 1H), 1.05 (s, 3H), 0.98 (s, 9H), 0.91 (s, 3H).

Example 79

Methyl ((2S)-1-[(1R,2S,5S)-2-{{(1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl}carbamoyl}-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl]-3,3-dimethyl-1-oxobutan-2-yl)carbamate (79)
Step 1. Synthesis of methyl (1R,2S,5S)-3-[(N-methoxycarbonyl)-3-methyl-L-valyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate (C56).

To a 0 °C solution of C52 (370 mg, 1.16 mmol) in dichloromethane (6 mL) were slowly added triethylamine (0.647 mL, 4.64 mmol) and methyl chloroformate (335 mg, 3.55 mmol). After the reaction mixture had been stirred at 20 °C for 16 hours, it was diluted in a drop-wise manner with saturated aqueous sodium carbonate solution (5 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 × 20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo; chromatography on silica gel (Gradient: 0% to 100% ethyl acetate in petroleum ether) provided C56 as a white gum. Yield: 115 mg, 0.338 mmol, 29%. LCMS m/z 341.1 [M+H]+. 1H NMR (400 MHz, chloroform-d) δ 5.29 (br d, J = 9.6 Hz, 1H), 4.46 (s, 1H), 4.23 (d, J = 9.9 Hz, 1H), 3.94 – 3.86 (m, 2H), 3.74 (s, 3H), 3.63 (br s, 3H), 1.49 – 1.41 (m, 2H), 1.04 (s, 3H), 1.03 (s, 9H), 0.91 (s, 3H).

Step 2. Synthesis of (1R,2S,5S)-3-[(N-methoxycarbonyl)-3-methyl-L-valyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (C57).

To a solution of C56 (115 mg, 0.338 mmol) in a mixture of methanol (2.0 mL), tetrahydrofuran (2.0 mL), and water (2 mL) was added lithium hydroxide monohydrate (28.4 mg, 0.677 mmol). The reaction mixture was stirred at room temperature (22 °C to 25 °C) for 16 hours, then concentrated in vacuo. The aqueous residue was partitioned between water (5 mL) and ethyl acetate (20 mL), whereupon the organic layer was discarded and the aqueous layer was adjusted to a pH of 1 to 2 by addition of concentrated hydrochloric acid. The resulting mixture was extracted three times with ethyl acetate; the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to provide C57 as a colorless gum. Yield: 100 mg, 0.306 mmol, 91%. LCMS m/z 327.2 [M+H]+. 1H NMR (400 MHz, chloroform-d) δ 5.42 (d, J = 9.9 Hz, 1H), 4.46 (s, 1H), 4.26 (d, J = 10.0 Hz, 1H), 3.96 (d, half of AB quartet, J = 10.5 Hz, 1H).
3.87 (dd, component of ABX system, J = 10.3, 5.4 Hz, 1H), 3.64 (s, 3H), 1.68 (d, half of AB quartet, J = 7.7 Hz, 1H), 1.50 (dd, component of ABX system, J = 7.6, 5.3 Hz, 1H), 1.06 (s, 3H), 1.01 (s, 9H), 0.91 (s, 3H).

5 Step 3. Synthesis of methyl ((2S)-1-[(1R,2S,5S)-2-(((2S)-1-amino-1-oxo-3-[(3S)-2-oxopyrrolidin-3-yl]propan-2-yl)carbamoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl]-3,3-dimethyl-1-oxobutan-2-yl)carbamate (C58).

To a 0 °C solution of C57 (100 mg, 0.306 mmol) and C16, HCl salt (75%, 84.8 mg, 0.306 mmol) in N,N-dimethylformamide (3 mL) was added O-(7-azabenzotriazol-1-y1)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU; 140 mg, 0.368 mmol), followed by drop-wise addition of a solution of 4-methylmorpholine (93 mg, 0.919 mmol) in N,N-dimethylformamide (1 mL). The reaction mixture was then warmed to room temperature (25 °C) and stirred for 16 hours, whereupon water (10 mL) was added. After solid sodium sulfate had been added to saturation, the resulting mixture was extracted with a mixture of chloroform and 2-propanol (4:1, 3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated in vacuo, and purified using silica gel chromatography (Gradient: 0% to 30% methanol in dichloromethane), affording C58 as a white solid. Yield: 93 mg, 0.19 mmol, 62%. LCMS m/z 480.0 [M+H]+. 1H NMR (400 MHz, chloroform-d) δ 8.30 (br s, 1H), 7.18 (br s, 1H), 5.98 (br s, 1H), 5.64 (br s, 1H), 5.58 – 5.42 (m, 1H), 4.49 – 4.37 (m, 1H), 4.29 (d, J = 10.0 Hz, 1H), 4.23 (s, 1H), 4.11 (dd, component of ABX system, J = 10.3, 5.5 Hz, 1H), 3.93 (d, half of AB quartet, J = 10.3 Hz, 1H), 3.64 (s, 3H), 3.43 – 3.29 (m, 2H), 2.55 – 2.33 (m, 2H), 2.15 – 1.81 (m, 3H), 1.54 – 1.47 (m, 1H), 1.45 (d, half of AB quartet, J = 7.7 Hz, 1H), 1.03 (s, 3H), 1.01 (s, 9H), 0.88 (s, 3H).

20 Step 4. Synthesis of methyl ((2S)-1-[(1R,2S,5S)-2-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)carbamoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl]-3,3-dimethyl-1-oxobutan-2-yl)carbamate (79).

To a suspension of C58 (93 mg, 0.19 mmol) in dichloromethane (5 mL) was added methyl N-(triethylammoniosulfonyl)carbamate, inner salt (Burgess reagent; 139 mg, 0.583 mmol), and the reaction mixture was stirred at 25 °C for 2 hours. It was then diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL); the combined organic layers were washed with saturated aqueous sodium chloride solution (2 x 10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 100% ethyl acetate in petroleum ether, followed by a
gradient of 0% to 20% methanol in dichloromethane) afforded methyl [(2S)-1-[(1R,2S,5S)-2-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)carbamoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (79) as a white solid. Yield: 7.0 mg, 15 μmol, 8%. LCMS *m/z* 462.2 [M+H]⁺. ¹H NMR (400 MHz, chloroform-d) δ 8.13 (br d, J = 7.0 Hz, 1H), 5.68 (br s, 1H), 5.34 (br d, J = 9.9 Hz, 1H), 4.95 – 4.85 (m, 1H), 4.26 (s, 1H), 4.23 (d, J = 10.0 Hz, 1H), 3.94 (dd, component of ABX system, J = 10.1, 4.5 Hz, 1H), 3.88 (d, half of AB quartet, J = 10.3 Hz, 1H), 3.63 (s, 3H), 3.45 – 3.29 (m, 2H), 2.62 – 2.50 (m, 1H), 2.46 – 2.28 (m, 2H), 2.02 – 1.93 (m, 1H), 1.92 – 1.79 (m, 1H), 1.6 – 1.49 (m, 2H, assumed; partially obscured by water peak), 1.06 (s, 3H), 0.98 (s, 9H), 0.90 (s, 3H).

Example 80

\[ N-(\text{Trifluoroacetyl})-L\text{-valyl-}(4R)-N\{1S\}-1\text{-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl\}-4-\text{(trifluoromethyl)}-L\text{-prolinamide (80)} \]
Step 1. Synthesis of 2-benzyl 1-tert-butyl (2S,4R)-4-(trifluoromethyl)pyrrolidine-1,2-dicarboxylate (C59).

A mixture of (4R)-1-(tert-butoxycarbonyl)-4-(trifluoromethyl)-L-proline (400 mg, 1.41 mmol), benzyl bromide (0.335 mL, 2.82 mmol), and sodium bicarbonate (593 mg, 7.06 mmol) in N,N-dimethylformamide (8 mL) was stirred for 15 hours at 25 °C. After the reaction mixture had been diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL), the combined organic layers were washed with saturated aqueous sodium chloride solution and with 5% aqueous lithium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 30% ethyl acetate in petroleum ether) provided C59 as a colorless oil. By ¹H NMR analysis, this material existed as a mixture of rotamers. Yield: 355 mg, 0.951 mmol, 67%. ¹H NMR (400 MHz, chloroform-d) δ 7.44 – 7.28 (m, 5H), 5.29 – 5.07 (m, 2H), [4.54 (br d, J = 8.6 Hz) and 4.40 (br dd, J = 8.5, 2 Hz), total 1H], 3.87 – 3.70 (m, 1H), [3.58 (dd, J = 11.2, 7.4 Hz) and 3.49 (dd, J = 11.0, 7.9 Hz), total 1H], 3.13 – 2.95 (m, 1H), 2.47 – 2.27 (m, 1H), 2.25 – 2.11 (m, 1H), [1.46 (s) and 1.33 (s), total 9H].

Step 2. Synthesis of benzyl (4R)-4-(trifluoromethyl)-L-proline, hydrochloride salt (C60).

To a 0 °C solution of C59 (200 mg, 0.536 mmol) in ethyl acetate (3 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M; 6 mL, 24 mmol). After the reaction mixture had been stirred at room temperature (28 °C) for 3 hours, it was
concentrated in vacuo to afford C60 as a white solid; this material was taken directly to the following step. LCMS m/z 274.0 [M+H]⁺.


O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU; 277 mg, 0.728 mmol) and 4-methylmorpholine (184 mg, 1.82 mmol) were added to a 0 °C mixture of C60 (from the previous step; ≤0.536 mmol) and N-(tert-butoxycarbonyl)-L-valine (158 mg, 0.727 mmol) in N,N-dimethylformamide (3 mL). The reaction mixture was stirred at 0 °C for 1 hour, whereupon it was poured into ice water (15 mL) and extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed sequentially with 1 M hydrochloric acid, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated in vacuo. Purification via silica gel chromatography (Gradient: 0% to 40% ethyl acetate in petroleum ether) provided C61 as a colorless gum. Yield: 230 mg, 0.487 mmol, 91% over 2 steps. LCMS m/z 495.0 [M+Na⁺]. 1H NMR (400 MHz, chloroform-d), characteristic peaks: δ 7.40 – 7.30 (m, 5H), 5.17 (AB quartet, JAB = 12.3 Hz, ΔνAB = 12.6 Hz, 2H), 4.21 (dd, J = 9.3, 6.8 Hz, 1H), 4.00 – 3.86 (m, 2H), 3.18 – 3.04 (m, 1H), 2.36 (ddd, component of ABXY system, J = 13.5, 9, 9 Hz, 1H), 2.20 (ddd, component of ABXY system, J = 13.4, 7.4, 3.5 Hz, 1H), 2.05 – 1.94 (m, 1H), 1.42 (s, 9H), 0.98 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H).


To a 0 °C solution of C61 (230 mg, 0.487 mmol) in ethyl acetate (2 mL) was added a solution of hydrogen chloride in ethyl acetate (4 M; 4 mL, 16 mmol). The reaction mixture was stirred at room temperature (28 °C) for 1 hour, whereupon LCMS analysis indicated conversion to C62. LCMS m/z 373.1 [M+H]⁺. Concentration of the reaction mixture in vacuo provided C62 as a white solid, which was taken directly to the following step.

Step 5. Synthesis of benzyl N-(trifluoroacetyl)-L-valyl-(4R)-4-(trifluoromethyl)-L-prolinate (C63).

A solution of trifluoroacetic anhydride (154 mg, 0.733 mmol) in dichloromethane (0.5 mL) was added to a 0 °C suspension of C62 (from the previous step; ≤0.487 mmol)
in dichloromethane (3 mL). After 3 minutes, a solution of triethylamine (148 mg, 1.46 mmol) in dichloromethane (0.5 mL) was added in a drop-wise manner, and stirring was continued at 25 °C for 3 hours. After dilution with dichloromethane (5 mL), the reaction mixture was washed with saturated aqueous sodium carbonate solution (10 mL) and with saturated aqueous sodium chloride solution (15 mL), dried, filtered, and concentrated in vacuo; silica gel chromatography (Gradient: 0% to 30% ethyl acetate in petroleum ether) afforded C63 as a colorless oil. Yield: 129 mg, 0.275 mmol, 56% over 2 steps. LCMS m/z 491.2 [M+Na+].

Step 6. Synthesis of N-(trifluoroacetyl)-L-valyl-(4R)-4-(trifluoromethyl)-L-proline (C64).

To a 28 °C solution of C63 (129 mg, 0.275 mmol) in methanol (3 mL) was added palladium on carbon (10%, 29.3 mg, 27.5 μmol), whereupon the mixture was hydrogenated at 15 psi for 16 hours. Filtration provided a filter cake, which was washed with methanol (10 mL); the combined filtrates were concentrated in vacuo to afford C64 as a light-yellow solid. Yield: 80 mg, 0.21 mmol, 76%. LCMS m/z 401.0 [M+Na+].

Step 7. Synthesis of N-(trifluoroacetyl)-L-valyl-(4R)-4-(trifluoromethyl)-L-prolyl-3-[[3(S)-2-oxopyrrolidin-3-yl]-L-alaninamide (C65).

O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU; 88.5 mg, 0.233 mmol) and 4-methylmorpholine (64.2 mg, 0.635 mmol) were added to a 0 °C solution of C64 (80 mg, 0.21 mmol) and C16 (78.8 mg, 0.287 mmol) in N,N-dimethylformamide (3 mL). After the reaction mixture had been stirred at 0 °C for 2 hours, it was treated with water (10 mL) and aqueous citric acid solution (1 M; 10 mL, 10 mmol), then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed sequentially with saturated aqueous sodium bicarbonate solution (15 mL) and saturated aqueous sodium chloride solution (15 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Purification via silica gel chromatography (Gradient: 0% to 10% methanol in dichloromethane) provided C65 as a white solid. Yield: 72 mg, 0.14 mmol, 67%. LCMS m/z 532.2 [M+H]+.


Methyl N-(triethylammoniosulfonfyl)carbamate, inner salt (Burgess reagent; 96.9 mg, 0.407 mmol) was added to a mixture of C65 (72 mg, 0.14 mmol) in dichloromethane (5 mL), and the reaction mixture was stirred at room temperature
overnight. After dilution with water (15 mL), the mixture was extracted with dichloromethane (3 x 15 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (2 x 20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel chromatography (Gradient: 0% to 10% methanol in dichloromethane) afforded N-(trifluoroacetyl)-L-valyl-[(4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-(trifluoromethyl)-L-prolinamide (80) as a white solid. Yield: 30.9 mg, 60.2 μmol, 43%. LCMS m/z 536.1 [M+Na⁺]. ¹H NMR (400 MHz, DMSO-d₆), characteristic peaks: δ 9.89 (d, J = 7.8 Hz, 1H), 9.06 (d, J = 8.4 Hz, 1H), 7.69 (s, 1H), 4.96 (ddd, J = 10.6, 8.4, 5.5 Hz, 1H), 4.38 (dd, J = 7.9, 6.3 Hz, 1H), 4.28 (dd, J = 9.8, 7.8 Hz, 1H), 4.07 – 3.94 (m, 2H), 3.20 – 3.00 (m, 2H), 2.5 – 2.41 (m, 1H, assumed; partially obscured by solvent peak), 2.38 – 2.28 (m, 1H), 2.19 – 2.02 (m, 4H), 1.78 – 1.61 (m, 2H), 0.92 (d, J = 7 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H).

Examples 81-84

Example 81: (1R,2S,5S)-N-[(1S)-1-cyano-2-[(3R)-5-hydroxy-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide

Example 82: (1R,2S,5S,6R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6-(hydroxymethyl)-6-methyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide
Example 83: (1R,2S,5S,6S)-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6-(hydroxymethyl)-6-methyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide

Example 84: (1R,2S,5S)-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-3-[4-hydroxy-3-methyl-N-(trifluoroacetyl)-L-valyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

The compounds of Examples 81-84 were obtained by biotransformation pathways, both in vitro and in vivo, from (1R,2S,5S)-N-{(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide (the compound of Example 13) as follows. In in vitro studies, (1R,2S,5S)-N-{(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide was incubated with mouse, rat, hamster, rabbit, monkey or human liver microsomes (see Table M1 below) or with rat, monkey or human hepatocytes (see Table M2 below). Alternatively, in in vivo studies (1R,2S,5S)-N-{(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide was administered to rat and monkey. Samples of rat plasma, urine and bile and monkey plasma were obtained. The resulting metabolites were then analyzed using HPLC/MS and the resulting oxidative metabolite compounds of Examples 81-84 were detected and obtained. In addition to the compounds of Examples 81-84 an additional metabolite, (1R,2S,5S)-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxylic acid, resulting from hydrolytic cleavage, was observed in the in vivo studies.

Table M1: Compounds obtained from liver microsomes

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Table M2: Compounds of Examples 81-84 obtained from Hepatocytes

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Table M3: Compounds of Examples 81-84 obtained in vivo in the Rat or Monkey

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<th>Monkey Plasma</th>
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In tables M1, M2 and M3 the following abbreviations are used: - = not detected; + = detected by mass spectrometry and minor UV peak; ++ = detected by mass spectrometry and moderate UV peak; +++ = detected by mass spectrometry and major UV peak; t = trace, detected by mass spectrometry only.

Antiviral activity from SARS-CoV-2 infection

The ability of compounds to prevent SARS-CoV-2 coronavirus-induced cell death or cytopathic effect can be assessed via cell viability, using an assay format that utilizes luciferase to measure intracellular ATP as an endpoint. In brief, VeroE6 cells that are enriched for hACE2 expression were batched inoculated with SARS-CoV-2 (USA_WA1/2020) at a multiplicity of infection of 0.002 in a BSL-3 lab. Virus-inoculated cells were then added to assay-ready compound plates at a density of 4,000 cells/well. Following a 3-day incubation, a time at which virus-induced cytopathic effect is 95% in the untreated, infected control conditions, cell viability was evaluated using Cell Titer-Glo (Promega), according to the manufacturer’s protocol, which quantitates ATP levels. Cytotoxicity of the compounds was assessed in parallel non-infected cells. Test compounds are tested either alone or in the presence of the P-glycoprotein (P-gp) inhibitor CP-100356 at a concentration of 2 μM. The inclusion of CP-100356 is to
assess if the test compounds are being effluxed out of the VeroE6 cells, which have high levels of expression of P-glycoprotein. Percent effect at each concentration of test compound was calculated based on the values for the no virus control wells and virus-containing control wells on each assay plate. The concentration required for a 50% response (EC50) value was determined from these data using a 4-parameter logistic model. EC50 curves were fit to a Hill slope of 3 when >3 and the top dose achieved ≥ 50% effect. If cytotoxicity was detected at greater than 30% effect, the corresponding concentration data was eliminated from the EC50 determination.

For cytotoxicity plates, a percent effect at each concentration of test compound was calculated based on the values for the cell-only control wells and hyamine-containing control wells on each assay plate. The CC50 value was calculated using a 4-parameter logistic model. A TI was then calculated by dividing the CC50 value by the EC50 value.

SARS-CoV-2 Coronavirus 3C Protease FRET Assay and Analysis

The proteolytic activity of the main protease, 3CLpro, of SARS-CoV-2 was monitored using a continuous fluorescence resonance energy transfer (FRET) assay. The SARS-CoV-2 3CLpro assay measures the activity of full-length SARS-CoV-2 3CL protease to cleave a synthetic fluorogenic substrate peptide with the following sequence: Dabcyl-KTSAVLQ-SGFRKME-Edans modelled on a consensus peptide (V. Grum-Tokars et al. 2018). Evaluating the 3C-like protease activity of SARS-coronavirus: recommendations for standardized assays for drug discovery. Virus Research 133 (2008) 63–73). The fluorescence of the cleaved Edans peptide (excitation 340 nm / emission 490 nm) is measured using a fluorescence intensity protocol on a Flexstation reader (Molecular Devices). The fluorescent signal is reduced in the present of PF-835231, a potent inhibitor of SARS-CoV-2 3CLpro. The assay reaction buffer contained 20 mM Tris-HCl (pH 7.3), 100 mM NaCl, 1 mM EDTA and 25 μM peptide substrate. Enzyme reactions were initiated with the addition of 15 nM SARS-CoV-2 3CL protease and allowed to proceed for 60 minutes at 23 °C. Percent inhibition or activity was calculated based on control wells containing no compound (0% inhibition/100% activity) and a control compound (100% inhibition/0% activity). IC50 values were generated using a four-parameter fit model using ABASE software (IDBS). Ki values were fit to the Morrison equation with the enzyme concentration parameter fixed to 15 nM, the Km parameter fixed to 14 μM and the substrate concentration parameter fixed to 25 μM using ABASE software (IDBS).
Proteolytic activity of SARS-CoV-2 Coronavirus 3CL protease is measured using a continuous fluorescence resonance energy transfer assay. The SARS-CoV-2 3CLpro FRET assay measures the protease catalyzed cleavage of TAMRA-SITSAVLQSGFRMK-(DABCYL)-OH to TAMRA - SITSAVLQ and SGFRMK(DABCYL)-OH. The fluorescence of the cleaved TAMRA (ex. 558 nm / em. 581 nm) peptide was measured using a TECAN SAFIRE fluorescence plate reader over the course of 10 min. Typical reaction solutions contained 20 mM HEPES (pH 7.0), 1 mM EDTA, 4.0 μM FRET substrate, 4% DMSO and 0.005% Tween-20. Assays were initiated with the addition of 25 nM SARS 3CLpro (nucleotide sequence 9985-10902 of the Urbani strain of SARS coronavirus complete genome sequence (NCBI accession number AY278741)). Percent inhibition was determined in duplicate at 0.001 mM level of inhibitor. Data was analyzed with the non-linear regression analysis program Kalidagraph using the equation:

\[
FU = \text{offset} + (\text{limit})(1 - e^{-k_{obs}t})
\]

where offset equals the fluorescence signal of the un-cleaved peptide substrate, and limit equals the fluorescence of fully cleaved peptide substrate. The kobs is the first order rate constant for this reaction, and in the absence of any inhibitor represents the utilization of substrate. In an enzyme start reaction which contains an irreversible inhibitor, and where the calculated limit is less than 20% of the theoretical maximum limit, the calculated kobs represents the rate of inactivation of coronavirus 3C protease. The slope (kobs / I) of a plot of kobs vs. [I] is a measure of the avidity of the inhibitor for an enzyme. For very fast irreversible inhibitors, kobs/I is calculated from observations at only one or two [I] rather than as a slope.

Table 2. Biological activity and IUPAC name for Examples 1 – 84.

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<th>Example Number</th>
<th>Geometric Mean ( K_i ) (μM)</th>
<th>Count Used ( K_i ) (μM)</th>
<th>Geometric Mean ( EC_{50} ) (μM)</th>
<th>Count Used ( EC_{50} ) (μM)</th>
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- $N$-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)-4-methyl-$N^2$-[(propan-2-yloxy)acetyl]-L-leucinamide
- $N$-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)-$N^2$-[(cyclohexyloxy)acetyl]-4-methyl-L-leucinamide
- $N$-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)-4-methyl-$N^2$-(4,4,4-trifluoro-3-methylbutanoyl)-L-leucinamide
- $N$-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)-$N^2$-[(2S)-2-(dimethylamino)-2-phenylacetyl]-4-methyl-L-leucinamide
- $N^2$-[(trans-4-cyanocyclohexyl)carbonyl]-$N$-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)-4-methyl-L-leucinamide
- $N^2$-[(trans-4-cyanocyclohexyl)carbonyl]-$N$-((1R)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)-4-methyl-L-leucinamide
- $N$-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)-$N^2$-[(2-cyclohexyloxy)propanoyl]-4-methyl-L-leucinamide
- $N$-((1R)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)-$N^2$-[(2-cyclohexyloxy)propanoyl]-4-methyl-L-leucinamide
- $N$-((2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-4-hydroxy-1H-indole-2-carboxamidine
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\[N^2-[(2S)-1-\{((1S)-1-cyano-2-[(3S)-2-oxypyrrolidin-3-yl]ethyl}amino)-4-methyl-1-oxopentan-2-yl\}-5-hydroxy-4-methoxy-1H-indole-2-carboxamide\]

\[N^2-[(4-chloro-1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]-N^2-[(1S)-1-cyano-2-[(3S)-2-oxypyrrolidin-3-yl]ethyl}]-4-methyl-L-leucinamide\]

\[N^2-[(1S)-1-cyano-2-[(3S)-2-oxypyrrolidin-3-yl]ethyl}-N^2-[(2R)-2-(dimethylamino)-2-phenylacety]-4-methyl-L-leucinamide\]

\[N^2-[(2S)-1-\{((1S)-1-cyano-2-[(3S)-2-oxypyrrolidin-3-yl]ethyl}amino)-4,4-dimethyl-1-oxopentan-2-yl\}-4-methoxy-3-(trifluoromethyl)-1H-indole-2-carboxamide\]

\[N^2-[(2S)-1-\{((1S)-1-cyano-2-[(3S)-2-oxypyrrolidin-3-yl]ethyl}amino)-4,4-dimethyl-1-oxopentan-2-yl\}-4-methoxy-7-(trifluoromethyl)-1H-indole-2-carboxamide\]

\[N^2-[(2S)-1-\{((1S)-1-cyano-2-[(3S)-2-oxypyrrolidin-3-yl]ethyl}amino)-4,4-dimethyl-1-oxopentan-2-yl\}-4-methoxy-3,7-bis(trifluoromethyl)-1H-indole-2-carboxamide\]

\[N^2-[(2S)-1-\{((1S)-1-cyano-2-[(3S)-2-oxypyrrolidin-3-yl]ethyl}amino)-4,4-dimethyl-1-oxopentan-2-yl\}-4-methoxy-3,5-bis(trifluoromethyl)-1H-indole-2-carboxamide\]

\[N^2-[(2S)-1-\{((1S)-1-cyano-2-[(3S)-2-oxypyrrolidin-3-yl]ethyl}amino)-4,4-dimethyl-1-oxopentan-2-yl\}-4-methoxy-3,6-bis(trifluoromethyl)-1H-indole-2-carboxamide^2\]
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<td>3</td>
<td>N.D.</td>
<td>(N)-((2S)-1-{((1S)-1\text{-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl}amino)-4,4\text{-dimethyl-1-oxopentan-2-yl}}-4-(\text{trifluoromethyl})-1H\text{-indole-2-carboxamide})</td>
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<td>(6\text{-chloro-}N)-((2S)-1-{((1S)-1\text{-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl}amino)-4\text{-methyl-1-oxopentan-2-yl}}-1H\text{-indole-2-carboxamide})</td>
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<td>(4\text{-chloro-}N)-((2S)-1-{((1S)-1\text{-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl}amino)-4\text{-methyl-1-oxopentan-2-yl}}-1H\text{-indole-2-carboxamide})</td>
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N²-[(4-chloro-1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]-N-(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-L-leucinamide

3-acetyl-N-[((2S)-1-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide

Diastereomer 1: (2S,4R)-4-tert-butyl-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-{N-[(trifluoromethyl)sulfonyl]-L-valyl}piperidine-2-carboxamide

Diastereomer 2: (2S,4R)-4-tert-butyl-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-1-{N-[(trifluoromethyl)sulfonyl]-L-valyl}piperidine-2-carboxamide

3-methyl-N-(trifluoroacetyl)-L-valyl-(4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-(trifluoromethyl)-L-prolinamide

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(methylcarbamoyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide
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<td>81</td>
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<td>2</td>
<td>0.690</td>
<td>3</td>
<td>(1R,2S,5S)-(N)-(1S)-1-cyano-2-{(3R)-5-hydroxy-2-oxopyrrolidin-3-yl}[ethyl]-6,6-dimethyl-3-[3-methyl-(N)-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide</td>
</tr>
<tr>
<td>82</td>
<td>0.139</td>
<td>1</td>
<td>N.D.</td>
<td>N.D.</td>
<td>(1R,2S,5S,6R)-(N)-(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}[ethyl]-6-(hydroxymethyl)-6-methyl-3-[3-methyl-(N)-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide</td>
</tr>
<tr>
<td>83</td>
<td>0.092</td>
<td>1</td>
<td>N.D.</td>
<td>N.D.</td>
<td>(1R,2S,5S,6S)-(N)-(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}[ethyl]-6-(hydroxymethyl)-6-methyl-3-[3-methyl-(N)-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide</td>
</tr>
<tr>
<td>84</td>
<td>0.003</td>
<td>1</td>
<td></td>
<td></td>
<td>(1R,2S,5S)-(N)-(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}[ethyl]-3-[4-hydroxy-3-methyl-(N)-(trifluoroacetyl)-L-valyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide</td>
</tr>
</tbody>
</table>

1. Not determined.

2. The regiochemistry of Example 41 was not rigorously determined; other possible structures for this example are \(N\)-\{(2S)-1-\{(1S)-1-cyano-2-\{(3S)-2-oxopyrrolidin-3-yl\}[ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl\}-4-methoxy-5,6-bis(trifluoromethyl)-1H-
indole-2-carboxamide and N-((2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-6,7-bis(trifluoromethyl)-1H-indole-2-carboxamide.

Predicted Pharmacokinetic Parameters of (1R,2S,5S)-N-((1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide (the compound of Example 13) in Humans

Based on physiologically based pharmacokinetic (PBPK) modeling of in-vitro data incorporating CLint from human liver microsomes and CLbile from human hepatocytes under sandwich-cultured conditions, the predicted human plasma CL and Vss of (1R,2S,5S)-N-((1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide are 5.9 mL/min/kg and 0.97 L/kg, respectively, providing an effective half-life, t1/2, of 1.9 hours. A target Ceff of 0.16 μM (unbound plasma concentration) was defined based on antiviral inhibition data obtained from in vitro studies of (1R,2S,5S)-N-((1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide with either VeroE6 cells in the presence of a P-gp inhibitor (EC90 value of 0.156 μM) or in a differentiated normal human bronchial epithelial (dNHBE) cell assay (EC90 value of 0.149 μM). A dose of 380 mg of (1R,2S,5S)-N-((1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide administered orally three times a day (TID) is projected to cover the efficacious unbound concentration of 0.16 μM at Cmin.

All patents and publications described hereinabove are hereby incorporated by reference in their entirety. While the invention has been described in terms of various preferred embodiments and specific examples, the invention should be understood as not being limited by the foregoing detailed description, but as being defined by the appended claims and their equivalents.
WHAT IS CLAIMED IS:

1. A compound of Formula I

or a pharmaceutically acceptable salt thereof;

wherein

\( R^1 \) is selected from the group consisting of \( C_1-C_6 \) alkyl which is optionally substituted with a cyano or with one to five fluoro; \( C_2-C_6 \) alkynyl; and \( (C_3-C_6 \text{ cycloalkyl})-C_1-C_3 \) alkyl which is optionally substituted with one to two substituents selected from trifluoromethyl and \( C_1-C_3 \) alkyl or with one to five fluoro;

\( R^2 \) is hydrogen or \( R^2 \) and \( R^1 \) taken together with the nitrogen and carbon atoms to which they are attached are a pyrrolidine or piperidine ring which is optionally substituted with one to four \( R^{2a} \);

\( R^{2a} \) at each occurrence is independently selected from the group consisting of fluoro, \( C_1-C_6 \) alkyl optionally substituted with one to three fluoro and \( C_1-C_6 \) alkoxy optionally substituted with one to three fluoro; or two \( R^{2a} \) groups when attached to adjacent carbons and taken together with the carbons to which they are attached are a fused \( C_3-C_6 \) cycloalkyl which is optionally substituted with one to four \( R^{2b} \); or two \( R^{2a} \) groups when attached to the same carbon and taken together with the carbon to which they are attached are a spiro \( C_3-C_6 \) cycloalkyl which is optionally substituted with one to four \( R^{2b} \);

\( R^{2b} \) at each occurrence is independently selected from fluoro, \( C_1-C_3 \) alkyl optionally substituted with one to three fluoro and \( C_1-C_3 \) alkoxy optionally substituted with one to three fluoro;

\( R^3 \) is selected from the group consisting of \( C_1-C_6 \) alkyl, \( C_1-C_6 \) alkoxy, \( (C_1-C_6 \text{ alkoxy})-C_1-C_6 \) alkyl, \( C_2-C_6 \) alkynyl, \( C_2-C_6 \) alkynyloxy, \( C_3-C_{12} \) cycloalkyl optionally fused with a 5- to 6-
membered heteroaryl or phenyl, (C₅-C₁₂ cycloalkyl)-C₁-C₆ alkyl, C₅-C₁₂ cycloalkoxy, (C₃-
C₁₂ cycloalkoxy)-C₁-C₆ alkyl, 4- to 12-membered heterocycloalkyl which is optionally
fused with a 5- to 6-membered heteroaryl or phenyl and wherein said heterocycloalkyl
comprises one to four heteroatoms independently selected from N, O and S(O)ₓ, (4- to
12-membered heterocycloalkyl)-C₁-C₆ alkyl wherein said heterocycloalkyl moiety
comprises one to four heteroatoms independently selected from N, O and S(O)ₓ, C₅-C₁₀
aryl optionally fused with a C₄-C₆ cycloalkyl or a 4- to 7-membered heterocycloalkyl,
(C₆-C₁₀ aryl)-C₁-C₆ alkyl, 5- to 10-membered heteroaryl comprising one to five
heteroatoms independently selected from N, O and S, which is optionally fused with a
C₅-C₆ cycloalkyl; (5- to 10-membered heteroaryl)-C₁-C₆ alkyl wherein the heteroaryl
moiety comprises one to five heteroatoms independently selected from N, O and S; (C₆-
C₁₀ aryl)-(5- to 10-membered heteroaryl)- wherein the heteroaryl moiety comprises one
to five heteroatoms independently selected from N, O and S, (5- to 10-membered
heteroarylxy)-C₁-C₆ alkyl wherein the heteroaryl moiety comprises one to five
heteroatoms independently selected from N, O and S; (5- to 6-membered heteroaryl)-
(5- to 6-membered heteroaryl)- wherein each heteroaryl moiety comprises one to four
heteroatoms independently selected from N, O and S; (4- to 7-membered
heterocycloalkyl)-(5- to 6-membered heteroaryl)- wherein the heterocycloalkyl moiety
comprises one to three heteroatoms independently selected from N, O and S(O)ₓ, and the
heteroaryl moiety comprises one to four heteroatoms independently selected from
N, O and S; (5- to 6-membered heterocycloalkyl)-(4- to 7-membered heterocycloalkyl)-
wherein the heterocycloalkyl moiety comprises one to three heteroatoms independently
selected from N, O and S(O)ₓ, and the heteroaryl moiety comprises one to four
heteroatoms independently selected from N, O and S; wherein each R³ group is
optionally substituted with one to five R⁴;

R⁴ at each occurrence is independently selected from the group consisting of oxo, halo,
hydroxy, cyano, phenyl, benzyl, amino, (C₁-C₆ alkyl)amino optionally substituted with
one to five fluoro, di(C₁-C₆ alkyl)amino optionally substituted with one to ten fluoro, C₁-
C₆ alkyl optionally substituted with one to five fluoro, C₁-C₆ alkoxy optionally substituted
with one to five fluoro, C₁-C₆ alkoxy-C₁-C₃ alkyl optionally substituted with one to five
fluoro, C₃-C₆ cycloalkyl optionally substituted with one to three fluoro or C₁-C₃ alkyl, C₁-
C₆ alkyl-C(O)NH- optionally substituted with one to five fluoro, C₁-C₆ alkyl-S(O)ₓ₂NH-
optionally substituted with one to five fluoro, C₁-C₆ alkyl-C(O)- optionally substituted with
one to five fluoro, C₁-C₆ alkyl-S(O)ₓ- optionally substituted with one to five fluoro; and
n at each occurrence is independently selected from 0, 1 and 2.

2. The compound of claim 1 wherein $R^1$ is selected from the group consisting of (CH$_3$)$_2$CHCH$_2$-, (CH$_3$)$_3$CCH$_2$-, cyanomethyl, 2-cyanoethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 3,3,3-trifluoro-2-methylpropyl, cyclopropylmethyl, (2,2-difluorocyclopropyl)methyl, [1-(trifluoromethyl)cyclopropyl]methyl, (2-methylcyclopropyl)methyl, (3,3-difluorocyclobutyl)methyl, cyclopentylmethyl and propynyl; and $R^2$ is hydrogen; or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 wherein $R^2$ and $R^1$ taken together with the nitrogen and carbon atoms to which they are attached are a pyrrolidine or piperidine ring which is optionally substituted with one to four $R^{2a}$; or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3 wherein $R^{2a}$ at each occurrence is independently selected from the group consisting of fluoro, methyl, isopropyl, trifluoromethyl and tert-butoxy; or two $R^{2a}$ groups when attached to adjacent carbons and taken together with the carbons to which they are attached are a fused cyclopentane or cyclopropane which is optionally substituted with one to four $R^{2b}$; or two $R^{2a}$ groups when attached to the same carbon and taken together with the carbon to which they are attached are a spirocyclopropane ring which is optionally substituted with one to four $R^{2b}$; or a pharmaceutically acceptable salt thereof.

5. The compound of claim 4 wherein $R^{2b}$ at each occurrence is independently selected from the group consisting of fluoro, methyl and methoxy; or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1 selected from the group consisting of formulae la through lg.
or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1 selected from the group consisting of formulae Ia through Ii
or a pharmaceutically acceptable salt thereof.

8. The compound of claim 7 selected from the group consisting of
or a pharmaceutically acceptable salt thereof.

9. The compound of claim 8 wherein \( R^3 \) is selected from the group consisting of \( C_1-C_6 \) alkyl and \((C_3-C_6 \text{ cycloalkyl})-C_1-C_3 \) alkyl; each of which is substituted with one to four \( R^4 \); or a pharmaceutically acceptable salt thereof.

10. The compound of claim 9 wherein \( R^3 \) is selected from the group consisting of \((CH_3)_2CHCH(R^4)-, (CH_3)\text{CCH}(R^4)-\) and \((\text{cyclohexyl})\text{CH}(R^4)\)-; or a pharmaceutically acceptable salt thereof.

11. The compound of claim 10 selected from the group consisting of
or a pharmaceutically acceptable salt thereof.

12. The compound of claim 11 wherein \( R^4 \) is selected from the group consisting of \((C_1-\)C_6 alkyl)amino optionally substituted with one to five fluoro, \( C_1-C_6 \) alkyl-C(O)NH- optionally substituted with one to five fluoro, and \( C_1-C_6 \) alkyl-S(O)_2NH- optionally substituted with one to five fluoro; or a pharmaceutically acceptable salt thereof.

13. The compound of claim 12 wherein \( R^4 \) is selected from the group consisting of \( CF_3C(O)NH- \), \( CF_3S(O)_2NH- \), \( CH_3C(O)NH- \), \( CH_3CH_2C(O)NH- \) and \( CF_3CH_2NH- \); or a pharmaceutically acceptable salt thereof.

14. The compound of claim 13 wherein \( R^4 \) is \( CF_3C(O)NH- \) or \( CF_3S(O)_2NH- \); or a pharmaceutically acceptable salt thereof.
15. The compound of any one of claims 1 to 8 wherein \( R^3 \) is a 4- to 12-membered heterocycloalkyl which is optionally fused with a 5- to 6-membered heteroaryl or phenyl and wherein said heterocycloalkyl comprises one to four heteroatoms independently selected from N, O and S(O)\(_n\); or is a (4- to 12-membered heterocycloalkyl)-C\(_1\)-C\(_6\) alkyl wherein said heterocycloalkyl moiety comprises one to four heteroatoms independently selected from N, O and S(O)\(_n\); each of which is optionally substituted with one to five R\(^4\); or a pharmaceutically acceptable salt thereof.

16. The compound of claim 15 wherein the 4- to 12-membered heterocycloalkyl moiety in \( R^3 \) is selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, oxetanyl, tetrahydrofuranyl, pyranyl, 2-oxo-1,3-oxazolidinyl, oxabicyclo[2.2.1]heptyl, 1-oxa-8-azaspiro[4.5]decyl, 1,1-dioxido-1,2-thiazolidinyl and 1,1-dioxido-1,2-thiazinanyl; each of which is optionally substituted with one to three R\(^4\); or a pharmaceutically acceptable salt thereof.

17. The compound of any one of claims 1 to 8 wherein \( R^3 \) is selected from the group consisting of phenyl, benzyl, phenethyl, a 5- to 10-membered heteroaryl comprising one to five heteroatoms independently selected from N, O and S; (5- to 10-membered heteroaryl)-C\(_1\)-C\(_6\) alkyl wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S; and a (5- to 10-membered heteroaryl(\(_{\text{oxy}}\))-C\(_1\)-C\(_6\) alkyl wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S; each of which is optionally substituted with one to five R\(^4\); or a pharmaceutically acceptable salt thereof.

18. The compound of claim 17 wherein the 5- to 10-membered heteroaryl moiety in \( R^3 \) is selected from the group consisting of imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, benzimidazolyl, pyridinopyrrolyl, quinolinyl, quinoxalinyl, benzotriazolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b][1,3]thiazolyl, 4H-furo[3,2-b]pyrrolyl, 4H-thieno[3,2-b]pyrrolyl, [1,2,4]triazolo[1,5-a]pyrimidinyl, [1,2,3]triazolo[1,5-a]pyridinyl and naphthyridinyl; each of which is optionally substituted with one to four R\(^4\); or a pharmaceutically acceptable salt thereof.

19. The compound of claim 18 wherein \( R^3 \) is indolyl; which is optionally substituted with one to four R\(^4\); or a pharmaceutically acceptable salt thereof.

20. The compound of claim 19 wherein \( R^3 \) is indol-2-yl; which is optionally substituted with one to four R\(^4\); and R\(^4\) at each occurrence is independently selected from the group
consisting of fluoro, chloro, bromo, hydroxy, methyl, ethyl, propyl, isopropyl, 1-methylpropyl, butyl, tert-butyl, acetyl, methoxy, ethoxy, propoxy, butoxy, trifluoromethyl, trifluoromethoxy, cyclohexyl and diethylamino; or a pharmaceutically acceptable salt thereof.

21. The compound of claim 20 of the formula

or a pharmaceutically acceptable salt thereof.

22. The compound of claim 21 wherein R³ is selected from the group consisting of 1H-indol-2-yl, 7-fluoro-4-methoxy-1H-indol-2yl, 4-methoxy-7-(trifluoromethyl)-1H-indol-2-yl, 4-methoxy-1H-indol-2-yl, 4-(trifluoromethoxy)-1H-indol-2-yl, 6-(trifluoromethyl)-1H-indol-2-yl, 4-methoxy-3,6,7-tris(trifluoromethyl)-1H-indol-2-yl, 3-fluoro-4-methoxy-1H-indol-2-yl and 3,5-difluoro-4-methoxy-1H-indol-2-yl; or a pharmaceutically acceptable salt thereof.

23. The compound of claim 1 wherein R³ is C₁-C₅ alkoxy; or a pharmaceutically acceptable salt thereof.

24. The compound of claim 23 wherein R³ is selected from the group consisting of methoxy, ethoxy and prop-2-oxo; or a pharmaceutically acceptable salt thereof.

25. The compound of claim 1 wherein R³ is selected from the group consisting of C₃-C₁₂ cycloalkyl optionally fused with a 5- to 6-membered heterocaryl or phenyl, (C₃-C₁₂ cycloalkyl)-C₁-C₅ alkyl, C₃-C₁₂ cycloalkoxy and (C₃-C₁₂ cycloalkoxy)-C₁-C₅ alkyl; each of which is optionally substituted with one to three R⁴; or a pharmaceutically acceptable salt thereof.

26. The compound of claim 25 wherein R³ is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-(cyclohexyloxy)ethyl, cyclohexoxymethyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl and
cyclohexylethyl; each of which is optionally substituted with one to three \( R^4 \); or a pharmaceutically acceptable salt thereof.

27. The compound of claim 17 wherein \( R^3 \) is selected from the group consisting of phenyl, benzyl and phenethyl, each of which is optionally substituted with one to three \( R^4 \); or a pharmaceutically acceptable salt thereof.

28. The compound of claim 27 wherein \( R^4 \) is selected from the group consisting of fluoro, chloro, dimethylamino, trifluoromethyl, \( CF_3C(O)NH^- \) and \( CF_3S(O)NH^- \); or a pharmaceutically acceptable salt thereof.

29. A compound selected from the group consisting of

N-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(2R)-2-(dimethylamino)-2-[4-(trifluoromethyl)phenyl]acetyl]-4-methyl-L-leucinamide; N-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(2R)-2-(dimethylamino)-2-[3-(trifluoromethyl)phenyl]acetyl]-4-methyl-L-leucinamide; N-\{[(2S)-1-(((1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-6-(trifluoromethyl)-1H-indole-2-carboxamide; N-\{[(2S)-1-(((1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-6-(trifluoromethyl)-1H-indole-2-carboxamide; N-\{[(2S)-1-(((1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-3,6,7-tris(trifluoromethyl)-1H-indole-2-carboxamide; N-\{[(2S)-1-(((1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-4-(trifluoromethoxy)-1H-indole-2-carboxamide; N-\{[(2S)-1-(((1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-4-(trifluoromethoxy)-1H-indole-2-carboxamide; N-\{[(2S)-1-(((1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-3-fluoro-4-methoxy-1H-indole-2-carboxamide; N-\{[(2S)-1-(((1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-3,5-difluoro-4-methoxy-1H-indole-2-carboxamide; N-\{[(2S)-1-(((1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-5,7-difluoro-4-methoxy-1H-indole-2-carboxamide;
N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-5-fluoro-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-3,5,7-tris(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-3,7-bis(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-5-(trifluoromethyl)-1H-indole-2-carboxamide;

7-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-7-methyl-1H-indole-2-carboxamide;

6-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

4-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

5-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-7-(trifluoromethyl)-1H-indole-2-carboxamide;

4,6-dichloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-4-(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-5-(trifluoromethyl)-1H-indole-2-carboxamide;

7-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;
N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-7-methyl-1H-indole-2-carboxamide;

6-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

4-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

5,7-dichloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

5-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-7-(trifluoromethyl)-1H-indole-2-carboxamide;

4,6-dichloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-4-(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-3-methyl-5-(trifluoromethyl)imidazo[2,1-b][1,3]thiazole-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N²-[4-methyl-2-(trifluoromethyl)-1,3-thiazol-5-yl]carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N²-[5-methyl-2-(trifluoromethyl)-1,3-thiazol-4-yl]carbonyl]-L-leucinamide;

N²-[(4-bromo-1-ethyl-3-methyl-1H-pyrazol-5-yl)carbonyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-L-leucinamide;

N²-[(4-chloro-1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-L-leucinamide;

3-acetyl-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;
N-{(2S)-1-[(1S)-1-cyano-2-[(3R)-2,5-dioxopyrrolidin-3-yl]ethyl]amino}-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-{(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4-methyl-1-oxopentan-2-yl]-4-hydroxy-1H-indole-2-carboxamide;

N-{(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4-methyl-1-oxopentan-2-yl]-5-hydroxy-4-methoxy-1H-indole-2-carboxamide;

N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[3,3-difluorocyclobutyl]acetyl]-4-methyl-L-leucinamide;

N^2-[(trans-4-cyanocyclohexyl)carbonyl]N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;

N^2-[(trans-4-cyanocyclohexyl)carbonyl]N-{(1R)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;

N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[2-(cyclohexyloxy)propanoyl]-4-methyl-L-leucinamide;

N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[cyclohexylmethoxycarbonyl]acetyl]-4-methyl-L-leucinamide;

N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[cyclohexylmethoxyacetyl]-4-methyl-L-leucinamide;

N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(2S)-2-(dimethylamino)-2-phenylacetyl]-4-methyl-L-leucinamide;

N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-(pyrrolidin-1-ylacetyl)-L-leucinamide;

N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(2R)-2-(dimethylamino)-2-phenylacetyl]-4-methyl-L-leucinamide;

N^2-[(4-chloro-1,3-dimethyl-1H-pyrazol-5-yl)carbonyl]N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;

N-{(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino}-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-3-(trifluoromethyl)-1H-indole-2-carboxamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-7-(trifluoromethyl)-1H-indole-2-carboxamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-3,7-bis(trifluoromethyl)-1H-indole-2-carboxamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-3,5-bis(trifluoromethyl)-1H-indole-2-carboxamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-3,6-bis(trifluoromethyl)-1H-indole-2-carboxamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-4-methoxy-3-(trifluoromethyl)-1H-indole-2-carboxamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]N^2-(cyclohexylcarbonyl)-4-methyl-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]N^2-(cyclohexylcarbonyl)-4-methyl-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[2-(trifluoromethyl)-1,3-thiazol-4-yl]carbonyl]-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[(propan-2-yloxy)acetyl]-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[cyclohexyloxy]acetyl]-4-methyl-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[4,4,4-trifluoro-3-methylbutanoyl]-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[4,4,4-trifluoro-3-methylbutanoyl]-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-3-methylimidazo[2,1-b][1,3]thiazole-2-carboxamide;
(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-5,5,5-trifluoro-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;
N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-7-fluoro-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

N²-[(4-bromo-1-ethyl-3-methyl-1H-pyrazol-5-yl)carbonyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-4-methoxy-7-(trifluoromethyl)-1H-indole-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N²-(2,6-dichlorobenzoyl)-4-methyl-L-leucinamide;

(2S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4,4-dimethyl-1-[3-methyl-N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

3-methyl-N-(trifluoroacetyl)-L-valyl-(4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-4-(trifluoromethyl)-L-prolinamide;

(2S,4S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[3-methyl-N-(trifluoromethyl)sulfonyl]-L-valyl)piperidine-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N²-[(2-(trifluoromethyl)-1,3-thiazol-5-yl)carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N²-[2-(dimethylamino)-2-phenylacetyl]-4-methyl-L-leucinamide;

N²-[(trans-4-cyanocyclohexyl)carbonyl]-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;

N²-[(trans-4-cyanocyclohexyl)carbonyl]-N-[(1R)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;
N-[(1R)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N\(^2\)-[2-(cyclohexyloxy)propanoyl]-4-methyl-L-leucinamide;

(2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

5-(butan-2-yl)-N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N\(^2\)-[(4,5-dichloro-1H-imidazol-2-yl)carbonyl]-4-methyl-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-N\(^2\)-[(4,5-dichloro-1H-pyrazol-3-yl)carbonyl]-4-methyl-L-leucinamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-2,3-dimethyl-4H-furo[3,2-b]pyrrole-5-carboxamide;

5-chloro-N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-(trifluoromethyl)-1H-benzimidazole-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-methoxy-1H-pyrrolo[3,2-b]pyridine-2-carboxamide;

5-chloro-N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-pyrrolo[3,2-b]pyridine-2-carboxamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-fluoro-1H-benzimidazole-2-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N\(^2\)-[(3-(propan-2-yl)-1H-pyrazol-5-y]carbonyl]-L-leucinamide;

N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-fluoro-1H-benzimidazole-2-carboxamide;

5-chloro-N-[(2S)-1-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-benzimidazole-2-carboxamide;
N-[(2S)-1-{{(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-5,6-difluoro-1H-benzimidazole-2-carboxamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-4H-thieno[3,2-b]pyrrole-5-carboxamide;

N-[(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[(3-(2-methylpropyl)-1H-pyrazol-5-yl)carbonyl]-L-leucinamide;

N^2-[[4-(3-chlorophenyl)-1H-imidazol-2-yl]carbonyl]-N-[(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-lecinamide;

N^2-[[3-tert-butyl-1H-pyrazol-5-yl]carbonyl]-N-[(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-lecinamide;

6-bromo-N-[(2S)-1-{{(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-1H-benzimidazole-2-carboxamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-5-methyl-1H-benzimidazole-2-carboxamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;

4,6-dichloro-N-[(2S)-1-{{(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-1H-benzimidazole-2-carboxamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-6-(1-methylcyclopropyl)-4-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

N^2-[[5-(2-chlorophenyl)-4-fluoro-1H-pyrazol-3-yl]carbonyl]-N-[(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-L-leucinamide;

N-[(2S)-1-{{(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl}amino}-4,4-dimethyl-1-oxopentan-2-yl]-2-methyl-4H-thieno[3,2-b]pyrrole-5-carboxamide;

N-[(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(3-(4-methoxyphenyl)-1H-pyrazol-5-yl)carbonyl]-4-methyl-L-leucinamide;

N-[(1S)-1-cyano-2-[3(S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(3-(2-methoxyphenyl)-1H-pyrazol-5-yl)carbonyl]-4-methyl-L-leucinamide;
N-[(1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl]-N'-[4-(4-methoxyphenyl)-1H-imidazol-2-yl]carbonyl]-4-methyl-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl]-4-methyl-N'-[3-(4-methylphenyl)-1H-pyrazol-5-yl]carbonyl]-L-leucinamide;

7-bromo-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-5-methyl-1H-indole-2-carboxamide;

7-bromo-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

(2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl]-4-methyl-1-[3-methyl-N-(methylsulfonyl)-L-valyl]piperidine-2-carboxamide;

(2S,4S)-N-[(1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl]-4-methyl-1-[N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

(2S,4S)-N-[(1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl]-4-methyl-1-[3-methyl-N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

(2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl]-4-methyl-1-[3-methyl-N-(trifluoroacetyl)-L-valyl]piperidine-2-carboxamide;

5-[(2S)-butan-2-yl]-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3',3',3'-trifluoro-N-(trifluoroacetyl)-L-isoleucyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;


(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[4-methyl-N-(trifluoroacetyl)-L-leucyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxoppyrrolidin-3-yl]ethyl]-3-[(2S)-2-(4,4-difluorocyclohexyl)-2-[trifluoroacetyl]amino]acetyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;
(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[3-cyclopentyl-N-(trifluoroacetyl)-L-alanyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[3-cyclohexyl-N-(trifluoroacetyl)-L-alanyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(trifluoroacetyl)-L-leucyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[6,6-difluoro-N-(trifluoroacetyl)-L-norleucyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[(2S)-4,4,4-trifluoro-2-[(trifluoroacetyl)amino]butanoyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[3-fluoro-N-(trifluoroacetyl)-L-valyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[(2S)-2-cyclopropyl-2-[(trifluoroacetyl)amino]acetyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[3-(3,3-difluorocyclobutyl)-N-(trifluoroacetyl)-L-alanyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(trifluoroacetyl)-O-(trifluoromethyl)-L-seryl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[(2S)-2-phenyl-2-[(trifluoroacetyl)amino]acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(trifluoroacetyl)-L-phenylalanyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[3,5-difluoro-N-(trifluoroacetyl)-L-phenylalanyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(trifluoroacetyl)-3-(trifluoromethyl)-L-phenylalanyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

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(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(2,2,2-
trifluoroethyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[(2S)-3-methyl-2-
[(trifluoroacetyl)amino]butyl]piperidine-2-carboxamide;

(2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[(2S)-3-methyl-2-
[(2,2,2-trifluoroethyl)amino]butyl]piperidine-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[N-(3,3,3-
trifluoropropanoyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[(N-
propanoyl-L-valyl)-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(2S,4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-1-[(N-(2,2,2-
trifluoroethyl)-L-valyl)piperidine-2-carboxamide;

N²-[(4-chloro-1-ethyl-3-methyl-1H-pyrazol-5-yl)carbonyl]-N-[(1S)-1-cyano-2-[(3S)-2-
oxopyrrolidin-3-yl]ethyl]-L-leucinamide;

5-chloro-N-[(2S)-1-([(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino)-4-methyl-1-
oxopentan-2-yl]-3-ethyl-1H-indole-2-carboxamide;

N-[(2S)-1-([(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino)-4-methyl-1-
oxopentan-2-yl]-5-cyclohexyl-1H-indole-2-carboxamide;

5-chloro-N-[(2S)-1-([(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino)-4-methyl-1-
oxopentan-2-yl]-3-methyl-1H-indole-2-carboxamide;

N-[(2S)-1-([(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino)-4-methyl-1-
oxopentan-2-yl]-3,5-dimethyl-1H-indole-2-carboxamide;

5-tert-butyl-N-[(2S)-1-([(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino)-4-methyl-1-
oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-([(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino)-4-methyl-1-
oxopentan-2-yl]-5-(propan-2-yl)-1H-indole-2-carboxamide;

N-[(2S)-1-([(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino)-4-methyl-1-
oxopentan-2-yl]-3-ethyl-1H-indole-2-carboxamide;
N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-6-ethyl-1H-indole-2-carboxamide;

N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-5-ethyl-1H-indole-2-carboxamide;

4-butoxy-N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-5-(trifluoromethoxy)-1H-indole-2-carboxamide;

N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-6-(diethylamino)-1H-indole-2-carboxamide;

4-bromo-N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

5-bromo-N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

6-bromo-N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-3-methyl-1H-indole-2-carboxamide;

N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-6-propoxy-1H-indole-2-carboxamide;

N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-7-fluoro-1H-indole-2-carboxamide;

N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-7-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-6-fluoro-1H-indole-2-carboxamide;

N-[(2S)-1-[[[1S]-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-5-fluoro-1H-indole-2-carboxamide;
N-[(2S)-1-{[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]amino}-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-{[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]amino}-4-methyl-1-oxopentan-2-yl]-5-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-{[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]amino}-4-methyl-1-oxopentan-2-yl]-4,5-dimethoxy-1H-indole-2-carboxamide;

N-[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]-4-methyl-N²-{[(4-methyl-1,3-thiazol-5-yl)carbonyl]-L-leucinamide;}

N-[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]-N²-(ethoxycarbonyl)-L-leucinamide;

N-[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]-N²-(ethoxycarbonyl)-4-methyl-L-leucinamide;

N-[(2S)-1-{[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]amino}-5,5,5-trifluoro-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]-4-methyl-N²-{[2-(trifluoromethyl)-1,3-oxazol-4-yl]carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]-4-methyl-N²-{[3-(trifluoromethyl)-1,2-thiazol-4-yl]carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]-4-methyl-N²-{[3-(trifluoromethyl)-1,2-oxazol-4-yl]carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]-N²-{[2-(trifluoromethyl)-1,3-thiazol-4-yl]carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]-5,5,5-trifluoro-N²-{[2-(trifluoromethyl)-1,3-thiazol-4-yl]carbonyl]-L-norvalinamide;

(4S)-N-[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]-5,5,5-trifluoro-N²-{[2-(trifluoromethyl)-1,3-thiazol-4-yl]carbonyl]-L-leucinamide;

(4R)-N-[(1S)-1-cyano-2-{(3S)-2-oxopyrrolidin-3-yl}ethyl]-5,5,5-trifluoro-N²-{[2-(trifluoromethyl)-1,3-thiazol-4-yl]carbonyl]-L-leucinamide;
N-[(2S)-1-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-3-cyclopentyl-1-oxopropan-2-yl]-2-(trifluoromethyl)-1,3-thiazole-4-carboxamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[[5-(trifluoromethyl)-1,2-thiazol-4-yl]carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[[5-(trifluoromethyl)-1,2-oxazol-4-yl]carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[[2-(trifluoromethyl)-1,3-oxazol-5-yl]carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[[2-(trifluoromethyl)-1,3-thiazol-5-yl]carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-5,5-trifluoro-4-methyl-N^2-[[2-(trifluoromethyl)-1,3-thiazol-4-yl]carbonyl]-L-leucinamide;

N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-[(2S)-2-methyltetrahydrofuran-2-yl]carbonyl]-L-leucinamide;

N-[(2S,4R)-1-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-5,5-trifluoro-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-[(2S,4S)-1-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-5,5-trifluoro-4-methyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-5,5-trifluoro-4,4-dimethyl-1-oxopentan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-3-cyclopentyl-1-oxopropan-2-yl]-4-methoxy-1H-indole-2-carboxamide;

5,7-dichloro-N-[(2S)-1-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

5-chloro-N-[(2S)-1-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-3-ethyl-1H-indole-2-carboxamide;

N-[(2S)-1-((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-cyclohexyl-1H-indole-2-carboxamide;
5-chloro-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-3-methyl-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-3,5-dimethyl-1H-indole-2-carboxamide;

5-tert-butyl-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-5-(propan-2-yl)-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-7-(propan-2-yl)-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-3-ethyl-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-6-ethyl-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-5-ethyl-1H-indole-2-carboxamide;

4-butoxy-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-5-(trifluoromethoxy)-1H-indole-2-carboxamide;

N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-6-((diethylamino)-1H-indole-2-carboxamide;

4-bromo-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

5-bromo-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

6-bromo-N-[(2S)-1-(((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino)-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;
N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-3-methyl-1H-indole-2-carboxamide;

N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-6-propoxy-1H-indole-2-carboxamide;

N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-4-methyl-1H-indole-2-carboxamide;

N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-methyl-1H-indole-2-carboxamide;

N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-6-methyl-1H-indole-2-carboxamide;

N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-7-fluoro-1H-indole-2-carboxamide;

N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-7-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-6-fluoro-1H-indole-2-carboxamide;

N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-fluoro-1H-indole-2-carboxamide;

N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-6-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-5-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4,4-dimethyl-1-oxopentan-2-yl]-4,5-dimethoxy-1H-indole-2-carboxamide;

5-(butan-2-yl)-N-[(2S)-1-[((1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl)amino]-4-methyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;
N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-7-(propan-2-yl)-1H-indole-2-carboxamide;

N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-4-methyl-1H-indole-2-carboxamide;

N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-5-methyl-1H-indole-2-carboxamide;

N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-6-methyl-1H-indole-2-carboxamide;

N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4-methyl-1-oxopentan-2-yl]-6-methoxy-1H-indole-2-carboxamide;

5-(butan-2-yl)-N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]amino]-4,4-dimethyl-1-oxopentan-2-yl]-1H-indole-2-carboxamide;

N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(2R)-2-cyclohexyl-2-methoxyacetyl]-L-leucinamide;

N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(2R)-2-(cyclohexyloxy)propanoyl]-L-leucinamide;

N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]-4-methyl-N^2-(4,4,4-trifluoro-3-methylbutanoyl)-L-leucinamide;

N^2-[(trans-4-cyanocyclohexyl)carbonyl]-N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]-L-leucinamide;

N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(1-ethyl-4-methyl-1H-pyrazol-5-yl)carbonyl]-L-leucinamide;

N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-(cyclohexylcarbonyl)-L-leucinamide;

N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-(cyclohexyloxyacetyl)-L-leucinamide;

N-[(S)-1-cyano-2-[(S)-2-oxopyrrolidin-3-yl]ethyl]-N^2-[(3,3-difluorocyclobutyl)acetyl]-L-leucinamide;
N-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}-N\(^2\)-\{(propan-2-yloxy)acetyl\}-L-leucinamide;

N-\{(2S)-1-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}amino\}-4-methyl-1-oxopentan-2-yl]-3-methylimidazo[2,1-b][1,3]thiazole-2-carboxamide;

N-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}-N\(^2\)-\{(2R)-2-cyclohexyl-2-methoxyacetyl\}-4-methyl-L-leucinamide;

N-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}-N\(^2\)-\{(1-ethyl-4-methyl-1H-pyrazol-5-yl)carbonyl\}-4-methyl-L-leucinamide;

N\(^2\)-\{2-chloro-4-(methylsulfonyl)benzoyl\}-N-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}-L-leucinamide;

N-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}-N\(^2\)-\{(2,6-dichlorobenzoyl\})-L-leucinamide;

(1R,2S,5S)-3-\{N-( tert-butil)sulfonyl\}-3-methyl-L-valyl]-N-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-3-\{\{(3R)-1-benzyl-5-oxopyrrolidin-3-yl\}carbonyl\}-N-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}-6,6-dimethyl-3-\{\{(3R)-5-oxo-1-phenylpyrrolidin-3-yl\}carbonyl\}-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-3-\{\{(3R)-1-tert-butil-5-oxopyrrolidin-3-yl\}carbonyl\}-N-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}-6,6-dimethyl-3-\{3-methylimidazo[2,1-b][1,3]thiazol-2-yl\}carbonyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}-6,6-dimethyl-3-\{2-(trifluoromethyl)-1,3-thiazol-4-yl\}carbonyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

N-\{(2S)-1-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}amino\}-3-cyclopropyl-1-oxopropan-2-yl]-4-methoxy-1H-indole-2-carboxamide; and

N-\{(2S)-1-\{(1S)-1-cyano-2-\[(3S)-2-oxopyrrolidin-3-yl\]ethyl\}amino\}-3-cyclopropyl-1-oxopropan-2-yl]-1H-indole-2-carboxamide;
or a pharmaceutically acceptable salt thereof.

30. A compound of claim 1 selected from the group consisting of

N-[(2S)-1-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]amino\}-4,4-dimethyl-1-oxopentan-2-yl]-7-fluoro-4-methoxy-1H-indole-2-carboxamide;

N-[(2S)-1-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]amino\}-4-methyl-1-oxopentan-2-yl]-4-methoxy-7-\{(trifluoromethyl)\}-1H-indole-2-carboxamide;

(1R,2S,5S)-N-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl\}-6,6-dimethyl-3-[\{N-(trifluoroacetyl)\}-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S)-N-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl\}-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)\}-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

N-[(2S)-1-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl]amino\}-4-methyl-1-oxopentan-2-yl]-7-fluoro-4-methoxy-1H-indole-2-carboxamide;

(2S,4S)-N-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl\}-4-methyl-1-[\{N-(trifluoroacetyl)\}-L-valyl]piperidine-2-carboxamide;

(2S,4S)-N-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl\}-4-methyl-1-[3-methyl-N-(trifluoroacetyl)\}-L-valyl]piperidine-2-carboxamide;

(1R,2S,5S)-N-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl\}-3-\{[(2S)-2-cyclohexyl-2-\{(trifluoroacetyl)\}-amino\}-acetyl\}-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(2S,4S)-N-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl\}-4-methyl-1-[3-methyl-N-(trifluoromethyl)sulfonfonyl\}-L-valyl]piperidine-2-carboxamide;

3-methyl-N-(trifluoroacetyl)\}-L-valyl-(4R)-N-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl\}-4-methyl-4-(trifluoromethyl)\}-L-prolinamide; and

(2S)-N-\{[(1S)-1-cyano-2-[[3S]-2-oxopyrrolidin-3-yl]ethyl\}-4,4-dimethyl-1-[3-methyl-N-(trifluoroacetyl)\}-L-valyl]piperidine-2-carboxamide;

or a pharmaceutically acceptable salt thereof.

31. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.
32. The pharmaceutical composition of claim 31 wherein the composition is in the form of an intravenous, subcutaneous or oral dosage form.

33. The pharmaceutical composition of claim 32 wherein the composition is in an oral dosage form.

34. The pharmaceutical composition of claim 31 further comprising an additional therapeutic agent.

35. The pharmaceutical composition of claim 34 wherein the pharmaceutical composition further comprises one or more of dexamethasone, azithromycin, and remdesivir.

36. A method of treating a coronavirus infection in a patient, the method comprising administering a therapeutically effective amount of a compound of any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof to a patient in need thereof.

37. The method of claim 36 wherein the coronavirus infection is COVID-19.

38. A method of treating a coronavirus infection in a patient, the method comprising administering a pharmaceutical composition of any one of claims 31 to 35 to a patient in need thereof.

39. The method of claim 38 wherein the coronavirus infection is COVID-19.

40. A method of inhibiting or preventing SARS-CoV-2 viral replication comprising contacting the SARS-CoV-2 coronavirus 3CL protease with a therapeutically effective amount of a compound of any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof.

41. A method of inhibiting or preventing SARS-CoV-2 viral replication in a patient comprising administering to the patient in need of inhibition of or prevention of SARS-CoV-2 viral replication a therapeutically effective amount of a compound of any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof.

42. Use of a compound of any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof for the treatment of a coronavirus infection.

43. The use of claim 42 wherein the coronavirus infection is COVID-19.
44. Use of a compound of any one of claims 1 to 30 or a pharmaceutically acceptable salt thereof for the preparation of a medicament that is useful for the treatment of a coronavirus infection.

45. The use of claim 44 wherein the coronavirus infection is COVID-19.

46. A compound of Formula I'

```
\[
\begin{array}{c}
\text{O} \\
\text{R}^3 \\
\text{N} \\
\text{R}^1 \\
\text{R}^2 \\
\text{D} \\
\text{H} \\
\text{O} \\
\text{H} \\
\text{N} \\
\text{C} \\
\text{N} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\end{array}
\]
```

or a pharmaceutically acceptable salt thereof;

wherein

R at each occurrence is independently hydroxy or oxo;

p is 0, 1 or 2;

R₁ is selected from the group consisting of C₁-C₆ alkyl which is optionally substituted with a cyano or with one to five fluoro; C₂-C₆ alkynyl; and (C₃-C₆ cycloalkyl)-C₁-C₆ alkyl which is optionally substituted with one to two substituents selected from trifluoromethyl and C₁-C₆ alkyl or with one to five fluoro;

R₂ is hydrogen or R₂ and R¹ taken together with the nitrogen and carbon atoms to which they are attached are a pyrrolidine or piperidine ring which is optionally substituted with one to four R²a;

R²a at each occurrence is independently selected from the group consisting of fluoro, hydroxy, C₁-C₆ alkyl optionally substituted with one to three fluoro and C₁-C₆ alkoxy optionally substituted with one to three fluoro; or two R²a groups when attached to adjacent carbons and taken together with the carbons to which they are attached are a fused C₃-C₆ cycloalkyl which is optionally substituted with one to four R²b; or two R²a groups when attached to the same carbon and taken together with the carbon to which
they are attached are a spiro C₅-C₆ cycloalkyl which is optionally substituted with one to four R³;

R³ at each occurrence is independently selected from fluoro, hydroxy, C₁-C₆ alkyl optionally independently substituted with one to three fluoro or hydroxy and C₁-C₃ alkoxy optionally independently substituted with one to three fluoro or hydroxy;

R³ is selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, (C₁-C₆ alkoxy)-C₁-C₆ alkyl, C₂-C₆ alkynyl, C₂-C₆ alkynloxy, C₃-C₁₂ cycloalkyl optionally fused with a 5- to 6-membered heteroaryl or phenyl, (C₂-C₁₂ cycloalkyl)-C₁-C₆ alkyl, C₃-C₁₂ cycloalkoxy, (C₃-C₁₂ cycloalkoxy)-C₁-C₆ alkyl, 4- to 12-membered heterocycloalkyl optionally fused with a 5- to 6-membered heteroaryl or phenyl and wherein said heterocycloalkyl comprises one to four heteroatoms independently selected from N, O and S(O)ₓₜ, (4- to 12-membered heterocycloalkyl)-C₁-C₆ alkyl wherein said heterocycloalkyl moiety comprises one to four heteroatoms independently selected from N, O and S(O)ₓₜ, C₆-C₁₀ aryl optionally fused with a C₅-C₆ cycloalkyl or a 4- to 7-membered heterocycloalkyl, (C₆-C₁₀ aryl)-C₁-C₆ alkyl, 5- to 10-membered heteroaryl comprising one to five heteroatoms independently selected from N, O and S, which is optionally fused with a C₅-C₆ cycloalkyl; (5- to 10-membered heteroaryl)-C₁-C₆ alkyl wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S; (C₆-C₁₀ aryl)-(5- to 10-membered heteroaryl)- wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S, (5- to 10-membered heterocycloalkyl)-C₁-C₆ alkyl wherein the heteroaryl moiety comprises one to five heteroatoms independently selected from N, O and S; (C₆-C₁₀ aryl)-(5- to 6-membered heteroaryl)- wherein each heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S; (4- to 7-membered heterocycloalkyl)-(5- to 6-membered heteroaryl)- wherein the heterocycloalkyl moiety comprises one to three heteroatoms independently selected from N, O and S(O)ₓₜ and the heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S; (5- to 6-membered heteroaryl)-(4- to 7-membered heterocycloalkyl)- wherein the heterocycloalkyl moiety comprises one to three heteroatoms independently selected from N, O and S(O)ₓₜ and the heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S; wherein each R³ group is optionally substituted with one to five R⁴;

R⁴ at each occurrence is independently selected from the group consisting of oxo, halo, hydroxy, cyano, phenyl, benzyl, amino, (C₁-C₆ alkyl)amino optionally substituted with
one to five fluoro, di(C₁-C₅ alkyl)amino optionally substituted with one to ten fluoro, C₁-C₆ alkyl optionally substituted with one to five fluoro, C₁-C₆ alkoxy optionally substituted with one to five fluoro, C₁-C₃ alkoxy-C₁-C₃ alkyl optionally substituted with one to five fluoro, C₃-C₆ cycloalkyl optionally substituted with one to three fluoro or C₁-C₃ alkyl, C₁-C₆ alkyl-C(O)NH- optionally substituted with one to five fluoro, C₁-C₆ alkyl-OC(O)NH- optionally substituted with one to five fluoro or with one R⁵, C₁-C₆ alkyl-NHC(O)NH- optionally substituted with one to five fluoro or with one R⁵, C₁-C₆ alkyl-S(O)₂NH- optionally substituted with one to five fluoro or with one R⁵, C₁-C₆ alkyl-C(O)- optionally substituted with one to five fluoro or with one R⁵, C₁-C₆ alkyl-S(O)ₙ- optionally substituted with one to five fluoro or with one R⁵;

R⁵ is selected from phenyl, phenoxy, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkoxy, 4- to 7-membered heterocycloalkyl- wherein the heterocycloalkyl moiety comprises one to three heteroatoms independently selected from N, O and S(O)ₙ and 5- to 6-membered heteroaryl- wherein the heteroaryl moiety comprises one to four heteroatoms independently selected from N, O and S; wherein each R⁵ is optionally independently substituted with one to three halo, C₁-C₅ alkyl and C₁-C₃ alkoxy; and

n at each occurrence is independently selected from 0, 1 and 2.

47. A compound of claim 46 selected from the group consisting of

(2S,4R)-4-tert-buty1-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-1-[(N-[[trifluoromethyl]sulfonyl]-L-valyl)piperidine-2-carboxamide;

(2R,4S)-4-tert-buty1-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-1-[(N-[[trifluoromethyl]sulfonyl]-L-valyl)piperidine-2-carboxamide;

3-methyl-N-(trifluoroacetyl)-L-valyl-(4R)-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-4-(trifluoromethyl)-L-prolinamide;

(1R,2S,5S)-N-{(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl}-6,6-dimethyl-3-[3-methyl-N-(methylcarbamoyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

methyl [(2S)-1-[(1R,2S,5S)-2-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]carbamoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate;
(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3R)-5-hydroxy-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S,6R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6-(hydroxymethyl)-6-methyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;

(1R,2S,5S,6S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6-(hydroxymethyl)-6-methyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; and

N-(trifluoroacetyl)-L-valyl-(4R)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-4-(trifluoromethyl)-L-prolinamide;

or a pharmaceutically acceptable salt thereof.

48. A method of treating a coronavirus infection in a patient, the method comprising administering a therapeutically effective amount of a compound of any one of claims 46 to 47 or a pharmaceutically acceptable salt thereof to a patient in need thereof.

49. The method of claim 48 wherein the coronavirus infection is COVID-19.

50. The method of claim 48 wherein an additional therapeutic agent is administered and the additional therapeutic agent is selected from the group consisting of remdesivir, galidesivir, favilavir/avifavir, mulpipiravir, AT-527, AT-301, BLD-2860, favipiravir, camostat, SLV213, emtricitabine/tenofovir, clevudine, dalcatrapib, boceprevir, ABX464, dexamethasone, hydrocortisone, convalescent plasma, gelsolin (Rhu-p65N), regdanvimab (Regkriova), ravaluzumab (Ultomiris), VIR-7831/VIR-7832, BRL-196/BRL-198, COVI-AMG/COVI DROPS (STI-2020), bamlanivimab (LY-CoV555), mavrilmab, leronlimab (PRO140), AZD7442, lenzilumab, infliximab, adalimumab, JS 016, STI-1499 (COVI GUARD), lanadelumab (Takhyzo), canakinumab (Ilaris), gimsilumab, otlimab, casirivimab/imdevimab (REGN-Cov2), MK-7110 (CD24Fc/SACCOVID), heparin, apixaban, tocilizumab (Actemra), sarilumab (Kevzara), apilimod dimesylate, DNL758, PB1046, dapagliflozin, abivirntib, ATR-002, bemcentinib, acalabrutinib, losmapimod, famotidine, ritonavir, niclosamide and diminazene.
51. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 46 to 47 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

52. The compound (1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof.

53. A pharmaceutical composition comprising a therapeutically effective amount of (1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

54. A method of treating a coronavirus infection in a patient, the method comprising administering a therapeutically effective amount of (1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof.

55. The method of claim 55 wherein the coronavirus infection is COVID-19.

56. The method of claim 54 or 55 wherein (1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof is administered orally.

57. The method of claim 56 wherein 50 mg to 1500 mg of (1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof is administered each day.

58. The method of claim 57 wherein 380 mg of (1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof is administered three times a day.

59. The method of claim 57 wherein the (1R,2S,5S)-N-[(1S)-1-Cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-6,6-dimethyl-3-[3-methyl-N-(trifluoroacetyl)-L-valyl]-3-
azabicyclo[3.1.0]hexane-2-carboxamide; or a pharmaceutically acceptable salt thereof is administered as an oral suspension, capsule or tablet.

60. The method of claim 59 wherein a tablet is administered.
ABSTRACT OF THE INVENTION

The invention relates to compounds of Formula I’

wherein \( R, R^1, R^2, R^3 \) and \( p \) are as defined herein, pharmaceutical compositions comprising the compounds, methods of treating coronavirus infection such as COVID-19 in a patient by administering therapeutically effective amounts of the compounds, and methods of inhibiting or preventing replication of coronaviruses such as SARS-CoV-2 with the compounds.
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<tr>
<td><strong>First Named Inventor/Applicant Name:</strong> Dafydd Rhys Owen</td>
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**Payment information:**

- **Submitted with Payment:** yes
- **Payment Type:** DA
- **Payment was successfully received in RAM:** $1140
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### Information:

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National Stage of an International Application under 35 U.S.C. 371
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NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82A) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

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<tr>
<td>First Named Inventor</td>
<td>Dafydd Rhys Owen, et al.</td>
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<td>Title</td>
<td>Nitrile-Containing Antiviral Compounds</td>
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**SIGNATURE of Applicant or Patent Practitioner**

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<tr>
<th>Signature</th>
<th>John A. Wichtowski /</th>
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<tr>
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<td>01/29/2021</td>
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<tr>
<td>Name</td>
<td>John A. Wichtowski</td>
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NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

*Total of 1 pg of 82A forms are submitted.*

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

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Pfizer Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer’s title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer’s title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature: Lisa A. Samuels

Date (Optional): 

Name: Lisa A. Samuels

Title: Assistant General Counsel, Pfizer Inc.

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of 2 page of 609/C forms are submitted.

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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<td><strong>EFS ID:</strong> 41789128</td>
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<tr>
<td><strong>Application Number:</strong> 63143435</td>
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<tr>
<td><strong>International Application Number:</strong></td>
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<td><strong>Confirmation Number:</strong> 3679</td>
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<tr>
<td><strong>Title of Invention:</strong> Nitrile-Containing Antiviral Compounds</td>
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<tr>
<td><strong>First Named Inventor/Applicant Name:</strong> Dafydd Rhys Owen</td>
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| **Correspondence Address:** Pfizer Inc.  
**Attn:** Legal Patent Department, Chief IP Counsel  
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New York NY 10017  
US 212-733-2323  
PfizerPatentDocketing@pfizer.com |
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| **Receipt Date:** 29-JAN-2021 |
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