223002

FORM – 7A

THE PATENTS ACT, 1970

(39 OF 1970)

&

THE PATENTS RULES, 2003

REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT

(See section 25 (1) and rule 55)

We, **NATCO PHARMA LTD.**, an Indian Company at Natco House, Road No. 2, Banjara Hills, Hyderabad – 500 033, India hereby give representation by way of opposition to the grant of patent in respect of Patent Application No. **806/DELNP/2010** dated February 5, 2010 assigned to **BRISTOL-MYERS SQUIBB COMPANY** having office at Route 206 and Provice Line Road, Princeton, New Jersey 08543, U.S.A. It is published under section 11A in the Official Journal of Indian Patent Office dated July 30, 2010.

The impugned Patent Application is opposed on the following grounds:-

a. **U/S 25 (1) (e):** that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in section 25 (1) (b) or having regard to what was used in India before the priority date of the applicant's claim;

b. **U/S 25 (1) (f):** that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act;

c. **U/S 25 (1) (g):** that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;

Our address for service in India is

S. MAJUMDAR & CO., 5, Harish Mukherjee Road, Calcutta - 700 025, State of West Bengal. Phone: 0-33-4557484/4557485/4557486; Fax: 0-33-4557487/4557488. Email: cal@patentindia.com.

Dated this the 5th day of November, 2015

Of S. Majumdar & Co.
Opponent's Agent

To

The Controller of Patents
The Patent Office,
At Delhi

223915

BEFORE THE CONTROLLER OF PATENTS,
NEW DELHI

OPPOSITION UNDER SECTION 25(1) TO PATENT APPLICATION No. 806/DELNP/2010

Natco Pharma Ltd.

..... Opponent

-vs-

Bristol-Myers Squibb Company

.... Applicant

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BEFORE THE CONTROLLER OF PATENTS,
NEW DELHI

In the matter of section 25(1) of The Patents Act, 1970 *as amended by* The Patents (Amendment) Act 2005,

-And-

In the matter of The Patents Rules, 2003 as *amended by* The Patent (Amendment) Rules 2006

-And-

IN THE MATTER of Patents Application No. 806/DELNP/2010 dated February 5, 2010 (International Filing date July 31, 2008), assigned to Bristol-Myers Squibb Company having office at Route 206 and Provice Line Road, Princeton, New Jersey 08543, U.S.A

.... APPLICANT

-And-

IN THE MATTER of Opposition to the grant of a patent thereto NATCO PHARMA LTD., an Indian Company at Natco House, Road No. 2, Banjara Hills, Hyderabad – 500 033.

...OPPONENT

REPRESENTATION UNDER SECTION 25(1)

We, *NATCO PHARMA LTD.*, an Indian Company at Natco House, Road No. 2, Banjara Hills, Hyderabad – 500 033, (hereinafter called 'Opponent') make the following representation under Section 25(1) of the Act in opposing the grant of patent on the application indicated in the cause title.

1 Locus standi

Locus standi is not a condition precedent for an opposition under Section 25(1).

2 Grounds of opposition

The application is opposed on the following grounds:

a. Section 25(1) (e)-Obviousness/lack of inventive step

that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in Section 25(1) (b) or having regard to what was used in India before the priority date of the Applicant's claim.

b. Section 25(1) (f)-Not an invention

that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act;

c. Section 25(1) (g) - Insufficiency

that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;

3 Analysis of the Applicant's specification

3.1 Patent Application No: **806/DELNP/2010** entitled "CRYSTALLINE FORM OF METHYL ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-

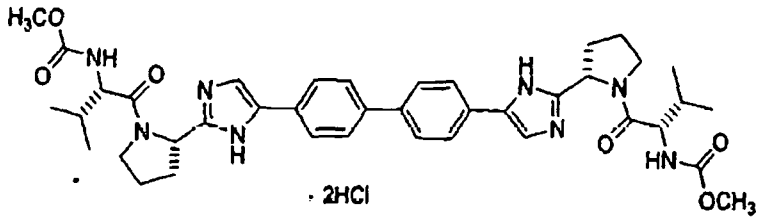
((METHOXYCARBONYL)AMINO)-3-METHYLBUTANOYL)-2-PYRROLIDINYL)-1H-IMIDAZOL-5-YL)-4-BIPHENYLYL)-1H-IMIDAZOL-2-YL)-1-PYRROLIDINYL)CARBONYL)-2-METHYLPROPYL)CARBAMATE DIHYDROCHLORIDE SALT" dated February 5, 2010. It is published under section 11A in the Official Journal of Indian Patent Office dated July 30, 2010. There is no notification of grant of patent on this application and it is presumed that a patent has not yet been granted and thus the present pre-grant representation made by the Opponent. The impugned patent application claims a priority of USA dated August 8, 2007, priority Document No: 60/954,592. The instant patent application has been nationalized from International Application No: PCT/US2008/071734 dated July 31, 2008; International Publication No: WO 2009/020828.

3.2 The impugned patent application relates to a crystalline form of methyl ((1S)-1-(((2S)-2-(5-(4,-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride salt. The impugned patent application also generally relates to a pharmaceutical composition comprising a crystalline form, as well of methods of using a crystalline form in the treatment of Hepatitis C virus (HCV) and methods for obtaining such crystalline form.

3.3 The alleged problem which the impugned patent application discloses i.e. *"The compound methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate is useful for the treatment of HCV infection. Due to the difficulty in crystallizing this compound, formation of pure product has not been reproducible."* (paragraph bridging pages 1 and 2)

3.4 The alleged solution disclosed in the impugned patent application i.e., *"It has been found that the dihydrochloride salt, represented by formula (I) and herein referred to as Compound (I), can be repeatedly crystallized into one particular polymorph, herein referred to as Form N-2, that offers high aqueous solubility and excellent purification capacity."* (page 2)

3.5 The impugned patent application disclosure provides Form N-2 of



characterized by one or more of the following:

a) a unit cell with parameters substantially equal to the following:

Cell dimensions: a = 7.5680 Å

b= 9.5848 Å

c = 16.2864 Å

α = 74.132 degrees

ß = 84.132 degrees

γ = 70.646 degrees

Space group P1

Molecules/unit cell 1

wherein measurement of said crystalline form is at a temperature between about 20 °C to about 25 °C;

b) characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 + 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1,22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 20 calibrated with a NIST other suitable standard; and/or c) a melt with decomposition endotherm with onset typically in the range of 225-245 °C.

3.6 By virtue of the chemical structure of the compound of the impugned patent application it is bound to form the dihydrochloride salt.

3.7 It is pertinent to note that the impugned patent application while describing the method of preparation of the N-2 form of Compound (I) admittedly sets forth *'General Preparation of Crystalline Materials'* from pages 9 to 11, with pages 11 to 12 describing various techniques to ***characterize*** the Form N-2 of Compound (I).

4. **Applicant's Claims.**

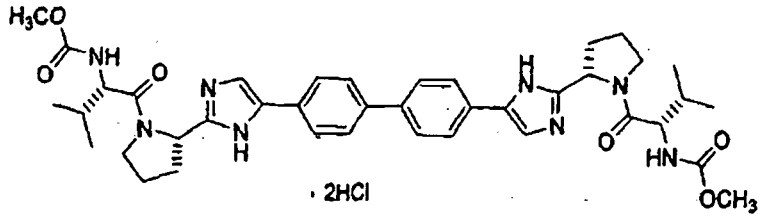
4.1 The impugned Patent Application no. 806/DELNP/2010 contains a statement of 20 claims, of which 10 are independent claims.

4.2 The said 20 claims have been amended in Reply dated May 27, 2015 to various objections the First Examination Report October 29, 2014.

4.3 Presently there are 12 claims of which claim 1 is an independent claim.

4.4 The said claim 1 is reproduced below for ready reference:

"Form N-2 of



characterized by one or more of the following:

a) a unit cell with parameters substantially equal to the following:

Cell dimensions: a = 7.5680 Å

b= 9.5848 Å

c = 16.2864 Å

α = 74.132 degrees

ß = 84.132 degrees

γ = 70.646 degrees

Space group P1

Molecules/unit cell 1

wherein measurement of said crystalline form is at a temperature between about 20 °C to about 25 °C;

b) characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 + 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1,22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 20 calibrated with a NIST other suitable standard; and/or

c) a melt with decomposition endotherm with onset typically in the range of 225-245 °C."

4.5 The complete specification of impugned application along with the original as-filed claims as downloaded from IPAIRS is annexed hereto as "**Annexure A**" for ready reference. Also annexed hereto is a copy of the amended claims referred to hereinabove as downloaded from IPAIRS as **"Annexure B"**.

4.6 In the event the claims are amended and the present representation does not automatically address the subject matter of the amended claims, the Opponent craves leave to file a fresh or supplementary representation, to address the amendments.

4.7 The Opponent has examined and carefully considered the complete specification of the application under opposition and wishes to draw the attention of the Ld. Controller to the most salient features therein under the grounds of opposition discussed hereinafter.

4.8 Having regard to the aforesaid discussions in relation to the alleged invention of the Applicant, the Opponent now proceeds to deal with the various grounds of opposition.

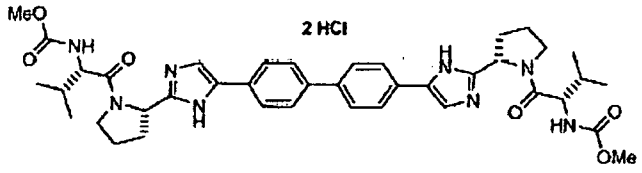
5 **Preliminary Objections:**

5.1 The Opponent at the very outset states that the subject-matter of the claims of the impugned patent application already forms part of the subject-matter of an earlier application filed by the same Applicant for which the later of the two priorities of the earlier application is dated on the same date as the priority for the impugned patent application. The said earlier application is Patent Application No: 853/DELNP/2009 entitled "Hepatitis C Virus Inhibitors" dated February 5, 2009 against which the Opponent herein has filed a pre-grant opposition. The said patent application is published under section 11A in the Official Journal of Indian Patent Office dated June 12, 2009. The said patent application claims a priority of US 60/836,996 dated August 11, 2006, priority Document No: US 11/835,462 dated August 8, 2007 and has been nationalized from International Application No: PCT/US2007/075544 dated August 9, 2007; International Publication No: WO 2008/021927. A copy of the aforesaid Patent Application 853/DELNP/2009 is annexed herewith and marked **'Annexure C'**.

5.2 The Opponent states that the alleged invention of the impugned patent application forms the subject matter of the said earlier patent application 853/DELNP/2009

although for reasons best known to the Applicant it has not specifically claimed the said Form N-2 of Compound (I) of the impugned patent application i.e.

"Example 24-23



methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-l-((2S)-2-((methoxycarbonyl)amino)-3- methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)- 1 -pyrrolidinyl) carbonyl) -2-methylpropyl) carbamate

A 50 mL flask equipped with a stir bar was sequentially charged with 2.5 mL acetonitrile, 0.344 g (2.25 mmol, 2.5 equiv) hydroxy benzotriazole hydrate, 0.374 g (2.13 mmol, 2.4 equiv) N-(methoxycarbonyl)-L-valine, 0.400 g (2.09 mmol, 2.4 equiv) 1 -(3 -dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride and an additional 2.5 mL acetonitrile. The resulting solution was agitated at 20 0C for 1 hour and charged with 0.501 g (0.88 mmol, 1 equiv) Example A-le-4. The slurry was cooled to about 0 0C and 0.45 g (3.48 mmol, 4 equiv) diisopropylethylamine was added over 30 minutes while maintaining a temperature below 10 °C. The solution was slowly heated to 15 °C over 3 hours and held at 15 0C for 16 hours. The temperature was increased to 20 °C and stirred for 3.25 hours. The resulting solution was charged with 3.3 g of 13 wt% aqueous NaCl and heated to 50 °C for 1 hour. After cooling to 20 °C, 2.5 mL of isopropyl acetate was added. The rich organic phase was washed with 2 x 6.9 g of a 0.5 N NaOH solution containing 13 wt% NaCl followed by 3.3 g of 13 wt% aqueous NaCl. The mixture was then solvent exchanged into isopropyl acetate by vacuum distillation to a target volume of 10 mL. The resulting hazy solution was cooled to 20 0C and filtered through a 0.45 μm filter. The clear solution was then solvent exchanged into ethanol by vacuum distillation with a target volume of 3 mL. 1.67 mL (2.02 mmol, 2.3 equiv) of 1.21 M HCl in ethanol was added. The mixture was then stirred at

25 °C for 15 hours. The resulting slurry was filtered and the wet cake was washed with 2.5 mL of 2: 1 acetone:ethanol. The solids were dried in a vacuum oven at 50 0C to give 0.550 g (0.68 mmol, 77 %) of the desired product.

Recrystallization of Example 24-23

A solution of Example 24-23 prepared above was prepared by dissolving 0.520 g of the above product in 3.65 mL methanol. The solution was then charged with 0.078 g of type 3 Cuno Zeta loose carbon and allowed to stir for 0.25 hours. The mixture was then filtered and washed with 6 ml of methanol. The product rich solution was concentrated down to 2.6 mL by vacuum distillation. 7.8 mL acetone was added and allowed to stir at 25 0C for 15 h. The solids were filtered, washed with 2.5 mL 2: 1 acetone:ethanol and dried in a vacuum oven at 70 0C to give 0.406 g (57.0%) of the desired product as white crystals: 1H NMR (400 MHz, OMSO-d6, 80 0C): 8.02 (d, J=8.34 Hz, 4 H), 7.97 (s, 2 H), 7.86 (d, J=8.34 Hz, 4 H), 6.75 (s, 2 H), 5.27 (t, J=6.44 Hz, 2 H), 4.17 (t, J=6.95 Hz, 2 H), 3.97 - 4.11 (m, 2 H), 3.74 - 3.90 (m, 2 H), 3.57 (s, 6 H), 2.32 - 2.46 (m, 2 H), 2.09 - 2.31 (m, 6 H), 1.91 - 2.07 (m, 2 H), 0.88 (d, J=6.57 Hz, 6 H), 0.79 (d, J=6.32 Hz, 6 H); 13C NMR (75 MHz, DMSO-d6): δ 170.9, 156.9, 149.3, 139.1, 131.7, 127.1, 126.5, 125.9, 115.0, 57.9, 52.8, 51.5, 47.2, 31.1, 28.9, 24.9, 19.6, 17.7; IR (neat, cm^{-1}): 3385, 2971, 2873, 2669, 1731, 1650. Anal. Calcd for $C_{40}H_{52}N_8O_6Cl_2$: C, 59.18; H, 6.45; N, 13.80; Cl, 8.73. Found C, 59.98; H, 6.80; N, 13.68; Cl, 8.77. mp 267 °C (decomposed). Characteristic diffraction peak positions (degrees 2θ ± 0.1) @ RT, ***based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard are as follows: 10.3, 12.4, 12.8, 13.3, 13.6, 15.5, 20.3, 21.2, 22.4, 22.7, 23.7."*** (Pages 156 to 158)

5.3 The Opponent states that the Section 10(4) of the Patents Act provides that,

"Every complete specification shall –

..... (a) fully and particularly describe ***the invention*** *and its operation or use and the method by which it is to be performed;*

(c) end with a claim or claims defining the scope of ***the invention*** *for which protection is claimed:..."*

While Section 10(5) provides that, *"The claims or claims of a complete specification shall relate to a* ***single invention****, or to a group of inventions linked so as to form a single inventive concept, shall be clear and succinct and shall be fairly based on the matter disclosed in the specification..."*

5.4 The Opponent now draws the attention of the Ld. Controller to section 16 of the Patents Act which provides that, *"A person who has made an application for a patent under this Act may, at any time before the grant of a patent, if he so desires, or with a view to remedy the objection raised by the Controller on the ground that the* ***claims of the complete specification relate to more than one invention****, file a* ***further application*** *in respect of an invention* ***disclosed in the provisional or complete specification already filed in respect of the first-mentioned application****.*

(2) The further application under sub-section (1) shall be accompanied by a complete specification, ***but such complete specification shall not include any matter not in substance disclosed in the complete specification filed in pursuance of the first-mentioned application****..."*

5.5 Furthermore, section 59 also prohibits inclusion in claims by way of amendment such that *"any claim of the specification as amended would not fall wholly within the scope of a claim of the specification before the amendment..."*

5.6 The Opponent thus states that the Applicant has for whatever reason whether mistakenly or otherwise, not claimed the said Form N-2 of Compound (I) in the 853/DELNP/2009 patent application although disclosed in it. Now that it has not claimed the said compound disclosed in 853/DELNP/2009, it would be *estopped* by Statute from filing a claim in that regard. Thus, not having filed a claim for the said compound in the 853/DELNP/2009 patent application, the same Applicant herein cannot be permitted to take an indirect route to secure what it cannot do directly by including the details of the same compound in another provisional application by design in order to seek extension of term of monopoly on an alleged invention. The Opponent states that permitting such an indirect attempt by a person to secure what it directly cannot be permitted to do would strike at the very root of the Patents Act.

5.7 The Opponent states that a serious view ought to be taken of the attempt of the Applicant herein to knowingly secure a patent in contravention of the provisions of the Act, with a deliberate motive of securing a patent term extension. The Opponent states that such deliberate attempt is clear from the fact that not even a mention of any co-pending application has been made in the impugned patent application.

5.8 The Opponent states that the Ld. Controller is empowered by the Patents Act to thwart any such attempt by the Applicant. Section 12 of the Patents Act mandates that, *"....the application and specification and other documents related thereto shall be referred at the earliest by the Controller to an examiner for making a report to him in respect of the following matters, namely:-*

(a) whether the application and the specification and other documents relating thereto are in accordance with the requirements of this Act and of any rules made thereunder;

(b) whether there is any lawful ground of objection to the grant of the patent under this Act in pursuance of the application;..."

Section 15 provides that,

"Power of Controller to refuse or require amended applications, etc., in certain case
Where the Controller is satisfied that the application or any specification or any other document filed in pursuance thereof does not comply with the requirements of this Act or of any rules made thereunder, the Controller may refuse the application or may require the application, specification or the other documents, as the case may be, to be amended to his satisfaction before he proceeds with the application and refuse the application on failure to do so."

5.9 The Opponent states that the Applicant ought to be made answerable to such a serious objection and that the Ld. Controller being fully empowered can raise the said objection with the Applicant. The Opponent states that the present opposition being a pre-grant opposition and in aid of Examination, the said objection has been brought to the attention of the Ld. Controller.

5.10 The Opponent states that in view of the same the impugned patent application ought to be refused at the very threshold.

5.11 Without prejudice to the said preliminary objection, the Opponent shall hereinafter deal with the grounds of the instant opposition to the impugned patent application.

6 <u>Prior arts (published prior to the priority dated of the impugned patent application) relied on in the present opposition representation</u>

- **Exhibit D1: WO2004005264** entitled "Imidazole compounds and human cellular proteins casein kinase I alpha, delta and epsilon as targets for medical intervention against hepatitis C virus infection" published on January 15, 2004; annexed herewith as Exhibit D1 and referred as 'D1'.
- **Exhibit D2: EP0480714A2** entitled "HIV protease inhibitors having symmetrical structure" published on April 15, 1992; annexed herewith as Exhibit D2 and referred as D2.
- **Exhibit D3**: Article entitled: "Structure of the Zinc-Binding Domain of an Essential Replicase Component of Hepatitis C Virus Reveals a Novel Fold" by

Tellinghuisen et al published in **Nature** in **May 2005;** annexed herewith as Exhibit D3 and referred as D3.

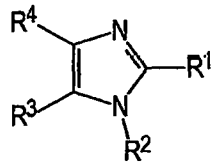
- **Exhibit D4:** Article entitled **"Synthesis of bridged aromatic 4(S), 4' (S) diimidazoldes"** by Herman Schubert et al **published in 1963** in Journal of Practical Chemistry, 4 Series, Volume 22; annexed herewith along with English translation as Exhibit D4 and herein after referred as D4.
- **Exhibit D5: WO2003099274** entitled "Hepatitis C Virus inhibitors" published on December 4, 2003; annexed herewith as Exhibit D5 and herein after referred as D5.
- **Exhibit D6:** '*Pharmaceutical Salts; Stephen M. Berge et al.; Vol. 66, No. 1, January 1977';* annexed herewith as Exhibit D6 and herein after referred as D6.
- **Exhibit D7:** *'Review - Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations; Stephen Byrn et al.; Pharmaceutical Research, Vol. 12, No. 7, 1995';* annexed herewith as Exhibit D7 and herein after referred as D7.
- **Exhibit D8:** Copies of relevant pages from *'Remington: The Science and Practice of Pharmacy 20th Edition 2000; Volume 1; Lippincott Williams & Wilkins; Chapter 36 – Separation';* annexed herewith as Exhibit D8 and herein after referred as D8.

7 OBVIOUSNESS AND LACK OF INVENTIVE STEP [Section 25(1) (e)]:

7.1 **Exhibit D1: WO2004005264** entitled "Imidazole compounds and human cellular proteins casein kinase I apha, delta and epsilon as targets for medical intervention against hepatitis C virus infection" published on January 15, 2004. **(Annexed hereto as Exhibit D1; hereinafter referred to as D1).** D1 teaches novel compounds for prophylaxis and/or treatment of Hepatitis C Virus infection and disease caused by such infections.

7.2 The Opponent states that D1 relates to imidazole molecules specifically used against hepatitis C virus and those which are drawn to the structures that encompass the similar sequence of heterocycles as that of the compounds of the impugned application. D1 discloses imidazole compounds that are useful against

hepatitis C viral infections and these compounds act by inhibition of NS5A Protein and also discloses the use of the compounds in other diseases associated therewith. The general structure as disclosed in D1, disclosed at pages 4, is represented here below for ready reference:

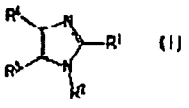


(I)

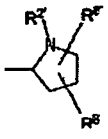
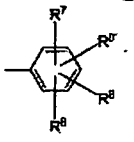
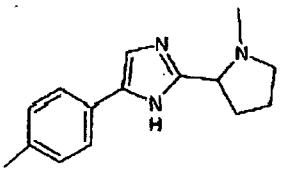
8

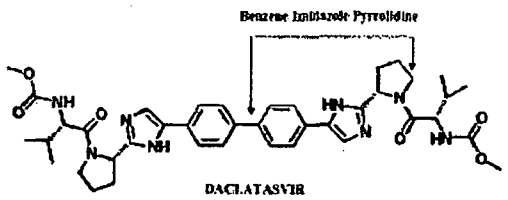
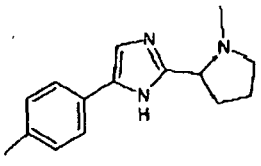
9 **Figure 3**

7.3 By substituting various structural nodes of figure 3 of D1, it is possible to arrive at ***one phenyl ring connected to an imidazole ring which is further connected to a pyrrolidine nucleus,*** which is the basic structural skeleton of the compounds of the impugned application. This can be shown by selecting below substituents in the general structure disclosed by D1, represented here below for ready reference:

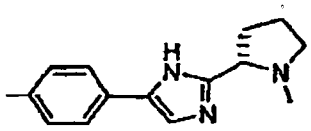


(I)

R^1	R^2	R^3	R^4
	H		H
			
Wherein R^6, R^7, R^8 and $R^{8'}$ are H.			

(Present Application)	D1 (Prior Art)
 DACLATASVIR	 Benzene Imidazole Pyrrolidine

7.4 Since the person skilled in the art could derive from D1 that the class of phenyl- imidazoles-pyrrolidine with additional terminal heterocycles are suitable as agents to treat HCV. In other words the following fraction of compound of formula I of the impugned application is taught in the prior art and known to have Hepatitis C virus inhibiting properties.



7.5 Further Exhibit D1 discloses 'phenyl- imidazole-pyrrolidine' moiety for HCV replication inhibition in particular NS5A inhibitor. Thus phenyl-imidazole-pyrrolidine containing compounds have been known to exhibit NS5A inhibitory activity.

7.6 The compound of formula I of the impugned application is 'symmetric molecule' (dimer) such that one-half of the left structure is equal to other half in the right.

7.7 The proposed compound families of the impugned application are obvious solution to the problem of providing further HCV agents.

7.8 The Opponent states that structures of D1 and the compound of the impugned patent have similarities in the basic 'phenyl imidazole pyrrolidine ring. The structural similarities in the markush structure of D1 and claim 1 of the impugned invention as highlighted above. Therefore claim 1 and its dependent claims of the impugned application are obvious in light of D1.

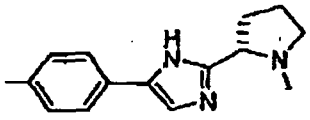
7.9 **Exhibit D2: EP0480714 A2 entitled "HIV protease inhibitors having symmetrical structure" published on April 15, 1992; hereinafter referred as D2.**

7.10 D2 essentially teaches compounds that have symmetrical structure as protease inhibitors. Compounds of the form: **J-B-B-G-B-B-J** where in G is dipeptide isostere, B is amino acid or analog and J a small terminal group. These compounds are useful for inhibition of HIV protease and in treatment of AIDS.

7.11 Teachings of D2 are significant as it teaches the "symmetric" molecule. HIV protease *is a dimer with a 2-fold axis of symmetry*, a property unique to

retroviral proteases compared to proteases of mammalian origin (page 2, line 25-26 of D2). Further it is taught that the symmetrical nature of compounds of D2 offers the possibility of overcoming the high mutation rate of HIV virus, for as HIV mutates through its inaccurate reverse transcriptase, the viral protease must retain the ability to cleave substrate with a 2 fold axis.

7.12 The Opponent states that symmetric molecule *per se* has been known for inhibitors of dimer with two-fold axis of symmetry. D1 teaches:



for inhibition of HCV replication and D2 teaches use of symmetric molecule for a dimer protease inhibitor. D1 read with D2 clearly teaches compound of formula I of the impugned application when a 'symmetric molecule of phenyl imidazole pyrrolidine ring is prepared'.

7.13 With the structural and functional similarities therefore there is clear motivation for the person skilled in the art to derive the structure in the compound claimed in impugned patent application from the teachings of D1 combined with D2.

7.14 **Exhibit D3: Article entitled "Structure of the Zinc-Binding Domain of an Essential Replicase Component of Hepatitis C Virus Reveals a Novel Fold" by Tellinghuisen et al published in 'Nature' in May 2005; herein after referred as D3.**

7.15 The abstract of D3 teaches that RNA replication machine of HDV is a multi-subunit membrane-associated complex. The non-structural protein NS5A is an active HCV replicase component, a pivotal regulator of replication and modulator of cellular processes spanning from innate immunity to dysregulated cell growth NS5A is a large phosphoprotein (56-58 kDa) with an amphipathic alpha-helix at its N-terminus that promotes membrane association. The structure of domain I (amino acids 36-198) as taught in D3 reveals two identical monomers per asymmetric unit packed as dimer via contacts near the N-terminal ends of the molecules (page 1 of D3).

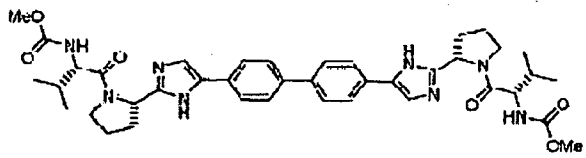
7.16 The Opponent states that D3 essentially teaches structure of replicase component of Hepatitis C virus. D3 teaches that structure of domain I (amino acids 36-198) reveals two identical monomers per asymmetric unit packed as a dimer. Further on page 2 of D3, third paragraph, analysis of molecular surface

of domain I of NS5A is taught. The teaching that flows from D3 is that NS5A protein is a dimer. Figure 4 discloses NS5A domain I dimer with potential interaction surfaces. On page 4, first line of D3 it is taught that "*the crystal structure of domain I region of NS5A provides the first molecular view of this important protein, and perhaps a new class of viral replicase proteins. The high-resolution view of domain I has practical application for anti-viral drug design and provides a rational framework for experimentally addressing NS5A function in the replicase and in the regulation of cellular processes.*"

7.17 The Opponent states that NS5A protein is a dimer and that a high resolution view could aid in anti-viral drug design. D2 teaches HIV protease inhibitors with symmetric molecules to address dimer with a 2-fold axis of symmetry. On similar lines when D3 teaches NS5A protein as a dimer and the 'portion' of phenyl-imidazole-pyrrolidine structure is taught, an avenue is available for a person skilled in the art to prepare symmetric molecule as inhibitor of NS5A dimer.

7.18 As is known from D3, that NS5A protein is a dimer and would eventually require a symmetric molecule. D2 teaches that symmetric molecule is beneficial for inhibition of HIV protease which is a dimer.

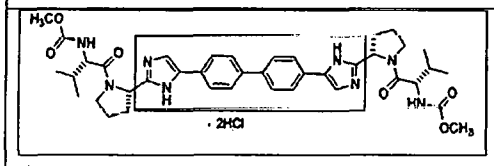
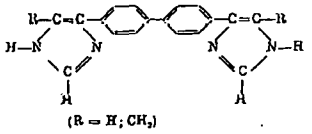
7.19 The Opponent states that the structural similarity suggests that D3 read along with D1 and D2 would motivate the person skilled in the art to derive the base



form i.e. of the compound claimed in the impugned patent application from the teachings of the prior art.

7.20 **Exhibit D4: Article entitled "Synthesis of bridged aromatic 4(S), 4'(S) diimidazoldes" by Herman Schubert et al published in 1963 in Journal of Practical Chemistry, 4 Series, Volume 22; annexed herewith along with English translation as Exhibit D4 and herein after referred as D4.**

7.21 The teachings of the said prior art is set out below with one of the compounds of the impugned application. D4 teaches bi-phenyl imidazole structure as mentioned below.

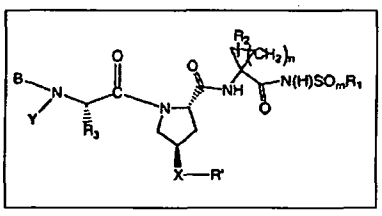
Claimed compound in the impugned application	D4
	

7.22 From the aforesaid it is known that biphenyl imidazole containing symmetric compounds were known.

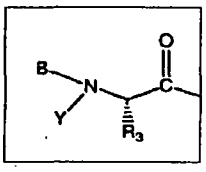
7.23 The Opponent state that the markush structures of D4 and the impugned patent application have similarities in the basic biphenyl imidazole ring and the different points of attachments of the substitucnts around the same. There are structural and functional similarities in both.

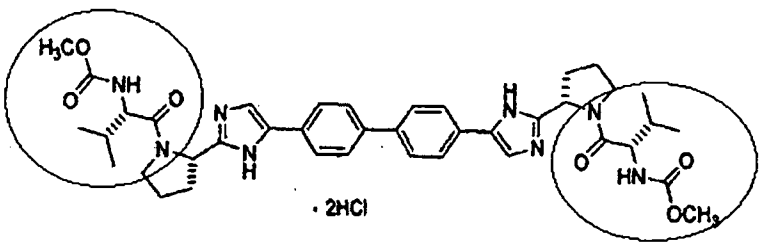
7.24 **Exhibit D5: WO2003099274 entitled "Hepatitis C Virus" published on December 4, 2003; herein after referred as D5.**

7.25 D5 discloses hepatitis C virus inhibitors of compound of formula I



7.26 The compounds taught in D5 are HCV inhibitors.

7.27 The Opponent states that  attached to compound of formula I of D5, when B is H; Y is C1-C6 alkyl; R3 is C1-C8 alkyl from substitutions mentioned on page 3 of the D5 teaches alkyl glycine component attached to pyrrolidine of the compound (*reproduced below*) of the impugned application.



7.28 It is clear that the alkyl glycine component is taught in D5.

7.29 The Opponent states that D1 teaches moiety for HCV replication inhibition in particular NS5A inhibitor; D2 teaches molecule with symmetrical structure; D3 teaches the NS5A protein to be a dimer. Further D4 teaches biphenyl-imidazole containing symmetric compounds and D5 teaches alkyl glycine attached to the pryrrolidine ring of compounds disclosed therein.

7.30 The Opponent state that a person skilled in the art is not a dullard and therefore equipped with the teachings of D1 to D3 and looking for alternatives would try and combine the substituents from these prior art documents and try to develop a compound with reasonable expectation of success. In the present case the documents in combination provide enough direction (*spring-board*) to combine the same and look for the activities. In any event both D1 and D2 refer to HCV inhibitory activity likewise the impugned patent application. Thus looking for alternate compounds and combining the structure of the prior arts and verify the feasibility of arriving at a compound or its effects does not involve inventive faculty. The Opponent states that since the substituent are added separately there is clear chance of tweaking the point of attachment during preparation and look for the effects. Thus a person skilled in the art looking for alternate compounds from those of the cited art is motivated to alter the point of attachment of the substituent and experiment further. It is already known from D5 that the substituent 'alkyl glycine component' are workable for Hepatitis C virus inhibitors so a person skilled in the art would try and change the point of attachment of the same with reasonable expectation of success. Further from D1 and D2/D3 there is clear teaching that each of the changes in position of the substituent is workable for similar purpose.

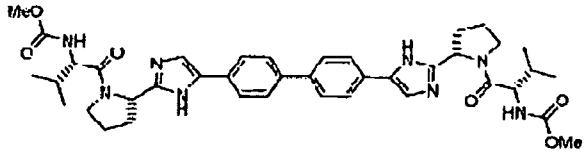
7.31 The Opponent further states that once a compound has been made, preparing various salts of it and checking for polymorphs is something done in the normal course of development.

7.32 In this regards, the Opponent relies on the publication '*Pharmaceutical Salts; Stephen M. Berge et al.; Vol. 66, No. 1, January 1977*' - **Exhibit D6** hereinafter referred to as D6. D6 discloses on page 1 that, *"The chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form, choosing appropriate salt...."*

7.33 D6 further discloses on page 5 that, *"The salt form is known to influence a number of physicochemical properties of the parent compound including dissolution rate, solubility, stability, and hygroscopicity. These properties, in turn, affect the availability and formulation characteristics of the drug. Consequently, the pharmaceutical industry has systematically engaged in extensive preformulation studies of the physicochemical properties of each new drug entity to determine the most suitable form for drug formulation..... ."*

7.34 The said publication D6 also discloses on page 2 that, *"The relative frequency with which each salt type has been used is calculated as a percentage, based on the total number of anionic or cationic salts in use through 1974. Because of simple availability and physiological reasons, the monoprotic hydrochlorides have been by far the most frequent choice of the available anionic salt-forming radicals... For similar reasons, sodium has been the most predominant cation...."*

7.35 The compound i.e.



has two salt forming groups and thus dihydrochloride will be formed.

7.36 The Opponent now relies on a *'Review - Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations; Stephen Byrn et al.; Pharmaceutical Research, Vol. 12, No. 7, 1995'* which is annexed herewith and marked ***'Exhibit D7'*** herein after referred to as D7.

7.37 The said document discloses that identifying new polymorphs is part of an ongoing strategy i.e.,

"Interest in the subject of pharmaceutical solids stems in part from the Food and Drug Administration's (FDA's) drug substance guideline that states "appropriate" analytical procedures should be used to detect polymorphic, hydrated, or amorphous forms of the drug substance. These guidelines suggest the importance of controlling the crystal from of the drug substance. The guideline also states that it is the Applicant's responsibility to control the

crystal form of the drug substance and, if bioavailability is affected, to demonstrate the suitability of the control methods.

Thus, while it is clear that the New Drug Application (NDA) should contain information on solid state properties, particularly when bioavailability is an issue, the Applicant may be unsure about how to scientifically approach the gathering of information and perhaps what kind of information is needed. This review is intended to provide a strategic approach to remove much of this uncertainty by presenting concepts and ideas in the form of flow charts rather than a set of guidelines or regulations. This is especially important because each individual compound has its own peculiarities which require flexibility in approach. The studies proposed herein are part of the Investigational New Drug (IND) process.

Solid drug substances display a wide and largely unpredictable variety of solid state properties. Nevertheless, application of basic physicochemical principles combined with appropriate analytical methodology can provide a strategy for scientific and regulatory decisions related to solid state behavior in the majority of cases. By addressing fundamental questions about solid state behavior at an early stage of drug development, both the Applicant and the FDA are in a better position to assess the possible effects of any variations in the solid state properties of the drug substance. The resulting early interaction of the parties with regard to this area would not only tend to ensure uniformity of the materials used throughout the clinical trials but also fully resolve solid state issues before the critical stages of drug development. A further benefit of these scientific studies is the development of a meaningful set of solid state specifications which critically describe the solid form of the drug substance. These specifications would thus also facilitate the approval of a change in supplier or chemical process." (Columns 1 to 2 on page 945)

7.38 The document (D7) further discloses decisions trees which provide the approach to be taken for identifying solid state forms such as polymorphs, etc.,

"We have chosen to present this approach in the form of a series of decision trees, or flow charts (algorithms), one for each of the most common solid state forms. The charts are accompanied by examples from the literature

representing the kind of data that would be useful in supporting the various decisions.

Decision trees provide conceptual frameworks for understanding how the justification for different crystal forms might be presented in the drug application. Industry may wish to use these decision trees as a strategic tool to organize the gathering of information early in the drug development process. Put another way, these decision trees provide a thought process that will lead to development of the most appropriate analytical controls. One should also note that it is the responsibility of the industry to select the appropriate test or tests to identify the phase of the solid and determine its relevant pharmaceutical properties. This approach is superior to simply performing a broad range of tests without regard to their relevance.

We should point out that, form a regulatory standpoint, if a company can establish a specification/test to ensure production of a well defined solid form of the drug substance, then it is not necessary to do all of the physical/chemical testing outlined in the decision trees. From a scientific standpoint, however, such an approach is risky since new forms may appear unpredictably during various stages of the development process. The appearance of these new form usually slows the drug approval process and makes planning difficult."(Columns 2 on page 945 and column 1 on page 946)

7.39 The document (D7) reiterates that it is advisable to investigate the drug substance for the existence of polymorphs and hydrates since these may be encountered at any stage of the drug manufacturing process or upon storage of the drug substance or dosage form.

7.40 The said document provides the strategy which needs to be adopted to identify polymorphs

"A. Formation of Polymorphs—Have Polymorphs been Discovered?

The first step in the polymorphs decision tree is to crystallize the substance form a number of different solvents in order to attempt to answer the question: Are polymorphs possible? ***Solvents should include those used in the final crystallization steps and those used during formulation and processing and may also include water, methanol, ethanol, propanol, isopropanol, acetone, acetone, acetonitrile, ethyl acetate, hexance and mixtures if appropriate.*** *New crystal forms can often be obtained by cooling hot saturated solutions or*

partly evaporating clear saturated solutions. The solids produced are analyzed using X-ray diffraction and at least one of the other methods. In these analyses, care must be taken to show that the method of sample preparation (i.e. drying, grinding) has not affected the solid form. If the analyses show that the solids obtained are identical (e.g. have the same X-ray diffraction patterns and IR spectra) then the answer to the question "Are polymorphs possible?" is "No", and further research is not needed. The work of Miyamae et al. serves as a good example of solid state studies of a drug substance which exists as polymorphs (1). Powder diffraction showed that there were two crystal forms (see Figure 2).

These workers also carried out single crystal analysis of the two crystal forms of the compound. The structures are shown in Figure 3. While such studies are not required, and indeed sometimes not possible, they provide an unequivocal confirmation of the existence of polymorphs. Moreover, once the single crystal structure of a phase has been determined, it is possible to calculate the corresponding X-ray powder pattern. This provides and irrefutable standard for identifying the phase by that method.

The DSC thermal curves of the two forms are slightly different, as shown in Figure 4 and thus may not be the preferred way of differentiating these polymorphs..."(Column 2 on page 946 to column 1 on page 947)

7.41 The decision tree for polymorphs is set-out below (Page 946):

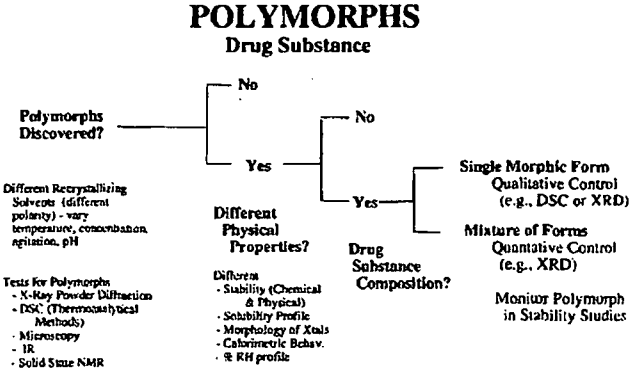
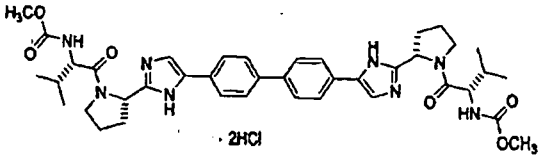


Figure 1. Flow chart/decision tree for polymorphs.

7.42 The Opponent states that evidently the first step of the decision tree involves using different recrystallizing solvents (different polarity) and varying temperature, concentration, ***agitation***, pH. The solvents used ***should include those used in the final crystallization steps and those used during formulation and processing and may also include water, methanol, ethanol, propanol, isopropanol, acetone, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate.***

7.43 Furthermore the temperature range for arriving at the alleged inventive crystal of the impugned patent is "***then stirred at temperatures between 0°C and 90°C followed by isolation of the crystals.***"

7.44 The Opponent states that the fact that recrystallization is used for purification is well-known in the art and is not something surprising. The Opponent states that the same is evident from *'Remington: The Science and Practice of Pharmacy 20th Edition 2000; Volume 1; Lippincott Williams & Wilkins; Chapter 36 – Separation'* – **Exhibit D8** hereinafter referred to as D8, which at page 678 discloses that, *"One of the most important uses of precipitation is in the purification of solids. The process as applied to purification is termed recrystallization...."*

7.45 From the aforesaid, the Form N-2 of  of the impugned application claimed in claim 1 and dependent claims 2 to 4 are clearly obvious and lacking in any inventive step. The Opponent states that it is only in dependent claims that purity as a characterizing feature appear and even then there is no data in the specification in support of any alleged advantage such as purity and aqueous solubility, let alone repeated cystallization. All claims dependent on claim 1 do not by themselves add any inventive merit to the alleged invention and thus ought to be rejected *in toto*.

7.46 Consequently, on the basis of the Exhibits presented, the Opponent humbly implores that the impugned patent application ought to be rejected on this ground.

8 **Not an Invention / Not Patentable within the meaning of the Act [Section 25(1) (f)]**

8.3 **Section 2(1) (ja)**

8.3.1 The Opponent states that the claimed invention does not meet the requirements of section 2(1)(j) and section 2(1)(ja) by virtue of being devoid of inventive step. The Opponent states that the invention should be a technical advancement over the prior art or it should show economic significance or both and should not be obvious to a person skilled in the art.

8.3.2 The Opponent relies on paragraph 7 and the same is not reproduced here for the sake of brevity and states that the Applicant has not provided technical advancement over prior art.

8.3.3 There is also no technical advancement in light of the case made out in paragraph 7. Thus the alleged invention is obvious and does not involve any inventive step and hence the invention does not satisfy requirements of 2(1) (j) and 2 (1) (ja) and therefore is not an invention within the meaning of this Act.

8.3.4 The impugned application is liable to be rejected on this ground.

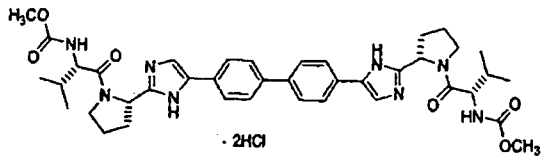
8.4 **Claims not patentable as per section 3(d)**

8.4.1 The Opponent states that the alleged invention claimed in claim 1 of the impugned patent application and in the dependent claims falls under the mischief of 3 (d) which clearly states that the mere discovery of a new form of a known substance which does not result in the enhancement of known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant is not patentable under this Act.

8.4.2 The Opponent states that an earlier application has been filed by the Applicant which is Patent Application No: 853/DELNP/2009 entitled "Hepatitis C Virus Inhibitors" dated February 5, 2009 against which the Opponent herein has preferred a pre-grant opposition. The said patent application is published under section 11A in the Official Journal of Indian Patent Office dated June 12, 2009. The said patent application claims a priority of US 60/836,996 dated August 11, 2006 and US 11/835,462 and has been nationalized from

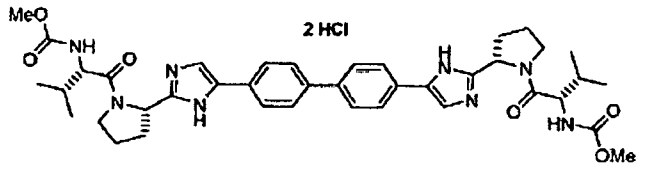
International Application No: PCT/US2007/075544 dated August 9, 2007; International Publication No: WO 2008/021927.

8.4.3 The Opponent states that the alleged invention of the impugned patent application forms the subject matter of the said earlier patent application 853/DELNP/2009 although for reasons best known to the Applicant it has not specifically claimed the said Form N-2 of



of the impugned patent application i.e.

"Example 24-23



methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-l-((2S)-2-((methoxycarbonyl)amino)-3- methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)- 1 -pyrrolidinyl) carbonyl) -2-methylpropyl) carbamate

A 50 mL flask equipped with a stir bar was sequentially charged with 2.5 mL acetonitrile, 0.344 g (2.25 mmol, 2.5 equiv) hydroxy benzotriazole hydrate, 0.374 g (2.13 mmol, 2.4 equiv) N-(methoxycarbonyl)-L-valine, 0.400 g (2.09 mmol, 2.4 equiv) 1 -(3 -dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride and an additional 2.5 mL acetonitrile. The resulting solution was agitated at 20 0C for 1 hour and charged with 0.501 g (0.88 mmol, 1 equiv) Example A-le-4. The slurry was cooled to about 0 0C and 0.45 g (3.48 mmol, 4 equiv) diisopropylethylamine was added over 30 minutes while maintaining a temperature below 10 °C. The solution was slowly heated to 15 °C over 3 hours and held at 15 0C for 16 hours. The temperature was increased to 20 °C and stirred for 3.25 hours. The resulting solution was charged with 3.3 g of 13 wt% aqueous NaCl

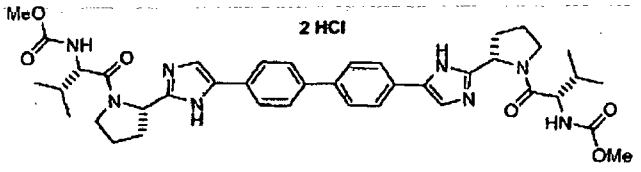
and heated to 50 °C for 1 hour. After cooling to 20 °C, 2.5 mL of isopropyl acetate was added. The rich organic phase was washed with 2 x 6.9 g of a 0.5 N NaOH solution containing 13 wt% NaCl followed by 3.3 g of 13 wt% aqueous NaCl. The mixture was then solvent exchanged into isopropyl acetate by vacuum distillation to a target volume of 10 mL. The resulting hazy solution was cooled to 20 0C and filtered through a 0.45 μm filter. The clear solution was then solvent exchanged into ethanol by vacuum distillation with a target volume of 3 mL. 1.67 mL (2.02 mmol, 2.3 equiv) of 1.21 M HCl in ethanol was added. The mixture was then stirred at 25 °C for 15 hours. The resulting slurry was filtered and the wet cake was washed with 2.5 mL of 2: 1 acetone:ethanol. The solids were dried in a vacuum oven at 50 0C to give 0.550 g (0.68 mmol, 77 %) of the desired product.

Recrystallization of Example 24-23

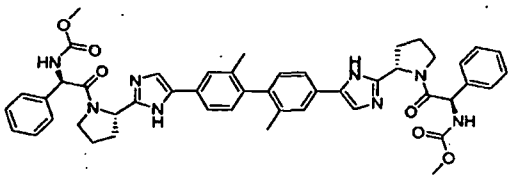
A solution of Example 24-23 prepared above was prepared by dissolving 0.520 g of the above product in 3.65 mL methanol. The solution was then charged with 0.078 g of type 3 Cuno Zeta loose carbon and allowed to stir for 0.25 hours. The mixture was then filtered and washed with 6 ml of methanol. The product rich solution was concentrated down to 2.6 mL by vacuum distillation. 7.8 mL acetone was added and allowed to stir at 25 0C for 15 h. The solids were filtered, washed with 2.5 mL 2: 1 acetone:ethanol and dried in a vacuum oven at 70 0C to give 0.406 g (57.0%) of the desired product as white crystals: 1H NMR (400 MHz, OMSO-d6, 80 0C): 8.02 (d, J=8.34 Hz, 4 H), 7.97 (s, 2 H), 7.86 (d, J=8.34 Hz, 4 H), 6.75 (s, 2 H), 5.27 (t, J=6.44 Hz, 2 H), 4.17 (t, J=6.95 Hz, 2 H), 3.97 - 4.11 (m, 2 H), 3.74 - 3.90 (m, 2 H), 3.57 (s, 6 H), 2.32 - 2.46 (m, 2 H), 2.09 - 2.31 (m, 6 H), 1.91 - 2.07 (m, 2 H), 0.88 (d, J=6.57 Hz, 6 H), 0.79 (d, J=6.32 Hz, 6 H); 13C NMR (75 MHz, DMSO-d6): δ 170.9, 156.9, 149.3, 139.1, 131.7, 127.1, 126.5, 125.9, 115.0, 57.9, 52.8, 51.5, 47.2, 31.1, 28.9, 24.9, 19.6, 17.7; IR (neat, cm^{-1}): 3385, 2971, 2873, 2669, 1731, 1650. Anal. Calcd for $C_{40}H_{52}N_8O_6Cl_2$: C, 59.18; H, 6.45; N, 13.80; Cl, 8.73. Found C, 59.98; H, 6.80; N, 13.68; Cl, 8.77. mp 267 °C (decomposed). Characteristic diffraction peak positions (degrees 2θ ± 0.1)

*@ RT, **based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard are as follows: 10.3, 12.4, 12.8, 13.3, 13.6, 15.5, 20.3, 21.2, 22.4, 22.7, 23.7.**"* (Pages 156 to 158)

The Opponent states that while the said



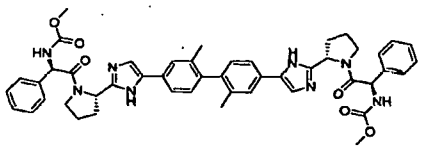
*with Characteristic diffraction peak positions (degrees 2θ ± 0.1) @ RT, **based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard are as follows: 10.3, 12.4, 12.8, 13.3, 13.6, 15.5, 20.3, 21.2, 22.4, 22.7, 23.7.**"* are based on the later priority document US 11/835,462 dated August 8, 2007 (annexed herewith and marked ***Annexure D***), the compound *per se* i.e.



formed a part of the earlier priority document US 60/836,996 dated August 11, 2006 (copy of which is annexed herewith and marked ***'Annexure E'***) and in fact forms a part of the 853/DELNP/2009 patent application.

8.4.4 Thus, at the highest the alleged inventive compound claimed in the impugned patent application is merely a new form of a known substance without demonstration of any enhanced efficacy.

8.4.5 The Opponent states that the said compound



was known to the Applicant much before the impugned patent application and the use of it was also known and for which it has sought a patent without demonstration of any enhanced efficacy over what was already known.

8.4.6 In view of the above, the alleged invention in the alleged invention claimed in claim 1 and the dependent claims of the impugned application is not patentable as per Section 3 (d) of the Act and thus the impugned patent application ought to be rejected.

8.5 Claims not patentable as per section 3(i)

8.5.1 The Opponent states that claim 12 i.e.

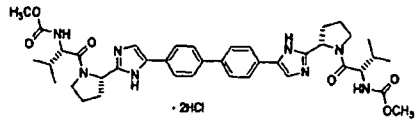
"12. A compound as claimed in any one of claims 1 to 4 for use in a method of treating HCV infection." squarely falls within section 3(i) and ought to be rejected being a method of treatment claim.

8.6 Claims not patentable under section 3(e):

8.6.1 The Opponent states that claims 5 to 11 being mere combinations (admixtures) without demonstration of any synergy squarely fall within the section 3(e) and ought to be rejected.

9 Insufficiency of Description [Section 25(1) (g)]

9.3 The Opponent states that the complete specification of the alleged invention does not sufficiently and clearly describe the invention or the method by which it is to be performed. The Opponent states that it is a well settled rule that the specification should clearly and fairly describe the invention and disclose the best mode of working the invention so that the person skilled in the art could perform the invention without any undue efforts and it is hereby stated that the Applicant has failed to do so.

9.4 The complete specification of impugned application is premised on the allegedly inventive Form N-2 of  being such that as a result of being the dihydrochloride salt can be repeatedly crystallized into one particular polymorph that offers high aqueous solubility and excellent purification capacity.

9.5 The Opponent states that clearly it is the capacity for purification and not the extent of purification that is sought to be projected as an advantage. The examples provided merely disclose that the purified compound (I) has been

formed while not providing the extent of purity. The Opponent states that yet the impugned patent application seeks to claim in the dependent claims 2 to 4, the extent of purity which would be dependent on a number of factors including the number of times of recrystallization, etc. and thus the invention claimed in the impugned patent application does have a basis in the specification and thus the invention is not sufficiently and clearly described nor the method by which it is to be performed is provided.

Accordingly, in view of the above-mentioned factors all the claims of impugned application are liable to be rejected on the various grounds made out by the Opponent in the present representation.

10 RELIEF(s) SOUGHT

The Opponent states that it has established and made out a case on each of the aforesaid grounds of opposition and prays to the Ld. Controller for the following relief(s):

1) Take on record the present representation;
2) Leave to file evidence;
3) Forward copy of reply of Applicant and evidence if any and any amendments filed;
4) Leave to file a replication to the reply of the Applicant and evidence;
5) Grant of hearing;
6) Refusal of the application *in toto*;
7) Such other relief or reliefs as the Controller may deem appropriate.

Dated this the 5th day of November 2015

Of S. Majumdar & Co
(Opponent's Agent)

To,

The Controller of Patents,
Patent office,
New Delhi

Enclosures:

- Annexure A;
- Annexure B;
- Annexure C;
- Exhibit D1;
- Exhibit D2;
- Exhibit D3;
- Exhibit D4;
- Exhibit D5;
- Exhibit D6;
- Exhibit D7;
- Exhibit D8;
- Annexure D;
- Annexure E.

ANNEXURE-A 31

8016 DELNP 2007

ORIGINAL

05 FEB 2010

FORM 2
THE PATENTS ACT 1970
[39 OF 1970]
&
THE PATENTS (AMENDMENT) RULES, 2006
COMPLETE SPECIFICATION

[See Section 10; rule 13]

"CRYSTALLINE FORM OF METHYL ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((METHOXYCARBONYL)AMINO)-3-METHYLBUTANOYL)-2-PYRROLIDINYL)-1H-IMIDAZOL-5-YL)-4-BIPHENYLYL)-1H-IMIDAZOL-2-YL)-1-PYRROLIDINYL)CARBONYL)-2-METHYLPROPYL)CARBAMATE DIHYDROCHLORIDE SALT"

BRISTOL-MYERS SQUIBB COMPANY, a corporation of the State of Delaware, of Route 206 and Province Line Road, Princeton, New Jersey 08543, United States of America,

The following specification particularly describes the invention and the manner in which it is to be performed:

CRYSTALLINE FORM OF METHYL ((1*S*)-1-(((2*S*)-2-(5-(4'-(2-((2*S*)-1-((2*S*)-2-((METHOXYCARBONYL)AMINO)-3-METHYLBUTANOYL)-2-PYRROLIDINYL)-1*H*-IMIDAZOL-5-YL)-4-BIPHENYLYL)-1*H*-IMIDAZOL-2-YL)-1-PYRROLIDINYL)CARBONYL)-2-METHYLPROPYL)CARBAMATE DIHYDROCHLORIDE SALT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S Provisional Application Serial Number 60/954,592 filed August 8, 2007.

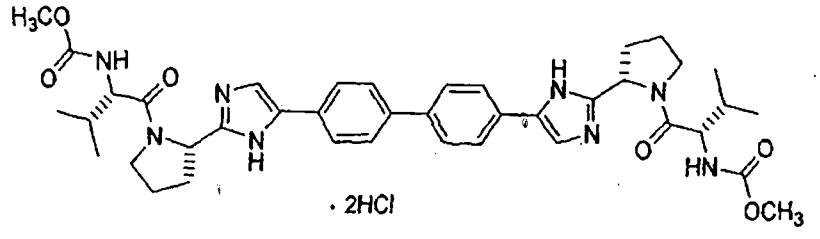
The present disclosure generally relates to a crystalline form of methyl ((1*S*)-1-(((2*S*)-2-(5-(4'-(2-((2*S*)-1-((2*S*)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride salt. The present disclosure also generally relates to a pharmaceutical composition comprising a crystalline form, as well of methods of using a crystalline form in the treatment of Hepatitis C virus (HCV) and methods for obtaining such crystalline form.

Hepatitis C virus (HCV) is a major human pathogen, infecting an estimated 170 million persons worldwide - roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma.

Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40 percent of patients. Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and unmet need to develop effective therapeutics for treatment of HCV infection.

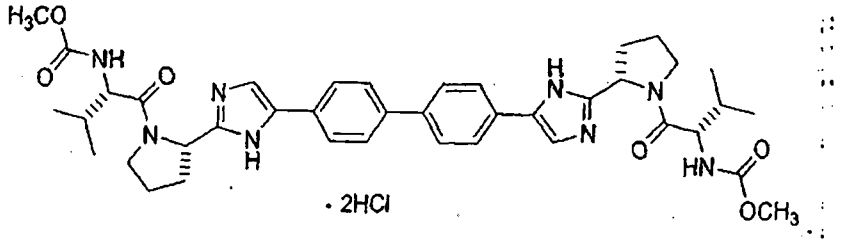
The compound methyl ((1*S*)-1-(((2*S*)-2-(5-(4'-(2-((2*S*)-1-((2*S*)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-

biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate is useful for the treatment of HCV infection. Due to the difficulty in crystallizing this compound, formation of pure product has not been reproducible. It has been found that the dihydrochloride salt, represented by formula (I) and herein referred to as Compound (I), can be repeatedly crystallized into one particular polymorph, herein referred to as Form N-2, that offers high aqueous solubility and excellent purification capacity.

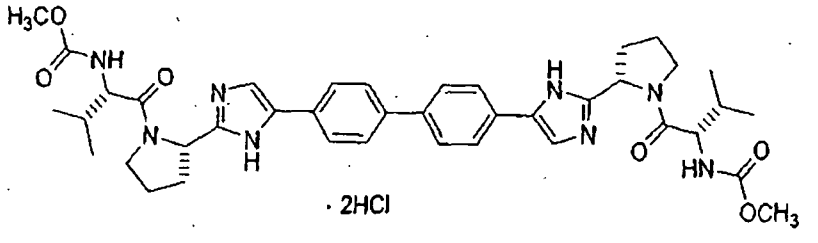


Compound (I)

In its first aspect the present disclosure provides Form N-2 of



In a second aspect the present disclosure provides Form N-2 of



characterized by the following unit cell parameters:

Cell dimensions: a = 7.5680 Å

b= 9.5848 Å

c = 16.2864 Å

α = 74.132 degrees

β = 84.132 degrees

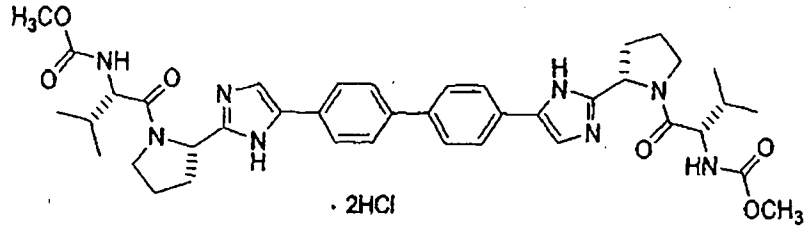
$\gamma = 70.646$ degrees

Space group P1

Molecules/unit cell 1

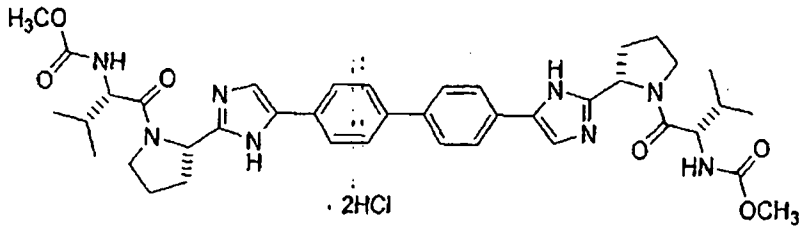
wherein measurement of said crystalline form is at a temperature between about 20 °C to about 25 °C.

In a third aspect the present disclosure provides Form N-2 of



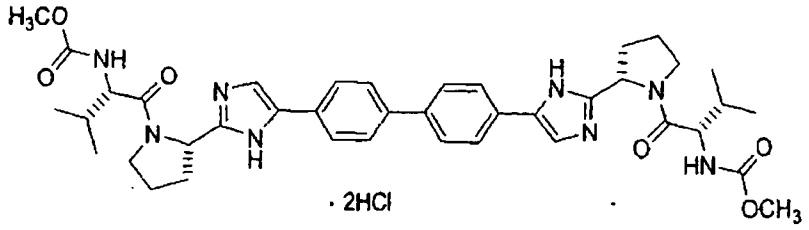
characterized by fractional atomic coordinates within the unit cell as listed in Table 3.

In a fourth aspect the present disclosure provides Form N-2 of



with characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard.

In a fifth aspect the present disclosure provides Form N-2 of



characterized by one or more of the following:

a) a unit cell with parameters substantially equal to the following:

Cell dimensions: a = 7.5680 Å

b= 9.5848 Å

c = 16.2864 Å

α = 74.132 degrees

β = 84.132 degrees

γ = 70.646 degrees

Space group P1

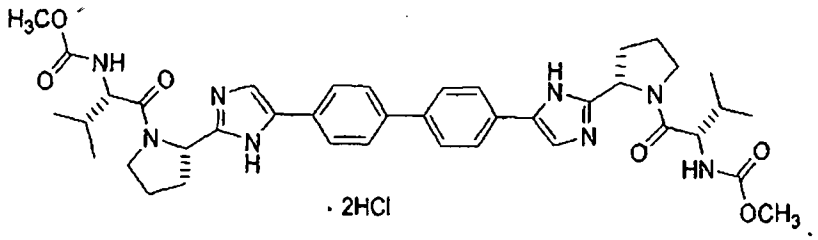
Molecules/unit cell 1

wherein measurement of said crystalline form is at a temperature between about 20 °C to about 25 °C;

b) characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard; and/or

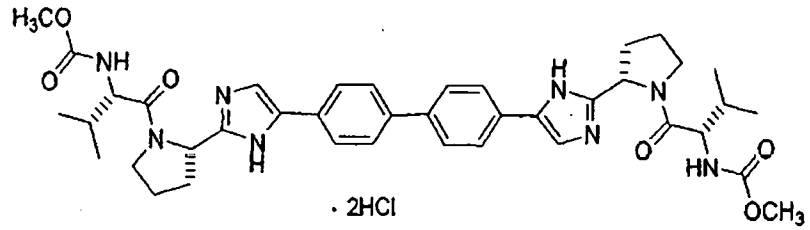
c) a melt with decomposition endotherm with onset typically in the range of 225-245 °C.

In a sixth aspect the present disclosure provides substantially pure Form N-2 of



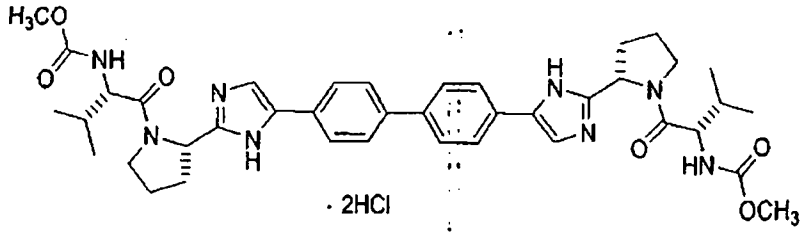
In a first embodiment of the sixth aspect said Form N-2 has a purity of at least 95 weight percent. In a second embodiment of the sixth aspect said Form N-2 has a purity of at least 99 weight percent.

In a seventh aspect the present disclosure provides substantially pure Form N-2 of



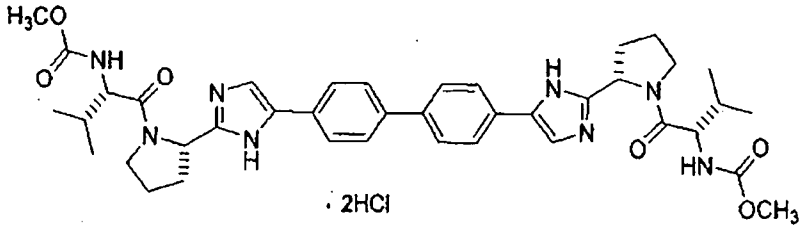
with characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard.

In an eighth aspect the present disclosure provides a pharmaceutical composition comprising Form N-2 of



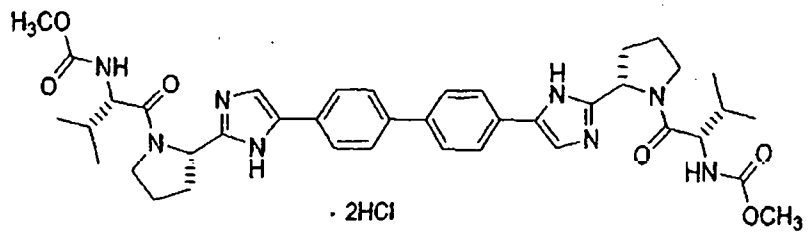
and a pharmaceutically acceptable carrier or diluent.

In a ninth aspect the present disclosure provides a pharmaceutical composition comprising substantially pure Form N-2 of



and a pharmaceutically acceptable carrier or diluent. In a first embodiment of the ninth aspect said Form N-2 has a purity of at least 95 weight percent. In a second embodiment of the ninth aspect said Form N-2 has a purity of at least 99 weight percent.

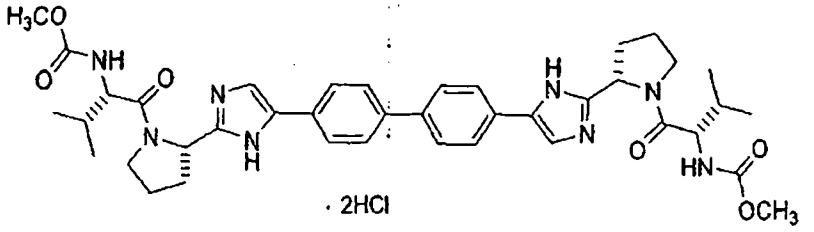
In a tenth aspect the present disclosure provides a pharmaceutical composition comprising Form N-2 of



in combination with one or two additional compounds having anti-HCV activity. In a first embodiment of the tenth aspect said Form N-2 has a purity of at least 90 weight percent. In a second embodiment of the tenth aspect said Form N-2 has a purity of at least 95 weight percent. In a third embodiment of the tenth aspect said Form N-2 has a purity of at least 99 weight percent.

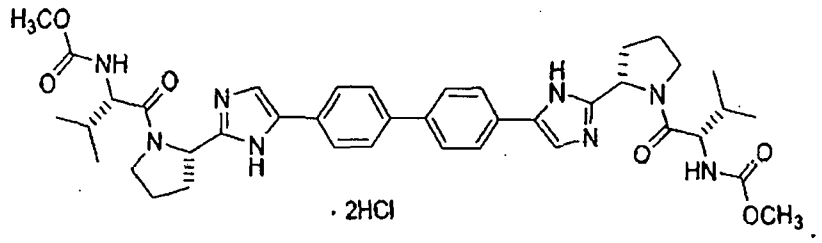
In a fourth embodiment of the tenth aspect at least one of the additional compounds having anti-HCV activity is an interferon or ribavirin. In a fifth embodiment of the tenth aspect the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a sixth embodiment of the tenth aspect the present disclosure provides a pharmaceutical composition comprising Form N-2 of



in combination with one or two additional compounds having anti-HCV activity wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

In an eleventh aspect the present disclosure provides a method of treating HCV infection in a mammal comprising administering to the mammal a therapeutically-effective amount of Form N-2 of



In a first embodiment of the eleventh aspect said Form N-2 has a purity of at least 90 weight percent. In a second embodiment of the eleventh aspect said Form N-2 has a purity of at least 95 weight percent. In a third embodiment of the eleventh aspect said Form N-2 has a purity of at least 99 weight percent. In a fourth embodiment of the eleventh aspect the mammal is a human.

Other embodiments of the present disclosure may comprise suitable combinations of two or more of embodiments and/or aspects disclosed herein.

Yet other embodiments and aspects of the disclosure will be apparent according to the description provided below.

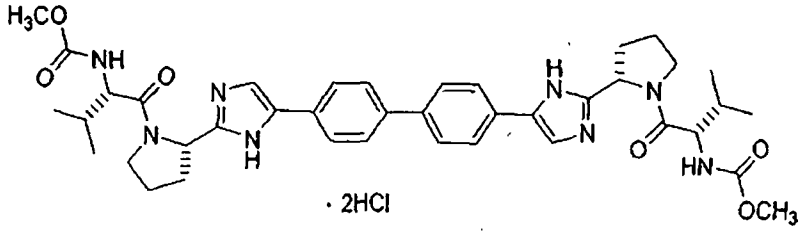
The compounds of the present disclosure also exist as tautomers; therefore the present disclosure also encompasses all tautomeric forms.

FIG. 1 illustrates experimental and simulated powdered X-Ray diffraction patterns (CuKα λ=1.54178 Å at T = room temperature) of the N-2 crystalline form of Compound (I).

FIG. 2 illustrates the differential scanning calorimetry pattern of the N-2 crystalline form of Compound (I).

FIG. 3 illustrates the solid state NMR spectrum of the N-2 crystalline form of Compound (I).

The disclosure relates to a crystalline form of Compound (I).



(I).

Definitions

As used herein "polymorph" refers to crystalline forms having the same chemical composition but different spatial arrangements of the molecules, atoms, and/or ions forming the crystal.

The term "pharmaceutically acceptable," as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable beneift/risk ratio.

The term "substantially pure," as used herein refers to Form N-2 of Compound (I) which is great than about 90% pure. This means that the polymorph of Compound (I) does not contain more than about 10% of any other compound, and, in particular, does not contain more than about 10% of any other form of Compound (I).

The term "therapeutically effective amount," as used herein, is intended to include an amount of the crystalline forms of Compound (I) that is effective when administered alone or in combination to treat Hepatitis C. The crystalline forms of Compound (I) and pharmaceutical compositions thereof may be useful in treating Hepatitis C. If Compound (I) is used in combination with another medication, the combination of compounds described herein may result in a synergistic combination. Synergy, as described for example by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*, 27-55, occurs when the effect of the compounds when administered in combination is greater than the effect of the compounds when administered alone as single agents.

The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder or condition, i.e., arresting its development; and/or (iii) relieving the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

In one embodiment the disclosure provides a crystalline form of Compound (I). This crystalline form of Compound (I) may be employed in pharmaceutical compositions which may optionally include one or more other components selected,

for example, from the group consisting of excipients, carriers, and one of other active pharmaceutical ingredients active chemical entities of different molecular structure.

In one embodiment the crystalline form has phase homogeneity indicated by less than 10 percent, in another embodiment the crystalline form has phase homogeneity indicated by less than 5 percent, and in another embodiment the crystalline form has phase homogeneity indicated by less than 2 percent of the total peak area in the experimentally measured PXRD pattern arising from the extra peaks that are absent from the simulated PXRD pattern. In another embodiment the crystalline form has phase homogeneity with less than 1 percent of the total peak area in the experimentally measured PXRD pattern arising from the extra peaks that are absent from the simulated PXRD pattern.

In one embodiment, a composition is provided consisting essentially of the crystalline form N-2 of Compound (I). The composition of this embodiment may comprise at least 90 weight percent of the crystalline form N-2 of Compound (I), based on the weight of Compound (I) in the composition. The remaining material comprises other form(s) of the compound and/or reaction impuritis and/or processing impurities arising from its preparation.

The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art, such as, for example, chromatography, nuclear magnetic resonance spectroscopy, mass spectrometry, or infrared spectroscopy.

General Preparation of Crystalline Materials:

Crystalline forms may be prepared by a variety of methods, including for example, crystallization or recrystallization from a suitable solvent, sublimation, growth from a melt, solid state transformation from another phase, crystallization from a supercritical fluid, and jet spraying. Techniques for crystallization or recrystallization of crystalline forms from a solvent mixture include, for example, evaporation of the solvent, decreasing the temperature of the solvent mixture, crystal seeding a supersaturated solvent mixture of the molecule and/or salt, freeze drying the solvent mixture, and addition of antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs. Crystals of drugs, including polymorphs,

methods of preparation, and characterization of drug crystals are discussed in *Solid-State Chemistry of Drugs*, S.R. Byrn, R.R. Pfeiffer, and J.G. Stowell, 2nd Edition, SSCI, West Lafayette, Indiana (1999).

For crystallization techniques that employ solvent, the choice of solvent or solvents is typically dependent upon one or more factors, such as solubility of the compound, crystallization technique, and vapor pressure of the solvent. Combinations of solvents may be employed, for example, the compound may be solubilized into a first solvent to afford a solution, followed by the addition of an antisolvent to decrease the solubility of the compound in the solution and to afford the formation of crystals. An antisolvent is a solvent in which the compound has low solubility.

In one method to prepare crystals, a compound is suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated to promote dissolution. The term "slurry", as used herein, means a saturated solution of the compound, which may also contain an additional amount of the compound to afford a heterogeneous mixture of the compound and a solvent at a given temperature.

Seed crystals may be added to any crystallization mixture to promote crystallization. Seeding may be employed to control growth of a particular polymorph or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in "Programmed Cooling of Batch Crystallizers," J.W. Mullin and J. Nyvlt, *Chemical Engineering Science*, **1971**, *26*, 369-377. In general, seeds of small size are needed to control effectively the growth of crystals in the batch. Seed of small size may be generated by sieving, milling, or micronizing of large crystals, or by micro-crystallization of solutions. Care should be taken that milling or micronizing of crystals does not result in any change in crystallinity of the desired crystal form (i.e., change to amorphous or to another polymorph).

A cooled crystallization mixture may be filtered under vacuum, and the isolated solids may be washed with a suitable solvent, such as cold recrystallization solvent, and dried under a nitrogen purge to afford the desired crystalline form. The isolated solids may be analyzed by a suitable spectroscopic or analytical technique, such as solid state nuclear magnetic resonance, differential scanning calorimetry, X-

Ray powder diffraction, or the like, to assure formation of the preferred crystalline form of the product. The resulting crystalline form is typically produced in an amount of greater than about 70 weight percent isolated yield, preferably greater than 90 weight percent isolated yield, based on the weight of the compound originally employed in the crystallization procedure. The product may be co-milled or passed through a mesh screen to delump the product, if necessary.

Crystalline forms may be prepared directly from the reaction medium of the final process for preparing Compound (I). This may be achieved, for example, by employing in the final process step a solvent or a mixture of solvents from which Compound (I) may be crystallized. Alternatively, crystalline forms may be obtained by distillation or solvent addition techniques. Suitable solvents for this purpose include, for example, the aforementioned non-polar solvents and polar solvents, including protic polar solvents such as alcohols, and aprotic polar solvents such as ketones.

The presence of more than one polymorph in a sample may be determined by techniques such as powder X-Ray diffraction (PXRD) or solid state nuclear magnetic resonance spectroscopy (SSNMR). For example, the presence of extra peaks in an experimentally measured PXRD pattern wehn compared with a simulated PXRD pattern may indicate more than one polymorph in the sample. The simulated PXRD may be calculated from single crystal X-Ray data. see Smith, D.K., "*A FORTRAN Program for Calculating X-Ray Powder Diffraction Patterns,*" Lawrence Radiation Laboratory, Livermore, California, UCRL-7196 (April 1963).

Characterization:

Form N-2 of Compound (I) can be characterized using various techniques, the operation of which are well known to those of ordinary skill in the art. Examples of characterization methods include, but are not limited to, single crystal X-Ray diffraction, powder X-Ray diffraction (PXRD), simulated powder X-Ray patterns (Yin, S.; Scaringe, R. P.; DiMarco, J.; Galella, M. and Gougoutas, J. Z., *American Pharmaceutical Review*, **2003**, *6*, 2, 80), differential scanning calorimetry (DSC), solid-state ^{13}C NMR (Earl, W.L. and Van der Hart, D. L., *J. Magn. Reson.*, **1982**, *48*, 35-54), Raman spectroscopy, infrared spectroscopy, moisture sorption isotherms, thermal gravimetric analysis (TGA), and hot stage techniques.

The forms may be characterized and distinguished using single crystal X-Ray diffraction, which is based on unit cell measurements of a single crystal of form N-2. A detailed description of unit cells is provided in Stout & Jensen, X-Ray Structure Determination: A Practical Guide, Macmillan Co., New York (1968), Chapter 3, which is herein incorporated by reference. Alternatively, the unique arrangement of atoms in spatial relation within the crystalline lattice may be characterized according to the observed fractional atomic coordinates. Another means of characterizing the crystalline structure is by powder X-Ray diffraction analysis in which the diffraction profile is compared to a simulated profile representing pure powder material, both run at the same analytical temperature, and measurements for the subject form characterized as a series of 2θ values.

One of ordinary skill in the art will appreciate that an X-Ray diffraction pattern may be obtained with a measurement of error that is dependent upon the measurement conditions employed. In particular, it is generally known that intensities in an X-Ray diffraction pattern may fluctuate depending upon measurement conditions employed. It should be further understood that relative intensities may also vary depending upon experimental conditions, and, accordingly, the exact order of intensity should not be taken into account. Additionally, a measurement error of diffraction angle for a conventional X-Ray diffraction pattern is typically about 5 percent or less, and such degree of measurement error should be taken into account as pertaining to the aforementioned diffraction angles. Consequently, it is to be understood that the crystal forms of the present disclosure are not limited to the crystal forms that provide X-Ray diffraction patterns completely identical to the X-Ray diffraction patterns depicted in the accompanying Figures disclosed herein. Any crystal form that provides and X-Ray diffraction pattern, DSC thermogram, or SSNMR spectrum substantiallyidentical to those disclosed in the accompanying Figures fall within the scope of the present disclosure. The ability to ascertain substantial identities of X-Ray diffraction patters is within the purview of one of ordinary skill in the art.

Utility:

The N-2 form of Compound (I), alone or in combination with other compounds, can be used to treat HCV infection.

The present disclosure also provides compositions comprising a therapeutically effective amount of the N-2 form of Compound (I) and at least one pharmaceutically acceptable carrier.

The active ingredient, i.e., form N-2 of Compound (I), in such compositions typically comprises from 0.1 weight percent to 99.9 percent by weight of the composition, and often comprises from about 5 to 95 weight percent. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable modifiers (such as calcium carbonate and magnesium oxide) to enhance the stability of the formulated compound or its delivery form. Formulations of the polymorph of the present disclosure may also contain additives for enhancement of absorption and bioavailability.

The pharmaceutical compositions of this disclosure may be administered orally, parenterally or via an implanted reservoir. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular,intra-articular, intrasynovial, intrasternal, intrathecal, and intralesional injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The details concerning the preparation of such compounds are known to those skilled in the art.

When orally administered, the pharmaceutical compositions of this disclosure may be administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, can also be added. For oral administration in a capsule form, useful carriers/diluents include lactose, high and low molecular weight polyethylene glycol, and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Other suitable carriers for the above noted compositions can be found in standard pharmaceutical texts, e.g. in "Remington's Pharmaceutical Sciences", 19th

ed., Mack Publishing Company, Easton, Penn., 1995. Further details concerning the design and preparation of suitable delivery forms of the pharmaceutical compositions of the disclosure are known to those skilled in the art.

Dosage levels of between about 0.05 and about 100 milligram per kilogram ("mg/kg") body weight per day, more specifically between about 0.1 and about 50 mg/kg body weight per day of the compounds of the disclosure are typical in a monotherapy for the prevention and/or treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 3 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, gender, diet, time of administration, the duration of treatment, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician. In one embodiment, unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the peptide. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

When the compositions of this disclosure comprise a combination of the polymorph of the disclosure and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent are usually present at dosage levels of between about 10 and 100 percent, and more preferably between about 10 and 80 percent of the dosage normally administered in a monotherapy regimen.

Administration of the one or more additional agents may occur prior to, after, or simultaneously with the polymorph of the present disclosure.

When the polymorph is formulated together with a pharmaceutically acceptable carrier, the resulting composition may be administered *in vivo* to mammals, such as man, to inhibit NS5A or to treat or prevent HCV virus infection. Such treatment may also be achieved using the polymorph of this disclosure in combination with agents which include, but are not limited to: Immunomodulatory agents, such as interferons; other antiviral agents such as ribavirin, amantadine; other inhibitors of NS5A; inhibitors of other targets in the HCV life cycle such as helicase, protease, polymerase, metalloprotease, or internal ribosome entry site; or combinations thereof. The additional agents may be combined with the polymorph of this disclosure to create a single dosage form. Alternatively these additional agents may be separately administered to a mammal as part of a multiple dosage form.

Table 1 below lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the disclosure can be administered with other anti-HCV activity compounds in combination therapy, either jointly or separately, or by combining the compounds into a composition.

Table 1

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
NIM811		Cyclophilin Inhibitor	Novartis
Zadaxin		Immunomodulator	Sciclone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Batabulin (T67)	Anticancer	β-tubulin inhibitor	Tularik Inc., South San Francisco, CA

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
ISIS 14803	Antiviral	antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV Inhibitor	Achillion / Gilead
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 2005	Antiviral	HCV Inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
HCV-796	Antiviral	NS5B Replicase Inhibitor	Wyeth / Viropharma
NM-283	Antiviral	NS5B Replicase Inhibitor	Idenix / Novartis
GL-59728	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
GL-60667	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
2'C MeA	Antiviral	NS5B Replicase Inhibitor	Gilead
PSI 6130	Antiviral	NS5B Replicase Inhibitor	Roche
R1626	Antiviral	NS5B Replicase Inhibitor	Roche
2'C Methyl adenosine	Antiviral	NS5B Replicase Inhibitor	Merck
JTK-003	Antiviral	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Levovirin	Antiviral	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Ribavirin	Antiviral	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Viramidine	Antiviral	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
SCH 503034	Antiviral	serine protease inhibitor	Schering Plough
Zadazim	Immune modulator	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Immunomodulator	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Immunosuppressant	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Civacir	Immunosuppressant	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferon	albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferon	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferon	IFN-ω	Intarcia Therapeutics
IFN-β and EMZ701	Interferon	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
Rebif	Interferon	IFN-β1a	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Intron A	Interferon	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Intron A and Zadaxin	Interferon	IFN-α2b/α1-thymosin	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferon	IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Actimmune	Interferon	INF-γ	InterMune Inc., Brisbane, CA
Interferon-β	Interferon	Interferon-β-1a	Serono
Multiferon	Interferon	Long lasting IFN	Viragen/Valentis
Wellferon	Interferon	lymphoblastoid IFN-αn1	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferon	natural IFN-α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN-α2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Pegasys and Ribavirin	Interferon	PEGylatcd IFN-α2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
PEG-Intron	Interferon	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	Interferon	PEGylated IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Liver protection	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Liver protection	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B Replicase Inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys

Another aspect of this disclosure provides methods of inhibiting HCV NS5A activity in patients by administering the polymorph of the present disclosure.

In one embodiment, these methods are useful in decreasing HCV NS5A activity in the patient. If the pharmaceutical composition comprises only the polymorph of this disclosure as the active component, such methods may additionally comprise the step of administering to said patient an agent selected from an immunomodulatory agent, an antiviral agent, an HCV NS5A inhibitor, or an inhibitor of other targets in the HCV life cycle such as, for example, helicase, polymerase, protease, or metalloprotease. Such additional agent may be administered to the patient prior to, concurrently with, or following the administration of the compounds of this disclosure.

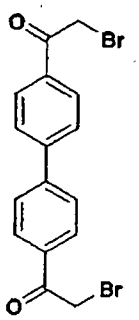
In another embodiment, these methods are useful for inhibiting viral replication in a patient. Such methods can be useful in treating or preventing HCV disease.

The polymorph of the disclosure may also be used as a laboratory reagent. The polymorph may be instrumental in providing research tools for designing of viral replication assays, validation of animal assay systems and structural biology studies to further enhance knowledge of the HCV disease mechanisms.

The polymorph of this disclosure may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, e.g., blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

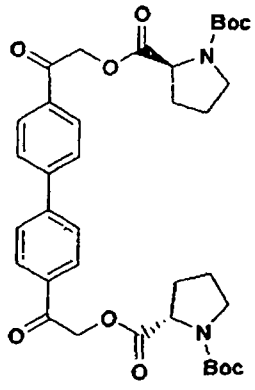
The following non-limiting examples are illustrative of the disclosure.

EXAMPLES



Preparation of Compound 2

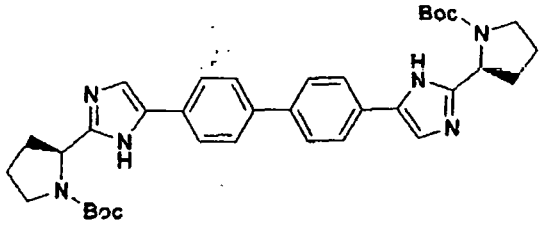
A 1 L, 3-neck round bottom flask, fitted with a nitrogen line, overhead stirrer and thermocouple, was charged with 20 g (83.9 mmol, 1 equiv) 1,1'-(biphenyl-4,4'-diyl)diethanone, 200 mL CH_2Cl_2 and 8.7 mL (27.1g, 169.3 mmol, 2.02 quiv) bromine. The mixture was allowed to stir under nitrogen for about 20 hours under ambient conditions. The resulting slurry was charged with 200 mL CH_2Cl_2 and concentrated down to about 150 mL *via* vacuum distillation. The slurry was then solvent exchanged into THF to a target volume of 200 mL *via* vacuum distillation. The slurry was cooled to 20-25 °C over 1 hour and allowed to stir at 20-25 °C for an additional hour. The off-white crystalline solids were filtered and washed with 150 mL CH_2Cl_2. The product was dried under vacuum at 60 °C to yield 27.4 g (69.2 mmol, 82%) of the desired product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.85 (m, 4H), 7.60-7.50 (m, 4H), 4.26 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 145.1, 133.8, 129.9, 127.9, 30.8; IR (KBr, cm-1) 3007, 2950, 1691, 1599, 1199; Anal calcd for $C_{16}H_{12}Br_2O_2$: C, 48.52; H, 3.05; Br, 40.34. Found: C, 48.53; H, 3.03; Br, 40.53. HRMS calcd for $C_{16}H_{13}Br_2O_2$ (M + H; DCI$^+$): 394.9282. Found: 394.9292. mp 224-226 °C.



Preparation of Compound 3

A 500 mL jacketed flask, fitted with a nitrogen line, thermocouple and overhead stirrer, was charged with 20 g (50.5 mmol, 1 equiv) of Compound 2, 22.8 g (105.9 moles, 2.10 equiv) 1-(*tert*-butoxycarbonyl)-L-proline and 200 mL acetonitrile. The slurry was cooled to 20 °C followed by the addition of 18.2 mL (13.5 g, 104.4 mmol, 2.07 equiv) DIPEA. The slurry was warmed to 25 °C and allowed to stir for 3

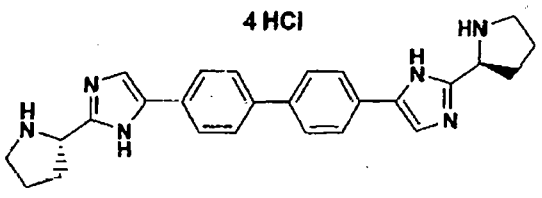
hours. The resulting clear, organic solution was washed with 3 x 100 mL 13 wt% aqueous NaCl. The rich acetonitrile solution was solvent exchanged into toluene (target volume = 215 mL) by vacuum distillation until there was less than 0.5 vol% acetonitrile.



Preparation of Compound 4

The toluene solution of Compound 3 was charged with 78 g (1.011 moles, 20 equiv) ammonium acetate and heated to 95-100 °C. The mixture was allowed to stir at 95-100 °C for 15 hours. After reaction completion, the mixture was cooled to 70-80 °C and charged with 7 mL acetic acid, 40 mL n-butanol, and 80 mL of 5 vol% aqueous acetic acid. The resulting biphasic solution was split while maintaining a temperature > 50 °C. The rich organic phase was charged with 80 mL of 5 vol% aqueous acetic acid, 30 mL acetic acid and 20 mL n-butanol while maintaining a temperature > 50 °C. The resulting biphasic solution was split while maintaining a temperature > 50 °C and the rich organic phase was washed with an additional 80 mL of 5 vol% aqueous acetic acid. The rich organic phase was then solvent exchanged into toluene to a target volume of 215 mL by vacuum distillation. While maintaining a temperature > 60 °C, 64 mL methanol was charged. The resulting slurry was heated to 70-75 °C and aged for 1 hour. The slurry was cooled to 20-25 °C over 1 hour and aged at that temperature for an additional hour. The slurry was filtered and the cake was washed with 200 mL 10:3 toluene:methanol. The product was dried under vacuum at 70 °C, resulting in 19.8 g (31.7 mmol, 63%) of the desired product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00-11.00 (s, 2H), 7.90-7.75 (m, 4H), 7.75-7.60 (m, 4H), 7.60-7.30 (s, 2H), 4.92-4.72 (m, 2H), 3.65-3.49 (m, 2H), 3.49-3.28 (m, 2H), 2.39-2.1 (m, 2H), 2.10-1.87 (m, 6H), 1.60-1.33 (s, 8H), 1.33-1.07 (s, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.1, 153.8, 137.5, 126.6, 125.0, 78.9, 78.5, 55.6, 55.0, 47.0, 46.7, 33.7, 32.2, 28.5, 28.2, 24.2, 23.5; IR (KBr, cm-1) 2975, 2876, 1663, 1407,

1156, 1125; HRMS calcd for $C_{36}H_{45}N_6O_4$ (M + H; ESI$^+$): 625.3502. Found: 625.3502. mp 190-195 °C (decomposed).

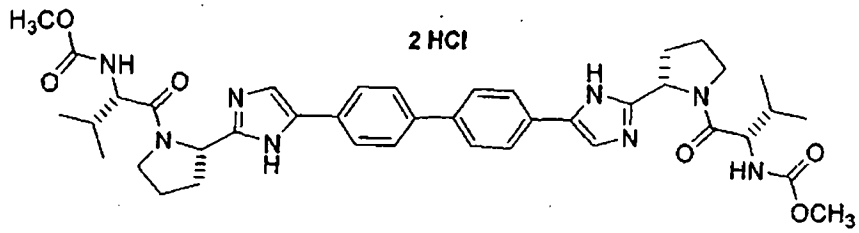


Preparation of Compound 5

To a 250 mL reactor equipped with a nitrogen line and overhead stirrer, 25.0 g of Compound 4 (40.01 mmol, 1 equiv) was charged followed by 250 mL methanol and 32.85 mL (400.1 mmol, 10 equiv) 6M aqueous HCl. The temperature was increased to 50 °C and agitated at 50 °C for 5 hours. The resulting slurry was cooled to 20-25 °C and held with agitation for about 18 hours. Filtration of the slurry afforded a solid which was washed successively with 100 mL 90% methanol/water (V/V) and 2 x 100 mL of methanol. The wet cake was dried in a vacuum oven at 50 °C overnight to give 18.12 g (31.8 mmol, 79.4%) of the desired product.

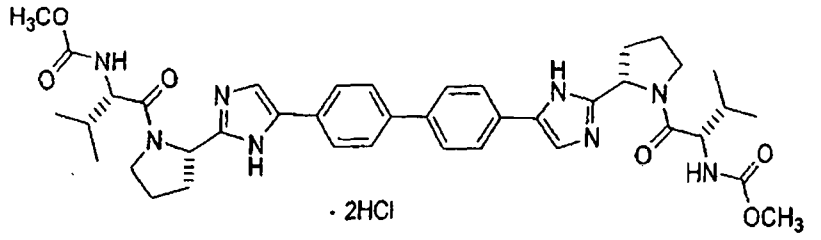
Recrystallization of Compound 5

To a 250 mL reactor equipped with a nitrogen line and an overhead stirrer, 17.8g of Compound 5 from above was charged followed by 72 mL methanol. The resulting slurry was agitated at 50 °C for 4 hours, cooled to 20-25 °C and held with agitation at 20-25 °C for 1 hour. Filtration of the slurry afforded a crystalline solid which was washed with 60 mL methanol. The resulting wet cake was dried in a vacuum oven at 50 °C for 4 days to yield 14.7 g (25.7 mmol, 82.6%) of the purified product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.5-10.25 (br, 2H), 10.1-9.75 (br, 2H), 8.19 (s, 2H), 7.05 (d, J = 8.4, 4H), 7.92 (d, J = 8.5, 4H), 5.06 (m, 2H), 3.5-3.35 (m, 4H), 2.6-2.3 (m, 4H), 2.25-2.15 (m, 2H), 2.18-1.96 (m, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 156.6, 142.5, 139.3, 128.1, 127.5, 126.1, 116.9, 53.2, 45.8, 29.8, 24.3; IR (KBr, cm^{-1}) 3429, 2627, 1636, 1567, 1493, 1428, 1028. Anal calcd for $C_{26}H_{32}N_6Cl_4$: C, 54.75; H, 5.65; Cl, 24.86; Adjusted for 1.9% water: C, 53.71; H, 5.76; N, 14.46; Cl, 24.39. Found: C, 53.74; H, 5.72; N, 14.50; Cl, 24.49; KF = 1.9. mp 240 °C (decomposed).



Preparation of Compound (I)

A 1 L jacketed flask equipped with a nitrogen line and an overhead stirrer was sequentially charged with 100 mL acetonitrile, 13.69 g (89.4 mmol, 2.5 equiv) hydroxybenzotriazole hydrate, 15.07 g (86 mmol, 2.4 equiv) *N*-(methoxycarbonyl)-L-valine, 16.46 g (85.9 mmol, 2.4 equiv) 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride and an additional 100 mL acetonitrile. The resulting solution was agitated at 20 °C for 1 hour and charged with 20.4 g (35.8 mmol, 1 equiv) of purified Compound 5. The slurry was cooled to about 0 °C and 18.47 g (142.9 mmol, 4 equiv) diisopropylethylamine was added over 30 minutes while maintaining a temperature below 10 °C. The solution was slowly heated to 15 °C over 3 hours and held at 15 °C for 12 hours. The resulting solution was charged with 120 mL 13 wt% aqueous NaCl and heated to 50 °C for 1 hour. After cooling to 20 °C, 100 mL of isopropyl acetate was added. The biphasic solution was filtered through a 0.45 μm filter and the mixture split. The rich organic phase was washed with 2 x 240 mL of a 0.5 N NaOH solution containing 13 wt% NaCl followed by 120 mL 13 wt% aqueous NaCl. The mixture was then solvent exchanged into isopropyl acetate by vacuum distillation with a target volume of 400 mL. The resulting hazy solution was cooled to 20 °C and filtered through a 0.45 μm filter. The clear solution was then solvent exchanged into ethanol by vacuum distillation with a target volume of 140 mL. While maintaining a temperature of 50 °C, 66.4 mL (82.3 mmol, 2.3 equiv) of 1.24M HCl in ethanol was added. The mixture was then charged with 33 mg (0.04 mmol, 0.001 equiv) of seed crystals of Compound (I) (see preparation below) and the resulting slurry was stirred at 50 °C for 3 hours. The mixture was cooled to 20 °C over 1 hour and aged at that temperature for an additional 22 hours. The slurry was filtered and the wet cake was washed with 100 mL of 2:1 acetone:ethanol. The solids were dried in a vacuum oven at 70 °C to give 22.15 g (27.3 mmol, 76.3%) of the desired product.



Carbon Treatment and Recrystallization of Compound (I)

A solution of Compound (I) was prepared by dissolving 3.17 g of Compound (I) from above in 22 mL methanol. The solution was passed through a 47mm Cuno Zeta Carbon® 53SP filter at ~5 psig at a flow rate of ~58mL/min. The carbon filter was rinsed with 32 mL of methanol. The solution was concentrated down to 16 mL by vacuum distillation. While maintaining a temperature of 40-50 °C, 15.9 mL acetone and 5 mg of seed crystals of Compound (I) (see procedure below) were added. The resulting slurry was then charged with 32 mL acetone over 30 minutes. The slurry was held at 50 °C for 2 hours, cooled to 20 °C over about 1 hour and held at 20 °C for about 20 hours. The solids were filtered, washed with 16 mL 2:1 acetone:methanol and dried in a vacuum oven at 60 °C to give 2.14 g (67.5%) of purified Compound (I): ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C): 8.02 (d, J=8.34 Hz, 4 H), 7.97 (s, 2 H), 7.86 (d, J=8.34 Hz, 4 H), 6.75 (s, 2 H), 5.27 (t, J=6.44 Hz, 2 H), 4.17 (t, J=6.95 Hz, 2 H), 3.97 - 4.11 (m, 2 H), 3.74 - 3.90 (m, 2 H), 3.57 (s, 6 H), 2.32 - 2.46 (m, 2 H), 2.09 - 2.31 (m, 6 H), 1.91 - 2.07 (m, 2 H), 0.88 (d, J=6.57 Hz, 6 H), 0.79 (d, J=6.32 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.9, 156.9, 149.3, 139.1, 131.7, 127.1, 126.5, 125.9, 115.0, 57.9, 52.8, 51.5, 47.2, 31.1, 28.9, 24.9, 19.6, 17.7; IR (neat, cm^{-1}): 3385, 2971, 2873, 2669, 1731, 1650. Anal. Calcd for $C_{40}H_{52}N_8O_6Cl_2$: C, 59.18; H, 6.45; N, 13.80; Cl, 8.73. Found C, 59.98; H, 6.80; N, 13.68; Cl, 8.77. mp 267 °C (decomposed).

Preparation of Seed Crystals of Compound (I)

A 250 mL round-bottom flask was charged with 6.0g (10.5 mmol, 1 equiv) Compound 5, 3.87g (22.1 mmol, 2.1 equiv) N-(methoxycarbonyl)-L-valine, 4.45g (23.2 mmol, 2.2 equiv) 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.289 g (2.14 mmol, 0.2 equiv) 1-hydroxybenzotriazole, and 30 mL acetonitrile. The resulting slurry was then charged with 7.33 mL (42.03 mmol, 4

equiv) diisopropylethylamine and allowed to stir at 24-30 °C for about 18 hours. The mixture was charged with 6 mL of water and heated to 50 °C for about 5 hours. The mixture was cooled and charged with 32 mL ethyl acetate and 30 mL water. The layers were separated and the rich organic layer was washed with 30 mL of 10 wt% aqueous $NaHCO_3$, 30 mL water, and 20 mL of 10 wt% aqueous NaCl. The rich organic layer was then dried over $MgSO_4$, filtered, and concentrated down to a residue. The crude material was then purified via flash chromatography (silica gel, 0-10% methanol in dichloromethane) to provide the free base of Compound (I).

The free-base of Compound (I) (0.03g) was dissolved in 1 mL isopropanol at 20 °C. Anhydrous HCl (70 μL, dissolved in ethanol, approximately 1.25M concentration) was added and the reaction mixture was stirred. To the solution was added methyl *tert*-butyl ether (1 mL) and the resulting slurry was stirred vigorously at 40 °C to 50 °C for 12 hours. The crystal slurry was cooled to 20 °C and filtered. The wet cake was air-dried at 20 °C. A white crystalline solid (Form N-2 of Compound (I)) was obtained.

Form N-2 was analyzed using one or more of the testing methods described below.

1 Single Crystal X-Ray Measurements

A Bruker APEX2 Kappa CCD diffractometer equipped with a rotating anode generator of Cu Kα radiation, (λ = 1.54178 Å) was used to collect diffraction data at the room temperature. Indexing and processing of the measured intensity data were carried out with the APEX2 software package/program suite (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27; BRUKER AXS, INc., 5465 East Cheryl Parkway, Madison, WI 53711 USA). The final unit cell parameters were determined using the entire data set.

The structure was solved by direct methods and refined by the full-matrix least-squares techniques, using the SHELXTL software package (Sheldrick, GM. 1997, SHELXTL. Structure Determination Programs. Version 5.10, Bruker AXS, Madison, Wisconsin, USA.). The function minimized in the refinements was $\Sigma w(|F_o| - |F_c|)^2$. R is defined as $\Sigma ||F_o| - |F_c||/\Sigma |F_o|$ while $R_w = [\Sigma_w(|F_o| - |F_c|)^2/\Sigma_w |Fo|^2]^{1/2}$,

where w is an appropriate weighting function based on errors in the observed intensities. Difference Fourier maps were examined at all stages of refinement. All non-hydrogen atoms were refined with anisotropic thermal displacement parameters. The hydrogen atoms associated with hydrogen bonding were located in the final difference Fourier maps while the positions of the other hydrogen atoms were calculated from an idealized geometry with standard bond lengths and angles. They were assigned isotropic temperature factors and included in structure factor calculations with fixed parameters.

The crystal data of the N-2 form is shown in Table 2. The fractional atomic coordinates are listed in Table 3. It should be understood by one of ordinary skill in the art that slight variations in the coordinates are possible and are considered to be within the scope the present disclosure.

Table 2. Crystal Data of Form N-2

Temperature	room temperature	
Wavelength	1.54178 Å	
Crystal system, space group	Triclinic, P1	
Unit cell dimensions	a = 7.5680(2) Å	alpha = 74.132(2) °
	b = 9.5848(3) Å	beta = 84.132(2) °
	c = 16.2864(5) Å	gamma = 70.646(2) °
Volume	1072.06(5) $Å^3$	
Z, Calculated density	1, 1.257 Mg/m^3	

Table 3. Atomic coordinates

Atom	*X*	*Y*	*Z*	*Atom*	*X*	*Y*	*Z*
C7	0.0807	-0.0688	0.0165	H3	0.0264	0.2281	-0.0035
C16	-0.5489	0.4635	-0.1121	H17	-0.7884	0.4046	-0.0848
C4	-0.0807	0.0688	-0.0165	H2	-0.2192	0.4393	-0.0575
C18	-0.7034	0.6975	-0.1863	H5	-0.2549	-0.0380	-0.0365
C13	0.5516	-0.4628	0.1105	H6	-0.5015	0.1728	-0.0892
C15	0.7037	-0.6988	0.1841	H9	0.5090	-0.1737	0.0755
C3	-0.0789	0.2157	-0.0218	H14	0.7875	-0.4013	0.0906

Atom	*X*	*Y*	*Z*	*Atom*	*X*	*Y*	*Z*
C10	0.3885	-0.3317	0.0771	H12	-0.0376	-0.2264	0.0165
C1	-0.3895	0.3303	-0.0781	H11	0.2109	-0.4403	0.0683
C17	-0.7335	0.4794	-0.1115	H8	0.2590	0.0389	0.0270
C2	-0.2275	0.3428	-0.0531	H19	0.8664	-0.8827	0.2693
C5	-0.2458	0.0584	-0.0412	H20A	0.6721	-0.9411	0.1489
C6	-0.3950	0.1847	-0.0720	H20B	0.8848	-1.0218	0.1745
C9	0.3978	-0.1858	0.0641	H22A	0.4299	-0.9831	0.2863
C14	0.7330	-0.4774	0.1143	H22B	0.5433	-1.0623	0.3720
C12	0.0728	-0.2143	0.0290	H24	0.4288	-0.8972	0.4553
C11	0.2233	-0.3439	0.0597	H29A	0.3610	-0.6896	0.7199
C8	0.2471	-0.0573	0.0347	H29B	0.5410	-0.6388	0.7042
C19	0.7480	-0.8565	0.2404	H29C	0.5552	-0.8060	0.7046
C20	0.7591	-0.9804	0.1959	H26A	0.0099	-0.5669	0.3086
C22	0.5494	-1.0075	0.3126	H26B	0.2158	-0.5619	0.2923
C24	0.3932	-0.7895	0.4232	H26C	0.1027	-0.5160	0.3723
C28	0.4299	-0.7573	0.5628	H25	0.2074	-0.8105	0.3478
C29	0.4783	-0.7007	0.6895	H21A	0.6629	-1.1660	0.2427
C26	0.1249	-0.5830	0.3353	H21B	0.8099	-1.1619	0.3036
C25	0.1972	-0.7461	0.3866	H27A	0.0368	-0.7163	0.4938
C21	0.7052	-1.0999	0.2661	H27B	0.1093	-0.8874	0.4894
C27	0.0588	-0.7834	0.4569	H27C	-0.0572	-0.7699	0.4319
C23	0.5435	-0.7711	0.3553	H30	-0.6271	0.8706	-0.2714
C30	-0.7440	0.8547	-0.2454	H31A	-0.9249	0.9498	-0.1547
C34	-0.8171	0.7743	-0.3628	H31B	-0.7674	1.0278	-0.1856
C31	-0.8522	0.9853	-0.2037	H33A	-1.1460	0.9828	-0.2916
C33	-1.0373	1.0092	-0.3191	H33B	-1.0659	1.0635	-0.3783
C32	-0.9782	1.1019	-0.2736	H32A	-1.0859	1.1679	-0.2499
C38	-0.8340	0.7734	-0.5748	H32B	-0.9111	1.1645	-0.3120
C36	-1.1117	0.7288	-0.3922	H36	-1.1758	0.7856	-0.3502
C39	-0.6953	0.7302	-0.7067	H39A	-0.7874	0.7037	-0.7301
C37	-1.0485	0.5605	-0.3464	H39B	-0.5733	0.6820	-0.7276
C35	-0.9477	0.7893	-0.4312	H39C	-0.7221	0.8392	-0.7235
N1	0.5385	-0.6067	0.1537	H37A	-1.1562	0.5276	-0.3279

Atom	*X*	*Y*	*Z*	*Atom*	*X*	*Y*	*Z*
N4	-0.5358	0.6044	-0.1590	H37B	-0.9757	0.5444	-0.2977
N2	0.8232	-0.6215	0.1585	H37C	-0.9736	0.5027	-0.3846
N3	-0.8254	0.6252	-0.1572	H35	-0.9995	0.8976	-0.4608
N6	-0.8719	0.8722	-0.3123	H1	0.4378	-0.6316	0.1597
N5	0.5974	-0.8687	0.3055	II4	-0.4338	0.6276	-0.1688
N8	-0.8375	0.7087	-0.4913	H2A	0.9413	-0.6576	0.1685
N7	0.3941	-0.6991	0.4812	H3A	-0.9442	0.6631	-0.1654
O4	-0.6651	0.6742	-0.3518	H8A	-0.7710	0.6146	-0.4726
O1	0.6094	-0.6663	0.3446	H7	0.3699	-0.6020	0.4611
O2	0.4413	-0.8890	0.6028	H40A	-1.1909	0.7164	-0.5066
O3	0.4448	-0.6524	0.5991	H40B	-1.3113	0.8675	-0.4819
O5	-0.9383	0.8955	-0.6125	H40C	-1.3481	0.7128	-0.4362
O6	-0.7001	0.6782	-0.6138				
C40	-1.2538	0.7592	-0.4606				
Cl1	-0.2486	0.7587	-0.1475				
Cl2	0.2421	-0.7524	0.1377				

2. *Powder X-Ray Diffraction*

About 200mg were packed into a Philips powder X-ray diffraction (PXRD) sample holder. The sample was transferred to a Philips MPD unit (45 KV, 40mA, Cu Kα). Data were collected at room temperature in the 2 to 32 2θ range (continuous scanning mode, scanning rate 0.03 degrees/sec., auto divergence and anti scatter slits, receiving slit: 0.2 mm, sample spinner: ON).

The results of the PXRD pattern and a simulated pattern calculated from the single crystal data are shown in FIG. 1.

Table 4 lists the characteristic PXRD peaks that describe Form N-2 of Compound (I).

Table 4. Characteristic diffraction peak positions (degrees 2θ ± 0.1) at room temperature, based on a high quality pattern collected with a diffractometer (cuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard.

Form N-2
10.3
12.4
12.8
13.3
13.6
15.5
20.3
21.2
22.4
22.7
23.7

3. *Differential Scanning Calorimetry*

Differential scanning calorimetry (DSC) experiments were performed in a TA Instruments ™ model Q2000, Q1000 or 2920. The sample (about 2-6mg) was weighed in an aluminum pan and recorded accurately to a hundredth of a milligram, and transferred to the DSC. The instrument was purged with nitrogen gas adt 50 mL/min. Data were collected between room temperature and 300 °C at 10 °C/min heating rate. The plot was made with the endothermic peaks pointing down.

The results are shown in FIG. 2.

4. *Solid-State NMR (SSNMR)*

All solid-state C-13 NMR measurements were made with a Bruker DSX-400, 400 MHz NMR spectromter. High resolution spectra were obtained using high-power proton decoupling and the TPPM pulse sequence and ramp amplitude cross-polarization (RAMP-CP) with magic-angle spinning (MAS) at approximately 12 kHz (A.E. Bennett et al. *J. Chem. Phys.* **1995**, *103*, 6951). (G. Metz, X. Wu, and S.O. Smith, *J. Magn. Reson. A.*, **1994**, *110*, 219-227). Approximately 70 mg of sample, packed into a canister-design zirconia rotor was used for each experiment. Chemical shifts (δ) were referenced to external adamantane with the high frequency resonance

being set to 38.56 ppm (W.L. Earl and D.L. VanderHart, *J. Magn. Reson.*, **1982**, *48*, 35-54).

The SSNMR spectrum is shown in FIG. 3.

Table 5 lists the characteristic SSNMR peaks that describe Form N-2 of Compound (I).

Table 5: SSNMR peak positions of Form N-2 of Compound (I). Peak positions δ (in ppm) relative to TMS scale.

Form N-2
14.8
15.3
19.6
20.4
25.1
25.6
28.4
29.3
29.3
30.1
32.3
46.8
51.6
54.3
55.2
57.5
57.8
58.2
111.7
113.1
125.4
127.4
128.5
132.6

133.7
138.8
150.5
151.9
156.7
169.9

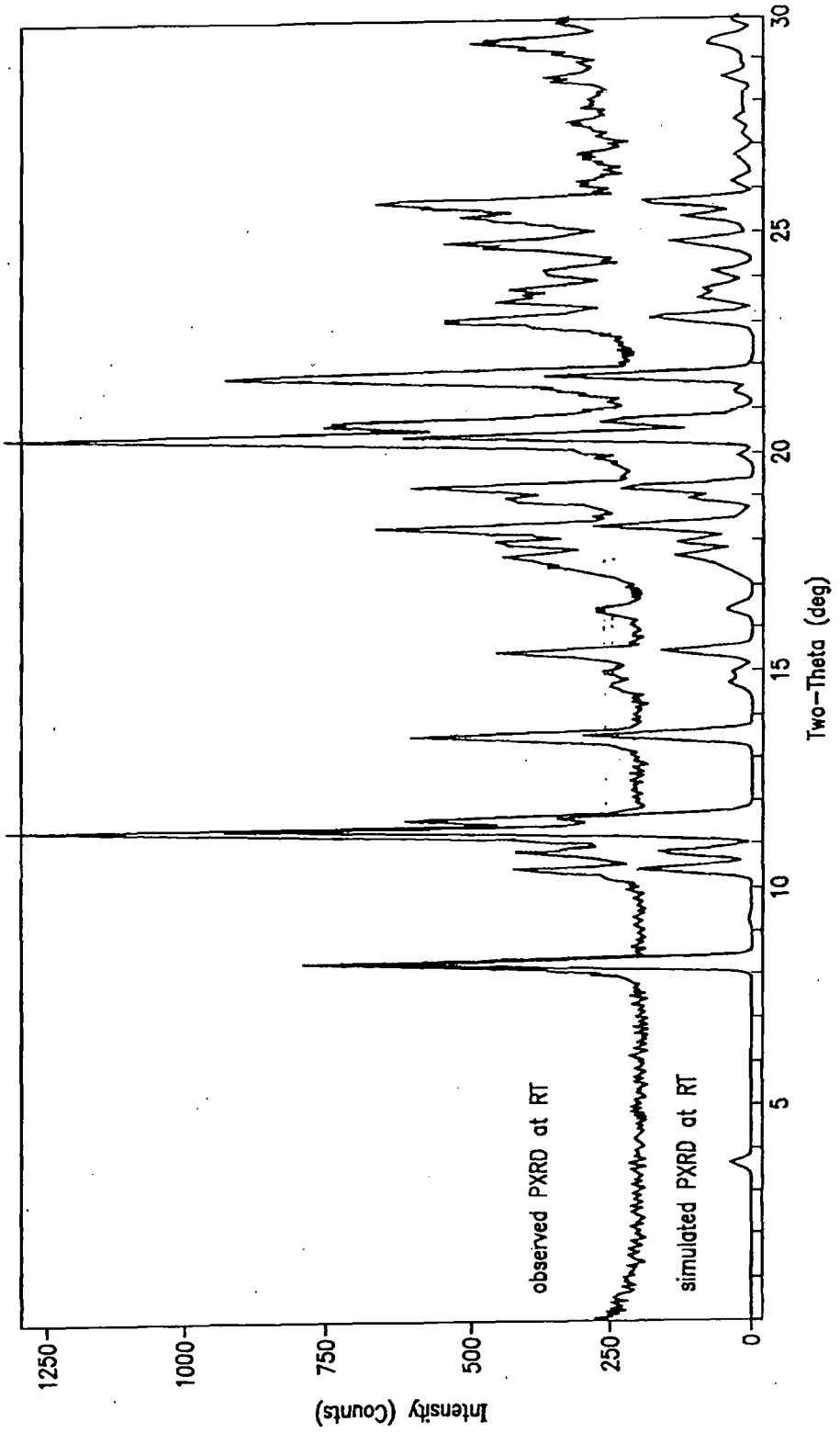


FIG. 1

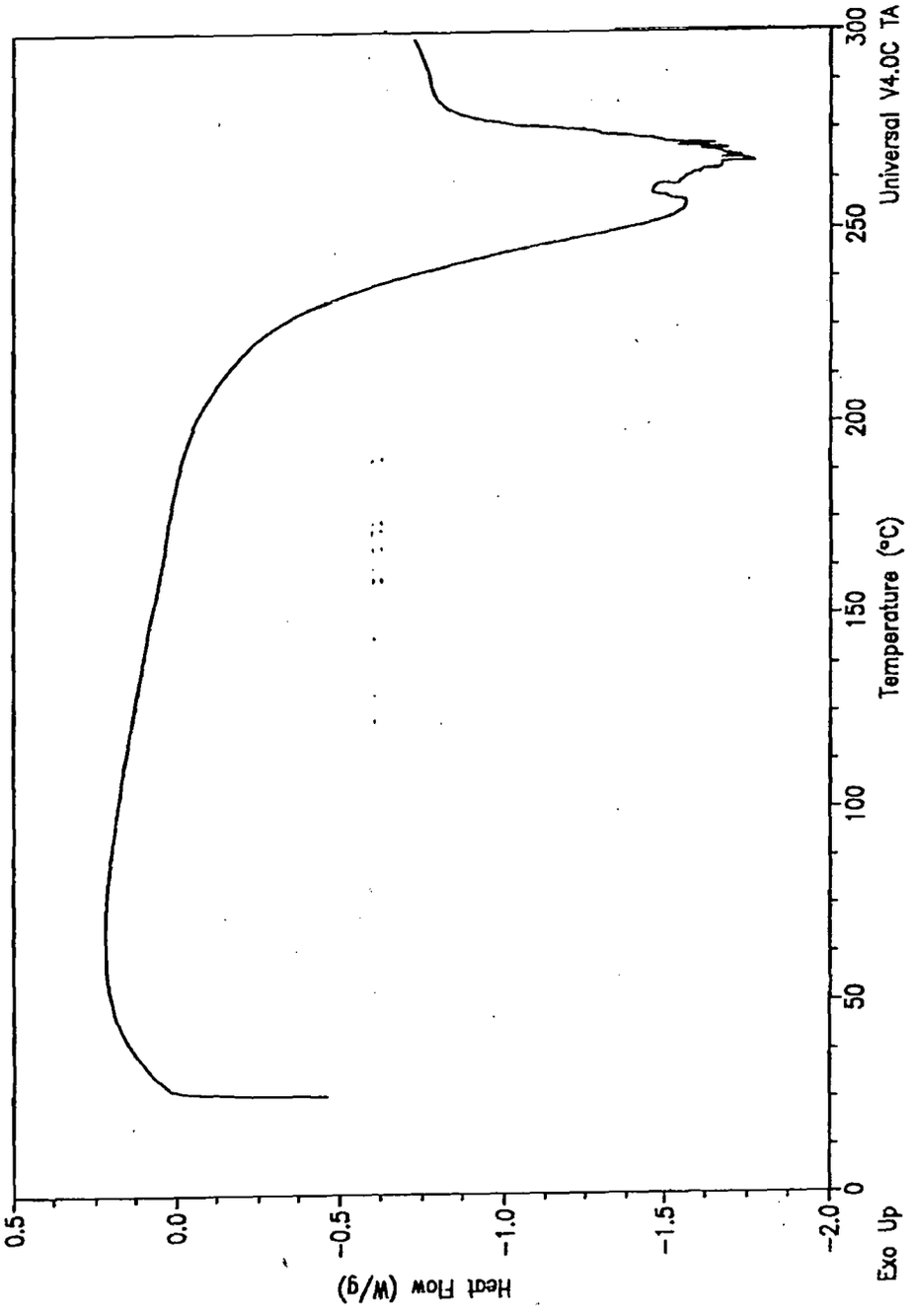


FIG. 2

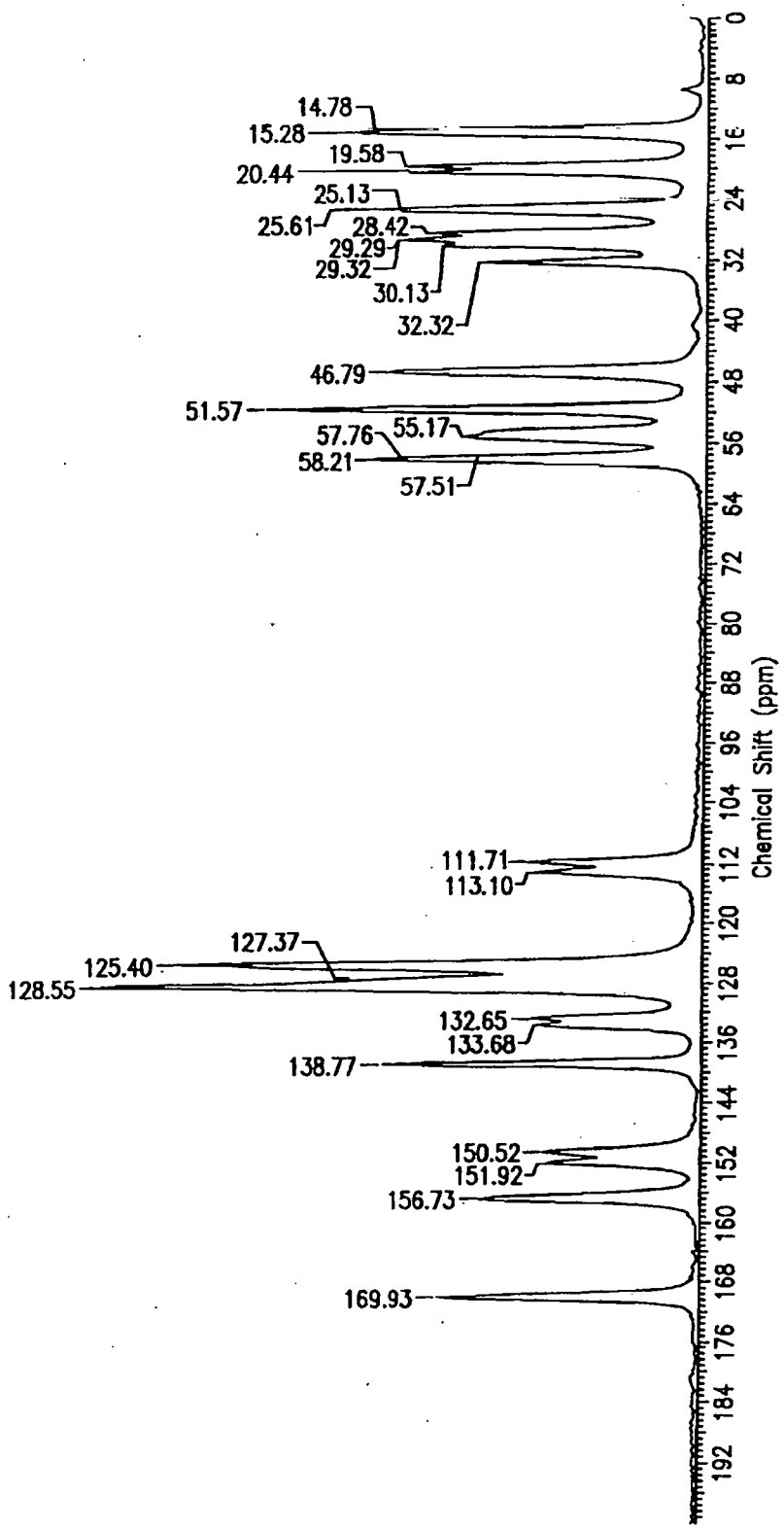
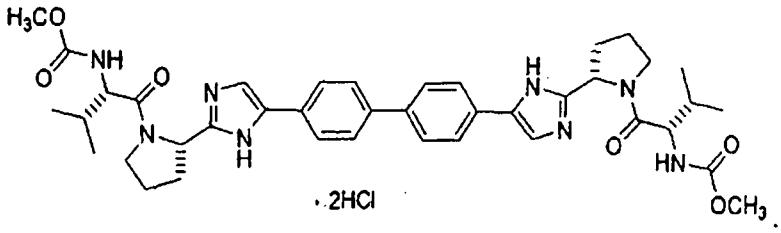


FIG. 3

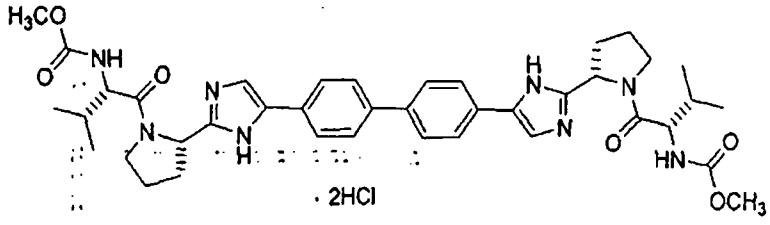
CLAIMS

What is claimed is:

1. Form N-2 of



2. Form N-2 of



characterized by the following unit cell parameters:

Cell dimensions: a = 7.5680 Å

b= 9.5848 Å

c = 16.2864 Å

α = 74.132 degrees

β = 84.132 degrees

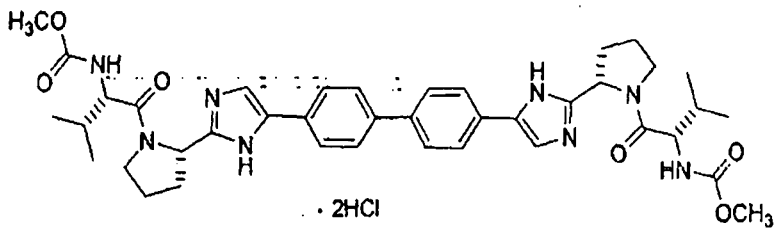
γ = 70.646 degrees

Space group P1

Molecules/unit cell 1

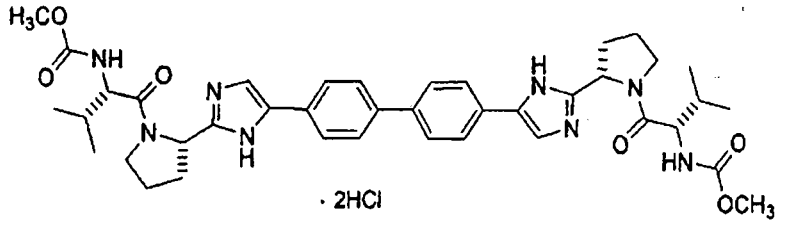
wherein measurement of said crystalline form is at a temperature between about 20 °C to about 25 °C.

3. Form N-2 of



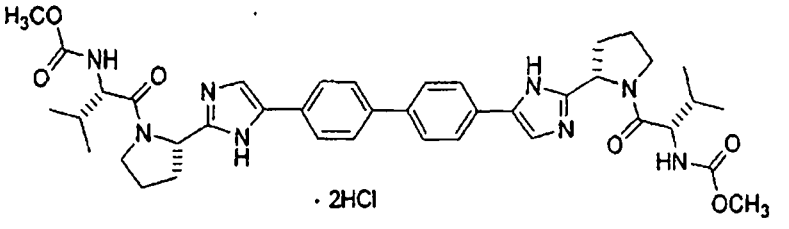
characterized by fractional atomic coordinates within the unit cell as listed in Table 3.

4. Form N-2 of



with characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C.

5. Form N-2 of



characterized by one or more of the following:

a) a unit cell with parameters substantially equal to the following:

Cell dimensions: a = 7.5680 Å

b= 9.5848 Å

c = 16.2864 Å

α = 74.132 degrees

β = 84.132 degrees

γ = 70.646 degrees

Space group P1

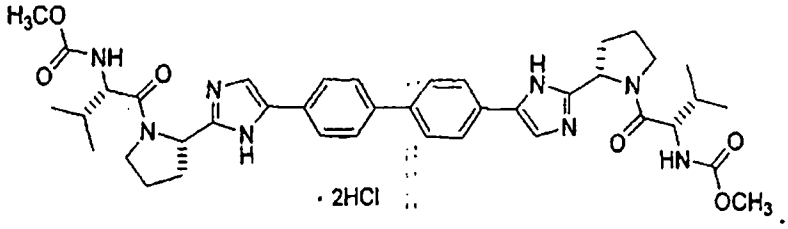
Molecules/unit cell 1

wherein measurement of said crystalline form is at a temperature between about 20 °C to about 25 °C;

b) characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C; and/or

c) a melt with decomposition endotherm with onset typically in the range of 225-245 °C.

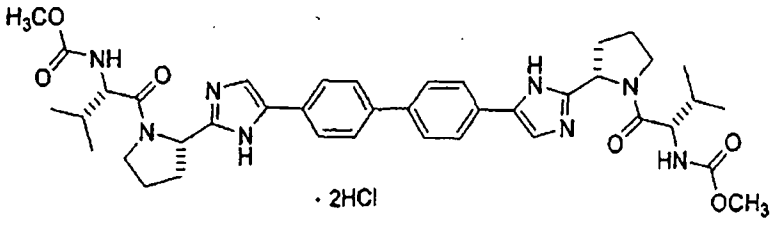
6. Substantially pure Form N-2 of



7. The form of Claim 6 wherein said Form N-2 has a purity of at least 95 weight percent.

8. The form of Claim 6 wherein said Form N-2 has a purity of at least 99 weight percent.

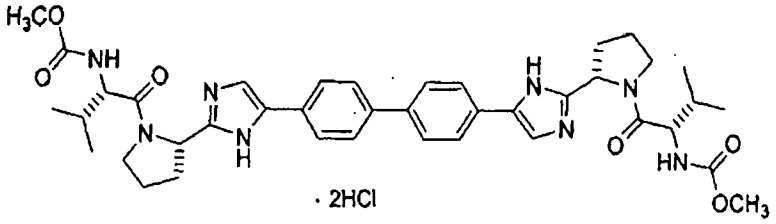
9. Substantially pure Form N-2 of



with characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0.1, 13.6 ± 0.1, 15.5 ± 0.1, 20.3 ±

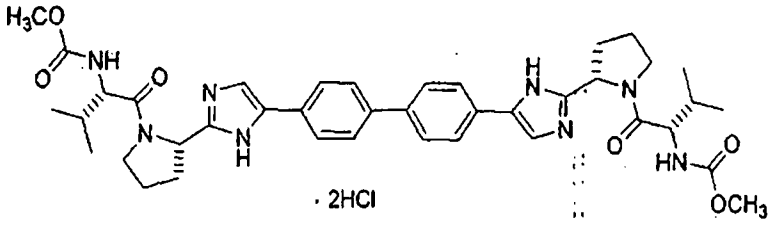
0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C.

10. A pharmaceutical composition comprising Form N-2 of



and a pharmaceutically acceptable carrier or diluent.

11. A pharmaceutical composition comprising substantially pure Form N-2 of

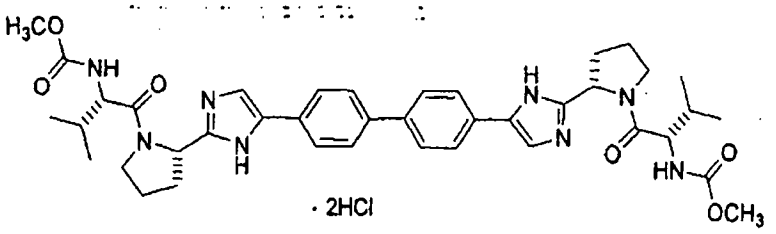


and a pharmaceutically acceptable carrier or diluent.

12. The pharmaceutical composition of Claim 11 wherein said Form N-2 has a purity of at least 95 weight percent.

13. The pharmaceutical composition of Claim 11 wherein said Form N-2 has a purity of at least 99 weight percent.

14. A pharmaceutical composition comprising Form N-2 of



in combination with one or two additional compounds having anti-HCV activity.

15. The pharmaceutical composition of Claim 14 wherein said Form N-2 has a purity of at least 90 weight percent.

16. The pharmaceutical composition of Claim 14 wherein said Form N-2 has a purity of at least 95 weight percent.

17. The pharmaceutical composition of Claim 14 wherein said Form N-2 has a purity of at least 99 weight percent.

18. The composition of Claim 14 wherein at least one of the additional compounds having anti-HCV activity is an interferon or ribavirin.

19. The composition of Claim 18 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

20. The composition of Claim 14 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

Dated this 05/02/2010

(HRISHIKESH RAY CHAUDHURY)
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANT[S]

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ABSTRACT

The present disclosure generally relates to a crystalline form of methyl ((1*S*)-1-(((2*S*)-2-(5-(4'-(2-((2*S*)-1-((2*S*)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1*H*-imidazol-5-yl)-4-biphenylyl)-1*H*-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride salt. The present disclosure also generally relates to a pharmaceutical composition comprising a crystalline form, as well of methods of using a crystalline form in the treatment of Hepatitis C and methods for obtaining such crystalline form.

ANNEXURE - B

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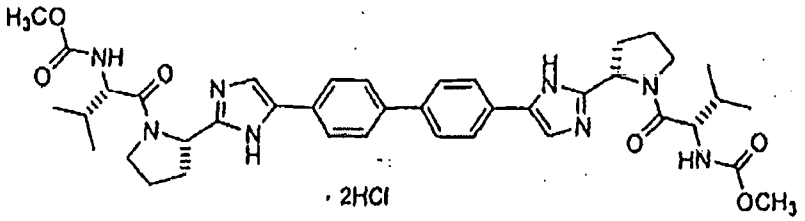
WE CLAIM:

1. Form N-2 of



characterized by one or more of the following:

a) a unit cell with parameters substantially equal to the following:

Cell dimensions: a = 7.5680 Å

b= 9.5848 Å

c = 16.2864 Å

α = 74.132 degrees

β = 84.132 degrees

γ = 70.646 degrees

Space group P1

Molecules/unit cell 1

wherein measurement of said crystalline form is at a temperature between 20°C to 25 °C;

b) characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1, 12.4 ± 0.1, 12.8 ± 0.1, 13.3 ± 0,1, 13.6 ± 0.1, 15.5 ± 0,1, 20.3 ± 0.1, 21.2 ± 0.1, 22.4 ± 0.1, 22.7 ± 0.1, and 23.7 ± 0.1 at a temperature between 20°C and 25 °C; and/or

c) a melt with decomposition endotherm with onset typically in the range of 225-245 °C.

2. The form as claimed in claim 1 having a purity of at least 90 weight percent.

3. The form as claimed in claim 2 having a purity of at least 95 weight percent.

4. The form as claimed in claim 2 having a purity of at least 99 weight percent.

5. A pharmaceutical composition comprising Form N-2 as claimed in any one of claims 1 to 4 and a pharmaceutically acceptable carrier or diluent, optionally in combination with one or two additional compounds having anti-HCV activity.

6. The pharmaceutical composition as claimed in claim 5 wherein said Form N-2, if combined with one or two additional compounds having anti-HCV activity, has a purity of at least 90 weight percent.

7. The pharmaceutical composition as claimed in claim 6 wherein said Form N-2, if combined with one or two additional compounds having anti-HCV activity, has a purity at least 95 weight percent.

8. The pharmaceutical composition as claimed in claim 6 wherein said Form N-2, if combined with one or two additional compounds having anti-HCV activity, has a purity at least 99 weight percent.

9. The composition as claimed in any one of claims 5 to 8 wherein at least one of the additional compounds having anti-HCV activity is an interferon or ribavirin.

10. The composition as claimed in claim 9 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

11. The composition as claimed in claim 5 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

12. A compound as claimed in any one of claims 1 to 4 for use in a method of treating HCV infection

Dated this 05/02/2010

[AMIT SAINI]
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

ANNEXURE – C

UU853 DELNP 77

-5 FEB 2009

FORM 2
THE PATENTS ACT 1970
[39 OF 1970]
&
THE PATENTS (AMENDMENT) RULES, 2006
COMPLETE SPECIFICATION

[See Section 10; rule 13]

"HEPATITIS C VIRUS INHIBITORS"

BRISTOL-MYERS SQUIBB COMPANY, a corporation of the State of Delaware, of Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, United States of America,

The following specification particularly describes the invention and the manner in which it is to be performed:

ORIGINAL

HEPATITIS C VIRUS INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial Number 60/836,996 filed August 11, 2006.

The present disclosure is generally directed to antiviral compounds, and more specifically directed to compounds which can inhibit the function of the NS5A protein encoded by Hepatitis C virus (HCV), compositions comprising such compounds, and methods for inhibiting the function of the NS5A protein.

HCV is a major human pathogen, infecting an estimated 170 million persons worldwide - roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma.

Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients. Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection.

HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins *via* translation of a single, uninterrupted, open reading frame.

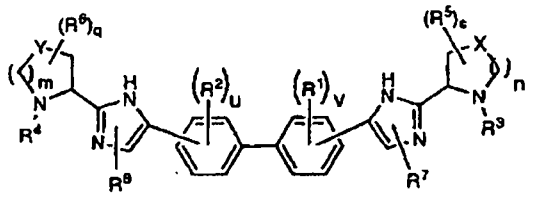
Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the

possible effect of genotypes on pathogenesis and therapy.

The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one is believed to be a metalloprotease and cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (also referred to herein as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B (also referred to herein as HCV polymerase) is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

Compounds useful for treating HCV-infected patients are desired which selectively inhibit HCV viral replication. In particular, compounds which are effective to inhibit the function of the NS5A protein are desired. The HCV NS5A protein is described, for example, in Tan, S.-L., Katzel, M.G. *Virology* 2001, *284*, 1-12; and in Park, K.-J.; Choi, S.-H, *J. Biological Chemistry* 2003.

In a first aspect the present disclosure provides a compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein

m and *n* are independently 0, 1, or 2;

q and s are independently 0, 1, 2, 3, or 4;

u and v are independently 0, 1, 2, or 3;

X is selected from O, S, S(O), SO_2, CH_2, CHR^5, and $C(R^5)_2$;

provided that when n is 0, X is selected from CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from O, S, S(O), SO_2, CH_2, CHR^6, and $C(R^6)_2$;

provided that when m is 0, Y is selected from CH_2, CHR^6, and $C(R^6)_2$;

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxy, hydroxyalkyl, $-NR^aR^b$, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl;

R^3 and R^4 are each independently selected from hydrogen, R^9-C(O)-, and R^9-C(S)-;

each R^5 and R^6 is independently selected from alkoxy, alkyl, aryl, halo, haloalkyl, hydroxy, and $-NR^aR^b$, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

R^7 and R^8 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, (NR^aR^b)carbonyl, and trialkylsilylalkoxyalkyl; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

In a first embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein m and n are each 1.

In a second embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

u and v are each independently 0, 1, or 2; and

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxyalkyl, (NR^aR^b)alkyl, and (NR^aR^b)carbonyl.

In a third embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

u and v are each independently 0 or 1; and

when present, R^1 and/or R^2 are halo.

In a fourth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

u and v are each independently 0 or 1; and

when present, R^1 and/or R^2 are halo, wherein the halo is fluoro.

In a fifth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of X and Y is S.

In a sixth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein X and Y are each S.

In a seventh embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein X is selected from CHR^5; and $C(R^5)_2$; and Y is selected from CH_2, CHR^6, and $C(R^6)_2$.

In an eighth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8 are independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl.

In a ninth embodiment of the first aspect the present dislcosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8 are each hydrogen.

In a tenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2; and

each R^5 and R^6 is independently selected from alkyl, aryl, halo, and hydroxy, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups.

In an eleventh embodiment of the first aspect the present dislcosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0 or 1; and

when present, R^5 and/or R^6 are each halo.

In a twelfth embodiment of the first aspect the present dislcosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0 or 1; and

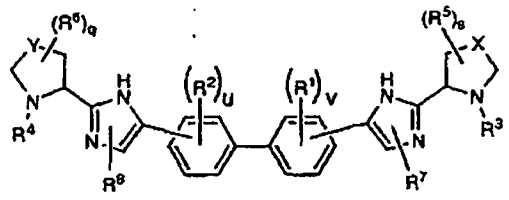
when present, R^5 and/or R^6 are each halo, wherein the halo is fluoro.

In a thirteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of R^3 and R^4 is hydrogen.

In a fourteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^3 and R^4 are each R^9-C(O)-.

In a fifteenth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein each R^9 is independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, -NR^cR^d, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

In a second aspect the present disclosure provides a compound of Formula (II)



(II),

or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2;

u and v are independently 0, 1, or 2;

X is selected from S, CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from S, CH_2, CHR^6, and $C(R^6)_2$;

each R^1 and R^2 is independently selected from alkoxy, alkoxyalkyl, alkyl, arylalkoxycarbonyl, carboxy, formyl, halo, haloalkyl, hydroxyalkyl, (NR^aR^b)alkyl,

and (NR^aR^b)carbonyl;

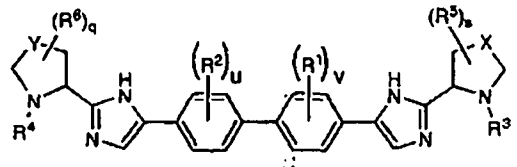
R^3 and R^4 are each independently selected from hydrogen and R^9-C(O)-;

each R^5 and R^6 is independently selected from alkyl, aryl, halo, and hydroxy, wherein the alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom, wherein the three- to six-membered ring is optionally substituted with one or two alkyl groups;

R^7 and R^8 are each independently selected from hydrogen, alkoxycarbonyl, alkyl, arylalkoxycarbonyl, carboxy, haloalkyl, and (NR^aR^b)carbonyl; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, heterocyclyl, heterocyclylalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

In a third aspect the present disclosure provides a compound of Formula (III)



(III);

or a pharmaceutically acceptable salt thereof, wherein

q and s are independently 0, 1, or 2;

u and v are independently 0 or 1;

X is selected from CH_2, CHR^5, and $C(R^5)_2$;

Y is selected from CH_2, CHR^6, and $C(R^6)_2$;

when present, R^1 and/or R^2 are halo, wherein the halo is fluoro;

R^3 and R^4 are each R^9-C(O)-;

when present, R^5 and/or R^6 are halo, wherein the halo is fluoro; and

each R^9 is independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonylalkyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, aryloxyalkyl, cycloalkyl, (cycloalkyl)alkenyl, (cycloalkyl)alkyl, cycloalkyloxyalkyl, haloalkyl, heterocyclyl, heterocyclylalkenyl, heterocyclylalkoxy, heterocyclylalkyl, heterocyclyloxyalkyl, hydroxyalkyl, $-NR^cR^d$, (NR^cR^d)alkenyl, (NR^cR^d)alkyl, and (NR^cR^d)carbonyl.

In a fourth aspect the present disclosure provides a compound selected from

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine);

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(diethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate;

methyl ((1S)-1-(((2S)-2-(4-(4'-(2-((2S)-4,4-difluoro-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-4-yl)-4-biphenylyl)-1H-imidazol-2-yl)-4,4-difluoro-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1S)-1-(((1R,3R,5R)-3-(5-(4'-(2-((1R,3R,5R)-2-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-azabicyclo[3.1.0]hex-3-yl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-2-azabicyclo[3.1.0]hex-2-yl)carbonyl)-2-methylpropyl)carbamate;

methyl ((1R)-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethyl)carbamate;

methyl ((1S)-2-methyl-1-(((2S)-2-(5-(4'-(2-((2S)-1-(N-2-pyrimidinyl-D-valyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)propyl)carbamate;

methyl ((1R)-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-2-(dimethylamino)-2-phenylacetyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-2-oxo-1-phenylethyl)carbamate;

dimethyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl((1R)-2-oxo-1-phenyl-2,1-ethanediyl)))biscarbamate;

(1R)-N,N-dimethyl-2-oxo-1-phenyl-2-((2S)-2-(5-(4'-(2-((2S)-1-((2R)-tetrahydro-2-furanylcarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)ethanamine;

methyl ((1S)-2-((2S)-2-(5-(4'-(2-((2S)-1-(N-(methoxycarbonyl)-L-alanyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)-1-methyl-2-oxoethyl)carbamate; and

methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3,3-dimethylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2,2-dimethylpropyl)carbamate;
or a pharmaceutically acceptable salt thereof.

In a first embodiment of the fifth aspect the pharmaceutically acceptable salt is a dihydrochloride salt.

In a sixth aspect the present disclosure provides a composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a first embodiment of the sixth aspect the composition further comprises one or two additional compounds having anti-HCV activity. In a second embodiment at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth embodiment of the sixth aspect the composition further comprises one or two additional compounds having anti-HCV activity wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

In a fifth embodiment of the sixth aspect the composition further comprises one or two additional compounds having anti-HCV activity wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

In an seventh aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In a first embodiment of the seventh aspect the method further comprises administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of formula (I), or a pharmaceutically

acceptable salt thereof. In a second embodiment at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth embodiment the method further comprises administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

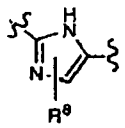
In a fifth embodiment the method further comprises administering one or two additional compounds having anti-HCV activity prior to, after or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B portein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

Other embodiments of the present disclosure may comprise suitable combinations of two or more of embodiments and/or aspects disclosed herein.

Yet other embodiments and aspects of the disclosure will be apparent according to the description provided below.

The compounds of the present disclosure also exist as tautomers; therefore the present disclosure also encompasses all tautomeric forms.

The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order accommodate a substitutent at any given location. For example, in the structure shown below



R^8 may be attached to either the carbon atom in the imidazole ring or, alternatively, R^8 may take the place of the hydrogen atom on the nitrogen ring to form an N-substituted imidazole.

It should be understood that the compounds encompassed by the present disclosure are those that are suitably stable for use as pharmaceutical agent.

It is intended that the definition of any substituent or variable (e.g., R^1, R^2, R^5, R^6, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, when u is 2, each of the two R^1 groups may be the same or different.

All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

As used in the present specification, the following terms have the meanings indicated:

As used herein, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

Unless stated otherwise, all aryl, cycloalkyl, and heterocyclyl groups of the present disclosure may be substituted as described in each of their respective definitions. For example, the aryl part of an arylalkyl group may be substituted as described in the definition of the term 'aryl'.

The term "alkenyl," as used herein, refers to a straight or branched chain group of two to six carbon atoms containing at least one carbon-carbon double bond.

The term "alkenyloxy," as used herein, refers to an alkenyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkenyloxycarbonyl," as used herein, refers to an alkenyloxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

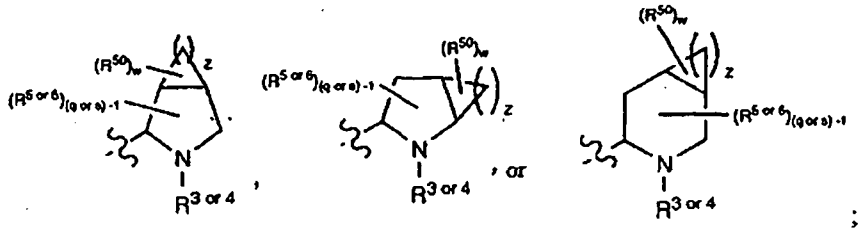
The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

The term "alkoxyalkylcarbonyl," as used herein, refers to an alkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxycarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxycarbonyl groups.

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to six carbon atoms. In the compounds of the present disclosure, when m and/or n is 1 or 2; X and/or Y is CHR^5 and/or CHR^6, respectively, and R^5 and/or R^6 is alkyl, each alkyl can optionally form a fused three- to six-membered ring with an adjacent carbon atom to provide one of the structures shown below:



where z is 1, 2, 3, or 4, w is 0, 1, or 2, and R^{50} is alkyl. When w is 2, the two R^{50} alkyl groups may be the same or different.

The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkylcarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkylcarbonyl groups.

The term "alkylcarbonyloxy," as used herein, refers to an alkylcarbonyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkylsulfanyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfur atom.

The term "alkylsulfonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "aryl," as used herein, refers to a phenyl group, or a bicyclic fused ring system wherein one or both of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a four- to six-membered aromatic or non-aromatic carbocyclic ring. The aryl groups of the present disclosure can be attached to the parent molecular moiety through any substitutable carbon atom in the group.

Representative examples of aryl groups include, but are not limited to, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, a second aryl group, arylalkoxy, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, $-NR^xR^y$, (NR^xR^y)alkyl, oxo, and $-P(O)OR_2$, wherein each R is independently selected from hydrogen and alkyl; and wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the second aryl group, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "arylalkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three aryl groups.

The term "arylalkoxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

The term "arylalkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three arylalkoxy groups.

The term "arylalkoxyalkylcarbonyl," as used herein, refers to an arylalkoxyalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "arylalkoxycarbonyl," as used herein, refers to an arylalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "arylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryl groups. The alkyl part of the arylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, and $-NR^cR^d$, wherein the heterocyclyl is further optionally substitued with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstituted arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and $-NR^xR^y$.

The term "arylalkylcarbonyl," as used herein, refers to an arylalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "arylcarbonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a carbonyl group.

The term "aryloxy," as used herein, refers to an aryl group attached to the parent molecular moiety through an oxygen atom.

The term "aryloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryloxy groups.

The term "aryloxycarbonyl," as used herein, refers to an aryloxy group attached to the parent molecular moiety through a carbonyl group.

The term "arylsulfonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a sulfonyl group.

The terms "Cap" and "cap" as used herein, refer to the group which is placed on the nitrogen atom of the terminal nitrogen-containing ring, i.e., the pyrrolidine rings of compound 1e. It should be understood that "Cap" or "cap" can refer to the reagent used to append the group to the terminal nitrogen-containing ring or to the fragment in the final product, i.e., "Cap-51" or "The Cap-51 fragment found in LS-19".

The term "carbonyl," as used herein, refers to -C(O)-.

The term "carboxy," as used herein, refers to $-CO_2H$.

The term "cyano," as used herein, refers to -CN.

The term "cycloalkyl," as used herein, refers to a saturated monocyclic, hydrocarbon ring system having three to seven carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. The cycloalkyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, aryl, cyano, halo, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, nitro, and $-NR^xR^y$, wherein the aryl and the heterocyclyl are futher optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, hydroxy, and nitro.

The term "(cycloalkyl)alkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three cycloalkyl groups.

The term "(cycloalkyl)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyl groups. The alkyl part of the (cycloalkyl)alkyl is further optionally substituted with one or two groups independently selected from hydroxy and $-NR^cR^d$.

The term "cycloalkyloxy," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "cycloalkyloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyloxy groups.

The term "cycloalkylsulfonyl," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through a sulfonyl group.

The term "formyl," as used herein, refers to -CHO.

The terms "halo" and "halogen," as used herein, refer to F, Cl, Br, or I.

The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkoxycarbonyl," as used herein, refers to a haloalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "haloalkyl," as used herein, refers to an alkyl group substituted by one, two, three, or four halogen atoms.

The term "heterocyclyl," as used herein, refers to a four-, five-, six-, or seven-membered ring containing one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur. The four-membered ring has zero double bonds, the five-membered ring has zero to two double bonds, and the six- and seven-membered rings have zero to three double bonds. The term "heterocyclyl" also includes bicyclic groups in which the heterocyclyl ring is fused to another monocyclic heterocyclyl group, or a four- to six-membered aromatic or non-aromatic carbocyclic ring; as well as bridged bicyclic groups such as 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2-azabicyclo[2.2.2]oc-3-tyl. The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through any carbon atom or nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, benzothienyl, furyl, imidazolyl, indolinyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, thiazolyl, thienyl, thiomorpholinyl, 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2-

azabicyclo[2.2.2]oc-3-yl. The heterocyclyl groups of the present disclosure are optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, arylalkyl, arylcarbonyl, cyano, halo, haloalkoxy, haloalkyl, a second heterocyclyl group, heterocyclylalkyl, heterocyclylcarbonyl, hydroxy, hydroxyalkyl, nitro, -NR^xR^y, (NR^xR^y)alkyl, and oxo, wherein the alkyl part of the arylalkyl and the heterocyclylalkyl are unsubstituted and wherein the aryl, the aryl part of the arylalkyl, the aryl part of the arylcarbonyl, the second heterocyclyl group, and the heterocyclyl part of the heterocyclylalkyl and the heterocyclylcarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "heterocyclylalkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three heterocyclyl groups.

The term "heterocyclylalkoxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an alkoxy group.

The term "heterocyclylalkoxycarbonyl," as used herein, refers to a heterocyclylalkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyl groups. The alkyl part of the heterocyclylalkyl is further optionally substituted with one or two additional groups independently selected from alkoxy, alkylcarbonyloxy, aryl, halo, haloalkoxy, haloalkyl, hydroxy, and -NR^cR^d, wherein the aryl is further optionally substitued with one or two substituents independently selected from alkoxy, alkyl, unsubstituted aryl, unsubstitued arylalkoxy, unsubstituted arylalkoxycarbonyl, halo, haloalkoxy, haloalkyl, hydroxy, and -NR^xR^y.

The term "heterocyclylalkylcarbonyl," as used herein, refers to a heterocyclylalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclylcarbonyl," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through a carbonyl group.

The term "heterocyclyloxy," as used herein, refers to a heterocyclyl group attached to the parent molecular moiety through an oxygen atom.

The term "heterocyclyloxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyloxy groups.

The term "heterocyclyloxycarbonyl," as used herein, refers to a heterocyclyloxy group attached to the parent molecular moiety through a carbonyl group.

The term "hydroxy," as used herein, refers to -OH.

The term "hydroxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three hydroxy groups.

The term "hydroxyalkylcarbonyl," as used herein, refers to a hydroxyalkyl group attached to the parent molecular moiety through a carbonyl group.

The term "nitro," as used herein, refers to $-NO_2$.

The term "$-NR^aR^b$," as used herein, refers to two groups, R^a and R^b, which are attached to the parent molecular moiety through a nitrogen atom. R^a and R^b are independently selected from hydrogen, alkenyl, and alkyl.

The term "(NR^aR^b)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^aR^b$ groups.

The term "(NR^aR^b)carbonyl," as used herein, refers to an $-NR^aR^b$ group attached to the parent molecular moiety through a carbonyl group.

The term "$-NR^cR^d$," as used herein, refers to two groups, R^c and R^d, which are attached to the parent molecular moiety through a nitrogen atom. R^c and R^d are independently selected from hydrogen, alkenyloxycarbonyl, alkoxyalkylcarbonyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylalkoxycarbonyl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxycarbonyl, arylsulfonyl, cycloalkyl, cycloalkylsulfonyl, formyl, haloalkoxycarbonyl, heterocyclyl, heterocyclylalkoxycarbonyl, heterocyclylalkyl, heterocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclyloxycarbonyl, hydroxyalkylcarbonyl, (NR^eR^f)alkyl, (NR^eR^f)alkylcarbonyl, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, -C(NCN)OR', and -C(NCN)NR^xR^y, wherein R' is selected from alkyl and unsubstituted phenyl, and wherein the alkyl part of the arylalkyl, the arylalkylcarbonyl, the heterocyclylalkyl, and the heterocyclylalkylcarbonyl are further optionally substituted with one $-NR^eR^f$ group; and wherein the aryl, the aryl part of the arylalkoxycarbonyl, the arylalkyl, the arylalkylcarbonyl, the arylcarbonyl, the aryloxycarbonyl, and the arylsulfonyl, the heterocyclyl, and the heterocyclyl part of the heterocyclylalkoxycarbonyl, the

heterocyclylalkyl, the heterocyclylalkylcarbonyl, the heterocyclylcarbonyl, and the heterocyclyloxycarbonyl are further optionally substituted with one, two, or three substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "(NR^cR^d)alkenyl," as used herein, refers to an alkenyl group substituted with one, two, or three $-NR^cR^d$ groups.

The term "(NR^cR^d)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^cR^d$ groups. The alkyl part of the (NR^cR^d)alkyl is further optionally substituted with one or two additional groups selected from alkoxy, alkoxyalkylcarbonyl, alkoxycarbonyl, alkylsulfanyl, arylalkoxyalkylcarbonyl, carboxy, heterocyclyl, heterocyclylcarbonyl, hydroxy, and (NR^cR^f)carbonyl; wherein the heterocyclyl is further optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, haloalkyl, and nitro.

The term "(NR^cR^d)carbonyl," as used herein, refers to an $-NR^cR^d$ group attached to the parent molecular moiety through a carbonyl group.

The term "$-NR^cR^f$," as used hercin, refers to two groups, R^e and R^f, which are attached to the parent molecular moiety through a nitrogen atom. R^e and R^f are independently selected from hydrogen, alkyl, unsubstituted aryl, unsubstituted arylalkyl, unsubstituted cycloalkyl, unsubstituted (cyclolalkyl)alkyl, unsubstituted heterocyclyl, unsubstituted heterocyclylalkyl, (NR^xR^y)alkyl, and (NR^xR^y)carbonyl.

The term "(NR^cR^f)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^cR^f$ groups.

The term "(NR^cR^f)alkylcarbonyl," as used herein, refers to an (NR^cR^f)alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "(NR^cR^f)carbonyl," as used herein, refers to an $-NR^cR^f$ group attached to the parent molecular moiety through a carbonyl group.

The term "(NR^cR^f)sulfonyl," as used herein, refers to an $-NR^cR^f$ group attached to the parent molecular moiety through a sulfonyl group.

The term "$-NR^xR^y$," as used herein, refers to two groups, R^x and R^y, which are attached to the parent molecular moiety through a nitrogen atom. R^x and R^y are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, unsubstituted aryl, unsubstituted arylalkoxycarbonyl, unsubstituted arylalkyl,

unsubstituted cycloalkyl, unsubstituted heterocyclyl, and $(NR^{x'}R^{y'})$carbonyl, wherein $R^{x'}$ and $R^{y'}$ are independently selected from hydrogen and alkyl.

The term "(NR^xR^y)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^xR^y$ groups.

The term "oxo," as used herein, refers to =O.

The term "sulfonyl," as used herein, refers to $-SO_2-$.

The term "trialkylsilyl," as used herein, refers to $-SiR_3$, wherein R is alkyl. The R groups may be the same or different.

The term "trialkylsilylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three trialkylsilyl groups.

The term "trialkylsilylalkoxy," as used herein, refers to a trialkylsilylalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "trialkylsilylalkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three trialkylsilylalkoxy groups.

Asymmetric centers exist in the compounds of the present disclosure. These centers are designated by the symbols "R" or "S", depending on the configuration of substituents around the chiral carbon atom. It should be understood that the disclosure encompasses all stereochemical isomeric forms, or mixtures thereof, which possess the ability to inhibit NS5A. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, or direct separation of enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art.

Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures thereof.

The term "compounds of the present disclosure", and equivalent expressions,

are meant to embrace compounds of Formula (I), and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof. Similarly, references to intermediates are meant to embrace their salts where the context so permits.

The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, dihydrobromide, diydrochloride, dihydroiodide, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxycthanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine,

procaine, dibenzylamine, N,N-dibenzylphenethylamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

When it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the disclosure further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "therapeutically effective amount," as used herein, refers to the total amount of each active component that is sufficient to show a meaningful patient benefit, e.g., a reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. The compounds of formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients. The term "pharmaceutically acceptable," as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day,

preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the present disclosure are typical in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Treatment may be initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

When the compositions of this disclosure comprise a combination of a compound of the present disclosure and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Oral administration or administration by injection are preferred.

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or

suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like. Lubricants used in these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is

imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax, or the like.

The compounds of formula (I), and pharmaceutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phopholipids, such as cholesterol, stearylamine, or phophatidylcholines.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palitoyl residues. Furthermore, the compounds may be coupled to a class of

biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research* 1986, *3*(6), 318.

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a course powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and soutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the

addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The term "patient" includes both human and other mammals.

The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient that may be predisposed to the disease, disorder, and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder, or condition, i.e., arresting its development; and (iii) relieving the disease, disorder, or condition, i.e., causing regression of the disease, disorder, and/or condition.

The compounds of the present disclosure can also be administered with a cyclosporin, for example, cyclosporin A. Cyclosporin A has been shown to be active against HCV in clinical trials (*Hepatology* 2003, *38*, 1282; *Biochem. Biophys. Res. Commun.* 2004, *313*, 42; *J. Gastroenterol.* 2003, *38*, 567).

Table 1 below lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the disclosure can be administered with other anti-HCV activity compounds in combination therapy, either jointly or separately, or by combining the compounds into a composition.

Table 1

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
NIM811		Cyclophilin Inhibitor	Novartis
Zadaxin		Immunomodulator	Sciclone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Batabulin (T67)	Anticancer	β-tubulin inhibitor	Tularik Inc., South San Francisco, CA

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
ISIS 14803	Antiviral	antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV Inhibitor	Achillion / Gilead
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 2005	Antiviral	HCV Inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
HCV-796	Antiviral	NS5B Replicase Inhibitor	Wyeth / Viropharma
NM-283	Antiviral	NS5B Replicase Inhibitor	Idenix / Novartis
GL-59728	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
GL-60667	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
2'C MeA	Antiviral	NS5B Replicase Inhibitor	Gilead

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
PSI 6130	Antiviral	NS5B Replicase Inhibitor	Roche
R1626	Antiviral	NS5B Replicase Inhibitor	Roche
2'C Methyl adenosine	Antiviral	NS5B Replicase Inhibitor	Merck
JTK-003	Antiviral	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Levovirin	Antiviral	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirin	Antiviral	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Viramidine	Antiviral	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
SCH 503034	Antiviral	serine protease inhibitor	Schering Plough
Zadazim	Immune modulator	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Immunomodulator	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Immunosuppressant	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Civacir	Immunosuppressant	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Albuferon - α	Interferon	albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferon	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferon	IFN-ω	Intarcia Therapeutics
IFN-β and EMZ701	Interferon	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
Rebif	Interferon	IFN-β1a	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Intron A	Interferon	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Intron A and Zadaxin	Interferon	IFN-α2b/α1-thymosin	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferon	IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Actimmune	Interferon	INF-γ	InterMune Inc., Brisbane, CA
Interferon-β	Interferon	Interferon-β-1a	Serono
Multiferon	Interferon	Long lasting IFN	Viragen/Valentis
Wellferon	Interferon	lymphoblastoid IFN-αn1	GlaxoSmithKline plc, Uxbridge, UK

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Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Omniferon	Interferon	natural IFN-α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN-α2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys and Ribavirin	Interferon	PEGylated IFN-α2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
PEG-Intron	Interferon	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	Interferon	PEGylated IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Liver protection	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Liver protection	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B Replicase Inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys

The compounds of the present disclosure may also be used as laboratory reagents. Compounds may be instrumental in providing research tools for designing of viral replication assays, validation of animal assay systems and structural biology studies to further enhance knowledge of the HCV disease mechanisms. Further, the compounds of the present disclosure are useful in establishing or determining the binding site of other antiviral compounds, for example, by competitive inhibition.

The compounds of this disclosure may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, e.g., blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

This disclosure is intended to encompass compounds having formula (I) when prepared by synthetic processes or by metabolic processes including those occurring in the human or animal body (*in vivo*) or processes occurring *In vitro*.

The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: HATU for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; Boc or BOC for tert-butoxycarbonyl; NBS for N-bromosuccinimide; tBu or t-Bu for tert-butyl; SEM for -(trimethylsilyl)ethoxymethyl; DMSO for dimethylsulfoxide; MeOH for methanol; TFA for trifluoroacetic acid; RT for room temperature or retention time (context will dictate); t_R for retention time; EDCI for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMAP for 4-dimethylaminopyridine; THF for tetrahydrofuran; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; *t*-Bu; DEA for diethylamine; HMDS for hexamethyldisilazide; DMF for N,N-dimethylformamide; Bzl for benzyl; EtOH for ethanol; iPrOH or i-PrOH for isopropanol; Me_2S for *dimethylsulfide*; Et_3N *or TEA for triethylamine*; *Ph for phenyl*; OAc for acetate; EtOAc for ethyl acetate; dppf for 1,1'-bis(diphenylphosphino)ferrocene; iPr_2EtN or DIPEA for diisopropylethylamine; Cbz for carbobenzyloxy; n-BuLi for n-butyllithium; ACN for acetonitrile; h or hr for hours; m or min for minutes; s for seconds; LiHMDS for lithium hexamethyldisilazide; DIBAL for diisobutyl aluminum hydride; TBDMSCl for tert-butyldimethylsilyl chloride; Me for methyl; ca. for about; OAc for acetate; iPr for isopropyl; Et for ethyl; Bn for benzyl; and HOAT for 1-hydroxy-7-azabenzotriazole.

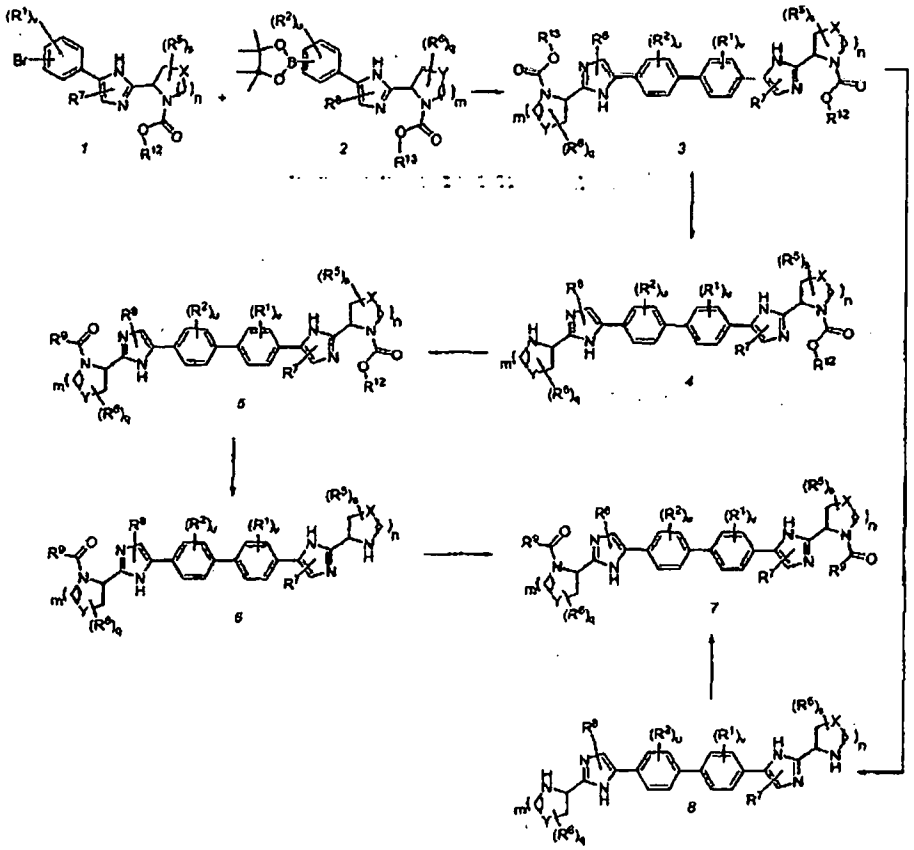
The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows:

The compounds and processes of the present disclosure will be better understood in connection with the following synthetic schemes which illustrate the

methods by which the compounds of the present disclosure may be prepared. Starting materials can be obtained from commercial sources or prepared by well-established literature methods known to those of ordinary skill in the art. It will be readily apparent to one of ordinary skill in the art that the compounds defined above can be synthesized by substitution of the appropriate reactants and agents in the syntheses shown below. It will also be readily apparent to one skilled in the art that the selective protection and deprotection steps, as well as the order of the steps themselves, can be carried out in varying order, depending on the nature of the variables to successfully complete the syntheses below. The variables are as defined above unless otherwise noted below.

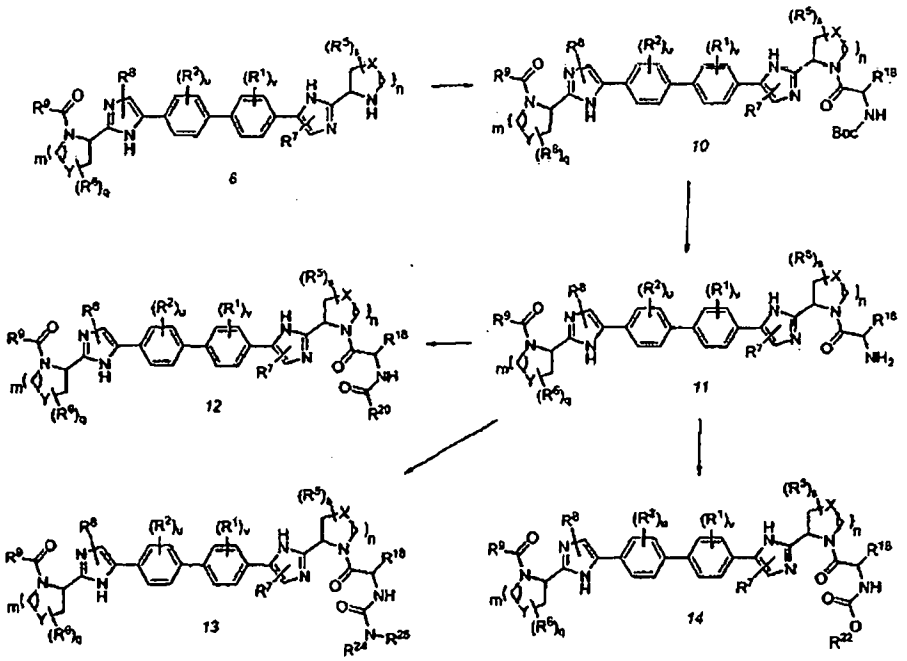
Scheme 1: Symmetric or Asymmetric Biphenyls

Aryl halide *1* and boronic ester *2* can be coupled to produce biaryl *3* using standard Suzuki-Miayura coupling conditions (*Angew Chem. Int. Ed. Engl* 2001, 40, 4544). It should be noted that the boronic acid analog of *2* may be used in place of the ester. Mono-deprotection of the pyrrolidine moiety may be accomplished when R^{12} and R^{13} are different. When R^{12} = benzyl, and R^{13} = t-butyl treatment to hydrogenolytic conditions produces *4*. For example, Pd/C catalyst in the presence of a base such as potassium carbonate can be used. Acylation of *4* can be accomplished under standard acylation conditions. A coupling reagent such as HATU in combination with an amine base such as Hunig's base can be used in this regard. Alternatively, *4* may be reacted with an isocyanate or carbamoyl chloride to provide compounds of formula *5* where R^9 is an amine. Further deprotection of *5* can be accomplished by treatment with strong acid such as HCl or trifluoroacetic acid. Standard conditions analogous to those used to convert *4* to *5* can be used to prepare *7* from *6*. In another embodiment where $R^{12} = R^{13}$ = t-Bu, direct conversion to *8* can be accomplished by treatment of *3* with strong acid such as HCl or trifluoroacetic acid. Conversion of *8* to *7* is accomplished in analogous fashion to the methods used to prepare *5* from *4* or *7* from *6*. In this instance however, the caps in *7* will be identical.



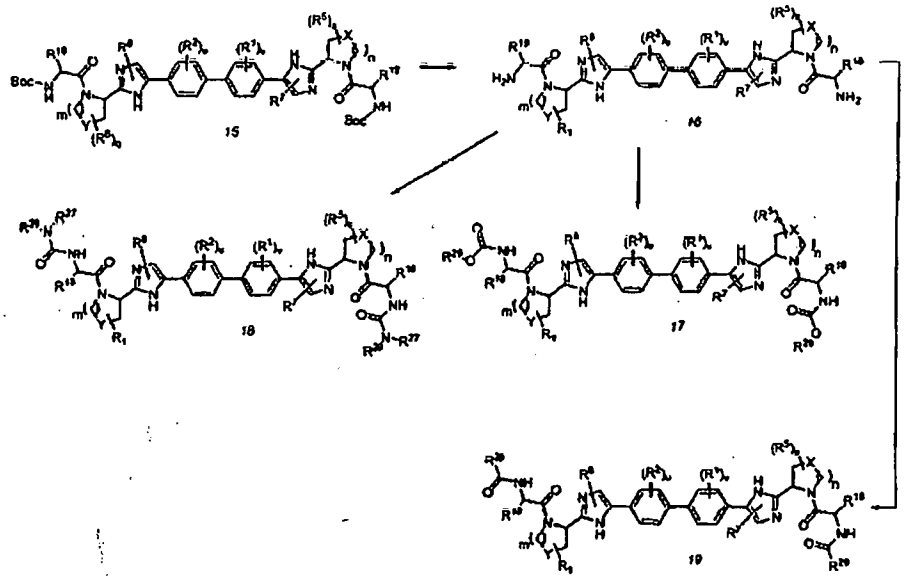
Scheme 2: Asymmetrically Capped Biphenyls

Conversion of *6* (from Scheme 1) to *10* can be done using standard amide coupling conditions such as HATU with an amine base, such as Hunig's base. Deprotection can be accomplished with strong acid such as HCl or trifluoroacetic acid affording *11*. Compound *11* can then be converted to *12*, *13*, or *14* using an acid chloride, an isocyanate or carbamoyl chloride, or a chloroformate respectively.



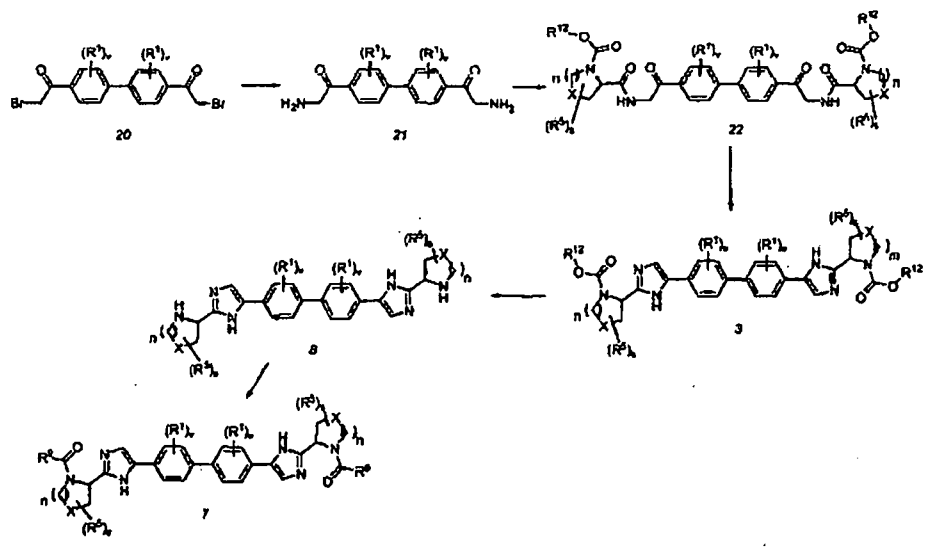
Scheme 3: Symmetric Cap Elaborated Biphenyls

Compound *15* (*15* = *7* (Scheme 1) wherein each R^9 is -CH(NHBoc)R^{18})can be converted to *16 via* treatment with strong acid such as HCl or trifluoroacetic acid. Compounds *17*, *18*, and *19* can be prepared from *16* by treating *16* with an appropriate chloroformate, isocyanate or carbamoyl chloride, or an acid chloride respectively.



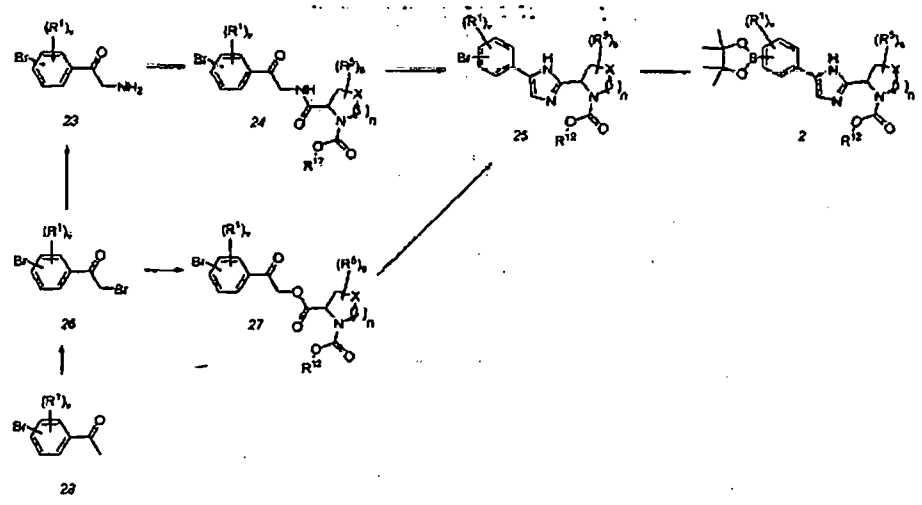
Scheme 4: Symmetric Biphenyls

Symmetrical biphenyl analogs (compounds of formula *7* where both halves of the molecule are equivalent) can be synthesized starting from bromoketone *20*. Amination by displacement with a nucleophile such as azide, phthalimide or preferably sodium diformylamide (Yinglin and Hongwen, *Synthesis* 1990, 122) followed by deprotection affords *21*. Condensation under standard amination conditions such as HATU and Hunig's base with an appropriately protected amino acid provides *22*. Heating with ammonium acetate under thermal or microwave conditions results in the formation of *3* which can be deprotected with strong acid such as HCl or trifluoroacetic acid ($R^{12} = R^{13}$ = t-Bu) or by hydrogenolysis with hydrogen gas and a transition metal catalyst such as Pd/C ($R^{12} = R^{13}$ = benzyl). Acylation can be affected with a carboxylic acid (R^9CO_2H) in a manner similar to the conversion of *21* to *22*. Urea formation can be accomplished by treatment with an appropriate isocycante ($R^9 = R^{24}R^{25}N$; R^{25} =H) or carbamoyl chloride ($R^9 = R^{24}R^{25}N$; R^{25} is other than hydrogen).



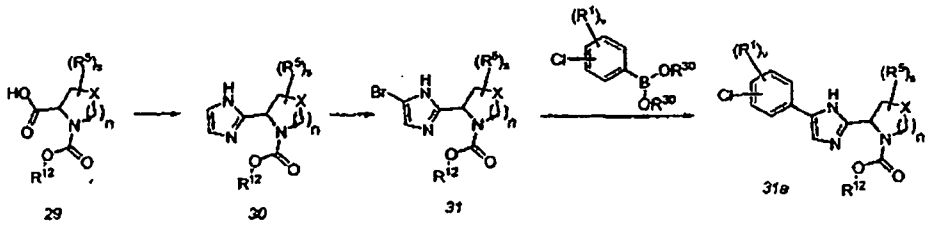
Scheme 5: Starting Materials 25 and 2

Scheme 5 describes the preparation of some of the starting materials required for the synthetic sequences depicted in Schemes 1-4. Key intermediate *25* (analogous to *1* in Scheme 1) is prepared from keto-amide *24* or keto-ester *27 via* heating with ammonium acetate under thermal or microwave conditions. Keto-amide *24* can be prepared from *23 via* condensation with an appropriate cyclic or acyclic amino acid under standard amide formation conditions. Bromide *26* can give rise to *23* by treatment with a nucleophile such as azide, phthalimide or sodium diformylamide (*Synthesis* 1990, 122) followed by deprotection. Bromide *26* can also be converted to *27* by reacting with an appropriate cyclic or acyclic N-protected amino acid in the presence of base such as potassium carbonate or sodium bicarbonate. Bromination of *28* with a source of bromonium ion such as bromine, NBS, or CBr_4 results in the formation of *26*. Bromide *25* can be converted to boronic ester *2 via* treatment with bis-pinacalotodiboron under palladium catalysis according to the method described in *Journal of Organic Chemistry* 1995, *60*, 7508, or variations thereof.



Scheme 6: Starting Material 31a

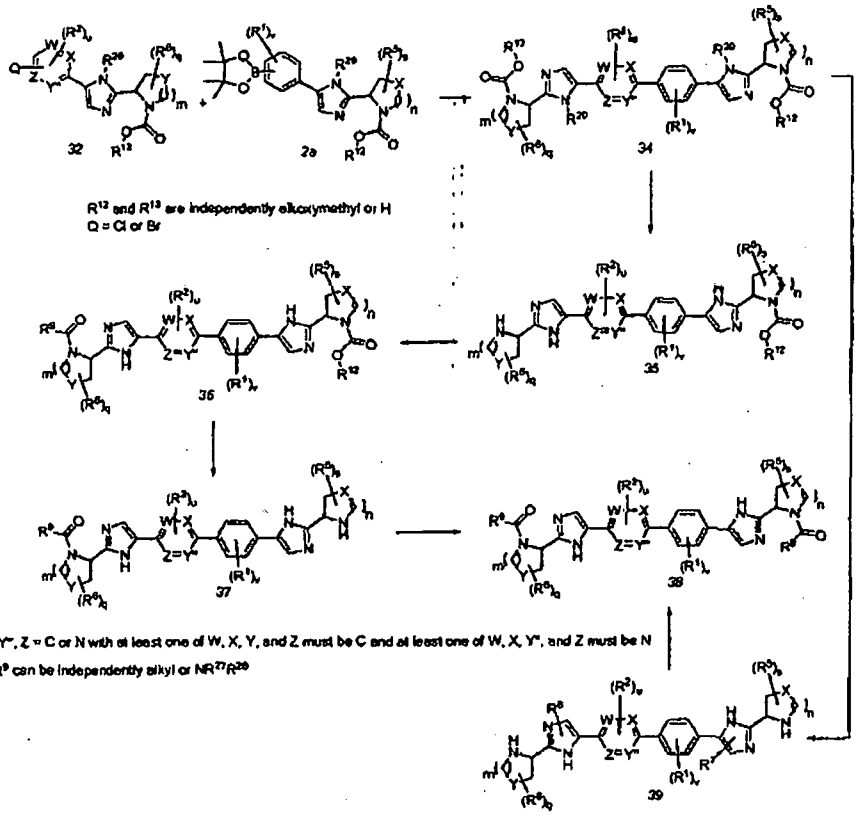
In another embodiment, starting materials such as *31a* (analogous to *25* in Scheme 5 and *1* in Scheme 1) may be prepared by reacting bromoimidazole derivatives *31* under Suzuki-type coupling conditions with a variety of chloro-substituted aryl boronic acids which can either be prepared by standard methodologies (see, for example, *Organic Letters* 2006, *8*, 305 and references cited therein) or purchased from commercial suppliers. Bromoimidazole *31* can be obtained by brominating imidazole *30* with a source of bromonium ion such as bromine, CBr_4, or N-bromosuccinimide. Imidazole *30* can be prepared from N-protected amino acids which are appropriately substituted by reacting with glyoxal in a methanolic solution of ammonium hydroxide.



Scheme 7: Heteroaryls

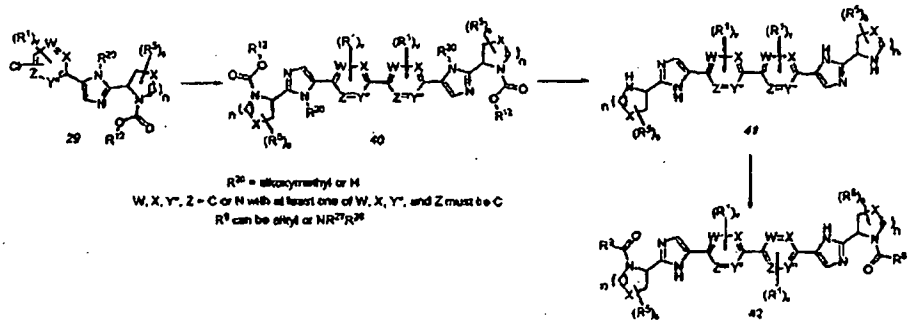
In yet another embodiment of the current disclosure, aryl halide *32* can be coupled under Suzuki-Miyaura palladium catalyzed conditions to form the heteroaryl derivative *34*. Compound *34* can be elaborated to *35* by treatment to hydrogenolytic conditions with hydrogen and a transition metal catalyst such as palladium on carbon

(R^{13} = benzyl). Acylation of *35* can be accomplished with an appropriate acid chloride (R^9COCl) in the presence of a base such as triethylamine, with an appropriately substituted carboxylic acid (R^9CO_2H) in the presence of a standard coupling reagent such as HATU, or with an isoscyanate ($R^{27}NCO$ wherein R^9 = $R^{27}R^{28}N$-; R^{28} =H)or carbamoyl chloride ($R^{27}R^{28}NCOCl$ wherein $R^9 = R^{27}R^{28}N$-). Compound *37* can be prepared from 36 (R^{12} = t-Bu) *via* treatment with strong acid such as HCl or trifluoroacetic acid. Acylation of the resulting amine in *37* to give *38* can be accomplished as in the transformation of *35* to *36*. In cases where $R^{12} = R^{13}$, *34* can be directly transformed into *39* by treatment with strong acid such as HCl or trifluoroacetic acid ($R^{12} = R^{13}$ = t-Bu) or by employing hydrogenolytic conditions with hydrogen and a transition metal catalyst such as palladium on carbon ($R^{12} = R^{13}$ = benzyl). Acylation of *39* can be accomplished in analogous fashion to that described for the transformation of *35* to *36*.



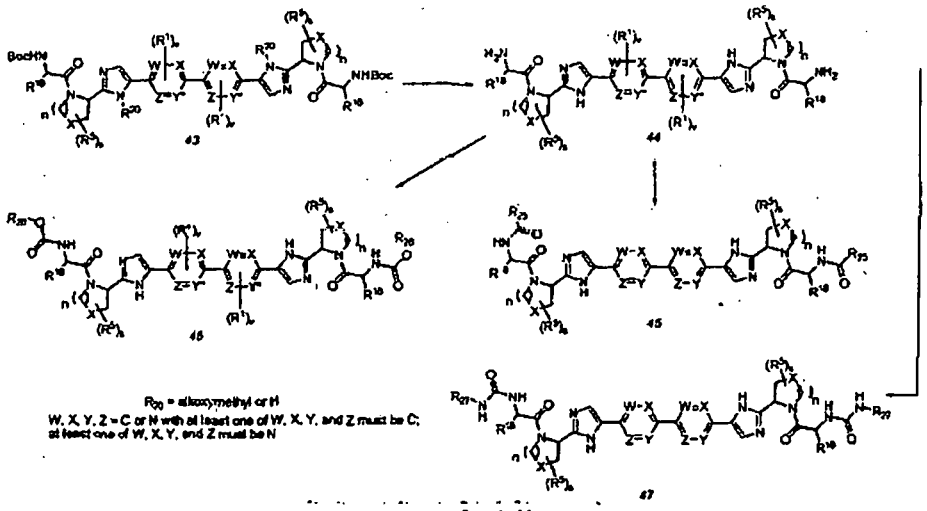
Scheme 8

Heteroaryl chloride *29* can be converted to symmetrical analog *40 via* treatment with a source of palladium such as dichlorobis(benzonitrile) palladium in the presence of tetrakis(dimethylamino)ethylene at elevated temperature. Removal of the SEM ether and Boc carbamates found in *40* can be accomplished in one step by treatment with a strong acid such as HCl or trifluoroacetic acid providing *41*. Conversion to *42* can be accomplished in similar fashion to the conditions used to convert *38* to *39* in Scheme 7.



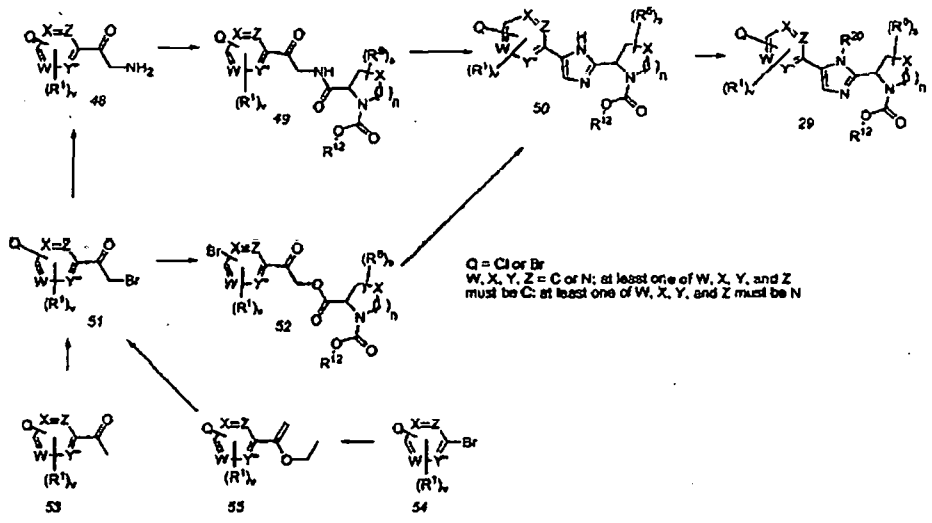
Scheme 9: Symmetric Cap Substituted Heteroaryls

Compound *43* (analogous to *42* wherein R_{23} = -CH(NHBoc)R_{24}) may be elaborated to *45*, *46*, and *47 via* similar methodologies to those described in Scheme 3. In cases where R_{20} = alkoxymethyl (ie; SEM), removal can be accomplished simultaneously with removal of the Boc carbamate (cf; *43* to *44*) using strong acid such as HCl or trifluoroacetic acid.



Scheme 10: Starting Material 29

Heteroaryl bromides *54* may be reacted with a vinyl stannane such as tributyl(1-ethoxyvinyl)tin in the presence of a source of palladium such as dichlorobis(triphenylphosphine)palladium (II) to provide *55* which can be subsequently transformed into bromoketone *51 via* treatment with a source of bromonium ion such as N-bromosuccinimide, CBr_4, or bromine. Alternatively, keto-substituted heteroaryl bromides *53* may be directly converted to *51 via* treatment with a source of bromonium ion such as bromine, CBr_4, or N-bromosuccinimide. Bromide *51* can be converted to aminoketone *48 via* addition of sodium azide, potassium phthalimide or sodium diformylamide (*Synthesis* 1990 122) followed by deprotection. Aminoketone *48* can then be coupled with an appropriately substituted amino acid under standard amide formation conditions (i.e.; a coupling reagent such as HATU in the presence of a mild base such as Hunig's base) to provide *49*. Compound *49* can then be further transformed into imidazole *50 via* reacting with ammonium acetate under thermal or microwave conditions. Alternatively, *51* can be directly reacted with an appropriately substituted amino acid in the presence of a base such as sodium bicarbonate or potassium carbonate providing *52* which can in turn be reacted with ammonium acetate under thermal or microwave conditions to provide *50*. Imidazole *50* can be protected with an alkoxylmethyl group by treatment with the appropriate alkoxymethyl halide such as 2-(trimethylsilyl)ethoxymethyl chloride after first being deprotonated with a strong base such as sodium hydride.



Scheme 11: Substituted Phenylglycine Derivatives

Substituted phenylglycine derivatives can be prepared by a number of methods shown below. Phenylglycine t-butyl ester can be reductively alkylated (pathyway A) with an appropriate aldehyde and a reductant such as sodium cyanoborohydride in acidic medium. Hydrolysis of the t-butyl ester can be accomplished with strong acid such as HCl or trifluoroacetic acid. Alternatively, phenylglycine can be alkylated with an alkyl halide such as ethyl iodide and a base such as sodium bicarbonate or potassium carbonate (pathway B). Pathway C illustrates reductive alkylation of phenylglycine as in pathway A followed by a second reductive alkylation with an alternate aldehyde such as formaldehyde in the presence of a reducing agent and acid. Pathway D illustrates the synthesis of substituted phenylglycines *via* the corresponding mandelic acid analogs. Conversion of the secondary alcohol to a competent leaving group can be accomplished with p-toluensulfonyl chloride. Displacement of the tosylate group with an appropriate amine followed by reductive removal of the benzyl ester can provide substituted phenylglycine derivatives. In pathway E a racemic substituted phenylglycine derivative is resolved by esterification with an enantiomerically pure chiral auxiliary such as but not limited to (+)-1-phenylethanol, (-)-1-phenylethanol, an Evan's oxazolidinone, or enantiomerically pure pantolactone. Separation of the diastereomers is accomplished *via* chromatography (silica gel, HPLC, crystallization,

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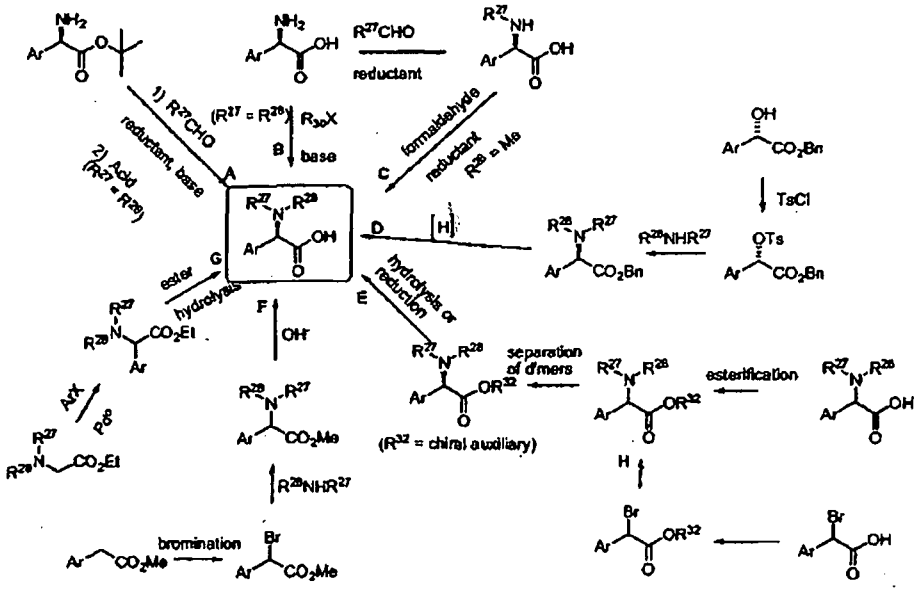
etc) followed by removal of the chiral auxiliary providing enantiomerically pure phenylglycine derivatives. Pathway H illustrates a synthetic sequence which intersects with pathway E wherein the aforementioned chiral auxiliary is installed prior to amine addition. Alternatively, an ester of an arylacetic acid can be brominated with a source of bromonium ion such as bromine, N-bromosuccinimide, or CBr_4. The resultant benzylic bromide can be displaced with a variety of mono- or disubstituted amines in the presence of a tertiary amine base such as triethylamine or Hunig's base. Hydrolysis of the methyl ester *via* treatment with lithium hydroxide at low temperature or 6N HCl at elevated temperature provides the substituted phenylglycine derivatives. Another method is shown in pathway G. Glycine analogs can be derivatized with a variety of aryl halides in the presence of a source of palladium (0) such as palladium bis(tributylphosphine) and base such as potassium phosphate. The resultant ester can then be hydrolyzed by treatment with base or acid. It should be understood that other well known methods to prepare phenylglycine derivatives exist in the art and can be amended to provide the desired compounds in this description. It should also be understood that the final phenylglycine derivatives can be purified to enantiomeric purity greater than 98%ee *via* preparative HPLC.



Scheme 12: Acylated Amino Acid Derivatives

In another embodiment of the present disclosure, acylated phenylglycine derivatives may be prepared as illustrated below. Phenylglycine derivatives whercin

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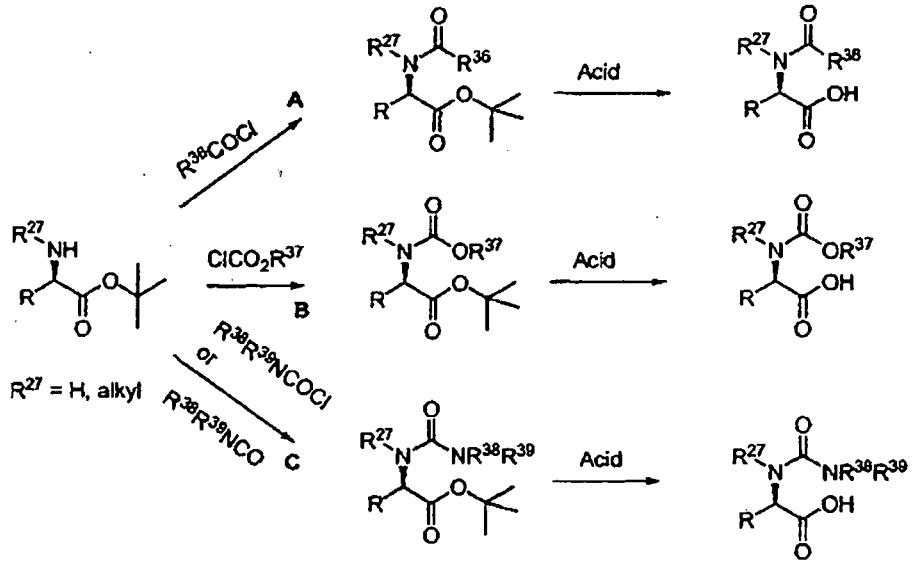
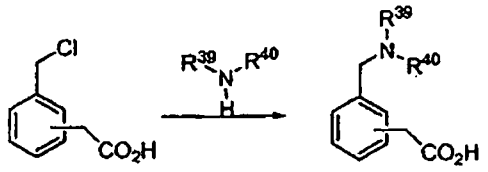
the carboxylic acid is protected as an easily removed ester, may be acylated with an acid chloride in the presence of a base such as triethylamine to provide the corresponding amides (pathway A). Pathway B illustrates the acylation of the starting phenylglycine derivative with an appropriate chloroformate while pathway C shows reaction with an appropriate isocyanate or carbamoyl chloride. Each of the three intermediates shown in pathways A – C may be deprotected by methods known by those skilled in the art (ie; treatment of the t-butyl ester with strong base such as HCl or trifluoroacetic acid).



Scheme 13

Amino-substituted phenylacetic acids may be prepared by treatment of a chloromethylphenylacetic acid with an excess of an amine.



Compound analysis conditions

Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters Micromass ZQ MS system. It should be

noted that retention times may vary slightly between machines. The LC conditions employed in determining the retention time (RT) were:

Condition 1

Column = Phenomenex-Luna 3.0X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 2

Column = Phenomenex-Luna 4.6X50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Slovent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 3

Column = HPLC XTERRA C18 3.0 x 50mm S7
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min
Wavelength = 220 nm

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Slovent A = 0.1% TFA in 10% methanol/90%H_2O

Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition M1

Column: Luna 4.6X 50 mm S10

Start %B = 0

Final %B = 100

Gradient time = 3 min

Stop time = 4 min

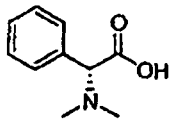
Flow rate = 4 mL/min

Solvent A: = 95% H_2O: 5% CH_3CN, 10 mm Ammonium acetate

Solvent B: = 5% H_2O : 95% CH_3CN; 10 mm Ammonium acetate

Synthesis of common caps

Cap-1



A suspension of 10% Pd/C (2.0g) in methanol (10 mL) was added to a mixture of (R)-2-phenylglycine (10g, 66.2 mmol), formaldehyde (33 mL of 37% wt. in water), 1N HCl (30 mL) and methanol (30 mL), and exposed to H_2 (60 psi) for 3 hours. The reaction mixture was filtered through diatomaceous earth (Celite®), and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of *Cap*-1 as a white needle (4.0 g). Optical rotation: -117.1° [c = 9.95 mg/mL in H_2O; λ = 589 nm]. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.43-7.34 (m, 5H), 4.14 (s, 1H), 2.43 (s, 6H); LC (Cond. 1): RT = 0.25; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.10; found 180.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$ 180.1025; found 180.1017.

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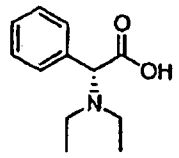
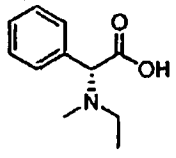
Cap-2



$NaBH_3CN$ (6.22g, 94 mmol) was added in portions over a few minutes to a cooled (ice/water) mixture of (R)-2-Phenylglycine (6.02 g, 39.8 mmol) and MeOH (100 mL), and stirred for 5 min. Acetaldehyde (10 mL) was added drop-wise over 10 min and stirring was continued at the same cooled temperature for 45 min and at ambient temperature for ~6.5 hr. The reaction mixture was cooled back with ice-water bath, treated with water (3 mL) and then quenched with a drop-wise addition of concentrated HCl over ~ 45 min until the pH of the mixture is ~ 1.5 – 2.0. The cooling bath was removed and the stirring was continued while adding concentrated HCl in order to maintain the pH of the mixture around 1.5-2.0. The reaction mixture was stirred over night, filtered to remove the white suspension, and the filtrate was concentrated *in vacuo*. The crude material was recrystallized from ethanol to afford the HCl salt of *Cap*-2 as a shining white solid in two crops (crop-1: 4.16 g; crop-2: 2.19 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 10.44 (1.00, br s, 1H), 7.66 (m, 2H), 7.51 (m, 3H), 5.30 (s, 1H), 3.15 (br m, 2H), 2.98 (br m, 2H), 1.20 (app br s, 6H). Crop-1: $[\alpha]^{25}$ -102.21° (c = 0.357, H_2O); crop-2: $[\alpha]^{25}$ -99.7° (c = 0.357, H_2O). *LC* (Cond. 1): RT = 0.43 min; *LC/MS*: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{18}NO_2$: 208.13; found 208.26

Cap-3



Acetaldehyde (5.0 mL, 89.1 mmol) and a suspension of 10% Pd/C (720 mg) in methanol/H_2O (4mL/1 mL) was sequentially added to a cooled (~ 15 °C) mixture of (R)-2-phenylglycine (3.096g, 20.48 mmol), 1N HCl (30 mL) and methanol (40 mL). The cooling bath was removed and the reaction mixture was stirred under a balloon of H_2 for 17 hours. An additional acetaldehyde (10 mL, 178.2 mmol) was

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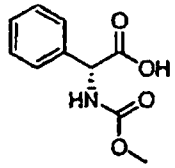
added and stirring continued under H_2 atmosphere for 24 hours [Note: the supply of H_2 was replenished as needed throughout the reaction]. The reaction mixture was filtered through diatomaceous earth (Celite®), and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol to provide the HCl salt of (R)-2-(ethylamino)-2-phenylacetic acid as a shining white solid (2.846g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 14.15 (br s, 1H), 9.55 (br s, 2H), 7.55-7.48 (m, 5H), 2.88 (br m, 1H), 2.73 (br m, 1H), 1.20 (app t, J = 7.2, 3H). LC (Cond. 1): RT = 0.39 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{14}NO_2$: 180.10; found 180.18.

A suspension of 10% Pd/C (536 mg) in methanol/H_2O (3 mL/1 mL) was added to a mixture of (R)-2-(ethylamino)-2-phenylacetic acid/HCl (1.492g, 6.918 mmol), formaldehyde (20 mL of 37% wt. in water), 1N HCl (20 mL) and methanol (23 mL). The reaction mixture was stirred under a balloon of H_2 for ~72 hours, where the H_2 supply was replenished as needed. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo*. The resulting crude material was recrystallized from isopropanol (50 mL) to provide the HCl salt of *Cap*-3 as a white solid (985 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 10.48 (br s, 1H), 7.59-7.51 (m, 5H), 5.26 (s, 1H), 3.08 (app br s, 2H), 2.65 (br s, 3H), 1.24 (br m, 3H). LC (Cond. 1): RT = 0.39 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.12; found 194.18; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{16}NO_2$: 194.1180; found 194.1181.

Cap-4

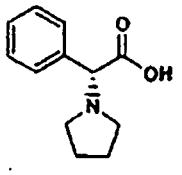


$ClCO_2Me$ (3.2 mL, 41.4 mmol) was added dropwise to a cooled (ice/water) THF (410 mL) semi-solution of (R)-tert-butyl 2-amino-2-phenylacetate/HCl (9.877 g, 40.52 mmol) and diisopropylethylamine (14.2 mL, 81.52 mmol) over 6 min, and stirred at similar temperature for 5.5 hours. The volatile component was removed *in vacuo*, and the residue was partitioned between water (100 mL) and ethyl acetate

(200 mL). The organic layer was washed with 1N HCl (25 mL) and saturated $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant colorless oil was triturated from hexanes, filtered and washed with hexanes (100 mL) to provide (R)-tert-butyl 2-(methoxycarbonylamino)-2-phenylacetate as a white solid (7.7 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.98 (d, J = 8.0, 1H), 7.37-7.29 (m, 5H), 5.09 (d, J = 8, 1H), 3.56 (s, 3H), 1.33 (s, 9H). LC (Cond. 1): RT = 1.53 min; ~90 % homogeneity index; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{14}H_{19}NNaO_4$: 288.12; found 288.15.

TFA (16 mL) was added dropwise to a cooled (ice/water) CH_2Cl_2 (160 mL) solution of the above product over 7 minutes, and the cooling bath was removed and the reaction mixture was stirred for 20 hours. Since the deprotection was still not complete, an additional TFA (1.0 mL) was added and stirring continued for an additional 2 hours. The volatile component was removed *in vacuo*, and the resulting oil residue was treated with diethyl ether (15 mL) and hexanes (12 mL) to provide a precipitate. The precipitate was filtered and washed with diethyl ether/hexanes (~1:3 ratio; 30 mL) and dried *in vacuo* to provide *Cap*-4 as a fluffy white solid (5.57 g). Optical rotation: -176.9° [c = 3.7 mg/mL in H_2O; λ = 589 nm]. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.84 (br s, 1H), 7.96 (d, J = 8.3, 1H), 7.41-7.29 (m, 5H), 5.14 (d, J = 8.3, 1H), 3.55 (s, 3H). LC (Cond. 1): RT = 1.01 min; >95 % homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.08; found 210.17; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{12}NO_4$ 210.0766; found 210.0756.

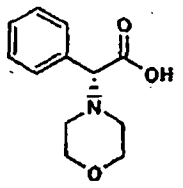
Cap-5



A mixture of (R)- 2-phenylglycine (1.0 g, 6.62 mmol), 1,4-dibromobutane (1.57 g, 7.27 mmol) and Na_2CO_3 (2.10 g, 19.8 mmol) in ethanol (40 mL) was heated at 100 °C for 21 hours. The reaction mixture was cooled to ambient temperature and filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethanol and acidified with 1N HCl to pH 3-4, and the volatile component was removed *in vacuo*. The resulting crude material was purified by a reverse phase

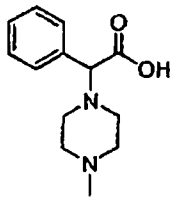
HPLC (water/methanol/TFA) to provide the TFA salt of *Cap*-5 as a semi-viscous white foam (1.0 g). ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 10.68 (br s, 1H), 7.51 (m, 5H), 5.23 (s, 1H), 3.34 (app br s, 2H), 3.05 (app br s, 2H), 1.95 (app br s, 4H); RT = 0.30 min (Cond. 1); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_2$: 206.12; found 206.25.

Cap-6



The TFA salt of *Cap*-6 was synthesized from (R)-2-phenylglycine and 1-bromo-2-(2-bromoethoxy)ethane by using the method of preparation of *Cap*-5. ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 12.20 (br s, 1H), 7.50 (m, 5H), 4.92 (s, 1H), 3.78 (app br s, 4H), 3.08 (app br s, 2H), 2.81 (app br s, 2H); RT = 0.32 min (Cond. 1); >98%; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.11; found 222.20; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_3$: 222.1130; found 222.1121.

Cap-7



Cap-7a: enantiomer-1
Cap-7b: enantiomer-2

A CH_2Cl_2 (200 mL) solution of p-toluenesulfonyl chloride (8.65 g, 45.4 mmol) was added dropwise to a cooled (-5 °C) CH_2Cl_2 (200 mL) solution of (S)-benzyl 2-hydroxy-2-phenylacetate (10.0 g, 41.3 mmol), triethylamine (5.75 mL, 41.3 mmol) and 4-dimethylaminopyridine (0.504 g, 4.13 mmol), while maintaining the temperature between -5 °C and 0 °C. The reaction was stirred at 0 °C for 9 hours, and then stored in a freezer (-25 °C) for 14 hours. It was allowed to thaw to ambient temperature and washed with water (200 mL), 1N HCl (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide benzyl 2-phenyl-2-

(tosyloxy)acetate as a viscous oil which solidified upon standing (16.5 g). The chiral integrity of the product was not checked and that product was used for the next step without further purification. ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 7.78 (d, J = 8.6, 2H), 7.43-7.29 (m, 10H), 7.20 (m, 2H), 6.12 (s, 1H), 5.16 (d, J = 12.5, 1H), 5.10 (d, J = 12.5, 1H), 2.39 (s, 3H). RT = 3.00 (Cond. 3); >90% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{22}H_{20}NaO_5S$: 419.09; found 419.04.

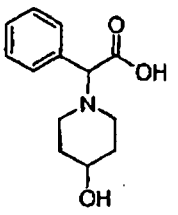
A THF (75 mL) solution of benzyl 2-phenyl-2-(tosyloxy)acetate (6.0 g, 15.1 mmol), 1-methylpiperazine (3.36 mL, 30.3 mmol) and N,N-diisopropylethylamine (13.2 mL, 75.8 mmol) was heated at 65 °C for 7 hours. The reaction was allowed to cool to ambient temperature and the volatile component was removed *in vacuo*. The residue was partitioned between ethylacetate and water, and the organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by flash chromatography (silica gel, ethyl acetate) to provide benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate as an orangish-brown viscous oil (4.56 g). Chiral HPLC analysis (Chiralcel OD-H) indicated that the sample is a mixture of enantiomers in a 38.2 to 58.7 ratio. The separation of the enantiomers were effected as follow: the product was dissolved in 120 mL of ethanol/heptane (1:1) and injected (5 mL/injection) on chiral HPLC column (Chiracel OJ, 5 cm ID x 50 cm L, 20 μm) eluting with 85:15 Heptane/ethanol at 75 mL/min, and monitored at 220 nm. Enantiomer-1 (1.474 g) and enantiomer-2 (2.2149 g) were retrieved as viscous oil. ^{1}H NMR ($CDCl_3$, δ = 7.26, 500 MHz) 7.44-7.40 (m, 2H), 7.33-7.24 (m, 6H), 7.21-7.16 (m, 2H), 5.13 (d, J = 12.5, 1H), 5.08 (d, J = 12.5, 1H), 4.02 (s, 1H), 2.65-2.38 (app br s, 8H), 2.25 (s, 3H). RT = 2.10 (Cond. 3); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19; found 325.20.

A methanol (10 mL) solution of either enantiomer of benzyl 2-(4-methylpiperazin-1-yl)-2-phenylacetate (1.0 g, 3.1 mmol) was added to a suspension of 10% Pd/C (120 mg) in methanol (5.0 mL). The reaction mixture was exposed to a balloon of hydrogen, under a careful monitoring, for <50 min. Immediately after the completion of the reaction, the catalyst was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo* to provide *Cap-7*, contaminated with phenylacetic acid as a tan foam (867.6 mg; mass is above the theoretical yield).

The product was used for the next step without further purification. ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 7.44-7.37 (m, 2H), 7.37-7.24 (m, 3H), 3.92 (s, 1H), 2.63-2.48 (app. bs, 2H), 2.48-2.32 (m, 6H), 2.19 (s, 3H); RT = 0.31 (Cond. 2); >90% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.14; found 235.15; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{19}N_2O_2$: 235.1447; found 235.1440.

The synthesis of *Cap*-8 and *Cap*-9 was conducted according to the synthesis of *Cap*-7 by using appropriate amines for the SN_2 displacement step (i.e., 4-hydroxypiperidine for *Cap*-8 and (S)-3-fluoropyrrolidine for *Cap*-9) and modified conditions for the separation of the respective stereoisomeric intermedites, as described below.

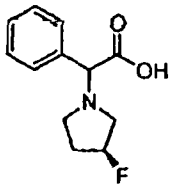
Cap-8



8a: enantiomer-1
8b: enantiomer-2

The enantiomeric separation of the intermediate benzyl 2-(4-hydroxypiperidin-1-yl)-2-phenyl acetate was effected by employing the following conditions: the compound (500 mg) was dissolved in ethanol/heptane (5 mL/45 mL). The resulting solution was injected (5 mL/injection) on a chiral HPLC column (Chiracel OJ, 2 cm ID x 25 cm L, 10 μm) eluting with 80:20 heptane/ethanol at 10 mL/min, monitored at 220 nm, to provide 186.3 mg of enantiomer-1 and 209.1 mg of enantiomer-2 as light-yellow viscous oils. These benzyl ester was hydrogenolysed according to the preparation of *Cap*-7 to provide *Cap*-8: ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 7.40 (d, J = 7, 2H), 7.28-7.20 (m, 3H), 3.78 (s 1H), 3.46 (m, 1H), 2.93 (m, 1H), 2.62 (m, 1H), 2.20 (m, 2H), 1.70 (m, 2H), 1.42 (m, 2H). RT = 0.28 (Cond. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.13; found 236.07; HRMS: Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_3$: 236.1287; found 236.1283.

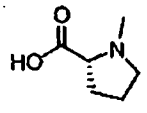
Cap-9



9a: diastereomer-1
9b: diastereomer-2

The diastereomeric separation of the intermediate benzyl 2-((S)-3-fluoropyrrolidin-1-yl)-2-phenylacetate was effected by employing the following conditions: the ester (220 mg) was separated on a chiral HPLC column (Chiracel OJ-H, 0.46 cm ID x 25 cm L, 5 μm) eluting with 95% CO_2 / 5% methanol with 0.1% TFA, at 10 bar pressure, 70 mL/min flow rate, and a temperature of 35 °C. The HPLC elute for the respective stereiosmers was concentrated, and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with an aqueous medium (10 mL water + 1 mL saturated $NaHCO_3$ solution). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 92.5 mg of fraction-1 and 59.6 mg of fraction-2. These benzyl esters were hydrogenolysed according to the preparation of *Cap*-7 to prepare Caps 9a and 9b. *Cap*-9a (diastereomer-1; the sample is a TFA salt as a result of purification on a reverse phase HPLC using H_2O/methanol/TFA solvent): ^{1}H NMR (DMSO-d_6, δ = 2.5, 400 MHz) 7.55-7.48 (m, 5H), 5.38 (d of m, *J* = 53.7, 1H), 5.09 (br s, 1H), 3.84-2.82 (br m, 4H), 2.31-2.09 (m, 2H). RT = 0.42 (Cond. 1); >95% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14; *Cap*-9b (diastereomer-2): ^{1}H NMR (DMSO-d_6, δ = 2.5, 400 MHz) 7.43-7.21 (m, 5H), 5.19 (d of m, *J* = 55.9, 1H), 3.97 (s, 1H), 2.95-2.43 (m, 4H), 2.19-1.78 (m, 2H). RT = 0.44 (Cond. 1); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{15}FNO_2$: 224.11; found 224.14.

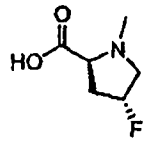
Cap-10



To a solution of D-proline (2.0 g, 17 mmol) and formaldehyde (2.0 mL of 37% wt. in H_2O) in methanol (15 mL) was added a suspension of 10% Pd/C (500 mg) in methanol (5 mL). The mixture was stirred under a balloon of hydrogen for 23

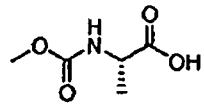
hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo* to provide *Cap*-10 as an off-white solid (2.15 g). ^1H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 3.42 (m, 1H), 3.37 (dd, *J* = 9.4, 6.1, 1H), 2.85-2.78 (m, 1H), 2.66 (s, 3H), 2.21-2.13 (m, 1H), 1.93-1.84 (m, 2H), 1.75-1.66 (m, 1H). RT = 0.28 (Cond. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_2$: 130.09; found 129.96.

Cap-11



A mixture of (2S,4R)-4-fluoropyrrolidine-2-carboxylic acid (0.50 g, 3.8 mmol), formaldehyde (0.5 mL of 37% wt. in H_2O), 12 N HCl (0.25 mL) and 10% Pd/C (50 mg) in methanol (20 mL) was stirred under a balloon of hydrogen for 19 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo*. The residue was recrystallized from isopropanol to provide the HCl salt of *Cap*-11 as a white solid (337.7 mg). ^1H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 5.39 (d m, *J* = 53.7, 1H), 4.30 (m, 1H), 3.90 (ddd, *J* = 31.5, 13.5, 4.5, 1H), 3.33 (dd, *J* = 25.6, 13.4, 1H), 2.85 (s, 3H), 2.60-2.51 (m, 1H), 2.39-2.26 (m, 1H). RT = 0.28 (Cond. 2); >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{11}FNO_2$: 148.08; found 148.06.

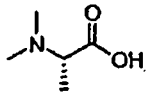
Cap-12



L-Alanine (2.0 g, 22.5 mmol) was dissolved in 10% aqueous sodium carbonate solution (50 mL), and a THF (50 mL) solution of methyl chloroformate (4.0 mL) was added to it. The reaction mixture was stirred under ambient conditions for 4.5 hours and concentrated *in vacuo*. The resulting white solid was dissolved in water and acidified with 1N HCl to a pH ~ 2-3. The resulting solutions was extracted with ethyl acetate (3 x 100 mL), and the combined organic phase was dried (Na_2SO_4),

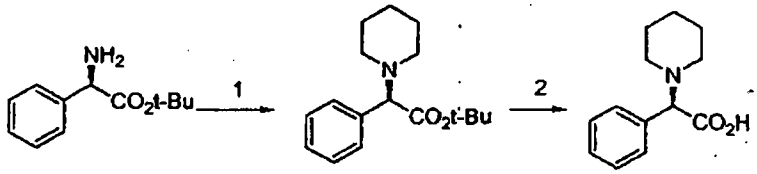
filtered, and concentrated *in vacuo* to provide a colorless oil (2.58 g). 500 mg of this material was purified by a reverse phase HPLC (H_2O/methanol/TFA) to provide 150 mg of *Cap*-12 as a colorless oil . ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) 7.44 (d, *J* = 7.3, 0.8H), 7.10 (br s, 0.2H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, *J* = 7.3, 3H).

Cap-13



A mixture of L-alanine (2.5 g, 28 mmol), formaldehyde (8.4 g, 37 wt. %), 1N HCl (30 mL) and 10% Pd/C (500 mg) in methanol (30 mL) was stirred under a hydrogen atmosphere (50 psi) for 5 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate was concentrated *in vacuo* to provide the HCl salt of *Cap*-13 as an oil which solidified upon standing under vacuum (4.4 g; the mass is above theoretical yield). The product was used without further purification. ^{1}H NMR (DMSO-d_6, δ = 2.5, 500 MHz) δ 12.1 (br s, 1H), 4.06 (q, *J* = 7.4, 1H), 2.76 (s, 6H), 1.46 (d, *J* = 7.3, 3H).

Cap-14



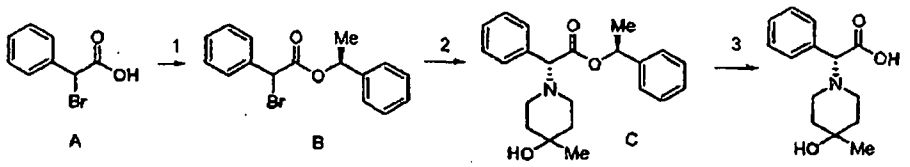
Cap-14

Step 1: A mixture of (R)-(-)-D-phenylglycine tert-butyl ester (3.00 g, 12.3 mmol), $NaBH_3CN$ (0.773 g, 12.3 mmol), KOH (0.690 g, 12.3 mmol) and acetic acid (0.352 mL, 6.15 mmol) were stirred in methanol at 0 °C. To this mixture was added glutaric dialdehyde (2.23 mL, 12.3 mmol) dropwise over 5 minutes. The reaction mixture was stirred as it was allowed to warm to ambient temperature and stirring was continued at the same temperature for 16 hours. The solvent was subsequently removed and the residue was partitioned with 10% aqueous NaOH and ethyl acetate. The organic phase was separated, dried ($MgSO_4$), filtered and concentrated to dryness to provide a clear oil. This material was purified by reverse-phase

preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the intermediate ester (2.70 g, 56%) as a clear oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53-7.44 (m, 3H), 7.40-7.37 (m, 2H), 3.87 (d, J = 10.9 Hz, 1H), 3.59 (d, J = 10.9 Hz, 1H), 2.99 (t, J = 11.2 Hz, 1H), 2.59 (t, J = 11.4 Hz, 1H), 2.07-2.02 (m, 2H), 1.82 (d, J = 1.82 Hz, 3H), 1.40 (s, 9H). LC/MS: Anal. Calcd. for $C_{17}H_{25}NO_2$: 275; found: 276 $(M+H)^+$.

Step 2: To a stirred solution of the intermediate ester (1.12g, 2.88mmol) in dichloromethane (10 mL) was added TFA (3 mL). The reaction mixture was stirred at ambient temperature for 4 hours and then it was concentrated to dryness to give a light yellow oil. The oil was purified using reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA). The appropriate fractions were combined and concentrated to dryness *in vacuo*. The residue was then dissolved in a minimum amount of methanol and applied to applied to MCX LP extraction cartridges (2 x 6 g). The cartridges were rinsed with methanol (40 mL) and then the desired compound was eluted using 2M ammonia in methanol (50 mL). Product-containing fractions were combined and concentrated and the residue was taken up in water. Lyophilization of this solution provided the title compound (0.492 g, 78%) as a light yellow solid. ^{1}HNMR (DMSO-d_6) δ 7.50 (s, 5H), 5.13 (s, 1H), 3.09 (br s, 2H), 2.92-2.89 (m, 2H), 1.74 (m, 4H), 1.48 (br s, 2H). LC/MS: Anal. Calcd. for $C_{13}H_{17}NO_2$: 219; found: 220 $(M+H)^+$.

Cap-15



Step 1; (S)-1-Phenylethyl 2-bromo-2-phenylacetate: To a mixture of α-bromophenylacetic acid (10.75 g, 0.050 mol), (S)-(-)-1-phenylethanol (7.94 g, 0.065 mol) and DMAP (0.61 g, 5.0 mmol) in dry dichloromethane (100 mL) was added solid EDCI (12.46 g, 0.065 mol) all at once. The resulting solution was stirred at room temperature under Ar for 18 hours and then it was diluted with ethyl acetate, washed (H_2O x 2, brine), dried (Na_2SO_4), filtered, and concentrated to give a pale

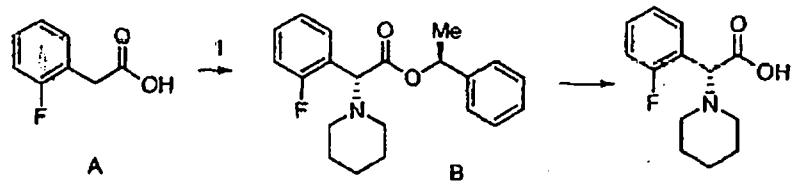
yellow oil. Flash chromatography (SiO_2/ hexane-ethyl acetate, 4:1) of this oil provided the title compound (11.64 g, 73%) as a white solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53-7.17 (*m*, 10H), 5.95 (q, *J* = 6.6 Hz, 0.5H), 5.94 (q, *J* = 6.6 Hz, 0.5H), 5.41 (s, 0.5H), 5.39 (s, 0.5H), 1.58 (d, *J* = 6.6 Hz, 1.5H), 1.51 (d, *J* = 6.6 Hz, 1.5H).

Step 2; (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (0.464 g, 1.45 mmol) in THF (8 mL) was added triethylamine (0.61 mL, 4.35 mmol), followed by tetrabutylammonium iodide (0.215 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-methyl-4-hydroxypiperidine (0.251 g, 2.18 mmol) in THF (2 mL) was added. The mixture was stirred for 1 hour at room temperature and then it was heated at 55-60 °C (oil bath temperature) for 4 hours. The cooled reaction mixture was then diluted with ethyl acetate (30 mL), washed (H_2O x2, brine), dried ($MgSO_4$), filtered and concentrated. The residue was purified by silica gel chromatography (0-60% ethyl acetate-hexane) to provide first the (S,R)-isomer of the title compound (0.306 g, 60%) as a white solid and then the corresponding (S,S)-isomer (0.120 g, 23%), also as a white solid. (S,R)-isomer: ^{1}HNMR (CD_3OD) δ 7.51-7.45 (m, 2H), 7.41-7.25 (m, 8H), 5.85 (q, *J* = 6.6 Hz, 1H), 4.05 (s, 1H), 2.56-2.45 (m, 2H), 2.41-2.29 (m, 2H), 1.71-1.49 (m, 4H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.18 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$. (S,S)-isomer: ^{1}HNMR (CD_3OD) δ 7.41-7.30 (m, 5H), 7.20-7.14 (m, 3H), 7.06-7.00 (m, 2H), 5.85 (q, *J* = 6.6 Hz, 1H), 4.06 (s, 1H), 2.70-2.60 (m, 1H), 2.51 (dt, *J* = 6.6, 3.3 Hz, 1H), 2.44-2.31 (m, 2H), 1.75-1.65 (m, 1H), 1.65-1.54 (m, 3H), 1.50 (d, *J* = 6.8 Hz, 3H), 1.20 (s, 3H). LCMS: Anal. Calcd. for $C_{22}H_{27}NO_3$: 353; found: 354 $(M+H)^+$.

Step 3; (R)-2-(4-Hydroxy-4-methylpiperidin-1-yl)-2-phenylacetic acid: To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-methylpiperidin-1-yl)-2-phenylacetate (0.185 g, 0.52 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the title compound (as TFA salt) as a pale bluish

solid (0,128 g, 98%). LCMS: Anal. Calcd. for $C_{14}H_{19}NO_3$: 249; found: 250 $(M+H)^+$.

Cap-16



(R)-Cap-16

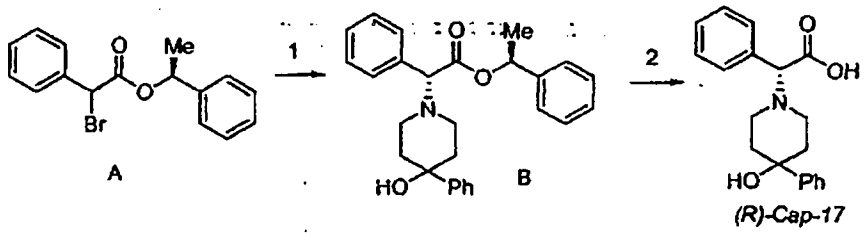
Step 1; (S)-1-Phenylethyl 2-(2-fluorophenyl)acetate: A mixture of 2-fluorophenylacetic acid (5.45 g, 35.4 mmol), (S)-1-phenylethanol (5.62 g, 46.0. mmol), EDCI (8.82 g, 46.0 mmol) and DMAP (0.561 g, 4.60 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 12 hours. The solvent was then concentrated and the residue partitioned with H_2O-ethyl acetate. The phases were separated and the aqueous layer back-extracted with ethyl acetate (2x). The combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Biotage/ 0-20% ethyl acetate-hexane) to provide the title compound as a colorless oil (8.38 g, 92%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.32 - 7.23 (m, 7H), 7.10-7.04 (m, 2), 5.85 (q, J = 6.5 Hz, 1H), 3.71 (s, 2H), 1.48 (d, J = 6.5 Hz, 3H).

Step 2; (R)-((S)-1-Phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate: To a solution of (S)-1-phenylethyl 2-(2-fluorophenyl)acetate (5.00 g, 19.4 mmol) in THF (1200 mL) at 0°C was added DBU (6.19 g, 40.7 mmol) and the solution was allowed to warm to room temperature while stirring for 30 minutes. The solution was then cooled to -78 °C and a solution of CBr_4 (13.5 g, 40.7 mmol) in THF (100 mL) was added and the mixture was allowed to warm to -10 °C and stirred at this temperature for 2 hours. The reaction mixture was quenched with saturated aq. NH_4Cl and the layers were separated. The aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. To the residue was added piperidine (5.73 mL, 58.1 mmol) and the solution was stirred at room temperature for 24 hours. The volatiles were then concentrated *in vacuo* and the residue was purified by silica

gel chromatography (Biotage/ 0-30% diethyl ether-hexane) to provide a pure mixture of diastereomers (2:1 ratio by ^{1}HNMR) as a yellow oil (2.07 g, 31%), along with unreacted starting material (2.53 g, 51%). Further chromatography of the diastereomeric mixture (Biotage/ 0-10% diethyl ether-toluene) provided the title compound as a colorless oil (0.737 g, 11%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.52 (ddd, J = 9.4, 7.6, 1.8 Hz, 1H), 7.33 – 7.40 (m, 1), 7.23 – 7.23 (m, 4H), 7.02 – 7.23 (m, 4H), 5.86 (q, J = 6.6 Hz, 1H), 4.45 (s, 1H), 2.39 – 2.45 (m, 4H), 1.52 – 1.58 (m, 4H), 1.40 – 1.42 (m, 1H), 1.38 (d, J = 6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{21}H_{24}FNO_2$: 341; found: 342 $(M+H)^+$.

Step 3; (R)-2-(2-fluorophenyl)-2-(piperidin-1-yl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(2-fluorophenyl)-2-(piperidin-1-yl)acetate (0.737 g, 2.16 mmol) and 20% $Pd(OH)_2/C$ (0.070 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 2 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®), and concentrated *in vacuo*. This provided the title compound as a colorless solid (0.503 g, 98%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.65 (ddd, J = 9.1, 7.6, 1.5 Hz, 1H), 7.47-7.53 (m, 1H), 7.21-7.30 (m, 2H), 3.07-3.13 (m, 4H), 1.84 (br s, 4H), 1.62 (br s, 2H). LCMS: Anal. Calcd. for $C_{13}H_{16}FNO_2$: 237; found: 238 $(M+H)^+$.

Cap-17

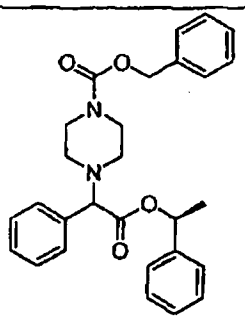


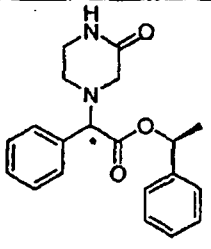
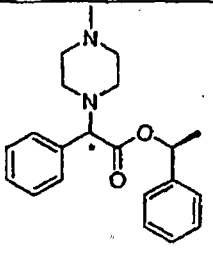
(R)-Cap-17

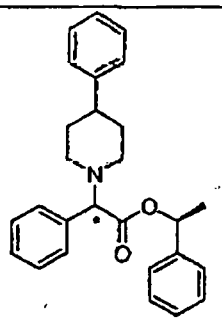
Step 1; (S)-1-Phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)- 2-phenylacetate: To a solution of (S)-1-phenylethyl 2-bromo-2-phenylacetate (1.50 g, 4.70 mmol) in THF (25 mL) was added triethylamine (1.31 mL, 9.42 mmol), followed by tetrabutylammonium iodide (0.347 g, 0.94 mmol). The reaction mixture was stirred at room temperature for 5 minutes and then a solution of 4-phenyl-4-hydroxypiperidine (1.00 g, 5.64 mmol) in THF (5 mL) was added. The mixture was stirred for 16 hours and then it was diluted with ethyl acetate (100 mL), washed (H_2O

x2, brine), dried ($MgSO_4$), filtered and concentrated. The residue was purified on a silica gel column (0-60% ethyl acetate-hexane) to provide an approximately 2:1 mixture of diastereomers, as judged by ^{1}HNMR. Separation of these isomers was performed using supercritical fluid chromatography (Chiralcel OJ-H, 30 x 250mm; 20% ethanol in CO_2 at 35 °C), to give first the (R)-isomer of the title compound (0.534 g, 27%) as a yellow oil and then the corresponding (S)-isomer (0.271 g, 14%), also as a yellow oil. (S,R)-isomer: ^{1}HNMR (400 MHz, CD_3OD) δ 7.55-7.47 (m, 4H), 7.44-7.25 (m, 10H), 7.25-7.17 (m, 1H), 5.88 (q, J = 6.6 Hz, 1H), 4.12 (s, 1H), 2.82-2.72 (m, 1H), 2.64 (dt, J = 11.1, 2.5 Hz, 1H), 2.58-2.52 (m, 1H), 2.40 (dt, J = 11.1, 2.5 Hz, 1H), 2.20 (dt, J = 12.1, 4.6 Hz, 1H), 2.10 (dt, J = 12.1, 4.6 Hz, 1H), 1.72-1.57 (m, 2H), 1.53 (d, J = 6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$; (S,S)-isomer: ^{1}HNMR (400 MHz, CD_3OD) δ 7.55-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.38-7.30 (m, 5H), 7.25-7.13 (m, 4H), 7.08-7.00 (m, 2H), 5.88 (q, J = 6.6 Hz, 1H), 4.12 (s, 1H), 2.95-2.85 (m, 1H), 2.68 (dt, J = 11.1, 2.5 Hz, 1H), 2.57-2.52 (m, 1H), 2.42 (dt, J = 11.1, 2.5 Hz, 1H), 2.25 (dt, J = 12.1, 4.6 Hz, 1H), 2.12 (dt, J = 12.1, 4.6 Hz, 1H), 1.73 (dd, J = 13.6, 3.0 Hz, 1H), 1.64 (dd, J = 13.6, 3.0 Hz, 1H), 1.40 (d, J = 6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{27}H_{29}NO_3$: 415; found: 416 $(M+H)^+$.

The following esters were prepared in similar fashion employing step 1 in the synthesis of *Cap*-17.

Intermediate-17a		Diastereomer 1: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.36 (d, J=6.41 Hz, 3H) 2.23 - 2.51 (m, 4H) 3.35 (s, 4H) 4.25 (s, 1H) 5.05 (s, 2H) 5.82 (d, J=6.71 Hz, 1H) 7.15 - 7.52 (m, 15H). LCMS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.55; Found: 459.44 $(M+H)^+$.

		Diastereomer 2: ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.45 (d, *J*=6.71 Hz, 3H) 2.27 - 2.44 (m, 4H) 3.39 (s, 4H) 4.23 (s, 1H) 5.06 (s, 2H) 5.83 (d, *J*=6.71 Hz, 1H) 7.12 (dd, *J*=6.41, 3.05 Hz, 2H) 7.19 - 7.27 (m, 3H) 7.27 - 7.44 (m, 10H). LCMS: Anal. Calcd. for: $C_{28}H_{30}N_2O_4$ 458.55; Found: 459.44 $(M+H)^+$.
Intermediate -17b		Diastereomer 1: RT = 11.76 min (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.4 Found: 339.39 $(M+H)^+$; Diastereomer 2: RT = 10.05 min (Cond'n II); LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_3$ 338.4; Found: 339.39 $(M+H)^+$.
Intermediate -17c		Diastereomer 1: T_R = 4.55 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.44 Found: 339.45 $(M+H)^+$; Diastereomer 2: T_R = 6.00 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{21}H_{26}N_2O_2$ 338.44 Found: 339.45 $(M+H)^+$.

Intermediate -17d		Diastereomer 1: RT = 7.19 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.52 Found: 400.48 $(M+H)^+$; Diastereomer 2: RT = 9.76 min (Cond'n I); LCMS: Anal. Calcd. for: $C_{27}H_{29}NO_2$ 399.52 Found: 400.48 $(M+H)^+$.

Chiral SFC Conditions for determining retention time for intermediates 17b-17d

Condition 1

Column: Chiralpak AD-H Column, 4.6X250 mm, 5µm

Solvents: 90% CO2 - 10% methanol with 0.1%DEA

Temp: 35 °C

Pressure: 150 bar

Flow rate: 2.0 mL/min.

UV monitored @ 220 nm

Injection: 1.0 mg/3mL methanol

Condition 2

Column: Chiralcel OD-H Column, 4.6X250 mm, 5µm

Solvents: 90% CO2 - 10% methanol with 0.1%DEA

Temp: 35 °C

Pressure: 150 bar

Flow rate: 2.0 mL/min.

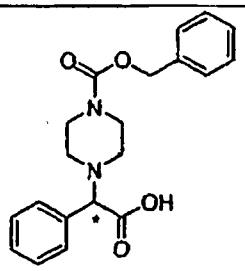
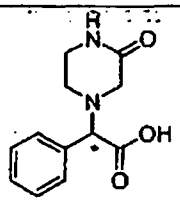
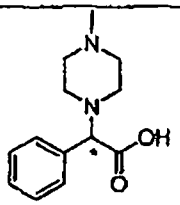
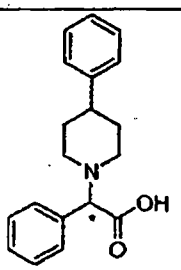
UV monitored @ 220 nm

Injection: 1.0 mg/mL methanol

Cap-17, Step 2; (R)-2-(4-Hydroxy-4-phenylpiperidin-1-yl)-2-phenylacetic acid: To a solution of (S)-1-phenylethyl (R)-2-(4-hydroxy-4-phenylpiperidin-1-yl)-2-

phenylacetate (0.350 g, 0.84 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL) and the mixture was stirred at room temperature for 2 hours. The volatiles were subsequently removed *in vacuo* and the residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 20 x 100mm; CH_3CN-H_2O-0.1% TFA) to give the title compound (as TFA salt) as a white solid (0.230 g, 88%). LCMS: Anal. Calcd. for $C_{19}H_{21}NO_3$: 311; found: 312 $(M+H)^+$.

The following carboxylic acids were prepared in a similar fashion:

Cap-17a		RT = 2.21 (Cond'n II); ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.20 - 2.35 (m, 2H) 2.34 - 2.47 (m, 2H) 3.37 (s, 4H) 3.71 (s, 1H) 5.06 (s, 2H) 7.06 - 7.53 (m, 10H). LCMS: Anal. Calcd. for: $C_{20}H_{22}N_2O_4$ 354.40; Found: 355.38 $(M+H)^+$.
Cap-17b		RT = 0.27 (Cond'n III); LCMS: Anal. Calcd. for: $C_{12}H_{14}N_2O_3$ 234.25; Found: 235.22 $(M+H)^+$.
Cap-17c		RT = 0.48 (Cond'n II); LCMS: Anal. Calcd. for: $C_{13}H_{18}N_2O_2$ 234.29; Found: 235.31 $(M+H)^+$.
Cap-17d		RT = 2.21 (Cond'n I); LCMS: Anal. Calcd. for: $C_{19}H_{21}NO_2$ 295.38; Found: 296.33 $(M+H)^+$.

LCMS Conditions for determining retention time for Caps 17a-17d

Condition 1

Column: Phenomenex-Luna 4.6 X 50 mm S10

Start % B = 0

Fianl % B = 100

Gradient Time = 4 min

Flow Rate = 4 mL/min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition 2

Column: Waters-Sunfire 4.6 X 50 mm S5

Start % B = 0

Fianl % B = 100

Gradient Time = 2 min

Flow Rate = 4 mL/min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Condition 3

Column: Phenomenex 10µ 3.0 X 50 mm

Start % B = 0

Fianl % B = 100

Gradient Time = 2 min

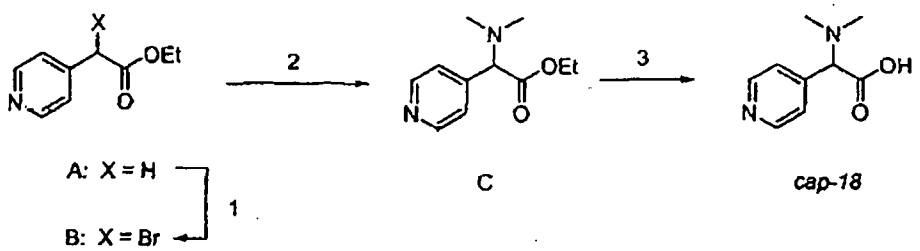
Flow Rate = 4 mL/min

Wavelength = 220

Solvent A = 10% methanol – 90% H_2O – 0.1% TFA

Solvent B = 90% methanol – 10% H_2O – 0.1% TFA

Cap-18



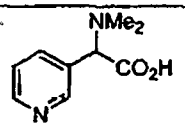
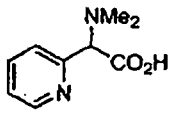
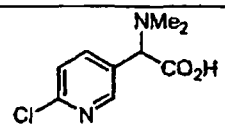
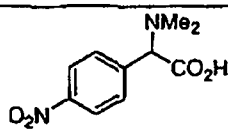
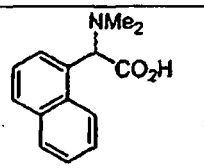
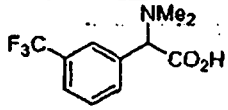
Step 1; (R,S)-Ethyl 2-(4-pyridyl)-2-bromoacetate: To a solution of ethyl 4-pyridylacetate (1.00 g, 6.05 mmol) in dry THF (150 mL) at 0 °C under argon was added DBU (0.99 mL, 6.66 mmol). The reaction mixture was allowed to warm to room temperature over 30 minutes and then it was cooled to -78 °C. To this mixture was added CBr_4 (2.21 g, 6.66 mmol) and stirring was continued at -78 °C for 2 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl and the phases were separated. The organic phase was washed (brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting yellow oil was immediately purified by flash chromatography (SiO_2/ hexane-ethyl acetate, 1:1) to provide the title compound (1.40 g, 95%) as a somewhat unstable yellow oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.62 (dd, J = 4.6, 1.8 Hz, 2H), 7.45 (dd, J = 4.6, 1.8 Hz, 2H), 5.24 (s, 1H), 4.21-4.29 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H). LCMS: Anal. Calcd. for $C_9H_{10}BrNO_2$: 242, 244; found: 243, 245 $(M+H)^+$.

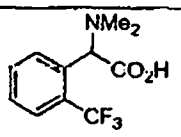
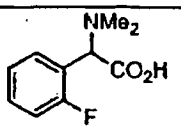
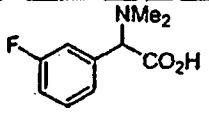
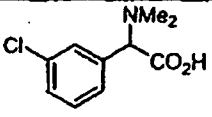
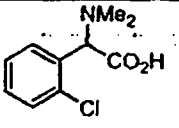
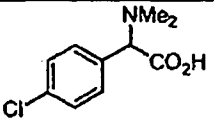
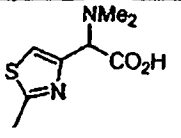
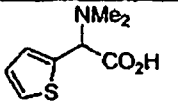
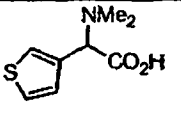
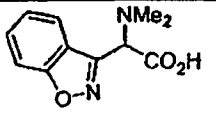
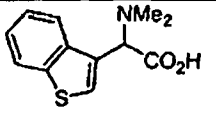
Step 2; (R,S)-Ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-bromoacetate (1.40 g, 8.48 mmol) in DMF (10 mL) at room temperature was added dimethylamine (2M in THF, 8.5 mL, 17.0 mmol). After completion of the reaction (as judged by tlc) the volatiles were removed *in vacuo* and the residue was purified by flash chromatography (Biotage, 40+M SiO_2 column; 50%-100% ethyl acetate-hexane) to provide the title compound (0.539 g, 31%) as a light yellow oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 6.0 Hz, 2H), 7.36 (d, J = 6.0 Hz, 2H), 4.17 (m, 2H), 3.92 (s, 1H), 2.27 (s, 6H), 1.22 (t, J = 7.0 Hz). LCMS: Anal. Calcd. for $C_{11}H_{16}N_2O_2$: 208; found: 209 $(M+H)^+$.

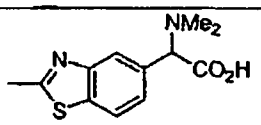
Step 3; (R,S)-2-(4-Pyridyl)-2-(N,N-dimethylamino)acetic acid: To a solution of (R,S)-ethyl 2-(4-pyridyl)-2-(N,N-dimethylamino)acetate (0.200 g, 0.960 mmol) in a mixture of THF-methanol-H_2O (1:1:1, 6 mL) was added powdered LiOH (0.120 g,

4.99 mmol) at room temperature. The solution was stirred for 3 hours and then it was acidified to pH 6 using 1N HCl. The aqueous phase was washed with ethyl acetate and then it was lyophilized to give the dihydrochloride of the title compound as a yellow solid (containing LiCl). The product was used as such in subsequent steps. ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 5.7 Hz, 2H), 7.34 (d, J = 5.7 Hz, 2H), 3.56 (s, 1H), 2.21 (s, 6H).

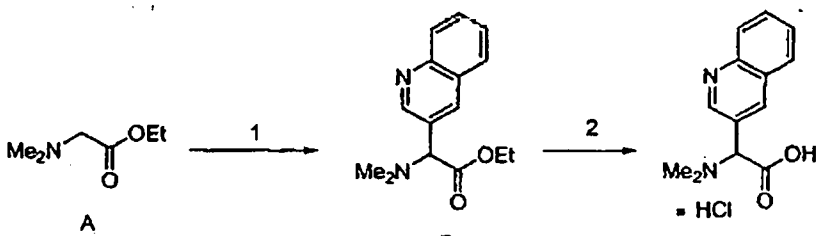
The following examples were prepared in similar fashion using the method described in Example 4;

Cap-19		LCMS: Anal. Calcd. for $C_9H_{12}N_2O_2$: 180; found: 181 $(M+H)^+$.
Cap-20		LCMS: no ionization. ^{1}HNMR (400 MHz, CD_3OD) δ 8.55 (d, J = 4.3 Hz, 1H), 7.84 (app t, J = 5.3 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.37 (app t, J = 5.3 Hz, 1H), 4.35 (s, 1H), 2.60 (s, 6H).
Cap-21		LCMS: Anal. Calcd. for $C_9H_{11Cl}N_2O_2$: 214, 216; found: 215, 217 $(M+H)^+$.
Cap-22		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-23		LCMS: Anal. Calcd. for $C_{14}H_{15}NO_2$: 247; found: 248 $(M+H)^+$.
Cap-24		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.

Cap-25		LCMS: Anal. Calcd. for $C_{11}H_{12}F_3NO_2$: 247; found: 248 $(M+H)^+$.
Cap-26		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$.
Cap-27		LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 247; found: 248 $(M+H)^+$.
Cap-28		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 217 $(M+H)^+$.
Cap-29		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 217 $(M+H)^+$.
Cap-30		LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 217 $(M+H)^+$.
Cap-31		LCMS: Anal. Calcd. for $C_8H_{11}N_2O_2S$: 200; found: 201 $(M+H)^+$.
Cap-32		LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.
Cap-33		LCMS: Anal. Calcd. for $C_8H_{11}NO_2S$: 185; found: 186 $(M+H)^+$.
Cap-34		LCMS: Anal. Calcd. for $C_{11}H_{12}N_2O_3$: 220; found: 221 $(M+H)^+$.
Cap-35		LCMS: Anal. Calcd. for $C_{12}H_{13}NO_2S$: 235; found: 236 $(M+H)^+$.

Cap-36		LCMS: Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: 250; found: 251 $(M+H)^+$.

Cap-37



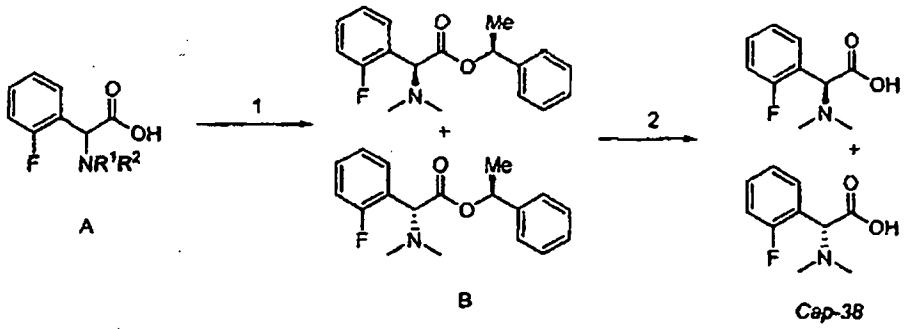
A B *cap-37*

Step 1; (R,S)-Ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)-acetate: A mixture of ethyl N,N-dimethylaminoacetate (0.462 g, 3.54 mmol), K_3PO_4 (1.90 g, 8.95 mmol), $Pd(t\text{-}Bu_3P)_2$ (0.090 g, 0.176 mmol) and toluene (10 mL) was degassed with a stream of Ar bubbles for 15 minutes. The reaction mixture was then heated at 100 °C for 12 hours, after which it was cooled to room temperature and poured into H_2O. The mixture was extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified first by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-5 mM NH_4OAc) and then by flash chromatography (SiO_2/ hexane-ethyl acetate, 1:1) to provide the title compound (0.128 g, 17%) as an orange oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 2.0 Hz, 1H), 8.32 (d, J = 2.0 Hz, 1H), 8.03-8.01 (m, 2H), 7.77 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 7.62 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 4.35 (s, 1H), 4.13 (m, 2H), 2.22 (s, 6H), 1.15 (t, J = 7.0 Hz, 3H). LCMS: Anal. Calcd. for $C_{15}H_{18}N_2O_2$: 258; found: 259 $(M+H)^+$.

Step 2; (R,S) 2-(Quinolin-3-yl)-2-(N,N-dimethylamino)acetic acid: A mixture of (R,S)-ethyl 2-(quinolin-3-yl)-2-(N,N-dimethylamino)acetate (0.122 g, 0.472 mmol) and 6M HCl (3 mL) was heated at 100 °C for 12 hours. The solvent was removed *in vacuo* to provide the dihydrochloride of the title compound (0.169 g, >100%) as a light yellow foam. The unpurified material was used in subsequent

steps without further purification. LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_2$: 230; found: 231 $(M+H)^+$.

Cap-38



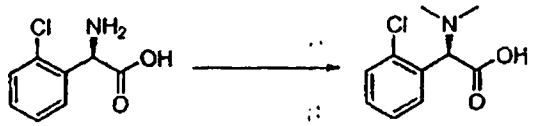
Step 1; (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate and (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate: To a mixture of (RS)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid (2.60 g, 13.19 mmol), DMAP (0.209 g, 1.71 mmol) and (S)-1-phenylethanol (2.09 g, 17.15 mmol) in CH_2Cl_2 (40 mL) was added EDCI (3.29 g, 17.15 mmol) and the mixture was allowed to stir at room temperature for 12 hours. The solvent was then removed *in vacuo* and the residue partitioned with ethyl acetate-H_2O. The layers were separated, the aqueous layer was back-extracted with ethyl acetate (2x) and the combined organic phases were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Biotage/ 0-50% diethyl ether-hexane). The resulting pure diastereomeric mixture was then separated by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA) to give first (S)-1-phenethyl (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetate (0.501 g, 13%) and then (S)-1-phenethyl (S)-2-(dimethylamino)-2-(2-fluorophenyl)-acetate (0.727 g. 18%), both as their TFA salts. (S,R)-isomer: ^{1}HNMR (400 MHz, CD_3OD) δ 7.65 - 7.70 (m, 1H), 7.55-7.60 (ddd, J = 9.4, 8.1, 1.5 Hz, 1H), 7.36-7.41 (m, 2H), 7.28-7.34 (m, 5H), 6.04 (q, J = 6.5 Hz, 1H), 5.60 (s, 1H), 2.84 (s, 6H), 1.43 (d, J = 6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 $(M+H)^+$; (S,S)-isomer: ^{1}HNMR (400 MHz, CD_3OD) δ 7.58-7.63 (m, 1H), 7.18-7.31 (m, 6H), 7.00 (dd, J = 8.5, 1.5 Hz, 2H), 6.02 (q, J = 6.5

Hz, 1H), 5.60 (s, 1H), 2.88 (s, 6H), 1.54 (d, J = 6.5 Hz, 3H). LCMS: Anal. Calcd. for $C_{18}H_{20}FNO_2$: 301; found: 302 $(M+H)^+$.

Step 2; (R)-2-(dimethylamino)-2-(2-fluorophenyl)acetic acid: A mixture of (R)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt (1.25 g, 3.01 mmol) and 20% $Pd(OH)_2/C$ (0.125 g) in ethanol (30 mL) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®), and concentrated *in vacuo*. This gave the title compound as a colorless solid (0.503 g, 98%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.53-7.63 (m, 2H), 7.33-7.38 (m, 2H), 5.36 (s, 1H), 2.86 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}FNO_2$: 197; found: 198 $(M+H)^+$.

The S-isomer could be obtained from (S)-((S)-1-phenylethyl) 2-(dimethylamino)-2-(2-fluorophenyl)acetate TFA salt in similar fashion.

Cap-39



cap-39

A mixture of (R)-(2-chlorophenyl)glycine (0.300 g, 1.62 mmol), formaldehyde (35% aqueous solution, 0.80 mL, 3.23 mmol) and 20% $Pd(OH)_2/C$ (0.050 g) was hydrogenated at room temperature and atmospheric pressure (H_2 balloon) for 4 hours. The solution was then purged with Ar, filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC (Primesphere C-18, 30 x 100mm; CH_3CN-H_2O-0.1% TFA) to give theTFA salt of the title compound (R)-2-(dimethylamino)-2-(2-chlorophenyl)acetic acid as a colorless oil (0.290 g, 55%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.59-7.65 (m, 2H), 7.45-7.53 (m, 2H), 5.40 (s, 1H), 2.87 (s, 6H). LCMS: Anal. Calcd. for $C_{10}H_{12}ClNO_2$: 213, 215; found: 214, 216 $(M+H)^+$.

Cap-40

cap-40

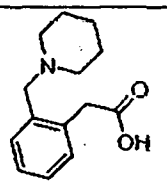
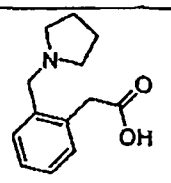
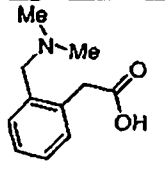
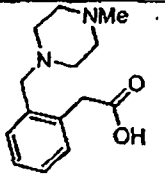
To an ice-cold solution of (R)-(2-chlorophenyl)glycine (1.00 g, 5.38 mmol) and NaOH (0.862 g, 21.6 mmol) in H_2O (5.5 mL) was added methyl chloroformate (1.00 mL, 13.5 mmol) dropwise. The mixture was allowed to stir at 0 °C for 1 hour and then it was acidified by the addition of conc. HCl (2.5 mL). The mixture was extracted with ethyl acetate (2x) and the combined organic phase was washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the title compound (R)-2-(methoxycarbonylamino)-2-(2-chlorophenyl)acetic acid as a yellow-orange foam (1.31 g, 96%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 – 7.43 (m, 2H), 7.29 – 7.31 (m, 2H), 5.69 (s, 1H), 3.65 (s, 3H). LCMS: Anal. Calcd. for $C_{10}H_{10}ClNO_4$: 243, 245; found: 244, 246 $(M+H)^+$.

Cap-41

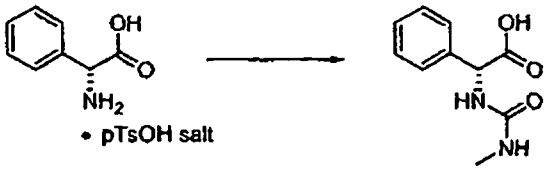
cap-41

To a suspension of 2-(2-(chloromethyl)phenyl)acetic acid (2.00 g, 10.8 mmol) in THF (20 mL) was added morpholine (1.89 g, 21.7 mmol) and the solution was stirred at room temperature for 3 hours. The reaction mixture was then diluted with ethyl acetate and extracted with H_2O (2x). The aqueous phase was lyophilized and the residue was purified by silica gel chromatography (Biotage/ 0-10% methanol-CH_2Cl_2) to give the title compound 2-(2-(Morpholinomethyl)phenyl)acetic acid as a colorless solid (2.22 g, 87%). ^{1}HNMR (400 MHz, CD_3OD) δ 7.37-7.44 (m, 3H), 7.29-7.33 (m, 1H), 4.24 (s, 2H), 3.83 (br s, 4H), 3.68 (s, 2H), 3.14 (br s, 4H). LCMS: Anal. Calcd. for $C_{13}H_{17}NO_3$: 235; found: 236 $(M+H)^+$.

The following examples were similarly prepared using the method described for *Cap*-41:

Cap-42		LCMS: Anal. Calcd. for $C_{14}H_{19}NO_2$: 233; found: 234 $(M+H)^+$.
Cap-43		LCMS: Anal. Calcd. for $C_{13}H_{17}NO_2$: 219; found: 220 $(M+H)^+$.
Cap-44		LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 194 $(M+H)^+$.
Cap-45		LCMS: Anal. Calcd. for $C_{14}H_{20}N_2O_2$: 248; found: 249 $(M+H)^+$.

Cap-45

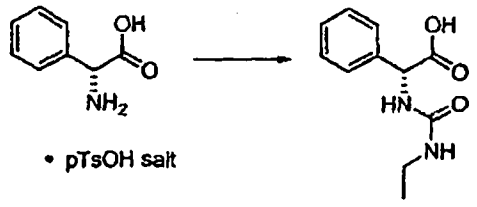


Cap-45

HMDS (1.85 mL, 8.77 mmol) was added to a suspension of (R)-2-amino-2-phenylacetic acid p-toluenesulfonate (2.83 g, 8.77 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 30 minutes. Methyl isocyanate (0.5 g, 8.77 mmol) was added in one portion stirring continued for 30 minutes. The reaction was quenched by addition of H_2O (5 mL) and the resulting precipitate was filtered, washed with H_2O and n-hexanes, and dried under vacuum. (R)-2-(3-methylureido)-

2-phenylacetic acid (1.5 g; 82 %).was recovered as a white solid and it was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.54 (d, *J*=4.88 Hz, 3H) 5.17 (d, *J*=7.93 Hz, 1H) 5.95 (q, *J*=4.48 Hz, 1H) 6.66 (d, *J*=7.93 Hz, 1H) 7.26 - 7.38 (m, 5H) 12.67 (s, 1H). LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_3$ 208.08 found 209.121 $(M+H)^-$; HPLC Phenomenex C-18 3.0 × 46 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 1.38 min, 90% homogeneity index.

Cap-46

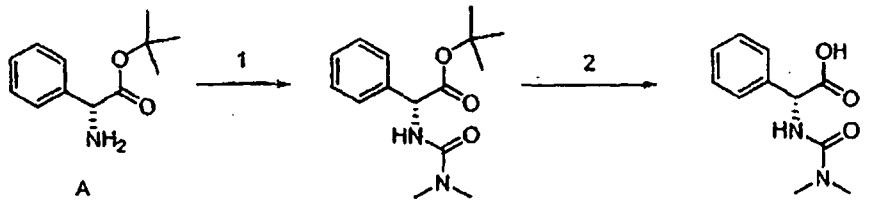


cap-46

The desired product was prepared according to the method described for *Cap-45*. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.96 (t, *J*=7.17 Hz, 3H) 2.94 - 3.05 (m, 2H) 5.17 (d, *J*=7.93 Hz, 1H) 6.05 (t, *J*=5.19 Hz, 1H) 6.60 (d, *J*=7.63 Hz, 1H) 7.26 - 7.38 (m, 5H) 12.68 (s, 1H). LCMS: Anal. Calcd. for $C_{11}H_{14}N_2O_3$ 222.10 found 209.121 $(M+H)^+$.

HPLC XTERRA C-18 3.0 × 506 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 0.87 min, 90% homogeneity index.

Cap-47



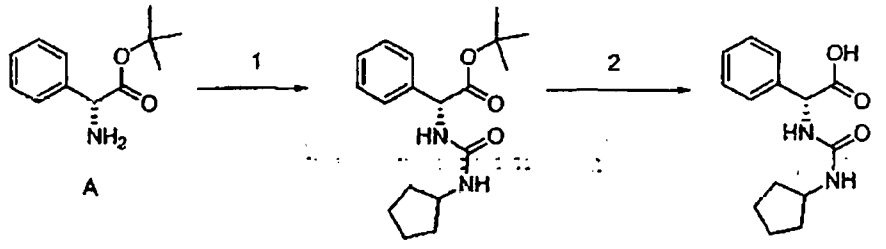
A B *Cap-47*

Step 1; (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate: To a stirred solution of (R)-tert–butyl-2-amino-2-phenylacetate (1.0 g, 4.10 mmol) and Hunig's

base (1.79 mL, 10.25 mmol) in DMF (40 mL) was added dimethylcarbamoyl chloride (0.38 mL, 4.18 mmol) dropwise over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was dissolved in ethyl acetate. The organic layer was washed with H_2O, 1N aq. HCl and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. (R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate was obtained as a white solid (0.86 g; 75%) and used without further purification. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.33 (s, 9H) 2.82 (s, 6H) 5.17 (d, J=7.63 Hz, 1H) 6.55 (d, J=7.32 Hz, 1H) 7.24 - 7.41 (m, 5H). LCMS: Anal. Calcd. for $C_{15}H_{22}N_2O_3$ 278.16 found 279.23 $(M+H)^+$; HPLC Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.26 min, 97% homogeneity index.

Step 2; (R)-2-(3,3-dimethylureido)-2-phenylacetic acid: To a stirred solution of ((R)-tert-butyl 2-(3,3-dimethylureido)-2-phenylacetate (0.86 g, 3.10 mmol) in CH_2Cl_2 (250 mL) was added TFA (15 mL) dropwise and the resulting solution was stirred at rt for 3 h. The desired compound was then precipitated out of solution with a mixture of EtOAC:Hexanes (5:20), filtered off and dried under reduced pressure. (R)-2-(3,3-dimethylureido)-2-phenylacetic acid was isolated as a white solid (0.59g, 86%) and used without further purification: ^1H NMR (500 MHz, DMSO-d_6) δ ppm 2.82 (s, 6H) 5.22 (d, J=7.32 Hz, 1H) 6.58 (d, J=7.32 Hz, 1H) 7.28 (t, J=7.17 Hz, 1H) 7.33 (t, J=7.32 Hz, 2H) 7.38 - 7.43 (m, 2H) 12.65 (s, 1H). LCMS: Anal. Calcd. for $C_{11}H_{14}N_2O_3$: 222.24; found: 223.21 $(M+H)^-$. HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 0.75 min, 93% homogeneity index.

Cap-48

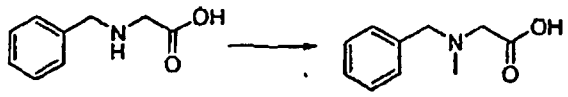


Step 1; (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate: To a stirred solution of (R)-2-amino-2-phenylacetic acid hydrochloride (1.0 g, 4.10 mmol) and Hunig's base (1.0 mL, 6.15 mmol) in DMF (15 mL) was added cyclopentyl isocyanate (0.46 mL, 4.10 mmol) dropwise and over 10 minutes. After stirring at room temperature for 3 hours, the reaction was concentrated under reduced pressure and the resulting residue was taken up in ethyl acetate. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate was obtained as an opaque oil (1.32 g; 100 %) and used without further purification. ^{1}H NMR (500 MHz, CD_3Cl-D) δ ppm 1.50 - 1.57 (m, 2H) 1.58 - 1.66 (m, 2H) 1.87 - 1.97 (m, 2H) 3.89 - 3.98 (m, 1H) 5.37 (s, 1H) 7.26 - 7.38 (m, 5H). LCMS: Anal. Calcd. for $C_{18}H_{26}N_2O_3$ 318.19 found 319.21 $(M+H)^+$; HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, RT = 2.82 min, 96% homogeneity index.

Step 2; (R)-2-(3-cyclopentylureido)-2-phenylacetic acid: To a stirred solution of (R)-tert-butyl 2-(3-cyclopentylureido)-2-phenylacetate (1.31 g, 4.10 mmol) in CH_2Cl_2 (25 mL) was added TFA (4 mL) and triethylsilane (1.64 mL; 10.3 mmol) dropwise, and the resulting solution was stirred at room temperature for 6 hours. The volatile components were removed under reduced pressure and the crude product was recrystallized in ethyl acetate/pentanes to yield (R)-2-(3-cyclopentylureido)-2-phenylacetic acid as a white solid (0.69 g, 64%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.17 - 1.35 (m, 2H) 1.42 - 1.52 (m, 2H) 1.53 - 1.64 (m, 2H) 1.67 - 1.80 (m, 2H) 3.75 - 3.89 (m, 1H) 5.17 (d, *J*=7.93 Hz, 1H) 6.12 (d, *J*=7.32 Hz, 1H) 6.48 (d, *J*=7.93 Hz, 1H) 7.24 - 7.40 (m, 5H) 12.73 (s, 1H). LCMS: Anal. Calcd. for $C_{14}H_{18}N_2O_3$:

262.31; found: 263.15 $(M+H)^+$. HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.24 min, 100% homogeneity index.

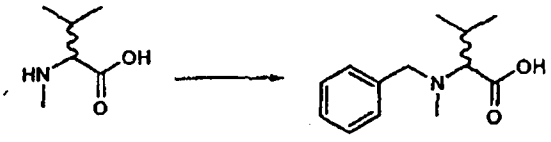
Cap-49



cap-49

To a stirred solution of 2-(benzylamino)acetic acid (2.0 g, 12.1 mmol) in formic acid (91 mL) was added formaldehyde (6.94 mL, 93.2 mmol). After five hours at 70 °C, the reaction mixture was concentrated under reduced pressure to 20 mL and a white solid precipitated. Following filtration, the mother liquors were collected and further concentrated under reduced pressure providing the crude product. Purification by reverse-phase preparative HPLC (Xterra 30 X 100 mm, detection at 220 nm, flow rate 35 mL/min, 0 to 35% B over 8 min; A = 90% water, 10 % methanol, 0.1% TFA, B = 10% water, 90 % methanol, 0.1% TFA) provided the title compound 2-(benzyl(methyl)-amino)acetic acid as its TFA salt (723 mg, 33%) as a colorless wax. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 2.75 (s, 3H) 4.04 (s, 2H) 4.34 (s, 2H) 7.29 - 7.68 (m, 5H). LCMS: Anal. Calcd. for: $C_{10}H_{13}NO_2$ 179.22; Found: 180.20 $(M+H)^+$.

Cap-50

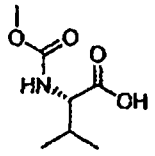


Cap-50

To a stirred solution of 3-methyl-2-(methylamino)butanoic acid (0.50 g, 3.81 mmol) in water (30 mL) was added K_2CO_3 (2.63 g, 19.1 mmol) and benzyl chloride (1.32 g, 11.4 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was extracted with ethyl acetate (30 mL x 2) and the aqueous layer was concentrated under reduced pressure providing the crude product which was purified by reverse-phase preparative HPLC (Xterra 30 x 100mm,

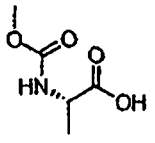
detection at 220 nm, flow rate 40 mL/min, 20 to 80% B over 6 min; A = 90% water, 10 % methanol, 0.1% TFA, B = 10% water, 90 % methanol, 0.1% TFA) to provide 2-(benzyl(methyl)amino)-3-methylbutanoic acid, TFA salt (126 mg, 19%) as a colorless wax. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.98 (d, 3H) 1.07 (d, 3H) 2.33 - 2.48 (*m*, 1H) 2.54 - 2.78 (*m*, 3H) 3.69 (s, 1H) 4.24 (s, 2H) 7.29 - 7.65 (m, 5H). LCMS: Anal. Calcd. for: $C_{13}H_{19}NO_2$ 221.30; Found: 222.28 $(M+H)^+$.

Cap-51



Na_2CO_3 (1.83g, 17.2 mmol) was added to NaOH (33 mL of 1M/H_2O, 33 mmol) solution of L-valine (3.9 g, 33.29 mmol) and the resulting solution was cooled with ice-water bath. Methyl chloroformate (2.8 mL, 36.1 mmol) was added drop-wise over 15 min, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 3.25 hr. The reaction mixture was washed with ether (50 mL, 3x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2, and extracted with CH_2Cl_2 (50 mL, 3x). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford *Cap-51* as a white solid (6 g). ^{1}H NMR for the dominant rotamer (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.54 (s, 1H), 7.33 (d, J = 8.6, 1H), 3.84 (dd, J = 8.4, 6.0, 1H), 3.54 (s, 3H), 2.03 (m, 1H), 0.87 (m, 6H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_7H_{14}NO_4$: 176.0923; found 176.0922

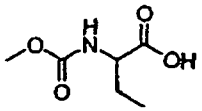
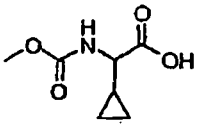
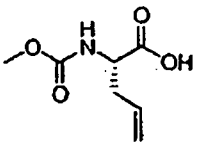
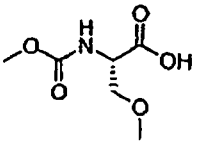
Cap-52

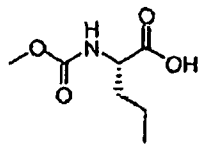
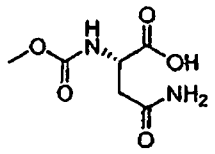
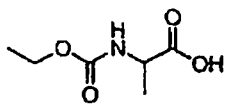
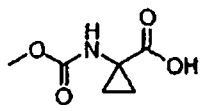
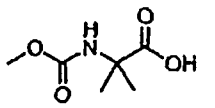


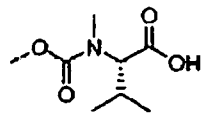
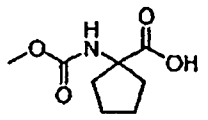
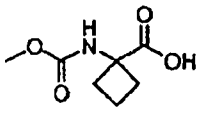
Cap-52 was synthesized from L-alanine according to the procedure described for the synthesis of *Cap-51*. For characterization purposes, a portion of the crude material was purified by a reverse phase HPLC (H_2O/MeOH/TFA) to afford *Cap-52* as a colorless viscous oil. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): 12.49 (br s,

1H), 7.43 (d, J = 7.3, 0.88H), 7.09 (app br's, 0.12H), 3.97 (m, 1H), 3.53 (s, 3H), 1.25 (d, J = 7.3, 3H).

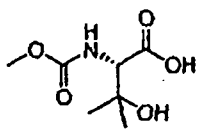
Cap-53 to -64 were prepared from appropriate starting materials according to the procedure described for the synthesis of *Cap*-51, with noted modifications if any.

Cap	Structure	Data
Cap-53a: (R) *Cap-53b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.51 (br s, 1H), 7.4 (d, J = 7.9, 0.9H), 7.06 (app s, 0.1H), 3.86-3.82 (m, 1H), 3.53 (s, 3H), 1.75-1.67 (m, 1H), 1.62-1.54 (m, 1H), 0.88 (d, J = 7.3, 3H). RT = 0.77 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.06; found 184.07. HRMS Calcd. for $[M+Na]^+$ $C_6H_{11}NNaO_4$: 184.0586; found 184.0592.
Cap-54a: (R) *Cap-54b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.48 (s, 1H), 7.58 (d, J = 7.6, 0.9H), 7.25 (app s, 0.1H), 3.52 (s, 3H), 3.36-3.33 (m, 1H), 1.10-1.01 (m, 1H), 0.54-0.49 (m, 1H), 0.46-0.40 (m, 1H), 0.39-0.35 (m, 1H), 0.31-0.21 (m, 1H). HRMS Calcd. for $[M+H]^+$ $C_7H_{12}NO_4$: 174.0766; found 174.0771
Cap-55		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.62 (s, 1H), 7.42 (d, J = 8.2, 0.9H), 7.07 (app s, 0.1H), 5.80-5.72 (m, 1H), 5.10 (d, J = 17.1, 1H), 5.04 (d, J = 10.4, 1H), 4.01-3.96 (m, 1H), 3.53 (s, 3H), 2.47-2.42 (m, 1H), 2.35-2.29 (m, 1H).
Cap-56		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.75 (s, 1H), 7.38 (d, J = 8.3, 0.9H), 6.96 (app s, 0.1H), 4.20-4.16 (m, 1H), 3.60-3.55 (m, 2H), 3.54 (s, 3H), 3.24 (s, 3H).

Cap-57		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.50 (s, 1H), 8.02 (d, *J* = 7.7, 0.08H), 7.40 (d, *J* = 7.9, 0.76H), 7.19 (d, *J* = 8.2, 0.07H), 7.07 (d, *J* = 6.7, 0.09H), 4.21-4.12 (m, 0.08H), 4.06-3.97 (m, 0.07H), 3.96-3.80 (m, 0.85H), 3.53 (s, 3H), 1.69-1.51 (m, 2H), 1.39-1.26 (m, 2H), 0.85 (t, *J* = 7.4, 3H). LC (Cond. 2): RT = 1.39 LC/MS: Anal. Calcd. for $[M+H]^+$ $C_7H_{14}NO_4$: 176.09; found 176.06.
Cap-58		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.63 (bs, 1H), 7.35 (s,1H), 7.31 (d, *J* = 8.2, 1H), 6.92 (s, 1H), 4.33-4.29 (m, 1H), 3.54 (s, 3H), 2.54(dd, *J* = 15.5, 5.4, 1H), 2.43 (dd, *J* = 15.6, 8.0, 1H). RT = 0.16 min (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_6H_{11}N_2O_5$: 191.07; found 191.14.
Cap-59a: (R) *Cap-59b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.49 (br *s*, 1H), 7.40 (d, *J* = 7.3, 0.89H), 7.04 (br s, 0.11H), 4.00-3.95 (m, 3H), 1.24 (d, *J* = 7.3, 3H), 1.15 (t, *J* = 7.2, 3H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; found 162.0771.
Cap-60		The crude material was purified with a reverse phase HPLC (H_2O/MeOH/TFA) to afford a colorless viscous oil that crystallized to a white solid upon exposure to high vacuum. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.38 (br s, 1H), 7.74 (s, 0.82H), 7.48 (s, 0.18H), 3.54/3.51 (two s, 3H), 1.30 (m, 2H), 0.98 (m, 2H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{10}NO_4$: 160.0610; found 160.0604.
Cap-61		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.27 (br s, 1H), 7.40 (br s, 1H), 3.50 (s, 3H), 1.32 (s, 6H). HRMS: Anal. Calcd. for $[M+H]^+$ $C_6H_{12}NO_4$: 162.0766; found 162.0765.

Cap-62		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.74 (br s, 1H), 4.21 (d, *J* = 10.3, 0.6H), 4.05 (d, *J* = 10.0, 0.4H), 3.62/3.60 (two singlets, 3H), 3.0 (s, 3H), 2.14-2.05 (m, 1H), 0.95 (d, *J* = 6.3, 3H), 0.81 (d, *J* = 6.6, 3H). LC/MS: Anal. Calcd. for $[M-H]^-$ $C_8H_{14}NO_4$: 188.09; found 188.05.
Cap-63		[Note: the reaction was allowed to run for longer than what was noted for the general procedure.] ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.21 (br s, 1H), 7.42 (br s, 1H), 3.50 (s, 3H), 2.02-1.85 (m, 4H), 1.66-1.58 (m, 4H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{14}NO_4$: 188.09; found 188.19.
Cap-64		[Note: the reaction was allowed to run for longer than what was noted for the general procedure.] ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.35 (br s, 1H), 7.77 (s, 0.82H), 7.56/7.52 (overlapping br s, 0.18H), 3.50 (s, 3H), 2.47-2.40 (m, 2H), 2.14-2.07 (m, 2H), 1.93-1.82 (m, 2H).

Cap-65

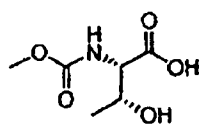


Methyl chloroformate (0.65 mL, 8.39 mmol) was added dropwise over 5 min to a cooled (ice-water) mixture of Na_2CO_3 (0.449 g, 4.23 mmol), NaOH (8.2 mL of 1M/H_2O, 8.2 mmol) and (*S*)-3-hydroxy-2-(methoxycarbonylamino)-3-methylbutanoic acid (1.04 g, 7.81 mmol). The reaction mixture was stirred for 45 min, and then the cooling bath was removed and stirring was continued for an additional 3.75 hr. The reaction mixture was washed with CH_2Cl_2, and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 1-2. The volatile component was removed *in vacuo* and the residue was

taken up in a 2:1 mixture of MeOH/CH_2Cl_2 (15 mL) and filtered, and the filterate was rotervaped to afford *Cap*-65 as a white semi-viscous foam (1.236 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 6.94 (d, *J* = 8.5, 0.9 H), 6.53 (br s, 0.1H), 3.89 (d, *J* = 8.8, 1H), 2.94 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H).

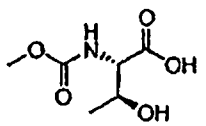
Cap-66 and -67 were prepared from appropriate commercially available starting materials by employing the procedure described for the synthesis of *Cap*-65.

Cap-66



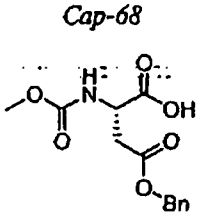
^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.58 (br s, 1H), 7.07 (d, *J* = 8.3, 0.13H), 6.81 (d, *J* = 8.8, 0.67H), 4.10-4.02 (m, 1.15H), 3.91 (dd, *J* = 9.1, 3.5, 0.85H), 3.56 (s, 3H), 1.09 (d, *J* = 6.2, 3H). [Note: only the dominant signals of NH were noted].

Cap-67



^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 12.51 (br s, 1H), 7.25 (d, *J* = 8.4, 0.75H), 7.12 (br d, *J* = 0.4, 0.05H), 6.86 (br s, 0.08H), 3.95-3.85 (m, 2H), 3.54 (s, 3H), 1.08 (d, *J* = 6.3, 3H). [Note: only the dominant signals of NH were noted]

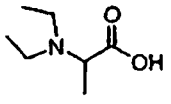
Cap-68



Methyl chloroformate (0.38 ml, 4.9 mmol) was added drop-wise to a mixture of 1N NaOH (aq) (9.0 ml, 9.0 mmol), 1M $NaHCO_3$ (aq) (9.0 ml, 9.0 mol), L-aspartic acid β-benzyl ester (1.0 g, 4.5 mmol) and Dioxane (9 ml). The reaction mixture was

stirred at ambient conditions for 3 hr, and then washed with Ethyl acetate (50 ml, 3x). The aqueous layer was acidified with 12N HCl to a pH ~ 1-2, and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford *Cap*-68 as a light yellow oil (1.37g; mass is above theoretical yield, and the product was used without further purification). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 12.88 (br s, 1H), 7.55 (d, J = 8.5, 1H), 7.40-7.32 (m, 5H), 5.13 (d, J = 12.8, 1H), 5.10 (d, J = 12.9, 1H), 4.42-4.38 (m, 1H), 3.55 (s, 3H), 2.87 (dd, J = 16.2, 5.5, 1H), 2.71 (dd, J =16.2, 8.3, 1H). LC (Cond. 2): RT = 1.90 min; LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{13}H_{16}NO_6$: 282.10; found 282.12.

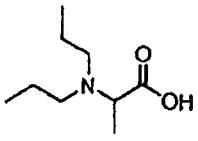
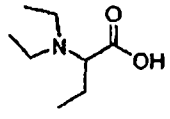
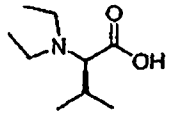
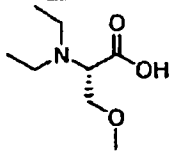
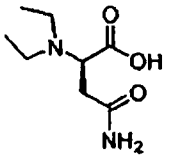
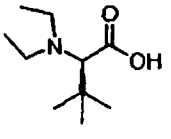
Cap-69a and -69b



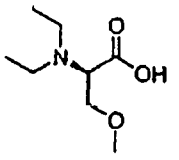
Cap-69a: (R)-enantiomer
Cap-69b: (S)-enantiomer

$NaCNBH_3$ (2.416 g, 36.5 mmol) was added in batches to a chilled (~15 °C) water (17 mL)/MeOH (10 mL) solution of alanine (1.338 g, 15.0 mmol). A few minutes later acetaldehyde (4.0 mL, 71.3 mmol) was added drop-wise over 4 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 6 hr. An additional acetaldehyde (4.0 mL) was added and the reaction was stirred for 2 hr. Concentrated HCl was added slowly to the reaction mixture until the pH reached ~ 1.5, and the resulting mixture was heated for 1 hr at 40 °C. Most of the volatile component was removed *in vacuo* and the residue was purified with a Dowex ® 50WX8-100 ion-exchange resin (column was washed with water, and the compound was eluted with dilute NH_4OH, prepared by mixing 18 ml of NH_4OH and 282 ml of water) to afford *Cap*-69 (2.0 g) as an off-white soft hygroscopic solid. ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.44 (q, J = 7.1, 1H), 2.99-2.90 (m, 2H), 2.89-2.80 (m, 2H), 1.23 (d, J = 7.1, 3H), 1.13 (t, J = 7.3, 6H).

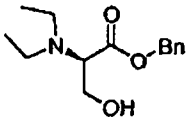
Cap-70 to -74 were prepared according to the procedure described for the synthesis of *Cap*-69 by employing appropriate starting materials.

Cap-70a: (R) *Cap-70b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 3.42 (q, *J* = 7.1, 1H), 2.68-2.60 (*m*, 4H), 1.53-1.44 (m, 4H), 1.19 (d, *J* = 7.3, 3H), 0.85 (t, *J* = 7.5, 6H). LC/MS: Anal. Calcd. for $[M+H]^-$ $C_9H_{20}NO_2$: 174.15; found 174.13.
Cap-71a: (R) *Cap-71b*: (S)		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 3.18-3.14 (m, 1H), 2.84-2.77 (m, 2H), 2.76-2.68 (m, 2H), 1.69-1.54 (m, 2H), 1.05 (t, *J* = 7.2, 6H), 0.91 (t, *J* = 7.3, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{18}NO_2$: 160.13; found 160.06.
Cap-72		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 2.77-2.66 (m, 3H), 2.39-2.31 (m, 2H), 1.94-1.85 (m, 1H), 0.98 (t, *J* = 7.1, 6H), 0.91 (d, *J* = 6.5, 3H), 0.85 (d, *J* = 6.5, 3H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_9H_{20}NO_2$: 174.15; found 174.15.
Cap-73		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 9.5 (br s, 1H), 3.77 (dd, *J* = 10.8, 4.1,1H), 3.69-3.61 (m, 2H), 3.26 (s, 3H), 2.99-2.88 (m, 4H), 1.13 (t, *J* = 7.2, 6H).
Cap-74		^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 500 MHz): δ 7.54 (s, 1H), 6.89 (s, 1H), 3.81 (t, *J* = 6.6, k,1H), 2.82-2.71 (m, 4H), 2.63 (dd, *J* = 15.6, 7.0, 1H), 2.36 (dd, *J* = 15.4, 6.3, 1H), 1.09 (t, *J* = 7.2, 6H). RT = 0.125 minutes (Cond. 2); LC/MS: Anal. Calcd. for $[M+H]^+$ $C_8H_{17}N_2O_3$: 189.12; found 189.13.
Cap-74x		LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{22}NO_2$: 188.17; found 188.21

Cap-75



Cap-75, step a



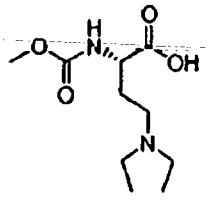
$NaBH_3CN$ (1.6 g, 25.5 mmol) was added to a cooled (ice/water bath) water (25 ml)/methanol (15 ml) solution of H-D-Ser-OBzl HCl (2.0 g, 8.6 mmol). Acetaldehyde (1.5 ml, 12.5 mmol) was added drop-wise over 5 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 2 hr. The reaction was carefully quenched with 12N HCl and concentrated *in vacuo*. The residue was dissolved in water and purified with a reverse phase HPLC ($MeOH/H_2O$/TFA) to afford the TFA salt of (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate as a colorless viscous oil (1.9g). ^1H *NMR (DMSO-*d_6, $\delta = 2.5$ ppm, 500 MHz): δ 9.73 (br s, 1H), 7.52-7.36 (m, 5H), 5.32 (d, J = 12.2, 1H), 5.27 (d, J = 12.5, 1H), 4.54-4.32 (m, 1H), 4.05-3.97 (m, 2H), 3.43-3.21 (m, 4H), 1.23 (t, J = 7.2, 6H). LC/MS (Cond. 2): RT = 1.38 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{22}NO_3$: 252.16; found 252.19.

Cap-75

NaH (0.0727 g, 1.82 mmol, 60%) was added to a cooled (ice-water) THF (3.0 mL) solution of the TFA salt (R)-benzyl 2-(diethylamino)-3-hydroxypropanoate (0.3019 g, 0.8264 mmol) prepared above, and the mixture was stirred for 15 min. Methyl iodide (56 µL, 0.90 mmol) was added and stirring was continued for 18 hr while allowing the bath to thaw to ambient condition. The reaction was quenched with water and loaded onto a MeOH pre-conditioned MCX (6 g) cartridge, and washed with methanol followed by compound elution with 2N NH_3/Methanol. Removal of the volatile component *in vacuo* afforded *Cap*-75, contaminated with

(R)-2-(diethylamino)-3-hydroxypropanoic acid, as a yellow semi-solid (100 mg). The product was used as is without further purification.

Cap-76

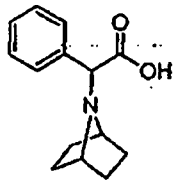


$NaCNBH_3$ (1.60 g, 24.2 mmol) was added in batches to a chilled (~15 °C) water/MeOH (12 mL each) solution of (*S*)-4-amino-2-(tert-butoxycarbonylamino) butanoic acid (2.17 g, 9.94 mmol). A few minutes later acetaldehyde (2.7 mL, 48.1 mmol) was added drop-wise over 2 min, the cooling bath was removed, and the reaction mixture was stirred at ambient condition for 3.5 hr. An additional acetaldehyde (2.7 mL, 48.1 mmol) was added and the reaction was stirred for 20.5 hr. Most of the MeOH component was removed *in vacuo*, and the remaining mixture was treated with concentrated HCl until its pH reached ~ 1.0 and then heated for 2 hr at 40 °C. The volatile component was removed *in vacuo*, and the residue was treated with 4 M HCl/dioxane (20 mL) and stirred at ambient condition for 7.5 hr. The volatile component was removed *in vacuo* and the residue was purified with Dowex ® 50WX8-100 ion-exchange resin (column was washed with water and the compound was eluted with dilute NH_4OH, prepared from 18 ml of NH_4OH and 282 ml of water) to afford intermediate (S)-2-amino-4-(diethylamino)butanoic acid as an off-white solid (1.73 g).

Methyl chloroformate (0.36 mL, 4.65 mmol) was added drop-wise over 11 min to a cooled (ice-water) mixture of Na_2CO_3 (0.243 g, 2.29 mmol), NaOH (4.6 mL of 1M/H_2O, 4.6 mmol) and the above product (802.4 mg). The reaction mixture was stirred for 55 min, and then the cooling bath was removed and stirring was continued for an additional 5.25 hr. The reaction mixture was diluted with equal volume of water and washed with CH_2Cl_2 (30 mL, 2x), and the aqueous phase was cooled with ice-water bath and acidified with concentrated HCl to a pH region of 2. The volatile component was then removed *in vacuo* and the crude material was free-based with MCX resin (6.0g; column was washed with water, and sample was eluted with 2.0 M

NH_3/MeOH) to afford impure *Cap*-76 as an off-white solid (704 mg). ^{1}H NMR (MeOH-d_4, δ = 3.29 ppm, 400 MHz): δ 3.99 (dd, J = 7.5, 4.7, 1H), 3.62 (s, 3H), 3.25-3.06 (m, 6H), 2.18-2.09 (m, 1H), 2.04-1.96 (m, 1H), 1.28 (t, J = 7.3, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{10}H_{21}N_2O_4$: 233.15; found 233.24.

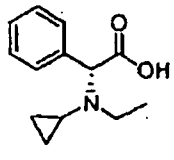
Cap-77a and -77b



Cap-77a: enantiomer-1
Cap-77b: enantiomer-2

The synthesis of *Cap*-77 was conducted according to the procedure described for *Cap*-7 by using 7-azabicyclo[2.2.1]heptane for the SN_2 displacement step, and by effecting the enantiomeric separation of the intermediate benzyl 2-(7-azabicyclo[2.2.1]heptan-7-yl)-2-phenylacetate using the following condition: the intermediate (303.7 mg) was dissolved in ethanol, and the resulting solution was injected on a chiral HPLC column (Chiracel AD-H column, 30 x 250 mm, 5 um) eluting with 90% CO_2-10% EtOH at 70 mL/min, and a temperature of 35 °C to provide 124.5 mg of enantiomer-1 and 133.8 mg of enantiomer-2. These benzyl esters were hydrogenolysed according to the preparation of *Cap*-7 to provide *Cap*-77: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.55 (m, 2H), 7.38-7.30 (m, 3H), 4.16 (s, 1H), 3.54 (app br s, 2H), 2.08-1.88 (m, 4 H), 1.57-1.46 (m, 4H). LC (Cond. 1): RT = 0.67 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}BrNO_2$: 232.13; found 232.18. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{14}H_{18}BrNO_2$: 232.1338; found 232.1340.

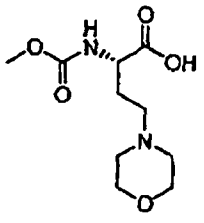
Cap-78



$NaCNBH_3$ (0.5828 g, 9.27 mmol) was added to a mixture of the HCl salt of (*R*)-2-(ethylamino)-2-phenylacetic acid (an intermediate in the synthesis of *Cap*-3; 0.9923 mg, 4.60 mmol) and (1-ethoxycyclopropoxy)trimethylsilane (1.640 g, 9.40

mmol) in MeOH (10 mL), and the semi-heterogeneous mixture was heated at 50 °C with an oil bath for 20 hr. More (1-ethoxycyclopropoxy)trimethylsilane (150 mg, 0.86 mmol) and $NaCNBH_3$ (52 mg, 0.827 mmol) were added and the reaction mixture was heated for an additional 3.5 hr. It was then allowed to cool to ambient temperature and acidified to a ~ pH region of 2 with concentrated HCl, and the mixture was filtered and the filtrate was rotervaped. The resulting crude material was taken up in *i*-PrOH (6 mL) and heated to effect dissolution, and the non-dissolved part was filtered off and the filtrate concentrated *in vacuo*. About 1/3 of the resultant crude material was purified with a reverse phase HPLC (H_2O/MeOH/TFA) to afford the TFA salt of *Cap*-78 as a colorless viscous oil (353 mg). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz; after D_2O exchange): δ 7.56-7.49 (m, 5H), 5.35 (S, 1H), 3.35 (m, 1H), 3.06 (app br s, 1H), 2.66 (m, 1H), 1.26 (t, J = 7.3, 3H), 0.92 (m, 1H), 0.83-0.44 (m, 3H). LC (Cond. 1): RT = 0.64 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.13; found 220.21. HRMS: Anal. Calcd. for $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.1338; found 220.1343.

Cap-79



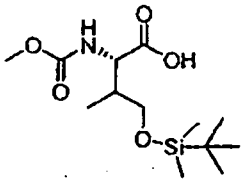
Ozone was bubbled through a cooled (-78 °C) CH_2Cl_2 (5.0 mL) solution *Cap*-55 (369 mg, 2.13 mmol) for about 50 min until the reaction mixture attained a tint of blue color. Me_2S (10 pipet drops) was added, and the reaction mixture was stirred for 35 min. The -78 °C bath was replaced with a -10 °C bath and stirring continued for an additional 30 min, and then the volatile component was removed *in vacuo* to afford a colorless viscous oil.

$NaBH_3CN$ (149 mg, 2.25 mmol) was added to a MeOH (5.0 mL) solution of the above crude material and morpholine (500 µL, 5.72 mmol) and the mixture was stirred at ambient condition for 4 hr. It was cooled to ice-water temperature and treated with concentrated HCl to bring its pH to ~2.0, and then stirred for 2.5 hr. The

volatile component was removed *in vacuo*, and the residue was purified with a combination of MCX resin (MeOH wash; 2.0 N NH_3/MeOH elution) and a reverse phase HPLC (H_2O/MeOH/TFA) to afford *Cap*-79 containing unknown amount of morpholine.

In order to consume the morpholine contaminant, the above material was dissolved in CH_2Cl_2 (1.5 mL) and treated with Et_3N (0.27 mL, 1.94 mmol) followed by acetic anhydride (0.10 mL, 1.06 mmol) and stirred at ambient condition for 18 hr. THF (1.0 mL) and H_2O (0.5 mL) were added and stirring continued for 1.5 hr. The volatile component was removed *in vacuo*, and the resultant residue was passed through MCX resin (MeOH wash; 2.0 N NH_3/MeOH elution) to afford impure *Cap*-79 as a brown viscous oil, which was used for the next step without further purification.

Cap-80a and -80b



Cap-80a: S/S-diastereomer
Cap-80b: S/R-diastereomer

$SOCl_2$ (6.60 mL, 90.5 mmol) was added drop-wise over 15 min to a cooled (ice-water) mixture of (S)-3-amino-4-(benzyloxy)-4-oxobutanoic acid (10.04g, 44.98 mmol) and MeOH (300 mL), the cooling bath was removed and the reaction mixture was stirred at ambient condition for 29 hr. Most of the volatile component was removed *in vacuo* and the residue was carefully partitioned between EtOAc (150 mL) and saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (150 mL, 2x), and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford (S)-1-benzyl 4-methyl 2-aminosuccinate as a colorless oil (9.706g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.40-7.32 (m, 5H), 5.11 (s, 2H), 3.72 (app t, J = 6.6, 1H), 3.55 (s, 3H), 2.68 (dd, J = 15.9, 6.3, 1H), 2.58 (dd, J = 15.9, 6.8, 1H), 1.96 (s, 2H). LC (Cond. 1): RT = 0.90 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{12}H_{16}NO_4$: 238.11; found 238.22.

$Pb(NO_3)_2$ (6.06 g, 18.3 mmol) was added over 1 min to a CH_2Cl_2 (80 mL) solution of (S)-1-benzyl 4-methyl 2-aminosuccinate (4.50 g, 19.0 mmol), 9-bromo-9-

phenyl-9*H*-fluorene (6.44 g, 20.0 mmol) and Et_3N (3.0 mL, 21.5 mmol), and the heterogeneous mixture was stirred at ambient condition for 48 hr. The mixture was filtered and the filtrate was treated with $MgSO_4$ and filtered again, and the final filtrate was concentrated. The resulting crude material was submitted to a Biotage purification (350 g silica gel, CH_2Cl_2 elution) to afford (S)-1-benzyl 4-methyl 2-(9-phenyl-9H-fluoren-9-ylamino)succinate as highly viscous colorless oil (7.93 g). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 7.82 (m, 2H), 7.39-7.13 (m, 16H), 4.71 (d, J = 12.4, 1H), 4.51 (d, J = 12.6, 1H), 3.78 (d, J = 9.1, NH), 3.50 (s, 3H), 2.99 (m, 1H), 2.50-2.41 (m, 2H, partially overlapped with solvent). LC (Cond. 1): RT = 2.16 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{28}NO_4$: 478.20; found 478.19.

LiHMDS (9.2 mL of 1.0 M/THF, 9.2 mmol) was added drop-wise over 10 min to a cooled (-78 °C) THF (50 mL) solution of (S)-1-benzyl 4-methyl 2-(9-phenyl-9H-fluoren-9-ylamino)succinate (3.907 g, 8.18 mmol) and stirred for ~1 hr. MeI (0.57 mL, 9.2 mmol) was added drop-wise over 8 min to the mixture, and stirring was continued for 16.5 hr while allowing the cooling bath to thaw to room temperature. After quenching with saturated NH_4Cl solution (5 mL), most of the organic component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (100 mL) and water (40 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the resulting crude material was purified with a Biotage (350 g silica gel; 25% EtOAc/hexanes) to afford 3.65 g of a 2S/3S and 2S/3R diastereomeric mixtures of 1-benzyl 4-methyl 3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)succinate in ~1.0:0.65 ratio (^1H NMR). The stereochemistry of the dominant isomer was not determined at this juncture, and the mixture was submitted to the next step without separation. Partial ^1H NMR data (DMSO-d_6, δ = 2.5 ppm, 400 MHz): major diastereomer, δ 4.39 (d, J = 12.3, 1H of CH_2), 3.33 (s, 3H, overlapped with H_2O signal), 3.50 (d, J = 10.9, NH), 1.13 (d, J = 7.1, 3H); minor diastereomer, δ 4.27 (d, J =12.3, 1H of CH_2), 3.76 (d, J = 10.9, NH), 3.64 (s, 3H), 0.77 (d, J = 7.0, 3H). LC (Cond. 1): RT = 2.19 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{32}H_{30}NO_4$: 492.22; found 492.15.

Diisobutylaluminum hydride (20.57 ml of 1.0 M in hexanes, 20.57 mmol) was added drop-wise over 10 min to a cooled (-78 °C) THF (120 mL) solution of (2S)-1-benzyl 4-methyl 3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)succinate (3.37

g, 6.86 mmol) prepared above, and stirred at -78 °C for 20 hr. The reaction mixture was removed from the cooling bath and rapidly poured into ~1M H_3PO_4/H_2O (250 mL) with stirring, and the mixture was extracted with ether (100 mL, 2x). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to chromatography (25% EtOAc/hexanes; gravity elution) to afford 1.1g of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate, contaminated with benzyl alcohol, as a colorless viscous oil and (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate containing the (2S,3R) stereoisomer as an impurity. The later sample was resubmitted to the same column chromatography purification conditions to afford 750 mg of purified material as a white foam. [Note: the (2S, 3S) isomer elutes before the (2S,3R) isomer under the above condition]. (2S, 3S) isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.81 (m, 2H), 7.39-7.08 (m, 16H), 4.67 (d, J = 12.3, 1H), 4.43 (d, J = 12.4, 1H), 4.21 (app t, J = 5.2, OH), 3.22 (d, J = 10.1, NH), 3.17 (m, 1H), 3.08 (m, 1H), ~2.5 (m, 1H, overlapped with the solvent signal), 1.58 (m, 1H), 0.88 (d, J = 6.8, 3H). LC (Cond. 1): RT = 2.00 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; found 464.22. (2S, 3R) isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): 7.81 (d, J = 7.5, 2H), 7.39-7.10 (m, 16H), 4.63 (d, J= 12.1, 1H), 4.50 (app t, J = 4.9, 1H), 4.32 (d, J = 12.1, 1H), 3.59-3.53 (m, 2H), 3.23 (m, 1H), 2.44 (dd, J = 9.0, 8.3, 1H), 1.70 (m, 1H), 0.57 (d, J = 6.8, 3H). LC (Cond. 1): RT = 1.92 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{31}H_{30}NO_3$: 464.45; found 464.52.

The relative stereochemical assignments of the DIBAL-reduction products were made based on NOE studies conducted on lactone derivatives prepared from each isomer by employing the following protocol: LiHMDS (50 µL of 1.0 M/THF, 0.05 mmol) was added to a cooled (ice-water) THF (2.0 mL) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate (62.7 mg, 0.135 mmol), and the reaction mixture was stirred at similar temperature for ~2 hr. The volatile component was removed *in vacuo* and the residue was partitioned between CH_2Cl_2 (30 mL), water (20 mL) and saturated aqueous NH_4Cl solution (1 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*, and the resulting crude material was submitted to a Biotage purification (40 g silica gel; 10-15% EtOAc/hexanes) to afford (3S,4S)-4-methyl-3-(9-phenyl-9*H*-fluoren-9-

ylamino)dihydrofuran-2(3*H*)-one as a colorless film of solid (28.1 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate was elaborated similarly to (3S,4R)-4-methyl-3-(9-phenyl-9*H*-fluoren-9-ylamino)dihydrofuran-2(3*H*)-one. (3S,4S)-lactone isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.83 (d, *J* = 7.5, 2H), 7.46-7.17 (m, 11H), 4.14 (app t, *J* = 8.3, 1H), 3.60 (d, *J* = 5.8, NH), 3.45 (app t, *J* = 9.2, 1H), ~2.47 (m, 1H, partially overlapped with solvent signal), 2.16 (m, 1H), 0.27 (d, *J* = 6.6, 3H). LC (Cond. 1): RT = 1.98 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; found 378.42. (3S,4R)-lactone isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.89 (d, *J* = 7.6, 1H), 7.85 (d, *J* = 7.3, 1H), 7.46-7.20 (m, 11H), 3.95 (dd, *J* = 9.1, 4.8, 1H), 3.76 (d, *J* = 8.8, 1H), 2.96 (d, *J* = 3.0, NH), 2.92 (dd, *J* = 6.8, 3, NCH), 1.55 (m, 1H), 0.97 (d, *J* = 7.0, 3H). LC (Cond. 1): RT = 2.03 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{24}H_{21}NNaO_2$: 378.15; found 378.49.

TBDMS-Cl (48 mg, 0.312 mmol) followed by imidazole (28.8 mg, 0.423 mmol) were added to a CH_2Cl_2 (3 ml) solution of (2S,3S)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate (119.5 mg, 0.258 mmol), and the mixture was stirred at ambient condition for 14.25 hr. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with water (15 mL), and the organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resultant crude material was purified with a Biotage (40 g silica gel; 5% EtOAc/hexanes) to afford (2S,3S)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate, contaminated with TBDMS based impurities, as a colorless viscous oil (124.4 mg). (2S,3R)-benzyl 4-hydroxy-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was elaborated similarly to (2S,3R)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate. (2S,3S)-silyl ether isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.82 (d, *J* = 4.1, 1H), 7.80 (d, *J* = 4.0, 1H), 7.38-7.07 (m, 16 H), 4.70 (d, *J* = 12.4, 1H), 4.42 (d, *J* = 12.3, 1H), 3.28-3.19 (m, 3H), 2.56 (dd, *J* = 10.1, 5.5, 1H), 1.61 (m, 1H), 0.90 (d, *J* = 6.8, 3H), 0.70 (s, 9H), -0.13 (s, 3H), -0.16 (s, 3H). LC (Cond. 1, where the run time was extended to 4 min): RT = 3.26 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{37}H_{44}NO_3Si$: 578.31; found 578.40. (2S,3R)-silyl ether isomer: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 7.82 (d, *J* = 3.0, 1H), 7.80 (d, *J* = 3.1, 1H), 7.39-7.10 (m,

16H), 4.66 (d, J = 12.4, 1H), 4.39 (d, J = 12.4, 1H), 3.61 (dd, J = 9.9, 5.6, 1H), 3.45 (d, J = 9.5, 1H), 3.41 (dd, J = 10, 6.2, 1H), 2.55 (dd, J = 9.5, 7.3, 1H), 1.74 (m, 1H), 0.77 (s, 9H), 0.61 (d, J = 7.1, 3H), -0.06 (s, 3H), -0.08 (s, 3H).

A balloon of hydrogen was attached to a mixture of (2S,3S)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9*H*-fluoren-9-ylamino)butanoate (836 mg, 1.447 mmol) and 10% Pd/C (213 mg) in EtOAc (16 mL) and the mixture was stirred at room temperature for ~ 21 hr, where the balloon was recharged with H_2 as necessary. The reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of diatomaceous earth (Celite-545®), and the pad was washed with EtOAc (200 mL), EtOAc/MeOH (1:1 mixture, 200 mL) and MeOH (750 mL). The combined organic phase was concentrated, and a silica gel mesh was prepared from the resulting crude material and submitted to a flash chromatography (8:2:1 mixture of EtOAc/i-PrOH/H_2O) to afford (2S,3S)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid as a white fluffy solid (325 mg). (2S,3R)-benzyl 4-(tert-butyldimethylsilyloxy)-3-methyl-2-(9-phenyl-9H-fluoren-9-ylamino)butanoate was similarly elaborated to (2S,3R)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid. (2S,3S)-amino acid isomer: ^{1}H NMR (Methanol-d_4, δ = 3.29 ppm, 400 MHz), 3.76 (dd, J = 10.5, 5.2, 1H), 3.73 (d, J = 3.0, 1H), 3.67 (dd, J = 10.5, 7.0, 1H), 2.37 (m, 1H), 0.97 (d, J = 7.0, 3H), 0.92 (s, 9H), 0.10 (s, 6H). LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; found 248.44. (2S,3R)-amino acid isomer: ^{1}H NMR (Methanol-d_4, δ = 3.29 ppm, 400 MHz), 3.76-3.75 (m, 2H), 3.60 (d, J = 4.1, 1H), 2.16 (m, 1H), 1.06 (d, J = 7.3, 3H), 0.91 (s, 9H), 0.09 (s, 6H). Anal. Calcd. for $[M+H]^+$ $C_{11}H_{26}NO_3Si$: 248.17; found 248.44.

Water (1 mL) and NaOH (0.18 mL of 1.0 M/H_2O, 0.18 mmol) were added to a mixture of (2S,3S)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid (41.9 mg, 0.169 mmol) and Na_2CO_3 (11.9 mg, 0.112 mmol), and sonicated for about 1 min to effect dissolution of reactants. The mixture was then cooled with an ice-water bath, methyl chloroformate (0.02 mL, 0.259 mmol) was added over 30 s, and vigorous stirring was continued at similar temperature for 40 min and then at ambient temperature for 2.7 hr. The reaction mixture was diluted with water (5 mL), cooled with ice-water bath and treated drop-wise with 1.0 N HCl aqueous solution (~0.23 mL). The mixture was further diluted with water (10 mL) and extracted with CH_2Cl_2

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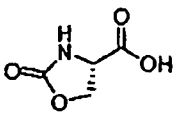
(15 mL, 2x). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford *Cap*-80a as an off-white solid. (2S,3R)-2-amino-4-(tert-butyldimethylsilyloxy)-3-methylbutanoic acid was similarly elaborated to *Cap*-80b. *Cap*-80a: ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz), 12.57 (br s, 1H), 7.64 (d, J = 8.3, 0.3H), 7.19 (d, J = 8.8, 0.7H), 4.44 (dd, J = 8.1, 4.6, 0.3H), 4.23 (dd, J = 8.7, 4.4, 0.7H), 3.56/3.53 (two singlets, 3H), 3.48-3.40 (m, 2H), 2.22-2.10 (m, 1H), 0.85 (s, 9H), ~0.84 (d, 0.9H, overlapped with t-Bu signal), 0.79 (d, J = 7, 2.1H), 0.02/0.01/0.00 (three overlapping singlets, 6H). LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; found 328.46. *Cap*-80b: ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm, 400 MHz), 6.00 (br d, J = 6.8, 1H), 4.36 (dd, J = 7.1, 3.1, 1H), 3.87 (dd, J = 10.5, 3.0, 1H), 3.67 (s, 3H), 3.58 (dd, J = 10.6, 4.8, 1H), 2.35 (m, 1H), 1.03 (d, J = 7.1, 3H), 0.90 (s, 9H), 0.08 (s, 6H). LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{13}H_{27}NNaO_5Si$: 328.16; found 328.53. The crude products were utilized without further purification.

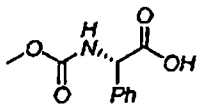
Cap-81



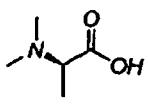
Prepared according to the protocol described by Falb et al. *Synthetic Communications* 1993, *23*, 2839.

Cap-82 to Cap-85

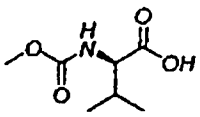
Cap-82 to *Cap*-85 were synthesized from appropriate starting materials according to the procedure described for *Cap*-51. The samples exhibited similar spectral profiles as that of their enantiomers (i.e., *Cap*-4, *Cap*-13, *Cap*-51 and *Cap*-52, respectively)



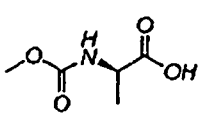
Cap-82



Cap-83



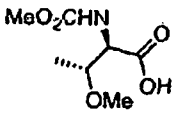
Cap-84



Cap-85

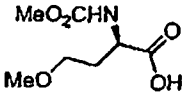
169

Cap-86



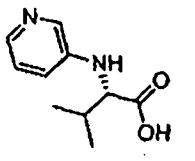
To a mixture of O-methyl-L-threonine (3.0 g, 22.55 mmol), NaOH (0.902 g, 22.55 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (1.74 mL, 22.55 mmol) dropwise at 0°C. The mixture was allowed to stir for 12 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2x250 mL) and 10% MeOH in CH_2Cl_2 (250 mL) and the combined organic phases were concentrated under *in vacuo* to afford a colorless oil (4.18 g, 97%) which was of sufficient purity for use in subsequent steps. ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.19 (s, 1H), 3.92-3.97 (m, 1H), 3.66 (s, 3H), 1.17 (d, J = 7.7 Hz, 3H). LCMS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 190 $(M-H)^-$.

Cap-87



To a mixture of L-homoserine (2.0 g, 9.79 mmol), Na_2CO_3 (2.08 g, 19.59 mmol) in H_2O (15 mL) was added $ClCO_2Me$ (0.76 mL, 9.79 mmol) dropwise at 0°C. The mixture was allowed to stir for 48 h and acidified to pH 1 using 1N HCl. The aqueous phase was extracted with EtOAc and (2X250 mL) and the combined organic phases were concentrated under *in vacuo* to afford a colorless solid (0.719 g, 28%) which was of sufficient purity for use in subsequent steps. ^{1}HNMR (400 MHz, $CDCl_3$) δ 4.23 (dd, J = 4.5, 9.1 Hz, 1H), 3.66 (s, 3H), 3.43-3.49 (m, 2H), 2.08 – 2.14 (m, 1H), 1.82 – 1.89 (m, 1H). LCMS: Anal. Calcd. for $C_7H_{13}NO_5$: 191; found: 192 $(M+H)^+$.

Cap-88



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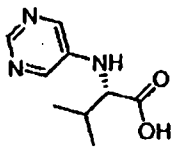
A mixture of L-valine (1.0 g, 8.54 mmol), 3-bromopyridine (1.8 mL, 18.7 mmol), K_2CO_3 (2.45 g, 17.7 mmol) and CuI (169 mg, 0.887 mmol) in DMSO (10 mL) was heated at 100°C for 12h. The reaction mixture was cooled to rt, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H_2O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and loaded onto a pad of cation exchange resin (Strata) (ca. 25g). The pad was washed with H_2O (200 mL), MeOH (200 mL), and then NH_3 (3M in MeOH, 2X200 mL). The appropriate fractions was concentrated *in vacuo* and the residue (ca. 1.1 g) was dissolved in H_2O, frozen and lyophyllized. The title compound was obtained as a foam (1.02 g, 62%). ^{1}HNMR (400 MHz, DMSO-d_6) δ 8.00 (s, br, 1H), 7.68 – 7.71 (m, 1H), 7.01 (s, br, 1H), 6.88 (d, J = 7.5 Hz, 1H), 5.75 (s, br, 1H), 3.54 (s, 1H), 2.04 – 2.06 (m, 1H), 0.95 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). LCMS: Anal. Calcd. for $C_{10}H_{14}N_2O_2$: 194; found: 195 $(M+H)^+$.

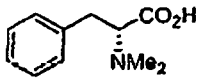
Cap-89



A mixture of L-valine (1.0 g, 8.54 mmol), 5-bromopyrimidine (4.03 g, 17.0 mmol), K_2CO_3 (2.40 g, 17.4 mmol) and CuI (179 mg, 0.94 mmol) in DMSO (10 mL) was heated at 100°C for 12h. The reaction mixture was cooled to RT, poured into H_2O (ca. 150 mL) and washed with EtOAc (x2). The organic layers were extracted with a small amount of H_2O and the combined aq phases were acidified to ca. pH 2 with 6N HCl. The volume was reduced to about one-third and 20g of cation exchange resin (Strata) was added. The slurry was allowed to stand for 20 min and loaded onto a pad of cation exchange resin (Strata) (ca. 25g). The pad was washed with H_2O (200 mL), MeOH (200 mL), and then NH_3 (3M in MeOH, 2x200 mL). The appropriate fractions was concentrated *in vacuo* and the residue (ca. 1.1 g) was dissolved in H_2O, frozen and lyophyllized. The title compound was obtained as a foam (1.02 g, 62%). ^{1}HNMR (400 MHz, CD_3OD) showed the mixture to contain valine and the purity

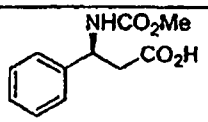
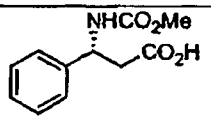
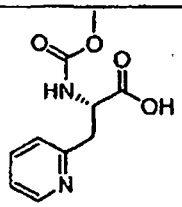
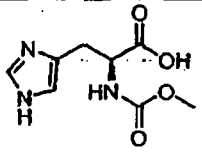
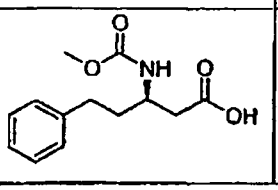
could not be estimated. The material was used as is in subsequent reactions. LCMS: Anal. Calcd. for $C_9H_{13}N_3O_2$: 195; found: 196 $(M+H)^+$.

Cap–90



Cap-90 was prepared according to the method described for the preparation of *Cap*-1. The crude material was used as is in subsequent steps. LCMS: Anal. Calcd. for $C_{11}H_{15}NO_2$: 193; found: 192 $(M-H)^-$.

The following caps were prepared according to the method of example 51:

Cap	Structure	LCMS
Cap-91		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-92		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-93		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-94		LCMS: Anal. Calcd. for $C_9H_{11}N_3O_4$: 213; found: 214 $(M+H)^+$.
Cap-95		LCMS: Anal. Calcd. for $C_{13}H_{17}NO_4$: 251; found: 250 $(M-H)^-$.

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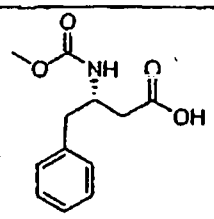
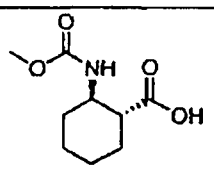
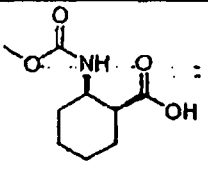
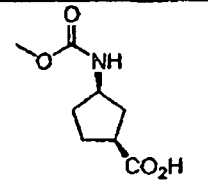
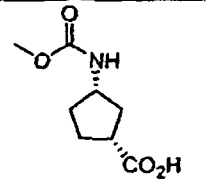
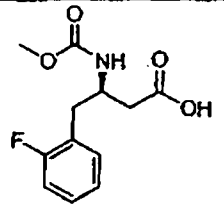
Cap-96		LCMS: Anal. Calcd. for $C_{12}H_{15}NO_4$: 237; found: 236 $(M-H)^-$.
Cap-97		LCMS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 200 $(M-H)^-$.
Cap-98		LCMS: Anal. Calcd. for $C_9H_{15}NO_4$: 201; found: 202 $(M+H)^+$.
Cap-99		^{1}HNMR (400 MHz, CD_3OD) δ 3.88 – 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 – 1.94 (m, 3H), 1.45 – 1.71 (m, 2H).
Cap-99a		^{1}HNMR (400 MHz, CD_3OD) δ 3.88 – 3.94 (m, 1H), 3.60, 3.61 (s, 3H), 2.80 (m, 1H), 2.20 (m 1H), 1.82 – 1.94 (m, 3H), 1.45 – 1.71 (m, 2H).
Cap-100		LCMS: Anal. Calcd. for $C_{12}H_{14}NO_4F$: 255; found: 256 $(M+H)^+$.

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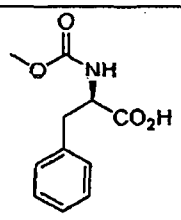
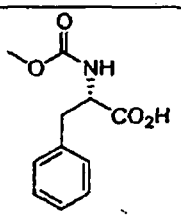
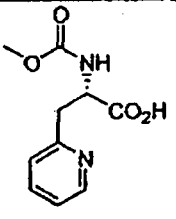
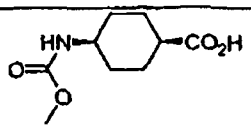
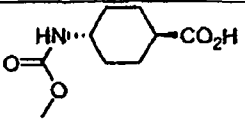
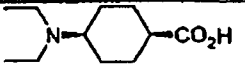
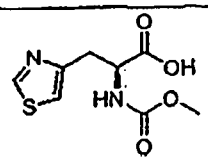
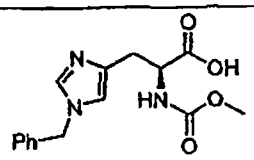
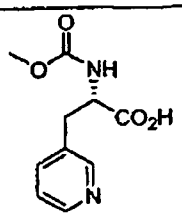
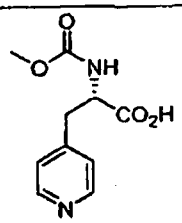
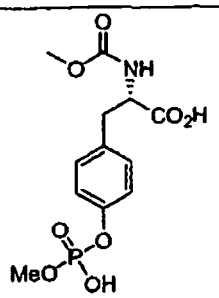
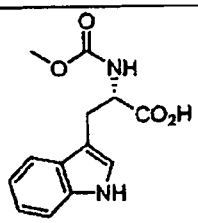
Cap-101		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$.
Cap-102		LCMS: Anal. Calcd. for $C_{11}H_{13}NO_4$: 223; found: 222 $(M-H)^-$
Cap-103		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-104		^{1}HNMR (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.50 – 3.53 (m, 1H), 2.66 – 2.69 and 2.44 – 2.49 (m, 1H), 1.91 – 2.01 (m, 2H), 1.62 – 1.74 (m, 4H), 1.51 – 1.62 (m, 2H).
Cap-105		^{1}HNMR (400 MHz, CD_3OD) δ 3.60 (s, 3H), 3.33 – 3.35 (m, 1H, partially obscured by solvent), 2.37 – 2.41 and 2.16 – 2.23 (m, 1H), 1.94 – 2.01 (m, 4H), 1.43 – 1.53 (m, 2H), 1.17 – 1.29 (m, 2H).
Cap-106		^{1}HNMR (400 MHz, CD_3OD) δ 3.16 (q, J = 7.3 Hz, 4H), 2.38 - 2.41 (m, 1H), 2.28 – 2.31 (m, 2H), 1.79 – 1.89 (m, 2H), 1.74 (app, ddd J = 3.5, 12.5, 15.9 Hz, 2H), 1.46 (app

		dt J = 4.0, 12.9 Hz, 2H), 1.26 (t, J = 7.3 Hz, 6H).
Cap-107		LCMS: Anal. Calcd. for $C_8H_{10}N_2O_4S$: 230; found: 231 $(M+H)^+$.
Cap-108		LCMS: Anal. Calcd. for $C_{15}H_{17}N_3O_4$: 303; found: 304 $(M+H)^+$.
Cap-109		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-110		LCMS: Anal. Calcd. for $C_{10}H_{12}N_2O_4$: 224; found: 225 $(M+H)^+$.
Cap-111		LCMS: Anal. Calcd. for $C_{12}H_{16}NO_8P$: 333; found: 334 $(M+H)^+$.
Cap-112		LCMS: Anal. Calcd. for $C_{13}H_{14}N_2O_4$: 262; found: 263 $(M+H)^+$.

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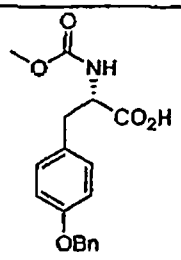
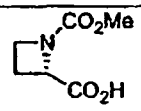
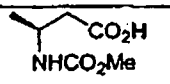
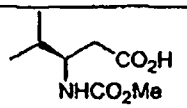
Cap-113		LCMS: Anal. Calcd. for $C_{18}H_{19}NO_5$: 329; found: 330 $(M+H)^+$.
Cap-114		^{1}HNMR (400 MHz, $CDCl_3$) δ 4.82 – 4.84 (m, 1H), 4.00 – 4.05 (m, 2H), 3.77 (s, 3H), 2.56 (s, br, 2H)
Cap-115		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.13 (s, br, 1H), 4.13 (s, br, 1H), 3.69 (s, 3H), 2.61 (d, J = 5.0 Hz, 2H), 1.28 (d, J = 9.1 Hz, 3H).
Cap-116		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.10 (d, J = 8.6 Hz, 1H), 3.74 – 3.83 (m, 1H), 3.69 (s, 3H), 2.54 – 2.61 (m, 2H), 1.88 (sept, J = 7.0 Hz, 1H), 0.95 (d, J = 7.0 Hz, 6H).

Cap-117 to Cap-123

For the preparation of caps *Cap*-117 to *Cap*-123 the the Boc amino acids were commercially available and were deprotected by treatment with 25% TFA in CH_2Cl_2. After complete reaction as judged by LCMS the solvents were removed *in vacuo* and the corresponding TFA salt of the amino acid was carbamoylated with methyl chloroformate according to the procedure for *Cap*-51.

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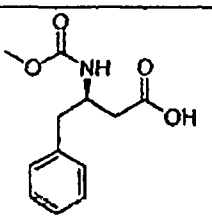
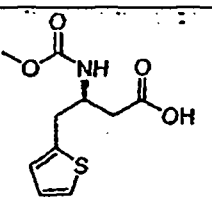
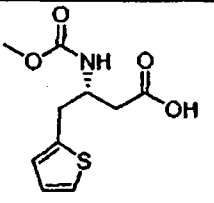
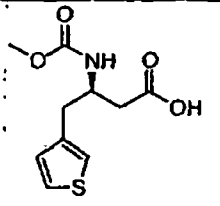
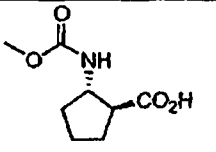
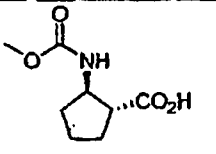
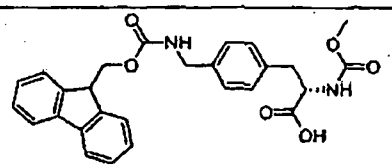
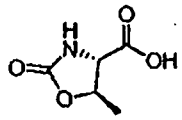
Cap	Structure	LCMS
Cap-117		LCMS: Anal. Calcd. for $C_{12}H_{15}NO_4S$: 237; found: 238 $(M+H)^+$.
Cap-118		LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$.
Cap-119		LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$.
Cap-120		LCMS: Anal. Calcd. for $C_{10}H_{13}NO_4S$: 243; found: 244 $(M+H)^+$.
Cap-121		^{1}HNMR (400 MHz, $CDCl_3$) δ 4.06 – 4.16 (m, 1H), 3.63 (s, 3H), 3.43 (s, 1H), 2.82 and 2.66 (s, br, 1H), 1.86 – 2.10 (m, 3H), 1.64 – 1.76 (m, 2H), 1.44 – 1.53 (m, 1H).
Cap-122		^{1}HNMR (400 MHz, $CDCl_3$) δ 5.28 and 5.12 (s, br, 1H), 3.66 (s, 3H), 2.64 – 2.74 (m, 1H), 1.86 - 2.12 (m, 3H), 1.67 – 1.74 (m, 2H), 1.39 – 1.54 (m, 1H).

Cap-123		LCMS: Anal. Calcd. for $C_{27}H_{26}N_2O_6$: 474; found: 475 $(M+H)^+$.

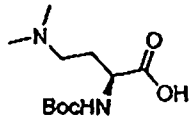
Preparation of *Cap*-124 . (4S,5R)-5-methyl-2-oxooxazolidine-4-carboxylic acid



cap-124

The hydrochloride salt of L-threonine tert-butyl ester was carbamoylated according to the procedure for *Cap*-51. The crude reaction mixture was acidified with 1N HCl to pH~1 and the mixture was extracted with EtOAc (2X50 mL). The combined organic phases were concentrated *in vacuo* to give a colorless which solidified on standing. The aqueous layer was concentrated *in vacuo* and the resulting mixture of product and inorganic salts was triturated with EtOAc-CH_2Cl_2-MeOH (1:1:0.1) and then the organic phase concentrated *in vacuo* to give a colorless oil which was shown by LCMS to be the desired product. Both crops were combined to give 0.52 g of a solid. ^{1}HNMR (400 MHz, CD_3OD) δ 4.60 (m, 1H), 4.04 (d, J = 5.0 Hz, 1H), 1.49 (d, J = 6.3 Hz, 3H). LCMS: Anal. Calcd. for $C_5H_7NO_4$: 145; found: 146 $(M+H)^+$.

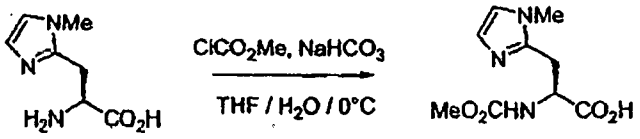
Preparation of *Cap*-125. (S)-2-(tert-butoxycarbonylamino)-4-(dimethylamino)butanoic acid.



cap-125

Cap-125 was prepared according to the procedure for the preparation of *Cap*-1. The crude product was used as is in subsequent reactions. LCMS: Anal. Calcd. for $C_{11}H_{22}N_2O_4$: 246; found: 247 $(M+H)^+$.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1-methyl-1H-imidazol-2-yl)propanoic acid (*Cap*-126).



cj-25 *cap-126*

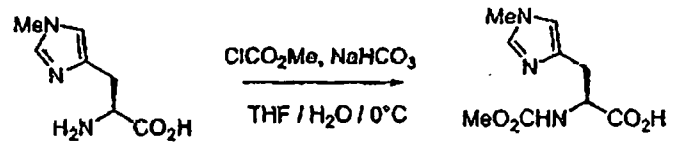
This procedure is a modification of that used to prepare *Cap*-51. To a suspension of (S)-2-amino-3-(1-methyl-1H-imidazol-2-yl)propanoic acid (0.80 g, 4.70 mmol) in THF (10mL) and H_2O (10 mL) at 0°C was added $NaHCO_3$ (0.88 g, 10.5 mmol). The resulting mixture was treated with $ClCO_2Me$ (0.40 mL, 5.20 mmol) and the mixture allowed to stir at 0°C. After stirring for ca. 2h LCMS showed no starting material remaining. The reaction was acidified to pH 2 with 6 N HCl.

The solvents were removed *in vacuo* and the residue was suspended in 20 mL of 20% MeOH in CH_2Cl_2. The mixture was filtered and concentrated to give a light yellow foam (1.21 g,). LCMS and ^{1}H NMR showed the material to be a 9:1 mixture of the methyl ester and the desired product. This material was taken up in THF (10mL) and H_2O (10mL), cooled to 0°C and LiOH (249.1 mg, 10.4 mmol) was added. After stirring ca. 1h LCMS showed no ester remaining. Therefore the mixture was acidified with 6N HCl and the solvents removed *in vacuo*. LCMS and ^{1}H NMR confirm the absence of the ester. The title compound was obtained as its HCl salt contaminated with inorganic salts (1.91 g, >100%). The compound was used as is in subsequent steps without further purification.

^{1}HNMR (400 MHz, CD_3OD) δ 8.84, (s, 1H), 7.35 (s, 1H), 4.52 (dd, J = 5.0, 9.1 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (dd, J = 4.5, 15.6 Hz, 1H, partially obscured by solvent), 3.12 (dd, J = 9.0, 15.6 Hz, 1H).

LCMS: Anal. Calcd. for $C_{17}H_{15}NO_2$: 392; found: 393 $(M+H)^+$.

Preparation of (*S*)-2-(methoxycarbonylamino)-3-(1-methyl-1H-imidazol-4-yl)propanoic acid (*Cap*-127).



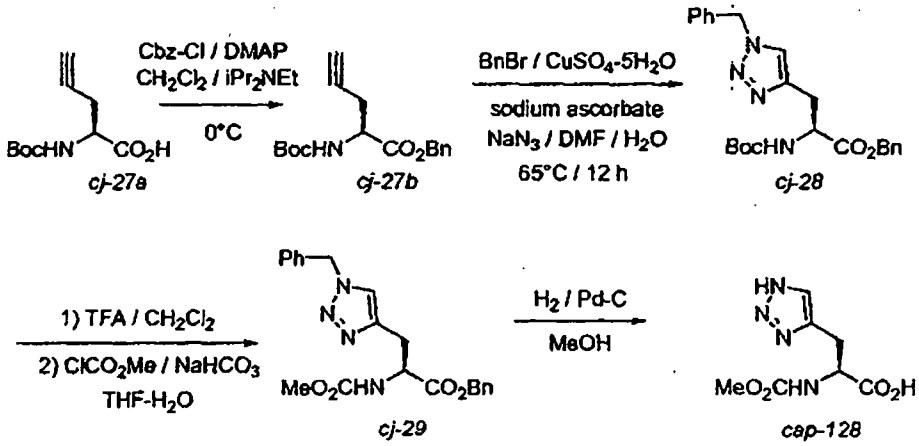
cj-26 *cap-127*

Cap-127 was prepared according to the method for *Cap*-126 above starting from (S)-2-amino-3-(1-methyl-1H-imidazol-4-yl)propanoic acid (1.11 g, 6.56 mmol), $NaHCO_3$ (1.21 g, 14.4 mmol) and $ClCO_2Me$ (0.56 mL, 7.28 mmol). The title compound was obtained as its HCl salt (1.79 g, >100%) contaminated with inorganic salts. LCMS and ^1H NMR showed the presence of ca. 5% of the methyl ester. The crude mixture was used as is without further purification.

^{1}HNMR (400 MHz, CD_3OD) δ 8.90 (s, 1H), 7.35 (s, 1H), 4.48 (dd, J = 5.0, 8.6 Hz, 1H), 3.89 (s, 3H), 3.62 (s, 3H), 3.35 (m, 1H), 3.08 (m, 1H).

LCMS: Anal. Calcd. for $C_{17}H_{15}NO_2$: 392; found: 393 $(M+H)^+$.

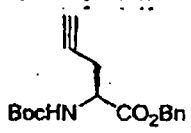
Preparation of (*S*)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid (*Cap*-128).



cj-27a *cj-27b* *cj-28*

cj-29 *cap-128*

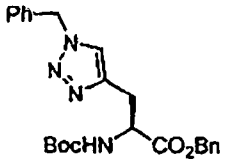
Step 1. Preparation of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (cj-27b).



cj-27b

To a solution of cj-27a (1.01 g, 4.74 mmol), DMAP (58 mg, 0.475 mmol) and iPr_2NEt (1.7 mL, 9.8 mmol) in CH_2Cl_2 (100 mL) at 0°C was added Cbz-Cl (0.68 mL, 4.83 mmol). The solution was allowed to stir for 4 h at 0°C, washed (1N $KHSO_4$, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (TLC 6:1 hex:EtOAc) to give the title compound (1.30 g, 91%) as a colorless oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.35 (d, br, J = 8.1 Hz, 1H), 5.23 (d, J = 12.2 Hz, 1H), 5.17 (d, J = 12.2 Hz, 1H), 4.48 – 4.53 (m, 1H), 2.68 – 2.81 (m, 2H), 2.00 (t, J = 2.5 Hz, 1H), 1.44 (s, 9H). LCMS: Anal. Calcd. for $C_{17}H_{21}NO_4$: 303; found: 304 $(M+H)^+$.

Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (cj-28).

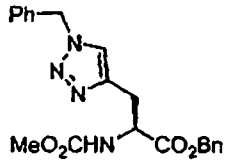


cj-28

To a mixture of (S)-benzyl 2-(tert-butoxycarbonylamino)pent-4-ynoate (0.50 g, 1.65 mmol), sodium ascorbate (0.036 g, 0.18 mmol), $CuSO_4$-$5H_2O$ (0.022 g, 0.09 mmol) and NaN_3 (0.13 g, 2.1 mmol) in DMF-H_2O (5 mL, 4:1) at rt was added BnBr (0.24 mL, 2.02 mmol) and the mixture was warmed to 65°C . After 5h LCMS indicated low conversion. A further portion of NaN_3 (100 mg) was added and heating was continued for 12h. The reaction was poured into EtOAc and H_2O and shaken. The layers were separated and the aqueous layer extracted 3x with EtOAc and the combined organic phases washed (H_2O x3, brine), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash (Biotage, 40+M 0-5% MeOH in CH_2Cl_2; TLC 3% MeOH in CH_2Cl_2) to afford a light yellow oil which solidified on

standing (748.3 mg, 104%). The NMR was consistent with the desired product but suggests the presence of DMF. The material was used as is without further purification. ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.84 (s, 1H), 7.27 – 7.32 (m, 10H), 5.54 (s, 2H), 5.07 (s, 2H), 4.25 (m, 1H), 3.16 (dd, J = 1.0, 5.3 Hz, 1H), 3.06 (dd, J = 5.3, 14.7 Hz), 2.96 (dd, J = 9.1, 14.7 Hz, 1H), 1.31 (s, 9H).
LCMS: Anal. Calcd. for $C_{24}H_{28}N_4O_4$: 436; found: 437 $(M+H)^+$.

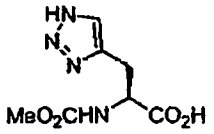
Step 2. Preparation of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (cj-29).



cj-29

A solution of (S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(tert-butoxycarbonylamino)propanoate (0.52 g, 1.15 mmol) in CH_2Cl_2 was added TFA (4 mL). The mixture was allowed to stir at room temperature for 2h. The mixture was concentrated *in vacuo* to give a colorless oil which solidified on standing. This material was dissolved in THF-H_2O and cooled to 0°C. Solid $NaHCO_3$ (0.25 g, 3.00 mmol) was added followed by $ClCO_2Me$ (0.25 mL, 3.25 mmol). After stirring for 1.5h the mixture was acidified to pH~2 with 6N HCl and then poured into H_2O-EtOAc. The layers were separated and the aq phase extracted 2x with EtOAc. The combined org layers were washed (H_2O, brine), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a colorless oil (505.8 mg, 111%, NMR suggested the presence of an unidentified impurity) which solidified while standing on the pump. The material was used as is without further purification. ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.27 – 7.32 (m, 10H), 5.54 (s, 2H), 5.10 (d, J = 12.7 Hz, 1H), 5.06 (d, J = 12.7 Hz, 1H), 4.32 – 4.37 (m, 1H), 3.49 (s, 3H), 3.09 (dd, J = 5.6, 14.7 Hz, 1H), 2.98 (dd, J = 9.6, 14.7 Hz, 1H). LCMS: Anal. Calcd. for $C_{21}H_{22}N_4O_4$: 394; found: 395 $(M+H)^+$.

Step 3. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid (*Cap*-128).

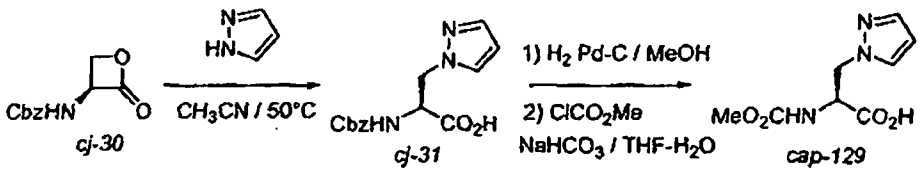


Cap-128

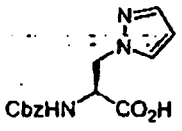
(S)-benzyl 3-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(methoxycarbonylamino)propanoate (502 mg, 1.11 mmol) was hydrogenated in the presence of Pd-C (82 mg) in MeOH (5 mL) at atmospheric pressure for 12h. The mixture was filtered through diatomaceous earth (Celite®) and concentrated *in vacuo*. (S)-2-(methoxycarbonylamino)-3-(1H-1,2,3-triazol-4-yl)propanoic acid was obtained as a colorless gum (266 mg, 111%) which was contaminated with ca. 10% of the methyl ester. The material was used as is without further purification.

^{1}HNMR (400 MHz, DMSO-d_6) δ 12.78 (s, br, 1H), 7.59 9s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 4.19 – 4.24 (m, 1H), 3.49 (s, 3H), 3.12 (dd, J = 4.8 Hz, 14.9 Hz, 1H), 2.96 (dd, J = 9.9, 15.0 Hz, 1H). LCMS: Anal. Calcd. for $C_7H_{10}N_4O_4$: 214; found: 215 $(M+H)^+$.

Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (*Cap*-129).



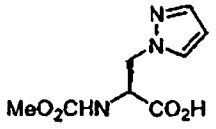
Step 1. Preparation of (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (cj-31).



cj-31

A suspension of (S)-benzyl 2-oxooxetan-3-ylcarbamate (0.67 g, 3.03 mmol), and pyrazole (0.22 g, 3.29 mmol) in CH_3CN (12 mL) was heated at 50°C for 24h. The mixture was cooled to rt overnight and the solid filtered to afford (S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (330.1 mg). The filtrate was concentrated *in vacuo* and then triturated with a small amount of CH_3CN (ca. 4 mL) to afford a second crop (43.5 mg). Total yield 370.4 mg (44%).
m.p. 165.5 – 168°C. lit m.p. 168.5 – 169.5 Vederas et al. *J. Am. Chem. Soc.* 1985, *107*, 7105.
^{1}HNMR (400 MHz, CD_3OD) δ 7.51 (d, J = 2.0, 1H), 7.48 (s, J = 1.5 Hz, 1H), 7.24 – 7.34 (m, 5H), 6.23 m, 1H), 5.05 (d, 12.7 H, 1H), 5.03 (d, J = 12.7 Hz, 1H), 4.59 – 4.66 (m, 2H), 4.42 – 4.49 (m, 1H). LCMS: Anal. Calcd. for $C_{14}H_{15}N_3O_4$: 289; found: 290 $(M+H)^+$.

Step 2. Preparation of (S)-2-(methoxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (*Cap*-129).



cap-129

(S)-2-(benzyloxycarbonylamino)-3-(1H-pyrazol-1-yl)propanoic acid (0.20 g, 0.70 mmol) was hydrogenated in the presence of Pd-C (45 mg) in MeOH (5 mL) at atmospheric pressure for 2h. The product appeared to be insoluble in MeOH, therefore the rxn mixture was diluted with 5mL H_2O and a few drops of 6N HCl. The homogeneous solution was filtered through diatomaceous earth (Celite®), and the MeOH removed *in vacuo*. The remaining solution was frozen and lyophyllized to give a yellow foam (188.9 mg). This material was suspended in THF-H_2O (1:1, 10mL) and then cooled to 0°C. To the cold mixture was added $NaHCO_3$ (146.0 mg, 1.74 mmol) carefully (evolution of CO_2). After gas evolution had ceased (ca. 15 min) $ClCO_2Me$ (0.06 mL, 0.78 mmol) was added dropwise. The mixture was allowed to stir for 2h and was acidified to pH~2 with 6N HCl and poured into EtOAc. The layers were separated and the aqueous phase extract with EtOAC (x5).

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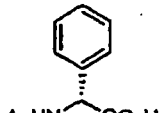
The combined organic layers were washed (brine), dried (Na_2SO_4), filtered, and concentrated to give the title compound as a colorless solid (117.8 mg, 79%). ^{1}HNMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.63 (d, J = 2.6 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 1.5 Hz, 1H), 6.19 (app t, J = 2.0 Hz, 1H), 4.47 (dd, J = 3.0, 12.9 Hz, 1H), 4.29 – 4.41 (m, 2H), 3.48 (s, 3H). LCMS: Anal. Calcd. for $C_8H_{11}N_3O_4$: 213; found: 214 $(M+H)^+$.

Cap-130. N-Acetyl –(R)-Phenylglycine



cap-130

Cap-130 was prepared by acylation of commercially available (R)-phenylglycine analgous to the procedure given in: Calmes, M.; Daunis, J.; Jacquier, R.; Verducci, J. *Tetrahedron*, 1987, *43*(10), 2285.

EXAMPLES

The present disclosure will now be described in connection with certain embodiments which are not intended to limit its scope. On the contrary, the present disclosure covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include specific embodiments, will illustrate one practice of the present disclosure, it being understood that the examples are for the purposes of illustration of certain embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

Solution percentages express a weight to volume relationship, and solution ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker 300, 400, or 500 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel (SiO_2) according to Still's flash chromatography technique (*J. Org. Chem.* **1978**, *43*, 2923).

Purity assessment and low resolution mass analysis were conducted on a Shimadzu LC system coupled with Waters Micromass ZQ MS system. It should be noted that retention times may vary slightly between machines. The LC conditions employed in determining the retention time (RT) were:

Condition 1

Column = Phenomenex-Luna 3.0X 50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 4 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 2

Column = Phenomenex-Luna 4.6X50 mm S10
Start %B = 0
Final %B = 100
Gradient time = 2 min
Stop time = 3 min
Flow Rate = 5 mL/min
Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Condition 3

Column = HPLC XTERRA C18 3.0 x 50mm S7
Start %B = 0
Final %B = 100
Gradient time = 3 min
Stop time = 4 min
Flow Rate = 4 mL/min

Wavelength = 220 nm
Solvent A = 0.1% TFA in 10% methanol/90%H_2O
Solvent B = 0.1% TFA in 90% methanol/10% H_2O

Method A: LCMS – Xterra MS C-18 3.0 x 50mm, 0 to 100% B over 30.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

Method B: HPLC – X-Terra C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA

Method C: HPLC – YMC C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.2% H_3PO_4, B = 90% methanol 10% water 0.2% H_3PO_4.

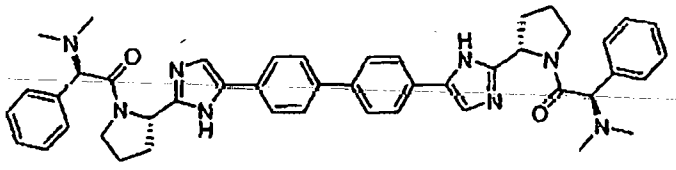
Method D: HPLC – Phenomenex C-18 4.6 x 150mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.2% H_3PO_4, B = 90% methanol 10% water 0.2% H_3PO_4

Method E: LCMS – Gemini C-18 4.6 x 50mm, 0 to 100% B over 10.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

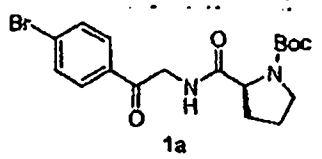
Method F: LCMS-Luna C-18 3.0 x 50mm, 0 to 100% B over 7.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate.

Example 1

(1R,1'R)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(2S)-2,1-pyrrolidinediyl))bis(N,N-dimethyl-2-oxo-1-phenylethanamine)



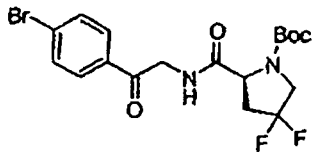
Example 1, Step a



1a

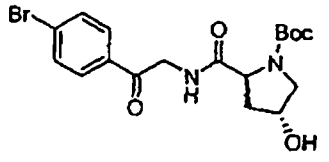
N,N-Diisopropylethylamine (18 mL, 103.3 mmol) was added dropwise, over 15 minutes, to a heterogeneous mixture of *N*-Boc-L-proline (7.139 g, 33.17 mmol), HATU (13.324 g, 35.04 mmol), the HCl salt of 2-amino-1-(4-bromophenyl)ethanone (8.127 g, 32.44 mmol), and DMF (105 mL), and stirred at ambient condition for 55 minutes. Most of the volatile component was removed *in vacuo*, and the resulting residue was partitioned between ethyl acetate (300 mL) and water (200 mL). The organic layer was washed with water (200 mL) and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. A silica gel mesh was prepared from the residue and submitted to flash chromatography (silica gel; 50-60 % ethyl acetate/hexanes) to provide ketoamide 1a as a white solid (12.8 g). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 8.25-8.14 (*m*, 1H), 7.92 (br d, *J* = 8.0, 2H), 7.75 (br d, *J* = 8.6, 2H), 4.61 (dd, *J* = 18.3, 5.7, 1H), 4.53 (dd, *J* = 18.1, 5.6, 1H), 4.22-4.12 (m, 1H), 3.43-3.35 (m, 1H), 3.30-3.23 (m, 1H), 2.18-2.20 (m, 1H), 1.90-1.70 (m, 3H), 1.40/1.34 (two app br s, 9H). LC (Cond. 1): RT = 1.70 min; LC/MS: Anal. Calcd. for $[M+Na]^+$ $C_{18}H_{23}BrN_2NaO_4$: 433.07; found 433.09.

Analogous compounds such as intermediate 1-1a to 1-5a can be prepared by incorporating the appropriately substituted amino acid and aryl bromide isomer.



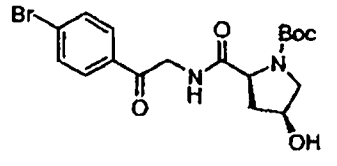
1-1a

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.35/1.40 (two br s, 9H), 2.27-2.42 (m, 1H), 2.73-2.95 (m, 1H), 3.62-3.89 (m, 2H), 4.36-4.50 (m, 1H), 4.51-4.60 (m, 1H), 4.62-4.73 (m, 1H), 7.75 (d, *J*=8.24 Hz, 2H), 7.92 (d, *J*=7.63 Hz, 2H), 8.31-8.49 (m, 1H). HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.59 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{18}H_{21}BrF_2N_2O_4$: 446.06; found: 445.43 $(M-H)^-$.



1-2a

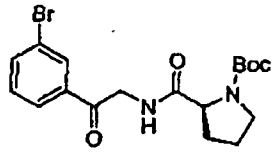
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm (8.25 1H, s), 7.91 (2H, d, *J*=8.24Hz), 7.75 (2H, d, *J*=8.24 Hz), 4.98 (1H, s), 4.59-4.63 (1H, m), 4.46-4.52 (1H, m), 4.23 (1H, m), 3.37 (1H, s), 3.23-3.28 (1H, m), 2.06 (1H, m), 1.88 (1H, s), 1.38 (3H, s), 1.33 (6H, s). LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA mobile phase, RT = 3.34 minutes, Anal Calcd. for $C_{18}H_{23}BrN_2O_5$ 427.30; found 428.08 $(M+H)^+$.



1-3a

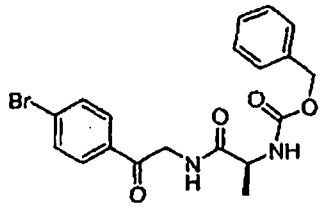
^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.30 (1H, s) 7.93-7.96 (2H, m) 7.76 (2H d, *J*=8.24 Hz) 5.13 (1H, s) 4.66-4.71 (1H, m) 4.52-4.55 (1H, m) 4.17 (1H, m) 3.51 (1H,

s) 3.16-3.19 (1H, m) 2.36 (1H, m) 1.78 (1H, s) 1.40 (s, 3H), 1.34 (s, 6H). LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 3.69 minutes, Anal Calcd. for $C_{18}H_{23}BrN_2O_5$ 427.30; found 428.16 $(M+H)^+$.



1-4a

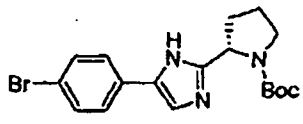
^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.29-1.47 (m, 9H), 1.67-1.90 (m, 3H), 2.00-2.20 (m, 1H), 3.23-3.30 (m, 1H), 3.34-3.44 (m, 1H), 4.16 (dd, 1H), 4.57 (q, 2H), 7.51 (t, *J*=7.78 Hz, 1H), 7.86 (dd, *J*=7.93, 1.22 Hz, 1H), 7.98 (d, *J*=7.63 Hz, 1H), 8.11 (s, 1H), 8.15-8.29 (m, 1H). LC/MS $(M+Na)^+$ = 433.12/435.12.



1-5a

LCMS conditions: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume. RT = 1.93 min; LRMS: Anal. Calcd. for $C_{15}H_{18}BrN_2O_4$ 418.05; found: 419.07 $(M+H)^+$.

Example 1, Step b



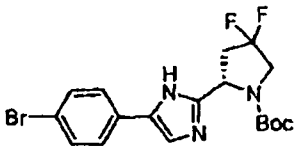
1b

A mixture of ketoamide 1a (12.8 g, 31.12 mmol) and NH_4OAc (12.0 g, 155.7 mmol) in xylenes (155 mL) was heated in a sealed tube at 140 °C for 2 hours. The volatile component was removed *in vacuo*, and the residue was partitioned carefully between ethyl acetate and water, whereby enough saturated $NaHCO_3$ solution was added so as to make the pH of the aqueous phase slightly basic after the shaking of the biphasic system. The layers were separated, and the aqueous layer was extracted with an additional ethyl acetate. The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was recrystallized from ethyl acetate/hexanes to provide two crops of imidazole 1b as a light-yellow dense solid, weighing 5.85 g. The mother liquor was concentrated *in vacuo* and submitted to a flash chromatography (silica gel; 30% ethyl acetate/hexanes) to provide an additional 2.23 g of imidazole 1b. ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.17/11.92/11.86 (m, 1H), 7.72-7.46/7.28 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.30-1.75 (m, 4H), 1.40/1.15 (app br s, 9H). LC (Cond. 1): RT = 1.71 min; >98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.10; found 391.96; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{18}H_{23}BrN_3O_2$: 392.0974; found 392.0959

The optical purity of the two samples of 1b were assessed using the chiral HPLC conditions noted below (ee > 99% for the combined crops; ee = 96.7% for the sample from flash chromatography):

Column: Chiralpak AD, 10 um, 4.6 x 50 mm
Solvent: 2% ethanol/heptane (isocratic)
Flow rate: 1 mL/min
Wavelength: either 220 or 254 nm
Relative retention time: 2.83 minutes (*R*), 5.34 minutes (*S*)

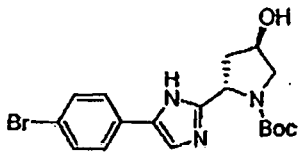
Analogous compounds such as intermediates 1-1b to 1-4b can be prepared by incorporating the appropriate ketoamide.



1-1b

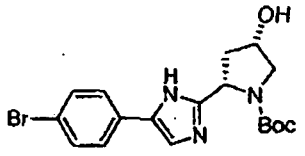
191

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.17/1.40 (two br s, 9H), 2.50-2.74 (m, *J*=25.64 Hz, 1H), 2.84-3.07 (m, 1H), 3.88 (d, *J*=10.07 Hz, 2H), 5.03 (s, 1H), 7.50 (d, *J*=8.55 Hz, 2H), 7.60 (s, 1H), 7.70 (d, *J*=8.55 Hz, 2H), 12.10 (s, 1H). HPLC XTERRA C-18 4.6 × 30 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.59 minutes, 99% homogeneity index; LCMS: Anal. Calcd. for $C_{18}H_{20}BrF_2N_3O_2$: 428.27; found: 428.02 $(M)^+$.



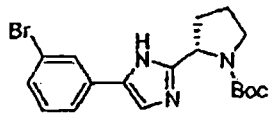
1-2b

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.89-11.99 (1H, m), 7.68 (2H, d, *J*=8.54 Hz), 7.52-7.59 (1H, m), 7.48 (2H, d, *J*=8.54 Hz), 4.80 (1H, m), 4.33 (1H, s), 3.51-3.60 (1H, m), 3.34 (1H, d, *J*=10.99 Hz), 2.14 (1H, s), 1.97-2.05 (1H, m), 1.37 (3H, s), 1.10 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (RT= 3.23 min) Anal Calcd. for $C_{18}H_{22}BrN_3O_3$ 408.30; found 409.12 $(M+H)^+$.



1-3b

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.06-12.24 (1H, m), 7.58-7.69 (5H, m), 4.84-4.95 (1H, m), 4.34 (1H, s), 3.61 (1H, s), 3.34-3.40 (1H, m), 2.52 (1H, s), 1.92-2.20 (1H, m), 1.43 (3H, s), 1.22 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (RT= 3.41 min) Anal Calcd. for $C_{18}H_{22}BrN_3O_3$ 408.30; found 409.15 $(M+H)^+$.



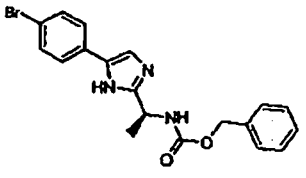
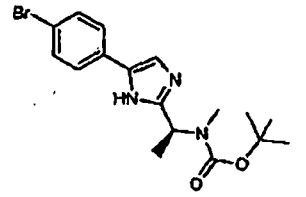
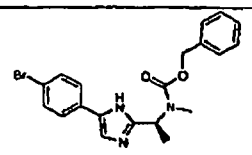
1-4b

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.98-1.51 (m, 9H), 1.82-2.12 (m, 3H), 2.31-2.48 (m, 1H), 3.30-3.51 (m, 1H), 3.52-3.66 (m, 1H), 4.88-5.16 (m, 1H), 7.47 (t, *J*=7.93 Hz, 1H), 7.61 (d, *J*=7.93 Hz, 1H), 7.81 (d, *J*=7.93 Hz, 1H), 8.04 (s, 1H), 8.12 (d, *J*=28.38 Hz, 1H), 14.65 (s, 1H). LC/MS $(M+H)^+$ = 391.96/393.96.

Additional imidazole analogs made following procedures similar to those described above.

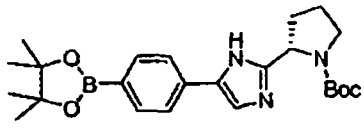
LC conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Example	Structure	Data
1-5b		RT = 1.70 minutes (condition 2, 98%); LRMS: Anal. Calcd. for $C_{19}H_{18}BrN_3O_2$ 399.05; found: 400.08 $(M+H)^+$.
1-6b		RT = 1.64 minutes (condtion 2, 98%); LRMS: Anal. Calcd. for $C_{17}H_{22}N_3O_2$ 379.09; found: 380.06 $(M+H)^+$.
1-7b		RT = 2.28 minutes (95%); LRMS: Anal. Calcd. for $C_{20}H_{21}BrN_3O_2$

		414.08; found: 414.08 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{20}H_{21}BrN_3O_2$ 414.0817; found: 414.0798 $(M+H)^+$.

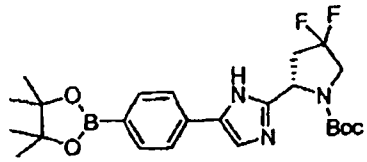
Example 1, Step c



1c

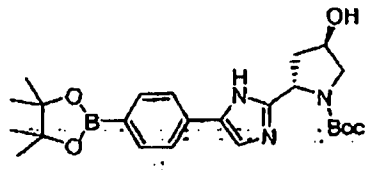
$Pd(Ph_3P)_4$ (469 mg, 0.406 mmol) was added to a pressure tube containing a mixture of bromide 1b (4.008 g, 10.22 mmol), bis(pinacolato)diboron (5.422 g, 21.35 mmol), potassium acetate (2.573g, 26.21 mmol) and 1,4-dioxane (80 mL). The reaction flask was purged with nitrogen, capped and heated with an oil bath at 80 °C for 16.5 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was partitioned carefully between CH_2Cl_2 (150 mL) and an aqueous medium (50 mL water + 10 mL saturated $NaHCO_3$ solution). The aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting material was purified with flash chromatography (sample was loaded with eluting solvent; 20-35% ethyl acetate/CH_2Cl_2) to provide boronate 1c, contaminated with pinacol, as an off-white dense solid; the relative mole ratio of 1c to pinacol was about 10:1 (^{1}H NMR). The sample weighed 3.925 g after ~2.5 days exposure to high vacuum. ^{1}H NMR (DMSO-d_6, δ= 2.5 ppm, 400 MHz): 12.22/11.94/ 11.87 (m, 1H), 7.79-7.50/ 7.34-7.27 (m, 5H), 4.86-4.70 (m, 1H), 3.52 (app br s, 1H), 3.36 (m, 1H), 2.27-1.77 (m, 4H), 1.45-1.10 (m, 21H). LC (Cond. 1): RT = 1.64 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{24}H_{35}BN_3O_4$: 440.27; found 440.23.

Analogous compounds such as intermediates 1-1c to 1-4c can be prepared by incorporating the appropriate aryl bromide.



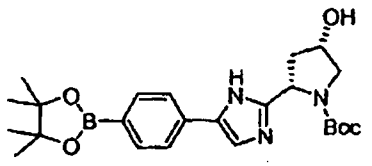
1-1c

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.16 (s, 8H), 1.29 (s, 13H), 2.51-2.72 (m, 1H), 2.84-3.03 (m, 1H), 3.79-4.00 (m, 2H), 4.88-5.21 (m, 1H), 7.62 (d, *J*=7.93 Hz, 2H), 7.67 (s, 1H), 7.76 (d, *J*=7.93 Hz, 2H), 12.11/12.40 (two br s, 1H). HPLC GEMINI C-18 4.6 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 95% water, 5% acetonitrile, 0.1% NH_4OAc, B = 5% water, 95% acetonitrile, 0.1% NH_4OAc, RT = 1.62 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{34}H_{32}BF_2N_3O_4$: 475.34; found: 474.78 $(M-H)^-$.



1-2c

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.97 (1H, m), 7.62-7.75 (5H, m), 5.05 (1H d, *J*=3.36 Hz), 4.82 (m, 1H), 4.35 (m, 1H), 3.58 (1H, m), 2.389 (1H, s), 2.17 (1 H, m), 1.38 (3H, s), 1.30 (12H, s), 1.1 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 5% acetonitrile, 95% water, 10mm ammonium acetate, B = 95% acetonitrile, 5% water, 10mm ammonium acetate, RT= 3.63 minutes, Anal. Calcd. for $C_{24}H_{34}BN_3O_5$ 455.30; found 456.31 $(M+H)^+$.

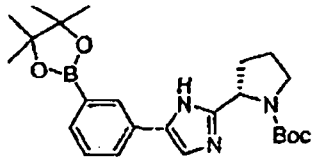


1-3c

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.05-12.24 (1H, m), 7.61-7.73 (5H, m), 4.83-5.01 (1H, m), 4.33 (1H, s), 3.54-3.63 (1H, m), 3.39-3.80 (1H, m), 2.38-2.49

195

(1H, m), 1.98-2.01 (1H, m), 1.42 (3H, s), 1.34 (12H, s), 1.21 (6H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 3.64 minutes, Anal. Calcd. for $C_{24}H_{34}BN_3O_5$ 455.30; found 456.30 $(M+H)^+$.



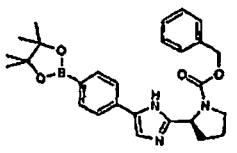
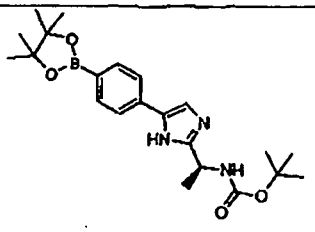
1-4c

^1H NMR (500 MHz, DMSO-d_6) δ ppm 1.02-1.54 (m, 21H), 1.75-2.07 (m, 3H), 2.09-2.33 (m, 1H), 3.32-3.44 (m, 1H), 3.55 (s, 1H), 4.69-4.94 (m, 1H), 7.33 (t, *J*=7.32 Hz, 1H), 7.41-7.57 (m, 2H), 7.84 (d, *J*=7.32 Hz, 1H), 8.08 (s, 1H), 11.62-12.07 (m, 1H). LC/MS $(M+H)^+$ = 440.32.

Additional boronic esters: Conditions for 1-5c through 1-10c

LCMS conditions: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 μL injection volume.

1-5c		RT = 1.84 minutes (condition 2); LCMS: Anal. Calcd. for $C_{27}H_{32}BN_3O_4$ 473; found: 474 $(M+H)^+$.
1-6c		RT = 1.84 minutes (condition 2); LCMS: Anal. Calcd. for $C_{22}H_{32}BN_3O_4$ 413; found: 414 $(M+H)^+$.

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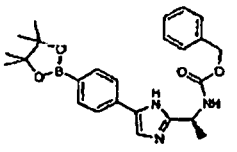
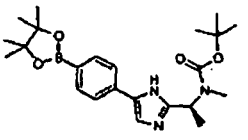
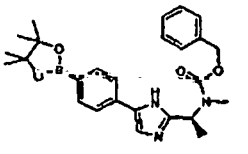
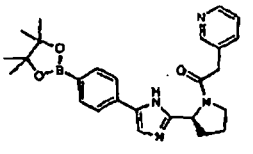
1-7c		RT = 1.85 minutes (condition 2); LRMS: Anal. Calcd. for $C_{25}H_{31}BN_3O_4$ 448; found: 448 $(M+H)^+$.
1-8c		RT = 2.49 (76%, boronic ester) and 1.81 (21.4%, boronic acid); LCMS: Anal. Calcd. for $C_{23}H_{35}N_3O_4B$ 428.27; found: 428.27 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{23}H_{35}N_3O_4B$ 428.2721; found: 428.2716 $(M+H)^+$.
1-9c		RT = 2.54 (74.2%, boronic ester) and 1.93 (25.8%, boronic acid); LRMS: Anal. Calcd. for $C_{26}H_{33}N_3O_4B$ 462.26; found: 462.25 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{26}H_{33}N_3O_4B$ 462.2564; found: 462.2570 $(M+H)^+$.
1-10c		RT = 1.91 (64.5 %, boronic ester) and 1.02 (33.8 %, boronic acid); LRMS: Anal. Calcd. for $C_{26}H_{32}N_4O_3{}^{10}B$ 458.26; found: 458.28 $(M+H)^+$; HRMS: Anal. Calcd. for $C_{26}H_{32}N_4O_3{}^{10}B$ 458.2604; found: 458.2617 $(M+H)^+$.

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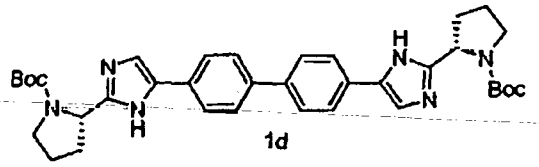
Example 1, Step d

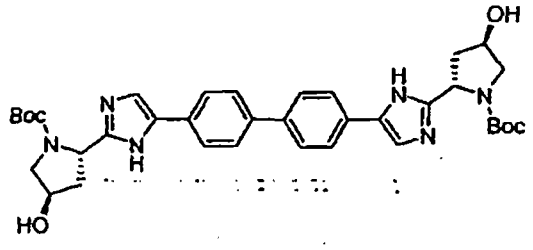
di-tert-butyl (2S,2'S)-2,2'-(4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl))di(1-pyrrolidinecarboxylate)



1d

$Pd(Ph_3P)_4$ (59.9 mg, 0.0518 mmol) was added to a mixture of bromide 1b (576.1 mg, 1.469 mmol), boronate 1c (621.8 mg, 1.415 mmol), $NaHCO_3$ (400.4 mg, 4.766 mmol) in 1,2-dimethoxyethane (12 mL) and water (4 mL). The reaction mixture was flushed with nitrogen, heated with an oil bath at 80 °C for 5.75 hours, and then the volatile component was removed *in vacuo*. The residue was partitioned between 20% methanol/ $CHCl_3$ (60 mL) and water (30 mL), and the aqueous phase was extracted with 20% methanol/$CHCl_3$ (30 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. A silica gel mesh was prepared from the resulting crude material and submitted to flash chromatography (ethyl acetate) to provide dimer 1d, contaminated with Ph_3PO, as an off-white solid (563 mg). ^1H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 12.21-12-16/11.95-11.78 (m, 2H), 7.85-7.48/ 7.32-7.25 (m, 10H), 4.90-4.71 (m, 2H), 3.60-3.32 (m, 4H), 2.30-1.79 (m, 8H), 1.46-1.10 (m, 18H). LC (Cond. 1b): RT = 1.77 min; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{36}H_{45}BN_6O_4$: 625.35; found 625.48.

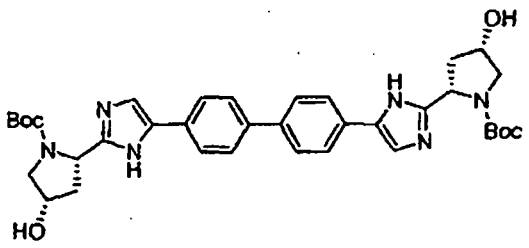
Additional symmetric analogs can be prepared in similar fashion.



1-1d

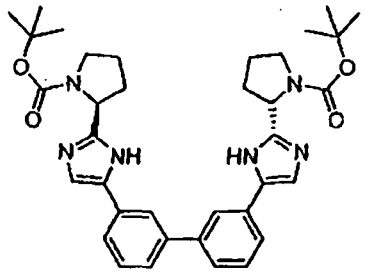
Example 1-1d was prepared using intermediates 1-2c and 1-2b. ^1H NMR (500 MHz, DMSO-d_6) δ ppm 11.94-12.22 (2H, m) 7.53-7.82 (10H, m) 4.82-4.92 (2 H, m) 4.34-4.43 (2 H, m) 3.55-3.64 (2 H, m) 3.36 (2 H, d, J=11.29 Hz) 2.12-2.22 (2 H, m) 2.02-

2.11 (2 H, m) 1.40 (6 H, s) 1.14 (12 H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 3.32min, Anal. Calcd. for 656.79; found 657.40 $(M+H)^+$. Nominal/LRMS – $(M+H)^+$ 657.42, $(M-H)^-$ -655.28.



1-2d

Example 1-2d was prepared using intermediates 1-3b and 1-3c. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 12.00-12.20 (2H, m) 7.56-7.76 (10H, m) 4.90 (1H, s) 4.82 (1H, s) 4.25-4.34 (2H, m) 3.56 (2H, s) 3.34-3.47 (2H, m) 1.97-2.13 (4H, m) 1.39 (9H, m) 1.20 (9H, s); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA; RT= 3.35min, Anal. Calcd. for 656.79; found 657.30 $(M+H)^+$.

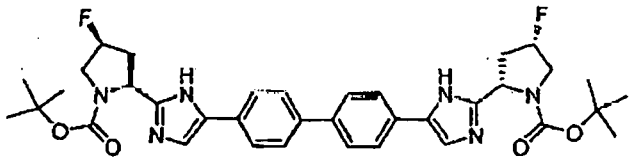


1-2d-1

tert-butyl (2S)-2-(4-(3'-(2-((2S)-1-(tert-butoxycarbonyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate

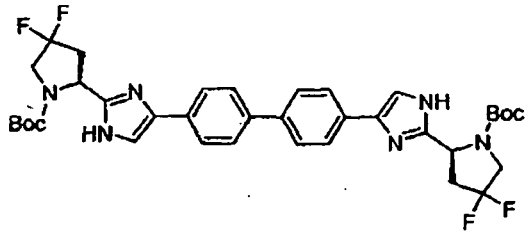
Example 1-2d-1 was prepared using intermediates 1-4c and 1-4b. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.09-1.51 (m, 18H), 1.84-2.15 (m, 6H), 2.34-2.50 (m, 2H).

3.35-3.52 (m, 2H), 3.54-3.67 (m, 2H), 5.08 (d, *J*=5.49 Hz, 2H), 7.68 (t, *J*=7.78 Hz, 2H), 7.78-7.92 (m, 4H), 8.11-8.30 (m, 4H), 14.81 (s, 2H). LC/MS $(M+H)^+ = 625.48$.



1-2d-2

Diol 1-1d (0.15g, 0.23mmol) was added as a solid to a solution of bis(2-methoxyethyl) aminosulfur trifluoride (0.1mL, 0.51mmol) in 1.0mL CH_2Cl_2 cooled to -78 °C. The reaction was stirred at -78 °C for two hours and then warmed to room temperature and stirred for 2 hours. The reaction was poured into saturated sodium bicarbonate solution and stirred until bubbling ceased. The layers were separated and the aqueous layer was extracted one time with CH_2Cl_2. The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The oil was triturated with CH_2Cl_2 and pentane to provide the desired product as a tan solid (0.092g, 61%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.76-11.94 (2H, m), 7.77 - 7.85 (4 H, m), 7.66 - 7.72 (4 H, m), 7.60 - 7.66 (2 H, m, *J*=11.60 Hz), 5.39 (1 H, s), 5.28 (1 H, s), 5.03 (2 H, s), 3.66 - 3.79 (4 H, m), 2.61 - 2.70 (2 H, m), 2.28 - 2.38 (2 H, m), 1.42 (10 H, s), 1.24 (8 H, s). LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (t_R = 3.58 min) Anal Calcd. for $C_{36}H_{42}F_2N_6O_4$ 660.70; found 661.68 $(M+H)^+$.

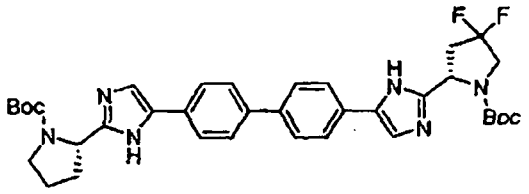


1-2d-3

Prepared from 1-1b and 1-1c in the same manner as the preparation of 1d from 1b and 1c. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.18/1.40 (two br. s., 18H),

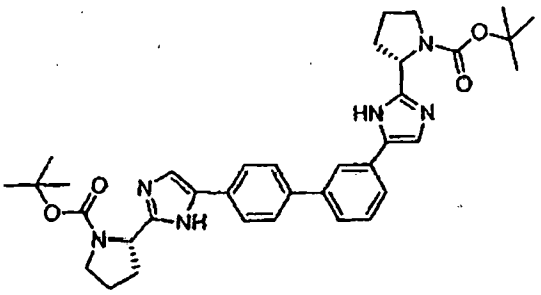
2.53 - 2.75 (m, J=25.94 Hz, 2H), 2.86 - 3.06 (m, 2H), 3.78 - 4.02 (m, 4H), 5.04 (br s, 2H), 7.17 – 8.24 (m, 10H), 12.07/12.37 (two br. s., 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 2 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.31 min, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{36}H_{40}F_4N_6O_4$: 696.73; found: 967.64 $(M+H)^+$.

Dissymmetric compounds such as intermediate 1-3d and 1-4d can be prepared by the same method. For example, reaction of 1-1c with 1b in the same manner as described above for the preparation of 1d provided 1-3d. Similarly, reaction of 1-4c with 1b in the same manner as described above for the preparation of 1d provideed 1-4d.



1-3d

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.40/1.18 (two br s, 18H), 1.90-2.02 (m, 2H), 2.02-2.12 (m, 1H), 2.28-2.46 (m, 2H), 2.68-2.87 (m, 1H), 3.35-3.49 (m, 1H), 3.53-3.62 (m, 1H), 3.82-4.10 (m, 2H), 4.92-5.11 (m, 1H), 5.28 (s, 1H), 7.79-8.00 (m, 8H), 8.03-8.25 (m, 2H), 13.77-15.16 (m, 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.22 minutes, 99% homogeneity index. LCMS: Anal. Calcd. for $C_{36}H_{42}F_2N_6O_4$: 660.75; found: 661.98 $(M+H)^+$.



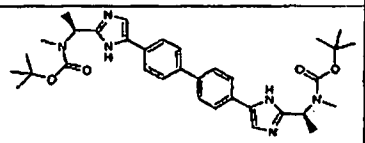
1-4d

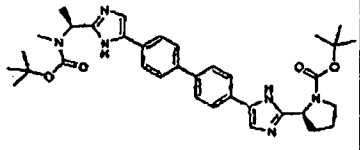
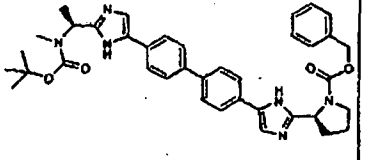
Example 1-4d was prepared from 1-4c and 1b in similar fashion to the preparation of 1d from 1b and 1c. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 0.99 - 1.60 (m, 18 H) 1.75 - 2.11 (m, *J*=73.24 Hz, 6 H) 2.12 - 2.32 (m, 2 H) 3.32 - 3.41 (m, 2 H) 3.56 (s, 2 H) 4.63 - 5.02 (m, 2 H) 6.98 - 8.28 (m, 10 H) 11.67 - 12.33 (m, 2 H); LC conditions: Phenomenex Luna 3.0 X 5.0mm S10, Solvent A – 0.1% TFA in 10% MeOH/90%H_2O, Solvent B - 0.1% TFA in 90% MeOH/10% H_2O, 0 to 100% B over 2min, Stop time = 3min, Flow rate = 4ml/min, Wavelength = 220nm, LC/MS $(M+H)^+$ = 625.32. Retention time = 1.438 min

Additional biphenyl analogs were prepared similarly.

LC conditions for Examples 1-5d through 1-7d: *Condition 1*: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 3 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

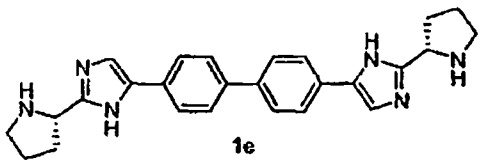
Condition 2: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

Example	*Compound Name*	*Structure*	*Characterization Data*
1-5d	di-tert-butyl (4,4'-biphenyldiylbis(1H-imidazole-5,2-diyl(1S)-1,1-ethanediyl))bis(meth	 Prepared from 1-8c and 1-6b	RT = 1.64 minutes (>95%); Condition 2; LCMS: Anal. Calcd $C_{34}H_{42}N_6O_4$

	ylcarbamate)		601.35; found: 601.48 $(M+H)^+$; LRMS: Anal. Calcd. for $C_{34}H_{44}N_6O_4$ 600.34; found: 601.32 $(M+H)^+$.
1-6d	tert-butyl (2S)-2-(5-(4'-(2-((1S)-1-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from 1-8c and 1b	RT = 1.63 minutes (>95%); Condition 2; LCMS: Anal. Calcd $C_{35}H_{45}N_6O_4$ 613.34; found: 613.56 $(M+H)^+$; LRMS: Anal. Calcd. for $C_{35}H_{44}N_6O_4$ 612.34; found: 613.33 $(M+H)^+$.
1-7d	benzyl (2S)-2-(5-(4'-(2-((1S)-1-((tert-butoxycarbonyl)(methyl)amino)ethyl)-1H-imidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1-pyrrolidinecarboxylate	 Prepared from 1-6b and 1-5c	RT = 1.65 minutes (>95%); Condition 2; LCMS: Anal. Calcd $C_{38}H_{43}N_6O_4$ 647.33; found: 647.44 $(M+H)^+$; LRMS: Anal. Calcd. for $C_{38}H_{42}N_6O_4$ 646.33; found: 647.34 $(M+H)^+$.

Example 1, Step e

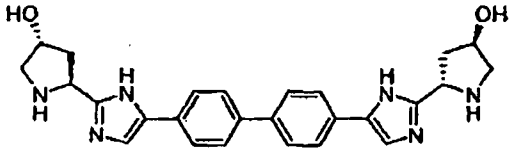
5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)



1e

A mixture of carbamate 1d (560 mg) and 25% TFA/CH_2Cl_2 (9.0 mL) was stirred at ambient condition for 3.2 hours. The volatile component was removed *in vacuo*, and the resulting material was free based using an MCX column (methanol wash; 2.0 M NH_3/methanol elution) to provide pyrrolidine 1e as a dull yellow solid (340 mg). ^{1}H NMR (DMSO-d_6, δ = 2.5 ppm, 400 MHz): δ 11.83 (br s, 2H), 7.80 (d, J = 8.1, 4H), 7.66 (d, J = 8.3, 4H), 7.46 (br s, 2H), 4.16 (app t, J = 7.2, 2H), 2.99-2.69 (m, 6H), 2.09-2.00 (m, 2H), 1.94-1.66 (m, 6H). LC (Cond. 1): RT = 1.27 min; > 98% homogeneity index; LC/MS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6$: 425.25; found 425.25; HRMS: Anal. Calcd. for $[M+H]^+$ $C_{26}H_{29}N_6$: 425.2454; found 425.2448

Additional analogs such as 1-1e to 1-4e can be prepared in a similar fashion.

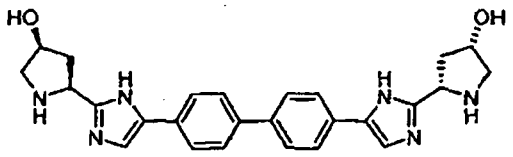


· 4 HCl

1-1e

To a solution of 1-1d (3R,3'R,5S,5'S)-tert-butyl 5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))bis(3-hydroxypyrrolidine-1-carboxylate) in 3mL dioxane was added 0.8mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 1-1e (3R,3'R,5S,5'S)-5,5'-(5,5'-(biphenyl-4,4'-diyl)bis(1H-imidazole-5,2-diyl))dipyrrolidin-3-oltetrahydrochloride (0.55g, 100%yield). Used without further purification.^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.33 (s, 2H), 9.85 (s, 2H), 8.09 (s, 2H), 8.01 (d, J=8.24 Hz, 4H), 7.88 (d, J=8.24 Hz, 4H), 5.14 (m, 2H), 4.62 (m, 2H), 3.61 (m, 2H),

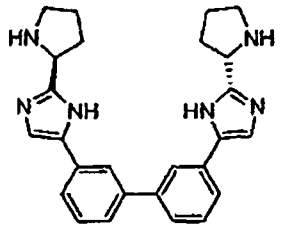
3.23 (d, J=11.29 Hz, 2H), 2.64 (m, 2H), 2.44 (dd, J=13.43, 6.71 Hz, 2H); LCMS – Waters-Sunfire C-18 4.6 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 1.35 minutes Anal. Calcd. for 456.30; found 457.25 $(M+H)^+$; Nominal/LRMS – $(M+H)^+$ 457.35.



· 4 HCl

1-2e

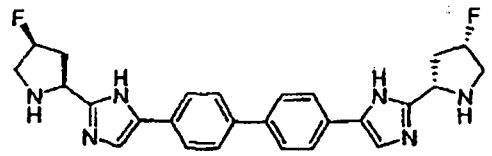
Example 1-2e was prepared in similar fashion to the method described for the preparation of 1-1e. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.32 (1 H, s) 8.01 (2 H, s) 7.97 (4 H, d, J=8.24 Hz) 7.86 (4 H, d, J=8.24 Hz) 5.01-5.10 (2 H, m) 4.52-4.60 (2 H, m) 3.36-3.45 (2 H, m) 3.25 (2 H, s) 2.60-2.68 (2 H, m) 2.40-2.48 (2 H, m); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, RT= 2.10min., Anal. Calcd. for 456.30; found 457.22 $(M+H)^+$



1-2e-1

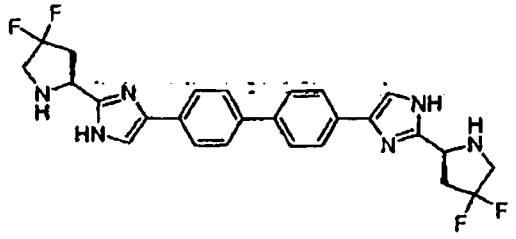
2-((2S)-2-pyrrolidinyl)-4-(3'-(2-((2S)-2-pyrrolidinyl)-1H-imidazol-5-yl)-3-biphenylyl)-1H-imidazole

Example 1-2e-1 was prepared from 1-2d-1 in similar fashion described for the preparation of 1-1e. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.74-2.44 (m, 12H), 4.83 (s, 2H), 7.37-7.72 (m, 4H), 7.74-8.03 (m, 4H), 8.10 (s, 2H), 9.14 (s, 2H), 9.81 (s, 2H). LC/MS $(M+H)^+$ = 425.30.



1-2e-2

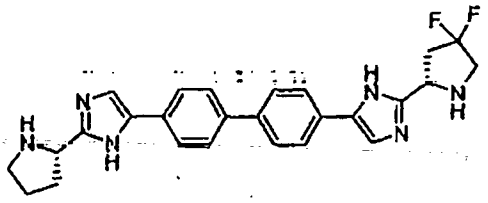
To a solution of 1-2d-2 (0.084g, 0.13mmol) in 1mL dioxane was added 0.5mL of a 4.0M solution of HCl in dioxane. The reaction was stirred for 2 hours at room temperature and concentrated under reduced pressure. The resulting tan solid was dried under vacuum to give 1-2e-2 (0.077g, 100%yield). The compound was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (2H, s), 7.97 (4H, d, *J*=8.55 Hz), 7.85 (4H, d, *J*=8.24 Hz), 5.63 (1H, s), 5.52 (1H, s), 5.09 - 5.17 (2H, m), 3.67 - 3.74 (2H, m), 3.63 - 3.67 (2H, m), 3.07 - 3.14 (1H, m), 2.89 - 2.96 (1H, m), 2.81 - 2.87 (2H, m); LCMS – Phenomenex C-18 3.0 x 50mm, 0 to 100% B over 4.0 minute gradient, 1 minute hold time, A = 10% methanol 90% water 0.1% TFA, B = 90% methanol 10% water 0.1% TFA, (t_R= 2.22 min) Anal Calcd. for $C_{26}H_{26}F_2N_6$ 460.53; found 461.37 $(M+H)^+$.



1-2e-3

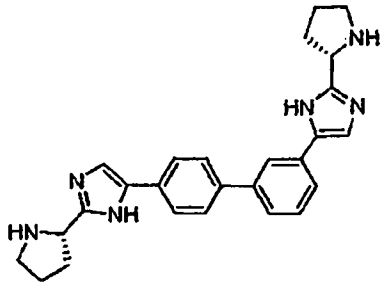
Prepared from 1-2d-3 in the same manner as the preparation of 1-1e from 1-1d. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.97 - 3.13 (m, 4H), 3.64 - 3.91 (m, 4H), 5.16 (d, *J*=6.41 Hz, 2H), 7.84 (d, *J*=7.93 Hz, 4H), 7.96 (d, *J*=7.93 Hz, 4H), 8.00 (s, 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minutes hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 1.66 min, 92% homogeneity index. LCMS: Anal. Calcd. for $C_{26}H_{24}F_4N_6$: 496.50; found: 495.53 $(M-H)^-$.

Analogous dissymmetric compounds such as intermediates 1-3e and 1-4e can be prepared by the same method.



1-3e

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.87-2.09 (m, 1H), 2.13-2.26 (m, 1H), 2.37-2.47 (m, 2H), 2.92-3.12 (m, 2H), 3.37 (s, 1H), 3.40-3.49 (m, 1H), 3.67-3.91 (m, 2H), 4.96-5.05 (m, 1H), 5.14 (t, *J*=8.70 Hz, 1H), 7.86 (t, *J*=9.00 Hz, 4H), 7.93-8.03 (m, 5H), 8.10 (s, 1H), 10.26/9.75 (two br s., 2H); HPLC XTERRA C-18 3.0 × 50 mm, 0 to 100% B over 4 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.2% H_3PO_4, B = 10% water, 90% methanol, 0.2% H_3PO_4, RT = 0.8622 minutes, 99% homogeneity index; LCMS: Anal. Calcd. for $C_{26}H_{26}F_2N_6$: 460.52; found: 461.45 $(M+H)^+$.



1-4e

Example 1-4e was prepared from 1-4d in similar fashion to that described for the preparation of 1-1e from 1-1d. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.90 - 2.13 (m, 2 H) 2.12 - 2.31 (m, 2 H) 2.36 - 2.60 (m, 4 H) 3.29 - 3.55 (m, 4 H) 5.00 (s, 2 H) 7.35 - 8.50 (m, 10 H) 9.76 (s, 2 H) 10.12 - 10.45 (m, 2 H). LC conditions: Phenomenex Luna 3.0 X 5.0mm S10, Solvent A – 0.1% TFA in 10% MeOH/90%H_2O, Solvent B - 0.1% TFA in 90% MeOH/10% H_2O, 0 to 100% B over 2min, Stop time = 3min, Flow rate = 4ml/min, Wavelength = 220nm, LC/MS $(M+H)^+$ = 425.28. Retention time = 0.942 min

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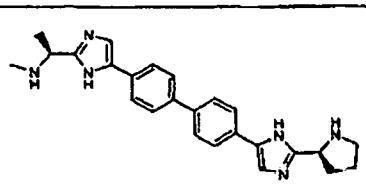
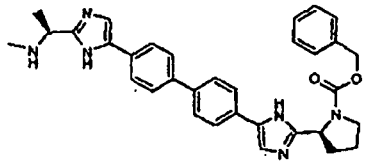
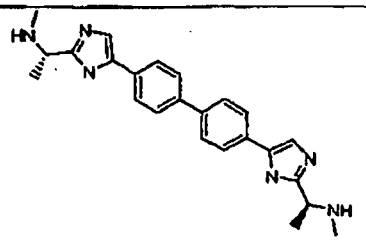
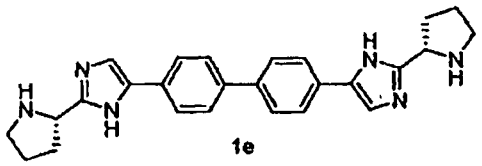
Additional analogs were prepared similarly:

Example	Compound Name	Structure	Data
1-5e		 Prepared from 1-6d	RT = 1.37 min; LCMS: Anal. Calcd. for $C_{25}H_{28}N_6$ 412; found: 413 $(M+H)^+$.
1-6e		 Prepared from 1-7d	RT = 1.43 min; LCMS: Anal. Calcd. for $C_{33}H_{35}N_6O_2$ 547; found: 547 $(M+H)^+$.
1-7e		 Prepared from 1-5d	RT = 1.12 min; LRMS: Anal. Calcd. for $C_{24}H_{28}N_6$ 400.24; found: 401.22 $(M+H)^+$.

LC Conditions for 1-5e through 1-7e: Phenomenex LUNA C-18 4.6 × 50 mm, 0 to 100% B over 2 minutes, 1 minute hold time, A = 90% water, 10% methanol, 0.1% TFA, B = 10% water, 90% methanol, 0.1% TFA, 220nm, 5 µL injection volume.

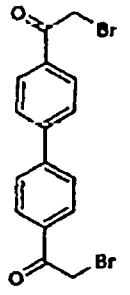
Alternative Synthesis of Example 1, Step e

5,5'-(4,4'-biphenyldiyl)bis(2-((2S)-2-pyrrolidinyl)-1H-imidazole)



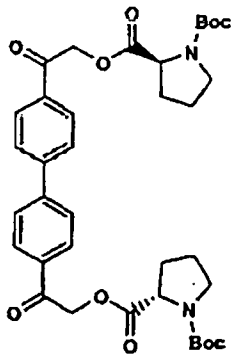
1e

Example A-1e-1



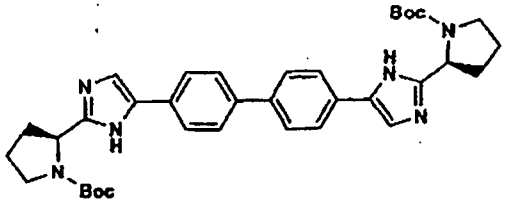
A 1 L, 3-neck round bottom flask, fitted with a nitrogen line, overhead stirrer and thermocouple was charged with 20 g (83.9 mmol, 1 equiv) 1,1'-(biphenyl-4,4'-diyl)diethanone, 200 mL CH_2Cl_2 and 8.7 mL (27.1g, 169.3 mmol, 2.02 quiv) bromine. The mixture was allowed to stir under nitrogen for about 20h under ambient conditions. The resulting slurry was charged with 200 mL CH_2Cl_2 and concentrated down to about 150 mL *via* vacuum distillation. The slurry was then solvent exchanged into THF to a target volume of 200 mL *via* vacuum distillation. The slurry was cooled to 20-25 °C over 1h and allowed to stir at 20-25 °C for an additional hour. The off-white crystalline solids were filtered and washed with 150 mL CH_2Cl_2. The product was dried under vacuum at 60 °C to provide 27.4 g (69.2 mmol, 82%) of the desired product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.85 (m, 4H), 7.60-7.50 (m, 4H), 4.26 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 145.1, 133.8, 129.9, 127.9, 30.8; IR (KBr, cm-1) 3007, 2950, 1691, 1599, 1199; Anal calcd for $C_{16}H_{12}Br_2O_2$: C, 48.52; H, 3.05; Br, 40.34. Found: C, 48.53; H, 3.03; Br, 40.53. HRMS calcd for $C_{16}H_{13}Br_2O_2$ (M + H; DCI$^+$): 394.9282. Found: 394.9292. mp 224-226 °C.

Example A-1e-2



A 500 mL jacketed flask, fitted with a nitrogen line, thermocouple and overhead stirrer, was charged with 20 g (50.5 mmol, 1 equiv) of Example A-1e-1, 22.8 g (105.9 moles, 2.10 equiv) 1-(*tert*-butoxycarbonyl)-L-proline, and 200 mL acetonitrile. The slurry was cooled to 20 °C followed by the addition of 18.2 mL (13.5 g, 104.4 mmol, 2.07 equiv) DIPEA. The slurry was warmed to 25 °C and allowed to stir for 3h. The resulting clear, organic solution was washed with 3 x 100 mL 13 wt% aqueous NaCl. The rich acetonitrile solution was solvent exchanged into toluene (target volume = 215 mL) by vacuum distillation until there was less than 0.5 vol% acetonitrile.

Example A-1e-3



The above toluene solution of Example A-1e-2 was charged with 78 g (1.011 moles, 20 equiv) ammonium acetate and heated to 95-100 °C. The mixture was allowed to stir at 95-100 °C for 15h. After reaction completion, the mixture was cooled to 70-80 °C and charged with 7 mL acetic acid, 40 mL n-butanol, and 80 mL of 5 vol% aqueous acetic acid. The resulting biphasic solution was split while maintaining a temperature > 50 °C. The rich organic phase was charged with 80 mL of 5 vol% aqueous acetic acid, 30 mL acetic acid and 20 mL n-butanol while