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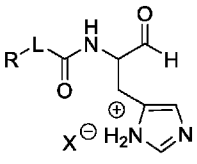

(I)

(57) Abstract: The present invention relates to a peptide-histidinal conjugates compound of formula (I) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof. The present invention also provides a process for preparation of compound of formula (I) and its use as antimalarial agents.

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PEPTIDE-HISTIDINAL CONJUGATES AS AN ANTI-MALARIAL AGENTS

TECHNICAL FIELD OF THE INVENTION

The present invention relates to novel synthetic compounds having biological activity. Specifically, the present invention relates to a peptide-histidinal conjugate compound of formula (I) useful as an anti-malarial agent. Also, the present invention relates to a process for preparation of peptide-histidinal conjugate compounds of formula (I).

BACKGROUND OF THE INVENTION

Malaria is a global health issue, particularly in developing and poorer countries. The latest World Malaria Report revealed 241 million malaria cases in 2020, as compared to 227 million in 2019. It was estimated that 627000 malaria deaths occurred in 2020 - an increase of 69000 deaths compared to the previous year. Most people die from malaria caused by P. falciparum, the most common pathogenic parasite for humans. Most of the causes of morbidity are frequently reported in Africa, South East Asia, and South America, particularly in pregnant women and children under five years old. Clinical malaria cases were treated with chloroquine until a few decades ago. Due to drug resistance issues, chloroquine has become less effective in recent years, especially in certain geographic locations. So far, resistance has only been reported in two species, P. falciparum and P. vivax. Although there is a lack of new antimalarial drugs in development, the ones that are reaching the market may not fight resistant strains. As a result of rising drug resistance and the lack of an effective malarial vaccine, finding new, effective, safe, and affordable drugs for malaria treatment via novel targets is one of the most challenging global health priorities.

Article titled “Mutations in the P. falciparum Digestive Vacuole Transmembrane Protein PfCRT and Evidence for Their Role in Chloroquine Resistance” by Fidock et.al. published in Mol Cell. 2000 October; 6(4): 861–871 reports the Mutations in 13-exon gene, PfCRT may result in altered chloroquine flux or reduced drug binding to hematin through an effect on digestive vacuole pH.

Article titled “Chloroquine Resistance in Plasmodium falciparum Malaria Parasites Conferred by pfcrt Mutations” by Sidhu et. al. published in Science. 2002 October 4; 298(5591): 210–213 reports conclusive evidence that mutant haplotypes of the pfcrt gene product of Asian, African, or South American origin confer chloroquine resistance with characteristic verapamil reversibility and reduced chloroquine accumulation. pfcrt mutations increased susceptibility to artemisinin and quinine and

minimally affected amodiaquine activity; hence, these antimalarials warrant further investigation as agents to control chloroquine-resistant falciparum malaria.

Article titled "Artemisinin, the Magic Drug Discovered from Traditional Chinese Medicine" published in Engineering 5 (2019) 32–39 reviews the Artemisinin and its derivatives use as a influential class of drugs in the fight against malaria

The existing large numbers of antimalarial therapies are based on interfering in the heme polymerization process at the erythrocytic stage. Until a few decades ago, chloroquine was the standard drug of choice for treating clinical malaria cases. However, in recent times, chloroquine does not cure as many cases as it used to, based on location owing to drug resistance issues.

Therefore, there is need in prior art to synthesize potent and selective inhibitors of malarial cysteine protease such as falcipain-2 (FP-2) and falcipain-3 (FP-3) by designing novel class of peptide-histidinal conjugates.

Further, it is desirable to produce the molecules that could be used as antimalarial drugs, allowing for the development of novel treatments which might reduce the burden of resistance to antimalarial drugs.

OBJECTIVE OF THE INVENTION

The main objective of the present invention is to provide peptide-histidinal conjugates useful as an anti-malarial agent.

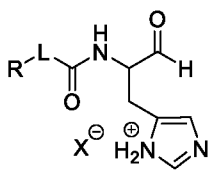
Another objective of the present invention is to provide a process for preparation of peptide-histidinal conjugates.

Another objective of the present invention is to provide peptide-histidinal conjugates compounds for inhibition of cysteine and aspartic acid proteases.

SUMMARY OF THE INVENTION

The primary objective of the present invention is to provide Peptide-histidinal conjugate compounds useful as an anti-malarial agent.

In an aspect, the present invention relates to a peptide histidinal conjugate of compound of formula (I) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a pharmaceutically acceptable solvate thereof:



Formula (I)

wherein:

L is direct bond, $CH(R^1)$, $(CH(R^1))nNR^4CHR^5$, $(CH(R^1))nCONR^2CHR^3$, $(CH(R^1))n\ SO_2NR^2CHR^3$, or $(CH(R^1))nNR^4CHR^5CONR^6CHR^7$, wherein n is 0 or 1;

R is aryl, heterocyclyl, alkyl, NH-aryl, SO_2-aryl, or aryl-heterocyclyl, wherein the aryl, heterocyclyl, alkyl is substituted or unsubstituted;

R^1 is hydrogen, alkyl, or aryl; wherein the alkyl and aryl is substituted or unsubstituted;

R^2 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^3 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^4 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^5 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^6 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^7 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted and

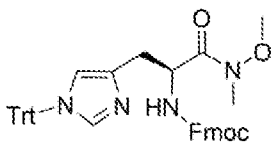
X is CF_3COO^-, or Cl^-.

In yet another aspect, the peptide-histidinal conjugate compounds of formula (I) useful for inhibition of cysteine and aspartic acid proteases.

In an aspect, the present invention provides a process for the preparation of histidinal peptide conjugate compounds of formula (I) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate thereof, wherein the process comprising the steps of:

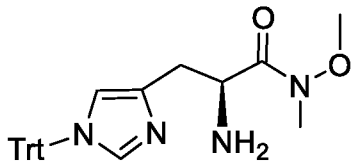
Formula (I)

a) coupling N^{α}-(((9H-fluoren-9-yl) methoxy) carbonyl)-N^{τ}-trityl-L-histidine with aminating agent or base in the presence of coupling reagent(s) in solvent to obtain precursor **1**



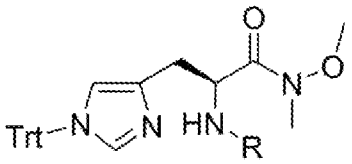
Precursor 1;

b) deprotecting Fmoc of precursor **1** of step a) by treating the precursor 1 in presence of *tert*-butylamine in a solvent at temperature in the range of 25-35 °C for time period in the range of 3 to 5 hrs to obtain an intermediate

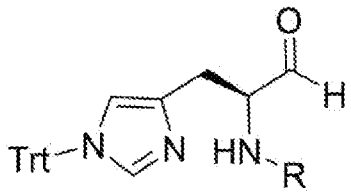


Intermediate;

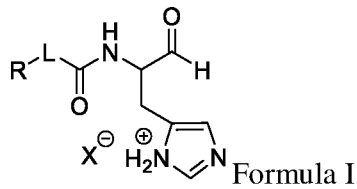
c) coupling the intermediate obtained in step (b) with R-carboxylic acid in the presence of coupling reagent(s) in solvent to furnish compound selected from formula **2a-h**



d) Formula **2a-h** reducing the compound obtained in step (c) using lithium aluminium hydride ($LiAlH_4$) in solvent at temperature in the range of 0 to -20 °C for time period of 45 to 120 minutes to obtain the compound selected from Formula **3a-h**



e) Formula **3a-h;** deprotecting compound obtained in step (d) using salt precursor trifluoroacetic acid (TFA) in solvent at temperature in the range of 25 to 40°C for the time period in the range of 1 to 2 hours to obtain the histidinal peptide conjugate compound of formula (I) with salt form selected from compounds **4a-h;**.



Formula I

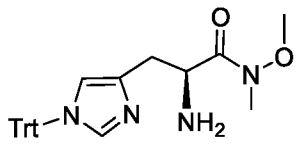
wherein X is trifluoroacetate salt, and HCl salt, and R is the same as defined in claim 1, and wherein the compounds **4a-h** recite X as trifluoroacetate salt form**.**

In another aspect, said R-carboxylic acid (**1a-h**) is selected from 2-methylbenzoic acid (**a**), 1-hydroxy-2-naphthoic acid (**b**), 3-hydroxy-2-naphthoic acid (**c**), benzo[b]thiophene-2-carboxylic acid (**d**), (S)-2-(6-methoxynaphthalen-2-yl) propanoic acid (**e**), 2-propylpentanoic acid (**f**), 2-(2-((2,6-dichlorophenyl)

amino) phenyl) acetic acid (**g**), and 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl) methyl)-[1,1'-biphenyl]-2-carboxylic acid (**h**).

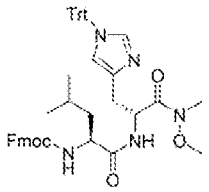
In another aspect, the present invention provides a process for the preparation of peptide-histidinal conjugate compounds of formula (I), wherein the process comprising the steps of:

i. deprotecting **precursor 1** by treating the precursor 1 in presence of *tert*-butylamine in a solvent at temperature in the range of 25-35 °C for time period in the range of 3 to 5 hrs to obtain an intermediate



Intermediate;

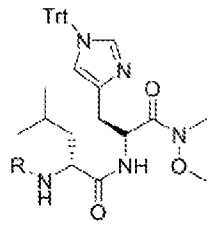
ii. coupling Fmoc-Leu-OH with the **precursor 1** as obtained in step (i) in the presence of coupling reagent(s) in solvent to obtain intermediate **5**



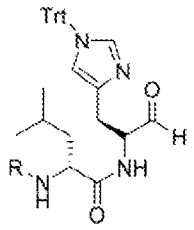
intermediate **5;**

iii. deprotecting Fmoc of the intermediate **5** of step (ii) by treating the intermediate **5** in presence of *tert*-butylamine in a solvent at temperature in the range of 25-35 °C for time period in the range of 3 to 5 hrs to obtain an intermediate;

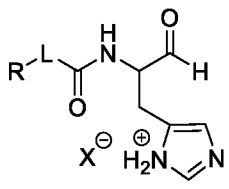
iv. coupling the intermediate obtained in step (iii) with R-carboxylic acid in the presence of coupling reagent(s) in solvent to furnish compound selected from compounds of formula **6a-k**;



v. Formula **6a-k** reducing the compound obtained in step (iv) using lithium aluminium hydride ($LiAlH_4$) in solvent at 0 to -20°C to obtain the compound selected from compounds of formula 7a-k



vi. formula **7a-k** deprotecting compound obtained in step (v) using salt precursor TFA in solvent at temperature in the range of 25 to 40°C for the time period in the range of 2 to 3 hours to obtain the histidinal peptide conjugate compound of formula (I) with trifluoroacetate salt form selected from compounds **8a-k;**



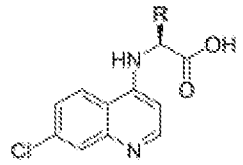
Formula I

wherein X is trifluoroacetate salt and HCl salt, and R is the same as defined in claim 1, and wherein the compounds **8a-k** recite X as trifluoroacetate salt form.

In another aspect, said R-carboxylic acids are selected from (**a-k**) 2-methylbenzoic acid (**a**), 1H-indole-2-carboxylic acid (**b**), 1-hydroxy-2-naphthoic acid (**c**), 3-hydroxy-2-naphthoic acid (**d**), benzo[b]thiophene-2-carboxylic acid (**e**), (S)-2-(6-methoxynaphthalen-2-yl) propanoic acid (**f**), 2-propylpentanoic acid (**g**), 2-(2-((2,6-dichlorophenyl) amino) phenyl) acetic acid (**h**), 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl) methyl)-[1,1'-biphenyl]-2-carboxylic acid (**i**), 5-(dimethylamino) naphthalene-1-sulfonic acid (**j**), and 5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl) pentanoic acid (**k**).

In another aspect, the present invention relates to a process for the preparation of peptide-histidinal conjugate compounds of formula (I), comprising the steps of:

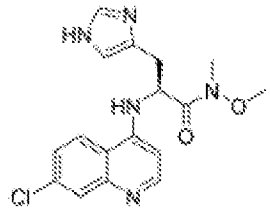
i) coupling compound **10c** with *N, O*-dimethylhydroxylamine to obtain compound **11**



a. R = L-His; b. R = L-Leu; c. R = L-Ala

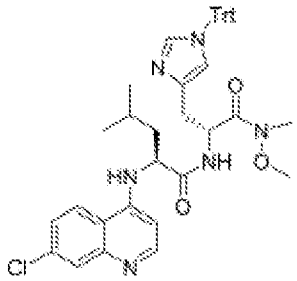
10c

compound 10 (a to c) wherein ;



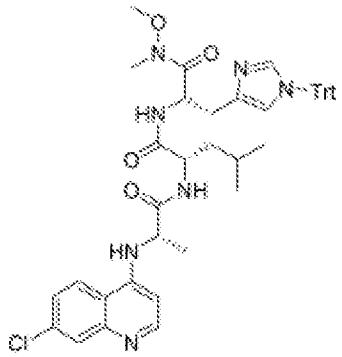
compound 11;

ii) reacting compound **10b** with precursor **1** in presence of coupling reagent(s) to afford compound



13 ;

(iii)reacting compound **10a** with intermediate **5** in presence of coupling reagent(s) to afford compound



16 ;

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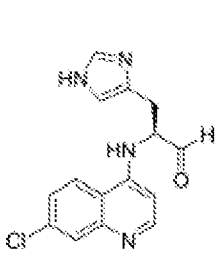
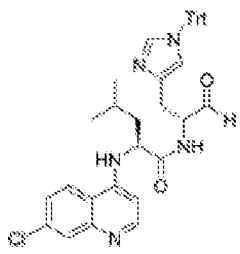
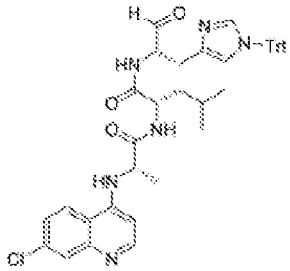
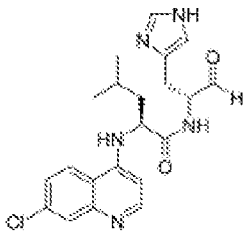
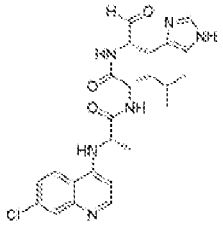
iii) deducing the compounds obtained in step (i), (ii), (iii) using lithium aluminium hydride ($LiAlH_4$) in dry THF at -20°C to obtain the compounds **12, 14, 17**

12; **14**; **17**; and

iv) deprotecting compound 12, 14 or 17 obtained in step (iv) using trifluororacetic acid in solvent at temperature in the range of 25 to 40°C for the time period in the range of 2 to 3 hours to produce histidinal-based trifluoroacetate salt compounds **15** and **18**

15; and **18**.

In another aspect, the coupling agent used in step a) is selected from HBTU, HOBt and EDC·HCl or mixtures thereof.

In another aspect, the aminating agent is selected from DIPEA, DMF, and N, O-dimethyl hydroxylamine. HCl.

In another aspect, the precursor salt is selected from trifluororacetic acid and 4M HCl in 1,4-Dioxane.

In another aspect, the solvent is selected from polar or non-polar solvent, and protic or aprotic solvent.

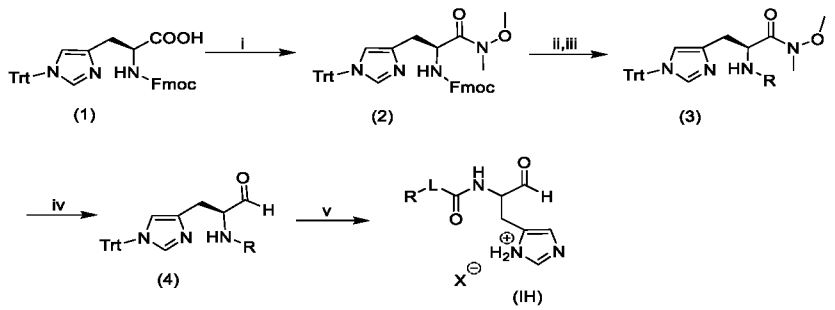
In another aspect, the base is selected from organic base and inorganic base.

In another aspect, the solvent is selected from DMF, THF, lower (C1-C5) alcohol, nitrile, ketone, halogenated hydrocarbon, TFA or combinations thereof.

In another aspect, the organic base is selected from ethylamine, triethylamine, DIPEA, and pyridine.

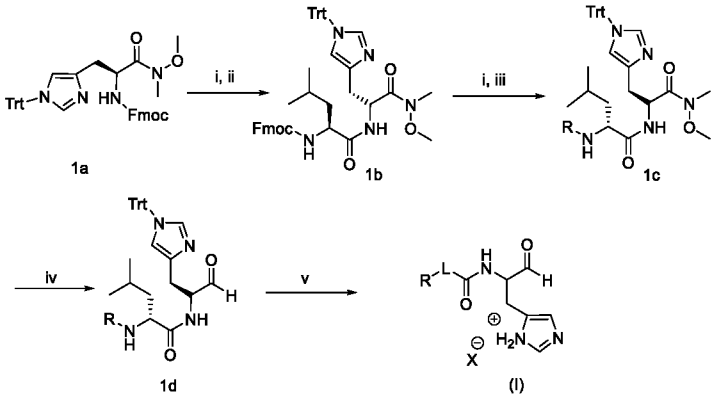
In another aspect, the inorganic base is selected from sodium hydroxide, alkali or alkaline earth metal carbonate and bicarbonate or combination thereof.

The scheme for the synthesis of compound of formula I according to said process steps i) to v) is provided below in Scheme 1:



Scheme 1.

The scheme for the synthesis of compound of formula I according to said process steps i) to vi) is provided below in Scheme 2:



Scheme 2.

In another aspect, the present invention provides a pharmaceutical composition comprising the compound of formula I as claimed in claim 1 and pharmaceutically acceptable excipient(s).

In another aspect, the present invention provides a method of inhibition of malaria cysteine proteases by contacting *P.falciparum* with the compound of formula I as claimed in claim 1 or the pharmaceutical composition as claimed in claim 17.

BRIEF DESCRIPTION OF THE DRAWINGS:

Fig 1: Scheme 3. Synthesis of **4a-h**. Reagents and conditions. (i) HBTU/HOBt, DIPEA, DMF, N, O-dimethylhydroxylamine. HCl, DMF, rt, 4h; (ii) 50% tert-Butylamine in DCM, 45 min, rt; (iii) HBTU/EDC.HCl/HOBt, DIPEA, DMF, R= carboxylic acids; (iv) LiAlH4, dry THF, -20oC, 1h, citric acid; (v) 60% TFA in DCM, 2 - 4h rt. Note: EDC.HCl instated of HBTU for synthesis of compound 4b and 4c.

Fig 2: Scheme 4. Synthesis of 8a-k. Reagents and conditions. (i) 50% tert-Butylamine in DCM, 45 min, rt; (ii) HBTU/HOBt/DIPEA, Fmoc-L-Leu-OH, DMF, rt, 12h; (iii) HBTU/HOBt/EDC.HCl, DIPEA, DMF, R= carboxylic acids; (iv) LiAlH4, dry THF, -20oC, 1h, citric acid; (v) 60% TFA in DCM, 2h rt. Note: (iii) EDC.HCl instated of HBTU for synthesis of compound 6c and 6d.

Fig 3: Scheme 5. Synthesis of 12, 15 and 18. Reagents and conditions. (i) amino acids, phenol, 1500 C, 1-6h; (ii) HBTU/HOBt, DIPEA, DMF, N, O-dimethylhydroxylamine. HCl, DMF, rt, 4h; (iii) free amine of 1 (scheme 1), HBTU/HOBt, DIPEA, DMF; (iv) free amine of 5 (scheme 2); (v) LiAlH4, dry THF, -20oC, 1h.; (vi) 60% TFA in DCM, 2-3h rt.

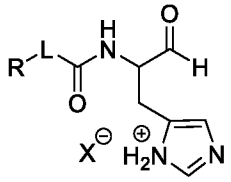
Fig 4: Phenotypic assays to determine effect of inhibitors on food vacuole. The top panel shows microscopic appearance of control parasites (1% DMSO treatment) while the middle and lower panels show appearance of parasites when treated with various inhibitors. All inhibitors were used at 25 μM concentration and two representative microscopic images are shown for each inhibitor. The white arrowheads indicate the swollen food vacuoles (due to accumulation of undigested hemoglobin) when parasites are treated with E64, 8g, and 8j compounds for 24 h and 36 h.

ABBREVIATIONS: t-Boc = tert-butyloxycarbonyl; HBTU = 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOBt = Hydroxy benzotriazoleEDC.HCl N-Ethyl-N′-(3-dimethylaminopropyl) carbodiimide hydrochloride; DIPEA- N, N-Diisopropylethylamine; DCM-dichloromethane; THF-Tetrahydrofuran; DMF- Dimethylformamide; TFA- Trifluoroacetic acid.

DETAILED DESCRIPTION OF THE INVENTION

The present invention has designed novel class of peptide-histidinal conjugates of compound of formula **(I)** that is potent and selective inhibitors of malarial cysteine protease such as falcipain-2 (FP-2) and falcipain-3 (FP-3).

In an embodiment, the present invention relates to a peptide histidinal conjugate of compound of formula (I) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a pharmaceutically acceptable solvate thereof:



(I)

wherein:

L is direct bond, $CH(R^1)$, $(CH(R^1))nNR^4CHR^5$, $(CH(R^1))nCONR^2CHR^3$, $(CH(R^1))nSO_2NR^2CHR^3$, or $(CH(R^1))nNR^4CHR^5CONR^6CHR^7$, wherein n is 0 or 1;

R is aryl, heterocyclyl, alkyl, NH-aryl, SO_2-aryl, or aryl-heterocyclyl, wherein the aryl, heterocyclyl, alkyl is substituted or unsubstituted;

R^1 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^2 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^3 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^4 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

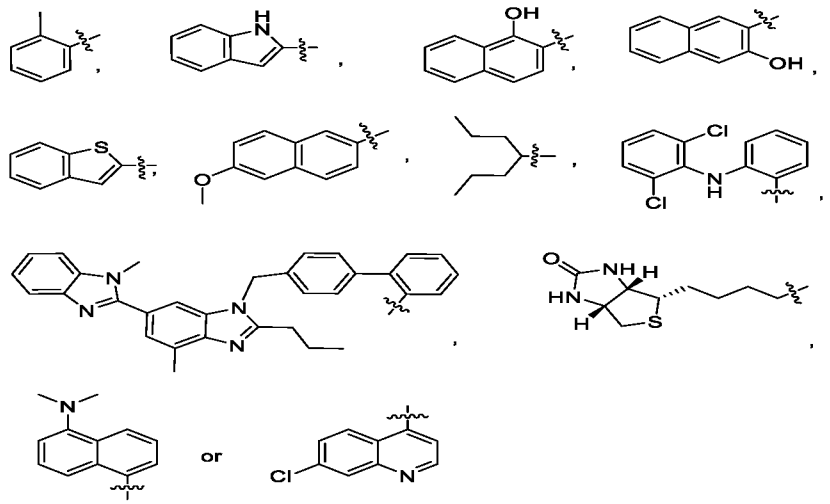
R^5 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^6 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted; and

R^7 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted.

X is CF_3COO^-, or Cl^-.

In another embodiment of the present invention, R is selected from the group consisting of:



In another embodiment of the present invention, the peptide-histidinal conjugates compound of formula (I) is selected from the group consisting of:

(S)-5-(2-(2-methylbenzamido)-3-oxopropyl)-1H-imidazol-1-ium **(4a);**

(S)-5-(2-(1-hydroxy-2-naphthamido)-3-oxopropyl)-1H-imidazol-1-ium **(4b);**

(S)-5-(2-(3-hydroxy-2-naphthamido)-3-oxopropyl)-1H-imidazol-1-ium **(4c);**

(S)-5-(2-(benzo[b]thiophene-2-carboxamido)-3-oxopropyl)-1H-imidazol-1-ium **(4d);**

5-((S)-2-((S)-2-(6-methoxynaphthalen-2-yl) propanamido)-3-oxopropyl)-1H-imidazol-1-ium **(4e);**

(S)-5-(3-oxo-2-(2-propylpentanamido) propyl)-1H-imidazol-1-ium **(4f);**

(S)-5-(2-(2-(2-((2, 6-dichlorophenyl) amino) phenyl) acetamido)-3-oxopropyl)-1H-imidazol-1-ium **(4g);**

(S)-5-(2-(4'-((1, 7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d] imidazol]-3'-yl) methyl)-[1, 1'-biphenyl]- 2-carboxamido)-3-oxopropyl)-1H-imidazol-1-ium **(4h);**

5-((S)-2-((S)-4-methyl-2-(2-methylbenzamido) pentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8a);**

5-((S)-2-((S)-2-(1H-indole-2-carboxamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8b);**

5-((S)-2-((S)-2-(1-hydroxy-2-naphthamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8c);**

5-((S)-2-((S)-2-(3-hydroxy-2-naphthamido)-4-methylpentanamido)-3-oxopropyl)- 1H-imidazol-1-ium **(8d);**

5-((S)-2-((S)-2-(benzo[b]thiophene-2-carboxamido)-4-methylpentanamido)-3-oxopropyl) -1H-imidazol-1-ium **(8e);**

5-((S)-2-((S)-2-((S)-2- (6-methoxynaphthalen-2-yl) propanamido)-4-methylpentan amido)-3-oxopropyl)-1H-imidazol-1-ium **(8f);**

5-((S)-2-((S)-4-methyl-2-(2-propylpentanamido) pentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8g);**

5-((S)-2-((S)-2-(2-(2-((2, 6-dichlorophenyl) amino) phenyl) acetamido)-4-methylpentan amido)-3-oxopropyl)-1H-imidazol-1-ium **(8h);**

5-((S)-2-((S)-2-(4'-((1, 7'-dimethyl-2'-propyl-1H,3'H-[2, 5'-bibenzo[d]imidazol]-3'-yl) methyl)- [1, 1'-biphenyl]-2-carboxamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8i);**

5-((S)-2-((S)-2-((5-(dimethylamino) naphthalene)-1-sulfonamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8j);**

5-((S)-2-((S)-4-methyl-2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl) pentanamido) pentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8k);**

(S)-2-((7-chloroquinolin-4-yl) amino)-3-(1H-imidazol-5-yl) propanal **(12)**;

5-((S)-2-((S)-2-((7-chloroquinolin-4-yl) amino)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(15);** and

5-((S)-2-((S)-2-((S)-2-((7-chloroquinolin-4-yl)amino)propanamido)-4-methylpentan amido)-3-oxopropyl)-1H-imidazol-1-ium **(18).**

In another embodiment, the compounds of present invention are in the form of trifluoroacetate or chloride salt.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein and the appended claims. These

definitions should not be interpreted in the literal sense as they are not intended to be general definitions and are relevant only for this application.

The term “L as direct bond” used herein means that the L group without being present (or as absent), making direct bond between R- group and -CO- group.

The term, “alkyl”, as used herein, refers to the radical of saturated aliphatic groups, including straight or branched-chain alkyl groups having eight or fewer carbon atoms in its backbone, for instance, C1-C8alkyl for straight chain and C3-C8 for branched chain. As used herein, C1-C8alkyl refers to an alkyl group having from 1 to 8 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, sec-butyl, isobutyl, *tert*-butyl, isopentyl, 2-methylbutyl and 3-methylbutyl.

Furthermore, unless stated otherwise, the alkyl group can be unsubstituted or substituted with one or more substituents, for example, from one to four substituents, independently selected from the group consisting of tetrahydro-1H-thieno[3,4-d] imidazol-2(3H)-one, alkoxy, halogen, hydroxy, cyano, nitro and amino. Examples of substituted alkyl include, but are not limited to hydroxymethyl, 2-chlorobutyl, trifluoromethyl and aminoethyl.

The term, "halogen" as used herein refers to chlorine, fluorine, bromine or iodine atom.

The term, “alkoxy" refers to a (C1-C8) alkyl having an oxygen radical attached thereto. Representative examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy and *tert*-butoxy. Furthermore, unless stated otherwise, the alkoxy groups can be unsubstituted or substituted with one or more groups. A substituted alkoxy refers to alkoxy substituted with one or more groups, particularly one to four groups independently selected from the groups indicated above as the substituents for the alkyl group.

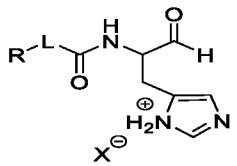
The term “aryl" as used herein refers to monocyclic, bicyclic or tricyclic hydrocarbon groups having 6 to 14 ring carbon atoms, wherein at least one carbocyclic ring is having a π electron system. Examples of aryl ring systems include, but are not limited to, phenyl, naphthyl, biphenyl, anthracenyl and phenanthrenyl. Unless indicated otherwise, aryl group can be unsubstituted or substituted with one or more substituents, for example 1 -4 substituents independently selected from the group consisting of halogen, alkyl, alkoxy, acetyl, 9H-carbazol-9-yl, (1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d] imidazol]-3'-yl) methyl, hydroxy, phenyl, cyano, nitro, -COOH and NR^aR^b; wherein R^a and R^b is hydrogen, substituted or unsubstituted aryl or heteroaryl.

As used herein, the terms "heterocyclyl" or "heterocyclic" whether used alone is a 3-12 membered saturated or partially unsaturated, monocyclic or bicyclic ring system, including spiro ring systems, containing one to four heteroatoms independently selected from the group consisting of O, N and S.

Representative examples of heterocyclyls include, but are not limited to, pyrrolyl, pyrrolidinyl, pyrazolyl, imidazolyl, pyrazinyl, piperazinyl, oxazolyl, oxadiazolyl, isoxazolyl, triaziolyl, thiazolyl, tetrazolyl, furyl, thienyl, purinyl, pyridinyl, pyridazinyl, pyrimidinyl, piperidyl, benzoxazolyl, benzothiazolyl, benzofuranyl, purinyl, benzimidazolyl, benzoxazolyl, indolyl, indazolyl, isoindolyl, isothiazolyl, isoquinolyl, isoquinolyl, morpholinyl, thiomorpholinyl, thiomorpholinyl-1, 1-dioxide, quinoxalinyl, quinolinyl and thiophenyl. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S, S-dioxide. Heterocyclyl having an aromatic ring containing heteroatoms are herein referred to by the customary term "heteroaryl". Within the context of the present invention and as used herein, the term "heteroaryl" refers to a 5-12 membered aromatic monocyclic or bicyclic ring system containing one to four heteroatoms independently selected from: nitrogen, sulphur and oxygen. Representative examples of heteroaryls include, but are not limited to, pyrrole, pyrazole, imidazole, pyrazine, furan, thiophene, oxazole, thiazole, benzimidazole, benzoxazole, benzothiazole, benzofuran, indole, indazole, isoindole, isoquinoline, isooxazole, triazine, purine, pyridine, quinoline, oxadiazole, thiene, pyridazine, pyrimidine, isothiazole, quinoxaline (benzopyrine) and tetrazole. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S, S-dioxide.

A heterocyclyl or heteroaryl group can be unsubstituted or substituted with one or more groups independently selected from group consisting of halogen, hydroxy, oxo, cyano, (C_1-C_8)-alkyl, halo(C_1-C_8)-alkyl, (C_1-C_8)-alkoxy, halo(C_1-C_8)-alkoxy, (C_3-C_{12})-cycloalkyl, hydroxy, cyano, nitro, amine, and COOH. The substituents can be present on either ring carbon or ring nitrogen atom(s). The substituents can be present at one or more positions provided that stable molecule results.

In another aspect, the present invention relates to a process for synthesis of peptide-histidinal conjugate compound of formula (I) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a pharmaceutically acceptable solvate thereof;



Formula (I)

wherein the process comprising the steps of:

a) coupling Fmoc-His (Trt)-OH with *N, O*-dialkyllhydroxylamine in the presence of coupling reagents in solvent to obtain precursor **1**;

b) deprotecting Fmoc of **1** by *tert*-butylamine in solvent;

c) coupling the intermediate obtained in step (i) with carboxylic acids in the presence of coupling reagents in solvent to furnish compounds **2a-h**;

d) reducing the compounds obtained in step (iii) using lithium aluminium hydride (LiAlH4) in dry THF at -20°C to obtain the compounds **3a-h**;

e) deprotecting compounds obtained in step (iv) using 60% TFA in DCM at temperature in the range of room temperature to 40°C for the time period in the range of 1 to 2 hours to produce histidinal-based trifluoroacetate salt compounds **4a-h**;

wherein said carboxylic acids are selected from (**1a-h**) 2-methylbenzoic acid (**a**), 1-hydroxy-2-naphthoic acid (**b**), 3-hydroxy-2-naphthoic acid (**c**), benzo[b]thiophene-2-carboxylic acid(**d**), (S)-2-(6-methoxynaphthalen-2-yl) propanoic acid (**e**), 2-propylpentanoic acid(f), 2-(2-((2,6-dichlorophenyl) amino) phenyl) acetic acid (**g**), and 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl) methyl)-[1,1'-biphenyl]-2-carboxylic acid (**h**).

The process is depicted in **Figure 1 Scheme 3.** According to process, Fmoc-His (Trt)-OH was coupled with *N, O*-dimethylhydroxylamine in the presence of coupling agents to obtain precursor **1**, a common intermediate for scaffolds **4a-h**. Further removing Fmoc of **1** by *tert*-butylamine followed by coupling with different carboxylic acids in presence of HBTU/HOBt/EDC.HCl and DIPEA in DMF to obtain compounds **2a-h**. Hydride reduction of compounds **2a-h** using lithium aluminium hydride ($LiAlH_4$) in dry THF at -20°C to get the compounds **3a-h**, followed by the deprotection of the *trityl* protecting group with 60% TFA in DCM at room temperature for 2 hours to produce the heteroaryl/aliphatic histidinal trifluoroacetate salt **4a-h**.

In yet another embodiment, the present invention provides a process for synthesis of peptide-histidinal conjugate compound of formula (I) comprising the steps of;

i. deprotecting **precursor 1**by *tert*-butylamine in solvent;

ii. coupling Fmoc-Leu-OH with **precursor 1** obtained in step (i) in the presence of coupling reagents in solvent to obtain intermediate **5**;

iii. deprotecting Fmoc by *tert*-butylamine in solvent;

iv. coupling the intermediate obtained in step (i) with carboxylic acids in the presence of coupling reagents in solvent to furnish compounds **6a-k**;

v. reducing the compounds obtained in step (iii) using lithium aluminium hydride ($LiAlH_4$) in dry THF at -20°C to obtain the compounds **7a-k**, and

vi. deprotecting compounds obtained in step (iv) using 60% TFA in DCM at temperature in the range of room temperature to 40°C for the time period in the range of 2 to 3 hours to produce histidinal-based trifluoroacetate salt compounds **8a-k;**

wherein said carboxylic acids are selected from (**a-k**), 2-methylbenzoic acid (**a**), 1H-indole-2-carboxylic acid (**b**), 1-hydroxy-2-naphthoic acid (**c**), 3-hydroxy-2-naphthoic acid(**d**), benzo[b]thiophene-2-carboxylic acid (**e**), (S)-2-(6-methoxynaphthalen-2-yl) propanoic acid (**f**), 2-propylpentanoic acid (**g**), 2-(2-((2,6-dichlorophenyl) amino) phenyl) acetic acid(**h**), 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl) methyl)-[1,1'-biphenyl]-2-carboxylic acid (**i**), 5-(dimethylamino) naphthalene-1-sulfonic acid (**j**), **and** 5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl) pentanoic acid (**k**)

The process is depicted in **Figure 2 Scheme 4.** According to the process, precursor **1** was first deprotected using *tert*-butylamine, then coupling with Fmoc-Leu-OH to obtain a common intermediate **5**. Deprotection of **5** followed by coupling with different carboxylic acids afforded compounds **6a-k.** Hydride reduction of compounds **6a-k** by using $LiAlH_4$ in dry THF under inert conditions followed by deprotecting aldehydes **7a-k** with 60% TFA in dichloromethane at temperature in the range of room temperature to 40°C for the time period in the range of 2 to 3 hours remove their trityl protecting groups to obtain histidinal-based scaffold **8a-k** as trifluoroacetate salts.

In still another embodiment, the present invention provides process for the synthesis of peptide-histidinal conjugate compound of formula (I) comprising the steps of:

i) reacting 4, 7-dichloroquinoline **9** with the amino acids, at temperature in the range of 140 to 150°C for the time period of 1-6h to obtain compounds **10 a-c** as reported in literature.[1]

ii) coupling Compound **10c** with *N, O*-dimethylhydroxylamine to obtain compound **11**;

iii) reacting compound **10b** with precursor **1** in presence of coupling reagents to afford compound **13**

iv) reacting compound **10a** with intermediate **5** in presence of coupling reagents to afford compound **16**

v) deducing the compounds obtained in step (i), (ii), (iii) using lithium aluminium hydride ($LiAlH_4$) in dry THF at -20°C to obtain the compounds **12, 14, 17**;

vi) deprotecting compounds obtained in step (iv) using 60% TFA in DCM at temperature in the range room temperature to 40°C for the time period in the range of 2 to 3 hours to produce histidinal-based trifluoroacetate salt compounds **15** and **18**;

wherein said amino acids are selected from **a-c** L-alanine (**a**), L-leucine (**b**) and L-histidine (**c**).

The process is depicted in **Figure 3 Scheme 5**. According to the process 4, 7-dichloroquinoline **9** (commercially available) was first reacted with the amino acids at temperature in the range of 140°C to150°C for 1-6h to obtain compounds **10 a-c**, following literature protocols.[1] Coupling **10c** with *N, O*-dimethylhydroxylamine to obtain compound **11** followed by hydride reduction to furnish compound **12**. Reacting compound **10b** with the free amine of compound **1** in presence of coupling reagents followed reduction with $LiAlH_4$ at -20°C in dry THF to get compound **14**. *D*eprotecting trityl by using 60% TFA in solvent at temperature in the range of room temperature to 40°C for the time period in the range of 1 to 2 hours to furnish compound **15**. Reacting compound **10a** with the free amine of compound **5** in the presence of coupling reagents followed by reduction with $LiAlH_4$ at -20°C in dry THF to furnish compound **17**. Deprotecting trityl group using 60% TFA in solvent at temperature in the range of room temperature to 40°C for the time period in the range of 1 to 2 hours to yield compound **18**.

The solvent for the process is selected from polar or non-polar, protic or aprotic solvent such as lower alcohols, nitriles, ketones, halogenated hydrocarbons, TFA or combinations thereof.

The base for the reaction is selected from organic base such as ethylamine, triethylamine, DIPEA, pyridine or from inorganic base such as sodium hydroxide, alkali or alkaline earth metal carbonates and bicarbonates or combination thereof.

The coupling agent for reaction is selected from HBTU, EDC.HCl, or HOBt.

In yet another preferred embodiment, the peptide-histidinal conjugate compounds of formula (I) are useful for inhibition of cysteine and aspartic acid proteases.

Peptide-histidinal conjugate compounds of formula (I) tested to determine whether they could inhibit blood cells infected with *P. falciparum*.

Inventor observed that the majority of molecules were found to be active against *P. falciparum* strains. Further the inhibitory potency (EC_{50}) of compounds of present invention is within the micromolar range, between 8.1μM to 0.01 μ M.

Importantly, it was noted that histidinal-containing leucine and aromatic/aliphatic compounds are having good antimalarial activity. Particularly, the compounds 8g (EC50 of 0.018 μM), 8h (EC50 of 0.06 μM), and 15 (EC50 of 0.02 μM) were found to have nanomolar inhibition potency against the parasites.

EXAMPLES

Following examples are given by way of illustration and therefore should not be construed to limit the scope of the invention.

[A] Synthesis of compounds of formula I

Example 1: (9H-fluoren-9-yl) methyl (S)-(1-(methoxy (methyl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) carbamate (1): A mixture of Fmoc-His (*Trt*)-OH (1g, 1.61 mmol, 1 equiv.), HBTU (0.73 g, 1.93 mmol, 1.2 equiv), and HOBt (0.21g, 1.61 mmol,1 equiv) were dissolved in DMF at ice temperature and *N, N*-diisopropylethylamine was added (0.82 mL, 4.84 mmol, 3 equiv.) and stirred for 20 min. Then *N* O-dimethylhydroxylamine hydrochloride (0.31g, 3.23 mmol, 2 equiv.) was added and stirred for 5 h at room temperature. The reaction mixture was diluted with ice-cold water (20 mL), and the resulting solid precipitate was filtered under vacuum, and the solid residue was dissolved in ethyl acetate (30 mL) and washed with dilute citric acid, $NaHCO_3$ solution, and brine solution, and dried over Na_2SO_4. The product obtained after evaporating solvent was pure enough and carried forward for next reactions. **Yield:** 0.9g, (84%); mp: 70-75°C; R_f = 0.5 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_D$ = -3.55°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.75 - 7.74 (d, *J* = 7.5 Hz, 2 H), 7.38 (t, *J* = 6.9 Hz, 2 H), 7.38 -7.32 (m, 3 H), 7.31 - 7.30 (m, 11 H), 7.13 - 7.11 (m, 7 H), 6.60 (s, 1 H), 6.11 (d, *J* = 7.6 Hz, 1 H), 4.98 - 4.95 (d, *J* = 5.4 Hz, 1 H), 4.31 - 4.23 (m, 2 H), 4.17(d, *J* = 7.5 Hz, 1 H), 3.77 (s, 3 H), 3.16 - 3.09 (s, 3 H), 2.98 - 2.96 (m, 2H); Calcd m/z: $[M+H]^+$ for; $C_{42}H_{39}N_4O_4$; 663.2966; Found 663.2953.

Example 2: (S)-N-(1-(methoxy(methyl) amino)-1-oxo-3-(1-trityl-1H- imidazol-4-yl) propan-2-yl)-2-methylbenzamide (2a): Fmoc deprotection was done first, as follows. Fmoc compound **1** (0.678g, 1 mmol, 1equiv.) was taken in 50% solution of *tert*-butylamine in DCM (30mL) and stirred at room temperature for 45 min, and the reaction mixture was concentrated under vacuum. The resulting semisolid residue was washed with diethyl ether (3 x 5 mL). The free amine of **1** (0.440g, 1 mmol, 1 equiv.) was added to a reaction mixture containing *O*-toluic acid (0.136 g, 1 mmol, 1 equiv.), HBTU (0.456g, 1.2 mmol, 1.2 equiv), HOBt (0.135g, 1 mmol, 1 equiv) and *N, N*-diisopropylethylamine (0.347 mL, 2 mmol, 2 equiv.) in DMF (12mL). The solution was stirred at room temperature for overnight. Then, the reaction mixture was diluted with ice cold water (20 mL), and extracted with ethyl acetate (2 x 30 mL). It was successively washed with dilute aqueous citric acid solution, $NaHCO_3$ solution, and brine solution, dried over Na_2SO_4 and concentrated under vacuum, then purified with

neutral allumimium oxide packed column chromatography. The mobile phase starting from pet-ether and gradually increasing polarity with dichloromethane and then 3% methanol/DCM afforded **2a** as white solid. **Yield:** 0.4g, (70%); mp: 75 - 80°C; R_f = 0.45 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_D$ = -10.64°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.5 Hz, 1 H), 7.29 (s, 1 H), 7.29 (d, *J* = 5.3 Hz, 10 H), 7.28 (d, *J* = 8.1 Hz, 2 H), 7.12 - 7.09 (m, 8 H), 6.57 (s, 1 H), 5.33 - 5.32 (d, *J* = 19.0 Hz, 1 H), 3.83 (s, 3 H), 3.17 (s, 3 H), 3.10 - 3.03 (dd, *J* = 5.6, 9.1 Hz, 2 H), 2.42 (s, 3 H); Calcd m/z: $[M+H]^+$ for $C_{35}H_{35}N_4O_3$; 559.2704; Found 559.2701.

Example 3: (S)-1-hydroxy-N-(1-(methoxy(methyl) amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)-2-naphthamide (2b): Using 1-hydroxy-2-naphthoic acid, **2b** was synthesized following the analogous procedure of **2a** White solid (note: in place of HBTU, we used EDC.HCl as a coupling agent); **Yield:** 0.56g, (75%); mp: 85-90°C; R_f = 0.6 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_D$ = 26.42 (c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 13.67 (bs, 1H), 8.38 (d, *J* = 8.1 Hz, 1 H), 8.36 (d, *J* = 7.3 Hz, 1 H), 7.72 (bs., 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.50 (m, 3 H), 7.46 - 7.28 (m, 11 H), 7.26 (d, *J* = 6.1 Hz, 6 H), 7.58 (s, 1 H), 5.33 (m, 1 H), 3.86 (s., 3 H), 3.19 - 3.13 (m, 3 H), 3.11 - 3.109 (m, 3H); Calcd m/z: $[M+H]^+$ for $C_{38}H_{35}N_4O_4$; 611.2653; Found 611.2648.

Example 4: (S)-3-hydroxy-N-(1-(methoxy(methyl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)-2-naphthamide (2c): Using 2-hydroxy-3-naphthoic acid, **2c** was synthesized following the analogous procedure of **2a**. White solid (note: in place of HBTU, we used EDC.HCl as a coupling agent); **Yield:** 0.38g (62%); $[\alpha]^{27}_D$ = 22.42°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 13.62 (bs, 1H), 8.33 (m, 2 H), 8.30 (m, 1H); 7.74 (bs., 1 H), 7.72 (d, *J* = 8.1 Hz, 1 H), 7.54 - 7.46 (m, 2 H), 7.47 - 7.36 (m, 1 H), 7.27 - 7.22 (m, 10 H), 7.20 (d, *J* = 8.8 Hz, 1 H), 7.03 - 7.02 (m, 6 H), 6.76 (s, 1 H), 5.42 (m, 1 H), 3.89 (bs., 3 H), 3.31 (m, 2 H), 3.26 - 3.121; Calcd m/z: $[M+H]^+$ for $C_{38}H_{35}N_4O_4$; 611.2653; Found 611.2640.

Example 5: (S)-N-(1-(methoxy(methyl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) benzo [b] thiophene-2-carboxamide (2d): Using benzo[b]thiophene-2-carboxylic acid, **2d** was synthesized following the analogous procedure of **2a**. **2d** was obtained as a white solid: **Yield:** 0.35g, (58%); mp:80-84°C; R_f = 0.55 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_D$ = -13.60°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.83 (bs., 1 H), 7.81-7.78 (m, 2 H), 7.42 (m, 1 H), 7.31 - 7.30 (m, 12 H), 7.13 - 7.11 (m, 7 H), 6.59 (s, 1 H), 5.30 (d, *J* = 5.9 Hz, 1 H), 3.86 (s, 3 H), 3.19 (m, 3 H), 3.12 - 3.08 (m, 2 H); Calcd m/z: $[M+H]^+$ for $C_{36}H_{33}N_4O_3$; 601.2268; Found 601.2266.

Example 6: (S)-N-methoxy -2-((S)-2-(6-methoxynaphthalen-2-yl) propanamido)-N-methyl-3-(1-trityl-1H-imidazol-4-yl) propanamide (2e): Using (S)-(+)-2-(6-methoxy-2-naphthyl) propionic acid, **2e** was synthesized following the analogous procedure of **2a**. **2e** was obtained as a white solid. **Yield:** 0.4g, (61%); $[\alpha]^{27}_{D}$ = -73.21°(c = 0.1, MeOH); mp: 60-65°C; R_f = 0.65 (silica gel TLC, 2% MeOH in DCM); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.61 - 7.60 (m, 3 H), 7.34 (d, *J* = 1.8 Hz, 1 H), 7.33 - 7.28 (m, 10 H), 7.08 - 7.03 (m, 9 H), 6.91 (d, *J* = 2.4 Hz, 1 H), 6.91 (bs., 1 H), 6.44 (s, 1 H), 5.07-5.02 (m, 1 H), 3.88 (s, 3 H), 3.74 (s, 3 H), 3.65 (q, *J* = 7.2 Hz, 1 H), 3.09 (s, 3 H), 2.89 (dq, *J* = 5.4, 14.6 Hz, 2 H), 1.54 (d, *J* = 7.3 Hz, 3 H); Calcd m/z: $[M+H]^+$ for $C_{41}H_{41}N_4O_4$; 653.3122; Found 653.3104.

Example 7: (S)-N-(1-(methoxy(methyl) amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)-2-propyl pentanamide (2f): Using 2-propylpentanoic acid, **2f** was synthesized following the analogous procedure of **2a**. **2f** was obtained as a white solid. **Yield:** 0.28g, (50%); mp: 65-70°C; R_f = 0.6 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_{D}$ = -8.80°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.34 - 7.32 (m, 10 H), 7.13 - 7.12 (m, 6 H), 6.80 (bs., 1 H), 6.55 (s, 1 H), 5.12 (d, *J* = 6.9 Hz, 1 H), 3.77 (s, 3 H), 3.13 (s, 3 H), 2.96 - 2.95 (d, *J* = 5.5 Hz, 2 H), 2.08 - 2.07 (d, *J* = 4.5 Hz, 1 H), 1.56 - 1.26 (m, 2 H), 1.38 - 1.14 (m, 7 H), 0.87 - 0.78 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{35}H_{43}N_4O_3$; 567.3330, Found 567.3332.

Example 8: (S)-2-(2-(2-((2, 6-dichlorophenyl) amino) phenyl) acetamido)-N-methoxy-N-methyl-3-(1-trityl-1H-imidazol-4-yl) propanamide (2g): Using 2-(2,6-dichloroanilino) phenylacetic Acid, **2g** was synthesized following the analogous procedure of **2a**. **2g** was obtained as a white solid: **Yield:** 0.287g, (59%): mp:95-99°C; R*f* = 0.55 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_{D}$ =-29.33° (c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.80 (s, 1 H), 7.33 - 7.31 (m, 12 H), 7.18 (d, *J* = 6.5 Hz, 1 H), 7.13 - 7.11 (m, 6 H), 7.05 - 7.03 (m, 2 H), 6.95 (t, *J* = 8.1 Hz, 1 H), 6.79 (t, *J* = 7.4 Hz, 1 H), 6.52 - 6.50 (m, 2 H), 5.14 - 5.10 (d, *J* = 6.3 Hz, 1 H), 3.76 (s, 3 H), 3.71 - 3.59 (m, 2 H), 3.14 (s, 3 H), 2.99 – 2.98 (d, *J* = 5.4 Hz, 2 H); Calcd m/z: $[M+H]^+$ for $C_{41}H_{38}N_5O_3$; 718.2346; Found 718.2345.

Example 9: (S)-4'-((1, 7'-dimethyl-2'-propyl-1H, 3'H-[2, 5'-bibenzo[d] imidazol]-3'-yl)methyl)-N-(1-(methoxy(methyl) amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) -[1, 1'-biphenyl]-2-carboxamide (2h): Using 4'-[[4-methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic acid, **2h** was synthesized following the analogous procedure of **2a**. **2h** was obtained as a white solid. Yield: 0.13g, (71%); mp. 105 -108°C; $[\alpha]^{25}_{D}$ = -

6.90°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.80 - 7.78 (dd, *J* = 2.8, 6.3 Hz, 1 H), 7.54 (d, *J* = 7.5 Hz, 1 H), 7.45 - 7.40 (m, 3 H), 7.32 - 7.30 (m, 4 H), 7.29 - 7.25 (m, 16 H), 7.09 (m, 6 H), 7.08 (d, *J* = 8.1 Hz, 2 H), 6.89 (bs., 1 H), 6.44 (s, 1 H), 5.39 (s, 2 H), 5.12 (bs., 1 H), 3.76 (s, 3 H), 3.62 (s, 3 H), 3.02 (s, 3 H), 2.93 - 2.89 (m, 2 H), 2.81 - 2.79 (m, 5 H), 1.87 - 1.85 (m, 2 H), 1.03-1.01 (t, *J* = 7.3 Hz, 3 H); Calcd m/z: $[M+H]^+$ for $C_{60}H_{57}N_8O_3$; 937.4548; Found 937.4568.

Example 10: (S)-2-methyl-N-(1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) benzamide (3a): The compound **2a** (0.30g, 0.536 mmol, 1 equiv.) was dissolved in dry THF under nitrogen atmosphere and cooled to -20°C, added $LiAlH_4$ (0.039g, 1 mmol, 2 equiv.), stirred for 1hour and the reaction progress was monitored by TLC. The resulting reaction mixture was quenched with dilute solution of citric acid (0.1 - 0.2mL), followed by the addition of ethyl acetate (30 mL). Afterwards, the combined organic layer was washed with dilute citric acid solution and $NaHCO_3$ and brine solutions, dried over Na_2SO_4 and then the organic solvent was concentrated under vacuum. The crude product was purified by Al_2O_3 packed column chromatography. The mobile phase was pet ether to dichloromethane. The compound **3a** was precipitated in 50% diethyl ether and hexane to yield a white solid.**Yield:** 0.22g, (82%); mp: 80 - 85°C; R_f = 0.5 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_D$ = -14.92°(c = 0.1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1 H), 7.52 (d, *J* = 6.6 Hz, 1 H), 7.42 (d, *J* = 7.6 Hz, 1 H), 7.32 - 7.26 (m, 12 H), 7.24 - 7.17 (m, 2 H), 7.13 - 7.06 (m, 6 H), 6.64 (s, 1 H), 4.84 (d, *J* = 6.2 Hz, 1 H), 3.24 (dd, *J* = 5.1, 15.0 Hz, 1 H), 3.15 (dd, *J* = 5.3, 15.1 Hz, 1 H), 2.45 (s, 3 H); Calcd m/z: $[M+H]^+$ for $C_{33}H_{30}N_3O_2$; 500.2333; Found 500.2320.

Example 11: (S)-1-hydroxy-N-(1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)-2-naphthamide (3b): The synthetic method of **3a** was adopted to synthesize **3b**. White solid;

Yield: 0.155g, (56%); mp:80-85°C; R_f = 0.5 (silica gel TLC, 70% ethyl acetate in pet. ether); $[\alpha]^{27}_D$ =-9.24°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 13.66 (bs, 1H); 9.66 (s, 1 H), 9.07 (d, *J* = 5.9 Hz, 1 H), 8.41 (d, *J* = 8.3 Hz, 1 H), 7.74 (d, *J* = 7.9 Hz, 1 H), 7.55 (m, 3 H), 7.45 - 7.32 (d, *J* = 1.1 Hz, 1 H), 7.32 - 7.26 (m, 10 H), 7.25 (s, 1 H), 7.10 - 7.09 (m, 6 H), 6.66 (s, 1 H), 4.79 (d, *J* = 5.5 Hz, 1 H), 3.24 (dd, *J* = 5.4, 15.0 Hz, 1 H), 3.12 (dd, *J* = 5.1, 15.0 Hz, 1 H); Calcd m/z: $[M+H]^+$ for $C_{36}H_{30}N_3O_3$; 552.2882; Found 552.2880.

Example 12: (S)-3-hydroxy-N-(1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)-2-naphthamide (3c): The synthetic method **3a** was used to synthesize **3c.** White solid;

Yield: 0.140g, (50%); mp:83-86°C; R_f = 0.45 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{27}_D$ =-9.10°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 11.81 (bs, 1H) 9.69 (s, 1 H), 9.22 - 9.21 (d, *J* = 5.8 Hz, 1 H), 8.21 (s, 1 H), 7.77 (d, *J* = 8.4 Hz, 1 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.46 - 7.43 (m, 2 H), 7.32 (m, 11 H), 7.11 - 7.08 (m, 7 H), 6.68 (s, 1 H), 4.83 - 4.80 (m, 1 H), 3.28 - 3.12 (m, 2 H); Calcd m/z: $[M+H]^+$ for $C_{36}H_{30}N_3O_3$; 522.5282; Found 522.5280.

Example 13: (S)-N-(1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) benzo[b]thiophene-2-carboxamide (3d): The synthetic method **3a** was used to synthesize **3d**. White solid;
Yield: 0.25g, (85%); mp: 75-80°C; R_f = 0.25 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_D$ = -17.28°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.70 (s, 1 H), 8.56 (d, *J* = 5.8 Hz, 1 H), 7.86 - 7.85 (m, 2 H), 7.44 - 7.33 (m, 2 H), 7.32 (m, 8 H), 7.31 (m, 2 H), 711. - 7.09 (m, 8 H), 6.66 (s, 1 H), 4.82 - 4.78 (d, *J* = 5.6 Hz, 1 H), 3.27 - 3.22 (s, 1 H), 3.14 - 3.09 - (d, *J* = 5.0 Hz, 1 H); Calcd m/z: $[M+H]^+$ for $C_{34}H_{28}N_3O_2S$; 542.1897; Found 542.1893.

Example 15: (S)-2-(6-methoxynaphthalen-2-yl)-N-((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) propanamide (3e): The synthetic method of **3a** was adopted to synthesize **3e.** White solid. Yield: 0.23g, (84%); R_f = 0.5 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_D$ =-5.32°(c = 0.1, MeOH); mp: 80-84°C; ^{1}H NMR (400MHz, $CDCl_3$) δ 9.52 - 9.41 (s, 1 H), 7.69 - 7.61 (m, 4 H), 7.32 - 7.29 (m, 13 H), 6.99 (td, *J* = 2.2, 8.9 Hz, 2 H), 6.98 - 6.97 (m, 7 H), 6.97 (dd, *J* = 1.3, 4.0 Hz, 1 H), 6.45 (d, *J* = 9.5 Hz, 1 H), 4.50 (d, *J* = 5.8 Hz, 1 H), 3.88 (s, 3 H), 2.98 (s, 2 H), 1.61-1.58 (dd, *J* = 3.5, 7.1 Hz, 3 H); Calcd m/z: $[M+H]^+$ for $C_{39}H_{36}N_3O_3$; 594.2751; Found 594.2339.

Example 16: (S)-N-(1-oxo-3-(1-trityl- 1H-imidazol-4-yl) propan-2-yl)-2-propylpentanamide (3f): The synthetic method of **3a** was adopted to synthesize **3f**. White solid. **Yield:** 0.2g (74%); R_f = 0.5 (silica gel TLC, 30% ethyl acetate in pet. ether); $[\alpha]^{25}_D$ = 27.66°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.59 (s, 1 H), 7.34 - 7.32 (m, 10 H), 7.10 - 7.07 (m, 6 H), 6.61 (s, 1 H), 4.61 - 4.57 (q, *J* = 5.8 Hz, 1 H), 3.14 (dd, *J* = 5.9, 15.0 Hz, 1 H), 2.96 (dd, *J* = 5.3, 15.0 Hz, 1 H), 2.17 (dt, *J* = 4.7, 9.3 Hz, 1 H), 1.64 (m, 4 H), 1.27 (m, 4 H), 0.98 - 0.76 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{33}H_{37}N_3O_2$; 508.2959; Found 508.2957.

Example 17: (S)-2-(2-((2, 6-dichlorophenyl) amino) phenyl)-N-(1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) acetamide (3g): The synthetic method of **3a** was adopted to synthesize **3g**. White

solid; **Yield:** 0.16g, (58%); R*f* = 0.4 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_D$ = -12.80°(c = 0.1, MeOH); mp: 70-75°C; ^{1}H NMR (400MHz, $CDCl_3$) δ 9.57 (s, 1 H), 7.73 (d, *J* = 6.6 Hz, 1 H), 7.55 (s, 1 H), 7.38 - 7.30 (m, 15 H), 7.15 - 7.03 (m, 10 H), 6.97 (t, *J* = 8.1 Hz, 2 H), 6.84 (t, *J* = 7.4 Hz, 1 H), 6.58 (s, 1 H), 6.51 (d, *J* = 8.0 Hz, 1 H), 4.77 - 4.49 (m, 1 H), 3.51 - 3.45 (m, 1 H), 3.12 (dd, *J* = 5.3, 15.0 Hz, 1 H), 2.98 (dd, *J* = 5.1, 15.1 Hz, 1 H); Calcd m/z: $[M+H]^+$ for $C_{39}H_{33}N_4O_2Cl_2$; 659.1975; Found 659.1971.

Example 18: (S)-4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl) methyl)-N-(1-oxo -3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)-[1,1'-biphenyl]-2-carboxamide (3h): The synthetic method of **3a** was adopted to synthesize **3h**. White solid; **Yield:** 0.07g, (74%); R_f = 0.36 (silica gel TLC, 2% MeOH in DCM); mp: 95-105°C; $[\alpha]^{27}_D$ = -6.80°(c = 0.1, MeOH); ^{1}H NMR (500MHz, $CDCl_3$) δ 9.42 (s, 1 H), 7.87 - 7.68 (m, 1 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.46 (d, *J* = 1.1 Hz, 1 H), 7.43 (s, 2 H), 7.39 - 7.32 (m, 3 H), 7.32 - 7.22 (m, 17 H), 7.17 (d, *J* = 6.8 Hz, 1 H), 7.14 - 7.06 (m, 1 H), 7.06 - 6.96 (m, 7 H), 6.48 (s, 1 H), 5.39 (s, 2 H), 4.55 (d, *J* = 6.5 Hz, 1 H), 3.82 - 3.64 (m, 3 H), 3.56 - 3.36 (m, 2 H), 3.04 - 2.81 (m, 3 H), 2.81 - 2.61 (m, 4 H), 1.97 - 1.79 (m, 2 H), 1.40 - 1.15 (m, 8 H), 1.15 - 0.95 (m, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H); Calcd m/z: $[M+H]^+$ for $C_{58}H_{51}N_7O_2$; 878.4182; Found 878.4160.

Example 19: (S)-5-(2-(2-methylbenzamido)-3-oxopropyl)-1H-imidazol-1-ium (4a):

The compound **3a** (0.25g, 0.5 mmol, 1 equiv.) was dissolved in a solution of 60% TFA in DCM and stirred at room temperature for 3-4 h and the complete deprotection was monitored by TLC. The resultant yellow solution was concentrated under the vacuum and the residual TFA was stripped off using co-evaporation with DCM (2 x 10 mL), and the solid residue was washed (3 x 5 mL) with diethyl ether to yield compound **4a** as white solid; **Yield:** 0.15g, (81%); R_f = 0.2 (silica gel TLC, 3% MeOH in DCM); mp: 70-75°C; $[\alpha]^{25}_D$ = 30.30°(c = 0.1, MeOH); ^{1}H NMR (400MHz, CD_3OD) δ 8.78 (s, 1 H), 7.34 - 7.27 (m, 3 H), 7.21- 7.12 (m, 3 H), 4.70 - 4.40 (m, 2 H), 3.29 (d, *J* = 15.5 Hz, 1 H), 2.95 (bs., 1 H), 2.23 (s, 3 H); Calcd m/z: $[M+H]^+$ for $C_{14}H_{16}N_3O_2$; 258.1237; Found 258.1234.

Example 20: (S)-5-(2-(1-hydroxy-2-naphthamido)-3-oxopropyl)-1H-imidazol-1-ium (4b): The synthetic method of **4a** was adopted to synthesize **4b**. White solid; **Yield:** 0.06 g (78%); R_f = 0.2 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{27}_D$ = -17.28°(c = 0.1, MeOH); mp: 65-70°C; ^{1}H NMR (400MHz, CD_3OD) δ 8.74 (s, 1 H), 8.31-8.29 (d, *J* = 8.3 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.69 - 7.68 (m, 2 H),

7.58 (s, 2 H), 7.49 (d, *J* = 7.4 Hz, 1 H), 7.32 (s, 1 H), 7.30 - 7.25 (m, 3 H), 4.79 -4.57 (bs., 2 H), 3.50 (d, *J* = 7.0 Hz, 1 H), 3.23 - 3.10 (t, *J* = 7.0 Hz, 2 H); Calcd m/z: $[M+H]^+$ for $C_{17}H_{16}N_3O_3$; 310.1186; Found 310.1182.

Example 21: (S)-5-(2-(3-hydroxy-2-naphthamido)-3-oxopropyl)-1H-imidazol-1-ium (4c): The synthetic method of **4a** was adopted to synthesize **4c**. White solid; **Yield:** 0.072g, (75%); R_f = 0.2 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{25}_D$ = 7.90°(c = 0.1, MeOH); mp: 80 - 85°C; ^{1}H NMR (400MHz, CD_3OD) δ 8.74 – 8.73 (m, 1 H), 8.44 - 8.38 (d, *J* = 4.8 Hz, 1 H), 7.82 - 7.79 (d, *J* = 8.1 Hz, 1 H), 7.66 - 7.64 (d, *J* = 8.3 Hz, 1 H), 7.46 (dt, *J* = 1.1, 7.6 Hz, 1 H), 7.33 - 7.28 (m, 2 H), 7.22 (s, 1 H),4.77 - 4.76 (m,1H), 4.59-4.53 (m, 1 H); 3.05 (s, 2 H); Calcd m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}N_3O_3$; 310.1186; Found 310.1179. Calcd m/z: $[M+H]^+$ Calcd for $C_{17}H_{16}N_3O_3$; 310.1186; Found 310.1179.

Example 22: (S)-5-(2-(benzo[b]thiophene-2-carboxamido)-3-oxopropyl)-1H-imidazol-1-ium (4d): The synthetic method of **4a** was adopted to synthesize **4d**. White solid; **Yield:** 0.11g, (72%); R_f = 0.2 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{27}_D$ = -17.28°(c = 0.1, MeOH); mp: 80-85°C; ^{1}H NMR (400MHz CD_3OD) δ 8.73 (bs., 1 H), 7.97 (s, 1 H), 7.89 (*δ*, *J* = 7.1 Hz, 2 H), 7.44 - 7.41 (m, 2 H), 7.28 (s, 1 H), 4.76 - 4.73 (m, 1 H), 4.44 (bs., 2 H), 3.76 - 3.65 (m, 2 H), 3.51 - 3.42 (m, 1 H), 3.28 - 3.13 (m, 1 H), 3.13 - 2.95 (m, 1 H); Calcd m/z: [M+H]+ for $C_{15}H_{14}N_3O_2S$; 300.0801; Found 300.0793.

Example 23: 5-((S)-2-((S)-2-(6-methoxynaphthalen-2-yl)propanamido)-3-oxopropyl) -1H-imidazol-1-ium (4e): The synthetic method of **4a** was adopted to synthesize **4e**. White solid; **Yield:** 0.12g, (85%); R_f = 0.2 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{25}_D$ = 36.18° (c = 0.1, MeOH); mp: 100-105°C; ^{1}H NMR (400MHz, CD_3OD) δ 8.70 (bs., 1 H), 8.24 (s, 1 H), 7.70 - 7.66 (m, 4 H), 7.58 (s, 1 H), 7.38 (d, *J* = 8.5 Hz, 1 H), 7.25 - 7.18 (m, 3 H), 7.12 (t, *J* = 9.7 Hz, 2 H), 6.75 (m, 1 H), 4.62 - 4.61 (dd, *J* = 3.4, 7.2 Hz, 1 H), 4.46 (dd, *J* = 3.6, 10.1 Hz, 1 H), 4.26 - 4.12 (m, 2 H), 3.90 (s, 3 H), 3.77 - 3.68 (m, 3 H), 3.09 (d, *J* = 15.5 Hz, 1 H), 2.98 (d, *J* = 14.0 Hz, 1 H), 2.77 (m, 2 H), 1.46 -1.39 (dd, *J* = 7.0, 18.9 Hz, 5 H), 1.16-1.10 (d, *J* = 6.1 Hz, 6 H): Calcd m/z: $[M+H]^+$ for $C_{20}H_{22}N_3O_3$; 352.1656; Found 352.1656.

Example 24: (S)-5-(3-oxo-2-(2-propylpentanamido) propyl)-1H-imidazol-1-ium (4f): The synthetic method of **4a** was adopted to synthesize **4f**. White solid; **Yield:** 0.12g (80%); $[\alpha]^{27}_D$ = 3.80°(c = 0.1, MeOH); mp: 60 - 65°C; ^{1}H NMR (400MHz, CD_3OD) δ 8.78 (d, *J* = 1.3 Hz, 1 H), 7.44 - 7.27 (m, 2 H), 4.31- 4.28 (tdd, *J* = 3.9, 5.5, 11.3 Hz, 1 H), 3.32 (m, 1 H), 2.88 (ddd, *J* = 3.9, 11.4, 15.4 Hz, 2 H), 2.19

(m, 1 H), 1.29 – 1.25 (m, 8 H), 0.91 - 0.80 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{14}H_{24}N_3O_2$; 352.1656; Found 352.1656.

Example 25: (S)-5-(2-(2-(2-((2, 6-dichlorophenyl) amino)phenyl)acetamido)-3-oxopropyl)-1H-imidazol-1-ium (4g): The synthetic method of **4a** was adopted to synthesize **4g**. White solid; **Yield:** 0.12g, (74%); mp: 75-80°C; R_f = 0.2 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{27}_D$ = 25.80°(c = 0.1, MeOH); ^{1}H NMR (400MHz, CD_3OD) δ 8.41 - 8.39 (m, 1 H), 7.30 - 7.28 (m, 3 H), 7.25 - 7.11 (m, 2 H), 7.08 - 7.06 (m, 1 H), 6.98 (t, *J* = 8.2 Hz, 2 H), 6.83 - 6.78 (m, 2 H), 6.27 - 6.25 (d, *J* = 8.0 Hz, 1 H), 4.54 – 4.52 (t, *J* = 4.4 Hz, 1 H), 4.16 (t, *J* = 11.8 Hz, 1 H), 3.57 (dd, *J* = 3.8, 13.4 Hz, 1 H), 3.49 - 3.45 (d, *J* = 13.4 Hz, 1 H), 3.38 - 3.35 (m, 1 H), 2.99 (dt, *J* = 3.5, 15.4 Hz, 1 H), 2.75 (m, 1 H); Calcd m/z: $[M+H]^+$ for $C_{20}H_{19}N_4O_2Cl_2$; 417.0880; Found 417.0882.

Example 26: (S)-5-(2-(4'-((1, 7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d] imidazol]-3'-yl) methyl)-[1, 1'-biphenyl]- 2-carboxamido)-3-oxopropyl)-1H-imidazol-1-ium (4h): A synthetic method of **4a** was used to synthesize **4h**. White solid; **Yield:** 0.123g, (69%); $[\alpha]^{27}_D$ = -6.80°(c = 0.1, MeOH); mp: 80-85°C; ^{1}H NMR (400MHz, CD_3OD) δ 8.78 - 8.77 (t, *J* = 1.6 Hz, 1 H), 7.92 - 7.87 (m, 2 H), 7.70 - 7.76 (m, 1 H), 7.71 (s, 1 H), 7.69 - 7.61 (m, 2 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.45 - 7.65 (m, 1 H), 7.42 - 7.40 (m, 4 H), 7.26 - 7.24 (m, 4 H), 5.76 (s, 2 H), 4.39 (m, 1H),4.38 (m, 1H), 4.01 (s, 3 H), 3.33 - 3.29 (m, 3 H), 3.19 (t, *J* = 7.4 Hz, 2 H), 2.79 (s, 3 H), 1.90 (dd, *J* = 2.2, 7.7 Hz, 2 H), 1.29 - 1.16 (m, 2 H) 1.14 - 1.01 (m, 3 H); Calcd m/z: $[M+H]^+$ for $C_{39}H_{38}N_7O_2$; 636.3081; Found 636.3081.

Example 27: (9H-fluoren-9-yl) methyl ((S)-1-(((S)-1-(methoxy(methyl) amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino)-4-methyl-1-oxopentan-2-yl) carbamate (5): The synthetic method of **2** was adopted to synthesize compound **5**. White solid. **Yield:** 0.45g, (58 %); mp:85-90°C; R_f = 0.65 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_D$ = 0.76°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 2 H), 7.57 - 7.51 (m, 2 H), 7.37 (t, *J* = 7.5 Hz, 3 H), 7.31 - 7.25 (m, 12 H), 7.10 - 7.08 (m, 6 H), 6.52 (s, 1 H), 5.58 (d, *J* = 8.3 Hz, 1 H), 5.06 (bs., 1 H), 4.40 (bs., 1 H), 4.38 - 4.31 (m, 2 H), 4.28 - 4.16 (d, *J* = 7.0 Hz, 1 H), 3.76 (s, 3 H), 3.12 (s, 3 H), 2.97 (d, *J* = 5.3 Hz, 2 H), 2.09 (s, 3 H), 1.69 - 1.67 (m, 2 H), 1.47 (bs, 1H), 0.93 – 0.87 (t, *J* = 5.8 Hz, 6 H); Calcd m/z: $[M+H]^+$ Calcd for $C_{48}H_{50}N_5O_5$; 776.3806; Found 776.3815.

Example 28: N-((S)-1-(((S)-1-(methoxy(methyl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino)-4-methyl-1-oxopentan-2-yl)-2-methylbenzamide (6a): Fmoc deprotection was

done first, as follows. Fmoc compound **5** (0.675g, 1 mmol, 1equiv.) was taken in 50% solution of *tert*-butylamine in DCM (30mL) and stirred at room temperature for 45 min, and the reaction mixture was concentrated under vacuum. The resulting semisolid residue was washed with pet-ether (3 x 5 mL). The free amine of **1** (0.4g, 0.72 mmol, 1 equiv.) was added to a reaction mixture containing *O*-toluic acid (0.1 g, 0.73 mmol, 1.02 equiv.), HBTU (0.456 g, 1.2 mmol, 1.2 equiv), HOBt (0.135g, 1 mmol, 1 equiv) and *N, N*-diisopropylethylamine (0.347 mL, 2 mmol, 2 equiv.) in DMF (12mL). The solution was stirred at room temperature for overnight. Then, the reaction mixture was diluted with ice cold water (20 mL), and extracted with ethyl acetate (2 x 30 mL). It was successively washed with dilute aqueous citric acid solution, $NaHCO_3$ solution, and brine solution, dried over Na_2SO_4 and concentrated under vacuum., then purified with neutral allumimium oxide packed column chromatography. The mobile phase starting from pet-ether and gradually increasing polarity with dichloromethane and then 3% methanol/DCM afforded **2a** as white solid. **Yield:** (0.34g), 70%; mp: 72-77°C; R_f = 0.45 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{24}_D$ = -2.4°(c = 0.1, MeOH); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.0 Hz, 1 H), 7.44 - 7.35 (m, 1 H), 7.34 (m, 9 H), 7.29 - 7.26 (m, 2 H), 7.12 (d, *J* = 7.9 Hz, 1 H), 7.11-7.10 (m, 7 H), 6.71 - 6.70 (d, *J* = 7.9 Hz, 1 H), 6.55 (s, 1 H), 5.14 – 5.12 (d, *J* = 7.0 Hz, 1 H), 4.78 - 4.76 (m, 1 H), 3.77 (s, 3 H), 3.13 (s, 3 H), 3.01 - 2.99 (m, 2 H), 2.44 (s, 3 H), 1.82 - 1.80 (m, 2 H), 1.62 - 1.60 (m, 1 H), 1.28 - 1.23 (m, 3 H), 1.01 - 0.98 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{41}H_{46}N_5O_4$; 772.3544; Found 772.3522.

Example 29: N-((S)-1-(((S)-1-(methoxy(methyl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino)-4-methyl-1-oxopentan-2-yl)-1H-indole-2-carboxamide(6b): Using 1H-indole-2-carboxylic acid, **6b** was synthesized following the analogous procedure of **2a**. **6b** was obtained as a white solid. Yield: 0.45g, (58 %); mp: 80-85°C; R_f = 0.45 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{24}_D$ = -3.4°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.42 (bs., 1 H), 7.60 (bs., 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 7.30 - 7.22 (m, 14 H), 7.08 (m, 2 H), 7.07 (m, 4 H), 6.89 (s, 1 H), 6.53 (s, 1 H), 5.17 - 5.15(m, 1 H), 4.87- 4.83 (m, 1 H), 3.77 (s, 3 H), 3.14 (s, 3 H), 2.99 - 2.95 (m, 2 H), 1.87 - 1.65 (m, 3 H), 1.26 (m, 1H), 0.97 - 0.74 (m, 6 H); Calcd m/z: $[M+H]^+$ Calcd for $C_{42}H_{45}N_6O_4$; 697.3497; Found 697.3479.

Example 30: 1-hydroxy-N-((S)-1-(((S)-1-(methoxy(methyl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino)-4-methyl-1-oxopentan-2-yl)-2-naphthamide (6c): Using 1-hydroxy-2-naphthoic acid, **6c** was synthesized following the analogous procedure of **2a**. **6c** was obtained as a

white solid. (Note: EDC.HCl was used in place of HBTU). **Yield:** 0.45g, (62%); mp: 80-85°C; R_f = 0.45 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{24}_D$ = 2.80°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 13.89 (bs., 1 H), 8.83 (bs, 1H), 8.35 (bs, 1H), 7.98, (s,1H), 7.72 (bs., 1 H), 7.61 - 7.51 (m, 1 H), 7.40 - 7.38 (m, 9 H), 7.04 (m, 6 H), 6.74 (s, 1 H), 5.19-5.17 (bs., 1 H), 4.94 (t, *J* = 8.5 Hz, 1 H), 3.72 (s, 3 H), 3.15 (d, *J* = 6.0 Hz, 2 H), 3.72 (s, 3 H), 2.05 - 1.02 (m, 1 H), 1.81 - 1.74 (m, 2 H), 0.94 - 0.93 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{44}H_{46}N_5O$, 724.3493 Found, 724.3475.

Example 31: 3-hydroxy-N-((S)-1-(((S)-1-(methoxy (methyl) amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino)-4-methyl-1-oxopentan-2-yl)-2-naphthamide (6d): Using 3-hydroxy-2-naphthoic acid, **6d** was synthesized following the analogous procedure of **2a**. **6d** was obtained as a white solid. (Note: in place of HBTU we used EDC.HCl). **Yield:** 0.4g, (55 %); $[\alpha]^{24}_D$ = -2.43°(c = 0.1, MeOH); mp: 85-90°C; ^{1}H NMR (400MHz, $CDCl_3$) δ 11.74 (bs., 1 H), 9.04 (bs., 1 H), 8.90 (bs., 1 H), 8.00 - 7.95 (m, 2 H), 7.60 (d, *J* = 8.4 Hz, 1 H), 7.39 (d, *J* = 8.4 Hz, 1 H), 7.38 - 7.33 (m, 9 H), 7.06 - 7.04 (dd, *J* = 2.0, 7.4 Hz, 5 H), 6.73 (s, 1 H), 5.17 (bs., 1 H), 4.92 - 4.90 (t, *J* = 8.1 Hz, 1 H), 3.71 - 3.66 (m, 3 H), 3.15 - 3.14 (m, 2 H), 3.010 - 3.06 (m, 3 H), 1.99 (t, *J* = 10.3 Hz, 1 H), 1.78 - 1.74 (m, 2 H), 1.29 - 1.21 (m, 2 H), 0.95 - 0.87 (m, 6 H); Calcd m/z: $[M+H]^+$ Calcd for $C_{44}H_{46}N_5O_5$ Exact Mass: 724.3493 found, 724.3475.

Example 32: N-((S)-1-(((S)-1-(methoxy (methyl) amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino)-4-methyl-1-oxopentan-2-yl) benzo[b]thiophene-2-carboxamide(6e): Using benzo[b] thiophene-2-carboxylic, **6e** was synthesized following the analogous procedure of **2a**. **6e** was obtained as a white solid. **Yield:** 0.454g, (64%); mp: 70-75°C; R*f* = 0.35 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{24}_D$ = -2.50°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.81 - 7.78 (m, 3 H), 7.74 (d, *J* = 7.6 Hz, 1 H), 7.44 (d, *J* = 7.1 Hz, 1 H), 7.40 - 7.38 (m, 2 H), 7.30 - 7.27 (m, 9 H), 7.20 (t, *J* = 7.8 Hz, 1 H), 7.09 - 7.04 (m, 6 H), 6.54 (s, 1 H), 5.11 - 5.9 (d, *J* = 5.5 Hz, 1 H), 4.79 - 4.76 (m, 1 H), 3.76 (s, 3 H), 3.12 (s, 3 H), 2.99 - 2.95 (m, 2 H), 1.81 - 1.76 (m, 2 H), 1.66 - 1.62 (m, 1 H), 0.98 - 0.93 (dd, *J* = 6.1, 15.4 Hz, 6 H); Calcd m/z: $[M+H]^+$ Calcd for $C_{42}H_{43}N_5O_4S$ Exact Mass: 714.3109, Found, 714.3112.

Example 33: (S)-N-((S)-1-(methoxy(methyl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)-2-((S)-2-(6-methoxynaphthalen-2-yl) propanamido)-4-methylpentan amide (6f): Using (S)-2-(6-methoxynaphthalen-2-yl) propanoic acid, **6f** was synthesized following the analogous procedure of

6a. **6f** was obtained as a white solid. **Yield:** 0.55g ,(71%); mp: 96-100°C; R*f* = 0.45 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{24}_{D}$ = -2.4°(c = 0.1, MeOH; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (t, *J* = 7.7 Hz, 3 H), 7.68 (s, 1 H), 7.32 - 7.30 (m, 10 H), 7.10 – 7.09 (m, 9 H), 6.46 (s, 1 H), 6.13-6.11 (bs., 1 H), 5.00 (m, 1 H), 4.50 – 4.49 (m, 3 H), 3.73 - 3.70 (m, 3 H), 2.89 - 2.82 (m, 2 H), 1.61-1.55 (d, *J* = 7.3 Hz, 4 H), 1.37 - 1.33 (s, 4 H), 1.28 (m, 1 H), 0.88 -0.87(d, *J* = 12.9 Hz, 2 H), 0.84 - 0.83 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{47}H_{52}N_5O_5$ Exact Mass: 766.3963 found, 766.3445.

Example 34: (S)-N-((S)-1-(methoxy(methyl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)-4-methyl-2-(2-propylpentanamido) pentanamide (6g): Using 2-propylpentanoic acid, **6g** was synthesized following the analogous procedure of **6a**. **6g** was obtained as a white solid (Note: EDC.HCl was used in place of HBTU). **Yield:** (0.3g), 73%; $[\alpha]^{24}_{D}$ = -97.18°(c = 0.1, MeOH); mp: 70-75°C; R*f* = 0.4 (silica gel TLC, 2% MeOH in DCM); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.35 - 7.34 (m, 9 H), 7.33 - 7.13 (m, 1 H), 7.12 - 7.10 (m, 7 H), 7.29, (bs, 1H), 6.53, (s, 1H), 6.29 (d, *J* = 8.4 Hz, 1 H), 5.09 -5.07, (d, *J* = 7.0 Hz, 1 H), 3.74 (s, 3 H), 3.10 (s, 3 H), 2.96 - 2.94 (d, *J* = 5.6 Hz, 2 H), 2.07 (bs, 1H), 1.82 (m, 1 H), 1.65 (m, 3 H), 1.65 - 1.59 (m, 3 H), 1.26 - 1.21 (m, 3 H), 0.93 - 0.87 (m, 7 H), 0.88 - 0.80 (m, 6 H); Calcd m/z: $[M+H]^+$ Calcd for $C_{41}H_{54}N_5O_4$; 680.4170; Found 680.4139.

Example 35: (S)-2-(2-(2-((2, 6-dichlorophenyl) amino) phenyl) acetamido)-N-((S)-1-(methoxy(methyl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl)propan-2-yl)-4-methylpentanamide (6h): Using 2-(2-((2,6-dichlorophenyl)amino)phenyl)acetic acid, **6h** was synthesized following the analogous procedure of **6a**. **6h** was obtained as a white solid. **Yield:** 0.45g, (54%); mp: 90 - 95°C; R_f = 0.5 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_{D}$=-2.96°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.61 (s, 1 H), 7.33 - 7.30 (m, 13 H), 7.12 - 7.10 (m, 8 H), 7.08 - 7.01 (m, 1 H), 6.96 (t, *J* = 8.1 Hz, 1 H), 6.90 - 6.81 (m, 1 H), 6.67 (d, *J* = 8.4 Hz, 1 H), 6.50 - 6.48 (m, 1 H), 5.04 -5.02 (d, *J* = 7.1 Hz, 1 H), 4.56 - 4.54 (d, *J* = 5.3 Hz, 1 H), 3.73 (s, 3 H), 3.67 (s, 2 H), 3.10 (s, 3 H), 2.89 – 2.88 (d, *J* = 4.9 Hz, 1 H), 1.92 (s, 3 H), 1.66 - 1.59 (m, 2 H), 1.44 (m, 1 H), 1.27 (m, 2 H), 0.90 - 0.83 (m, 7 H); Calcd m/z: $[M+H]^+$ for $C_{47}H_{49}N_6O_4Cl_2$; 831.3187; Found 831.3327.

Example 36: 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl) methyl)-N-((S)-1-(((S)-1-(methoxy (methyl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino)-4-methyl-1-oxopentan-2-yl)-[1,1'-biphenyl]-2-carboxamide (6i): Using 2 4'-((1,7'-dimethyl-2'-propyl-

1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl)methyl)-[1,1'-biphenyl]-2-carboxylic acid, **6i** was synthesized following the analogous procedure of **6a**. **6i** was obtained as a white solid.

Yield: 0.23g (56%); mp: 85-90°C; R_f = 0.50 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{27}_D$=12.96°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.79 (dd, *J* = 2.7, 6.2 Hz, 1 H), 7.56 (d, *J* = 7.3 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.37 - 7.31 (m, 6 H), 7.28 (d, *J* = 1.8 Hz, 7 H), 7.24 - 7.18 (m, 2 H), 7.15 - 7.07 (m, 4 H), 7.07 - 7.01 (m, 5 H), 6.60 - 6.51 (m, 1 H), 6.46 (s, 1 H), 5.45 - 5.36 (m, 2 H), 5.03 (d, *J* = 7.3 Hz, 1 H), 4.59 - 4.45 (m, 1 H), 3.74 (s, 3 H), 3.72 - 3.66 (m, 3 H), 3.07 - 3.01 (m, 3 H), 2.94 - 2.89 (m, 2 H), 2.76 (s, 3 H), 1.94 - 1.79 (m, 3 H), 1.54 (ddd, *J* = 5.2, 8.6, 13.5 Hz, 1 H), 1.48 - 1.34 (m, 1 H), 1.34 - 1.20 (m, 3 H), 1.12 - 0.97 (m, 3 H), 0.97 - 0.83 (m, 3 H), 0.80 - 0.76 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{66}H_{67}N_9O_4$;1050.5389; Found 1050.5416.

Example 37: (S)-2-((5-(dimethylamino)naphthalene)-1-sulfonamido)-N-((S)-1-(methoxy(methyl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl)propan-2-yl)-4-methylpentanamide (6j): The dansyl chloride (269 mg, 1 mmol, 1 equiv.) was dissolved in DMF and cooled at ice temperature then DIPEA (0.521 mL, 3 mmol, 3 equiv.) was added and stirred for 5 min then free amine of compound **3**, (0.633g, 1.14 mmol, 1.2 equiv.) was added and stirred for 5 h at room temperature. The reaction mixture was diluted with cold water and product was extracted with ethyl acetate. (2x20mL) The combined organic layer was subsequently washed with cold water, dilute citric acid, saturated solution of $NaHCO_3$ and brine solution respectively, dried over Na_2SO_4**,** the organic layer was concentrated under vacuum and resultant residue purified by column chromatography, on neutral Al_2O_3 using pet-ether to DCM to 5% methanol as mobile phase to get compound **6j** as white solid. **Yield:** 0.4g (51%); $[\alpha]^{24}_D$=-42.00°(c = 0.1, MeOH); mp: 110-115°C; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.5 Hz, 1 H), 8.46 (d, *J* = 8.8 Hz, 1 H), 8.31 (dd, *J* = 1.1, 7.3 Hz, 1 H), 7.53 (m, 2 H), 7.36 - 7.33 (m, 11 H), 7.16 - 7.12 (m, 8 H), 6.48 (s, 1 H), 5.71 - 5.69 (d, *J* = 7.5 Hz, 1 H), 4.72 - 4.68 (m, 1 H), 3.63 (s, 4 H), 3.06 (s, 3 H), 2.84 (s, 8 H), 1.40 (bs., 2 H), 0.66 (d, *J* = 6.3 Hz, 3 H), 0.49 (d, *J* = 6.0 Hz, 3 H); Calcd m/z: $[M+H]^+$ for $C_{45}H_{51}N_6O_5$; 787.3636; Found 787.3617.

Example 38: (S)-N-((S)-1-(methoxy(methyl)amino)-1-oxo-3-(1-trityl-1H-imidazol-5-yl) propan-2-yl)-4-methyl-2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl) pentanamido) pentanamide (6k): Using 5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl) pentanoic acid (biotin), **6k** was synthesized following the analogous procedure of **6a**. **6k** was obtained as a white solid. **Yield:** 0.46g (59%); mp: 80-85°C; $[\alpha]^{24}_D$=-3.12°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ

7.51 (d, *J* = 8.3 Hz, 1 H), 7.36 - 7.33 (m, 10 H), 7.12 - 7.09 (m, 6 H), 6.76 (bs., 1 H), 6.55 (s, 1 H), 5.96 (bs., 1 H), 5.13 (d, *J* = 6.8 Hz, 1 H), 4.56 (m, 1 H), 4.50 - 4.48 (m, 1 H), 4.31 - 4.28 (m, 1 H), 3.72 (s, 3 H), 3.21 - 3.14 (m, 1 H), 3.11 (s, 3 H), 2.94 - 2.92 (m, 3 H), 2.67 (d, *J* = 12.8 Hz, 1 H), 2.29 - 2.11 (m, 2 H), 1.74 (td, *J* = 7.2, 14.2 Hz, 2 H), 1.66 - 1.60 (m, 4 H), 1.55 - 1.45 (m, 1 H), 1.41 - 1.32 (m, 2 H), 0.88 (d, *J* = 5.9 Hz, 6 H); Calcd m/z: $[M+H]^+$ for $C_{43}H_{53}N_7O_5$; 780.3902; Found 780.3893.

Example 39: 2-methyl-N-((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino) pentan-2-yl) benzamide (7a): The synthetic method of **3a** was adopted to synthesize **7a**. White solid. **Yield:** 0.2g, (73%); mp: 70 - 75°C; R_f = 0.4 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_D$=-2.96°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.57 (d, *J* = 3.5 Hz, 1 H), 8.16 (m, 1 H), 7.43 (t, *J* = 8.4 Hz, 1 H), 7.34 - 7.32 (m, 9 H), 7.20 - 7.13 (m, 1 H), 7.07 - 7.05 (m, 7 H), 6.61 (s, 1 H), 6.28 (m, 1 H), 4.79 - 4.77 (td, *J* = 4.3, 8.5 Hz, 1 H), 4.59 (dd, *J* = 6.6, 11.9 Hz, 1 H), 3.13 - 3.12 (m, 1 H), 2.99 - 2.95 (m, 1 H), 2.42 - 2.40 (d, *J* = 8.4 Hz, 3 H), 1.85 - 1.76 (m, 2 H), 1.70 - 1.54 (m, 2 H), 1.01 - 0.94 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{39}H_{40}N_4O_2$; 613.3173; Found 613.3158.

Example 40: N-((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino) pentan-2-yl)-1H-indole-2-carboxamide(7b): The synthetic method of **3a** was adopted to synthesize **7b.** Light yellow solid; **Yield:** 0.2 g, (73%); mp: 70-75°C; R_f = 0.43 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{24}_D$=5.50°(c = 0.1, MeOH); $[\alpha]^{27}_D$ = -12.80°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.55 (d, *J* = 7.5 Hz, 1 H), 9.46 (m, 1 H), 8.33 (m, 1 H), 7.57 (dd, *J* = 5.5, 7.8 Hz, 1 H), 7.31 - 7.26 (m, 12 H), 7.20 - 7.04 (m, 3 H), 7.07 - 6.85 (m, 6 H), 6.61 - 6.58 (d, *J* = 11.1 Hz, 1 H), 4.88 - 4.84 (m, 1 H), 4.62 - 4.54 (m, 1 H), 3.08 - 2.98 (m, 2 H), 1.86 - 1.69 (m, 1 H), 1.37 - 1.26 (m, 2 H), 0.97 - 0.88 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{40}H_{40}N_5O_3$; 638.3126; Found 638.3099.

Example 41: 1-hydroxy-N-((S)-4 -methyl-1-oxo-1-(((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino) pentan-2-yl)-2-naphthamide (7c): The synthetic method of **3a** was adopted to synthesize **7c**. White solid**. Yield:** 0.2g, (72%); mp: 65-70°C; $[\alpha]^{25}_D$= 36.41°(c = 0.1, MeOH); ^{1}H NMR (400MHz,$CDCl_3$) δ 13.58 (bs, 1 H), 9.55 – 9.53 (d, *J* = 6.8 Hz, 1 H), 8.36 (d, *J* = 8.3 Hz, 1 H), 8.20 (m, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.63 - 7.53 (m, 1 H), 7.53 - 7.47 (m, 1 H), 7.44 (t, *J* = 9.1 Hz, 1 H), 7.30 - 7.27 (m, 11 H), 7.01 - 7.12 (m, 2 H), 7.01 (m, 1 H), 7.00 (m, 6 H), 6.58 (m, 1 H), 4.86 - 4.84 (m, 1 H), 4.63 - 4.62 (m, 1 H), 3.10 (ddd, *J* = 2.9, 5.3, 14.9 Hz, 1 H), 3.09 - 2.98 (m, 1 H), 1.74 - 1.73 (m, 2 H), 1.22 (m, 1H), 1.01 - 0.95 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{42}H_{41}N_4O_4$; 665.3122; Found 638.3094.

Example 42: 3-hydroxy-N-((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino) pentan-2-yl)-2-naphthamide (7d): The synthetic method of **3a** was adopted to synthesize **7d**. White solid; **Yield:** 0.195g (70%); mp: 68-73°C; $[\alpha]^{24}_{D}$ 11.31°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.55 - 9.51(m, 1 H), 8.20 (s, 1 H), 8.11 (d, *J* = 6.9 Hz, 1 H), 7.63 (d, *J* = 8.3 Hz, 1 H), 7.53 (d, *J* = 8.4 Hz, 1 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 7.30 - 7.29 (m, 11 H), 7.26 - 7.18 (m, 2 H), 7.18 - 7.11 (m, 2 H), 7.06 – 7.02 (m, 6 H), 6.58 (m, 1 H), 4.87 (d, *J* = 5.3 Hz, 1 H), 4.63 - 4.62 (d, *J* = 6.9 Hz, 1 H), 3.10 (d, *J* = 5.0 Hz, 1 H), 3.09 - 2.99 (m, 1 H), 1.89 (s, 1 H), 1.80 - 1.26 (m, 3 H), 0.98 (td, *J* = 3.1, 6.1 Hz, 6 H); Calcd m/z: $[M+H]^+$ for $C_{42}H_{41}N_4O_4$; 665.3122; Found 665.3098.

Example 43: N-((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino) pentan-2-yl) benzo[b]thiophene-2-carboxamide(7e): The synthetic method of **3a** was adopted to synthesize **7e**. White solid; **Yield:** 0.22g (79%); mp: 82-87°C; $[\alpha]^{27}_{D}$=-2.99°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.55 – 9.53 (d, *J* = 7.5 Hz, 1 H), 8.29 - 8.28 (m, 1 H), 7.81 - 7.79 (dd, *J* = 2.7, 7.4 Hz, 1 H), 7.46 - 7.35 (m, 2 H), 7.32 - 7.28 (m, 10 H), 7.26 (d, *J* = 6.9 Hz, 1 H), 7.04 (m, 7 H), 7.00 (d, *J* = 8.1 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 6.60 - 6.59 (d, *J* = 3.5 Hz, 1 H), 4.81 - 4.80 (m, 1 H), 4.62 - 4.60 (m, 1 H), 3.13 - 3.08 (m, 1 H), 3.00 - 2.99 (td, *J* = 5.6, 15.0 Hz, 1 H), 1.83 - 1.73 (m, 4 H), 1.29- 1.20 (m, 3 H), 1.00 - 0.94 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{42}H_{41}N_4O_4$; 655.2737; Found 655.2737.

Example 44: (S)-2-((S)-2-(6-methoxynaphthalen-2-yl) propanamido)-4-methyl-N-((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) pentanamide(7f): The synthetic method of **3a** was adopted to synthesize **7f.** White solid; **Yield:** 0.2g (72%); mp: 80-85°C; $[\alpha]^{27}_{D}$=14.04°(c = 0.1, MeOH; ^{1}H NMR (400MHz, $CDCl_3$) δ 9.53 - 9.46 (d, *J* = 2.1 Hz, 1 H), 7.69 (m, 4 H), 7.41 - 7.31 (m, 11 H), 7.10 - 7.08 (m, 8 H), 6.58 - 6.56 (m, 1 H), 5.94 - 5.92 (d, *J* = 6.3 Hz, 1 H), 4.54 - 4.48 (m, 2 H), 3.92 - 3.90 (m, 3 H), 3.74 - 3.71 (m, 1 H), 3.49 - 3.47 (dd, *J* = 5.4, 15.1 Hz, 1 H), 2.89 - 2.86 (m, 2 H), 1.60 - 1.46 (m, 4 H), 1.46 - 1.35 (m, 1 H), 1.26 (s, 1 H), 0.89 - 0.83 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{45}H_{47}N_4O_4$; 707.3592; Found 707.3563.

Example 45: (S)-4-methyl-N-((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)-2-(2-propylpentan amidopentanamide (7g): The synthetic method of **3a** was adopted to synthesize **7g**. White solid; **Yield:** 0.75g (82%); mp: 70-75°C; $[\alpha]^{27}_{D}$=0.96°(c = 0.1, MeOH); mp: 60-65°C; R_f = 0.5

(silica gel TLC, 70% ethyl acetate in pet. ether); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.54 (d, *J* = 2.9 Hz, 1 H), 7.92 - 7.90 (m, 1 H), 7.36 - 7.33 (m, 10 H), 7.11 - 7.08 (m, 6 H), 6.63 (d, *J* = 3.1 Hz, 1 H), 6.07-6.05 (d, *J* = 8.3 Hz, 1 H), 4.62 - 4.54 (m, 2 H), 3.14 - 3.09 (m, 1 H), 2.96 (m, 1 H), 2.10 (m, 1H), 1.65 - 1.58 (m, 5 H), 1.26 - 1.25 (m, 7 H), 0.94 - 0.82 (m, 12 H); Calcd m/z: $[M+H]^+$ for $C_{39}H_{49}N_3O_4$; 621.3799; Found 621.3785.

Example 46: (S)-2-(2-(2-((2,6-dichlorophenyl) amino) phenyl) acetamido)-4-methyl-N-((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) pentanamide (7h): The synthetic method of **4a** was adopted to synthesize **7h**. White solid; **Yield:** 0.15g (53%); mp: 86-90°C; R_f = 0.5 (silica gel TLC, 70% ethyl acetate in pet. ether); $[\alpha]^{27}_D$ = 14.46°(c = 0.1, MeOH); ^{1}H NMR (500MHz, $CDCl_3$) δ 9.47 (s, 1 H), 7.89 (d, *J* = 6.9 Hz, 1 H), 7.59 - 7.44 (m, 1 H), 7.36 - 7.28 (m, 12 H), 7.15 (d, *J* = 7.4 Hz, 1 H), 7.13 - 7.03 (m, 7 H), 6.99 (t, *J* = 8.1 Hz, 1 H), 6.91 - 6.82 (m, 1 H), 6.62 - 6.57 (m, 1 H), 6.46 (d, *J* = 8.0 Hz, 2 H), 4.61 - 4.56 (m, 1 H), 4.53 - 4.52 (d, *J* = 6.4 Hz, 1 H), 3.72 - 3.66 (m, 2 H), 3.02 (dd, *J* = 5.3, 15.0 Hz, 1 H), 2.83 (dd, *J* = 5.0, 15.0 Hz, 1 H), 1.77 - 1.72 (m, 5 H), 1.62 - 1.40 (m, 3 H), 1.26 (bs., 2 H), 0.89 - 0.83 (m, 6 H), Calcd m/z: $[M+H]^+$ for $C_{45}H_{43}N_5O_3Cl_2$; 771.2743; Found 772.2811.

Example 47: 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl) methyl)-N-((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) amino) pentan-2-yl)-[1,1'-biphenyl]-2-carboxamide (7i): The synthetic method of **4a** was adopted to synthesize **7i**. White solid; **Yield:** 0.07g, (73%); mp: 75-80°C; R_f = 0.5 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_D$ = -12.04° (c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.44 - 943 (d, *J* = 4.5 Hz, 1 H), 7.91 (d, *J* = 6.8 Hz, 1 H), 7.80 - 7.67 (m, 1 H), 7.60 (dd, *J* = 7.3, 15.2 Hz, 1 H), 7.49 - 7.40 (m, 3 H), 7.39 - 7.27 (m, 18 H), 7.26 - 7.20 (m, 4 H), 7.16 - 7.01 (m, 12 H), 6.56 (d, *J* = 3.5 Hz, 2 H), 6.12 (s, 1 H), 6.05 (d, *J* = 8.1 Hz, 1 H), 5.43 (s, 3 H), 4.60 - 4.34 (m, 3 H), 3.87 - 3.66 (m, 4 H), 3.47 (s, 1 H), 3.13 - 2.85 (m, 5 H), 2.76 (s, 4 H), 2.09 - 1.96 (m, 4 H), 1.89 (qd, *J* = 7.4, 15.1 Hz, 3 H), 1.33 - 1.20 (m, 4 H), 1.12 - 0.99 (m, 4 H), 0.92 - 0.82 (m, 4 H), 0.76 (q, *J* = 6.2 Hz, 6 H); Calcd m/z: $[M+H]^+$ for $C_{64}H_{63}N_8O_3$; 991.5018; Found 991.4998

Example 48: (S)-2-((5-(dimethylamino) naphthalene)-1-sulfonamido)-4-methyl-N-((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) pentanamide (7j): The synthetic method of **4a** was adopted to synthesize **7j**. White solid; **Yield:** 0.08g (72%); mp: 90-95°C; $[\alpha]^{27}_D$=-37.62°(c = 0.1, MeOH); ^{1}H NMR (400MHz,$CDCl_3$) δ 9.08 (s, 1 H), 8.51 (d, *J* = 8.5 Hz, 1 H), 8.31 (d, *J* = 8.6 Hz, 1 H), 8.20 (d, *J* =

7.3 Hz, 1 H), 7.77 (d, *J* = 6.0 Hz, 1 H), 7.77 (t, *J* = 8.1 Hz, 2 H), 7.45 - 7.39 (m, 2 H), 7.38 - 7.28 (m, 9 H), 7.11 - 7.09 (m, 7 H), 6.57 (s, 1 H), 4.25 (d, *J* = 5.5 Hz, 1 H), 3.72 (bs., 1 H), 2.89 - 2.83 (m, 6 H), 2.82 - 2.66 (m, 2 H), 1.41 - 1.31 (m, 3 H), 0.67 (d, *J* = 5.6 Hz, 3 H), 0.43 (d, *J* = 5.0 Hz, 3 H); Calcd m/z: $[M+H]^+$ for $C_{43}H_{46}N_5O_4S$; 728.3265; Found 728.3251.

Example 49: (S)-4-methyl-N-((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)-2-(5 -((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl) pentanamido) pentanamide (7k): The synthetic method of **4a** was adopted to synthesize **7k**. White solid; **Yield:** 0.3g, (63%); mp: 70-75°C; $[\alpha]^{24}_D$= 17.07°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.53 - 9.49 (m, 1 H), 7.99-7.98 (d, *J* = 6.6 Hz, 1 H), 7.59 (m, 13 H), 7.34-7.33 (s, 3 H), 7.11 - 7.09 (m, 8 H), 6.80 (bs., 1 H), 6.62 - 6.57 (m, 1 H), 6.17 (bs., 1 H), 4.56 - 4.53 (m, 2 H), 4.48 - 4.46 (m, 2 H), 4.30 (d, *J* = 4.1 Hz, 2 H), 3.11 (m, 2 H), 2.87 (d, *J* = 5.9 Hz, 1 H), 2.27 - 2.20 (m, 3 H), 1.66, (d, *J* = 12.6 Hz, 2 H), 1.42 (m, 3 H), 1.29 - 1.22 (m, 8 H), 1.22- 1.21 (m, 3 H), 1.35 - 1.24 (m, 6 H), 1.24 - 1.18 (m, 2 H), 0.91 - 0.87 (m, 9 H), 0.80 (d, *J* = 5.4 Hz, 2 H); Calcd m/z: $[M+H]^+$ for $C_{64}H_{62}N_8O_3$; 721.0713; Found 721.3541.

Example 50: 5-((S)-2-((S)-4-methyl-2-(2-methylbenzamido)pentanamido)-3-oxopropyl)-1H-imidazol-1-ium (8a): The synthetic method of **4a** was adopted to synthesize **8a**. White solid**; Yield :**0.06g (82%); R*f* = 0.2 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{25}_D$ = 12.89°(c = 0.1, MeOH); mp: 70-75°C; ^{1}H NMR (400MHz, CD_3OD) δ 8.78 - 8.73 (bs., 1 H), 7.33 - 7.23 (m, 6 H), 4.67 - 4.66 (dd, *J* = 1.9, 3.4 Hz, 1 H), 4.56 - 4.22 (m, 1 H), 4.47 (m, 1 H), 4.22 (m, 1 H), 3.29 (m, 1 H), 3.14 - 2.94 (m, 1 H), 2.37 - 2.35 (m, 3 H), 1.82 - 1.70 (m, 1 H), 1.70 - 1.60 (m, 1 H), 1.60 - 1.36 (m, 2 H), 1.08 - 0.86 (m, 6 H); Calcd m/z: $[M+H]^+$ for ;$C_{20}H_{27}N_4O_3$; 371.2078; Found 371.2071.

Example 51: 5-((S)-2-((S)-2-(1H-indole-2-carboxamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium (8b): The synthetic method of **4a** was adopted to synthesize **8b**. Light yellow solid; **Yield:** 0.1g (84%); mp: 72-76°C; R*f* = 0.2 (silica gel TLC, 4% MeOH in DCM); $[\alpha]^{24}_D$=-27.0°(c = 0.1, MeOH); ^{1}H NMR (500MHz, CD_3OD) δ 8.92 (s, 1 H), 7. (d, *J* = 7.9 Hz, 1 H), 7.48 - 7.46 (m, 2 H), 7.45 - 7.28 (m, 2 H), 7.24 - 7.11 (m, 3 H), 7.09 (m, 2 H), 6.99 (s, 1 H), 6.52 (s, 1 H), 5.12 (bs., 1 H), 3.78 – 3.69(d, *J* = 4.4 Hz, 1 H), 1.66 - 1.56 (m, 1 H), 1.55 (dd, *J* = 6.6, 13.9 Hz, 1 H), 1.40 (dd, *J* = 6.9, 13.2 Hz, 1 H), 1.11 (bs., 1 H), 1.00 - 0.93 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{21}H_{26}N_5O_3$; 396.2030; Found 396.2016.

Example 52: 5-((S)-2-((S)-2-(1-hydroxy-2-naphthamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium (8c): The synthetic method of **4a** was adopted to synthesize **8c**.

White solid; **Yield:** 0.6g (74%) $[\alpha]^{27}_{D}$=-21.00°(c = 0.1, MeOH); mp: 80-85°C; R_f = 0.2 (silica gel TLC, 4% MeOH in DCM); ^{1}H NMR (400MHz, CD_3OD) δ8.83-8.13 (m, 1H), 7.82 - 7.77 (m, 1 H), 7.77 - 7.72 (m, 3 H), 7.57 - 7.51 (m, 3H), 7.30 - 6.70 (m, 1H), 5.93 - 5.91(m, 1H), 5.79 (m, 1H), 5.20 (m, 1H), 4.67 (s, 2H), 3.40 (m, 2H), 3.90 (m, 2H), 1.84-1.69 (m, 2H), 0.98 - 0.80 (m, 6H); Calcd m/z: $[M+H]^+$ for $C_{23}H_{27}N_4O_4$; 423.2027; Found 423.2013.

Example 53: 5-((S)-2-((S)-2-(3-hydroxy-2-naphthamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium (8d): The synthetic method of **4a** was adopted to synthesize **8d.** Brown solid; **Yield:** 0.13g, (80%); mp: 83-87°C; R*f* = 0.3 (silica gel TLC, 4% MeOH in DCM); $[\alpha]^{25}_{D}$=38.40°(c = 0.1, MeOH); ^{1}H NMR (400MHz, CD_3OD) δ 8.92 - 8.88 (s, 1 H), 8.54 - 8.51 (m, 2 H), 7.97 (d, *J* = 8.5 Hz, 1 H), 7.77 (s, 1 H), 7.59 (bs., 2 H), 7.48 - 7.43 (m, 3 H), 7.32 (s, 2 H), 7.25 (s, 1 H), 7.05 (s, 1 H), 5.73 - 5.71 (d, *J* = 9.0 Hz, 1 H), 5.36 - 5.33 (d, *J* = 11.1 Hz, 1 H), 4.58 (m, 1 H), 4.21-419 (m, 1 H), 3.31-3.15 (s, 2 H), 1.94 - 1.77 (m, 1 H), 1.13 (d, *J* = 6.1 Hz, 2 H), 1.06 – 1.00 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{23}H_{27}N_4O_4$; 423.2027; Found 423.2013.

Example 54: 5-((S)-2-((S)-2-(benzo[b]thiophene-2-carboxamido)-4-methylpentanamido)-3-oxopropyl) -1H-imidazol-1-ium (8e): The synthetic method of **4a** was adopted to synthesize **8e.** White solid. **Yield:** 0.12g, (78%); mp: 70-75C; R_f = 0.25 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{25}_{D}$=32.52°(c = 0.1, MeOH); ^{1}H NMR (400MHz, CD_3OD) δ 8.77 - 8.67 (t, *J* = 1.1 Hz, 1 H), 8.05 (m, 1 H), 7.89 - 7.88 (m, 2 H), 7.45 - 7.41 (m, 2 H), 7.30 (m, 1 H), 4.64-4.55 (m, 2 H), 4.48 (ddd, *J* = 3.9, 7.1, 10.5 Hz, 1 H), 4.19 (m, 2H), 3.31 - 3.29 (m, 1 H), 3.11 - 2.91 (m, 1 H), 1.75 - 1.64 (m, 1 H), 1.62 (m, 2 H), 0.97 - 0.91 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{21}H_{25}N_4O_3$; 413.1642; Found 413.1633.

Example 55: 5-((S)-2-((S)-2-((S)-2- (6-methoxynaphthalen-2-yl) propanamido)-4-methylpentan amido)-3-oxopropyl)-1H-imidazol-1-ium (8f): The synthetic method of **4a** was adopted to synthesize **8f**. White solid.**Yield:** 0.1g, (81%); mp: 93-98C; R_f = 0.2 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{27}_{D}$=10.9°(c = 0.1, MeOH); ^{1}H NMR (400MHz, CD_3OD) δ 8.55 (m, 1 H), 8.06 (m, 1 H), 7.67 - 7.59 (m, 3 H), 7.55 - 7.33 (m, 2 H), 7.09 (m, 1 H), 7.03 - 6.80 (m, 3 H), 4.79 - 4.32 (m, 2 H), 4.15 (m, 1 H), 3.82 - 3.76 (m, 4 H), 3.19 (d, *J* = 7.0 Hz, 1 H), 2.80-2.60 (m,1H), 2.50-2.30 (m, 1H), 3.03 - 2.74 (m, 1

H), 1.46 - 1.39 (m, 6 H), 0.99 - 0.77 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{26}H_{33}N_4O_4$; 424.2493; Found 424.2496.

Example 56: 5-((S)-2-((S)-4-methyl-2-(2-propylpentanamido)pentanamido)-3-oxopropyl)-1H-imidazol-1-ium (8g): The synthetic method of **4a** was adopted to synthesize **8g.** White solid; **Yield:** 0.5g, (63%); mp: 70 – 75C; R_f = 0.2 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{27}_D$=-2.88°(c = 0.1, MeOH); ^{1}H NMR (400MHz, CD_3OD) δ 8.78 - 8.73 (m, 1 H), 7.43-7.30 (m, 1 H), 7.29-7.24 (bs., 1 H), 4.60 - 4.48 (m, 1 H), 4.28 - 4.25 (m, 1 H), 4.20 (m, 1 H), 3.21 - 2.98 (m, 1 H), 2.98 - 2.77 (m, 1 H), 2.30 (tt, *J* = 4.7, 9.5 Hz, 1 H), 1.78 - 1.61 (m, 1 H), 1.61 - 1.43 (m, 4 H), 1.30 - 1.26 (m, 4 H), 0.95 - 0.84 (m, 14 H); Calcd m/z: $[M+H]^+$ for $C_{20}H_{35}N_4O_3$; 379.2704; Found 379.2695.

Example 57: 5-((S)-2-((S)-2-(2-(2-((2, 6-dichlorophenyl) amino) phenyl) acetamido)-4-methylpentan amido)-3-oxopropyl)-1H-imidazol-1-ium (8h): The synthetic method of **4a** was adopted to synthesize **8h**. White solid; **Yield:** 0.16g, (66%); mp: 88-93C; R_f = 0.2 (silica gel TLC, 4% MeOH in DCM); $[\alpha]^{27}_D$= -48.00°(c = 0.1, MeOH); ^{1}H NMR (500MHz, CD_3OD) δ 8.85 - 8.71 (m, 1H), 8.24 (m, 1H), 7.41 (d, *J* = 7.9 Hz, 3 H), 7.39 - 7.19 (m, 4 H), 7.09-7.06 (t, *J* = 7.4 Hz, 2 H), 6.91 (m, 1 H), 6.42 (d, *J* = 7.6 Hz, 1 H), 4.51 (d, *J* = 3.5 Hz, 1 H), 4.37 - 4.30 (m, 1 H), 4.12 (bs., 1 H), 3.74 - 3.73 (m, 2 H), 3.24 - 3.00 (m, 1 H), 2.83 - 2.82 (m, 1 H), 1.65 (bs., 1 H), 1.65 - 1.57 (m, 1 H), 1.46 (d, *J* = 7.9 Hz, 1 H), 1.17 - 0.95 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{26}H_{30}N_5O_3Cl_2$; 530.1711.

Example 58: 5-((S)-2-((S)-2-(4'-((1, 7'-dimethyl-2'-propyl-1H,3'H-[2, 5'-bibenzo[d]imidazol]-3'-yl) methyl)- [1, 1'-biphenyl]-2-carboxamido)-4-methyl pentanamido)-3-oxopropyl)-1H-imidazol-1-ium (8i): The synthetic method of **4a** was adopted to synthesize **8i**. White solid; **Yield:** 0.2g (83%); mp: 75-80C; $[\alpha]^{27}_D$=-2.9°(c = 0.1, MeOH); R_f = 0.5 (silica gel TLC, 4% MeOH in DCM). ^{1}H NMR (500MHz, CD_3OD) δ 8.52 (m 1 H), 8.05 (m, 1H), 7.80 (, *J* = 7.4 Hz, 1 H), 7.79 - 7.76 (m, 2 H), 7.63 - 7.62 (m, 2 H), 7.42 - 7.40 (m, 4 H), 7.32 - 7.30 (m, 3 H), 7.28 - 7.20 (m, 1 H), 7.15 (bs., 1 H), 5.84 - 5.76 (m, 2 H), 4.44 (bs,1H), 3.96 - 3.95 (m, 2 H), 3.64 (s, 1 H), 2.75 (s, 3 H), 1.88 - 1.84 (m, 2 H), 1.33 (bs., 2 H), 1.22 (bs., 1 H), 1.05 – 1.03 (m, 6 H), 0.77 - 0.67 (m, 4 H); Calcd m/z: $[M+H]^+$ for $C_{45}H_{49}N_8O_3$; 749.3922; Found 749.3893.

Example 59: 5-((S)-2-((S)-2-((5-(dimethylamino) naphthalene)-1-sulfonamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium(8j): The synthetic method of **4a** was adopted to synthesize **8j**. Light green solid; **Yield:** 0.12g, (81%); mp: 90-95C; $[\alpha]^{25}_D$ =3.6°(c = 0.1, MeOH); ^{1}H

NMR (400MHz, CD_3OD) δ 8.71 (d, *J* = 4.0 Hz, 1 H), 8.53 (d, *J* = 8.8 Hz, 1 H), 8.51 - 8.32 (m, 1 H), 8.17 - 8.18 (dd, *J* = 1.3, 7.4 Hz, 1 H), 7.57 - 7.52 (m, 2 H), 7.25 - 7.23 (m, 2 H), 4.49 - 4.30 (t, *J* = 4.0 Hz, 1 H), 3.40 - 3.35 (m, 3 H), 3.20 (m, 1H), 2.83 - 2.65 (m, 8 H), 1.24 (bs., 2 H), 1.20 - 1.07 (m, 1 H), 0.85 - 0.83 (m, 3 H), 0.49 - 0.48 (m, 3 H); Calcd m/z: $[M+H]^+$ for $C_{24}H_{32}N_5O_4S$; 486.2170; Found 486.2154.

Example 60: 5-((S)-2-((S)-4-methyl-2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl) pentanamido) pentanamido)-3-oxopropyl)-1H-imidazol-1-ium (8k): The synthetic method of **4a** was adopted to synthesize **8k.** White solid: **Yield:** 0.09g (68%); mp: 70 – 75°C; R_f = 0.3 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{24}_D$ = 40.00°(c = 0.1, MeOH); ^1H NMR (400MHz, CD_3OD) δ 8.77 - 8.72 (d, *J* = 19.5 Hz, 1 H), 7.41 - 7.23 (m, 2 H), 5.06 (d, *J* = 5.4 Hz, 1 H), 4.51 - 4.50 (m, 2 H), 4.29 - 4.24 (m, 2 H), 4.16 - 3.78 (m, 1 H), 3.43 - 3.39 (m, 2 H), 3.19 - 2.91 (m, 2 H), 2.71 (m, 1 H), 2.26 - 2.24 (d, *J* = 12.6 Hz, 1 H), 1.67 - 1.41 (m, 9 H), 1.07 - 0.80 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{22}H_{35}N_6O_4S$; 479.2435; Found 479.2435.

Example 61: (S)-2-((7-chloroquinolin-4-yl) amino)-3-(1H-imidazol-4-yl)-N-methoxy-N-methylpropanamide (11): Using compound **10c**, **11** was synthesized following the analogous procedure of compound **1** as white solid: **Yield:** 0.13g, (57%); mp: 85 – 89C; R_f = 0.2 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{27}_D$ = -17.28°(c = 0.1, MeOH); ^1H NMR (400MHz, $CDCl_3$) δ 8.35 - 8.34 (d, *J* = 5.4 Hz, 1 H), 7.84 – 7.81 (m, 2 H), 7.54 (s, 1 H), 7.28 - 7.26 (dd, *J* = 2.0, 8.9 Hz, 1 H), 6.87 (bs, 1H), 6.76 (s, 2 H), 6.23 - 6.22 (d, *J* = 5.4 Hz, 1 H), 4.90 (bs, 1H), 3.38 (s, 3 H), 3.29 – 2.80 (m, 5 H); Calcd m/z: $[M+H]^+$ for $C_{17}H_{18}N_2O_5Cl$; 360.1222, found 360.1217.

Example 62: (S)-2-((7-chloroquinolin-4-yl) amino)-3-(1H-imidazol-4-yl) propanal (12): The synthetic method of compound **2a** was adopted to synthesize **12**. Yellow solid: **Yield:** 0.16g, (63%); $[\alpha]^{27}_D$=-9.75°(c = 0.1, MeOH); mp: 68-73C; ^1H NMR (400MHz, CD_3OD) δ 8.35 (dd, *J* = 1.9, 6.0 Hz, 1 H), 8.26 - 8.24 (m, 1 H), 8.21 - 8.15 (m, 1 H), 7.75 (m, 1 H), 7.54 (s, 1 H), 7.45 – 7.42 (m, 1 H), 6.80 (s, 1 H), 6.58 - 6.56 (m, 1 H), 4.16 – 4.12 (qd, *J* = 4.1, 8.5 Hz, 1 H), 3.13 (dd, *J* = 3.8, 14.8 Hz, 1 H), 2.98 (td, *J* = 9.0, 14.9 Hz, 1 H); Calcd m/z: $[M+H]^+$ for $C_{15}H_{14}N_4O_1Cl$; 301.0851; Found 301.0855.

Example 63: (S)-2-((7-chloroquinolin-4-yl)amino)-N-((S)-1-(methoxy(methyl) amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl)propan-2-yl)-4-methylpentanamide (13): Using compound **10b, 13** was synthesized following the analogous procedure of **2a**. White solid. **Yield:** 0.51g, (70%); $[\alpha]^{27}_D$=-

2.28°(c = 0.1, MeOH), 80-85C; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.46 - 8.44 (dd, *J* = 5.4, 11.3 Hz, 1 H), 8.06 (bs, 1H), 7.89 - 7.81 (m, 2 H), 7.33 - 7.30 (m, 10 H), 7.01 - 6.99 (m, 5 H), 6.86 (s, 1 H), 6.46 (d, *J* = 5.5 Hz, 2 H), 6.41 (s, 1 H), 5.70 - 5.69 (d, *J* = 6.5 Hz, 1 H), 5.02 – 4.97 (m, 1 H), 4.12 (d, *J* = 2.8 Hz, 1 H), 3.80 - 3.76 (d, *J* = 12.4 Hz, 3 H), 3.14 (s, 1 H), 3.06 (s, 2 H), 2.95 – 3.94 (d, *J* = 5.0 Hz, 1 H), 2.84 - 2.83 (t, *J* = 5.4 Hz, 1 H), 1.94 (dd, *J* = 5.7, 13.7 Hz, 1 H), 1.87 - 1.79 (m, 3 H), 1.27 (m, 1H), 1.00 - 0.99 (d, *J* = 6.3 Hz, 3 H), 0.92 - 0.90 (m, 3 H); Calcd m/z: $[M+H]^+$ for $C_{42}H_{44}N_6O_3Cl$; 715.3158; Found 715.3133.

Example 64: (S)-2-((7-chloroquinolin-4-yl)amino)-4-methyl-N-((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)pentanamide (14): The synthetic method of compound **2a** was adopted to synthesize **14**. White solid; **Yield:** 0.5g, (76%); $[\alpha]^{27}_D$=-0.67°(c = 0.1, MeOH); mp: 70 – 75C; ^{1}H NMR (400MHz, $CDCl_3$) δ 9.52 - 9.31 (dd, 1H) 8.78 - 8.75 (m, 1H), 8.50 - 8.45 (dd, *J* = 5.3, 14.6 Hz, 1 H), 7.85 - 7.83 (m, 2 H), 7.35 - 7.30 (m, 12 H), 7.10 - 7.14 (m, 2H), 6.93 - 6.87 (m, 5 H), 6.45 - 6.44 (m, 1 H), 5.61 (m, 1 H), 4.54 - 4.53 (m, 1 H), 4.15 - 4.14 (m, 1H), 3.04 - 2.92 (m, 2 H), 2.05 – 2.01 (m, 1 H), 1.87 (dd, *J* = 6.3, 11.0 Hz, 2 H), 1.44 - 1.15 (m, 3 H), 1.03 - 0.94 (m, 3 H); Calcd m/z: $[M+H]^+$ for $C_{40}H_{39}N_5O_2Cl$; 656.2787; Found 656.2755.

Example 65: (S)-2-((S)-2-((7-chloroquinolin-4-yl) amino) propanamido)-N-((S)-1-(methoxy (methyl) amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl)-4-methylpentanamide (16): Using compound **10a**, **16** was synthesized following the analogous procedure of **6a**. White solid: **Yield:** 0.645g (82%); R_f = 0.4 (silica gel TLC, 2% MeOH in DCM); $[\alpha]^{27}_D$ = -28.62°(c = 0.1, MeOH); mp: 80 – 85C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 - 8.50 (d, *J* = 5.4 Hz, 1 H), 7.94 (dd, *J* = 1.9, 8.4 Hz, 1 H), 7.78 - 7.76 (dd, *J* = 6.3, 8.9 Hz, 1 H), 7.34 - 7.31 (m, 11 H), 7.30 (d, *J* = 1.1 Hz, 1 H), 7.09 - 7.00 (m, 6 H), 6.53 (d, *J* = 6.5 Hz, 1 H), 6.33 (t, *J* = 5.4 Hz, 1 H), 5.04 (bs., 1 H), 4.59 (d, *J* = 2.3 Hz, 1 H), 4.17 - 4.16 (d, *J* = 6.4 Hz, 1 H), 3.73 - 371 (d, *J* = 6.9 Hz, 3 H), 3.09 - 3.08 (d, *J* = 6.1 Hz, 3 H), 2.96 - 2.91 (m, 2 H), 2.04 (bs, 1 H), 1.61 - 1.59 (m, 6 H), 1.33 - 1.29 (m, 3 H), 0.92 - 0.86 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{45}H_{49}N_7O_4Cl$; 786.3529; Found 786.3526.

Example 66: (S)- 2-((S)-2-((7-chloroquinolin-4-yl) amino) propanamido)-4-methyl-N-((S)-1-oxo-3-(1-trityl-1H-imidazol-4-yl) propan-2-yl) pentanamide (17): The synthetic method of compound **3a** was adopted to synthesize **17**. Light yellow solid; **Yield:** 0.2g, (72%); $[\alpha]^{27}_D$=-2.90°(c = 0.1, MeOH); mp: 80-85C; ^{1}H NMR (500MHz, $CDCl_3$) δ 9.54 - 9.50 (m, 1 H), 8.46 (bs., 1 H), 7.94 (d, *J* = 7.8 Hz, 1

H), 7.75 (dd, *J* = 5.4, 8.6 Hz, 1 H), 7.33 (m, 11 H), 7.18 - 7.07 (m, 6 H), 6.62 (s, 1 H), 6.36 - 6.29 (m, 1 H), 5.87 (m, 1 H), 4.64 - 4.54 (m, 2 H), 4.19 - 4.16 (m, 1 H), 3.09 (bs., 1 H), 2.96-2.93 (dd, *J* = 5.1, 14.6 Hz, 2 H), 1.67 - 1.56 (m, 5H), 1.40 - 1.21 (m, 3 H), 0.92 - 0.80 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{43}H_{44}N_6O_3Cl$ 727.3158, found 727.3157.

Example 67: (S)-2-((7-chloroquinolin-4-yl) amino)-3-(1H-imidazol-4-yl)-N-methoxy-N-methylpropanamide (11): Using compound **10c**, **11** was synthesized following the analogous procedure of compound **1** as white solid: **Yield:** 0.13g, (57%); mp: 85 – 89C; R_f = 0.2 (silica gel TLC, 3% MeOH in DCM); $[\alpha]^{27}_D$ = -17.28°(c = 0.1, MeOH); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.35 - 8.34 (d, *J* = 5.4 Hz, 1 H), 7.84 – 7.81 (m, 2 H), 7.54 (s, 1 H), 7.28 - 7.26 (dd, *J* = 2.0, 8.9 Hz, 1 H), 6.87 (bs, 1H), 6.76 (s, 2 H), 6.23 - 6.22 (d, *J* = 5.4 Hz, 1 H), 4.90 (bs, 1H), 3.38 (s, 3 H), 3.29 – 2.80 (m, 5 H); Calcd m/z: $[M+H]^+$ for $C_{17}H_{18}N_2O_5Cl$; 360.1222, found 360.1217.

Example 68: (S)-2-((7-chloroquinolin-4-yl) amino)-3-(1H-imidazol-4-yl) propanal (12): The synthetic method of compound **2a** was adopted to synthesize **12**. Yellow solid: **Yield:** 0.16g, (63%); $[\alpha]^{27}_D$=-9.75°(c = 0.1, MeOH); mp: 68-73C; ^{1}H NMR (400MHz, CD_3OD) δ 8.35 (dd, *J* = 1.9, 6.0 Hz, 1 H), 8.26 - 8.24 (m, 1 H), 8.21 - 8.15 (m, 1 H), 7.75 (m, 1 H), 7.54 (s, 1 H), 7.45 – 7.42 (m, 1 H), 6.80 (s, 1 H), 6.58 - 6.56 (m, 1 H), 4.16 – 4.12 (qd, *J* = 4.1, 8.5 Hz, 1 H), 3.13 (dd, *J* = 3.8, 14.8 Hz, 1 H), 2.98 (td, *J* = 9.0, 14.9 Hz, 1 H); Calcd m/z: $[M+H]^+$ for $C_{15}H_{14}N_4O_1Cl$; 301.0851; Found 301.0855.

Example 69: 5-((S)-2-((S)-2-((7-chloroquinolin-4-yl) amino)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium (15): The synthetic method of compound **4a** was adopted to synthesize **15**. light yellow solid; **Yield:** 0.35g, (87%); $[\alpha]^{27}_D$=0.67°(c = 0.1, MeOH); mp: 98 -102C; ^{1}H NMR (400MHz, CD_3OD) δ 8.79 - 8.69 (dd, 1 H), 8.55 (m, 1 H), 8.46 (m, 1 H), 7.93 - 7.92 (m, 1 H), 7.88 - 7.70 (m, 1 H), 7.42 - 7.24(m, 4 H), 6.81 - 6.64 (m, 1 H), 4.64 - 4.61 (m, 1 H), 4.57-4.29 (bs., 1 H), 4.03 (t, *J* = 11.2 Hz, 1 H), 2.93-2.91 (d, *J* = 14.6 Hz, 1 H), 2.86 - 2.70 (m, 1 H), 1.76 (m, 1 H), 1.03 – 0.97(m, 2 H), 0.95- 0.91 (m, 6 H); Calcd m/z: $[M+H]^+$ for $C_{21}H_{25}N_5O_2Cl$; 414.1691; Found 414.1678.

Example 70: 5-((S)-2-((S)-2-((S)-2-((7-chloroquinolin-4-yl) amino) propanamido)-4-methylpentan amido)-3-oxopropyl)-1H-imidazol-1-ium (18): The synthetic method of compound **4a** was adopted to synthesize **18**. Light yellow solid; **Yield:** 0.150g, (86%); $[\alpha]^{27}_D$=-12.90°(c = 0.1, MeOH); mp: 90-95C; ^{1}H NMR (400MHz, CD_3OD) δ 8.78 (d, *J* = 7.3 Hz, 1 H), 8.58 - 8.48 (m, 1 H), 8.45 (m, 1 H), 7.93-7.91 (m, 1 H), 7.71 (m, 1 H), 7.53 - 7.34 (m, 1 H), 7.27 - 7.24 (m, 2 H), 6.69 - 6.67 (m, 1 H), 4.61 -

4.53 (m, 2 H), 4.34 - 4.33 (m, 1 H), 4.26 - 4.04 (m, 1 H), 3.11 (m, 1 H), 2.89 (m, 1 H), 1.71 - 1.68 (m, 3 H), 1.65 - 1.35 (m, 3 H), 1.34 - 1.26 (m, 1 H), 1.03 - 0.87 (m, 7 H); Calcd m/z: $[M+H]^+$ for $C_{24}H_{30}N_6O_3Cl$; 485.2062, found 485.2050.

[B] Assay protocol and results

Example 71: Protocol for laboratory culturing and developmental stage synchronization of the human malaria parasite P. falciparum: Asexual blood-stage *P. falciparum* (strain 3D7) parasites were cultured under optimal conditions of 37°C and 5% CO_2. These parasites are adapted to normoxic conditions and so the microaerophilic condition was not required. The culture medium consisted of 2% hematocrit with O+ human erythrocytes in RPMI1640 containing 25 mM HEPES, 50µg/ml Gentamicin sulfate, 2mM GlutaMAX 10 mg/L hypoxanthine, 2g/L sodium bicarbonate (Sigma-Aldrich), and 2.5g/L AlbuMAX II (Thermo Fisher Scientific). Parasites were synchronized using 5% sorbitol (Sigma-Aldrich) for enrichment of ring-stage parasites.[2] For synchronization, *P. falciparum* cultures were collected by centrifugation at 500 g for 5 min at 25°C and the parasitized RBC pellet was re-suspended in 5% sorbitol, followed by incubation at 37°C for 10 min. Following incubation, the cells were pelleted and washed with complete RPMI medium, before placing parasites back into culture flasks at 2% parasitaemia under optimal conditions.

Example 72: Preparation of stock solutions of inhibitor molecules:

Working stocks (1mM) for inhibitor molecules were prepared using cell culture grade DMSO (Sigma Aldrich, USA). Chloroquine and Atovaquone were used as standard positive controls in inhibition assays. These two drugs were dissolved in water and DMSO to make 1µM working stocks.

Example 73: Determining percentage growth inhibition and EC_{50} values for inhibitor compounds against blood-stage malaria parasites:

All the peptide-histidine conjugates (Series 1-3) were screened against *P. falciparum* for both their ability to parasite growth of inhibition and inhibitory potency EC_{50}. The compounds were used at a fixed concentration of 10 μM in the inhibition assays and all assays were carried out in a 96-well plate format under optimal growth conditions. Chloroquine (1μM) was used as a positive control for parasite killing in the assays. Complete RPMI medium was added into the wells of each 96-well plate pre-seeded with inhibitor molecules, followed by the addition of an infected RBCs culture. The final culture volume was 200 µl, the assays were set up in triplicates and the treated cultures were incubated for 60 h under optimal conditions for *P. falciparum* growth. After incubation, the cultures were lysed

with 0.05% triton X and stained with Sybr Green I nucleic acid stain (Invitrogen) to estimate the relative growth of parasites in presence of inhibitor molecule.[3] Fluorescence scan readings were obtained using the GloMax plate reader (Promega). Data were processed using Microsoft Excel to determine the percentage growth inhibition for the inhibitors tested and EC_{50} value was determined for those found to have >80% inhibition of growth at 10 μM. For determining the EC_{50}value a two-fold dilution series of the inhibitor starting at 10 μM as the highest concentration and ending at sub-nanomolar concentration was used. The EC_{50}value of the compounds of present invention is given in the table below.

Table 1: Inhibition of *p. falciparum* 3D7 (EC_{50}) growth *in vitro*

The (±) values indicate standard deviation of replicate samples (n-3).		
S.No.	Compound No.	EC_{50} (µM)
1	4a	8.19 ± 1.132
2	4b	6.74 ±0.919
3	4c	5.78 ± 1.654
4	4d	7.92 ± 0.384
5	4e	3.92 ± 1.762
6	4f	>10
7	4g	2.11 ± 0.035
8	4h	0.44 ± 0.039
9	8a	>10
10	8b	>10
11	8c	7.8 ± 0.22
12	8d	7.4 ±0.98
13	8e	0.432 ± 0.22
14	8f	8.7 ± 0.88
15	8g	0.018 ± 0.001
16	8h	0.069 ± 0.001
17	8i	2.43 ±1.365
19	8j	>10
20	8k	0.447 ± 0.2
21	12	0.1 ± 0.035
22	15	0.02 ± 0.002
23	18	0.31 ± 0.057
24	Chloroquine	0.018±0.003

Example 74: Phenotypic studies: Late ring stage parasites (6-10 hours after 5% sorbitol synchronization) were treated with 25 µM of compounds E64, 8e, 8g and 8j and incubated for 24 h and

36 h from the time of synchronization. At these time points, thin smears of the parasite culture were made on glass slides, stained with Giemsa stain and visualized by light microscopy using 100X oil immersion objective.

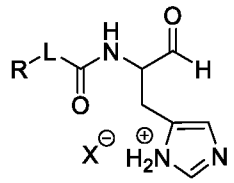
The falcipains are involved in hemoglobin breakdown. This was tested using the cysteine protease inhibitor E64 as a reference inhibitor (refer, figure 4). It was observed that compound 8g, and its biotinylated version 8j showed specific morphological changes in the food vacuole consistent with inhibition of hemoglobin digestion. Thus, 8g is a potent novel inhibitor of parasite falcipain-2/3 proteases capable of disrupting the food vacuole function and arresting parasite growth.

ADVANTAGES OF THE INVENTION

- Compounds can be claimed to be active in any parasite that uses cysteine protease, enzymes specifically found in falciparum
- Recently, malaria treatment failures have been reported for ACTs. Thus, aldehyde-based scaffolds might be useful against resistant strain.
- Modified chloroquine compounds might be able to access the target site, which is the food vacuole of the parasites.

We Claim:

1. A histidinal peptide conjugate compound of formula (I) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate thereof of formula I, represented by:



Formula (I)

wherein

L is direct bond either present or absent, wherein L is selected from $CH(R^1)$, $(CH(R^1))nNR^4CHR^5$, $(CH(R^1))nCONR^2CHR^3$, $(CH(R^1))nSO_2NR^2CHR^3$, or $(CH(R^1))nNR^4CHR^5CONR^6CHR^7$,

wherein n is 0 or 1;

R is aryl, heterocyclyl, alkyl, NH-aryl, SO_2-aryl, or aryl-heterocyclyl, wherein the aryl, heterocyclyl, alkyl is substituted or unsubstituted;

R^1 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^2 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^3 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^4 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

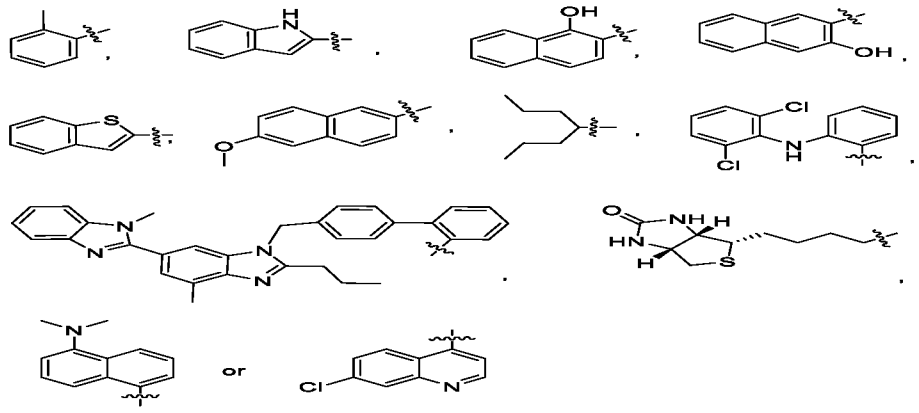
R^5 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^6 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted; and

R^7 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted.

X is CF_3COO^-, or Cl^-.

2. The histidinal peptide conjugate compound of formula (I) as claimed in claim 1, wherein R is selected from:



3. The histidinal peptide conjugate compound of formula (I) as claimed in claim 1, wherein the compound is selected from the group consisting of:

i. (S)-5-(2-(2-methylbenzamido)-3-oxopropyl)-1H-imidazol-1-ium **(4a);**

ii. (S)-5-(2-(1-hydroxy-2-naphthamido)-3-oxopropyl)-1H-imidazol-1-ium **(4b);**

iii. (S)-5-(2-(3-hydroxy-2-naphthamido)-3-oxopropyl)-1H-imidazol-1-ium **(4c);**

iv. (S)-5-(2-(benzo[b]thiophene-2-carboxamido)-3-oxopropyl)-1H-imidazol-1-ium **(4d);**

v. 5-((S)-2-((S)-2-(6-methoxynaphthalen-2-yl) propanamido)-3-oxopropyl)-1H-imidazol-1-ium **(4e);**

vi. (S)-5-(3-oxo-2-(2-propylpentanamido) propyl)-1H-imidazol-1-ium **(4f);**

vii. (S)-5-(2-(2-(2-((2, 6-dichlorophenyl) amino) phenyl) acetamido)-3-oxopropyl)-1H-imidazol-1-ium **(4g);**

viii. (S)-5-(2-(4'-((1, 7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d] imidazol]-3'-yl) methyl)-[1, 1'-biphenyl]- 2-carboxamido)-3-oxopropyl)-1H-imidazol-1-ium **(4h);**

ix. 5-((S)-2-((S)-4-methyl-2-(2-methylbenzamido) pentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8a);**

x. 5-((S)-2-((S)-2-(1H-indole-2-carboxamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8b);**

xi. 5-((S)-2-((S)-2-(1-hydroxy-2-naphthamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8c);**

xii. 5-((S)-2-((S)-2-(3-hydroxy-2-naphthamido)-4-methylpentanamido)-3-oxopropyl)- 1H-imidazol-1-ium **(8d);**

xiii. 5-((S)-2-((S)-2-(benzo[b]thiophene-2-carboxamido)-4-methylpentanamido)-3-oxopropyl) -1H-imidazol-1-ium **(8e);**

xiv. 5-((S)-2-((S)-2-((S)-2- (6-methoxynaphthalen-2-yl) propanamido)-4-methylpentan amido)-3-oxopropyl)-1H-imidazol-1-ium **(8f);**

xv. 5-((S)-2-((S)-4-methyl-2-(2-propylpentanamido) pentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8g);**

xvi. 5-((S)-2-((S)-2-(2-(2-((2, 6-dichlorophenyl) amino) phenyl) acetamido)-4-methylpentan amido)-3-oxopropyl)-1H-imidazol-1-ium **(8h);**

xvii. 5-((S)-2-((S)-2-(4'-((1, 7'-dimethyl-2'-propyl-1H,3'H-[2, 5'-bibenzo[d]imidazol]-3'-yl) methyl)-[1, 1'-biphenyl]-2-carboxamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8i);**

xviii. 5-((S)-2-((S)-2-((5-(dimethylamino) naphthalene)-1-sulfonamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8j);**

xix. 5-((S)-2-((S)-4-methyl-2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl) pentanamido) pentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8k);**

xx. (S)-2-((7-chloroquinolin-4-yl) amino)-3-(1H-imidazol-5-yl) propanal **(12)**;

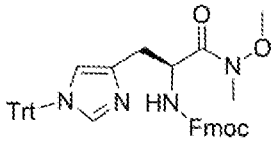
xxi. 5-((S)-2-((S)-2-((7-chloroquinolin-4-yl) amino)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(15);** and

xxii. 5-((S)-2-((S)-2-((S)-2-((7-chloroquinolin-4-yl)amino)propanamido)-4-methylpentan amido)-3-oxopropyl)-1H-imidazol-1-ium **(18).**

4. The histidinal peptide conjugate compound of formula (I) as claimed in claim 1, wherein the pharmaceutically acceptable salt form of the compound is selected from trifluoroacetate salt or chloride salt.

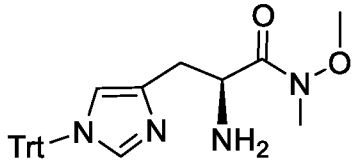
5. A process for the preparation of histidinal peptide conjugate compounds of formula (I) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate thereof as claimed in claim 1, wherein the process comprising the steps of:

a) coupling N^{α}-(((9H-fluoren-9-yl) methoxy) carbonyl)-N^{τ}-trityl-L-histidine with aminating agent or base in the presence of coupling reagent(s) in solvent to obtain precursor **1**



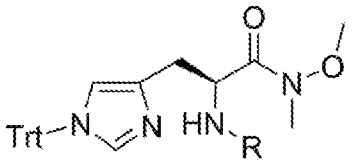
Precursor 1;

b) deprotecting Fmoc of precursor **1** of step a) by treating the precursor 1 in presence of *tert*-butylamine in a solvent at temperature in the range of 25-35 °C for time period in the range of 3 to 5 hrs to obtain an intermediate



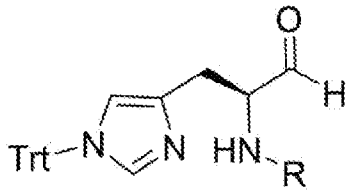
Intermediate;

c) coupling the intermediate obtained in step (b) with R-carboxylic acid in the presence of coupling reagent(s) in solvent to furnish compound selected from formula **2a-h**



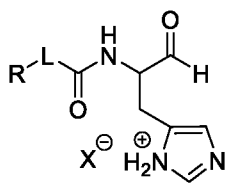
Formula **2a-h**

d) reducing the compound obtained in step (c) using lithium aluminium hydride ($LiAlH_4$) in solvent at temperature in the range of 0 to -20 °C for time period of 45 to 120 minutes to obtain the compound selected from Formula **3a-h**



Formula **3a-h;**

e) deprotecting compound obtained in step (d) using salt precursor trifluoroacetic acid (TFA) in solvent at temperature in the range of 25 to 40°C for the time period in the range of 1 to 2 hours to obtain the histidinal peptide conjugate compound of formula (I) with salt form selected from compounds **4a-h;**.



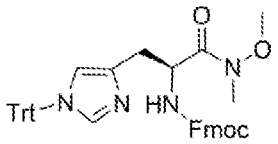
Formula I

wherein X is trifluoroacetate salt, and HCl salt, and R is the same as defined in claim 1, and wherein the compounds **4a-h** recite X as trifluoroacetate salt form.

6. The process as claimed in claim 5, wherein said R-carboxylic acid (**1a-h**) is selected from 2-methylbenzoic acid (**a**), 1-hydroxy-2-naphthoic acid (**b**), 3-hydroxy-2-naphthoic acid (**c**), benzo[b]thiophene-2-carboxylic acid (**d**), (S)-2-(6-methoxynaphthalen-2-yl) propanoic acid (**e**), 2-propylpentanoic acid (**f**), 2-(2-((2,6-dichlorophenyl) amino) phenyl) acetic acid (**g**), and 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl) methyl)-[1,1'-biphenyl]-2-carboxylic acid (**h**).

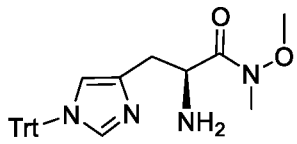
7. A process for the preparation of peptide-histidinal conjugate compounds of formula (I) as claimed in claim 1, wherein the process comprising the steps of:

(i) coupling N^{α}-(((9H-fluoren-9-yl) methoxy) carbonyl)-N^{τ}-trityl-L-histidine with aminating agent or base in the presence of coupling reagent(s) in solvent to obtain precursor **1**



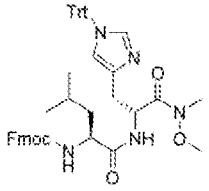
Precursor 1;

(ii) deprotecting **precursor 1** by treating the precursor 1 in presence of *tert*-butylamine in a solvent at temperature in the range of 25-35 °C for time period in the range of 3 to 5 hrs to obtain an intermediate



Intermediate;

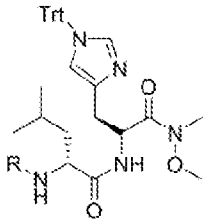
(iii)coupling Fmoc-Leu-OH with the **precursor 1** as obtained in step (i) in the presence of coupling reagent(s) in solvent to obtain intermediate **5**



intermediate **5;**

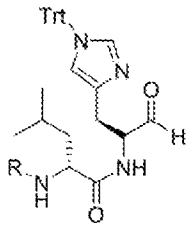
(iv) deprotecting Fmoc of the intermediate **5** of step (ii) by treating the intermediate **5** in presence of *tert*-butylamine in a solvent at temperature in the range of 25-35 °C for time period in the range of 3 to 5 hrs to obtain an intermediate;

(v) coupling the intermediate obtained in step (iii) with R-carboxylic acid in the presence of coupling reagent(s) in solvent to furnish compound selected from compounds of formula **6a-k**;



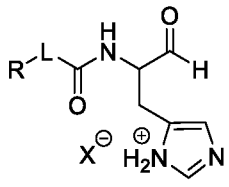
Formula **6a-k**

(vi) reducing the compound obtained in step (iv) using lithium aluminium hydride ($LiAlH_4$) in solvent at 0 to -20°C to obtain the compound selected from compounds of formula 7a-k



Formula **7a-k**

(vii) deprotecting compound obtained in step (v) using salt precursor TFA in solvent at temperature in the range of 25 to 40°C for the time period in the range of 2 to 3 hours to obtain the histidinal peptide conjugate compound of formula (I) with trifluoroacetate salt form selected from compounds **8a-k;**



Formula I

wherein X is trifluoroacetate salt and HCl salt, and R is the same as defined in claim 1, and wherein the compounds **8a-k** recite X as trifluoroacetate salt form.

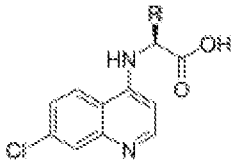
8. The process as claimed in claim 7, wherein said R-carboxylic acids are selected from (**a-k**) 2-methylbenzoic acid (**a**), 1H-indole-2-carboxylic acid (**b**), 1-hydroxy-2-naphthoic acid (**c**), 3-hydroxy-2-naphthoic acid (**d**), benzo[b]thiophene-2-carboxylic acid (**e**), (S)-2-(6-methoxynaphthalen-2-yl) propanoic acid (**f**), 2-propylpentanoic acid (**g**), 2-(2-((2,6-dichlorophenyl) amino) phenyl) acetic acid (**h**), 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl) methyl)-[1,1'-biphenyl]-2-carboxylic acid (**i**), 5-(dimethylamino) naphthalene-1-sulfonic acid (**j**), and 5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl) pentanoic acid (**k**).

9. A process for the preparation of peptide-histidinal conjugate compounds of formula (I) as claimed in claim 1, wherein the process comprising the steps of:

(i) reacting 4, 7-dichloroquinoline **9** with the amino acids, at temperature in the range of 140 to 150°C for the time period of 1-6h to obtain compounds **10 a-c**

wherein the amino acids are selected from **a-c** L-alanine (**a**), L-leucine (**b**) and L-histidine (**c**).

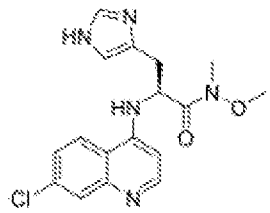
(ii) coupling the compound **10c** with *N, O*-dimethylhydroxylamine to obtain compound **11,**



a, R = L-His; b, R = L-Leu; c, R = L-Ala

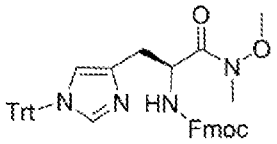
10c

compound 10 (a to c) wherein ;

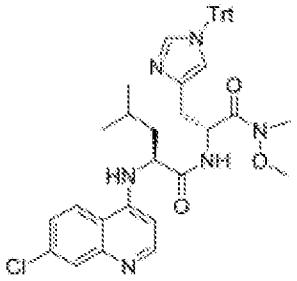


compound 11;

(iii) reacting compound **10b** with precursor **1,** wherein the precursor **1** is represented by

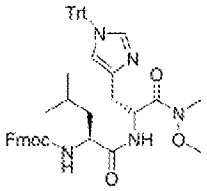


in presence of coupling reagent(s) to afford compound **13,**

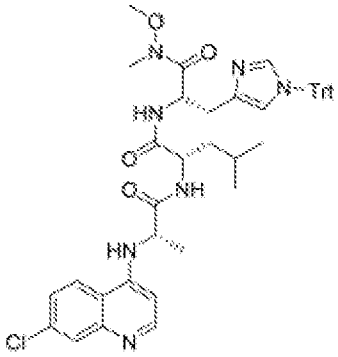


13

(iv)reacting compound **10a** with intermediate **5** wherein intermediate **5** is represented by

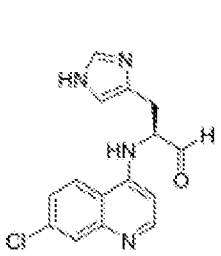
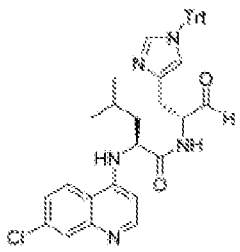
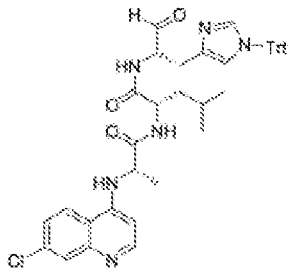


in presence of coupling reagent(s) to afford compound **16**



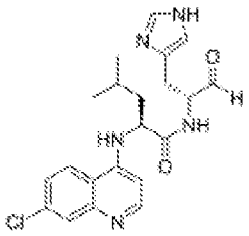
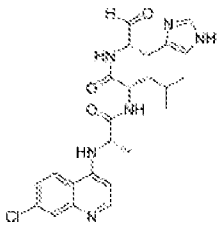
16

(v)deducing the compounds obtained in step (ii), (iii), (iv) using lithium aluminium hydride ($LiAlH_4$) in dry THF at -20°C to obtain the compounds **12, 14, 17**

12 **14** **17**

(vi) deprotecting the compounds 12, 14 or 17 obtained in step (v) using trifluororacetic acid in solvent at temperature in the range of 25 to 40°C for the time period in the range of 2 to 3 hours to produce histidinal-based trifluoroacetate salt compounds **15** and **18**

15 and **18**

10. The process as claimed in claim 5, 7 or 9, wherein the coupling agent used in step a) is selected from HBTU, HOBt and EDC·HCl or mixtures thereof.

11. The process as claimed in claim 5, 7 or 9, wherein the aminating agent is selected from DIPEA, DMF, and N, O-dimethyl hydroxylamine. HCl.

12. The process as claimed in claim 5, 7 or 9, wherein the precursor salt is selected from trifluororacetic acid and 4M HCl in 1,4-Dioxane.

13. The process as claimed in claim 5, 7 or 9, wherein the solvent is selected from polar or non-polar solvent, and protic or aprotic solvent.

14. The process as claimed in claim 5, 7 or 9, wherein the base is selected from organic base and inorganic base.

15. The process as claimed in claim 13, wherein the solvent is selected from DMF, THF, lower (C1-C5) alcohol, nitrile, ketone, halogenated hydrocarbon, TFA or combinations thereof;

16. The process as claimed in claim 14, wherein the wherein the organic base is selected from ethylamine, triethylamine, DIPEA, and pyridine; and wherein the inorganic base is selected from sodium hydroxide, alkali or alkaline earth metal carbonate and bicarbonate or combination thereof.

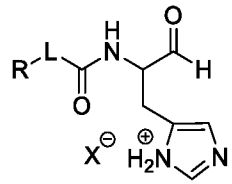
17. A pharmaceutical composition comprising the compound of formula I as claimed in claim 1 and a pharmaceutically acceptable excipient(s).

18. A method of treating malaria wherein, the method comprising administering therapeutically effective amount of the compound of Formula I as claimed in claim 1 or the pharmaceutical composition as claimed in claim 17 to reduce the malarial infection.

19. A method of inhibition of malaria cysteine proteases by contacting plasmodium with the compound of formula I as claimed in claim 1 or the pharmaceutical composition as claimed in claim 17.

AMENDED CLAIMS
received by the International Bureau on 22 May 2024 (22.05.2024)

1. A histidinal peptide conjugate compound of formula (I) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate thereof of formula I, represented by:



Formula (I)

wherein

L is either absent or selected from $CH(R^1)$, $(CH(R^1))nNR^4CHR^5$, $(CH(R^1))nCONR^2CHR^3$, $(CH(R^1))nSO_2NR^2CHR^3$, and $(CH(R^1))nNR^4CHR^5CONR^6CHR^7$,

wherein n is 0 or 1;

R is aryl, heterocyclyl, alkyl, NH-aryl, SO_2-aryl, or aryl-heterocyclyl, wherein the aryl, heterocyclyl, alkyl is substituted or unsubstituted;

R^1 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^2 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^3 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^4 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

R^5 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted;

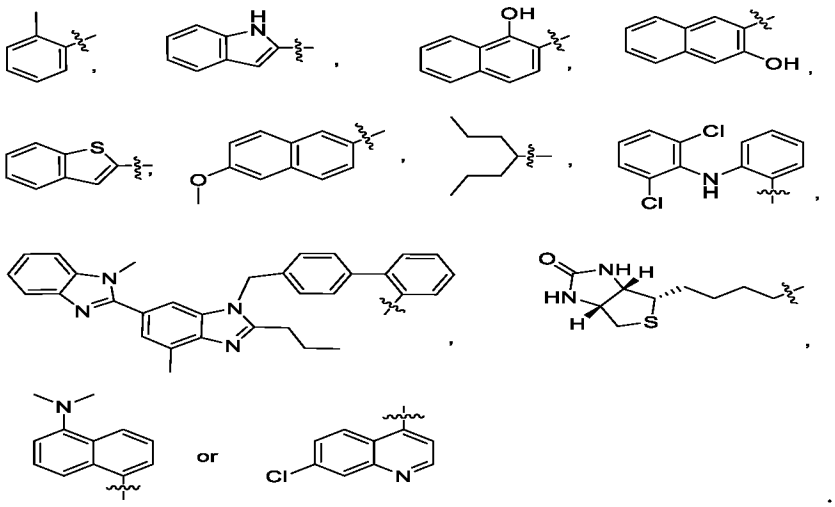
R^6 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted; and

R^7 is hydrogen, alkyl, or aryl; wherein the alkyl, aryl is substituted or unsubstituted.

X is CF_3COO^-, or Cl^-.

2. The histidinal peptide conjugate compound of formula (I) as claimed in claim 1, wherein R is selected from:

AMENDED SHEET (ARTICLE 19)



3. The histidinal peptide conjugate compound of formula (I) as claimed in claim 1, wherein the compound is selected from the group consisting of:

i. (S)-5-(2-(2-methylbenzamido)-3-oxopropyl)-1H-imidazol-1-ium **(4a);**

ii. (S)-5-(2-(1-hydroxy-2-naphthamido)-3-oxopropyl)-1H-imidazol-1-ium **(4b);**

iii. (S)-5-(2-(3-hydroxy-2-naphthamido)-3-oxopropyl)-1H-imidazol-1-ium **(4c);**

iv. (S)-5-(2-(benzo[b]thiophene-2-carboxamido)-3-oxopropyl)-1H-imidazol-1-ium **(4d);**

v. 5-((S)-2-((S)-2-(6-methoxynaphthalen-2-yl) propanamido)-3-oxopropyl)-1H-imidazol-1-ium **(4e);**

vi. (S)-5-(3-oxo-2-(2-propylpentanamido) propyl)-1H-imidazol-1-ium **(4f);**

vii. (S)-5-(2-(2-(2-((2, 6-dichlorophenyl) amino) phenyl) acetamido)-3-oxopropyl)-1H-imidazol-1-ium **(4g);**

viii. (S)-5-(2-(4'-((1, 7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d] imidazol]-3'-yl) methyl)-[1, 1'-biphenyl]- 2-carboxamido)-3-oxopropyl)-1H-imidazol-1-ium **(4h);**

ix. 5-((S)-2-((S)-4-methyl-2-(2-methylbenzamido) pentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8a);**

x. 5-((S)-2-((S)-2-(1H-indole-2-carboxamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8b);**

xi. 5-((S)-2-((S)-2-(1-hydroxy-2-naphthamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8c);**

xii. 5-((S)-2-((S)-2-(3-hydroxy-2-naphthamido)-4-methylpentanamido)-3-oxopropyl)- 1H-imidazol-1-ium **(8d);**

xiii. 5-((S)-2-((S)-2-(benzo[b]thiophene-2-carboxamido)-4-methylpentanamido)-3-oxopropyl) -1H-imidazol-1-ium **(8e);**

xiv. 5-((S)-2-((S)-2-((S)-2- (6-methoxynaphthalen-2-yl) propanamido)-4-methylpentan amido)-3-oxopropyl)-1H-imidazol-1-ium **(8f);**

xv. 5-((S)-2-((S)-4-methyl-2-(2-propylpentanamido) pentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8g);**

xvi. 5-((S)-2-((S)-2-(2-(2-((2, 6-dichlorophenyl) amino) phenyl) acetamido)-4-methylpentan amido)-3-oxopropyl)-1H-imidazol-1-ium **(8h);**

xvii. 5-((S)-2-((S)-2-(4'-((1, 7'-dimethyl-2'-propyl-1H,3'H-[2, 5'-bibenzo[d]imidazol]-3'-yl) methyl)-[1, 1'-biphenyl]-2-carboxamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8i);**

xviii. 5-((S)-2-((S)-2-((5-(dimethylamino) naphthalene)-1-sulfonamido)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8j);**

xix. 5-((S)-2-((S)-4-methyl-2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl) pentanamido) pentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(8k);**

xx. (S)-2-((7-chloroquinolin-4-yl) amino)-3-(1H-imidazol-5-yl) propanal **(12)**;

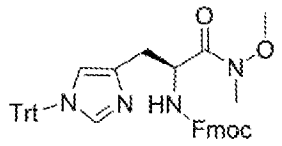
xxi. 5-((S)-2-((S)-2-((7-chloroquinolin-4-yl) amino)-4-methylpentanamido)-3-oxopropyl)-1H-imidazol-1-ium **(15);** and

xxii. 5-((S)-2-((S)-2-((S)-2-((7-chloroquinolin-4-yl)amino)propanamido)-4-methylpentan amido)-3-oxopropyl)-1H-imidazol-1-ium **(18).**

4. The histidinal peptide conjugate compound of formula (I) as claimed in claim 1, wherein the pharmaceutically acceptable salt form of the compound is selected from trifluoroacetate salt or chloride salt.

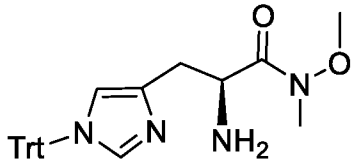
5. A process for the preparation of histidinal peptide conjugate compounds of formula (I) or a stereoisomer, a tautomer, a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate thereof as claimed in claim 1, wherein the process comprising the steps of:

a) coupling N^{α}-(((9H-fluoren-9-yl) methoxy) carbonyl)-N^{τ}-trityl-L-histidine with aminating agent or base in the presence of coupling reagent(s) in solvent to obtain precursor **1**



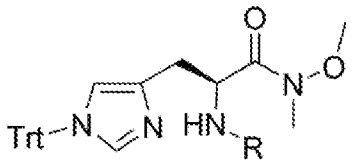
Precursor 1;

b) deprotecting Fmoc of precursor **1** of step a) by treating the precursor 1 in presence of *tert*-butylamine in a solvent at temperature in the range of 25-35 ºC for time period in the range of 3 to 5 hrs to obtain an intermediate



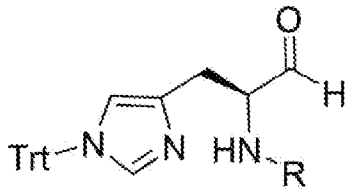
Intermediate;

c) coupling the intermediate obtained in step (b) with R-carboxylic acid in the presence of coupling reagent(s) in solvent to furnish compound selected from formula **2a-h**



Formula **2a-h**

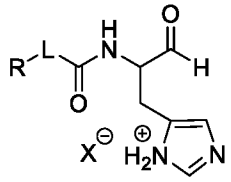
d) reducing the compound obtained in step (c) using lithium aluminium hydride ($LiAlH_4$) in solvent at temperature in the range of 0 to -20 °C for time period of 45 to 120 minutes to obtain the compound selected from Formula **3a-h**



Formula **3a-h;**

e) deprotecting compound obtained in step (d) using salt precursor trifluoroacetic acid (TFA) in solvent at temperature in the range of 25 to 40ºC for the time period in the range of 1 to 2 hours

to obtain the histidinal peptide conjugate compound of formula (I) with salt form selected from compounds **4a-h;**.



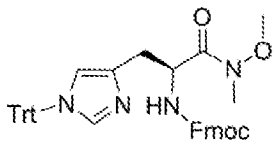
Formula I

wherein X is trifluoroacetate salt, and HCl salt, and R is the same as defined in claim 1, and wherein the compounds **4a-h** recite X as trifluoroacetate salt form**.**

6. The process as claimed in claim 5, wherein said R-carboxylic acid (**1a-h**) is selected from 2-methylbenzoic acid (**a**), 1-hydroxy-2-naphthoic acid (**b**), 3-hydroxy-2-naphthoic acid (**c**), benzo[b]thiophene-2-carboxylic acid (**d**), (S)-2-(6-methoxynaphthalen-2-yl) propanoic acid (**e**), 2-propylpentanoic acid (**f**), 2-(2-((2,6-dichlorophenyl) amino) phenyl) acetic acid (**g**), and 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl) methyl)-[1,1'-biphenyl]-2-carboxylic acid (**h**).

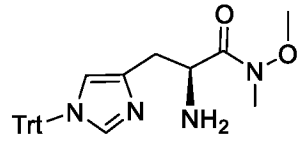
7. A process for the preparation of peptide-histidinal conjugate compounds of formula (I) as claimed in claim 1, wherein the process comprising the steps of:

(i) coupling N^{α}-(((9H-fluoren-9-yl) methoxy) carbonyl)-N^{τ}-trityl-L-histidine with aminating agent or base in the presence of coupling reagent(s) in solvent to obtain precursor **1**



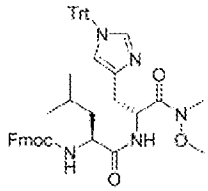
Precursor 1;

(ii) deprotecting **precursor 1** by treating the precursor 1 in presence of *tert*-butylamine in a solvent at temperature in the range of 25-35 ℃ for time period in the range of 3 to 5 hrs to obtain an intermediate



Intermediate;

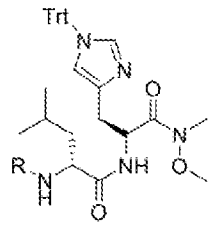
(iii)coupling Fmoc-Leu-OH with the **precursor 1** as obtained in step (i) in the presence of coupling reagent(s) in solvent to obtain intermediate **5**



intermediate **5;**

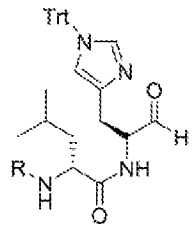
(iv)deprotecting Fmoc of the intermediate **5** of step (ii) by treating the intermediate **5** in presence of *tert*-butylamine in a solvent at temperature in the range of 25-35 ℃ for time period in the range of 3 to 5 hrs to obtain an intermediate;

(v) coupling the intermediate obtained in step (iii) with R-carboxylic acid in the presence of coupling reagent(s) in solvent to furnish compound selected from compounds of formula **6a-k**;



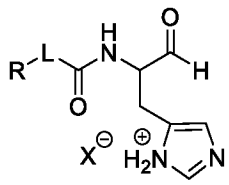
Formula **6a-k**

(vi)reducing the compound obtained in step (iv) using lithium aluminium hydride ($LiAlH_4$) in solvent at 0 to -20°C to obtain the compound selected from compounds of formula 7a-k



Formula **7a-k**

(vii) deprotecting compound obtained in step (v) using salt precursor TFA in solvent at temperature in the range of 25 to 40°C for the time period in the range of 2 to 3 hours to obtain the histidinal peptide conjugate compound of formula (I) with trifluoroacetate salt form selected from compounds **8a-k;**



Formula I

wherein X is trifluoroacetate salt and HCl salt, and R is the same as defined in claim 1, and wherein the compounds **8a-k** recite X as trifluoroacetate salt form.

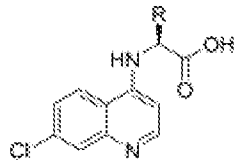
8. The process as claimed in claim 7, wherein said R-carboxylic acids are selected from (**a-k**) 2-methylbenzoic acid (**a**), 1H-indole-2-carboxylic acid (**b**), 1-hydroxy-2-naphthoic acid (**c**), 3-hydroxy-2-naphthoic acid (**d**), benzo[b]thiophene-2-carboxylic acid (**e**), (S)-2-(6-methoxynaphthalen-2-yl) propanoic acid (**f**), 2-propylpentanoic acid (**g**), 2-(2-((2,6-dichlorophenyl) amino) phenyl) acetic acid (**h**), 4'-((1,7'-dimethyl-2'-propyl-1H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl) methyl)-[1,1'-biphenyl]-2-carboxylic acid (**i**), 5-(dimethylamino) naphthalene-1-sulfonic acid (**j**), and 5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl) pentanoic acid (**k**).

9. A process for the preparation of peptide-histidinal conjugate compounds of formula (I) as claimed in claim 1, wherein the process comprising the steps of:

(i) reacting 4, 7-dichloroquinoline **9** with the amino acids, at temperature in the range of 140 to 150°C for the time period of 1-6h to obtain compounds **10 a-c**

wherein the amino acids are selected from **a-c** L-alanine (**a**), L-leucine (**b**) and L-histidine (**c**).

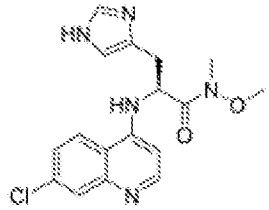
(ii) coupling the compound **10c** with *N, O*-dimethylhydroxylamine to obtain compound **11,**



a. R = L-His; b. R = L-Leu; c. R = L-Ala

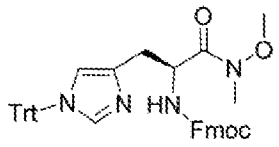
10c

compound 10 (a to c) wherein ;

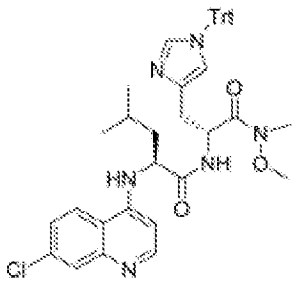


compound 11;

(iii) reacting compound **10b** with precursor **1,** wherein the precursor **1** is represented by

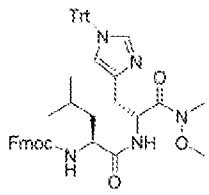


in presence of coupling reagent(s) to afford compound **13,**

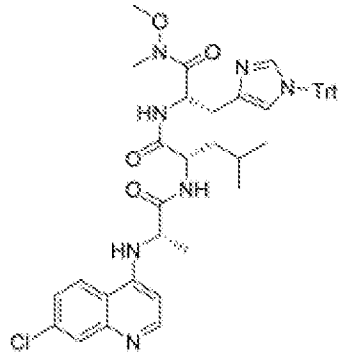


13

(iv)reacting compound **10a** with intermediate **5** wherein intermediate **5** is represented by

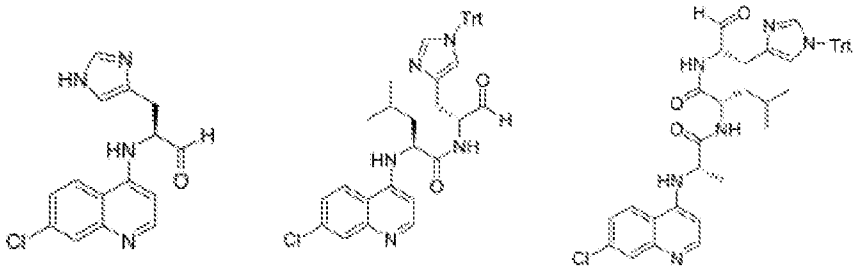


in presence of coupling reagent(s) to afford compound **16**



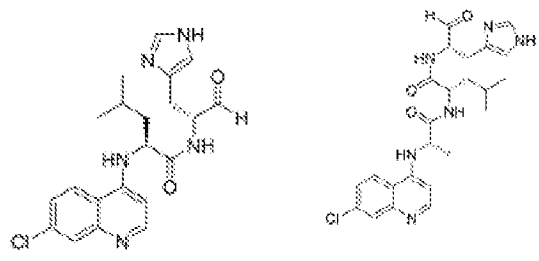
16

(v)deducing the compounds obtained in step (ii), (iii), (iv) using lithium aluminium hydride ($LiAlH_4$) in dry THF at -20°C to obtain the compounds **12, 14, 17**



12 **14** **17**

(vi) deprotecting the compounds 12, 14 or 17 obtained in step (v) using trifluororacetic acid in solvent at temperature in the range of 25 to 40°C for the time period in the range of 2 to 3 hours to produce histidinal-based trifluoroacetate salt compounds **15** and **18**



15 and **18**

10. The process as claimed in claim 5, 7 or 9, wherein the coupling agent used in step a) is selected from HBTU, HOBt and EDC·HCl or mixtures thereof.

11. The process as claimed in claim 5, 7 or 9, wherein the aminating agent is selected from DIPEA, DMF, and N, O-dimethyl hydroxylamine. HCl.

12. The process as claimed in claim 5, 7 or 9, wherein the precursor salt is selected from trifluororacetic acid and 4M HCl in 1,4-Dioxane.

13. The process as claimed in claim 5, 7 or 9, wherein the solvent is selected from polar or non-polar solvent, and protic or aprotic solvent.

14. The process as claimed in claim 5, 7 or 9, wherein the base is selected from organic base and inorganic base.

15. The process as claimed in claim 13, wherein the solvent is selected from DMF, THF, lower (C1-C5) alcohol, nitrile, ketone, halogenated hydrocarbon, TFA or combinations thereof;

16. The process as claimed in claim 14, wherein the wherein the organic base is selected from ethylamine, triethylamine, DIPEA, and pyridine; and wherein the inorganic base is selected from sodium hydroxide, alkali or alkaline earth metal carbonate and bicarbonate or combination thereof.

17. A pharmaceutical composition comprising the compound of formula I as claimed in claim 1 and a pharmaceutically acceptable excipient(s).

18. A method of treating malaria wherein, the method comprising administering therapeutically effective amount of the compound of Formula I as claimed in claim 1 or the pharmaceutical composition as claimed in claim 17 to reduce the malarial infection.

19. A method of inhibition of malaria cysteine proteases by contacting plasmodium with the compound of formula I as claimed in claim 1 or the pharmaceutical composition as claimed in claim 17.

STATEMENT UNDER ARTICLE 19

With reference to the search report and written opinion of ISA/IN, the applicant has amended claims to address the clarity objections.

- The Applicant submits that claim 1 has now been amended to address the clarity objection.

The Applicant undertakes that no new subject matter has been added in claims and the amended claims do not go beyond disclosure of international application as-filed.

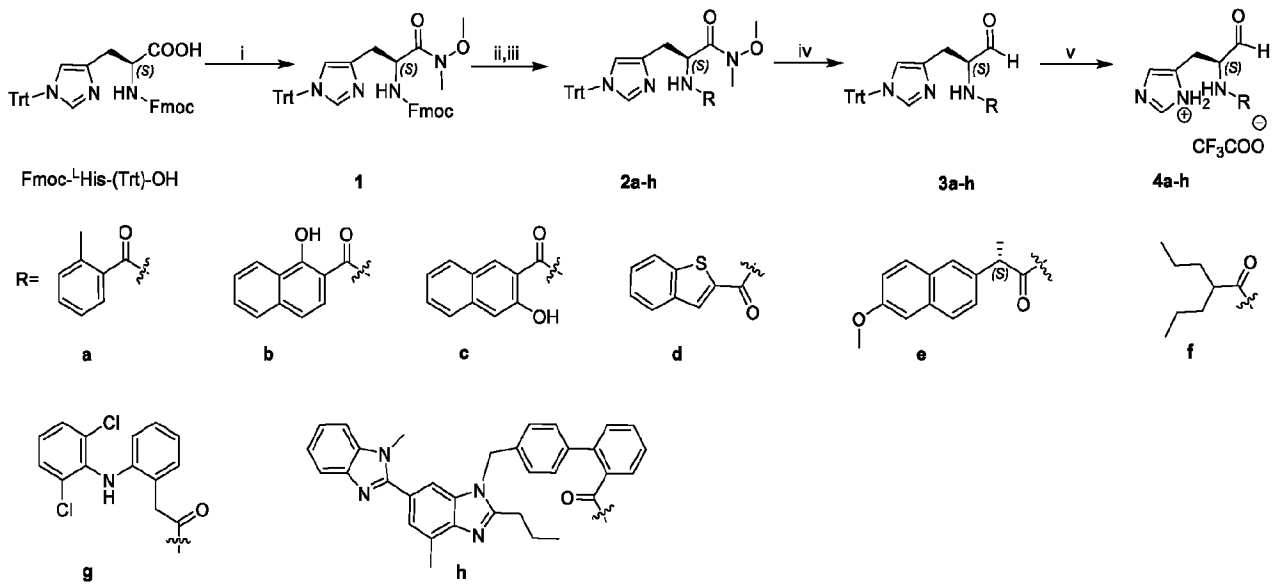


Fig 1

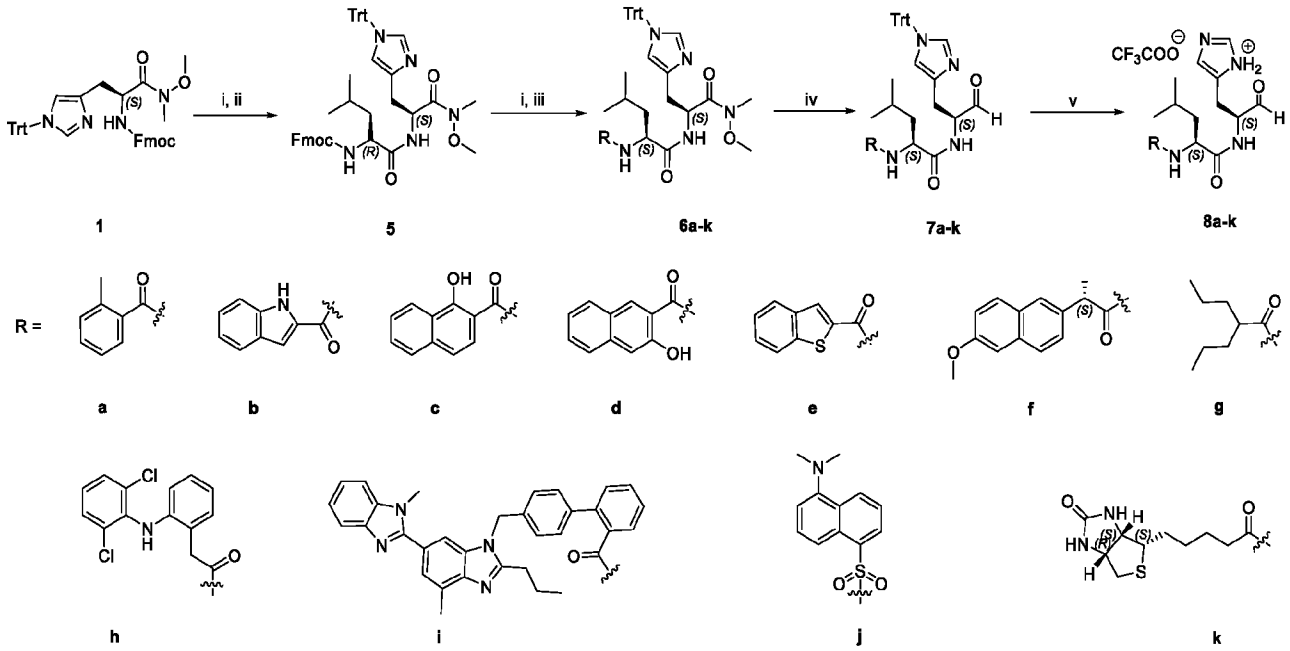


Fig 2

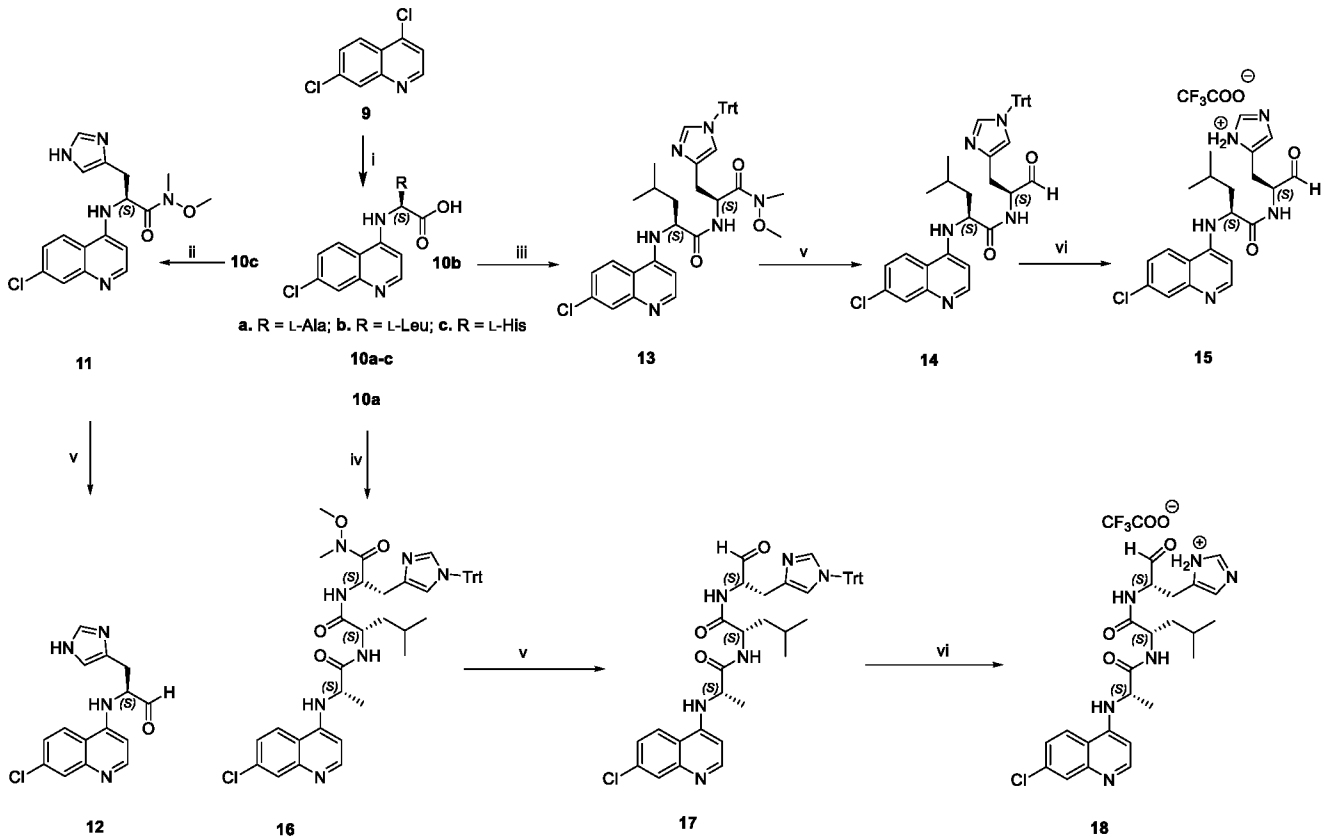

9
i
10b
10c
ii
iii
v
vi
a. R = L-Ala; b. R = L-Leu; c. R = L-His
11
10a-c
10a
13
14
15
v
iv
v
vi
12
16
17
18

Fig 3

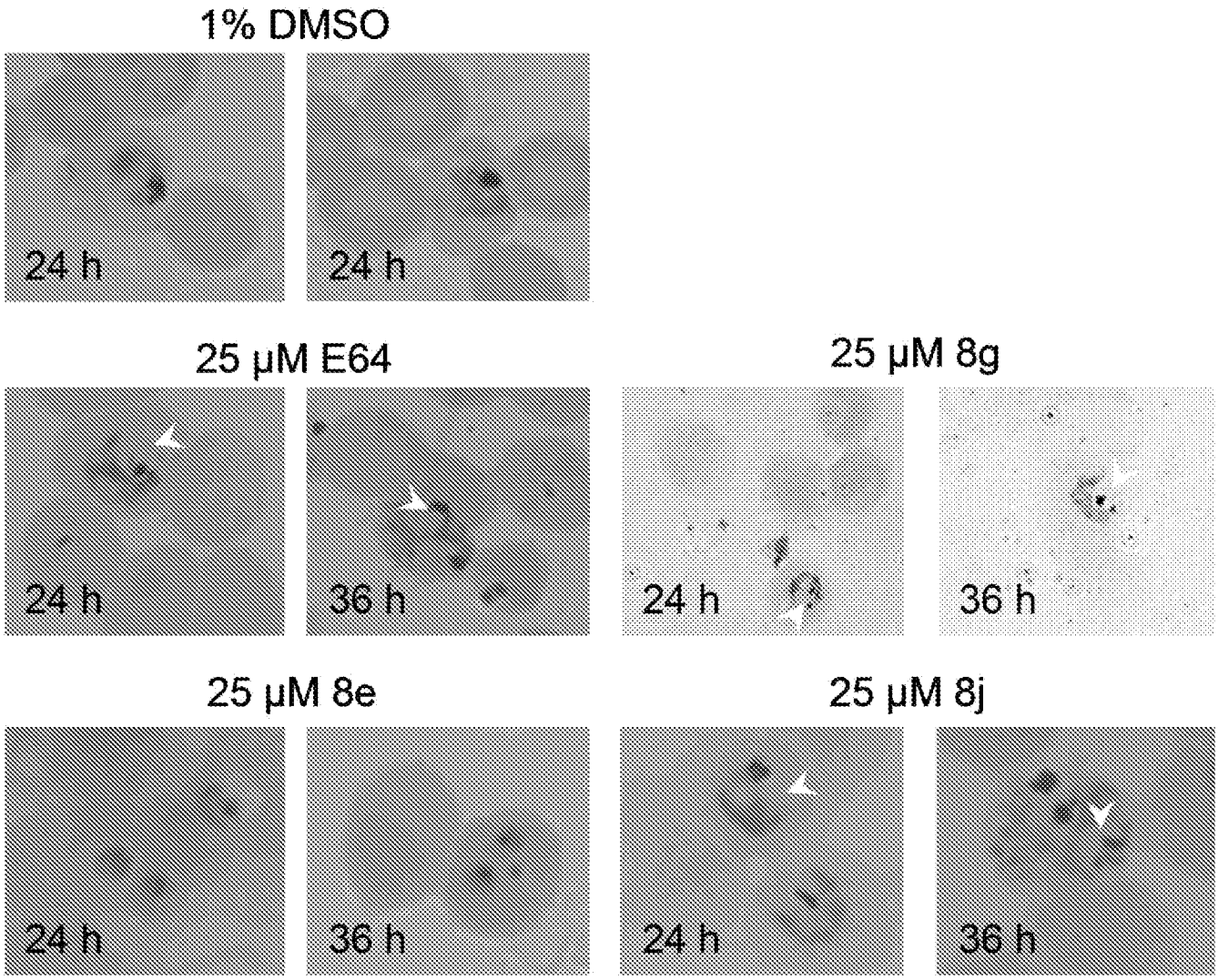

1% DMSO
24 h
24 h
25 µM E64
24 h
36 h
25 µM 8g
24 h
36 h
25 µM 8e
24 h
36 h
25 µM 8j
24 h
36 h

Fig 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2024/050002

A. CLASSIFICATION OF SUBJECT MATTER
C07D233/64,A61K31/435,C07D307/00 Version=2024.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K;C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Somanadhan, Brinda; Kotturi, Santosh R; Yan Leong, Chung; Glover, Robert P; Huang, Yicun; Flotow, Horst; Buss, Antony D; Lear, Martin J; Butler, Mark S (2013). Isolation and synthesis of falcitidin, a novel myxobacterial-derived acyl tetrapeptide with activity against the malaria target falcipain-2. The Journal of Antibiotics, 66(5), 259-264. doi:10.1038/ja.2012.123 Abstract, Figs 1 and 2, Scheme 1, Pages 1-6.	1-17
Y	Kotturi, Santosh R.; Somanadhan, Brinda; Ch'ng, Jun-Hong; Tan, Kevin S.-W.; Butler, Mark S.; Lear, Martin J. (2014), Diverted total synthesis of falcitidin acyl tetrapeptides as new antimalarial leads. Tetrahedron Letters, 55(11), 1949-1951. doi:10.1016/j.tetlet.2014.02.008. The whole document.	1-17
Y	Brinkmann, S., Semmler, S., Kersten, C., Patras, M.A., Kurz, M., Fuchs, N., Hammerschmidt, S.J., Legac, J., Hammann, P.E., Vilcinskas, A. and	1-17

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27-03-2024	27-03-2024
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Kamalesh Kumar Patel Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2024/050002

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-19
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claims 18-19 relates to a method for the treatment of cancer in human beings, which does not require an international search by the International Searching Authority by PCT Article 17(2)(a)(i) and [Rule 39.1(iv)].

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Rosenthal, P.J., 2022. Identification, characterization, and synthesis of natural parasitic cysteine protease inhibitors: pentacitidins are more potent falcitidin analogues. ACS Chemical Biology, 17(3), pp.576-589. Abstract, Fig 2, Scheme 1 and 2, Pages 15-16, 18.	