Summary

The β-hairpin peptidomimetics of the present invention are backbone cyclized peptidic compounds, built up from 13 amino acid residues, of the general formula

cyclo(-Xaa^1-Xaa^2-Thr^3-Xaa^4-Ser^5-Xaa^6-Xaa^7-Xaa^8-Xaa^9-Xaa^{10}-Xaa^{11}-Xaa^{12}-Xaa^{13}-)

(I),

and pharmaceutically acceptable salts thereof,

wherein

Xaa^1 is OctGly; Arg; hArg; Cha; a dipeptidic amino acid residue of type O; or of type P; as defined herein below; or an amino acid residue with delimited side chain-length of type Q; or of type R; as defined herein below;

Xaa^2 is Glu; Val; Leu; Nle; Phe; hPhe; DiHPhe; Tyr; hTyr; Trp; or a dipeptidic amino acid residue of type O; or of type P; as defined herein below;

Xaa^4 is Ala; AllylGly; Abu; or Val as defined herein below;

Xaa^6 is Ile; or OctGly as defined herein below;

Xaa^7 is Pro; or a N-substituted glycine of type I as defined herein below;

Xaa^8 is -B-CO- as defined herein below; or a N-substituted glycine of type I as defined herein below;

Xaa^9 is Gln; Tyr; or a β-amino acid residue of type N as defined herein below;

Xaa^{10} is Lys; Asn; Gly; a β-amino acid residue of type N as defined herein below; or a γ-amino acid residue of type M as defined herein below;

Xaa^{11} is hLeu; Ser; hSer; hSer(Me); Thr; alloThr; Asn; Gln; hGln; Dap; Tyr; His; or a γ-amino acid residue of type M as defined herein below;

Xaa^{12} is Gly; -A-CO- as defined herein below; a N-substituted glycine of type I as defined herein below; or the D-isomer of an amino acid residue of type C; or of type D; or of type E; or of type F; as defined herein below; and

Xaa^{13} is -B-CO- as defined herein below; a N-substituted glycine of type I as defined herein below; a β-amino acid residue of type N as defined herein below; a γ-amino acid residue of type M as defined herein below; -A-CO- as defined herein below; or the D-isomer of an amino acid residue of type C; or of type D; or of type E; or of type F; as defined herein below;

with the proviso that

- Xaa^{1} is a dipeptidic amino acid residue of type O; or of type P; as defined herein below;

and/or

- Xaa^{2} is a dipeptidic amino acid residue of type O; or of type P; as defined herein below;

and/or

- Xaa^{7} is a N-substituted glycine of type I as defined herein below;

and/or

- Xaa^{8} is Oic; 2Ind; Pip; Azt; or a N-substituted glycine of type I as defined herein below;

and/or

- Xaa^{9} is a β-amino acid residue of type N as defined herein below;

and/or

- Xaa^{10} is a β-amino acid residue of type N as defined herein below; or a γ-amino acid residue of type M as defined herein below;

and/or

- Xaa^{11} is a γ-amino acid residue of type M as defined herein below;

and/or

- Xaa^{12} is a N-substituted glycine of type I as described herein below; or the D-isomer of an amino acid residue of type C; or of type D; or of type E; or of type F; as defined herein below;

and/or

- Xaa^{13} is a N-substituted glycine of type I as described herein below;; a β-amino acid residue of type N as defined herein below;

a γ-amino acid residue of type M as defined herein below; -A-CO- as defined herein below; or the D-isomer of an amino acid residue of type C; or of type D; or of type E; or of type F; as defined herein below;

and with the further proviso that

- if Xaa^{11} is Tyr; or His, then

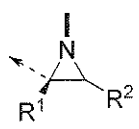
  Xaa^{1} is Arg; hArg; or a dipeptidic amino acid residue of type O; or of type P; as defined herein below;

  and/or

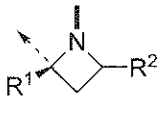
  Xaa^{2} is a dipeptidic amino acid residue of type O; or of type P; as defined herein below;

-B-CO- is a residue of an L-α-amino acid with B being a residue of formulae $-NR^{20}CH(R^{71})-$; $-NR^{20}CH(R^{72})-$; $-NR^{20}CH(R^{73})-$; $-NR^{20}CH(R^{74})-$; $-NR^{20}CH(R^{84})-$; or the enantiomer of one of the groups A1 to A37 and A105 as defined hereinafter;

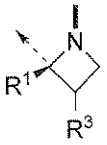
-A-CO- is a residue of an amino acid with A being a group of one of the formulae



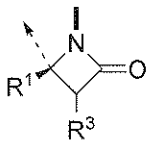
A1



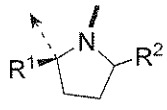
A2



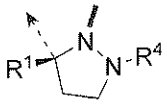
A3



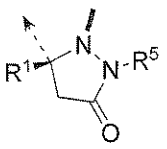
A4



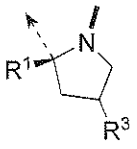
A5



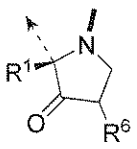
A6



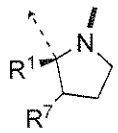
A7



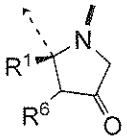
A8



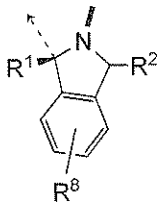
A9



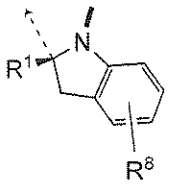
A10



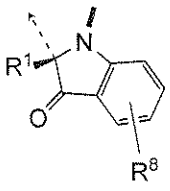
A11



A12



A13



A14

m is 2-4; o is 0-4; p is 1-4; q is 0-2; r is 1 or 2; s is 0 or 1;

the amino acid residue of type C is a residue of formula $-NR^{20}CH(R^{72})CO-$;
the amino acid residue of type D is a residue of formula $-NR^{20}CH(R^{73})CO-$;
the amino acid residue of type E is a residue of the formula $-NR^{20}CH(R^{74})CO-$;
the amino acid residue of type F is a residue of the formula $-NR^{20}CH(R^{84})CO-$;
the N-substituted glycine residue of type I is a residue of formula $-NR^{88}CH_2CO-$;
the amino acid residue of type M is a residue of one of the formulae
$-NR^{20}CH(R^{73})(CH_2)_2CO-$; $-NR^{20}CH(R^{74})(CH_2)_2CO-$; or $-NR^{20}CH(R^{84})(CH_2)_2CO-$;
the amino acid residue of type N is a residue of one of the formulae
$-NR^{20}CH(R^{72})(CH_2)CO-$; $-NR^{20}CH(R^{73})(CH_2)CO-$; $-NR^{20}CH(R^{74})(CH_2)CO-$, or
$-NR^{20}CH(R^{84})(CH_2)CO-$;
the amino acid residue of type O is a residue of formula $-NR^{20}CH(R^{89})CO-$;
the amino acid residue of type P is a residue of formula $-NR^{20}CH(R^{90})CO-$;
the amino acid residue of type Q is a residue of formula $-NR^{20}CH(R^{91})CO-$; and
the amino acid residue of type R is a residue of formula $-NR^{20}CH(R^{92})CO-$.

In one aspect, the present invention provides a compound as described herein of the formula I, in free form or in pharmaceutically acceptable salt form, for use as a medicament.

In another aspect, the present invention provides a compound as described herein of the formula I, in free form or in pharmaceutically acceptable salt form, having inhibitory activity against elastase for use in the treatment or prevention of lung cancer; breast cancer; psoriasis; alpha 1 antitrypsin deficiency; pulmonary emphysema; cystic fibrosis; chronic obstructive pulmonary disease; idiopathic pulmonary fibrosis; bronchiectasis; pulmonary hypertension; arterial pulmonary hypertension; cardiac hypertrophy; myocarditis; acute myocardial infarction; rheumatoid arthritis; osteoarthritis; atherosclerosis; multiple sclerosis; pancreatitis;

allergic rhinitis; systemic inflammatory respiratory syndrome; inflammatory dermatoses; inflammatory bowel disease; or Crohn's disease.

In yet another aspect, the present invention provides a pharmaceutical composition comprising a compound or a mixture of compounds as described herein of the formula I, in free form or in pharmaceutically acceptable salt form, and a pharmaceutically inert carrier, particularly in a form suitable for inhalation, for oral, topical, transdermal, injection, buccal, transmucosal, rectal, pulmonary or inhalation administration especially in the form of a tablet, dragee, capsule, solution, liquid, gel, plaster, cream, ointment, syrup, slurry, suspension, powder or suppository.

In yet another aspect, the present invention provides a compound as described herein of the formula I, in free form or in pharmaceutically acceptable salt form, for use as a pharmaceutically active substance having selective protease inhibitory activity, in particular against human neutrophil elastase, and/or anticancer activity and/or anti inflammatory activity and/or anti infective activity and/or anticardiovascular activity and/or antiimmunological activity and/or antineurodegenerative activity.

In yet another aspect, the present invention provides a compound as described herein, in free form or in pharmaceutically acceptable salt form, or a composition as described herein, for use as a medicament having inhibitory activity against elastase for the treatment or prevention of infections or diseases related to such infections; or cancer, such as lung cancer, or breast cancer, mediated or resulting from; or immunological diseases, such as psoriasis, mediated or resulting from; or pulmonary diseases, such as alpha 1 antitrypsin deficiency, pulmonary emphysema, cystic fibrosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, bronchiectasis, pulmonary hypertension, or arterial pulmonary hypertension, mediated or resulting from; or cardiovascular diseases, such as cardiac hypertrophy, myocarditis, or acute myocardial infarction, mediated or resulting from; or

neurodegenerative diseases mediated or resulting from; or inflammation or diseases related to inflammation, such as rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, pancreatitis, allergic rhinitis, systemic inflammatory respiratory syndrome, inflammatory dermatoses, inflammatory bowel disease, or Crohn's disease, mediated or resulting from elastase activity; or where immunological reaction is mediated or resulting from elastase activity.

In yet another aspect, the present invention provides the use of a compound as described herein, in free form or in pharmaceutically acceptable salt form, for the manufacture of a medicament having inhibitory activity against elastase for the treatment or prevention of infections or diseases related to such infections; or cancer, such as lung cancer, or breast cancer, mediated or resulting from; or immunological diseases, such as psoriasis, mediated or resulting from; or pulmonary diseases, such as alpha 1 antitrypsin deficiency, pulmonary emphysema, cystic fibrosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, bronchiectasis, pulmonary hypertension, or arterial pulmonary hypertension, mediated or resulting from; or cardiovascular diseases, such as cardiac hypertrophy, myocarditis, or acute myocardial infarction, mediated or resulting from; or neurodegenerative diseases mediated or resulting from; or inflammation or diseases related to inflammation, such as rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, pancreatitis, allergic rhinitis, systemic inflammatory respiratory syndrome, inflammatory dermatoses, inflammatory bowel disease, or Crohn's disease, mediated or resulting from elastase activity; or where immunological reaction is mediated or resulting from elastase activity.

In yet another aspect, the present invention provides the use of a pharmaceutically acceptable amount of a compound or pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of an infection or a disease or disorder associated with such an infection resulting from; or cancer mediated or resulting from; or immunological diseases mediated or resulting from; or

pulmonary diseases mediated or resulting from; or cardiovascular diseases mediated or resulting from; or neurodegenerative diseases mediated or resulting from; or inflammation mediated or resulting from elastase activity; or where immunological reaction is mediated or resulting from elastase activity, wherein said compound or pharmaceutical composition is to be administered to a subject in need thereof.

In accordance with the present invention these β-hairpin peptidomimetics can be prepared by a process which comprises

(a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product corresponds to Xaa^n, wherein n is 13, 8, 7, 6, 5 or 4, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(b) removing the N-protecting group from the product thus obtained;

(c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product corresponds to Xaa^{n-1}, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(d) removing the N-protecting group from the product obtained in step (c);

26. A compound according to anyone of claims 1 to 24 of the formula I, in free form or in pharmaceutically acceptable salt form, having inhibitory activity against elastase for the treatment or prevention of lung cancer; breast cancer; psoriasis; alpha 1 antitrypsin deficiency; pulmonary emphysema; cystic fibrosis; chronic obstructive pulmonary disease; idiopathic pulmonary fibrosis; bronchiectasis; pulmonary hypertension; arterial pulmonary hypertension; cardiac hypertrophy; myocarditis; acute myocardial infarction; rheumatoid arthritis; osteoarthritis; atherosclerosis; multiple sclerosis; pancreatitis; allergic rhinitis; systemic inflammatory respiratory syndrome; inflammatory dermatoses; inflammatory bowel disease; or Crohn's disease.

27. A pharmaceutical composition comprising a compound or a mixture of compounds according to any one of claims 1 to 24 of the formula I, in free form or in pharmaceutically acceptable salt form, and a pharmaceutically inert carrier, particularly in a form suitable for inhalation, for oral, topical, transdermal, injection, buccal, transmucosal, rectal, pulmonary or inhalation administration especially in the form of a tablet, dragee, capsule, solution, liquid, gel, plaster, cream, ointment, syrup, slurry, suspension, powder or suppository.

28. The use of a compound according to anyone of claims 1 to 24 of the formula I, in free form or in pharmaceutically acceptable salt form, as a pharmaceutically active substance having selective protease inhibitory activity, in particular against human neutrophil elastase, and/or anticancer activity and/or anti inflammatory activity and/or anti infective activity and/or anticardiovascular activity and/or antiimmunological activity and/or antineurodegenerative activity.

29. The use of a compound according to any one of claims 1 to 24, in free form or in pharmaceutically acceptable salt form, or a composition according to claim 27, as a medicament having inhibitory activity against elastase for the treatment or prevention of infections or diseases related to such infections; or cancer, such as lung

cancer, or breast cancer, mediated or resulting from; or immunological diseases, such as psoriasis, mediated or resulting from; or pulmonary diseases, such as alpha 1 antitrypsin deficiency, pulmonary emphysema, cystic fibrosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, bronchiectasis, pulmonary hypertension, or arterial pulmonary hypertension, mediated or resulting from; or cardiovascular diseases, such as cardiac hypertrophy, myocarditis, or acute myocardial infarction, mediated or resulting from; or neurodegenerative diseases mediated or resulting from; or inflammation or diseases related to inflammation, such as rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, pancreatitis, allergic rhinitis, systemic inflammatory respiratory syndrome, inflammatory dermatoses, inflammatory bowel disease, or Crohn's disease, mediated or resulting from elastase activity; or where immunological reaction is mediated or resulting from elastase activity.

30. The use of a compound according to any one of claims 1 to 24, in free form or in pharmaceutically acceptable salt form, for the manufacture of a medicament having inhibitory activity against elastase for the treatment or prevention of infections or diseases related to such infections; or cancer, such as lung cancer, or breast cancer, mediated or resulting from; or immunological diseases, such as psoriasis, mediated or resulting from; or pulmonary diseases, such as alpha 1 antitrypsin deficiency, pulmonary emphysema, cystic fibrosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, bronchiectasis, pulmonary hypertension, or arterial pulmonary hypertension, mediated or resulting from; or cardiovascular diseases, such as cardiac hypertrophy, myocarditis, or acute myocardial infarction, mediated or resulting from; or neurodegenerative diseases mediated or resulting from; or inflammation or diseases related to inflammation, such as rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, pancreatitis, allergic rhinitis, systemic inflammatory respiratory syndrome, inflammatory dermatoses, inflammatory bowel disease, or Crohn's disease, mediated

or resulting from elastase activity; or where immunological reaction is mediated or resulting from elastase activity.

31. A method of treating an infection or a disease or disorder associated with such an infection resulting from; or cancer mediated or resulting from; or immunological diseases mediated or resulting from; or pulmonary diseases mediated or resulting from; or cardiovascular diseases mediated or resulting from; or neurodegenerative diseases mediated or resulting from; or inflammation mediated or resulting from elastase activity; or where immunological reaction is mediated or resulting from elastase activity, comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound or pharmaceutical composition according to any of the claims 1 to 24 or 27.

32. A process for the manufacture of a compound as defined in any one of the claims 1 to 24 of the formula I comprising the steps of

(a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product corresponds to Xaa^{n}, wherein n is 13, 8, 7, 6, 5 or 4, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(b) removing the N-protecting group from the product thus obtained;

(c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product corresponds to Xaa^{n-1}, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(d) removing the N-protecting group from the product obtained in step (c);

(e) effecting steps substantially corresponding to steps (c) and (d) using appropriately N-protected derivatives of amino acids which in the desired end-product are in positions n-2 to 1, any functional group(s) which may be

present in said N-protected amino acid derivatives being likewise appropriately protected;

(f) if n is not 13, further effecting steps substantially corresponding to steps (c) and (d) using appropriately N-protected derivatives of amino acids which in the desired end-product are in positions 13 to n + 1, any functional group(s) which may be present in said N-protected amino acid derivatives being likewise appropriately protected;

(g) detaching the product thus obtained from the solid support;

(h) cyclizing the product cleaved from the solid support;

(i) removing any protecting groups present on functional groups of any members of the chain of amino acid residues; and

(j) if desired, converting the product thus obtained into a pharmaceutically acceptable salt or converting a pharmaceutically acceptable, or unacceptable, salt thus obtained into the corresponding free compound or into a different, pharmaceutically acceptable, salt.

26. A compound according to anyone of claims 1 to 24 of the formula I, in free form or in pharmaceutically acceptable salt form, having inhibitory activity against elastase for use in the treatment or prevention of lung cancer; breast cancer; psoriasis; alpha 1 antitrypsin deficiency; pulmonary emphysema; cystic fibrosis; chronic obstructive pulmonary disease; idiopathic pulmonary fibrosis; bronchiectasis; pulmonary hypertension; arterial pulmonary hypertension; cardiac hypertrophy; myocarditis; acute myocardial infarction; rheumatoid arthritis; osteoarthritis; atherosclerosis; multiple sclerosis; pancreatitis; allergic rhinitis; systemic inflammatory respiratory syndrome; inflammatory dermatoses; inflammatory bowel disease; or Crohn's disease.

27. A pharmaceutical composition comprising a compound or a mixture of compounds according to any one of claims 1 to 24 of the formula I, in free form or in pharmaceutically acceptable salt form, and a pharmaceutically inert carrier, particularly in a form suitable for inhalation, for oral, topical, transdermal, injection, buccal, transmucosal, rectal, pulmonary or inhalation administration especially in the form of a tablet, dragee, capsule, solution, liquid, gel, plaster, cream, ointment, syrup, slurry, suspension, powder or suppository.

28. A compound according to anyone of claims 1 to 24 of the formula I, in free form or in pharmaceutically acceptable salt form, for use as a pharmaceutically active substance having selective protease inhibitory activity, in particular against human neutrophil elastase, and/or anticancer activity and/or anti inflammatory activity and/or anti infective activity and/or anticardiovascular activity and/or antiimmunological activity and/or antineurodegenerative activity.

29. A compound according to any one of claims 1 to 24, in free form or in pharmaceutically acceptable salt form, or a composition according to claim 27, for use as a medicament having inhibitory activity against elastase for the treatment or prevention of infections or diseases related to such infections; or cancer, such as lung

cancer, or breast cancer, mediated or resulting from; or immunological diseases, such as psoriasis, mediated or resulting from; or pulmonary diseases, such as alpha 1 antitrypsin deficiency, pulmonary emphysema, cystic fibrosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, bronchiectasis, pulmonary hypertension, or arterial pulmonary hypertension, mediated or resulting from; or cardiovascular diseases, such as cardiac hypertrophy, myocarditis, or acute myocardial infarction, mediated or resulting from; or neurodegenerative diseases mediated or resulting from; or inflammation or diseases related to inflammation, such as rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, pancreatitis, allergic rhinitis, systemic inflammatory respiratory syndrome, inflammatory dermatoses, inflammatory bowel disease, or Crohn's disease, mediated or resulting from elastase activity; or where immunological reaction is mediated or resulting from elastase activity.

30. The use of a compound according to any one of claims 1 to 24, in free form or in pharmaceutically acceptable salt form, for the manufacture of a medicament having inhibitory activity against elastase for the treatment or prevention of infections or diseases related to such infections; or cancer, such as lung cancer, or breast cancer, mediated or resulting from; or immunological diseases, such as psoriasis, mediated or resulting from; or pulmonary diseases, such as alpha 1 antitrypsin deficiency, pulmonary emphysema, cystic fibrosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, bronchiectasis, pulmonary hypertension, or arterial pulmonary hypertension, mediated or resulting from; or cardiovascular diseases, such as cardiac hypertrophy, myocarditis, or acute myocardial infarction, mediated or resulting from; or neurodegenerative diseases mediated or resulting from; or inflammation or diseases related to inflammation, such as rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, pancreatitis, allergic rhinitis, systemic inflammatory respiratory syndrome, inflammatory dermatoses, inflammatory bowel disease, or Crohn's disease, mediated or resulting from elastase activity; or where immunological reaction is mediated or resulting from elastase activity.

31. The use of a pharmaceutically acceptable amount of a compound or pharmaceutical composition according to any of the claims 1 to 24 or 27 in the manufacture of a medicament for the treatment of an infection or a disease or disorder associated with such an infection resulting from; or cancer mediated or resulting from; or immunological diseases mediated or resulting from; or pulmonary diseases mediated or resulting from; or cardiovascular diseases mediated or resulting from; or neurodegenerative diseases mediated or resulting from; or inflammation mediated or resulting from elastase activity; or where immunological reaction is mediated or resulting from elastase activity, wherein said compound or pharmaceutical composition is to be administered to a subject in need thereof.

32. A process for the manufacture of a compound as defined in any one of the claims 1 to 24 of the formula I comprising the steps of

(a) coupling an appropriately functionalized solid support with an appropriately N-protected derivative of that amino acid which in the desired end-product corresponds to Xaa^n, wherein n is 13, 8, 7, 6, 5 or 4, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(b) removing the N-protecting group from the product thus obtained;

(c) coupling the product thus obtained with an appropriately N-protected derivative of that amino acid which in the desired end-product corresponds to Xaa^{n-1}, any functional group which may be present in said N-protected amino acid derivative being likewise appropriately protected;

(d) removing the N-protecting group from the product obtained in step (c);

(e) effecting steps substantially corresponding to steps (c) and (d) using appropriately N-protected derivatives of amino acids which in the desired end-product are in positions n-2 to 1, any functional group(s) which may be present in said N-protected amino acid derivatives being likewise appropriately protected;

(f) if n is not 13, further effecting steps substantially corresponding to steps (c) and (d) using appropriately N-protected derivatives of amino acids which in the desired end-product are in positions 13 to n + 1, any functional group(s) which may be present in said N-protected amino acid derivatives being likewise appropriately protected;

(g) detaching the product thus obtained from the solid support;

(h) cyclizing the product cleaved from the solid support;

(i) removing any protecting groups present on functional groups of any members of the chain of amino acid residues; and

(j) if desired, converting the product thus obtained into a pharmaceutically acceptable salt or converting a pharmaceutically acceptable, or unacceptable, salt thus obtained into the corresponding free compound or into a different, pharmaceutically acceptable, salt.