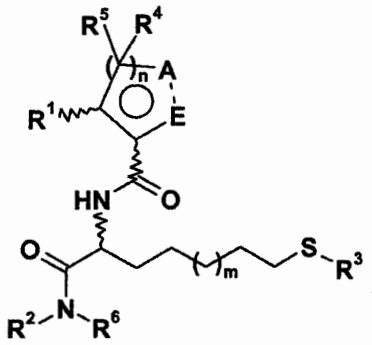
CLAIMS

1. A compound having the general Formula (I)



Formula I

wherein,

R^1 is H, (C_1-C_6)-alkyl or aryl; or alternatively

R^1 and one R^4, each being linked to two adjacent carbon atoms, in case n is 2 or 3, are taken together to form a cyclopropane ring;

R^2 is phenyl optionally substituted with halogen, benzyloxy, (C_1-C_3)-alkyl or CF_3; (C_3-C_6)-cycloalkyl; aryl-(C_1-C_6)-alkyl wherein the aryl is optionally substituted with benzyloxy, (C_1-C_3)-alkyl or CF_3;

R^3 is H, $PO(OH)_2$, or a group of Formula (II)

-(CO)-R^7 **Formula II**

R^7 is (C_1-C_7)-alkyl, (C_1-C_6)-alkoxy or -$CH(NH_2)R^8$;

R^8 is H, or the side chain of a natural α-amino acid;

R^4 and R^5 are at any occurrence independently H, halogen, (C_1-C_6)-alkyl, or alternatively,

when n is 2 or 3, one R^4 and one R^5, each being linked to two adjacent carbon atoms, are taken together to form a cyclopropane ring;

R^6 is H or alternatively,

R^2 and R^6 are taken together to form a five- to six-membered heterocycle which can be optionally fused with an aryl moiety;

-A-E- is -(CO)-(NR^9)- or -(NR^9)-(CO)-;

R^9 is H or (C_1-C_3)-alkyl;

m is an integer comprised between 0 to 3;

n is an integer comprised between 0 to 3 with the proviso that when is 2 or 3, each of R^4 and R^5 can adopt different meaning at each occurrence;

the symbol ~~ means that the carbon atom bearing said symbol can adopt a *R* or *S* configuration;

the symbol ○ can be absent, but if present it means that the cycle can be partially unsaturated with the proviso that when the carbon atom bearing R^4 is involved in a double bond, R^5 is absent;

their tautomers, their geometrical isomers, their optically active forms such as enantiomers, diastereomers and their racemate forms, as well as their pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein n is 1 or 2.

3. A compound according to claim 1, wherein m is 1 or 2.

4. A compound according to claims 1 to 2 selected from the group consisting of: thioacetic acid S-{(*S*)-6-[((*S*)-4-oxo-azetidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-[(*S*)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-(4-trifluoromethyl-benzylcarbamoyl)-hexyl] ester, thioacetic acid S-{(*S*)-6-(3-benzyloxy-benzylcarbamoyl)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-hexyl} ester, thioacetic acid S-{(*S*)-7-(3,4-dihydro-1H-isoquinolin-2-yl)-7-oxo-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-heptyl} ester, thioacetic acid S-[(S)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-(2-m-tolyl-ethylcarbamoyl)-hexyl] ester, thioacetic acid S-{(*S*)-6-[((*R*)-6-oxo-piperidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-p-tolylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-m-tolylcarbamoyl-hexyl} ester, thioacetic acid S-{(S)- 6-[((S)-6-oxo-piperidine-2-carbonyl)-amino]-6-cyclopentylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((3*R**,4*S**)-2-oxo-4-phenyl-pyrrolidine-3-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((3*R**,4*R**)-2-oxo-4-phenyl-pyrrolidine-3-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*R*)-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[(R*)-(2-oxo-piperidine-3-carbonyl)-amino]-6-phenyl carbamoyl-hexyl} ester, (*S*)-6-oxo-piperidine-2-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid ((*S*)-1-cyclopentylcarbamoyl-6-mercapto-hexyl)-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid [(*S*)-1-(3-benzyloxy-

benzylcarbamoyl)-6-mercapto-hexyl]-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid [(*S*)-6-mercapto-1-(4-trifluoromethyl-benzylcarbamoyl)-hexyl]-amide, (*S*)-4-oxo-azetidine-2-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (3S,4S)-2-oxo-4-phenyl-pyrrolidine-3-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (3R,4R)-2-oxo-4-phenyl-pyrrolidine-3-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (3R,4S)-2-oxo-4-phenyl-pyrrolidine-3-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (3S,4R)-2-oxo-4-phenyl-pyrrolidine-3-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid [(S)-1-(3,4-dihydro-1H-isoquinoline-2-carbonyl)-6-mercapto-hexyl]-amide, (*R*)-5-oxo-pyrrolidine-2-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid [(*S*)-6-mercapto-1-(2-m-tolyl-ethylcarbamoyl)-hexyl]-amide, (*R*)-2-oxo-piperidine-3-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (*S*)-2-oxo-piperidine-3-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (*R*)-6-oxo-piperidine-2-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, thiocarbonic acid ethyl ester {(*S*)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioisobutyric acid S-{(*S*)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*S*)-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*S*)-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-*m*-tolylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*R*)-1-methyl-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thiocarbonic acid ethyl ester {(*S*)-6-[((*R*)-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*R*)-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-*m*-tolylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*R*)-1-methyl-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-*m*-tolylcarbamoyl-hexyl} ester, thioacetic acid S-[(S)-6-[((R)-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-(3-trifluoromethyl-phenylcarbamoyl)-hexyl] ester, thioacetic acid S-{(*S*)-6-[((*S*)-1-methyl-6-oxo-piperidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, (*S*)-1-methyl-6-oxo-piperidine-2-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid ((*S*)-6-mercapto-1-m-tolylcarbamoyl-hexyl)-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid ((*S*)-6-mercapto-1-p-tolylcarbamoyl-hexyl)-amide,

and thioacetic acid S-{(*S*)-6-[((*S*)-6-oxo-1,2,3,6-tetrahydro-pyridine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester.

5. A pharmaceutical composition containing at least one compound according to claims 1-4 as the active ingredient in mixtures with at least one pharmaceutically acceptable vehicle and/or excipient.

6. Use of a compound according to any of claims 1-4 as a medicament.

7. Use according to claim 6 for the treatment of a pathological state for which the modulation of HDAC activity would result at improving the health of the patient.

8. Use according to claim 7 where the pathological state is a cancer disease, a neurodegenerative disease, an inflammatory disease, stroke, ischemia or Plasmodium infections.

9. Use according to claim 8 where the cancer disease is cancer of the breasts, pancreas, lung, colon, pleura, peritoneum, face and neck, kidney, bladder, brain, prostate, ovaries or eyes.

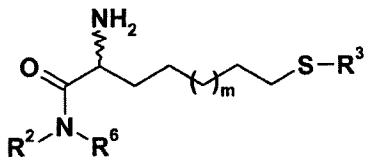
10. Use according to claim 9 where the cancer is a metastatic form of cancer.

11. Use according to claim 8 where the inflammatory disease is rheumatoid arthritis.

12. Use according to claim 8 where the neurodegenerative disease is Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis,

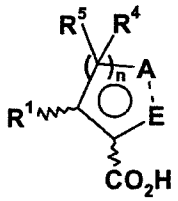
13. A method of treatment of a patient affected by a cancer disease comprising the administration of a compound according to claims 1-4.

14. Process for synthesizing compounds of claim 1, by reacting compounds of Formula (III)



Formula III

wherein R^2, R^3 and R^6 and m are as described in claim 1, with compounds of Formula (IV) salified or not

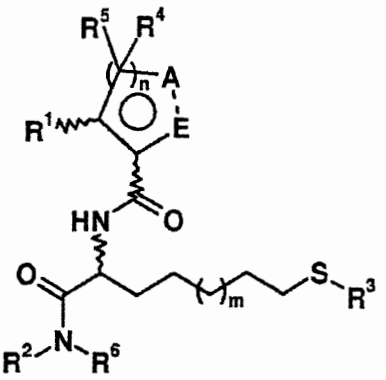


Formula IV

wherein R^1, R^4 and R^5 and n are as described in claim 1, in a polar aprotic solvent in the presence of a coupling agent.

Claims

1. A compound having the general Formula (I)



Formula I

wherein,

R^1 is H, (C_1-C_6)-alkyl or aryl; or alternatively
R^1 and one R^4, each being linked to two adjacent carbon atoms, in case n is 2 or 3, are taken together to form a cyclopropane ring;
R^2 is phenyl optionally substituted with halogen, benzyloxy, (C_1-C_3)-alkyl or CF_3; (C_3-C_6)-cycloalkyl; aryl-(C_1-C_6)-alkyl wherein the aryl is optionally substituted with benzyloxy, (C_1-C_3)-alkyl or CF_3;
R^3 is H, $PO(OH)_2$, or a group of Formula (II)

-(CO)-R^7 **Formula II**

R^7 is (C_1-C_7)-alkyl, (C_1-C_6)-alkoxy or -$CH(NH_2)R^8$;
R^8 is H, or the side chain of a natural α-amino acid selected from the group consisting of glycine, alanine, phenylalanine, valine, leucine, isoleucine, aspartic acid, asparagine, glutamic acid, glutamine, serine, lysine, histidine, methionine, proline, cysteine, threonine, tryptophan, arginine and tyrosine;
R^4 and R^5 are at any occurrence independently H, halogen, (C_1-C_6)-alkyl, or alternatively,
when n is 2 or 3, one R^4 and one R^5, each being linked to two adjacent carbon atoms, are taken together to form a cyclopropane ring;
R^6 is H or alternatively,
R^2 and R^6 are taken together to form a five- to six-membered heterocycle which can be optionally fused with an aryl moiety; **-A-E-** is -(CO)-(NR^9)- or -(NR^9)-(CO)-;
R^9 is H or (C_1-C_3)-alkyl;
m is an integer comprised between 0 to 3;
n is an integer comprised between 0 to 3 with the proviso that when is 2 or 3, each of
R^4 and R^5 can adopt different meaning at each occurrence;
the symbol ~~ means that the carbon atom bearing said symbol can adopt a *R* or *S* configuration;
the symbol O can be absent, but if present it means that the cycle can be partially unsaturated with the proviso that when the carbon atom bearing R^4 is involved in a double bond, R^5 is absent;

their tautomers, their geometrical isomers, their optically active forms such as enantiomers, diastereomers and their racemate forms, as well as their pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein n is 1 or 2.

3. A compound according to claim 1, wherein m is 1 or 2.

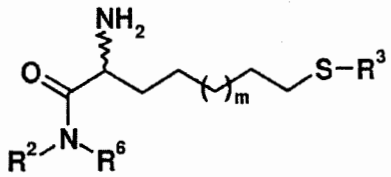
4. A compound according to claims 1 to 2 selected from the group consisting of:

thioacetic acid S-{(*S*)-6-[((*S*)-4-oxo-azetidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-[(*S*)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-(4-trifluoromethyl-benzylcarbamoyl)-hexyl] ester, thioacetic acid S-{(*S*)-6-(3-benzyloxy-benzylcarbamoyl)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-hexyl} ester, thioacetic acid S-{(*S*)-7-(3,4-dihydro-1H-isoquinolin-2-yl)-7-oxo-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-heptyl} ester, thioacetic acid S-[(S)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-(2-m-tolyl-ethylcarbamoyl)-hexyl] ester, thioacetic acid S-{(*S*)-6-[((*R*)-6-oxo-piperidine-2-carbonyl)-amino] -6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-p-tolylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-m-tolylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((S)-6-oxo-piperidine-2-carbonyl)-amino]-6-cyclopentylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((3*R**,4*S**)-2-oxo-4-phenyl-pyrrolidine-3-carbonyl)-amino] -6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((3*R**,4*R**)-2-oxo-4-phenyl-pyrrolidine-3-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*R*)-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[(*R**)-(2-oxo-piperidine-3-carbonyl)-amino]-6-phenyl carbamoyl-hexyl} ester, (*S*)-6-oxo-piperidine-2-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid ((*S*)-1-cyclopentylcarbamoyl-6-mercapto-hexyl)-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid [(*S*)-1-(3-benzyloxy-benzylcarbamoyl)-6-mercapto-hexyl]-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid [(*S*)-6-mercapto-1-(4-trifluoromethyl-benzylcarbamoyl)-hexyl]-amide, (*S*)-4-oxo-azetidine-2-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (3S,4S)-2-oxo-4-phenyl-pyrrolidine-3-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (3R,4R)-2-oxo-4-phenyl-pyrrolidine-3-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (3R,4S)-2-oxo-4-phenyl-pyrrolidine-3-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (3S,4R)-2-oxo-4-phenyl-pyrrolidine-3-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid [(*S*)-1-(3,4-dihydro-1H-isoquinoline-2-carbonyl)-6-mercapto-hexyl]-amide, (R)-5-oxo-pyrrolidine-2-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid [(*S*)-6-mercapto-1-(2-m-tolyl-ethylcarbamoyl)-hexyl]-amide, (*R*)-2-oxo-piperidine-3-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (*S*)-2-oxo-piperidine-3-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (R)-6-oxo-piperidine-2-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, thiocarbonic acid ethyl ester {(*S*)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioisobutyric acid S-{(*S*)-6-[((*S*)-6-oxo-piperidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*S*)-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*S*)-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-*m*-tolylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*R*)-1-methyl-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thiocarbonic acid ethyl ester {(*S*)-6-[((*R*)-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*R*)-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-*m*-tolylcarbamoyl-hexyl} ester, thioacetic acid S-{(*S*)-6-[((*R*)-1-methyl-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-*m*-tolylcarbamoyl-hexyl} ester, thioacetic acid S-[(S)-6-[((R)-5-oxo-pyrrolidine-2-carbonyl)-amino]-6-(3-trifluoromethyl-phenylcarbamoyl)-hexyl] ester, thioacetic acid S-{(*S*)-6-[((*S*)-1-methyl-6-oxo-piperidine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester, (*S*)-1-methyl-6-oxo-piperidine-2-carboxylic acid ((*S*)-6-mercapto-1-phenylcarbamoyl-hexyl)-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid ((*S*)-6-mercapto-1-m-tolylcarbamoyl-hexyl)-amide, (*S*)-6-oxo-piperidine-2-carboxylic acid ((*S*)-6-mercapto-1-p-tolylcarbamoyl-hexyl)-amide, and thioacetic acid S-{(*S*)-6-[((*S*)-6-oxo-1,2,3,6-tetrahydro-pyridine-2-carbonyl)-amino]-6-phenylcarbamoyl-hexyl} ester.

5. A pharmaceutical composition containing at least one compound according to claims 1-4 as the active ingredient in mixtures with at least one pharmaceutically acceptable vehicle and/or excipient.

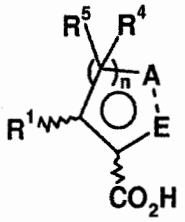
6. The compound according to any of claims 1-4 for use as a medicament.

7. Process for synthesizing compounds of claim 1, by reacting compounds of Formula (III)



Formula III

wherein R^2, R^3 and R^6 and m are as described in claim 1, with compounds of Formula (IV) salified or not



Formula IV

wherein R^1, R^4 and R^5 and n are as described in claim 1, in a polar aprotic solvent in the presence of a coupling agent.