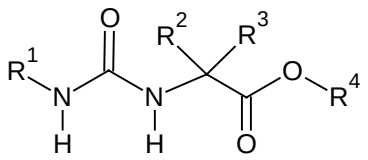
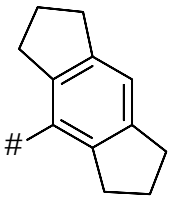
CLAIMS:

1. A compound of Formula (I) or pharmaceutically acceptable salt thereof:



in which:

R_1 is a 5 or 6 membered alkyl or aryl monocycle, having at least one group substituent comprising a (2-8C) alkyl **or** a 9 or 10 membered bicyclic partially unsaturated carbocyclic ring system, wherein said bicyclic ring system is optionally substituted by 1, 2, 3 or 4 substituents independently selected from (1-6C)alkyl, (2-6C)alkenylene, (2-6C)alkynylene, (3-8C)cycloalkyl, (1-3C)alkoxy, halo, oxo, hydroxy, cyano, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]-amino, CF_3, OCF_3, $S(O)_2CH_3$, $S(O)CH_3$, $S(O)_2NH_2$, $S(O)_2NHCH_3$, $S(O)_2N(CH_3)_2$, $NHS(O)_2CH_3$, and $N(CH_3)S(O)_2CH_3$ **or** a 12, 13, 14, 15, or 16 membered tricyclic partially unsaturated carbocyclic ring system, wherein said tricyclic ring system is an unsubstituted hexahydroindacene ring



wherein # denotes the bond to the nitrogen atom of Formula (I), or said tricyclic ring system is optionally substituted by 1, 2, 3 or 4 substituents independently selected from (1-6C)alkyl, (2-6C)alkenylene, (2-6C)alkynylene, (3-8C)cycloalkyl, (1-3C)alkoxy, halo, oxo, hydroxy, cyano, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]-amino, CF_3, OCF_3, $S(O)_2CH_3$, $S(O)CH_3$, $S(O)_2NH_2$, $S(O)_2NHCH_3$, $S(O)_2N(CH_3)_2$, $NHS(O)_2CH_3$, and $N(CH_3)S(O)_2CH_3$;

R_2 is H

R_3 is alkyl(C1-4)-**R_7**,

wherein **R_7** is selected from a 5 or 6 membered monocyclic aryl or non-aryl ring system comprising 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur, and a 3, 4, 5, or 6 membered monocyclic heterocyclyl ring system comprising 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein said heterocyclic **R_7** ring system is optionally substituted with 1 or more substituents independently selected from (1-6C) alkyl, alkylhydroxy, nitro, OH , $COCH_3$, halo, amino, cyano, and **R_8**,

or

wherein **R_7** is selected from a 5 or 6 membered monocyclic aryl or non-aryl ring system optionally comprising 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur, a 3, 4, 5 or 6 membered monocyclic heterocyclyl ring system optionally comprising 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, and a 3, 4, 5 or 6 membered saturated or partially unsaturated carbocyclic ring system, wherein the **R_7** ring system is substituted with 1 or more substituents independently selected from (1-6C) alkyl, alkylhydroxy, nitro, OH , COCH3, halo, amino, cyano, and **R_8**,

wherein **R_8** is, an optionally N-linked, 5 or 6 membered monocyclic heteroaryl ring comprising 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, or a 3, 4, 5 or 6 membered monocyclic heterocyclyl ring system comprising 1 heteroatom independently selected from oxygen, nitrogen and sulfur, said ring being optionally substituted with an alkyl, oxo, halo, or amino group; and

R_4 is H, alkyl, monocyclic alkyl, or monocyclic aryl group.

2. The compound of claim 1, wherein R_3 is methyl- R_7 or ethyl-R_7.

3. The compound according to claim 1 or claim 2, wherein R_7 is a monocyclic aryl,

optionally substituted with at least one hydroxyl group.

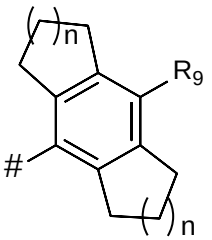
4. The compound according to claim 1 or claim 2, wherein R_7 is a monocyclic aryl with a cyano substitution.

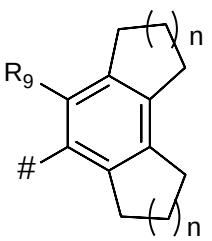
5. The compound according to claim 1 or claim 2, wherein R_7 is a 5 or 6 membered monocyclic aryl ring comprising 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur.

6. The compound according to any one of claims 1-5, wherein R_4 is alkyl (C1-C4) or cyclo alkyl (C3-C6).

7. The compound according to any one of claims 1-6, wherein R_1 is:

a 12, 13, 14, 15, or 16 membered tricyclic partially unsaturated carbocyclic ring system selected from the group consisting of

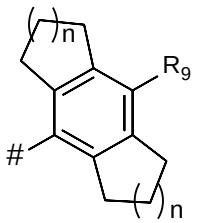


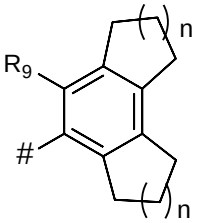
a and


a,

wherein # denotes the bond to the nitrogen atom of Formula (I); wherein n and n_a is an integer independently selected from 0, 1, 2, and 3; and wherein R_9 is selected from the group consisting of hydrogen, (1-6C)alkyl, (2-6C)alkenylene, (2-6C)alkynylene, (3-8C)cycloalkyl, halo, oxo, hydroxy, cyano, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]-amino, CF_3, OCF_3, $S(O)_2CH_3$, $S(O)CH_3$, $S(O)_2NH_2$, $S(O)_2NHCH_3$, $S(O)_2N(CH_3)_2$, $NHS(O)_2CH_3$, and $N(CH_3)S(O)_2CH_3$; or

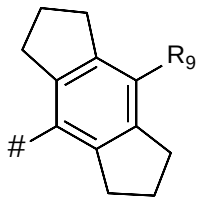
a 12, 13, 14, 15, or 16 membered tricyclic partially unsaturated carbocyclic ring system selected from the group consisting of

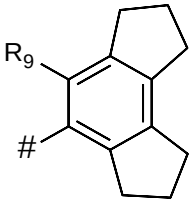


a and 

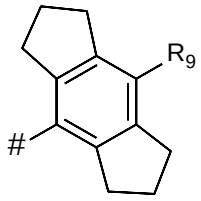
a,

wherein # denotes the bond to the nitrogen atom of Formula (I); wherein n and n_a is an integer independently selected from 0, 1, 2, and 3; and wherein R_9 is selected from the group consisting of hydrogen, (1-6C)alkyl, halo, CF_3, and OCF_3; or



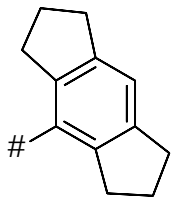
and 

wherein # denotes the bond to the nitrogen atom of Formula (I); and wherein R_9 is selected from the group consisting of hydrogen, (1-6C)alkyl, (2-6C)alkenylene, (2-6C)alkynylene, (3-8C)cycloalkyl, halo, oxo, hydroxy, cyano, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]-amino, CF_3, OCF_3, $S(O)_2CH_3$, $S(O)CH_3$, $S(O)_2NH_2$, $S(O)_2NHCH_3$, $S(O)_2N(CH_3)_2$, $NHS(O)_2CH_3$, and $N(CH_3)S(O)_2CH_3$; or



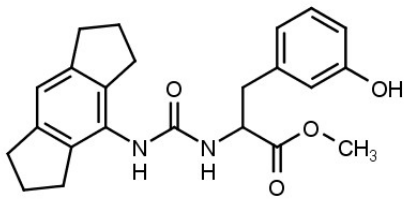
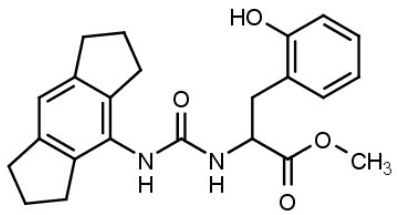
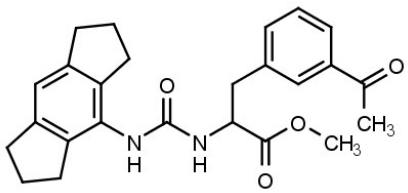
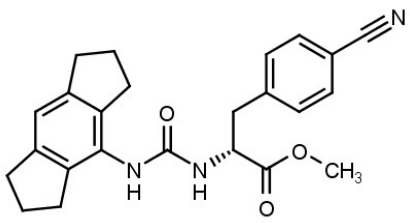
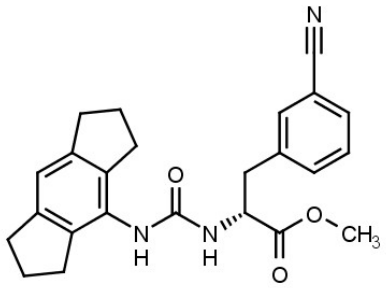
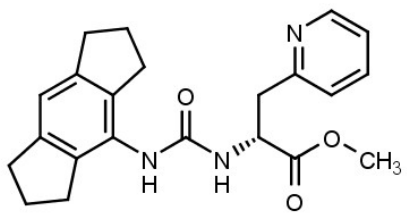
wherein # denotes the bond to the nitrogen atom of Formula (I); and wherein R_9 is selected from hydrogen, (1-6C)alkyl, halo, CF_3, and OCF_3; or

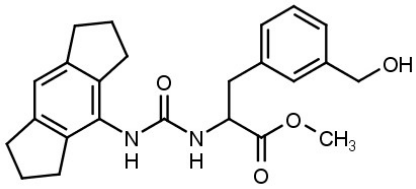
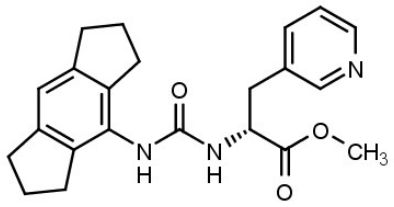
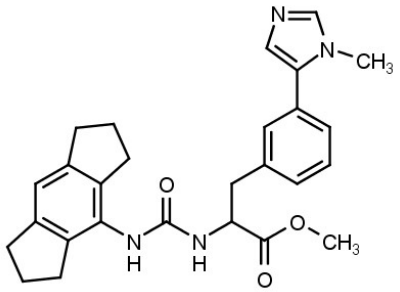
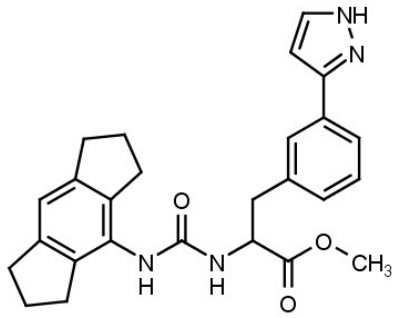
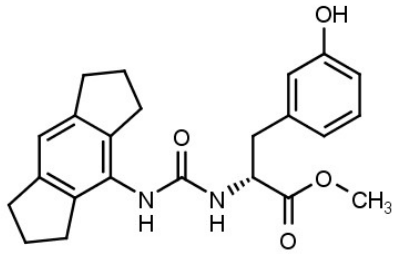
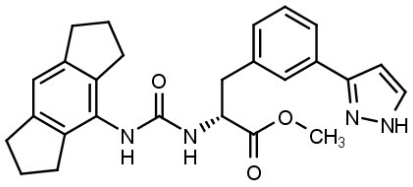
an unsubstituted hexahydroindacene ring:

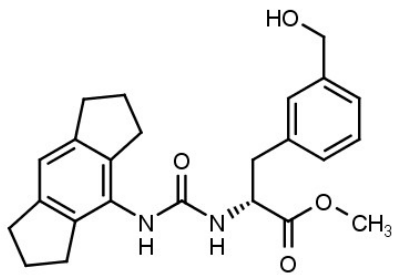
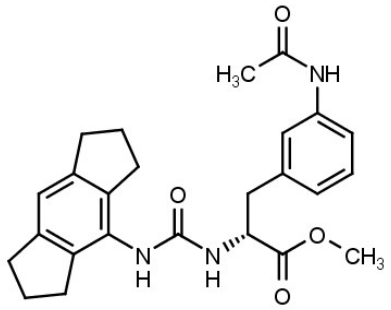
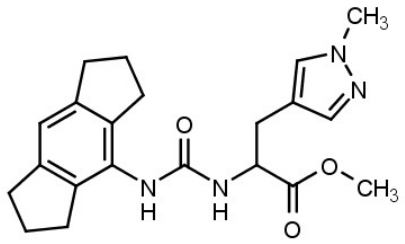
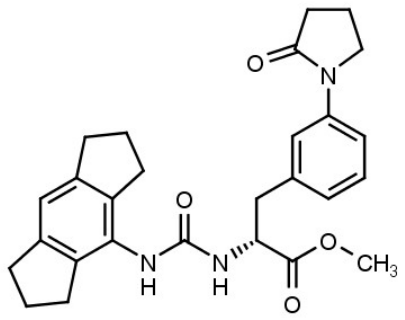
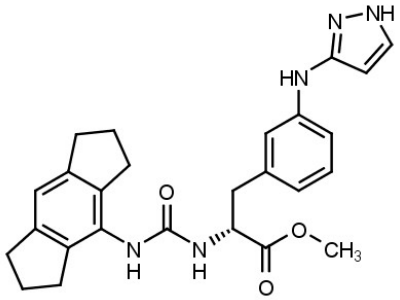


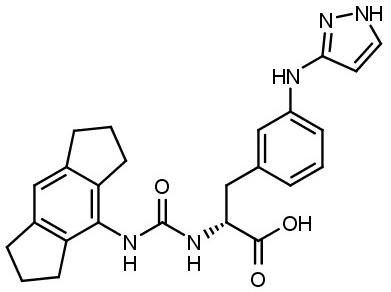
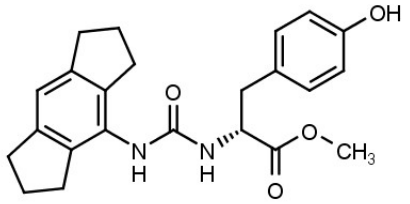
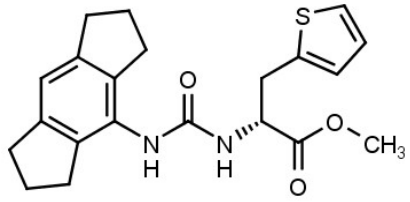
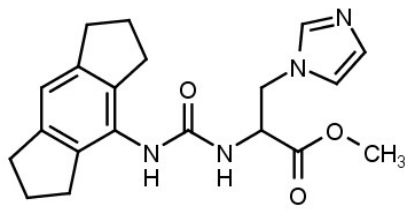
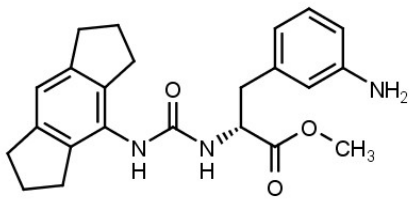
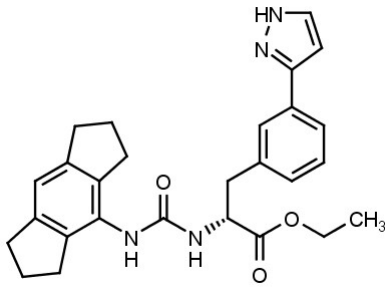
wherein # denotes the bond to the nitrogen atom of Formula (I).

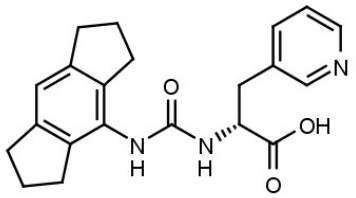
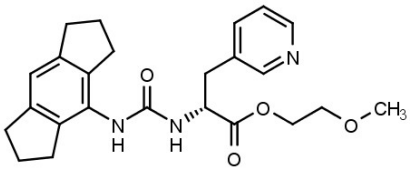
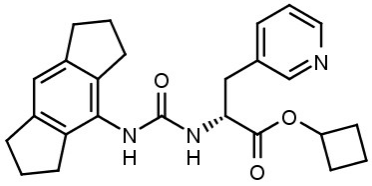
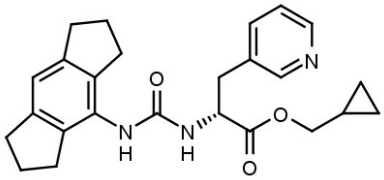
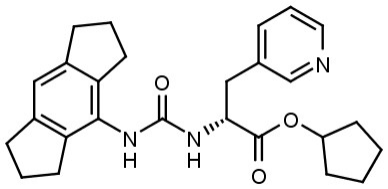
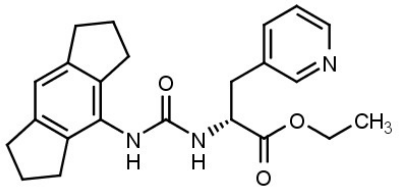
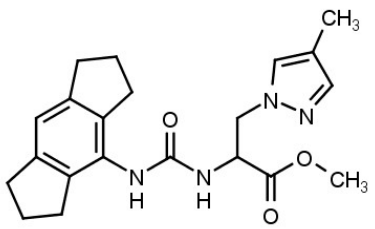
8. The compound according to any one of claims 1-7, wherein the compound is selected from the group consisting of:

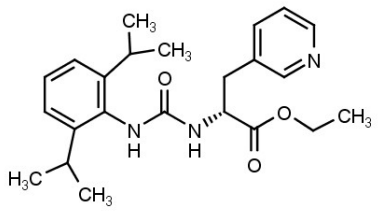
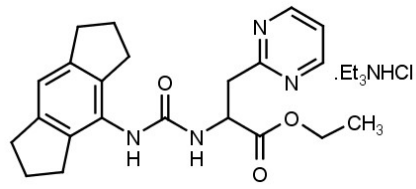
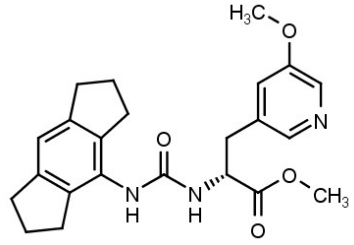
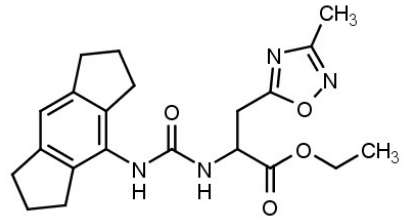
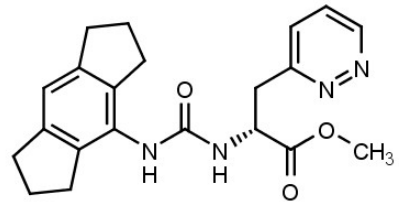
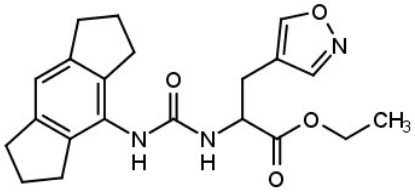
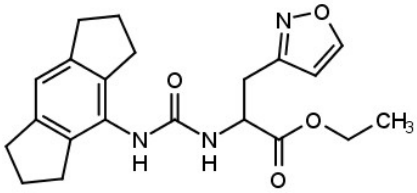
Structure	Name
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	Methyl2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(2-hydroxyphenyl)propanoate;
	methyl 3-(3-acetylphenyl)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}propanoate;
	methyl (2R)-3-(4-cyanophenyl)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}propanoate;
	methyl (2R)-3-(3-cyanophenyl)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}propanoate;
	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyridin-2-yl)propanoate;

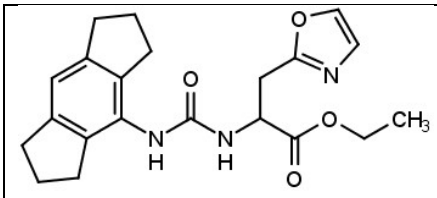
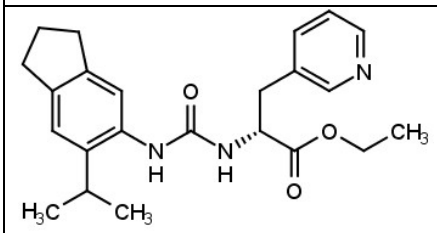
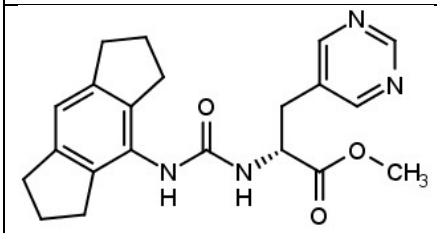
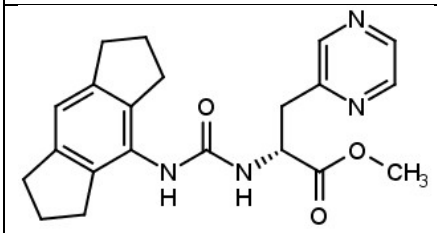
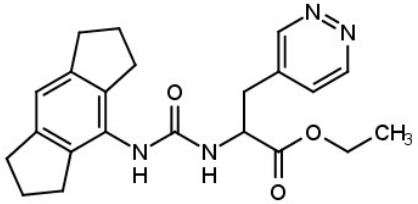
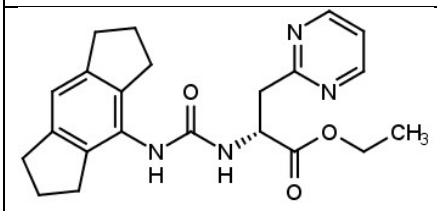
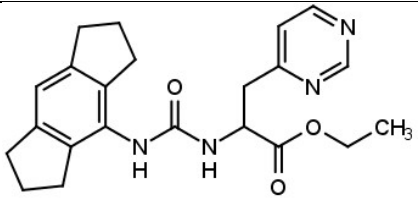
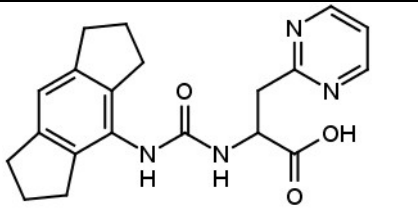
	methyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-[3-(hydroxymethyl)phenyl]propanoate;
	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyridin-3-yl)propanoate;
	methyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-[3-(1-methyl-1H-imidazol-5-yl)phenyl]propanoate;
	Methyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-[3-(1H-pyrazol-5-yl)phenyl]propanoate;
	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(3-hydroxyphenyl)propanoate;
	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-[3-(1H-pyrazol-3-yl)phenyl]propanoate;

	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-[3-(hydroxymethyl)phenyl]propanoate;
	methyl (2R)-3-(3-acetamidophenyl)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}propanoate;
	methyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(1-methyl-1H-pyrazol-4-yl)propanoate;
	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-[3-(2-oxopyrrolidin-1-yl)phenyl]propanoate;
	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-{3-[(1H-pyrazol-3-yl)amino]phenyl}propanoate;

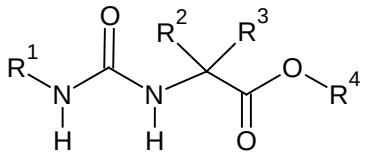
	(2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-[3-(1H-pyrazol-3-yl)phenyl]propanoic acid;
	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(4-hydroxyphenyl)propanoate;
	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(thiophen-2-yl)propanoate;
	methyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(1H-imidazol-1-yl)propanoate;
	methyl (2R)-3-(3-aminophenyl)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}propanoate;
	ethyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-[3-(1H-pyrazol-4-yl)phenyl]propanoate;

	(2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyridin-3-yl)propanoic acid;
	2-methoxyethyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyridin-3-yl)propanoate;
	cyclobutyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyridin-3-yl)propanoate;
	cyclopropylmethyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyridin-3-yl)propanoate;
	cyclopentyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyridin-3-yl)propanoate;
	ethyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyridin-3-yl)propanoate;
	methyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(4-methyl-1H-pyrazol-1-yl)propanoate;

	ethyl (2R)-2-({[2,6-bis(propan-2-yl)phenyl]carbamoyl}amino)-3-(pyridin-3-yl)propanoate;
	ethyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyrimidin-2-yl)propanoate;
	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(5-methoxypyridin-3-yl)propanoate;
	ethyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(3-methyl-1,2,4-oxadiazol-5-yl)propanoate;
	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyridazin-3-yl)propanoate;
	ethyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(1,2-oxazol-4-yl)propanoate;
	Ethyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(1,2-oxazol-3-yl)propanoate;

	ethyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(1,3-oxazol-2-yl)propanoate;
	ethyl (2R)-2-({[6-(propan-2-yl)-2,3-dihydro-1H-inden-5-yl]carbamoyl}amino)-3-(pyridin-3-yl)propanoate;
	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyrimidin-5-yl)propanoate;
	methyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyrazin-2-yl)propanoate;
	ethyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyridazin-4-yl)propanoate;
	ethyl (2R)-2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyrimidin-2-yl)propanoate;
	ethyl 2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyrimidin-4-yl)propanoate; and
	2-{[(1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl]amino}-3-(pyrimidin-2-yl)propanoic acid.

9. A compound of Formula (I), or a prodrug, or pharmaceutically acceptable salt thereof:



in which:

R_1 is a 5 or 6 membered alkyl or aryl monocycle, having at least one group substituent comprising a (2-8C) alkyl **or** a 9 or 10 membered bicyclic partially unsaturated carbocyclic ring system, wherein said bicyclic ring system is optionally substituted by 1, 2, 3 or 4 substituents independently selected from (1-6C)alkyl, (2-6C)alkenylene, (2-6C)alkynylene, (3-8C)cycloalkyl, (1-3C)alkoxy, halo, oxo, hydroxy, cyano, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]-amino, CF_3, OCF_3, $S(O)_2CH_3$, $S(O)CH_3$, $S(O)_2NH_2$, $S(O)_2NHCH_3$, $S(O)_2N(CH_3)_2$, $NHS(O)_2CH_3$, and $N(CH_3)S(O)_2CH_3$ **or** a 12, 13, 14, 15 or 16 membered tricyclic partially unsaturated carbocyclic ring system, wherein said tricyclic ring system is optionally substituted by 1, 2, 3 or 4 substituents independently selected from (1-6C)alkyl, (2-6C)alkenylene, (2-6C)alkynylene, (3-8C)cycloalkyl, (1-3C)alkoxy, halo, oxo, hydroxy, cyano, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]-amino, CF_3, OCF_3, $S(O)_2CH_3$, $S(O)CH_3$, $S(O)_2NH_2$, $S(O)_2NHCH_3$, $S(O)_2N(CH_3)_2$, $NHS(O)_2CH_3$, and $N(CH_3)S(O)_2CH_3$;

R_2 is H

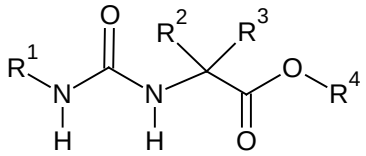
R_3 is alkyl(C1-4)-**R_7**,

wherein **R_7** is selected from a 5 or 6 membered monocyclic aryl or non-aryl ring system comprising 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur, and 3, 4, 5 or 6 membered monocyclic heterocyclyl ring system comprising 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, wherein said **R_7** ring

system is optionally substituted with 1 or more substituents independently selected from (1-6C) alkyl, alkylhydroxy, nitro, OH , $COCH_3$, halo, amino, cyano, an optionally N-linked 5 or 6 membered monocyclic heteroaryl ring comprising 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, and an optionally N-linked 3, 4, 5 or 6 membered monocyclic heterocyclyl ring system comprising 1 heteroatom independently selected from oxygen, nitrogen and sulfur, said ring being optionally substituted with an alkyl, oxo, halo, or amino group; and

R_4 is H, alkyl, monocyclic alkyl or monocyclic aryl group.

10. A compound of Formula (I), or a prodrug, or pharmaceutically acceptable salt thereof:



in which:

R_1 is a 5 or 6 membered alkyl or aryl monocycle, having at least one group substituent comprising a (2-8C) alkyl **or** a 9 or 10 membered bicyclic partially unsaturated carbocyclic ring system, wherein said bicyclic ring system is optionally substituted by 1, 2, 3 or 4 substituents independently selected from (1-6C)alkyl, (2-6C)alkenylene, (2-6C)alkynylene, (3-8C)cycloalkyl, (1-3C)alkoxy, halo, oxo, hydroxy, cyano, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]-amino, CF_3, OCF_3, $S(O)_2CH_3$, $S(O)CH_3$, $S(O)_2NH_2$, $S(O)_2NHCH_3$, $S(O)_2N(CH_3)_2$, $NHS(O)_2CH_3$, and $N(CH_3)S(O)_2CH_3$ **or** a 12, 13, 14, 15 or 16 membered tricyclic partially unsaturated carbocyclic ring system, wherein said tricyclic ring system is optionally substituted by 1, 2, 3 or 4 substituents independently selected from (1-6C)alkyl, (2-6C)alkenylene, (2-6C)alkynylene, (3-8C)cycloalkyl, (1-3C)alkoxy, halo, oxo, hydroxy, cyano, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]-amino, CF_3, OCF_3, $S(O)_2CH_3$, $S(O)CH_3$, $S(O)_2NH_2$, $S(O)_2NHCH_3$, $S(O)_2N(CH_3)_2$, $NHS(O)_2CH_3$, and $N(CH_3)S(O)_2CH_3$;

R_2 is H;

R_3 is alkyl(C1-4)-**R_7**,

wherein **R_7** is selected from a 5 or 6 membered monocyclic aryl or non-aryl ring system optionally comprising 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur, and 3, 4, 5 or 6 membered monocyclic heterocyclyl ring system optionally comprising 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur or a 3, 4, 5 or 6 membered saturated or partially unsaturated carbocyclic ring system and said **R_7** ring system is substituted with 1 or more substituents independently selected from (1-6C) alkyl, alkylhydroxy, nitro, OH , $COCH_3$, halo, amino, cyano, an optionally N-linked 5 or 6 membered monocyclic heteroaryl ring comprising 1 or 2 heteroatoms independently selected from oxygen, nitrogen and sulfur, and an optionally N-linked 3, 4, 5 or 6 membered monocyclic heterocyclyl ring system comprising 1 heteroatom independently selected from oxygen, nitrogen and sulfur, said ring being optionally substituted with an alkyl, oxo, halo, or amino group; and

R_4 is H, alkyl, monocyclic alkyl, or monocyclic aryl group.

11. A pharmaceutical composition comprising the compound according to any one of claims 1-10 or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

12. A method of inhibiting the NLRP3 inflammasome activity *in vitro*, said method comprising contacting a cell with an effective amount of the compound according to any one of claims 1-10 or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 11.

13. The compound according to any one of claims 1-10 or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 11, for use in therapy.

14. The compound according to any one of claims 1-10 or the pharmaceutically

acceptable salt thereof, or the pharmaceutical composition according to claim 11, for use in the treatment of a disorder in which inflammasome activity is implicated.

15. The compound according to any one of claims 1-10 or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 11, for use in the treatment of a disorder, wherein the disorder is a cancer being selected from gastrointestinal cancer, skin cancer, non-small-cell lung carcinoma, and colorectal adenocarcinoma.

16. The compound according to any one of claims 1-10 or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 11, for use in treatment of a disorder, wherein the disorder is an auto-inflammatory disorder, an autoimmune disorder, a neurodegenerative disease, or a cancer.

17. The compound according to any one of claims 1-10 or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 11, for use in treatment of a disorder, wherein the disorder is selected from cryopyrin-associated auto-inflammatory syndrome (CAPS) including familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome, neonatal-onset multisystem inflammatory disease (NOMID), familial Mediterranean fever, nonalcoholic fatty liver disease (NAFLD), gout, rheumatoid arthritis, Crohn's disease, COPD, fibrosis, obesity, type 2 diabetes, multiple sclerosis, neuro-inflammation occurring in protein misfolding diseases, Parkinson's disease, osteoarthritis, Non-alcoholic steatohepatitis (NASH), and Alzheimer's disease.

18. Use of the compound according to any one of claims 1-10 or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 11, in the preparation of a medicament for the treatment of a disorder in which inflammasome activity is implicated.

19. Use of the compound according to any one of claims 1-10 or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 11, in the

preparation of a medicament for the treatment of a disorder, wherein the disorder is a cancer being selected from gastrointestinal cancer, skin cancer, non-small-cell lung carcinoma, and colorectal adenocarcinoma.

20. Use of the compound according to any one of claims 1-10 or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 11, in the preparation of a medicament for the treatment of a disorder, wherein the disorder is an auto-inflammatory disorder, an autoimmune disorder, a neurodegenerative disease, or a cancer.

21. Use of the compound according to any one of claims 1-10 or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 11, in the preparation of a medicament for the treatment of a disorder, wherein the disorder is selected from cryopyrin-associated auto-inflammatory syndrome (CAPS) including familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), chronic infantile neurological cutaneous and articular (CINCA) syndrome, neonatal-onset multisystem inflammatory disease (NOMID), familial Mediterranean fever, nonalcoholic fatty liver disease (NAFLD), gout, rheumatoid arthritis, Crohn's disease, COPD, fibrosis, obesity, type 2 diabetes, multiple sclerosis, neuro-inflammation occurring in protein misfolding diseases, Parkinson's disease, osteoarthritis, Non-alcoholic steatohepatitis (NASH), and Alzheimer's disease.