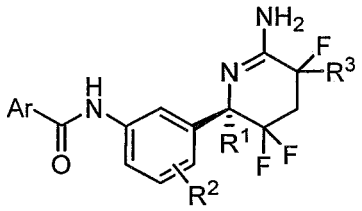
SUMMARY OF THE INVENTION

Contrary to the teachings of Ginman, et al. and Woltering, T. J., et al., the inventors have discovered a series of amidine compounds which are brain penetrant and are thus able to inhibit BACE1 in the brain after peripheral dose of said compounds. Accordingly, the present invention relates to said BACE1 inhibitors in combination with other compounds useful in the treatment neurodegenerative or cognitive disorders.

In an aspect, there is provided the use of a therapeutically effective amounts of 1) a BACE1 inhibitor of Formula I



Formula I

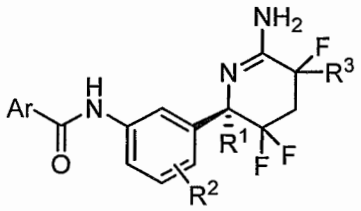
wherein Ar is selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, 1,2,4-triazolyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, 1,3,4-thiadiazolyl, isothiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, furazanyl and 1,2,4-thiadiazolyl and where the Ar is optionally substituted with one or more halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl or C_1-C_6 alkoxy;

R^1 is C_1-C_3 alkyl or C_1-C_3 fluoroalkyl;

R^2 is hydrogen, halogen, C_1-C_3 fluoroalkyl or C_1-C_3 alkyl;

R^3 is C_1-C_3 alkyl; or a pharmaceutically acceptable salt thereof; and 2) a compound useful in active or passive Tau immunotherapy, a compound useful in active or passive Aβ peptide immunotherapy, an NMDA receptor antagonists, an acetylcholine esterase inhibitor, an antiepileptic, an anti-inflammatory drug, a Tau protein aggregation inhibitor or an SSRI, in the manufacture of a medicament for treating a neurodegenerative or cognitive disorder, such as Alzheimer's disease.

In another aspect, there is provided a pharmaceutical composition comprising 1) a BACE1 inhibitor of Formula I



Formula I

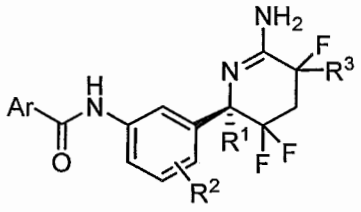
wherein Ar is selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, 1,2,4-triazolyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, 1,3,4-thiadiazolyl, isothiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, furazanyl and 1,2,4-thiadiazolyl and where the Ar is optionally substituted with one or more halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl or C_1-C_6 alkoxy;

R^1 is C_1-C_3 alkyl or C_1-C_3 fluoroalkyl;

R^2 is hydrogen, halogen, C_1-C_3 fluoroalkyl or C_1-C_3 alkyl;

R^3 is C_1-C_3 alkyl; or a pharmaceutically acceptable salt thereof and 2) a compound useful in active or passive Tau immunotherapy, a compound useful in active or passive Aβ peptide immunotherapy, an NMDA receptor antagonists, an acetylcholine esterase inhibitor, an antiepileptic, an anti-inflammatory drug, a Tau aggregation inhibitor or an SSRI and a pharmaceutically acceptable carrier.

Accordingly, in one embodiment the present invention relates to a method for the treatment of a neurodegenerative or cognitive disorder, the method comprising the combined administration to a patient in need thereof of therapeutically effective amounts of 1) a compound of Formula I



Formula I

wherein Ar is selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, 1,2,4-triazolyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, 1,3,4-thiadiazolyl, isothiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, furazanyl and 1,2,4-thiadiazolyl and where the Ar is optionally substituted with one or more halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl or C_1-C_6 alkoxy;

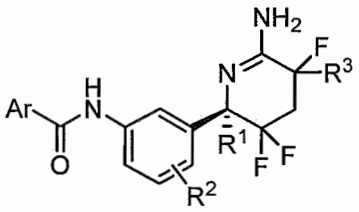
R^1 is C_1-C_3 alkyl or C_1-C_3 fluoroalkyl;

R^2 is hydrogen, halogen, C_1-C_3 fluoroalkyl or C_1-C_3 alkyl;
R^3 is C_1-C_3 alkyl; or a pharmaceutically acceptable salt thereof and 2) a compound useful in active or passive Tau immunotherapy, a compound useful in active or passive Aβ peptide immunotherapy, an NMDA receptor antagonists, an acetylcholine esterase inhibitor, an antiepileptic, an anti-inflammatory drug, a Tau aggregation inhibitor or an SSRI.

The present invention further provides a pharmaceutical composition comprising 1) a compound of Formula I or a pharmaceutically acceptable salt thereof and 2) a compound useful in active or passive Tau immunotherapy, a compound useful in active or passive Aβ peptide immunotherapy, an NMDA receptor antagonists, an acetylcholine esterase inhibitor, an

CLAIMS

1. Use of a therapeutically effective amounts of 1) a BACE1 inhibitor of Formula I



Formula I

wherein Ar is selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, 1,2,4-triazolyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, 1,3,4-thiadiazolyl, isothiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, furazanyl and 1,2,4-thiadiazolyl and where the Ar is optionally substituted with one or more halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl or C_1-C_6 alkoxy;

R^1 is C_1-C_3 alkyl or C_1-C_3 fluoroalkyl;

R^2 is hydrogen, halogen, C_1-C_3 fluoroalkyl or C_1-C_3 alkyl;

R^3 is C_1-C_3 alkyl; or a pharmaceutically acceptable salt thereof; and 2) a compound useful in active or passive Tau immunotherapy, a compound useful in active or passive Aβ peptide immunotherapy, an NMDA receptor antagonists, an acetylcholine esterase inhibitor, an antiepileptic, an anti-inflammatory drug, a Tau protein aggregation inhibitor or an SSRI, in the manufacture of a medicament for treating a neurodegenerative or cognitive disorder, such as Alzheimer's disease.

2. The use according to claim 1, wherein said BACE1 inhibitor is selected from the group consisting of

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluoro-phenyl)-5-fluoropicolinamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluoro-phenyl)-5-fluoropicolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluoro-phenyl)-5-chloropicolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-cyanopicolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-1-(difluoromethyl)-1*H*-pyrazole-3-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-methyloxazole-4-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)thiazole-2-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-bromo-1-methyl-1*H*-imidazole-2-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-methylthiazole-2-carboxamide,

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(trifluoromethyl)picolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrimidine-2-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-(difluoromethyl)oxazole-4-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-(fluoromethyl)oxazole-2-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-(fluoromethyl)thiazole-2-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(difluoromethyl)pyrazine-2-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypicolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-cyano-3-methylpicolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-3-methyl-1,2,4-oxadiazole-5-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-1-methyl-1*H*-1,2,4-triazole-3-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-1-(difluoromethyl)-1*H*-pyrazole-3-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(difluoromethyl)pyrazine-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrimidine-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-methylthiazole-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(trifluoromethyl)picolinamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-(difluoromethyl)oxazole-4-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-(fluoromethyl)oxazole-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-(fluoromethyl)thiazole-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-cyanopicolinamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-chloropicolinamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-methyloxazole-4-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methyl-1,2,4-oxadiazole-3-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)thiazole-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-bromo-1-methyl-1*H*-imidazole-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-1,4-dimethyl-1*H*-imidazole-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-3-methylisoxazole-5-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methylfuran-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-methyloxazole-5-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(methoxy-d_3)picolinamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-chlorobenzamide,

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(difluoromethoxy)picolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-3-fluoro-5-methoxypicolinamide;

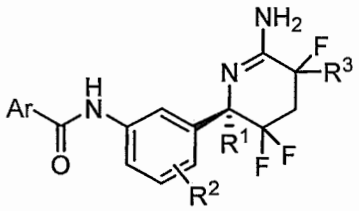
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4 fluorophenyl)-2,5-dimethyloxazole-4-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-5-(methoxy-*d3*)picolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-fluoro-3-methylpicolinamide;

or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising 1) a BACE1 inhibitor of Formula I



Formula I

wherein Ar is selected from the group consisting of phenyl, pyridyl, pyrimidyl, pyrazinyl, imidazolyl, pyrazolyl, 1,2,4-triazolyl, thiophenyl, thiazolyl, oxazolyl, isoxazolyl, 1,3,4-thiadiazolyl, isothiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, furazanyl and 1,2,4-thiadiazolyl and where the Ar is optionally substituted with one or more halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl or C_1-C_6 alkoxy;

R^1 is C_1-C_3 alkyl or C_1-C_3 fluoroalkyl;

R^2 is hydrogen, halogen, C_1-C_3 fluoroalkyl or C_1-C_3 alkyl;

R^3 is C_1-C_3 alkyl; or a pharmaceutically acceptable salt thereof and 2) a compound useful in active or passive Tau immunotherapy, a compound useful in active or passive Aβ peptide immunotherapy, an NMDA receptor antagonists, an acetylcholine esterase inhibitor, an antiepileptic, an anti-inflammatory drug, a Tau aggregation inhibitor or an SSRI and a pharmaceutically acceptable carrier.

4. The composition according to claim 3, wherein said BACE1 inhibitor is selected from the group consisting of
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-fluoropicolinamide;
N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-fluoropicolinamide;
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-chloropicolinamide;
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-cyanopicolinamide;
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide;
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-1-(difluoromethyl)-1*H*-pyrazole-3-carboxamide;
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-methyloxazole-4-carboxamide;
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)thiazole-2-carboxamide;
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-bromo-1-methyl-1*H*-imidazole-2-carboxamide;
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluoro-fphenyl)-4-methylthiazole-2-carboxamide,
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(trifluoromethyl)picolinamide;
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrimidine-2-carboxamide;
N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-(difluoromethyl)oxazole-4-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-(fluoromethyl)oxazole-2-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-(fluoromethyl)thiazole-2-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(difluoromethyl)pyrazine-2-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypicolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-cyano-3-methylpicolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-3-methyl-1,2,4-oxadiazole-5-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-1-methyl-1*H*-1,2,4-triazole-3-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-1-(difluoromethyl)-1*H*-pyrazole-3-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(difluoromethyl)pyrazine-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrazine-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methoxypyrimidine-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-methylthiazole-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(trifluoromethyl)picolinamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-(difluoromethyl)oxazole-4-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-(fluoromethyl)oxazole-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-(fluoromethyl)thiazole-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-cyanopicolinamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-chloropicolinamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-methyloxazole-4-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methyl-1,2,4-oxadiazole-3-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)thiazole-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-bromo-1-methyl-1*H*-imidazole-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-1,4-dimethyl-1*H*-imidazole-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-3-methylisoxazole-5-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-methylfuran-2-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-2-methyloxazole-5-carboxamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(methoxy-d_3)picolinamide;

N-(3-((2*R*,5*R*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-4-chlorobenzamide,

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-(difluoromethoxy)picolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-3-fluoro-5-methoxypicolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4 fluorophenyl)-2,5-dimethyloxazole-4-carboxamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-5-(methoxy-*d3*)picolinamide;

N-(3-((2*R*,5*S*)-6-amino-3,3,5-trifluoro-2,5-dimethyl-2,3,4,5-tetrahydropyridin-2-yl)-4-fluorophenyl)-5-fluoro-3-methylpicolinamide;
or a pharmaceutically acceptable salt thereof.

5. The use according to any one of claims 1 and 2, wherein a therapeutically effective amount of the two components (1) a compound of Formula I or a pharmaceutically acceptable salt thereof and (2) a compound useful in passive Aβ peptide immunotherapy which is an anti-Aβ peptide antibody are to be administered in combination, and wherein said anti-Aβ peptide antibody is selected from the group consisting of gantenerumab, solanezumab, aducanumab and crenezumab.

6. The use according to any one of claims 1 and 2, wherein a therapeutically effective amount of two components (1) a compound of Formula I or a pharmaceutically acceptable salt thereof and (2) a compound selected from the group consisting of a Tau protein aggregation inhibitor, such as TRX-0237, also known as Methylene Blue; and an SSRI (Selective Serotonin Reuptake Inhibitor), such as citalopram, are to be administered in combination.

7. The use according to any one of claims 1 and 2, wherein a therapeutically effective amount of two components (1) a compound of Formula I or a pharmaceutically acceptable salt thereof and (2) an anti-N3-pGlu Abeta monoclonal antibody, are to be administered in combination.

8. The method according to any one of claims 1 and 2, wherein a therapeutically effective amount of two components (1) a compound of Formula I or a pharmaceutically acceptable salt thereof and (2) a compound selected from the group consisting of an NMDA receptor antagonist, such as memantine; and an acetylcholine esterase inhibitor, such as donepezil, rivastigmine or galantamine, are to be administered in combination.

9. The use according to any one of claims 1 and 2, wherein a therapeutically effective amount of two components (1) a compound of Formula I or a pharmaceutically acceptable salt thereof and (2) a compound selected from an NSAID (non-steriod anti-inflammatory drugs); a TNFα inhibitor, such as etanercept; and p38 MAP kinase inhibitors, such as VX-745 (5-

(2,6-Dichlorophenyl)-2-((2,4-difluorophenyl)thio)-6H-pyrimido[1,6-b]pyridazin-6-one), are to be administered in combination.

10. The use according to any one of claims 1 and 2, wherein a therapeutically effective amount of two components (1) a compound of Formula I or a pharmaceutically acceptable salt thereof and (2) an antibody to hyperphosphorylated Tau, such as wherein the hyperphosphorylated Tau is selected from the group consisting of an antibody to the epitope pSer413 of hyperphosphorylated Tau protein, an antibody to the epitope pS409 of hyperphosphorylated Tau protein , an antibody to the epitope pS404 of hyperphosphorylated Tau protein, an antibody to the epitope pS396 of hyperphosphorylated Tau protein, an antibody to the conformation epitope pS396/pS404 of hyperphosphorylated Tau protein, an antibody to the epitope pS422 of hyperphosphorylated Tau protein, an antibody to the epitope pT212/pS214 of hyperphosphorylated Tau protein, and an antibody to the epitope pT231/pS235 of hyperphosphorylated Tau protein, are to be administered in combination.