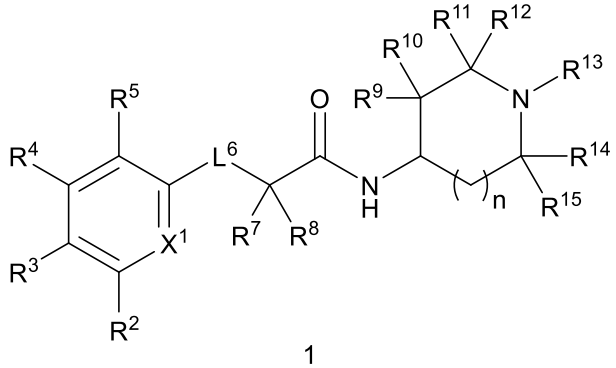
WHAT IS CLAIMED IS:

1. A compound of Formula 1,



1

or a pharmaceutically acceptable salt thereof in which:

X^1 is selected from N and CR^1;

n is selected from 0 and 1;

R^1, R^2, R^3, and R^4 are each independently selected from

(i) hydrogen, halo, hydroxy and cyano; and

(ii) C_{1-3} alkyl, C_{1-3} alkoxy and C_{3-6} cycloalkyl, each unsubstituted or substituted with 1 to 3 substituents independently selected from halo;

R^5 is hydrogen;

L^6 is selected from $-CH_2-$, $-N(R^6)-$, $*-N(R^6)CH_2-$ and -O-, wherein R^6 is selected from hydrogen and C_{1-3} alkyl, and * represents the point of attachment to an aromatic ring carbon atom;

R^7 and R^8 are each independently selected from halo and C_{1-3} alkyl, provided R^7 and R^8 are not both methyl; or R^7 and R^8, together with the carbon atom to which they are attached, form a cyclopropylidene;

R^9 is selected from

(i) hydrogen and halo; and

(ii) C_{1-3} alkyl and phenyl, each unsubstituted or substituted with 1 to 3 substituents independently selected from halo;

R^{10} is hydrogen; or

R^9 and R^{10}, together with the carbon atom to which they are attached, form a cyclopropylidene;

R^{11} is selected from hydrogen, halo and C_{1-3} alkyl which is unsubstituted or substituted with 1 to 3 substituents independently selected from halo, , and R^{12} is hydrogen; and

(a) R^{13} is selected from hydrogen and C_{1-3} alkyl; and

R^{14} and R^{15} are each hydrogen; or

(b) R^{13} and R^{14} together form a propane-1,3-diyl bridging the nitrogen and carbon atoms to which they are respectively attached; and

R^{15} is selected from hydrogen, halo, and C_{1-3} alkyl which is unsubstituted or substituted with 1 to 3 substituents independently selected from halo;

provided

(i) if X^1 is CR^1, L^6 is $-CH_2-$, and R^7 and R^8 form a cyclopropylidene, then at least one of R^1, R^2, R^3, R^4, R^5, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is not hydrogen;

(ii) if X^1 is CR^1, L^6 is $-CH_2-$, n is 0, R^1, R^2, R^4, R^5, R^{11}, R^{12}, R^{14} and R^{15} are each hydrogen, R^7 and R^8 form a cyclopropylidene, and R^9, R^{10} and R^{13} are each methyl, then R^3 is not fluoro or hydroxy;

(iii) if X^1 is CR^1, L^6 is $-CH_2-$, n is 0, R^1 is fluoro, R^2, R^3, R^4, R^5, R^{11}, R^{12}, R^{14} and R^{15} are each hydrogen, and R^7 and R^8 form a cyclopropylidene, then R^9, R^{10} and R^{13} are not all hydrogen and not all methyl;

(iv) if X^1 is CR^1, L^6 is $-CH_2-$, n is 1, R^1, R^2, R^3, R^4, R^5, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each hydrogen, and R^7 and R^8 form a cyclopropylidene, then R^9 is not methyl;

(v) if X^1 is CR^1, L^6 is $-CH_2-$, n is 1, R^1, R^2, R^3, R^4, R^5, R^9, R^{10}, R^{12}, R^{13}, R^{14} and R^{15} are each hydrogen, and R^7 and R^8 form a cyclopropylidene, then R^{11} is not methyl;

(vi) if X^1 is CR^1, n is 0, R^1, R^2, R^3, R^4, R^5, R^{11}, R^{12}, R^{14} and R^{15} are each hydrogen, R^7 and R^8 form a cyclopropylidene, R^9 and R^{10} are each methyl, and R^{13} is ethyl, then L^6 is not -O- or -NH-;

(vii) if X^1 is CR^1, L^6 is $-CH_2-$, n is 0, R^1, R^2, R^4, R^5, R^{11}, R^{12}, R^{14} and R^{15} are each hydrogen, R^7 and R^8 form a cyclopropylidene, R^9 and R^{10} are both methyl, and R^{13} is ethyl, then R^3 is not hydroxy;

(viii) if X^1 is CR^1, L^6 is $-CH_2-$, n is 1, R^7 and R^8 form a cyclopropylidene, and R^{13} and R^{14} together form a propane-1,3-diyl bridging the nitrogen and carbon atoms to which they

are respectively attached, then at least one of R^1, R^2, R^3, R^4, R^5, R^9, R^{10}, R^{11}, R^{12} and R^{15} is not hydrogen;

(ix) if X^1 is CR^1, L^6 is $-CH_2-$, n is 1, R^7 and R^8 form a cyclopropylidene, and R^{13} and R^{14} together form a propane-1,3-diyl bridging the nitrogen and carbon atoms to which they are respectively attached, and R^2, R^3, R^4, R^5, R^9, R^{10}, R^{11}, R^{12} and R^{15} are each hydrogen, then R^1 is not fluoro; and

(x) if X^1 is CR^1, L^6 is $-CH_2-$, n is 1, R^7 and R^8 form a cyclopropylidene, and R^{13} and R^{14} together form a propane-1,3-diyl bridging the nitrogen and carbon atoms to which they are respectively attached, and R^1, R^2, R^4, R^5, R^9, R^{10}, R^{11}, R^{12} and R^{15} are each hydrogen, then R^3 is not fluoro.

2. The compound or pharmaceutically acceptable salt according to claim 1, wherein X^1 is CR^1.

3. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 2, wherein R^1 is selected from hydrogen, halo, cyano, methyl, methoxy and cyclopropyl.

4. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 3, wherein R^2 is selected from hydrogen, halo, methyl and methoxy.

5. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 4, wherein R^3 is selected from hydrogen, halo and methyl.

6. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 5, wherein R^4 is selected from hydrogen, halo, methyl and methoxy.

7. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 6, wherein at least one of R^1, R^2, R^3, and R^4 is selected from

(i) halo, hydroxy and cyano; and

(ii) C_{1-3} alkyl, C_{1-3} alkoxy and C_{3-6} cycloalkyl, each unsubstituted or substituted with 1 to 3 substituents independently selected from halo .

8. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 7, wherein R^1 is hydrogen.

9. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 8, wherein L^6 is selected from $-CH_2-$ and -O-.

10. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 9, wherein R^7 and R^8 are each independently selected from fluoro and C_{1-3} alkyl, provided R^7 and R^8 are not both methyl, or R^7 and R^8, together with the carbon atom to which they are attached, form a cyclopropylidene.

11. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 10, wherein R^{11} is selected from hydrogen, halo and methyl, and R^{13} is selected from hydrogen and methyl.

12. The compound or pharmaceutically acceptable salt according to any one of claims 1 to 11, wherein n is 1.

13. The compound according to claim 1, which is selected from the following compounds:

(*R*)-1-(3-methylbenzyl)-*N*-(1-methylpyrrolidin-3-yl)cyclopropane-1-carboxamide;

N-(1-methyl-4-phenylpyrrolidin-3-yl)-1-(3-methylbenzyl)cyclopropane-1-carboxamide;

N-(*trans*-4-isopropyl-1-methylpyrrolidin-3-yl)-1-(3-methylbenzyl)cyclopropane-1-carboxamide;

N-(1,3-dimethylpiperidin-4-yl)-1-(3-methylbenzyl)cyclopropane-1-carboxamide;

N-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-1-(3-methylbenzyl)cyclopropane-1-carboxamide;

N-(1,4-dimethylpyrrolidin-3-yl)-1-(3-methylbenzyl)cyclopropane-1-carboxamide;

1-(2-chlorophenoxy)-*N*-(*trans*-3-ethyl-1-methylpiperidin-4-yl)cyclopropane-1-carboxamide;

1-(2-chlorophenoxy)-*N*-(1,2-dimethylpiperidin-4-yl)cyclopropane-1-carboxamide;

1-(2-chlorophenoxy)-*N*-(hexahydro-1*H*-pyrrolizin-1-yl)cyclopropane-1-carboxamide;

N-(*trans*-1,3-dimethylpiperidin-4-yl)-1-(4-fluorobenzyl)cyclopropane-1-carboxamide ;

N-(*trans*-1,3-dimethylpiperidin-4-yl)-1-(4-methylbenzyl)cyclopropane-1-carboxamide;

N-(*trans*-1,3-dimethylpiperidin-4-yl)-1-(2-methylbenzyl)cyclopropane-1-carboxamide;

1-(4-fluorobenzyl)-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)cyclopropane-1-carboxamide;

2,2-difluoro-2-phenoxy-*N*-(piperidin-4-yl)acetamide ;

1-(3-chlorobenzyl)-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)cyclopropane-1-carboxamide;

1-(2-methylbenzyl)-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)cyclopropane-1-carboxamide;

1-(2-chlorobenzyl)-*N*-(*trans*-1,3-dimethylpiperidin-4-yl)cyclopropane-1-carboxamide;

1-(4-chlorobenzyl)-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)cyclopropane-1-carboxamide;

N-(*trans*-1,3-dimethylpiperidin-4-yl)-1-(3-fluorobenzyl)cyclopropane-1-carboxamide;

N-(*trans*-3-ethyl-1-methylpiperidin-4-yl)-1-(3-methylbenzyl)cyclopropane-1-carboxamide;

1-(4-fluorobenzyl)-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)cyclopropane-1-carboxamide ;

1-(4-chlorobenzyl)-*N*-((3*S,*4*S*)-3-fluoropiperidin-4-yl)cyclopropane-1-carboxamide;

N-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-1-(2-methylbenzyl)cyclopropane-1-carboxamide;

2,2-difluoro-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)-2-phenoxyacetamide;

2,2-difluoro-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)-3-phenylpropanamide;

1-(3-chlorobenzyl)-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)cyclopropane-1-carboxamide;

2,2-difluoro-*N*-(1-methylpiperidin-4-yl)-2-phenoxyacetamide;

2,2-difluoro-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-2-phenoxyacetamide;

1-(4-fluoro-2-methylbenzyl)-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)cyclopropane-1-carboxamide;

1-(4-fluoro-3-methylbenzyl)-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)cyclopropane-1-carboxamide;

2-(2-cyanophenoxy)-2,2-difluoro-*N*-(piperidin-4-yl)acetamide;

2-(2-cyanophenoxy)-2,2-difluoro-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)acetamide;

2,2-difluoro-*N*-(piperidin-4-yl)-2-(*p*-tolyloxy)acetamide ;

N-((3*S*,4*S*)-1,3-dimethylpiperidin-4-yl)-1-(4-fluorobenzyl)cyclopropane-1-carboxamide;

1-(3-chlorobenzyl)-*N*-((3*S*,4*S*)-1,3-dimethylpiperidin-4-yl)cyclopropane-1-carboxamide;

1-(4-chlorobenzyl)-*N*-((3*S*,4*S*)-1,3-dimethylpiperidin-4-yl)cyclopropane-1-carboxamide;

N-((3*S*,4*S*)-1,3-dimethylpiperidin-4-yl)-1-(2-methylbenzyl)cyclopropane-1-carboxamide;

1-(4-chlorobenzyl)-*N*-((3*S*,4*S*)-3-fluoro-1-methylpiperidin-4-yl)cyclopropane-1-carboxamide;

N-((3*S*,4*S*)-1,3-dimethylpiperidin-4-yl)-2,2-difluoro-2-phenoxyacetamide;

1-(((6-chloropyridin-2-yl)(methyl)amino)methyl)-*N*-((2*R*,4*R*)-1,2-dimethylpiperidin-4-yl)cyclopropane-1-carboxamide;

(*R*)-2,2-difluoro-2-phenoxy-*N*-(5-azaspiro[2.4]heptan-7-yl)acetamide;

1-(2-fluorobenzyl)-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)cyclopropane-1-carboxamide;

1-(3-fluorobenzyl)-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)cyclopropane-1-carboxamide;

1-benzyl-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)cyclopropane-1-carboxamide;

N-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-1-(3-methoxybenzyl)cyclopropane-1-carboxamide;

N-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-1-(2-methoxybenzyl)cyclopropane-1-carboxamide;

2,2-difluoro-*N*-((2*S*,4*S*)-2-methylpiperidin-4-yl)-2-phenoxyacetamide;

2,2-difluoro-2-phenoxy-*N*-(5-azaspiro[2.5]octan-8-yl)acetamide;

2,2-difluoro-*N*-(*cis*-2-methylpiperidin-4-yl)-2-phenoxyacetamide;

2,2-difluoro-*N*-((2*R*,4*R*)-2-methylpiperidin-4-yl)-2-phenoxyacetamide;

2,2-difluoro-*N*-((2*R*,4*S*)-2-methylpiperidin-4-yl)-2-phenoxyacetamide;

2,2-difluoro-*N*-((2*S*,4*R*)-2-methylpiperidin-4-yl)-2-phenoxyacetamide;

2,2-difluoro-2-(2-fluorophenoxy)-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)acetamide;

2,2-difluoro-2-(3-fluorophenoxy)-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)acetamide;

2,2-difluoro-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)-2-(*o*-tolyloxy)acetamide;

2,2-difluoro-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)-2-(*m*-tolyloxy)acetamide;

2,2-difluoro-2-(4-fluorophenoxy)-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)acetamide;

1-(3-chlorophenoxy)-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)cyclopropane-1-carboxamide;

1-(2-cyclopropylphenoxy)-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)cyclopropane-1-carboxamide;

2-(2-chlorophenoxy)-2,2-difluoro-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)acetamide;

2-(3-chlorophenoxy)-2,2-difluoro-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)acetamide;

2-(4-chlorophenoxy)-2,2-difluoro-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)acetamide;

1-(3-fluoro-5-methoxybenzyl)-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)cyclopropane-1-carboxamide;

2,2-difluoro-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)-2-(*p*-tolyloxy)acetamide;

2-(2-chlorophenoxy)-2,2-difluoro-*N*-(piperidin-4-yl)acetamide;

2-(2-chlorophenoxy)-2,2-difluoro-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)acetamide; and

a pharmaceutically acceptable salt of any one of the aforementioned compounds.

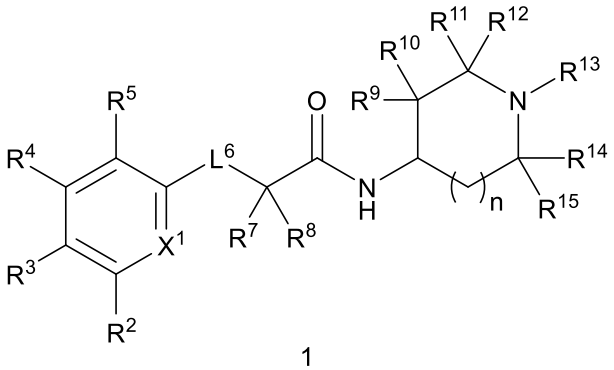
14. The compound of claim 1 or 13, wherein the compound is 3-(4-chlorophenyl)-2,2-dimethyl-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)propenamide or a pharmaceutically acceptable salt thereof.

15. The compound of claim 1 or 13, wherein the compound is 1-(3-chlorobenzyl)-*N*-((3*S*,4*S*)-3-methylpiperidin-4-yl)cyclopropane-1-carboxamide, or a pharmaceutically acceptable salt thereof.

16. The compound of claim 1 or 13, wherein the compound is 2-(2-cyclopropylphenoxy)-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)propenamide, or a pharmaceutically acceptable salt thereof.

17. A compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 16 for use as a medicament.

18. A compound of Formula 1,



1

or a pharmaceutically acceptable salt thereof for use as a medicament in which:

X^1 is selected from N and CR^1;

n is selected from 0 and 1;

R^1, R^2, R^3, R^4 and R^5 are each independently selected from

(i) hydrogen, halo, hydroxy and cyano; and

(ii) C_{1-3} alkyl, C_{1-3} alkoxy and C_{3-6} cycloalkyl, each unsubstituted or substituted with 1 to 3 substituents independently selected from halo;

L^6 is selected from $-CH_2-$, $-N(R^6)-$, $*-N(R^6)CH_2-$ and -O-, wherein R^6 is selected from hydrogen and C_{1-3} alkyl, and * represents the point of attachment to an aromatic ring carbon atom;

R^7 and R^8 are each independently selected from hydrogen, halo and C_{1-3} alkyl, wherein at least one of R^7 and R^8 is not hydrogen; or R^7 and R^8, together with the carbon atom to which they are attached, form a C_{3-6} cycloalkylidene;

R^9 and R^{10} are each independently selected from

(i) hydrogen and halo; and

(ii) C_{1-3} alkyl and phenyl, each unsubstituted or substituted with 1 to 3 substituents independently selected from halo; or

R^9 and R^{10}, together with the carbon atom to which they are attached, form a cyclopropylidene;

R^{11} and R^{12} are each independently selected from hydrogen, halo and C_{1-3} alkyl which is unsubstituted or substituted with 1 to 3 substituents independently selected from halo, provided no more than one of R^{11} and R^{12} is methyl; and

(a) R^{13} is selected from hydrogen and C_{1-3} alkyl; and

R^{14} and R^{15} are each independently selected from hydrogen, halo, and C_{1-3} alkyl which is unsubstituted or substituted with 1 to 3 substituents independently selected from halo, provided no more than one of R^{14} and R^{15} is methyl; or

(b) R^{13} and R^{14} together form a propane-1,3-diyl bridging the nitrogen and carbon atoms to which they are respectively attached; and

R^{15} is selected from hydrogen, halo, and C_{1-3} alkyl which is unsubstituted or substituted with 1 to 3 substituents independently selected from halo;

provided

(i) if X is CR^1, n is 1, L^6 is -O-, R^7 is methyl and R^8 is hydrogen, then at least one of R^1, R^2, R^3, R^4, R^5, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} or R^{15} is not hydrogen;

(ii) if X is CR^1, n is 1, L^6 is -O-, R^7 and R^8 are both methyl, and R^1, R^2, R^4, R^5, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each hydrogen, then R^3 is not chloro; and

(iii) if X is CR^1, n is 1, L^6 is -O-, R^7 is methyl or ethyl, R^1, R^2, R^3, R^4, R^5, R^8, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each hydrogen, then R^9 is not unsubstituted phenyl.

19. A pharmaceutical composition comprising:
a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 18; and a pharmaceutically acceptable excipient.

20. A compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 18 for use in treating a disease, disorder or condition selected from Alzheimer's disease, depression, anxiety, schizophrenia, bipolar disorder, autism, epilepsy, pain, and hyperactivity disorder.

21. A combination comprising a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 18, and at least one additional pharmacologically active agent selected from beta-secretase inhibitors, gamma-secretase inhibitors, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory drugs, vitamin E, anti-amyloid antibodies, antidepressants, antipsychotics, anxiolytics, and anticonvulsants.