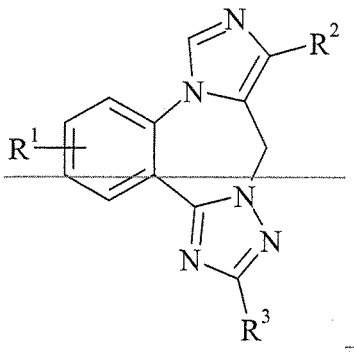
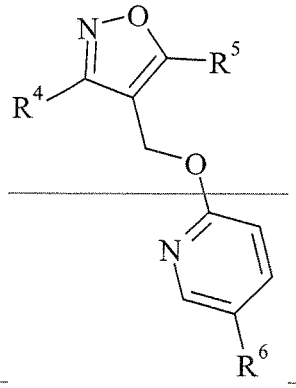
Claims

1. Use of a GABA A α5 negative allosteric modulator selected from (1,1-Dioxo-1,6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone ~~a compound of formula (I) or a compound of formula (II)~~



~~(I),~~



~~(II),~~

~~wherein~~

~~R^1 is hydrogen, halo, alkyl, haloalkyl, or cyano;~~

~~R^2 is hydrogen, halo, alkyl, haloalkyl, or cyano;~~

~~R^3 is hydrogen, alkyl, or heterocycloalkylalkyl, wherein heterocycloalkylalkyl is optionally substituted with one or more hydroxy, oxo, alkyl, alkoxy, haloalkyl, hydroxyalkyl, halo, or cyano;~~

~~R^4 is aryl or heteroaryl, each optionally substituted by one, two or three halo;~~

~~R^5 is hydrogen, alkyl, haloalkyl or hydroxyalkyl;~~

~~R^6 is $-C(O)-NR^7R^8$~~

~~R^7 is hydrogen;~~

~~R^8 is alkyl;~~

~~or R^7 and R^8 together with the nitrogen to which they are bound to form a heterocycloalkyl, or a heteroaryl, each optionally substituted with one or more hydroxy, oxo, alkyl, alkoxy, haloalkyl, hydroxyalkyl, halo, or cyano;~~

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for the treatment, prevention and/or delay of progression of CNS conditions related to excessive GABAergic inhibition in the cortex and hippocampus, wherein said CNS condition is selected from cognitive deficits in Down Syndrome, in autism or in neurofibromatosis type I or after stroke.

2. Use according to claim 1, wherein the excessive GABAergic inhibition in the cortex and hippocampus is caused by neurodevelopmental defects.

3. Use according to claim 2,wherein the CNS conditions are caused by neurodevelopmental defects which result in excessive GABAergic inhibition in the cortex and hippocampus.

4. Use according to any of claims 1 to 3, wherein said CNS condition is selected from cognitive deficits in Down Syndrome, in autism or in neurofibromatosis type I.

5. Use according to any of claims 1 to 4, wherein said CNS condition is cognitive deficits in Down Syndrome.

6. Use according to any of claims 1 to 4, wherein said CNS condition is cognitive deficits in autism.

7. Use according to any of claims 1 to 4, wherein said CNS condition is cognitive deficits in neurofibromatosis type I.

8. Use according to claim 1, wherein said CNS condition is characterized by disabilities after stroke.

9. Use according to any of claims 1 to 8, wherein said GABA A α5 negative allosteric modulator is binding to human GABA A α5β3γ2 receptor subtype with a binding selectivity of a factor of 10 or more as compared to binding affinities to human GABA A α1β2/3γ2, α2β3γ2 and α3β3γ2 receptor subtypes.

10. Use according to any of claims 1 to 9, wherein said GABA A α5 negative allosteric modulator exhibits a functional selectivity by acting as inverse agonist at human GABA A α5β3γ2 receptor subtype by reducing the effect of GABA by more than 30% and in addition affecting the effect of GABA at human GABA A α1β2/3γ2, α2β3γ2 and α3β3γ2 receptor subtypes by less than 15%.

~~11. Use according to any of claims 1 to 10, wherein said GABA A α5 negative allosteric modulator is selected from a compound of formula (I) as defined in claim 22, or a pharmaceutically acceptable salt thereof.~~

~~12. Use according to any of claims 1 to 11, wherein said GABA A α5 negative allosteric modulator is selected from a compound of formula (I), wherein R^1 is hydrogen, halo, haloalkyl, or cyano; R^2 is halo, or haloalkyl; R^3 is hydrogen, alkyl, or heterocycloalkylalkyl substituted with one oxo; or a pharmaceutically acceptable salt thereof.~~

~~13. Use according to any of claims 1 to 12, wherein said GABA A α5 negative allosteric modulator is selected from~~
~~3-Fluoro-10-fluoromethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;~~

3-Bromo-10-difluoromethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
3-Cyano-10-difluoromethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
10-Difluoromethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
3-Chloro-10-fluoromethyl-6-methyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
10-Chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
3,10-Dichloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
10-Chloro-3-cyano-6-methyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
10-Chloro-3-difluoromethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
3-Bromo-10-chloro-6-methyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
10-Bromo-3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
3-Bromo-10-methyl-6-(2-oxo-pyrrolidin-1-ylmethyl)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine; or a pharmaceutically acceptable salt thereof.

14. Use according to any of claims 1 to 10, wherein said GABA-A-α5 negative allosteric modulator is selected from a compound of formula (II) as defined in claim 1, or a pharmaceutically acceptable salt thereof.

15. Use according to any of claims 1 to 10 or 14, wherein said GABA-A-α5 negative allosteric modulator is selected from a compound of formula (II) wherein R^4 is aryl or heteroaryl, each optionally substituted by one halo; R^5 is alkyl; R^6 is C(O)-NR7R8; R^7 is hydrogen and R^8 is alkyl; or R^7 and R^8 together with the nitrogen to which they are bound to form a heterocycloalkyl optionally substituted with one or two oxo, or form a heteroaryl; or a pharmaceutically acceptable salt thereof.

16. Use according to any of claims 1 to 10, 14 or 15, wherein said GABA-A-α5 negative allosteric modulator is selected from:
N-Isopropyl-6-(5-methyl-3-phenyl-isoxazol-4-ylmethoxy)-nicotinamide;
(5,6-Dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-[6-(5-methyl-3-phenyl-isoxazol-4-ylmethoxy)-pyridin-3-yl]-methanone;
[6-(5-Methyl-3-phenyl-isoxazol-4-ylmethoxy)-pyridin-3-yl]-(2-oxa-6-aza-spiro[3.3]hept-6-yl)-methanone;
(1,1-Dioxo-1,6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone;
{6-[3-(4-Chloro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-morpholin-4-yl-methanone;
[6-(5-Methyl-3-pyridin-2-yl-isoxazol-4-ylmethoxy)-pyridin-3-yl]-morpholin-4-yl-methanone;
6-[3-(5-Fluoro-pyridin-2-yl)-5-methyl-isoxazol-4-ylmethoxy]-isopropyl-nicotinamide;
(1,1-Dioxo-1,6-thiomorpholin-4-yl)-{6-[3-(5-fluoro-pyridin-2-yl)-5-methyl-isoxazol-4-

~~ylmethoxy]-pyridin-3-yl}-methanone;~~
~~{6-[3-(5-Chloro-pyridin-2-yl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-thiomorpholin-4-yl-methanone; or a pharmaceutically acceptable salt thereof.~~

~~17. Use according to any of claims 1 to 10, 14 to 16, wherein said GABA A α5 negative allosteric modulator is (1,1-Dioxo-1,6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone or a pharmaceutically acceptable salt thereof.~~

~~18. Use according to any of claims 1 to 17, wherein said GABA A α5 negative allosteric modulator is used separately, sequentially or simultaneously in combination with a second active pharmaceutical compound.~~

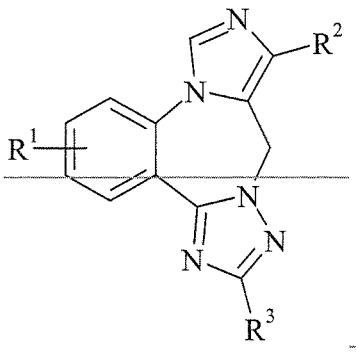
~~19~~11. A pharmaceutical composition comprising a GABA A α5 negative allosteric modulator according to any one of claims 1 to ~~18~~10 in a pharmaceutically acceptable form for the treatment, prevention and/or delay of progression of cognitive deficits in Down Syndrome, in autism, in neurofibromatosis type I, or for recovery after stroke.

~~20~~12. A GABA A α5 negative allosteric modulator according to any one of claims 1 to ~~18~~10 for the treatment, prevention and/or delay of progression of cognitive deficits in Down Syndrome, in autism, in neurofibromatosis type I, or for recovery after stroke.

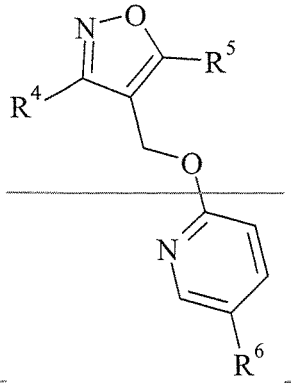
~~21~~13. A GABA A α5 negative allosteric modulator according to any one of claims 1 to ~~18~~10 for the preparation of medicaments for the treatment, prevention and/or delay of progression of cognitive deficits in Down Syndrome, in autism, in neurofibromatosis type I, or for recovery after stroke.

~~22~~14. The use of a GABA A α5 negative allosteric modulator according to any one of claims 1 to ~~18~~10 for the preparation of medicaments for the treatment, prevention and/or delay of progression of cognitive deficits in Down Syndrome, in autism, in neurofibromatosis type I, or for recovery after stroke.

~~23~~15. A GABA A α5 negative allosteric modulator selected from (1,1-Dioxo-1,6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxyl-pyridin-3-yl}-methanone ~~a compound of formula (I) or a compound of formula (II)~~



~~(I),~~



~~(II),~~

~~wherein~~

~~R^1 is hydrogen, halo, alkyl, haloalkyl, or cyano;~~

~~R^2 is hydrogen, halo, alkyl, haloalkyl, or cyano;~~

~~R^3 is hydrogen, alkyl, or heterocycloalkylalkyl, wherein heterocycloalkylalkyl is optionally substituted with one or more hydroxy, oxo, alkyl, alkoxy, haloalkyl, hydroxyalkyl, halo, or cyano;~~

~~R^4 is aryl or heteroaryl, each optionally substituted by one, two or three halo;~~

~~R^5 is hydrogen, alkyl, haloalkyl or hydroxyalkyl;~~

~~R^6 is -C(O)-NR7R8~~

~~R^7 is hydrogen;~~

~~R^8 is alkyl;~~

~~or R^7 and R^8 together with the nitrogen to which they are bound to form a heterocycloalkyl, or a heteroaryl, each optionally substituted with one or more hydroxy, oxo, alkyl, alkoxy, haloalkyl, hydroxyalkyl, halo, or cyano;~~

or a pharmaceutically acceptable salt thereof;

for the treatment, prevention and/or delay of progression of CNS conditions related to excessive GABAergic inhibition in the cortex and hippocampus, wherein said CNS condition is selected from cognitive deficits in Down Syndrome, in autism or in neurofibromatosis type I or after stroke.

~~24~~16. A GABA A α5 negative allosteric modulator according to claim ~~23~~15, wherein the excessive GABAergic inhibition in the cortex and hippocampus is caused by neurodevelopmental defects.

~~25~~17. A GABA A α5 negative allosteric modulator according to claim ~~23~~15, wherein the CNS condition is caused by neurodevelopmental defects which result in excessive GABAergic inhibition in the cortex and hippocampus.

~~26~~18. A GABA A α5 negative allosteric modulator according to any of claims ~~23~~15 to ~~25~~17, wherein said CNS condition is selected from cognitive deficits in Down Syndrome, in autism or in neurofibromatosis type I.

~~27~~19. A GABA A α5 negative allosteric modulator according to any of claims ~~23~~15 to ~~26~~18, wherein said CNS condition is cognitive deficits in Down Syndrome.

~~28~~20. A GABA A α5 negative allosteric modulator according to any of claims ~~23~~15 to ~~26~~18, wherein said CNS condition is cognitive deficits in autism.

~~29~~21. A GABA A α5 negative allosteric modulator according to any of claims ~~23~~15 to ~~26~~18, wherein said CNS condition is cognitive deficits in neurofibromatosis type I.

~~30~~22. A GABA A α5 negative allosteric modulator according to claim ~~23~~15, wherein said CNS condition is characterized by disabilities after stroke.

~~31~~23. A GABA A α5 negative allosteric modulator according to any of claims ~~23~~15 to ~~30~~22, wherein said GABA A α5 negative allosteric modulator is binding to human GABA A α5β3γ2 receptor subtype with a binding selectivity of a factor of 10 or more as compared to binding affinities to human GABA A α1β2/3γ2, α2β3γ2 and α3β3γ2 receptor subtypes.

~~32~~24. A GABA A α5 negative allosteric modulator according to any of claims ~~23~~15 or ~~31~~23, wherein said GABA A α5 negative allosteric modulator exhibits a functional selectivity by acting as inverse agonist at human GABA A α5β3γ2 receptor subtype by reducing the effect of GABA by more than 30% and in addition affecting the effect of GABA at human GABA A α1β2/3γ2, α2β3γ2 and α3β3γ2 receptor subtypes by less than 15%.

~~33. A GABA A α5 negative allosteric modulator according to any of claims 23 to 32, wherein said GABA A α5 negative allosteric modulator is selected from a compound of formula (I) as defined in claim 45, or a pharmaceutically acceptable salt thereof.~~

~~34. A GABA A α5 negative allosteric modulator according to any of claims 23 to 33, wherein said GABA A α5 negative allosteric modulator is selected from a compound of formula (I), wherein R^1 is hydrogen, halo, haloalkyl, or cyano; R^2 is halo, or haloalkyl; R^3 is hydrogen,~~

alkyl, or heterocycloalkylalkyl substituted with one oxo; or a pharmaceutically acceptable salt thereof.

35. A GABA-A α5 negative allosteric modulator according to any of claims 23 to 34, wherein said GABA-A α5 negative allosteric modulator is selected from
3-Fluoro-10-fluoromethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
3-Bromo-10-difluoromethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
3-Cyano-10-difluoromethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
10-Difluoromethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
3-Chloro-10-fluoromethyl-6-methyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
10-Chloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
3,10-Dichloro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
10-Chloro-3-cyano-6-methyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
10-Chloro-3-difluoromethyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
3-Bromo-10-chloro-6-methyl-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
10-Bromo-3-fluoro-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine;
3-Bromo-10-methyl-6-(2-oxo-pyrrolidin-1-ylmethyl)-9H-imidazo[1,5-a][1,2,4]triazolo[1,5-d][1,4]benzodiazepine; or a pharmaceutically acceptable salt thereof.

36. A GABA-A α5 negative allosteric modulator according to any of claims 23 to 32, wherein said GABA-A α5 negative allosteric modulator is selected from a compound of formula (II) wherein R^4, R^5, and R^6 are as defined in claim 24, or a pharmaceutically acceptable salt thereof.

37. A GABA-A α5 negative allosteric modulator according to any of claims 23 to 32 or 36, wherein said GABA-A α5 negative allosteric modulator is selected from a compound of formula (II) wherein R^4 is aryl or heteroaryl, each optionally substituted by one halo; R^5 is alkyl; R^6 is $C(O)NR^7R^8$; R^7 is hydrogen and R^8 is alkyl; or R^7 and R^8 together with the nitrogen to which they are bound to form a heterocycloalkyl optionally substituted with one or two oxo, or form a heteroaryl; or a pharmaceutically acceptable salt thereof.

38. A GABA-A α5 negative allosteric modulator according to any of claims 23 to 32, 36 or 37, wherein said GABA-A α5 negative allosteric modulator is selected from:
N-Isopropyl-6-(5-methyl-3-phenyl-isoxazol-4-ylmethoxy)-nicotinamide;
(5,6-Dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-[6-(5-methyl-3-phenyl-isoxazol-4-ylmethoxy)-pyridin-3-yl]-methanone;
[6-(5-Methyl-3-phenyl-isoxazol-4-ylmethoxy)-pyridin-3-yl]-(2-oxa-6-aza-spiro[3.3]hept-6-yl)-methanone;
(1,1-Dioxo-1,6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-

ylmethoxy]-pyridin-3-yl}-methanone;
{6-[3-(4-Chloro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-morpholin-4-yl-methanone;
[6-(5-Methyl-3-pyridin-2-yl-isoxazol-4-ylmethoxy)-pyridin-3-yl]-morpholin-4-yl-methanone;
6-[3-(5-Fluoro-pyridin-2-yl)-5-methyl-isoxazol-4-ylmethoxy]-isopropyl-nicotinamide;
(1,1-Dioxo-1,6-thiomorpholin-4-yl)-{6-[3-(5-fluoro-pyridin-2-yl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone;
{6-[3-(5-Chloro-pyridin-2-yl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-thiomorpholin-4-yl-methanone; or a pharmaceutically acceptable salt thereof.

39. A GABA-A α5 negative allosteric modulator according to any of claims 23 to 32, or 36 to 38, wherein said GABA-A α5 negative allosteric modulator is (1,1-Dioxo-1,6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone or a pharmaceutically acceptable salt thereof.

40. A GABA-A α5 negative allosteric modulator according to any of claims 23 to 39, wherein said GABA-A α5 negative allosteric modulator is used separately, sequentially or simultaneously in combination with a second active pharmaceutical compound.

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