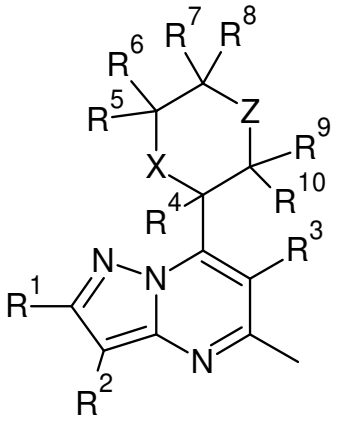
Claims

1. A compound of formula (I)



(I)

wherein

R^1 represents phenyl- or cyclohexyl group substituted by C_1-C_6alkyl or halo-C_1-C_6alkyl;

R^2 represents H or halogen;

R^3 represents H or C_1-C_6alkyl;

R^4 represents H; C_1-C_6alkyl or halo-C_1-C_6alkyl;

R^5 and R^6 may be each, independently H; C_1-C_6alkyl or halogen;

R^7 and R^8 may be each, independently H or C_1-C_6alkyl;

R^9 and R^{10} may be each, independently H or C_1-C_6alkyl or R^9 and R^{10} together may form oxo group;

X represents -CR^xR^y or -O- or -$S(O)_n$- group, wherein R^x and R^y may be each, independently H or C_1-C_6alkyl group and wherein n is 0 or 1 or 2;

Z represents -NR-; or -O-; or -$S(O)_2$- group wherein

R may be H or -$C(O)R^{11}$ or -$S(O)_2R^{12}$ group; aminocarbonyl-C_1-C_3alkyl; carboxy-C_1-C_3alkyl; cyano-C_1-C_3alkyl; C_1-C_5(cyclo)alkyl; saturated 4-6 membered heterocyclic ring with one O, or -$C(NH)(NH_2)$ group;

wherein R^{11} may be H; C_1-C_3alkyl; C_1-C_3alkoxy; deutero-C_1-C_3alkoxy; C_1-C_3alkoxy-C_1-C_3alkyl; C_1-C_3alkoxy-C_1-C_3alkoxy; methanesulphonyl-C_1-C_3alkyl; or R^{11} may be a saturated 3-6 membered carbocyclic ring, or a 4-6 membered saturated or unsaturated heterocyclic ring with one to three

hetero atoms selected from N, O or S; or amino, mono- or dialkylamino group; amino- C_1-C_3alkyl; hydroxy-C_1-C_3alkyl substituted by NH_2-group;

wherein R^{12} may be C_1-C_3alkyl; amino or dialkylamino group;

R^4 and CR^x may form a cycloalkyl ring;

or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

2. A compound according to claim 1 wherein

if X represents $-CR^xR^y$ then Z represents -NR- group; or

if X represents -O-; or -S(O)n- group then Z represents -NR- group; or

if X represents $-CR^xR^y$ group then Z represents -O-; or $-S(O)_2$- group.

3. A compound according to claim 2 wherein X represents $-CR^xR^y$ and Z represents -NR- group, wherein R may be $-C(O)R^{11}$.

4. A compound according to claim 2 wherein X represents -O- or $-S(O)_2$- group and Z represents -NR- group, where R may be $-C(O)R^{11}$ or $-S(O)_2R^{12}$ group.

5. A compound according to claim 1 selected from the group of

1-[(3*R*)-3-{6-ethyl-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-methylpiperidin-1-yl]ethan-1-one,

1-[(3*S*)-3-{6-ethyl-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3-methylpiperidin-1-yl]ethan-1-one,

1-{3-[5-methyl-6-(propan-2-yl)-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl]piperidin-1-yl}ethan-1-one,

1-[(3*R*)-3-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidin-1-yl]ethan-1-one,

1-[(3*S*)-3-{6-ethyl-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidin-1-yl]ethan-1-one,

(3*R*)-3-{6-ethyl-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-1-methanesulfonyl-3-methylpiperidine,

methyl (3*R*,4*S*)-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboxylate,

methyl (3*S*,4*R*)-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboxylate,

trans-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-4-methylpiperidine-1-carbaldehyde,

1-[*trans*-3-{6-ethyl-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-4-methylpiperidin-1-yl]ethan-1-one,

trans-4-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carbaldehyde,

methyl *trans*-3-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-4-methylpiperidine-1-carboxylate,

5-{5,6-dimethyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}-3,3-difluoropiperidine-1-carbaldehyde,

2-{6-ethyl-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carbaldehyde,

methyl (2*R*)-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carboxylate,

methyl *trans*-2-methyl-3-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}piperidine-1-carboxylate,

(2*R*)-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-sulfonamide,

methyl (2*R*,5*S*)-5-methyl-2-{5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carboxylate,

methyl (2*R*)-2-{3-fluoro-5-methyl-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidin-7-yl}morpholine-4-carboxylate,

5-methyl-7-[(3*R*)-oxan-3-yl]-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidine, and

5-methyl-7-[(3*S*)-oxan-3-yl]-2-[*trans*-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-*a*]pyrimidine.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof according to claim 1 as active ingredient and pharmaceutically acceptable carrier.

7. A combination comprising a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof according to claim 1 and one or more therapeutically active co-agents.

8. A process for manufacturing pharmaceutical composition having $GABA_B$ receptor positive allosteric modulator effect characterized by mixing a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof according to claim 1 and optical antipodes or racemates and/or salts thereof as active ingredients and pharmaceutically acceptable excipients.

9. A compound of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof according to claim 1 for use as $GABA_B$ receptor positive allosteric modulator.

10. A compound of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof according to claim 1 for use in the treatment or prevention of disorders associated with $GABA_B$ receptor positive allosteric modulator activity.

11. The compound for use according to claim 10 wherein the disorder associated with $GABA_B$ receptor positive allosteric modulator activity is selected from the group of psychiatric disorders (such as anxiety, panic disorder, posttraumatic disorder, depression, schizophrenia), neurodevelopmental disorders (such as autism spectrum disorder, obsessive-compulsive disorder, Fragile X syndrome), cognitive disorders, epilepsy, spasticity, skeletal muscle rigidity, spinal cord

injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, essential tremor, pain (neuropathic, visceral, osteoarthritic), substance abuse (cocaine, nicotine, alcohol), obesity, binge eating, asthma, cough, urinary incontinence, gastroesophageal reflux disease, transient lower esophageal sphincter relaxation, and irritable bowel syndrome.

12. The following compounds as an intermediate in the synthesis of the compounds of Formula (I):

(3S,4R)-4-methyl-3-{5-methyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-a]pyrimidin-7-yl}piperidine (Intermediate 213),

(3S)-3-{5-methyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-a]pyrimidin-7-yl}morpholine (Intermediate 222),

(3R)-3-{6-ethyl-5-methyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-a]pyrimidin-7-yl}-3-methylpiperidine (Intermediate 160),

(3S)-3-{6-ethyl-5-methyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-a]pyrimidin-7-yl}piperidine (Intermediate 168),

(2R,5S)-5-methyl-2-{5-methyl-2-[trans-4-(trifluoromethyl)cyclohexyl]pyrazolo[1,5-a]pyrimidin-7-yl}morpholine (Intermediate 189).