

addiction, substance abuse) and schizophrenia. *J. Clin. Psychiatry*, **2010**, *71*, S2, 14-9,
Pediatr. Drugs **2011**, *13*, 5, 291-302

Major depression: *BMC Psychiatry* **2011**, *11*, 86

Treatment resistant depression: *Journal of Psychopharmacology*, 0(0) 1- 16

5 Anxiety: *European Neuropsychopharmacology*, **2011**, *21*, 429-449

Bipolar disorders: *Encephale*, *International J. of Neuropsychopharmacology*, **2011**, *14*, 1029-
104, *International J. of Neuropsychopharmacology*, **2012**, 1-12; *J. of Neuropsychopharmacology*,
2011, *0*, 0, 1- 15

Mood disorders: *J. Psychopharmacol.* **2012**, Jan 11, *CNS Drugs*, **2010**, *2*, 131-61

10 Autism: *Current opinion in pediatrics*, **2011**, *23*, 621 – 627; *J. Clin. Psychiatry*, **2011**, *72*, 9,
1270-1276

Alzheimer's disease: *J. Clin. Psychiatry*, **2012**, *73*, 1, 121-128

Parkinson's disease: *Movement Disorders*, **2011**, *26*, 6

Chronic fatigue syndrome: *European Neuropsychopharmacology*, **2011**, *21*, 282-286

15 Borderline Personality disorder: *J. Clin. Psychiatry*, **2011**, *72*, 10, 1363-1365

J. Clin. Psychiatry, **2011**, *72*, 10, 1353-1362

Anti-inflammatory effects in arthritis: *European J. of Pharmacology*, **2012**, *678*, 55-60

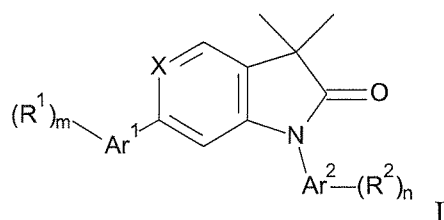
Objects of the embodiments disclosed herein are novel compounds of formula I and the use
of compounds of formula I and their pharmaceutically acceptable salts for the treatment of CNS
20 diseases related to positive (psychosis) and negative symptoms of schizophrenia, substance
abuse, alcohol and drug addiction, obsessive-compulsive disorders, cognitive impairment,
bipolar disorders, mood disorders, major depression, treatment resistant depression, anxiety
disorders, Alzheimer's disease, autism, Parkinson's disease, chronic pain, borderline personality
disorder, neurodegenerative disease, sleep disturbances, chronic fatigue syndrome, stiffness,
25 inflammatory disease, asthma, Huntington's disease, ADHD, amyotrophic lateral sclerosis,
epilepsy, effects in arthritis, autoimmune disease, viral and fungal infections, cardiovascular
diseases, ophthalmology and inflammatory retinal diseases and balance problems.

Further objects of the embodiments disclosed herein are medicaments containing such
novel compounds as well as methods for preparation of compounds of formula I, a combination
30 of compounds of formula I with marketed antipsychotics, antidepressants, anxiolytics or mood
stabilizers, and methods for the treatment of CNS disorders as mentioned above.

Encompassed by the present disclosure are corresponding prodrugs of compounds of

formula I.

In one aspect, there is provided a compound of formula



wherein

5

Ar¹ is phenyl or a five or six membered heteroaryl group, containing one, two or three heteroatoms, selected from N, S or O, wherein the N-heteroatom in the heteroaryl group may be oxidized to N⁺-(O⁻);

R¹ is C₁₋₇-alkyl, halogen, cyano or cycloalkyl;

10

Ar² is a five or six membered heteroaryl group, containing one, two, three or four heteroatoms, selected from N, S or O, wherein the N-heteroatom in the heteroaryl group may be oxidized to N⁺-(O⁻), or is benzo[b]thiophenyl;

R² is hydrogen, C₁₋₇-alkyl, halogen, cyano, C₁₋₇-alkyl substituted by hydroxyl, C₁₋₇-alkyl substituted by halogen, C₁₋₇-alkyl substituted by amino, C₁₋₇-alkyl substituted by alkoxy,

15 C₁₋₇-alkyl substituted by amide, or is cycloalkyl;

X is CH or N;

n is 1 or 2;

m is 1 or 2;

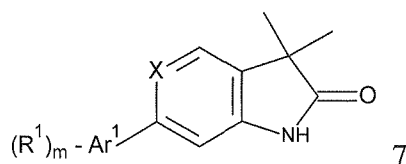
as well as with a pharmaceutically acceptable salt thereof, with a racemic mixture, or

20 with its

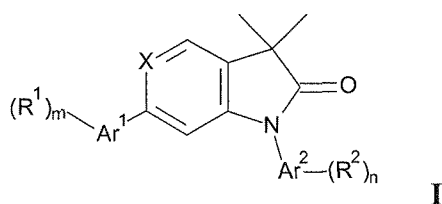
corresponding enantiomer and/or optical isomer and/or stereoisomer thereof.

In another aspect, there is provided a combination of a compound of formula I as defined herein together with an antipsychotic, antidepressant, anxiolytic or mood stabilizer.

In another aspect, there is provided a process for preparation of a compound of formula I as defined herein, reacting a compound of formula



with a compound of formula $(R^2)_n - Ar^2 - Y$ 8 to a compound of formula



wherein Y is Cl, Br or I and the R^1 , Ar^1 , X, R^2 , Ar^2 have the meaning as described herein, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

In another aspect, there is provided a compound as defined herein for use as therapeutically active substance.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a therapeutically active carrier for the treatment of CNS diseases related to positive (psychosis) and negative symptoms of schizophrenia, substance abuse, alcohol and drug addiction, obsessive-compulsive disorders, cognitive impairment, bipolar disorders, mood disorders, major depression, treatment resistant depression, anxiety disorders, Alzheimer's disease, autism, Parkinson's disease, chronic pain, borderline personality disorder, neurodegenerative disease, sleep disturbances, chronic fatigue syndrome, stiffness, inflammatory disease, asthma, Huntington's disease, ADHD, amyotrophic lateral sclerosis, epilepsy, arthritis, autoimmune disease, viral and fungal infections, cardiovascular diseases, ophthalmology and inflammatory retinal diseases.

In another aspect, there is provided use of a compound of formula I as defined herein for the manufacture of a medicament for the treatment of CNS diseases related to positive (psychosis) and negative symptoms of schizophrenia, substance abuse, alcohol and drug addiction, obsessive-compulsive disorders, cognitive impairment, bipolar disorders, mood disorders, major depression, treatment resistant depression, anxiety disorders, Alzheimer's disease, autism, Parkinson's disease, chronic pain, borderline personality disorder, neurodegenerative disease, sleep disturbances, chronic fatigue syndrome, stiffness, inflammatory disease, asthma, Huntington's disease, ADHD, amyotrophic lateral sclerosis, epilepsy, arthritis,

autoimmune disease, viral and fungal infections, cardiovascular diseases, ophthalmology and inflammatory retinal diseases.

In another aspect, there is provided a compound as defined herein for use in the treatment of CNS diseases related to positive (psychosis) and negative symptoms of schizophrenia, substance abuse, alcohol and drug addiction, obsessive-compulsive disorders, cognitive impairment, bipolar disorders, mood disorders, major depression, treatment resistant depression, anxiety disorders, Alzheimer's disease, autism, Parkinson's disease, chronic pain, borderline personality disorder, neurodegenerative disease, sleep disturbances, chronic fatigue syndrome, stiffness, inflammatory disease, asthma, Huntington's disease, ADHD, amyotrophic lateral sclerosis, epilepsy, arthritis, autoimmune disease, viral and fungal infections, cardiovascular diseases, ophthalmology and inflammatory retinal diseases.

A common antipsychotic drug for the treatment of schizophrenia is olanzapine. Olanzapine (Zyprexa) belongs to a drug class known as atypical antipsychotics. Other members of this class include for example clozapine (Clozaril), risperidone (Risperdal), aripiprazole (Abilify) and ziprasidone (Geodon).

Olanzapine is approved for the treatment of psychotic disorders, long term treatment of bipolar disorders and in combination with fluoxetine for the treatment of depressive episodes associated with bipolar disorders and for the treatment of resistant depression.

The compounds of the present invention may be combined with antipsychotic drugs like olanzapine (Zyprexa), clozapine (Clozaril), risperidone (Risperdal), aripiprazole (Abilify), amisulpride (Solian), asenapine (Saphris), blonanserin (Lonasen), clotiapine (Entumine), iloperidone (Fanapt), lurasidone (Latuda), mosapramine (Cremin), paliperidone (Invega), perospirone (Lullan), quetiapine (Seroquel), remoxipride (Roxiam), sertindole (Serdolect), sulpiride (Sulpirid, Eglonyl), ziprasidone (Geodon, Zeldox), zotepine (Nipolept), haloperidol (Haldol, Serenace), droperidol (Droleptan), chlorpromazine (Thorazine, Largactil), fluphenazine (Prolixin), perphenazine (Trilafon), prochlorperazine (Compazine), thioridazine (Mellaril, Melleril), trifluoperazine (Stelazine), triflupromazine (Vesprin), levomepromazine (Nozinan), promethazine (Phenergan), pimozide (Orap) and cyamemazine (Tercian).

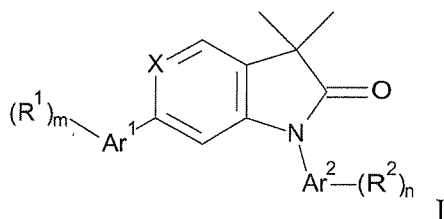
One preferred embodiment of the invention is a combination, wherein the marketed antipsychotic drug is olanzapine (Zyprexa), clozapine (Clozaril), risperidone (Risperdal), aripiprazole (Abilify) or ziprasidone.

Furthermore, the compounds of the present invention can be combined with antidepressants such as selective serotonin reuptake inhibitors [Citalopram (Celexa), Escitalopram (Lexapro, Cipralex), Paroxetine (Paxil, Seroxat), Fluoxetine (Prozac), Fluvoxamine

(Luvox), Sertraline (Zoloft, Lustral)], serotonin-norepinephrine reuptake inhibitors [Duloxetine (Cymbalta), Milnacipran (Ixel, Savella), Venlafaxine (Effexor), Desvenlafaxine (Pristiq), Tramadol (Tramal, Ultram), Sibutramine (Meridia, Reductil)], serotonin antagonist and reuptake inhibitors [Etooperidone (Axiomin, Etonin), Lubazodone (YM-992, YM-35,995), Nefazodone
5 (Serzone, Nefadar), Trazodone (Desyrel)], norepinephrine reuptake inhibitors [Reboxetine (Edronax), Viloxazine (Vivalan), Atomoxetine (Strattera)], norepinephrine-dopamine reuptake inhibitors [Bupropion (Wellbutrin, Zyban), Dexamethylphenidate (Focalin), Methylphenidate (Ritalin, Concerta)], norepinephrine-dopamine releasing agents [Amphetamine (Adderall), Dextroamphetamine (Dexedrine), Dextromethamphetamine (Desoxyn), Lisdexamfetamine

Claims

1. A compound of formula



wherein

- Ar¹ is phenyl or a five or six membered heteroaryl group, containing one, two or three heteroatoms, selected from N, S or O, wherein the N-heteroatom in the heteroaryl group may be oxidized to N⁺-(O⁻);
- R¹ is C₁₋₇-alkyl, halogen, cyano or cycloalkyl;
- Ar² is a five or six membered heteroaryl group, containing one, two, three or four heteroatoms, selected from N, S or O, wherein the N-heteroatom in the heteroaryl group may be oxidized to N⁺-(O⁻), or is benzo[b]thiophenyl;
- R² is hydrogen, C₁₋₇-alkyl, halogen, cyano, C₁₋₇-alkyl substituted by hydroxyl, C₁₋₇-alkyl substituted by halogen, C₁₋₇-alkyl substituted by amino, C₁₋₇-alkyl substituted by alkoxy, C₁₋₇-alkyl substituted by amide, or is cycloalkyl;
- X is CH or N;
- n is 1 or 2;
- m is 1 or 2;

as well as with a pharmaceutically acceptable salt thereof, with a racemic mixture, or with its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof.

2. A compound of formula I according to claim 1, wherein X is CH.

3. A compound of formula I according to claim 2, wherein Ar¹ and Ar² are both a six membered heteroaryl group, containing one, two or three heteroatoms, selected from N, S or O.

4. A compound of formula I according to claim 3, wherein the compounds are
- 3,3-Dimethyl-6-(2-methylpyrimidin-5-yl)-1-(pyridin-4-yl)indolin-2-one
- 3,3-Dimethyl-6-(2-methylpyrimidin-5-yl)-1-(pyridin-3-yl)indolin-2-one
- 3,3-Dimethyl-1-(2-methylpyridin-4-yl)-6-(2-methylpyrimidin-5-yl)indolin-2-one

3,3-dimethyl-1-(1-methyl-1H-imidazol-4-yl)-6-(2-methylpyridin-4-yl)-1H-pyrrolo[3,2-c]pyridin-2(3H)-one or
6-(4-fluorophenyl)-3,3-dimethyl-1-(2-methylpyrimidin-5-yl)-1H-pyrrolo[3,2-c]pyridin-2(3H)-one.

15. A combination of a compound of formula I according to any one of claims 1 - 14 together with an antipsychotic, antidepressant, anxiolytic or mood stabilizer.

16. A combination according to claim 15, wherein the antipsychotic drug is olanzapine (Zyprexa), clozapine (Clozaril), risperidone (Risperdal), aripiprazole (Abilify) or ziprasidone.

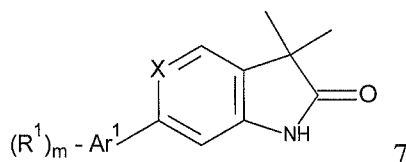
17. A combination according to claim 15, wherein the anti-depressive drug is citalopram (Celexa), escitalopram (Lexapro, Cipralex), paroxetine (Paxil, Seroxat), fluoxetine (Prozac), sertraline (Zoloft, Lustral) duloxetine (Cymbalta), milnacipran (Ixel, Savella), venlafaxine (Effexor), or mirtazapine (Remeron)

18. A combination according to claim 15, wherein the anxiolytic drug is alprazolam (Helex, Xanax, Xanor, Onax, Alprox, Restyl, Tafil, Paxal), chlordiazepoxide (Librium, Risolid, Elenium), clonazepam (Rivotril, Klonopin, Iktorivil, Paxam), diazepam (Antenex, Apaurin, Apzepam, Apozepam, Hexalid, Pax, Stesolid, Stedon, Valium, Vival, Valaxona), Estazolam (ProSom), eszopiclone (Lunesta), zaleplon (Sonata, Starnoc), zolpidem (Ambien, Nytamel, Stilnoct, Stilnox, Zoldem, Zolnod), pregabalin (Lyrica) or gabapentin (Fanatrex, Gabarone, Gralise, Neurontin, Nupentin).

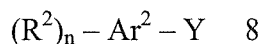
19. A combination according to claim 15, wherein the mood stabilizer is Carbamazepine (Tegretol), Lamotrigine (Lamictal), Lithium (Eskalith, Lithane, Lithobid), and Valproic Acid (Depakote).

20. A process for preparation of a compound of formula I as described in any one of claims 1 to 14

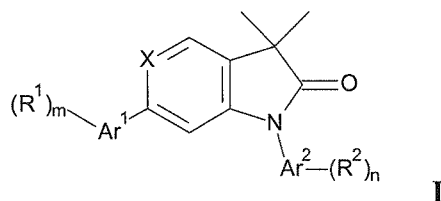
reacting a compound of formula



with a compound of formula



to a compound of formula



wherein Y is Cl, Br or I and the R^1 , Ar^1 , X, R^2 , Ar^2 have the meaning as described in any one of claims 1 to 14 and,

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

21. A compound according to any one of claims 1 – 14 for use as therapeutically active substance.

22. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 –14 and a therapeutically active carrier for the treatment of CNS diseases related to positive (psychosis) and negative symptoms of schizophrenia, substance abuse, alcohol and drug addiction, obsessive-compulsive disorders, cognitive impairment, bipolar disorders, mood disorders, major depression, treatment resistant depression, anxiety disorders, Alzheimer's disease, autism, Parkinson's disease, chronic pain, borderline personality disorder, neurodegenerative disease, sleep disturbances, chronic fatigue syndrome, stiffness, inflammatory disease, asthma, Huntington's disease, ADHD, amyotrophic lateral sclerosis, epilepsy, arthritis, autoimmune disease, viral and fungal infections, cardiovascular diseases, ophthalmology and inflammatory retinal diseases.

23. The use of a compound of formula I as claimed in any one of claims 1-14 for the manufacture of a medicament for the treatment of CNS diseases related to positive (psychosis) and negative symptoms of schizophrenia, substance abuse, alcohol and drug

addiction, obsessive-compulsive disorders, cognitive impairment, bipolar disorders, mood disorders, major depression, treatment resistant depression, anxiety disorders, Alzheimer's disease, autism, Parkinson's disease, chronic pain, borderline personality disorder, neurodegenerative disease, sleep disturbances, chronic fatigue syndrome, stiffness, inflammatory disease, asthma, Huntington's disease, ADHD, amyotrophic lateral sclerosis, epilepsy, arthritis, autoimmune disease, viral and fungal infections, cardiovascular diseases, ophthalmology and inflammatory retinal diseases.

24. A compound according to any one of claims 1 –14 for use in the treatment of CNS diseases related to positive (psychosis) and negative symptoms of schizophrenia, substance abuse, alcohol and drug addiction, obsessive-compulsive disorders, cognitive impairment, bipolar disorders, mood disorders, major depression, treatment resistant depression, anxiety disorders, Alzheimer's disease, autism, Parkinson's disease, chronic pain, borderline personality disorder, neurodegenerative disease, sleep disturbances, chronic fatigue syndrome, stiffness, inflammatory disease, asthma, Huntington's disease, ADHD, amyotrophic lateral sclerosis, epilepsy, arthritis, autoimmune disease, viral and fungal infections, cardiovascular diseases, ophthalmology and inflammatory retinal diseases.