**Claims**

1. 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide salt, which compound is crystalline and has an XRDP as shown in any one of figures 2-4.

2. 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine hydrobromide salt, which compound is crystalline and has XRPD reflections at approximately 6.89, 9.73, 13.78 and 14.62 (˚2Θ).

3. The compound according to claim 1 or 2, which compound has an XRDP as shown in figure 3.

4. The compound according to claim 3, which compound has a particle size distribution corresponding to
   D98%:650-680 µm; D50%: 230-250 µm; and D5%: 40-60 µm;
   D98%: 370-390; d50%: 100-120 µm; D5%: 5-15 µm;
   D98%: 100-125 µm; D50%: 15-25 µm; and D5%: µm; or
   D98%: 50-70 µm; D50%: 3-7 µm; and D5%: 0.5-2.

5. The compound according to any of claims 1-4 for use in therapy.

6. A pharmaceutical composition comprising a compound according to any of claims 1-4 together with a pharmaceutically acceptable excipient.

7. The composition according to claim 6 comprising a compound according to claim 2 or 3.

8. The composition according to claim 7, said composition being a tablet prepared by wet granulation and comprising anhydrous calcium hydrogen phosphate, corn starch, PVP-VA copolymer, microcrystalline cellulose, sodium starch glycolate, talc and magnesium stearate.

9. The composition according to claim 8 comprising

| | |
|---|---|
| HBr salt | 3-8% |
| Anhydrous calcium hydrogen phosphate | 35-45% |
| Com starch | 15-25% |
| PVP-VA copolymer | 2-6% |
| Microcrystalline cellulose | 20-30% |
| Sodium starch glycolate | 1-3% |
| Talc | 2-6% |
| Magnesium stearate | 0.5-2% |

10. The composition according to claim 8 comprising

| | |
|---|---|
| HBr salt | approximately 5% |
| Anhydrous calcium hydrogen phosphate | approximately 39% |
| Corn starch | approximately 20% |
| PVP-VA copolymer | approximately 3% |
| Microcrystalline cellulose | approximately 25% |
| Sodium starch glycolate | approximately 3% |
| Talc | approximately 4% |
| Magnesium stearate | approximately 1% |

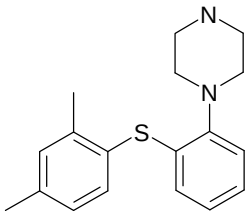
11. The use of a compound according to any of claims 1-4 for the preparation of a medicament for the treatment of depression, major depressive disorder, and cognitive impairment.

12. A compound according to any of claims 1-4 for use in the treatment of a disease selected from depression, major depressive disorder, and cognitive impairment.

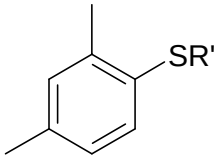
13. A crystalline form of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine pharmaceutically acceptable salts thereof, for use in the treatment of cognitive impairment.

14. A process for the preparation of

a crystalline form of 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine pharmaceutically acceptable salts thereof,



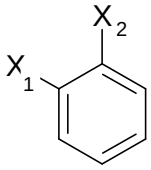

the process comprising reacting compound II




[II]

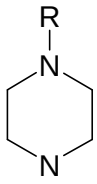
wherein R' represent hydrogen or a mono-valent metal ion,

with a compound of formula III




[III]

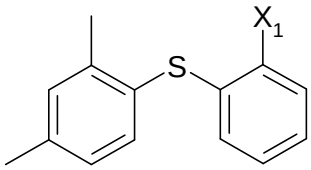
wherein X1 and X2 independently represent halogen, and a compound of formula IV




[IV]

wherein R represent hydrogen or a protecting group, in the presence of a solvent, a base and a palladium catalyst consisting of a palladium source and a phosphine ligand at a temperature between 60°C and 130°C.

15. The process according to claim 14, wherein compound II and compound III are reacted in a first reaction, and wherein the reaction product




for said first reaction is optionally isolated and purified, followed by a subsequent reaction with the compound IV.

16. The process according to claim 14, wherein compound II, compound III and compound IV are mixed together at the start of the process.

17. The process according to any of claims 14-16 wherein X1 and X2 independently represent Br or I.

18. The process according to claim 14, wherein $X_1$ represents Br and $X_2$ represents I.

19. The process according to any of claims 14-18, wherein said solvent is an aprotic solvent.

20. The process according to any of claims 14-19 wherein the solvent in selected from toluene, xylene, triethylamine, tributyl amine, dioxin or N-methylpyrrolidone.

21. The process according to claim 20, wherein the solvent is toluene.

22. The process according to any of claims 14-21, wherein the palladium source is selected from $Pddba_2$, $Pd(OAc)_2$ and $Pd_2dba_3$.

23. The process according to claim 22, wherein said palladium source is $Pddba_2$ or $Pd_2dba_3$

24. The process according to any of claim 14-23, wherein said phosphine ligand is selected from

2,2'-bis-diphenylphosphanyl-[1,1']binaphtalenyl (rac-BINAP),
1,1'-bis(diphenylphosphino)ferrocene (DPPF),
bis-(2-diphenylphosphinophenyl)ether (DPEphos),
tri-t-butyl phsophine (Fu's salt)
biphenyl-2-yl-di-t-butyl-phosphine, biphenyl-2-yl-dicyclohexyl-phosphine,
(2'-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethyl-amine,
[2'-(di-t-butyl-phosphanyl)-biphenyl-2-yl]-dimethyl-amine, and
dicyclohexyl-(2',4',6'-tri-propyl-biphenyl-2-yl)-phosphane.

25. The process according to claim 24, wherein said phosphine ligand is rac-BINAP.

26. The process according to any of claims 14-25, wherein said base is selected from NaO(t-Bu), KO(t-Bu), $Cs_2CO_3$, DBU and DABCO.

27. The process according to claim 26, wherein said base is NaO(t-Bu).

28. The process according to any of claims 14-27, wherein R represents hydrogen.

29. The process according to any of claims 14-28, wherein R represents a protecting group selected from Boc, Bn, Cbz, C(=O)Oet and Me.

30. The process according to any of claims 14-29, wherein R' is hydrogen.

31. The process according to any of claims 14-30, wherein the temperature is between 80°C and 120°C.

32. The process according to claim 16, comprising the steps of

a. Dissolving or dispersing 1-1.5 equivalents of compounds I, II and III in toluene to obtain mixture A;
b. Adding 1-2 mole-% of $Pddba_2$ and 1-2 mole-% of rac-BINAP together with 2-3 equivalents of NaO(t-Bu) to mixture A to obtain mixture B, which is heated to around 100°C until compound II and III are fully converted;

c. Increasing the temperature of the mixture obtained in step b to around 120°C until compound IV is fully converted; and
d. Optionally removing the protecting group by the addition of aqueous acid if compound IV is a protected piperazine.

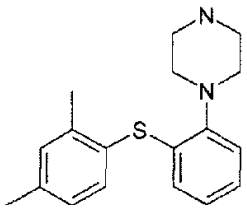
33. The process according to claim 16, wherein 1-1.5 equivalents of 2,4 dimethyl- thiol, 1-bromo-1-iodo-benzene (or 1,2 dibromo-benzene), and piperazine are dispersed in toluene followed by the addition of 2-5 equivalents NaO(t-Bu) and 1-2 mole-% $Pd_2dba_3$ and rac-BINAP dispersed in toluene to obtain a mixture which is heated to 100-130 °C for 2-10 hours to obtain the product 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine.

34. The process according to claim 33, wherein said mixture is heated to reflux for 3-5 hours, and which process is followed by a subsequent step in which the obtained product is further reacted with aqueous HBr to obtain the corresponding hydrobromic acid addition salt.

35. The process according to claim 16 wherein 2-5 equivalents of NaO(t-Bu), 2-5 equivalents piperazine, 0.2-0.6 mole-% $Pddba_2$, and 0.61 mole-% rac-BINAP are dispersed in toluene to obtain mixture A', to which mixture approximately 1 equivalent 2-bromo-iodobezene is added to obtain mixture B', to which mixture 1 equivalent 2,4-dimenthylthiopheno1 is added and the resulting mixture is heated to reflux for 3-7 hours to obtain 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]- piperazine.

36. The process according to claim 35, wherein said resulting mixture is heated to reflux for 4-6 hours, and which process is followed by a subsequent step in which the obtained product is further reacted with aqueous HBr to obtain the corresponding hydrobromic acid addition salt.

37. The process according to any of claims 14-33 with the additional step of adding aqueous HBr to the product




said product optionally being in a purified form, to obtain the corresponding hydrobromic acid salt.

38. A process for the manufacturing of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl}-piperazine hydrobromic acid addition salt in which process 1-1.5 equivalents of 2,4-dimethyl-thiol, 1-bromo-1-iodo-benzene (or 1,2-dibromo-benzene), and piperazine are dispersed in toluene followed by the addition of 2-5 equivalents NaO(t-Bu) and 1-2 mole-% $Pd_2dba_3$ and rac-BINAP dispersed in toluene to obtain a mixture which is heated to reflux 3-5 hours to obtain the product 1-[2-(2,4- dimethyl-phenylsulfanyl)-phenyl]-piperazine, which is further reacted with aqueous hydrobromic acid.

39. A process for the manufacturing of 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl}-piperazine hydrobromic acid addition salt in which process 2-5 equivalents of NaO(t-Bu), 2-5 equivalents piperazine, 0.2-0.6 mole-% $Pddba_2$, and 0.6-1 mole-% rac-BINAP are dispersed in toluene to obtain mixture A', to which mixture approximately 1 equivalent 2-bromo-iodobezene is added to obtain mixture B', to which mixture 1 equivalent 2,4-dimenthylthiophenol is added and the resulting mixture is heated to reflux for 4-6 hours to obtain 1-[2-(2,4-dimethyl- phenylsulfanyl)-phenyl]-piperazine, which is further reacted with aqueous hydrobromic acid.