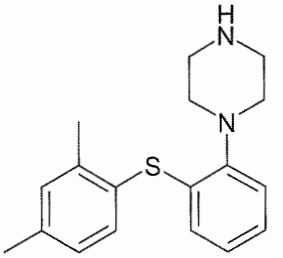
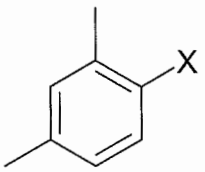
wherein impurities are reduced or eliminated. Accordingly, in one aspect, there is provided a process for the manufacture of

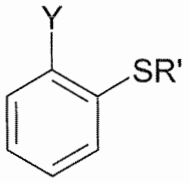


or pharmaceutically acceptable salts thereof (Compound I), said method comprising reacting a compound of formula II



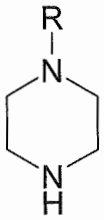
II

wherein X represents Br or I, with a compound of formula III



III

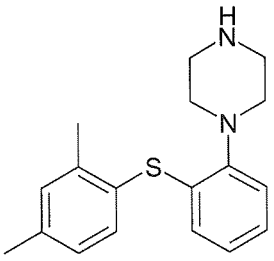
wherein Y represents Cl or Br and R' represents hydrogen or a metal ion, and a compound of formula IV



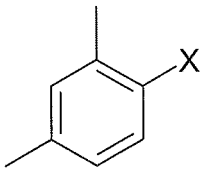
IV

wherein R represents hydrogen, 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 50°C and 130°C.

~~i~~In one embodiment the ~~invention~~ disclosure relates to a process for the manufacture of

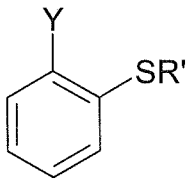


or pharmaceutically acceptable salts thereof (Compound I), said process comprising reacting a compound of formula II



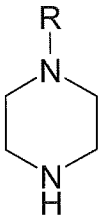
II

wherein X represents Br or I, with a compound of formula III



III

wherein Y represents Cl or Br and R' represents hydrogen or a metal ion, and a compound of formula IV

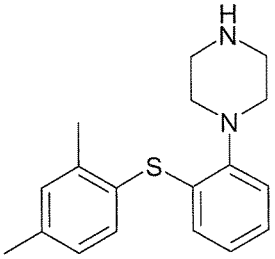


IV

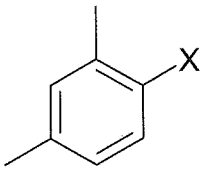
wherein R represents hydrogen or a protective group, in the presence of a solvent, a base and a palladium catalyst consisting of a palladium source and a phosphine ligand at a temperature between 50°C and 130°C, wherein when R represents a protective group, said protective group is removed in a subsequent step.

Claims

1. A process for the manufacture of

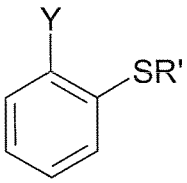


or pharmaceutically acceptable salts thereof (Compound I), said method comprising reacting a compound of formula II



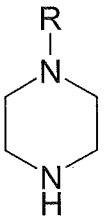
II

wherein X represents Br or I, with a compound of formula III



III

wherein Y represents Cl or Br and R' represents hydrogen or a metal ion, and a compound of formula IV



IV

wherein R represents hydrogen ~~or a protective 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 50°C and 130°C~~,~~

~~wherein when R represents a protective group, said protective group is removed in a subsequent step.~~

2. The process according to claim 1, wherein X represents I.

3. The process according to claims 1 or 2, wherein Y represents Br and R' represents H.

~~4. The process according to any of claims 1-3 wherein R represents H~~

~~5. The process according to any of claims 1-3, wherein R represents a protective group selected from C(=O)O-W, -C(=O)-W, boc, Bn and Cbz, wherein W represents alkyl or aryl.~~

~~6~~4. The process according to any of claims 1-~~5~~3, wherein said solvent is an aprotic solvent.

~~7~~5. The process according to claim ~~6~~4, wherein said solvent is toluene.

~~8~~6. The process according to any of claims 1-~~7~~5, wherein said palladium source is selected from $Pd(dba)_2$, $Pd(OAc)_2$ and Pd_2dba_3.

~~9~~7. The process according to claim ~~8~~6, wherein said palladium source is $Pd(dba)_2$ or $Pd(OAc)_2$.

~~10~~8. The process according to any of claims 1-~~9~~7, wherein said phosphine ligand is selected from
Racemic 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.

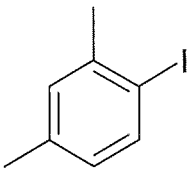
~~11~~9. The process according to claim ~~10~~8, wherein said phosphine ligand is 2,2'-bis-diphenylphosphanyl-[1,1']binaphtalenyl (rac-BINAP).

~~12~~10. The process according to any of claims 1-~~11~~9, wherein said base is selected from NaO(t-Bu), KO(t-Bu), K_2CO_3, Na_2CO_3, Cs_2CO_3, DBU and DABCO.

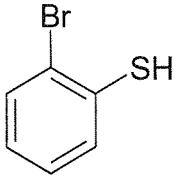
~~13~~11. The process according to claim ~~12~~10, wherein said base is NaO(t-Bu).

~~14~~12. The process according to any of claims 1-~~13~~11, which further comprises reacting the product obtained in said claims with an appropriate acid ~~to remove the protective group (when R is a protective group) and/or~~ to obtain the desired pharmaceutically acceptable salt.

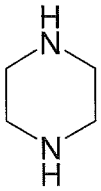
~~15~~13. The process according to claim 1, which comprises reacting



with



and



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 50°C and 130°C.

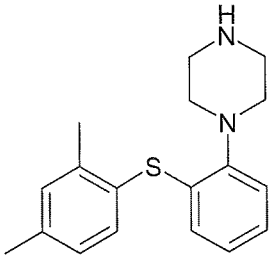
~~16~~14. The process according to claim ~~15~~13, which further comprises reacting the compound obtained in said claim with an acid to obtain a desired pharmaceutically acceptable salt of said compound.

~~17~~15. The process according to claim 1, comprising the steps of

a) Dissolving or dispersing 0.1 mole-% - 3 mole-% bis(dibenzylideneacetone)-palladium(0) and 0.5 mole-% – 4 mole-% racemic 2,2'-bis-diphenylphosphanyl-[1,1']binaphtalenyl and 2-6 equivalents base in toluene to obtain Mixture A;

b) adding 1 equivalent 1-iodo-2,4-dimethylbenzene, 0.8-1.2 equivalent 2-bromo thiophenol and 1-10 equivalents piperazine to Mixture A to obtain Mixture B; and

c) heating Mixture B to 80°C-120°C to obtain



; and

d) optionally adding an appropriate acid to the product obtained in step c) to obtain the corresponding salt.

~~18~~16. A process according to claim 1 comprising the steps of

a) Dissolving or dispersing 0.1 mole-% - 3 mole-% bis(dibenzylideneacetone)-palladium(0) and 0.5 mole-% – 4 mole-% racemic 2,2'-bis-diphenylphosphanyl-[1,1']binaphtalenyl, 1-10 equivalents piperazine and 2-6 equivalents base in toluene to obtain Mixture A;

b) adding 1 equivalent 1-iodo-2,4-dimethylbenzene and 0.8-1.2 equivalent 2-bromo thiophenol to Mixture A to obtain Mixture B; and

c) heating Mixture B to 80°C-120°C to obtain