Solid-phase chemistry is not feasible for pharmaceutical production involving manufacturing in ton-scale. The massive handling of resins that would be required and the costs associated are prohibitive. Additionally, the low yield obtained for votioxetine (only 17%) makes this manufacturing route unattractive.

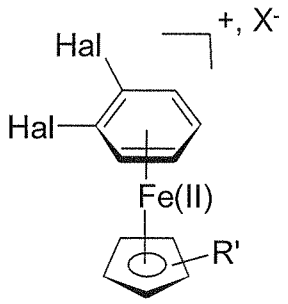
Large scale manufacturing of vortioxetine has been disclosed in WO 2007/144005 and WO 2010/094285. Piperazine, 2,4-dimethylthiophenol and 1,2-dihalogenbenzene are mixed e.g. in toluene together with a palladium catalyst to afford vortioxetine. Although this reaction provides high yield and can be handled in large scale, it requires the use of an expensive catalyst, i.e. palladium. Moreover, the reaction conditions are harsh employing elevated temperatures to obtain a satisfactory result, i.e. reflux temperatures or 80-120°C and the use of strong base.

The present invention provides a manufacturing process for vortioxetine which uses inexpensive starting materials, which can be run at mild conditions and which gives high yields.

Summary of the invention

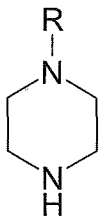
The present inventors have found that 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine (vortioxetine) or pharmaceutically acceptable salts thereof can be prepared in a reaction in which a suitable di-arene iron salt, i.e. optionally substituted 1,2-dihalogenbenzene-cyclopentadienyl-iron(II) salt is reacted with an optionally protected piperazine and 2,4-dimethylthiophenol(ate) followed by de-complexation of optionally substituted cyclopentadienyl iron and by de-protection of piperazine as required if protected piperazine is applied in the process to obtain 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine. A desired pharmaceutically acceptable salt may be obtained by subsequent reaction with a suitable acid.

In one aspect, the present disclosure relates to a process for the manufacture of vortioxetine or pharmaceutically acceptable salts thereof, which process comprises reacting a compound of formula I



[I]

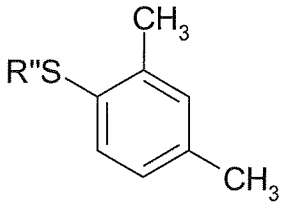
wherein each Hal independently represents fluoro or chloro; R' represents H or R' represents one or two moieties independently selected from CHO, COOH, COOR''' or $COONR_2$''', or R' represents one to five moieties independently selected from C_{1-6}-alkyl; R''' independently represents H or C_{1-6}-alkyl; and X^- represents a non-coordinating and non-nucleophilic anion, with a piperazine of formula II



[II]

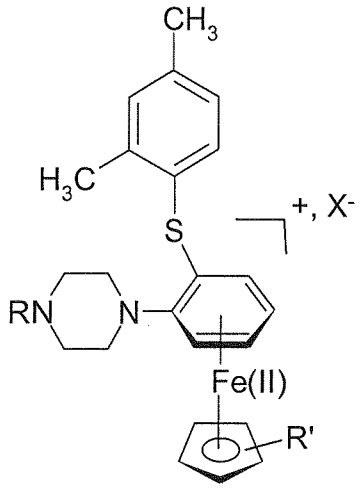
wherein R represents H,

and with a compound of formula III



[III]

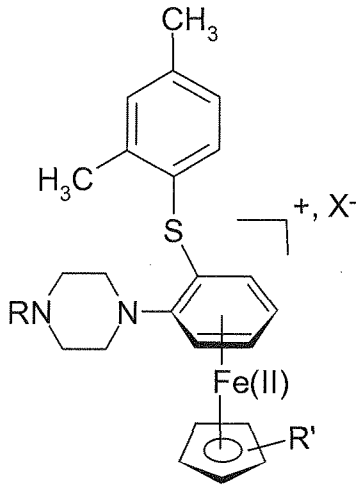
wherein R'' represents H or a cation and a base as required in a solvent to obtain a compound of formula IV



[IV]

followed by a de-complexation step in which the optionally substituted cyclopentadienyliron is de-complexed to obtain 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine (vortioxetine).

Accordingly, in one ~~aspect~~embodiment, the ~~invention~~ disclosure provides a process for the manufacture of vortioxetine or pharmaceutically acceptable salts thereof, which process comprises reacting a compound of formula I



[IV]

followed by a de-complexation step in which the optionally substituted cyclopentadienyliron is de-complexed, and a de-protection step as required in which the optionally protected piperazine moiety is de-protected to obtain 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine, i.e. vortioxetine.

The compound of formula I, the compound of formula II and the compound of formula III may be added to the reaction mixture in any sequence or simultaneously.

Another ~~aspect~~ embodiment relates to 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine and pharmaceutically acceptable salts thereof obtained in a process defined above.

Figures

Figure 1: Schematic depiction of a flow chemistry set-up for the reaction of the present invention. Compound of formula I is mixed with compound of formula II and compound of formula III to obtain vortioxetine following de-complexation and de-protection as required.

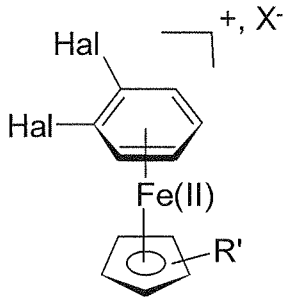
Detailed description of the invention

The compound of formula I comprises a di-halogen substituted benzene moiety which is η^6-bound to the metal centre of a cyclopentadienyl fragment. Said halogen is independently selected from fluoro and chloro. In one embodiment, the halogens are identical; in particular both halogens are chloro. In this embodiment, the di-arene iron compound can be made from very inexpensive starting materials, i.e. 1,2-di-chlorobenzene.

R' represents H or R' represents one or two moieties independently selected from CHO, COOH, COOR''' or $COONR_2$''', or R' represents one to five moieties

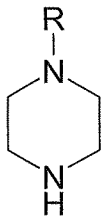
Claims

1. A process for the manufacture of vortioxetine or pharmaceutically acceptable salts thereof, which process comprises reacting a compound of formula I



[I]

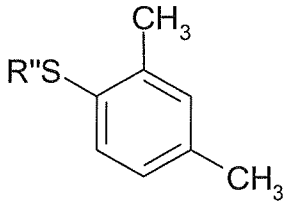
wherein each Hal independently represents fluoro or chloro; R' represents H or R' represents one or two moieties independently selected from CHO, COOH, COOR''' or $COONR_2$''', or R' represents one to five moieties independently selected from C_{1-6}-alkyl; R''' independently represents H or C_{1-6}-alkyl; and X^- represents a non-coordinating and non-nucleophilic anion, with ~~an optionally protected~~a piperazine of formula II



[II]

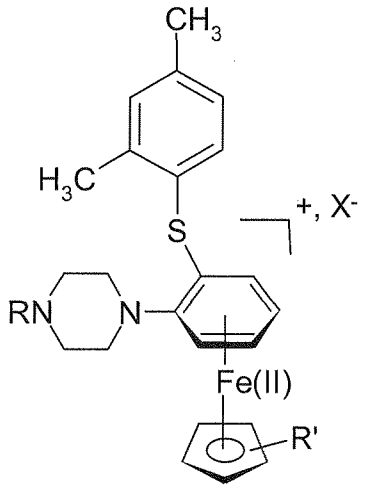
wherein R represents H ~~or a protetive group~~,

and with a compound of formula III



[III]

wherein R'' represents H or a cation and a base as required in a solvent to obtain a compound of formula IV



[IV]

followed by a de-complexation step in which the optionally substituted cyclopentadienyliron is de-complexed~~, and a de-protection step as required in which the optionally protected piperazine moiety is de-protected~~ to obtain 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine (vortioxetine).

2. The process according to claim 1, wherein Hal represents chloro.

3. The process according to claim 1or 2 wherein R' represents hydrogen.

~~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.~~

~~6. The process according to claim 5, wherein R represents a protective group selected from Boc, Fmoc, Bn and Cbz.~~

~~7~~4. The process according to any of claims 1-~~6~~3 wherein X^- is selected from PF_6^-, $AlCl_4^-$, ClO_4^-, BF_4^-, $[B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$, $B(C_6F_5)_4^-$ and $Al(OC(CF_3)_3)_4^-$.

~~8~~5. The process according to claim ~~7~~4, wherein X^- is PF_6^-.

96. The process according to any of claims 1-85, wherein said solvent is selected from toluene, THF (tetrahydrofuran), MTBE (methyl tertiary-butyl ether), water, ethanol, 2-propanol, NMP (N-Methyl-2-pyrrolidone), DMF (dimethylformamide), MIBK (methylisobutyl ketone), TEA (triethyl amine), DIPEA (N,N-diisopropylethylamine), DCM (dichloromethane), ethylacetate, isopropylacetate and combinations of these.

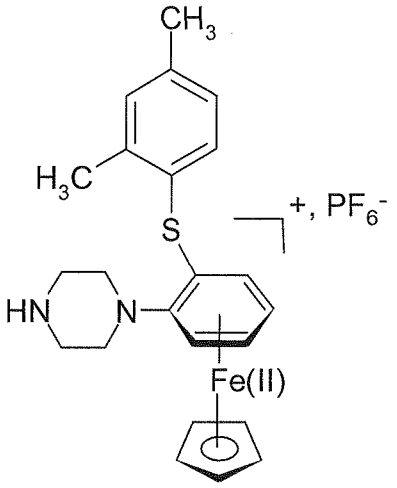
107. The process according to any of claims 1-96 wherein R'' represents H.

118. The process according to any of claims 1-107, wherein said de-complexation step comprises photolysis.

129. The process according to claim 1, wherein 1 equivalent of a compound of formula I is mixed with a compound of formula II (1-5 equivalents) and a compound of formula III (1-5 equivalents) in a solvent together with a base as required (more than 0.5 equivalent) to obtain a compound of formula IV followed by de-complexation ~~and removal of the protective group on the piperazine as required~~ to obtain 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine.

1310. The process according to claim 1, wherein 1 equivalent of a compound of compound of formula I is mixed with a base (between 0.5 and 20 equivalents), piperazine (1-5 equivalents) and 2,4-dimethyl thiophenol (1-5 equivalents) in a solvent to obtain a compound of formula IV, followed by de-complexation to obtain1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine.

1411. The process according to claim 1, wherein 1 equivalent of η^6-1,2-dichlorobenzene- η^5-cyclopentadienyliron(II) hexafluorophosphate is mixed with 1-5 equivalent base, 1-3 equivalents 2,4-dimethylthiophenol and 1-3 equivalents piperazine in a solvent at 10°C-50°C to obtain the compound of the formula



followed by de-complexation to obtain 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine.

~~15~~12. The process according to any of claims 1-~~14~~11, wherein the obtained 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine is reacted with a suitable acid to obtain the equivalent pharmaceutically acceptable salt.

~~16. 1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine and pharmaceutically acceptable salts thereof obtained in a process according to any of claims 1-15.~~