The synthesis of N-(2-(6-fluoro-lH-indol-3-yl)ethyl-(2,2,3,3-tetrafluoropropoxy) benzylamine, its use for the treatment of disorders such as cognitive dysfunction disorders, and pharmaceutical compositions comprising this substance are disclosed in U.S. Patent No. 7,157,488 ("the '488 patent"). The '488 patent further describes the preparation of the corresponding monohydrochloride salt.

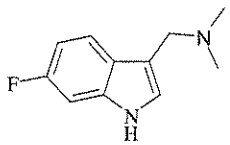
Although the synthetic methods disclosed in the above-identified reference suffices to prepare small quantities of material, it suffers from a variety of safety issues, low yields or processes that are not amendable to large scale synthesis. Thus, an unmet need exists to identify processes for the manufacture of the compound of Formula I.

Accordingly, the present invention describes an efficient and economical process for the preparation of the compound of Formula I that is useful for the production of kilogram quantities of material for preclinical, clinical and commercial use. In particular, the inventors have unexpectedly discovered the role of ammonia to prevent dimerization in connection with the reduction of the nitrile containing intermediate to the corresponding amine.

SUMMARY OF THE INVENTION

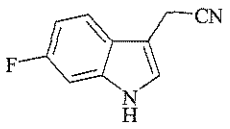
The present ~~invention~~disclosure relates to a process for the preparation of N-(2-(6-fluoro-lH-indol-3-yl)ethyl-(2,2,3,3-tetrafluoropropoxy)benzylamine, and pharmaceutically acceptable salts thereof, comprising the steps of:

(a) reacting 6-Fluoroindole with an iminium ion species generated in-situ from formaldehyde and dimethylamine in the presence of an acidic aqueous solution to produce the compound of Formula II



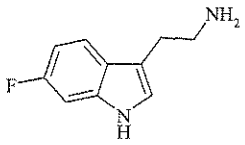
Formula II ;

(b) reacting the compound of Formula II with KCN in the presence of DMF/water to produce the compound of Formula III;



Formula III ;

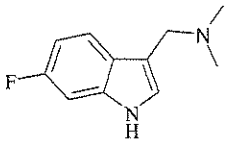
(c) hydrogenating the compound of Formula III with H_2 in the presence of NH_3 using a transition metal catalyst to produce the compound of Formula IV;



Formula IV ; and

(d) reacting the compound of Formula IV with 3-(2,2,3,3-tetrafluoropropoxy)benzaldehyde in the presence of a solvent followed by the addition of reducing agent.

A separate ~~aspect~~embodiment relates to a process for the preparation of the compound of formula II comprising the steps of:



Formula II

(a) mixing a solution of diethoxymethane, water and formic acid;

(b) adding the solution of step (a) to a mixture of 6-fluoroindole, methylamine and acetic acid; and

(c) adding an aqueous basic solution.

In one embodiment, the solution of step (a) is mixed at a temperature from about 75°C to about 85°C.

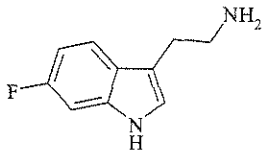
In another embodiment, the solution of step (a) is stirred for less than about 2 hours.

In yet another embodiment, the solution of step (a) is added to a mixture of 6-fluoroindole and acetic acid at a temperature from about 2-8 °C.

In another embodiment, the aqueous basic solution is NaOHaq.

In one embodiment, the yield is greater than 90%. In one embodiment, the yield is greater than 95%. In a separate embodiment, the yield is greater than 98%.

Another ~~aspect~~embodiment relates to a process for the preparation of the compound of formula IV comprising the steps of:

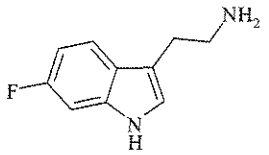


Formula IV

(a) mixing (6-fluoro-1H-indol-3-yl)acetonitrile, 25 % NH_3 in water and a transition metal catalyst in an alcoholic solvent; and

(b) hydrogenating the mixture with H_2.

In one aspect, there is provided a process for the preparation of the compound of formula IV, which comprises hydrogenating (6-fluoro-1H-indol-3-yl)acetonitrile in the presence of NH_3 in water using a transition metal catalyst:



Formula IV

In one embodiment, the transition metal catalyst is RaNi.

In another embodiment, the alcoholic solvent is methanol.

In yet another embodiment, the hydrogenation is run at a pressure of about 2.5 bars for about 16 hours.

In one embodiment, the hydrogenation is run at a temperature from about 55 °C to about 65 °C.

Yet another ~~aspect~~embodiment of the ~~invention~~disclosure relates to a process for the purification of 2-(6-fluoro-1H-indol-3-yl)-ethylamine comprising the steps of:

(a) dissolving 2-(6-Fluoro-1H-indol-3-yl)-ethylamine in an alcoholic solvent;

(b) adding a solution of L(+)-tartaric acid; and

(c) capturing the tartaric acid salt as a precipitate.

In one embodiment, the alcoholic solvent is methanol.