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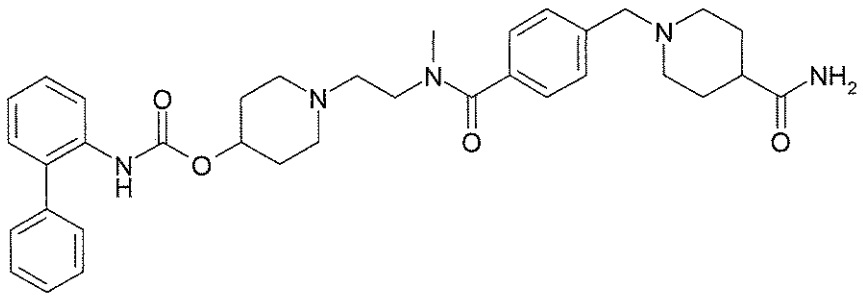
which is then isolated prior to being combined with isonipicotamide in the presence of a reducing agent to form the compound of formula I. The crystalline diphosphate is prepared by contacting the separated and purified compound of formula I with phosphoric acid. The crystalline freebase (Form III) can then be prepared from the crystalline diphosphate.

A need also exists for an efficient process of preparing the crystalline freebase (Form III). It is desirable to develop a process that does not first require preparation of the crystalline diphosphate. This invention addresses those needs.

## SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~disclosure relates to a process for preparing the crystalline freebase (Form III) of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl) benzoyl]methylamino}ethyl)piperidin-4-yl ester described in U.S. Patent Application Publication No. 2011/0015163 to Woollham. Form III is characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1; and further characterized by having five or more additional diffraction peaks at 2θ values selected from 8.8±0.1, 10.1±0.1, 11.4±0.1, 11.6±0.1, 14.8±0.1, 15.2±0.1, 16.1±0.1, 16.4±0.1, 16.9±0.1, 17.5±0.1, 18.2±0.1, 19.3±0.1, 19.9±0.1, 20.8±0.1, 21.1±0.1, 21.7±0.1, and 22.3±0.1.

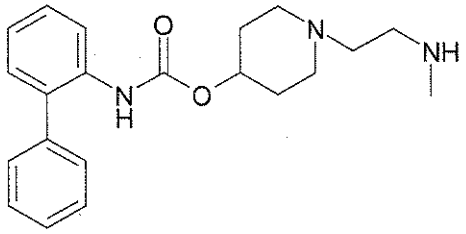
One aspect of the ~~invention~~present disclosure relates to a process for preparing a crystalline freebase (Form III) of the compound of formula I:



(I),

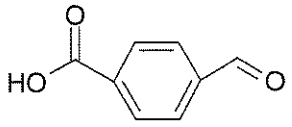
the process comprising the steps of:

(a) coupling a compound of formula 8:



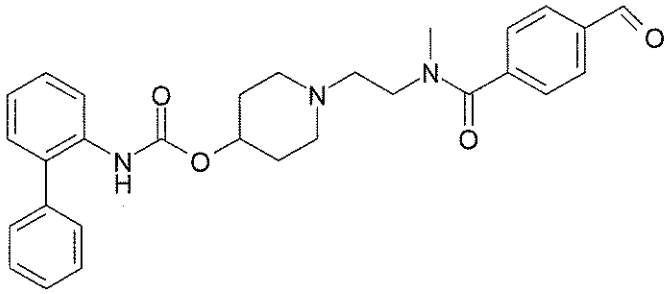
(8)

in the presence of a coupling reagent with a compound of formula 9:



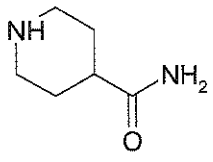
(9)

to yield the compound of formula 10:



(10);

(b) reductive amination of the compound of formula 10 and a compound of formula 11:



(11)

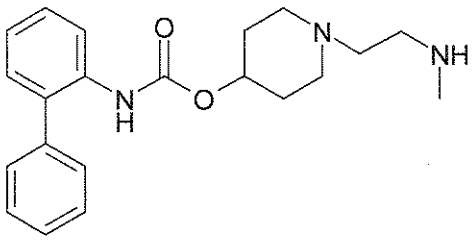
in the presence of a reducing agent to yield the compound of formula I, wherein azeotropic distillation of water is conducted at an elevated temperature prior to the addition of the reducing agent, and reductive amination is conducted at room temperature;

(c) contacting the product of step (b) with isopropyl acetate, optionally adding a seed crystal of the crystalline freebase (Form III) to form a solid, and isolating the resulting solid; and

(d) contacting the product of step (c) with toluene, optionally adding a seed crystal of the crystalline freebase (Form III) to form a solid, and isolating the resulting solid as the crystalline freebase (Form III); wherein step (a) and step (b) are conducted in the same reaction mixture without isolation of the intermediate from step (a).

The present ~~invention~~disclosure further relates to an improved process for preparing an

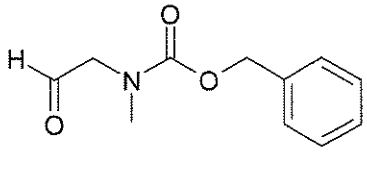
intermediate useful for preparing the crystalline freebase (Form III). Accordingly, another ~~aspect~~embodiment of the ~~invention~~present disclosure relates to a process for preparing a compound of formula 8:



(8),

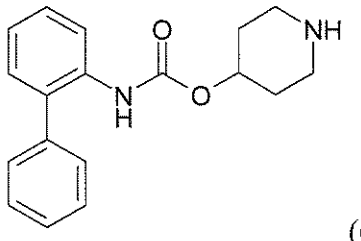
the process comprising the steps of:

(a) reductive amination of a compound of formula 3:



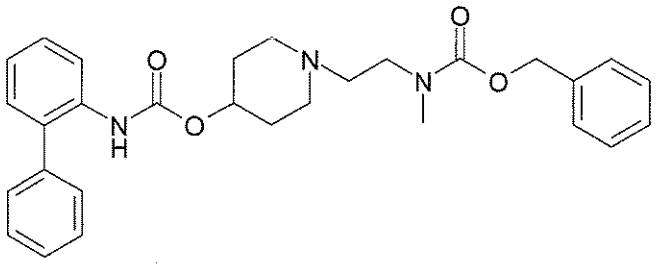
(3)

and a compound of formula 6:



(6);

in the presence of a reducing agent, to yield the compound of formula 7:

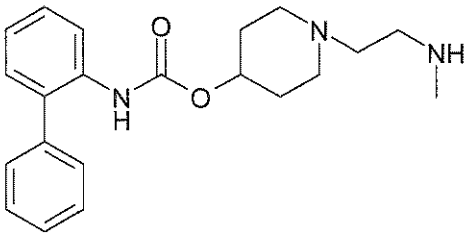


(7);

and

(b) debenzylation of the compound of formula 7 to yield the compound of formula 8; wherein step (a) and step (b) are conducted in the same reaction mixture without isolation of the intermediate from step (a).

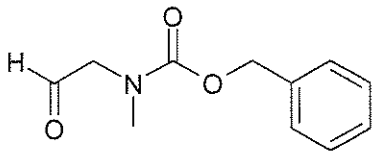
In an aspect, the present disclosure relates to a process for preparing a compound of formula 8:



(8),

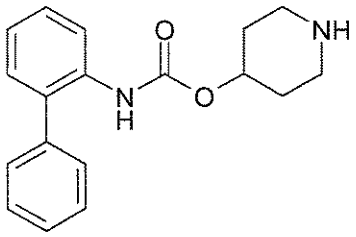
the process comprising the steps of:

(a) reductive amination of a compound of formula 3:



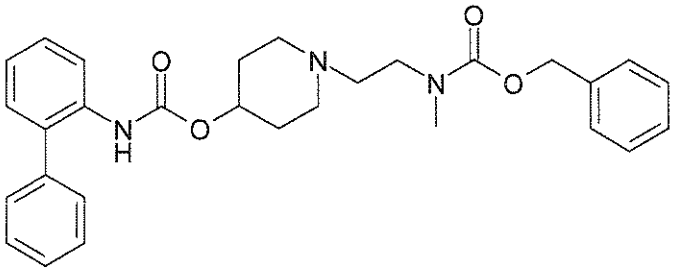
(3)

and a compound of formula 6:



(6);

in the presence of a reducing agent, to yield the compound of formula 7:



(7);

and

(b) debenzylation of the compound of formula 7 to yield the compound of formula 8; wherein step (a) and step (b) are conducted in the same reaction mixture without isolation of the intermediate from step (a); wherein steps (a) and (b) are conducted in methyltetrahydrofuran.

The present ~~invention~~disclosure also relates to an improved process for preparing a compound of formula 3: