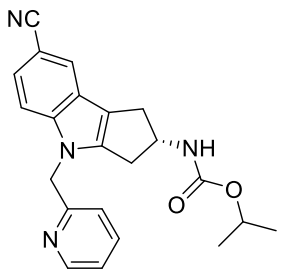
dysfunction, shrinking of the male sexual organs, hot flashes, osteoporosis, anemia, reduced muscle mass, decreased muscle strength, increase in body fat, and weight gain, due to the changes in the levels of the hormones testosterone and estrogen. Current treatments for the side effects associated with ADT are known in the art. See US 2009/0143344 (hot flashes – 5HT2A or D2R antagonist); US 2007/0281977 (hot flashes – muscarinic receptor antagonist); US 2008/0080143 (osteoporosis, bone fractures, loss of BMD, hot flashes gynochomastia, hair loss – torimifene). However, there remains a need in the art for alternate therapies wherein certain side effects of ADT may be reduced. In fact, until recently, intermittent androgen deprivation (IAD) was recommended to attempt to minimize the adverse effects of medical castration by withdrawing treatment in patients who have responded to ADT and then reinstituting ADT when there is evidence of recurrent or progressive disease. However, a trial of 1749 patients randomized to continuous ADT versus IAD for a median follow-up of 9.8 years demonstrated that continuous ADT is superior to IAD. A therapy to improve tolerability of the side effects of ADT could lead to improvements in compliance and result in better outcomes to patients.

Selective androgen receptor modulators (SARMs) have been found to display a differentiated profile of activity in androgenic tissues. In particular, such agents preferably display androgen agonist activity in anabolic tissues such as muscle or bone, yet are only partial agonists or even antagonists in other androgenic tissues such as the prostate or seminal vesicles. Thus, the use of an androgen receptor (AR) modulator may alleviate the symptoms of ADT for prostate cancer patients.

Summary

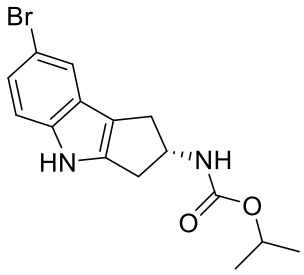
In an aspect of the present disclosure, there is provided a process for the preparation of the compound of Formula I



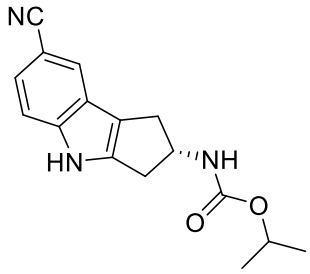
(Formula I)

comprising the steps of:

reacting $Zn(CN)_2$ with the compound of Formula II, thereby forming the compound of Formula III

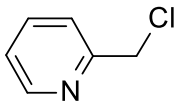


(Formula II)



(Formula III); and

forming the compound of Formula I by reacting the compound of Formula III with the compound of Formula IV



(Formula IV).

In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition in the manufacture of a medicament for treating the symptoms of secondary hypogonadism induced by androgen deprivation therapy, wherein the pharmaceutical composition comprises a substantially pure form of (S)-(7-cyano-4-pyridin-2-ylmethyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-2-yl)-carbamic acid isopropyl ester obtained by the process disclosed herein, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a substantially pure form of (S)-(7-cyano-4-pyridin-2-ylmethyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-2-yl)-carbamic acid isopropyl ester or a pharmaceutically acceptable salt thereof.

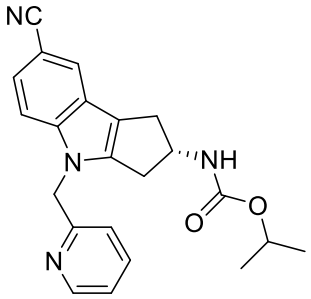
Description

Figure 1 illustrates that Example 1 resulted in no significant accrual of seminal vesicle weight after treatment of 8 weeks in a rat orchidectomized for 8 weeks and which was hyper responsive to any androgenic stimulation.

Figure 2 illustrates that Example 1 resulted in significant accrual of, lumbar vertebra trabecular bone mineral density (LV-TBMD) and showed a trend towards increase in lumbar vertebra trabecular bone mineral content (LV-TBMC), and cross-sectional area (LV-TA) after treatment of 8 weeks in a rat orchidectomized for 8 weeks.

WE CLAIM:

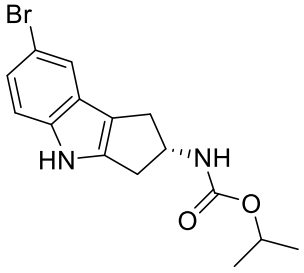
1. A process for the preparation of the compound of Formula I



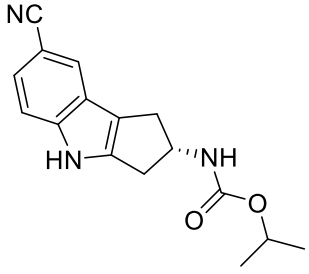
(Formula I)

comprising the steps of:

reacting $Zn(CN)_2$ with the compound of Formula II, thereby forming the compound of Formula III

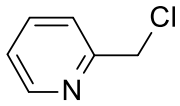


(Formula II)



(Formula III); and

forming the compound of Formula I by reacting the compound of Formula III with the compound of Formula IV



(Formula IV).

2. The process of claim 1, wherein the reaction of the compound of Formula II with $Zn(CN)_2$ to form a compound of Formula III comprises:

(i) reacting the compound of Formula II with $Zn(CN)_2$, $Zn(OAc)_2$, Zn, and $Pd(dppf)_2Cl_2 \cdot CH_2Cl_2$ in DMAC to form a compound of Formula III in solution;

(ii) adding water to precipitate and isolate the compound of Formula III from the solution;

(iii) dissolving the precipitated and isolated compound of Formula III in a mixture of MTBE and acetone to form a slurry;

(iv) filtering the slurry to produce a filtrate having a compound of Formula III; and

(v) treating the filtrate having the compound of Formula III with charcoal, $MgSO_4$, and FLORISIL™.

3. The process of claim 2, wherein the compound of Formula III is crystalized in the heptane.

4. The process of any one of claims 1-3, wherein the compound of formula I is produced by a process comprising the steps of:

(i) reacting the compound of Formula III with 2-picolyl chloride hydrochloride and K_2CO_3 in DMAC to give a compound of Formula I in solution; and

(ii) isolating the compound of Formula I by adding water to the solution formed in step (i) and filtering.

5. The process of claim 4, further comprising a step of recrystallizing the isolated compound of Formula I in EtOH to produce a crystalline form of a compound of Formula I.

6. Use of a pharmaceutical composition in the manufacture of a medicament for treating the symptoms of secondary hypogonadism induced by androgen deprivation therapy, wherein the pharmaceutical composition comprises a substantially pure form of (S)-(7-cyano-4-pyridin-2-ylmethyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-2-yl)-carbamic acid isopropyl ester obtained by the process according to any one of claims 1-5, or a pharmaceutically acceptable salt thereof.

7. The use according to claim 6, wherein said pharmaceutical composition is in the form of a capsule.

8. A substantially pure form of (S)-(7-cyano-4-pyridin-2-ylmethyl-1,2,3,4-tetrahydro-cyclopenta[b]indol-2-yl)-carbamic acid isopropyl ester or a pharmaceutically acceptable salt thereof.

9. The use according to claim 6, wherein the symptoms are the loss in bone mass, bone strength, muscle mass, or muscle strength.

10. The use according to claim 6, wherein the symptoms are loss of libido and hot flashes.

11. The process of claim 5, wherein the filtered isolate of the compound of Formula I is recrystallized at least three times in EtOH to produce the crystalline form of the compound of Formula I.