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Process for the preparation of 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one hydrochloride

MSN Laboratories Private Limited, R&D Center, Srinivasan Thirumalai Rajan, Sajja Eswaraiah, Vijayavitthal T. Mathad, Gandham Shyam Kiran babu, Lunavath Kumaraswamy

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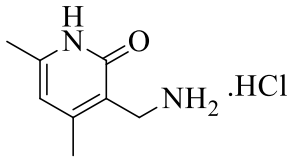
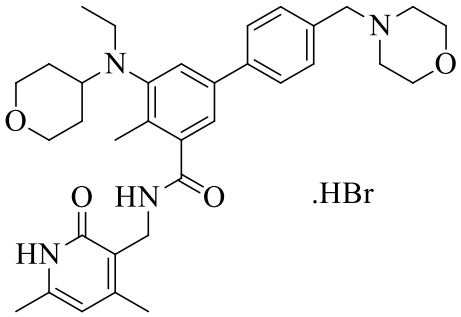
Abstract:

Process for the preparation of 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one hydrochloride of formula-1, which is represented by the following structural formula:



Formula-1

which is key intermediate for the preparation of Tazemetostat hydrobromide, which is chemically known as [1,1'-Biphenyl]-3-carboxamide, N-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-5[ethyl(tetrahydro-2H-pyran-4-yl)amino]-4-methyl-4'-(4-morpholinyl methyl)-, hydrobromide (1:1).



Tazemetostat hydrobromide

Introduction:

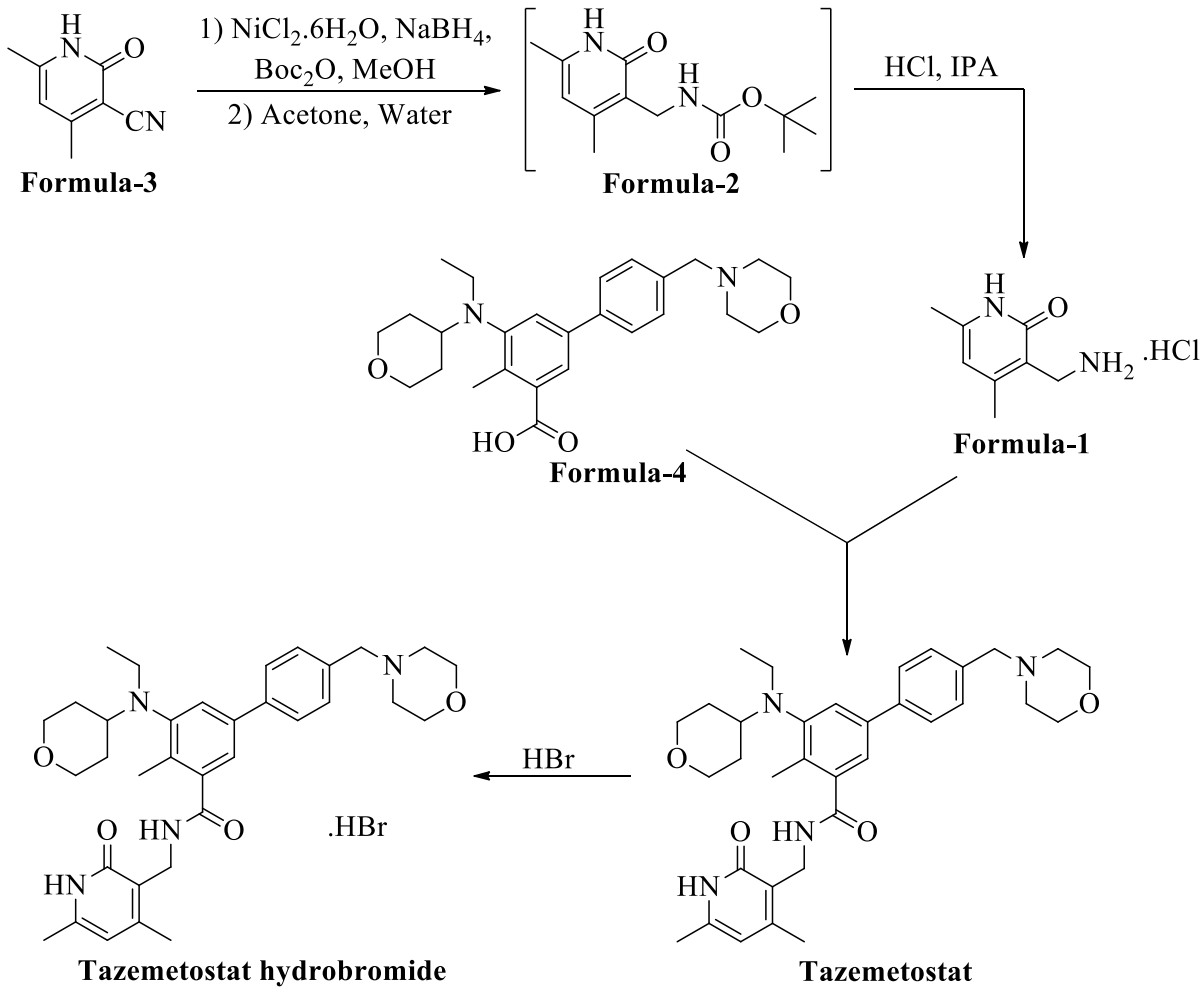
Tazemetostat is a selective, orally bioavailable, small molecule inhibitor of the enhancer of zeste homolog 2 (EZH2), a histone methyltransferase. EZH2 is the catalytic subunit of the polycomb repressive complex 2, catalyzing mono, di-, and trimethylation of lysine 27 of histone H3, which leads to repression (transcriptional regulation) of certain important gene sets such as tumor suppressors, differentiation markers, cell cycle regulators, and apoptotic machinery.

Tazemetostat is approved in US as TAZVERIK tablet for oral administration for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.

Tazemetostat is disclosed in US8410088 B2 and this patent also discloses process for the preparation of Tazemetostat trihydrochloride.

Tazemetostat hydrobromide is disclosed in US9394283 B2. This patent also discloses process for the preparation of Tazemetostat hydrobromide.

Disclosed herein the process for the preparation of Tazemetostat hydrobromide, schematically as mentioned below:



The compound of Formula-3 used in the present invention is prepared by method reported in Journal of the Chemical Society (1951), 3155-3174 or any other methods known in the art.

The compound of Formula-4 used in the present invention is prepared by method reported in US8410088 B2 or any other methods known in the art.

Experimental Section:

Example-1: Preparation of tert-butyl((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl) carbamate of Formula-2.

Methanol (3000.0 ml) was added to 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile of formula-3 at 25-30ºC. Di-tert-butyl dicarbonate (308.0 ml) and nickel chloride hexahydrate (159.3 gm) were added to the mixture at 25-30ºC and stirred for 20 minutes. Cooled the mixture to -15 to -10 ºC. Sodium borohydride (201.75 gm) was slowly added to the

mixture in lot wise at -15 to -10 ºC. Raised the temperature of the mixture to 0-5ºC and stirred for 2 hours. Water was added to the mixture at 0-5ºC. Raised the temperature of the mixture to 25-30ºC and stirred for 1 hour. Distilled off the solvent completely from the mixture under vacuum at below 60ºC. Mixture of methanol (600.0 ml) and ethyl acetate (2400.0 ml) were added to the obtained compound at 25-30ºC and stirred for 4 hours. Filtered the mixture through hyflow bed and washed with mixture of methanol and ethyl acetate. Distilled off the solvent completely from the filtrate under vacuum at below 60ºC. Sodium bicarbonate solution was added to the obtained compound at 25-30ºC and stirred for 3 hours. Filtered the solid, washed with water and dried. Mixture of acetone (840.0 ml) and water (160.0 ml) were added to the obtained compound at 25-30ºC and stirred for 15 minutes. Heated the mixture to 55-60ºC and stirred for 2 hours. Cooled the mixture to 25-30ºC and stirred for 15 minutes. Cooled the mixture to 0-5ºC and stirred for 3 hours. Filtered the solid and washed with acetone to get the title compound. Yield: 98.0 gm.

Example-2: Preparation of 3-(aminomethyl)-4,6-dimethylpyridin-2(1H)-one hydrochloride of Formula-1.

Isopropanol (250.0 ml) was added to the compound obtained in example-1 at 25-30ºC. Hydrochloric acid (170.0 ml) was slowly added to the mixture at 25-30ºC and stirred for 6 hours. Isopropanol (250.0 ml) was added to the mixture at 25-30ºC and stirred for 2 hours. Filtered the solid, washed with isopropanol and dried to get the title compound.
Yield: 58.0 gm; M.R: 313-315ºC.

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