June 2022

Improved process for the preparation of 4-Amino-3-fluorophenol

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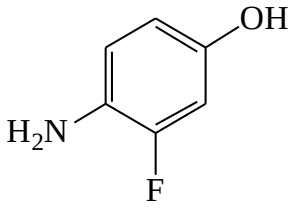
The present invention provides process for the preparation of 4-amino-3-fluorophenol, which is represented by the following structural formula-I:



Formula-I

4-Amino-3-fluorophenol compound of formula-I is useful for the preparation of Regorafenib.

Regorafenib is an oral multi-kinase inhibitor developed by Bayer, which targets angiogenic, stromal and oncogenic receptor tyrosine kinase (RTK). Regorafenib shows anti-angiogenic activity due to its dual targeted VEGFR2-TIE2 tyrosine kinase inhibition. Since 2009, it was studied as a potential treatment option in multiple tumour types. By 2015, it had two US approvals for advanced cancers.

The present invention provides improved process for the preparation of 4-amino-3-fluorophenol of formula-1, which provides Regorafenib with high yield and purity. In addition, the said process is cost effective and commercially viable.

The following example specifies the conditions of the process for the preparation of 4-amino-3-fluorophenol.

Example: Process for the preparation of 4-amino-3-fluorophenol.

Sodium carbonate (22.6 g) was slowly added to the mixture of sulfanilic acid (77.2 g) in water (450 ml) at 25-30°C. Cooled the mixture to 0°C to -5°C and aq. sodium nitrite (32.3 g) solution was slowly added to the mixture at the same temperature. Aqueous hydrochloric acid was added to the mixture at 0°C to -5°C and stirred the mixture for 60 minutes at the same temperature (mixture-1). Sodium hydroxide solution and sodium carbonate were added to the mixture of 3-fluorophenol (50 g) in water (250 ml) at 25-30°C and cooled the mixture to 5-10°C (mixture-2). Slowly added the mixture-2 to mixture-1 at 0°C to -5°C and stirred for 60 minutes at the same temperature. Treated the mixture with aq. Hydrochloric acid at 0-5°C. Allowed to heat the reaction mixture to 20-25°C. Ammonium chloride (143 g) and Iron powder (74.7 g) were slowly added to the mixture at 20-25°C. Stirred the mixture for 3 hours at 25-30°C. Ethyl acetate (300 ml) was added to the mixture and stirred for 15 minutes at 25-

30°C. Filtered the mixture. Separated and distilled-off the organic layer from filtrate. Cyclohexane was added to the mixture and stirred for 30 minutes. Filtered the mixture and dried to get the titled product as a solid.

Weight: 38.0 g

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