November 2022

Improved process for the preparation of 1-((4-fluorophenyl)carbamoyl) cyclopropanecarboxylic acid

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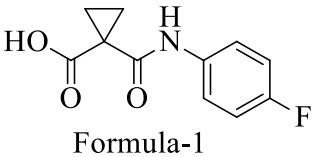
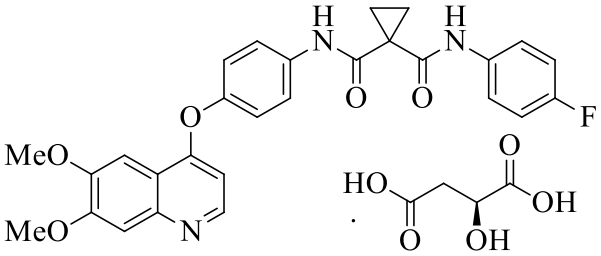
Abstract:

Improved process for the preparation of 1-((4-fluorophenyl)carbamoyl) cyclopropanecarboxylic acid of formula-1, which is represented by the following structural formula:



Formula-1

which is key intermediate for the preparation of Cabozantinib (S)-malate, which is chemically known as N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate.



Cabozantinib (S)-Malate

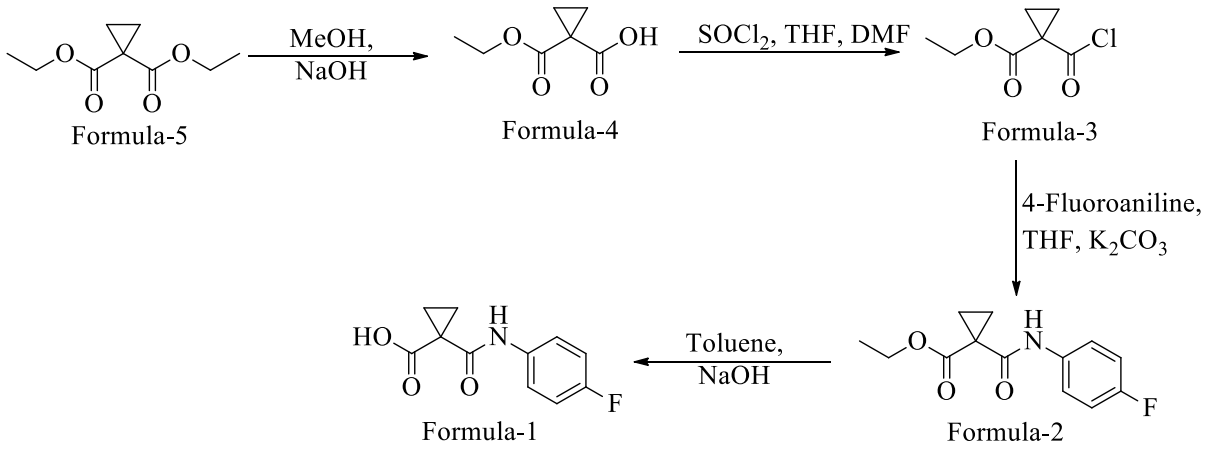
Introduction:

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in angiogenesis, invasion, or metastasis in renal cell carcinoma (RCC), including MET (hepatocyte growth factor [HGF] receptor protein) vascular endothelial growth factor receptors (VEGFRs) and AXL.

Cabozantinib has been approved by the USFDA under the trade names COMETRIQ and CABOMETYX. COMETRIQ for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC) and CABOMETYX for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

International (PCT) publication No. WO2005030140 A1 discloses Cabozantinib or a pharmaceutically acceptable salt and process for its preparation.

Disclosed herein the process for the preparation of 1-((4-fluorophenyl)carbamoyl) cyclopropanecarboxylic acid of formula-1, schematically as mentioned below:



The compound of Formula-5 used in the present invention is prepared by method reported in Synthesis (1987), (6), 565-566 or any other methods known in the art.

Experimental Section:

Example-1: Preparation of 1-(ethoxycarbonyl)cyclopropanecarboxylic acid of Formula-4.

Methanol (2500.0 ml) was added to diethyl cyclopropane-1,1-dicarboxylate of formula-5 (500.0 gm) at 25-30ºC and stirred for 20 minutes. Cooled the mixture to 0-5ºC. A solution of sodium hydroxide (129.0 gm) in water (500.0 ml) was slowly added to the mixture at 0-5ºC. Raised the temperature of the mixture to 25-30ºC and stirred for 7 hours. Distilled off the solvent completely from the mixture under vacuum at below 55ºC. Water (750.0 ml) was added to the obtained compound at 25-30ºC. Water and hydrochloric acid was added to the mixture at 25-30ºC and stirred for 15 minutes. Ethyl acetate (1250.0 ml) was added to the mixture at 25-30ºC and stirred for 15 minutes. Layers were separated and aqueous layer extracted with ethyl acetate. Layers were separated. Combined the total organic layers and dried with sodium sulphate. Distilled off the solvent completely from the organic layer under vacuum at below 55ºC to get the title compound.

Example-2: Preparation of ethyl 1-(chlorocarbonyl)cyclopropanecarboxylate of Formula-3.

The compound obtained in example-1 was dissolved in tetrahydrofuran (330.0 ml) and dimethylformamide (50.0 ml) at 25-30ºC and stirred for 15 minutes. Thionyl chloride (639.70 gm) was slowly added to the mixture at 25-30ºC and stirred for 7 hours to get the title

compound.

Example-3: Preparation of ethyl 1-((4-fluorophenyl)carbamoyl)cyclopropanecarboxylate of Formula-2.

The compound obtained in example-2 was slowly added to the mixture of water (1000.0 ml), tetrahydrofuran (750.0 ml), 4-flouroaniline (193.95 gm) and potassium carbonate (1112.9 gm) at 25-30ºC and stirred for 5 hours. Water (1250.0 ml) was added to the mixture at 25-30ºC and stirred for 20 minutes. Layers were separated and aqueous layer extracted with ethyl acetate. Combined the total organic layers and washed with water. Distilled off the solvent completely from the organic layer under vacuum at below 65ºC to get the title compound.

Example-4: Preparation of 1-((4-fluorophenyl)carbamoyl)cyclopropanecarboxylic acid of Formula-1.

Toluene (1000.0 ml) was added to the compound obtained in example-3 at 25-30ºC and stirred for 30 minutes. A solution of sodium hydroxide (161.29 gm) in water (1500.0 ml) was slowly added to the mixture at 25-30ºC and stirred for 8 hours. Layers were separated. Aqueous layer washed with toluene at 25-30ºC and stirred for 15 minutes. Layers were separated. Cooled the aqueous layer to 0-5ºC. Hydrochloric acid was slowly added to the aqueous layer at 0-5ºC and stirred for 2 hours. Filtered the solid, washed with water and dried to get the title compound. Yield: 298.0 gm.

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