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Improved process for the preparation of methyl 2-oxoindoline-6-carboxylate

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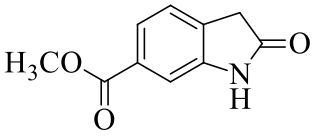
Abstract:

The present invention provides a process for the preparation of methyl 2-oxoindoline-6-carboxylate of formula-1, which is represented by the following structural formula:

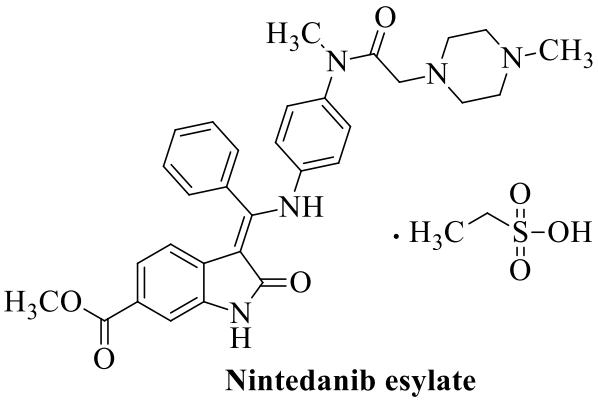


Formula-1

Introduction:

Methyl 2-oxoindoline-6-carboxylate of formula-1 is key intermediate for the preparation of Nintedanib esylate.

Nintedanib esylate is chemically known as 1H-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl)acetyl]amino]phenyl]amino]phenylmethylene]-2-oxo-,methyl ester, (3Z)-, ethanesulfonate (1:1).



Nintedanib esylate

Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors plateletderived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and VEGFR 1-3. Nintedanib binds competitively to the ATP binding pocket of these receptors and blocks the intracellular signalling. In addition, nintedanib inhibits Flt-3 (Fms-like tyrosine-protein kinase), Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn) and Src (proto-oncogene tyrosine-protein kinase src) kinases.

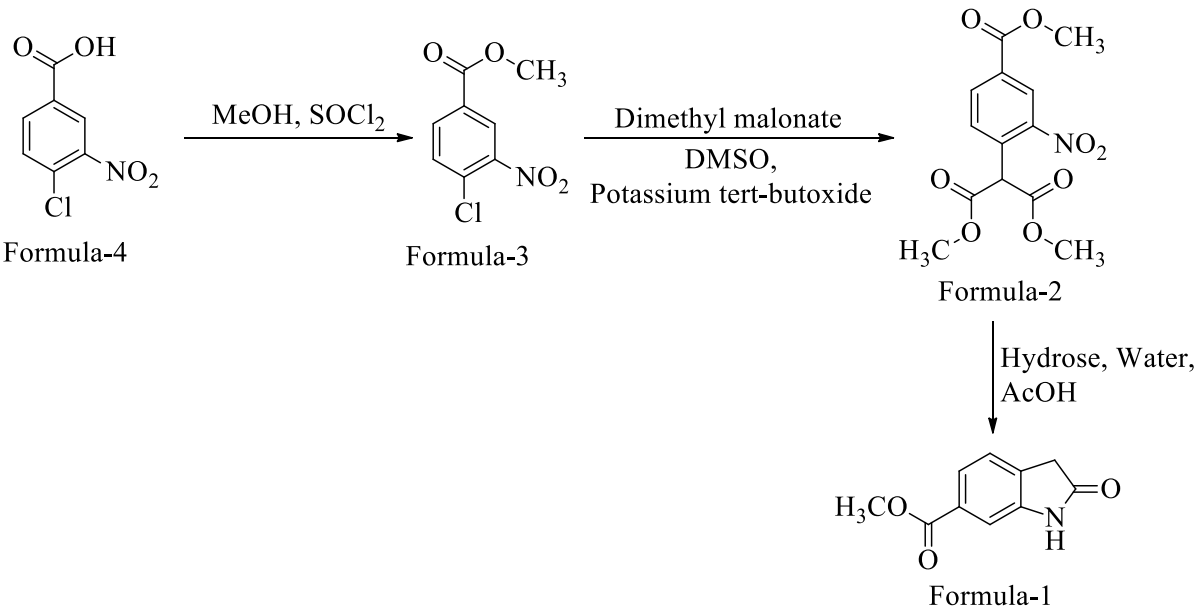
Nintedanib inhibits the activation of FGFR and PDGFR signalling cascades which are critically involved in proliferation, migration and differentiation of lung fibroblasts/myofibroblasts, the hallmark cells in the pathology of idiopathic pulmonary

fibrosis. The potential impact of VEGFR inhibition by nintedanib and the anti-angiogenic activity of nintedanib on IPF pathology are currently not fully elucidated. In preclinical disease models of lung fibrosis nintedanib exerts potent anti-fibrotic and anti-inflammatory activity. Nintedanib inhibits proliferation, migration and fibroblast to myofibroblast transformation of human lung fibroblasts from patients with IPF.

Nintedanib, marketed under the brand names Ofev and Vargatef, is a medication used for the treatment of idiopathic pulmonary fibrosis (IPF) and along with other medications for some types of non-small-cell lung cancer.

Nintedanib and its pharmaceutical acceptable salts was disclosed in US6762180 B1.

Disclosed herein the process for the preparation of methyl 2-oxoindoline-6-carboxylate of formula-1, schematically as mentioned below:



The compound of formula-4 used in the present invention can be prepared from any of the processes known in the art.

Experimental Section:

Example-1: Preparation of methyl 4-chloro-3-nitrobenzoate of Formula-3.

Methanol (500.0 ml) was added to 4-chloro-3-nitrobenzoic acid of formula-4 (100.0 gm) at 25-30ºC and stirred for 10 minutes. Thionyl chloride (30.0 gm) was slowly added to the mixture at 25-30ºC and stirred for 40 minutes. Heated the mixture to 60-65ºC and stirred for 3 hours. Distilled off the mixture and co-distilled with isopropanol. Isopropanol (300.0 ml) was

added to the obtained compound at 60-65ºC and stirred for 30 minutes. Cooled the mixture to 0-5ºC and stirred for 2 hours. Filtered the solid, washed with isopropanol and dried to get the title compound. Yield: 102 gm.

Example-2: Preparation of dimethyl [4-(methoxycarbonyl)-2-nitrophenyl]propanedioate of Formula-2.

Potassium tert-butoxide (52.0 gm) and dimethyl sulfoxide (150.0 ml) were added to dimethyl malonate (52.0 gm) at 25-30ºC. Cooled the mixture to 20-25ºC and stirred for 2 hours. Compound of formula-3 (50.0 gm) was slowly added to the mixture at 20-25ºC and stirred for 2 hours. Hydrochloric acid was added to the mixture at 20-25ºC. Sodium chloride (20.0 gm) and methyl tert-butyl ether (250.0 ml) were added to the mixture at 25-30ºC and stirred for 10 minutes. Layers were separated and aqueous layer was extracted with methyl tert-butyl ether. Distilled off the organic layer at below 50ºC to get the title compound. Yield: 53.0 gm.

Example-3: Preparation of methyl 2-oxoindoline-6-carboxylate of Formula-1.

Acetic acid (250.0 ml) was added to compound of formula-2 (50.0 gm) at 25-30ºC. Hydrose (83.9 gm) and water (250.0 ml) were added to the mixture at 25-30ºC and stirred for 10 minutes. Heated the mixture to 120-125ºC and stirred for 2 hours. Cooled the mixture to 15-20ºC. Ammonia (500.0 ml) was added to the mixture at 15-20ºC and stirred for 2 hours. Filtered the solid, washed with water and dried to get the title compound. Yield: 22.0 gm.

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