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(54) Title: POLYMORPH OF NINTEDANIB ETHANESULPHONATE, PROCESSES AND INTERMEDIATES THEREOF

Figure- 1

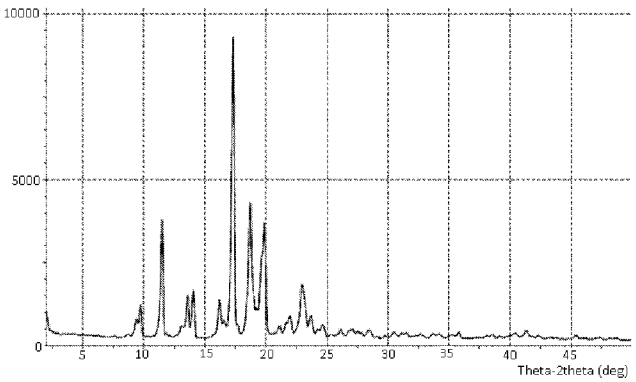
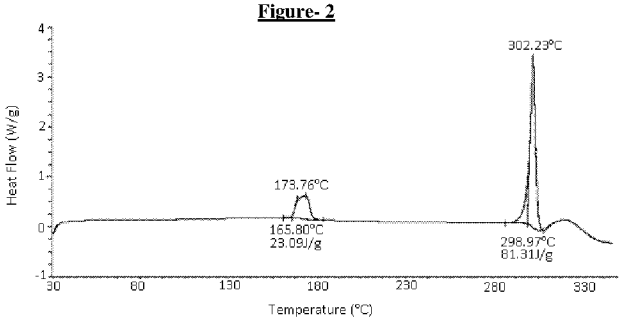


Figure- 2



(57) Abstract: The present invention provides novel crystalline Form of Nintedanib and process for its preparation. The present invention also provides to a novel process for the preparation of Nintedanib. The present invention further provides to novel intermediates used in the preparation of Nintedanib and process for their preparation.

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— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

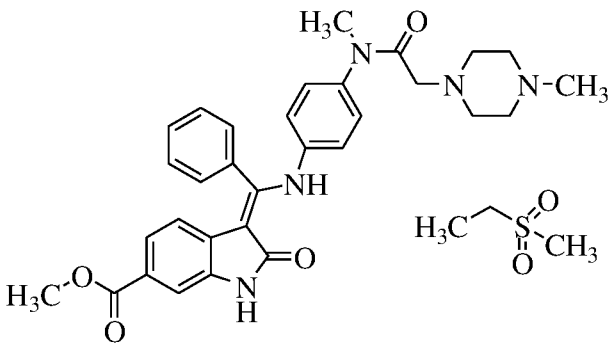
POLYMORPH OF NINTEDANIB ETHANESULPHONATE, PROCESSES AND INTERMEDIATES THEREOF

Field of the Invention

The present invention relates to novel crystalline Form of Nintedanib and process for its preparation. The present invention also relates to a novel process for the preparation of Nintedanib. The present invention further relates to novel intermediates used in the preparation of Nintedanib and process for their preparation.

Background of the Invention

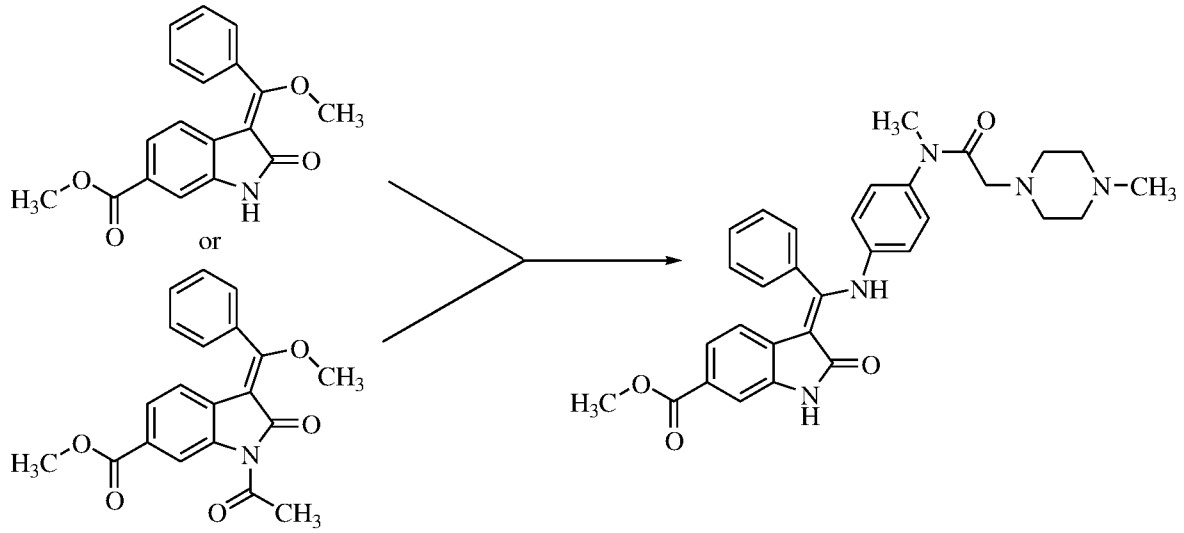
Nintedanib inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs).The chemical name of Nintedanib is1*H*-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl-(4-methyl-1-iperazinyl)acetyl]amino]phenyl]amino]phenylmethylene] -2-oxo-,methylester, (3Z)-, ethanesulfonate (1:1) and is structurally represented by compound of Formula I.



Formula I

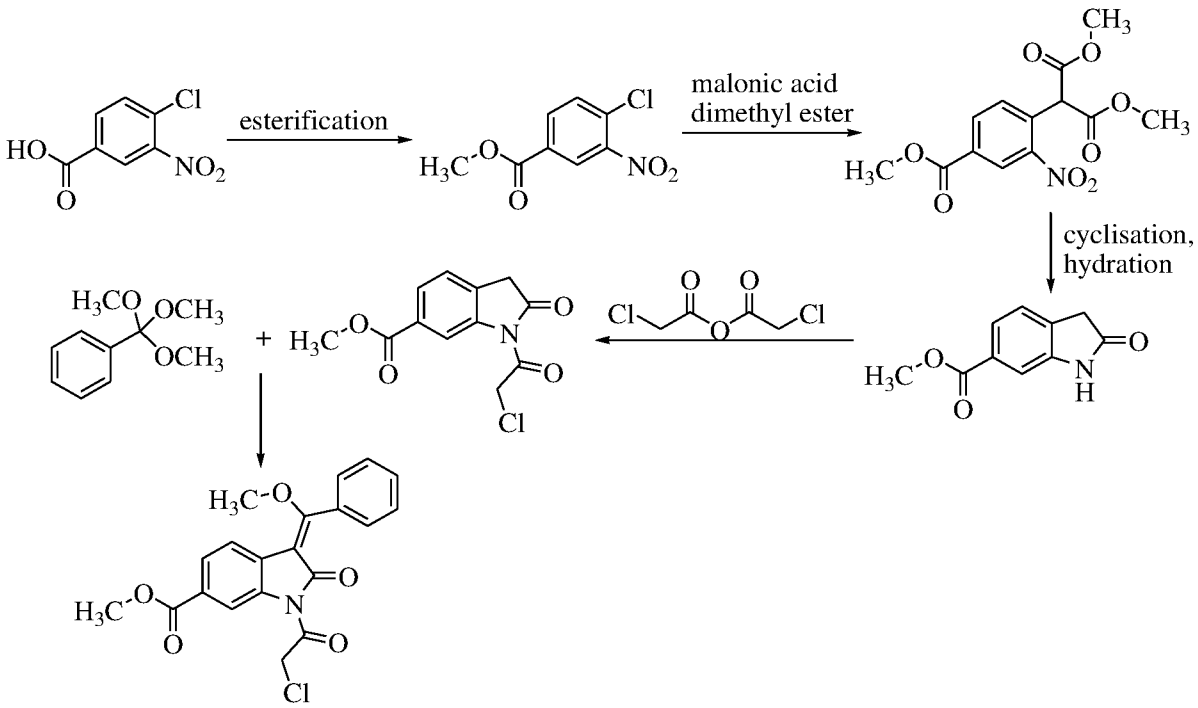
Nintedanib is marketed in the United States under the trade name OFEV and is indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

Nintedanib was first described and claimed in U.S. Pat.No. 6,762,180 and EP 1224 170. These patents disclose a process for the preparation of Nintedanib as depicted in scheme I given below:



Scheme-I

U.S.Pat.No. 8,067,617 discloses a process for the preparation of Nintedanib intermediate (Enolindole derivative), which is shown in the scheme-II given below:



Scheme-II

U.S.Pat. No. 7,119,093 discloses Nintedanib monoethanesulphonate in crystalline form characterised by X-ray powder diffraction pattern having 2θ values at 7.70, 8.78, 9.47, 9.82, 11.59, 11.93, 13.15, 13.69, 14.17, 16.32, 16.72, 16.92, 17.43, 17.77, 18.58, 18.81, 19.03, 19.73, 19.87, 20.03, 20.61, 20.83, 21.26, 21.76, 22.05, 22.19, 22.57, 23.10, 23.81, 24.69, 24.78, 24.91, 25.42, 26.24, 26.91, 27.19, 27.61, 27.95, 28.71, 29.25.

Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule may give rise to a variety of polymorphs having distinct crystal structures and physical properties like melting point, X-ray diffraction pattern, infrared absorption fingerprint and solid state NMR spectrum. One polymorph may give rise to thermal behaviour different from that of another polymorph. Thermal behaviour can be measured in the laboratory by such techniques as capillary melting point, thermo gravimetric analysis ("TGA") and differential scanning calorimetry ("DSC"), which have been used to distinguish polymorphic forms.

The differences in the physical properties of different polymorphs results from the orientation and intermolecular interactions of adjacent molecules or complexes in the bulk solid. Accordingly, polymorphs are distinct solids sharing the same molecular Formula yet having distinct advantageous physical properties compared to other polymorphs of the same composition or complex. Hence there remains a need for polymorphic forms which have properties suitable for pharmaceutical processing on a commercial scale.

Considering the importance of Nintedanib, there exists a need to develop an alternate and improved process for the preparation of Nintedanib with better yield. Further, the process involved should be simple, convenient and cost-effective for large scale production. The inventors of the present invention during their continuous efforts also developed a novel high melting stable polymorphic form of Nintedanib ethanesulfonate.

Objective of the Invention

The main objective of the present invention is to provide novel polymorph Form S of Nintedanib and process for its preparation.

Another objective of the present invention is to provide a robust and simple process for the preparation of Nintedanib monoethanesulphonate salt of Formula I with high yield and high purity.

In yet objective of the present invention is to provide a novel process for preparing Nintedanib monoethanesulphonate salt of Formula I, which is simple, industrially applicable and economically viable.

In yet another objective, the present invention relates to novel intermediates used in the preparation of Nintedanib and process for their preparation.

Summary of the Invention

Accordingly, the present invention provides a novel high melting crystalline Form S of Nintedanib ethanesulfonate of Formula I.

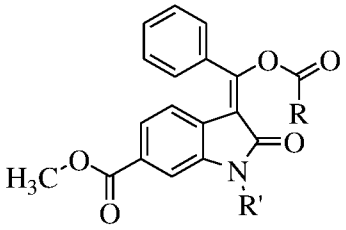
In one aspect, the present invention provides novel high melting crystalline Form S of Nintedanib ethanesulfonate of the Formula I having a DSC thermogram spectrum showing two characteristic endothermic peaks at 165-180° and at 295-305°C.

In another aspect, the present invention provides novel crystalline Form S of Nintedanib ethanesulfonate characterized by X-ray powder diffraction pattern having peaks at 9.38, 9.69, 11.47, 13.05, 13.56, 14.03, 16.18, 16.53, 17.29, 18.26, 18.96, 18.68, 19.22, 19.64, 19.86, 21.82, 22.99, 23.64 and 24.60 ± 0.2° 2θ values.

In another aspect, the present invention provides a process for the preparation of novel crystalline Form S of Nintedanib ethanesulfonate of Formula I which comprises the steps:
i) providing a solution of Nintedanib ethanesulfonate in a suitable solvent,
ii) crystallizing Nintedanib ethanesulfonate from the solution obtained in step (i) and
iii) isolating crystalline Form S of Nintedanib ethanesulfonate of Formula I.

In yet another aspect, the present invention provides a process for the preparation of novel crystalline Form S of Nintedanib ethanesulfonate of Formula I which comprises the steps:
i) providing a solution of Nintedanib ethanesulfonate in a suitable solvent,
ii) adding an anti-solvent to the solution obtained in step (i) and
iii) isolating crystalline Form S of Nintedanib ethanesulfonate of Formula I.

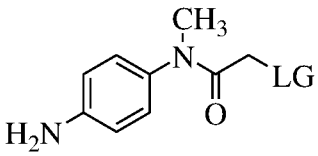
In yet another aspect, the present invention provides a novel process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:
i) reacting acetyl derivative of compound of Formula II



Formula II

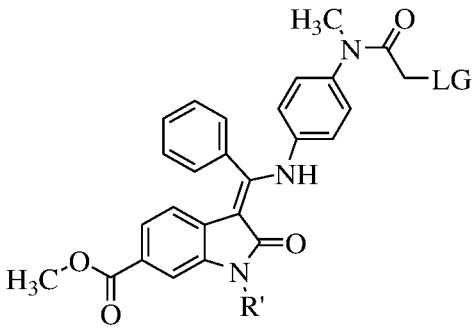
wherein R represents alkyl, aryl, halogen and R' is acetyl;

with a compound of Formula III,



Formula III

wherein LG is a leaving group in a solvent to obtain compound of Formula IV;



Formula IV

wherein LG and R' are as defined above;

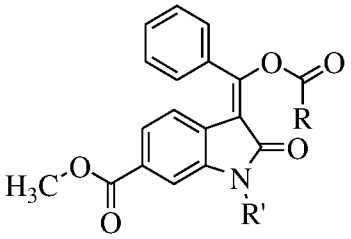
ii) reacting the compound of Formula IV with 1-methylpiperazine in a solvent to obtain Nintedanib free base of Formula I,

iii) reacting Nintedanib free base with ethane sulfonic acid in a solvent to obtain Nintedanib monoethane sulfonate,

iv) optionally recrystallization of Nintedanib ethanesulfonate.

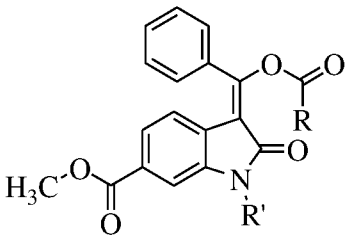
In another aspect, the present invention provides a novel process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) acetylating the compound of Formula II where R' is H to obtain a compound of Formula II where R' is acetyl using acetic anhydride,



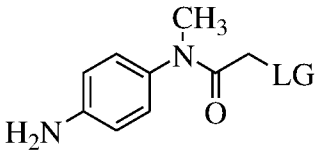
Formula II

ii) reacting acetyl derivative of compound of Formula II



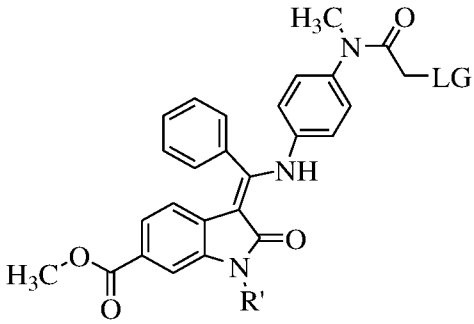
Formula II

wherein R represents alkyl, aryl, halogen and R' is acetyl; with a compound of Formula III,



Formula III

wherein LG is a leaving group in a solvent to obtain compound of Formula IV;



Formula IV

wherein LG and R' are as defined above;

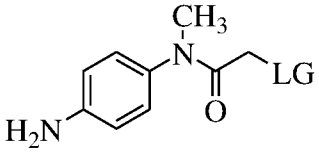
iii) reacting the compound of Formula IV (wherein R' is acetyl group) with 1-methylpiperazine in a solvent to obtain Nintedanib free base of Formula I,

iv) reacting Nintedanib free base with ethane sulfonic acid in a solvent to obtain Nintedanib monoethane sulfonate,

v) optionally recrystallization of Nintedanib ethanesulfonate.

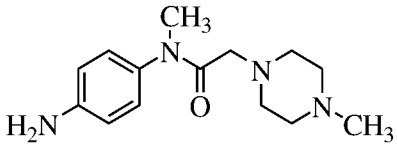
In yet another aspect, the present invention provides a novel process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) reacting the compound of Formula III



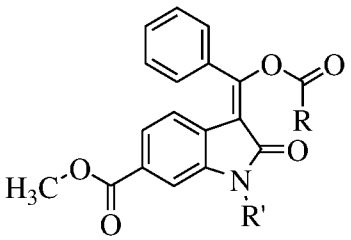
Formula III

wherein LG is a leaving group; with 1-methylpiperazine in a solvent to obtain compound of Formula VII



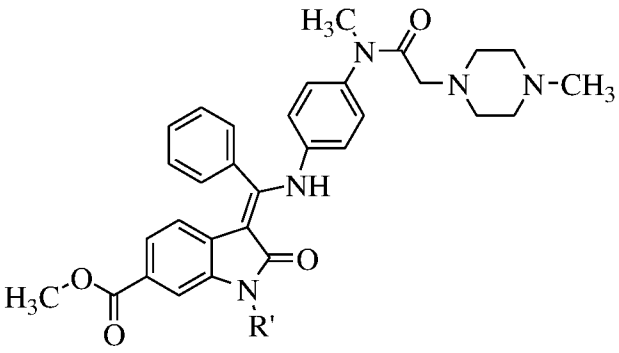
Formula VII

ii) reacting the compound of Formula VII with acetyl derivative of compound of Formula II



Formula II

wherein R represents alkyl, aryl, halogen and R' is acetyl; in a solvent to obtain compound of Formula VIII



Formula VIII

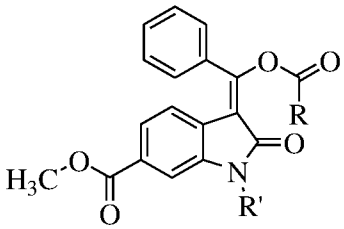
wherein R' is as defined above

iii) reacting compound of Formula VIII with 1-methylpiperazine in a solvent to obtain Nintedanib free base of Formula I,

iv) reacting Nintedanib free base with ethane sulfonic acid in a solvent to obtain Nintedanib monoethane sulfonate,

v) optionally recrystallization of Nintedanib ethanesulfonate.

In yet another aspect, the present invention relates to novel intermediate of acetyl derivative of compound of Formula II

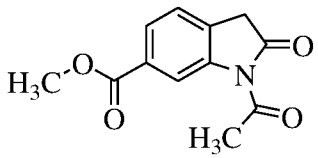


Formula II

wherein R represents alkyl, aryl, halogen and R' is acetyl.

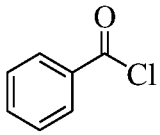
In yet another aspect, the present invention relates to process for the preparation of novel intermediate of acetyl derivative of compound of Formula II which comprises the steps of:

i) condensing methyl 2-oxoindoline-6-carboxylate of compound of Formula V.

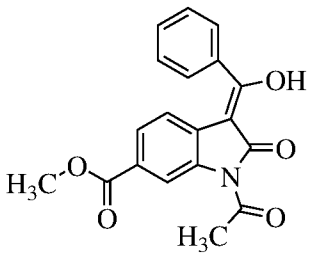


Formula V

with benzoyl chloride



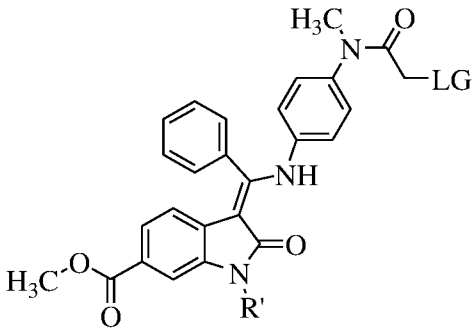
in a solvent in the presence of a base to give compound of Formula VI



Formula VI

ii) reacting compound of Formula VI with acetic anhydride to obtain acetyl derivative compound of Formula II.

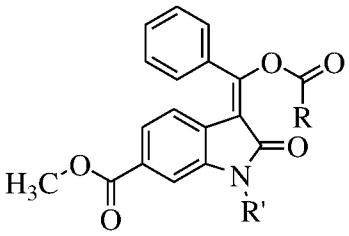
In yet another aspect, the present invention relates to novel intermediate of compound of Formula IV



Formula IV

wherein LG is a leaving group and aryl halide and R' is acetyl.

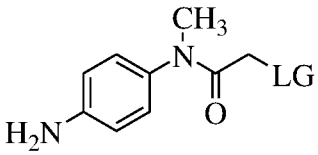
In yet another aspect, the present invention relates to a process for the preparation of novel intermediate compound of Formula IV which comprises reacting acetyl derivative of compound of Formula II



Formula II

wherein R represents alkyl, aryl, halogen and R' is acetyl;

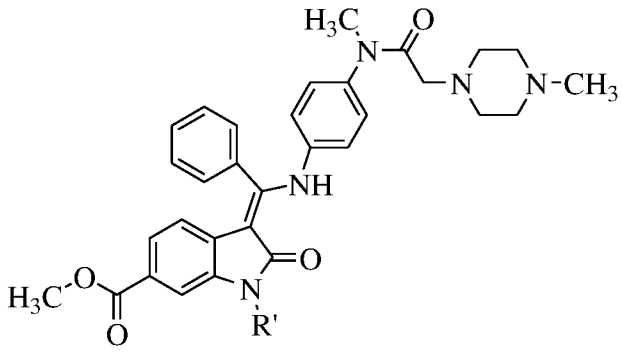
with a compound of Formula III



Formula III

wherein LG is leaving group to obtain compound of Formula IV.

In yet another aspect, the present invention provides a novel intermediate compound of Formula VIII

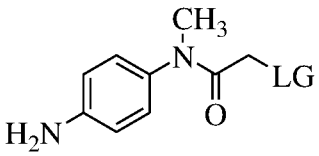


Formula VIII

wherein R' is as defined above.

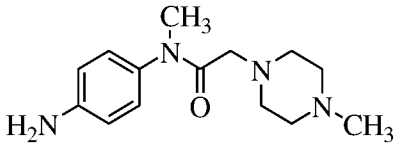
In yet another aspect, the present invention provides a process for the preparation of intermediate compound of Formula VIII which comprises the steps of:

i) reacting the compound of Formula III



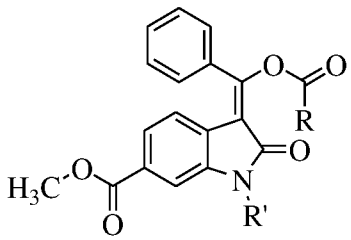
Formula III

wherein LG is a leaving group; with 1-methylpiperazine in a solvent to obtain compound of Formula VII



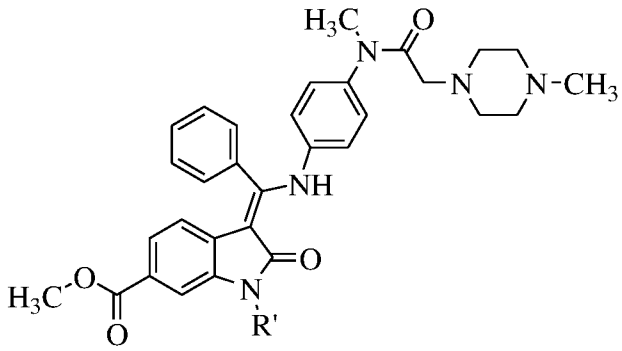
Formula VII

ii) reacting the compound of Formula VII with acetyl derivative of compound of Formula II



Formula II

wherein R represents alkyl, aryl, halogen and R' is acetyl; in a solvent to obtain compound of Formula VIII



Formula VIII

wherein R' is as defined above.

Brief Description of Drawings

Fig.1: Represents Differential Scanning Calorimetry (DSC) thermogram of novel crystalline Form S of Nintedanib ethanesulfonate.

Fig. 2: Represents X-ray powder diffraction pattern of novel crystalline Form S of Nintedanib ethanesulfonate.

Detailed Description of the Invention

The present invention provides a novel high melting crystalline Form S of Nintedanib ethanesulfonate of the Formula I having a *DSC* thermogram spectrum showing two endothermic peaks with a specific dehydration temperature at 165-180° and melting point at 295-305°C as depicted in Figure 1.

In one embodiment, the novel crystalline Form S of Nintedanib ethanesulfonate is also characterized by X-ray powder diffraction pattern having peaks at 11.47, 17.29, 18.68, 19.64, 19.86± 0.2° 2θ values.

In another embodiment novel crystalline Form S of Nintedanib ethane sulfonate is further characterized by X-ray powder diffraction pattern having additional peaks at 9.38, 9.69, 13.05, 13.56, 14.03, 16.18, 16.53, 18.26, 18.96, 19.22, 21.82, 22.99, 23.64 and 24.60± 0.2° 2θ values.

In yet another embodiment novel polymorph Form S of Nintedanib monoethane sulfonate is characterized by X-ray powder diffraction pattern having 2θ values, the interplanar spacing (d values) and relative intensities (I/I_0) as shown in the table given below:

S.No	2θ values	Interplanar spacing (d) [Å]	I/I_0
1.	9.38	9.42	6
2.	9.69	9.11	11
3.	11.47	7.70	39
4.	13.05	6.77	4
5.	13.56	6.52	14
6.	14.03	6.30	16
7.	16.18	5.47	12
8.	16.53	5.35	5
9.	17.29	5.12	100
10.	18.26	4.85	4
11.	18.68	4.74	44
12.	18.96	4.67	13
13.	19.22	4.61	8
14.	19.64	4.51	26
15.	19.86	4.46	37
16.	21.82	4.06	6
17.	22.99	3.86	17
18.	23.64	3.75	6
19.	24.60	3.61	4

As used herein the present invention, the term "suitable solvent" refers to the solvent selected from "polar protic solvents" such as water; "polar aprotic solvents" such as dimethylsulfoxide, dimethylacetamide, dimethyl formamide and the like; "nitrile solvents" such as acetonitrile, propionitrile, butyronitrile and isobutyronitrile and the like; "ether solvents" such as di-tert-butylether, diethylether, diisopropyl ether, 1,4-dioxane, methyltert-butylether, ethyl tert-butyl ether, tetrahydrofuran and dimethoxyethane; "alcohol solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol and t-butanol and the like; "chloro solvents" such as methylene chloride, ethylene dichloride, carbon tetra chloride, chloroform, chloro benzene

and the like; "hydrocarbon solvents" such as benzene, toluene, xylene, heptane, hexane and cyclohexane; "ketone solvents" such as acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone and the like; "esters solvents" such as ethyl acetate, methyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, isopropyl acetate and the like; and their mixtures thereof.

The crystallization and isolation of novel crystalline Form S of Nintedanib ethanesulfonate of Formula I according to the present invention is carried out using conventional methods used for crystallization and isolation of compounds known in the field.

In yet another embodiment the leaving group is selected from halogen (Cl, Br, F or I), tosyl, mesyl and the like.

In yet another embodiment suitable base used in the present invention is selected from ammonia, sodium methoxide, sodium ethoxide, potassium methoxide, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, potassium tert-pentoxide, sodium t-butoxide, potassium tert-butoxide, potassium n-butoxide, sodium hydride, triethylamine, N,N-diisopropylethylamine (DIPEA), pyridine and Dimethylaminopyridine (DMAP).

In a preferred embodiment, the present invention provides a process for the preparation of novel crystalline Form S of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) suspending crude Nintedanib ethanesulfonate in an alcoholic solvent,

ii) crystallizing Nintedanib ethanesulfonate from the solution obtained in step (i) and

iii) isolating crystalline Form S of Nintedanib ethanesulfonate of Formula I.

In a more preferred embodiment, the present invention provides a process for the preparation of novel crystalline Form S of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) suspending crude Nintedanib ethanesulfonate in methanol,

ii) crystallizing Nintedanib ethanesulfonate from the solution obtained in step (i) and

iii) isolating crystalline Form S of Nintedanib ethanesulfonate of Formula I.

In another preferred embodiment, the present invention provides a process for the preparation of novel crystalline Form S of Nintedanib ethanesulfonate of Formula I which comprises the steps:

i) dissolving crude Nintedanib ethanesulfonate in a suitable solvent

ii) adding an anti-solvent to the solution obtained in step (i) and

iii) isolating crystalline Form S of Nintedanib ethanesulfonate of Formula I.

In another more preferred embodiment, the present invention provides a process for the preparation of novel crystalline Form S of Nintedanib ethanesulfonate of Formula I which comprises the steps:

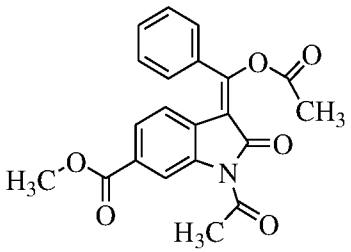
i) dissolving crude Nintedanib ethanesulfonate in methanol,

ii) adding isopropanol to the solution obtained in step (i) and

iii) isolating crystalline Form S of Nintedanib ethanesulfonate of Formula I.

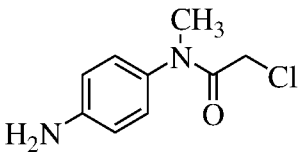
In yet another preferred embodiment, the present invention provides a novel process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) reacting acetyl derivative of compound of Formula IIa



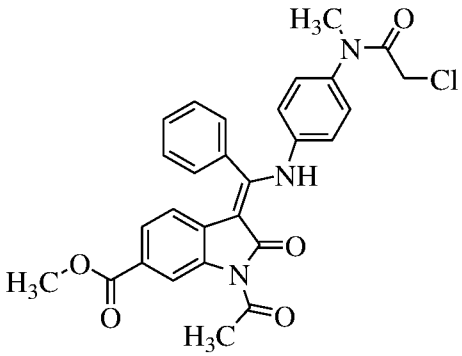
Formula IIa

with a compound of Formula IIIa,



Formula IIIa

in a solvent to obtain compound of Formula IVa;



Formula IVa

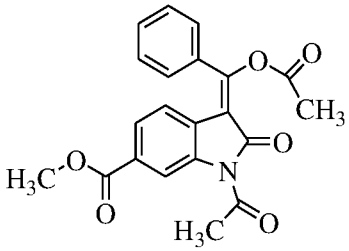
ii) reacting the compound of Formula IVa with 1-methylpiperazine in a solvent to obtain Nintedanib free base of Formula I;

iii) reacting Nintedanib free base with ethane sulfonic acid in a solvent to obtain Nintedanib monoethane sulfonate;

iv) optionally recrystallization of Nintedanib ethanesulfonate.

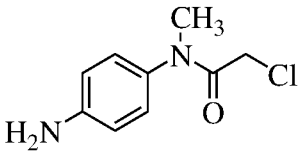
In yet another more preferred embodiment, the present invention provides a novel process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) reacting acetyl derivative of compound of Formula IIa



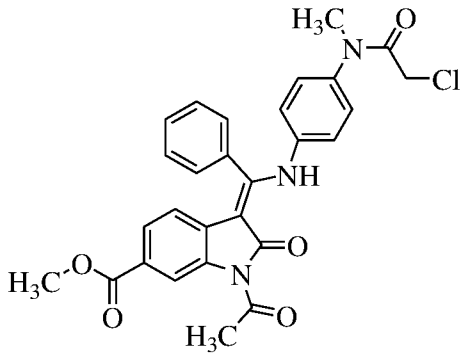
Formula IIa

with a compound of Formula IIIa,



Formula IIIa

in a mixture of methanol and DMF to obtain compound of Formula IVa;



Formula IVa

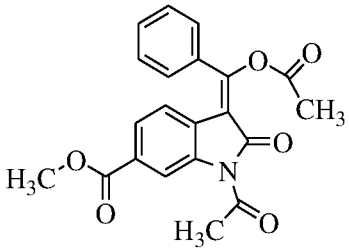
ii) reacting the compound of Formula IVa with 1-methylpiperazine in DMF to obtain Nintedanib free base of Formula I;

iii) reacting Nintedanib free base with ethane sulfonic acid in methanol to obtain Nintedanib monoethane sulfonate;

iv) optionally recrystallization of Nintedanib ethanesulfonate.

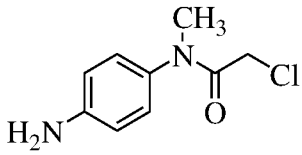
In yet another preferred embodiment, the present invention provides a novel process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) reacting acetyl derivative of compound of Formula IIa



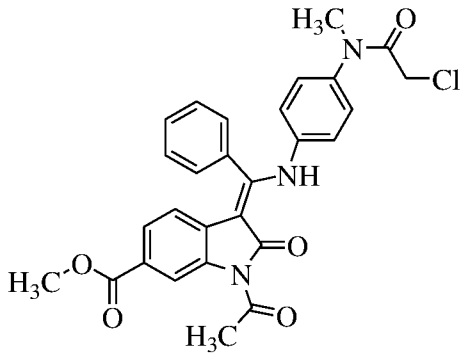
Formula IIa

with a compound of Formula IIIa,



Formula IIIa

in a solvent to obtain compound of Formula IVa;



Formula IVa

ii) reacting the compound of Formula IVa with 1-methylpiperazine in a solvent to obtain Nintedanib free base of Formula I;

iii) reacting Nintedanib free base with ethane sulfonic acid in a solvent to obtain Nintedanib monoethane sulfonate;

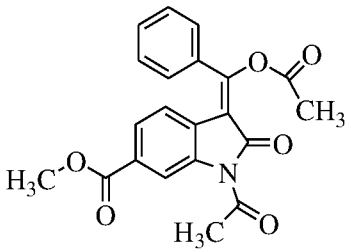
iv) suspending the crude Nintedanib ethanesulfonate obtained step (iii) in a solvent,

v) crystallizing Nintedanib ethanesulfonate from the solution obtained in step (iv) and

vi) isolating crystalline Form S of Nintedanib ethanesulfonate of Formula I.

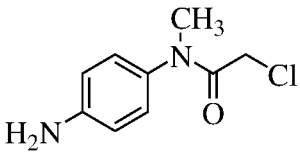
In yet another more preferred embodiment, the present invention provides a novel process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) reacting acetyl derivative of compound of Formula IIa



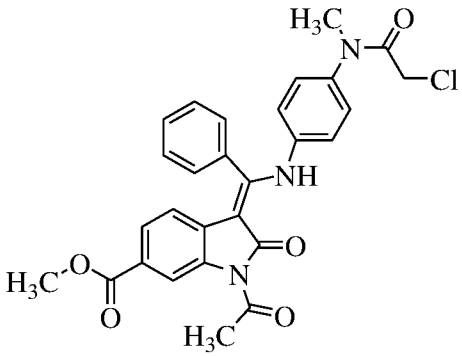
Formula IIa

with a compound of Formula IIIa,



Formula IIIa

in a mixture of methanol and DMF to obtain compound of Formula IVa;



Formula IVa

ii) reacting the compound of Formula IVa with 1-methylpiperazine in DMF to obtain Nintedanib free base of Formula I;

iii) reacting Nintedanib free base with ethane sulfonic acid in methanol to obtain Nintedanib monoethane sulfonate;

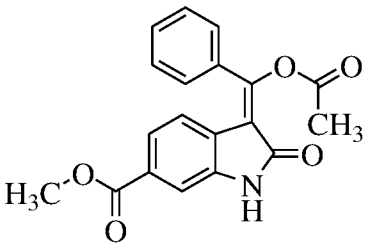
iv) suspending the crude Nintedanib ethanesulfonate obtained step (iii) in methanol,

v) crystallizing Nintedanib ethanesulfonate from the solution obtained in step (iv) and

vi) isolating crystalline Form S of Nintedanib ethanesulfonate of Formula I.

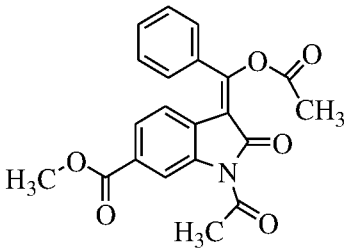
In yet another preferred embodiment, the present invention provides a novel process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) acetylating the compound of Formula IIb



Formula IIb

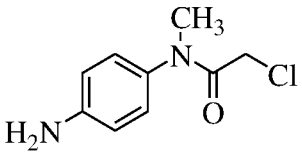
to obtain a compound of Formula IIa



Formula IIa

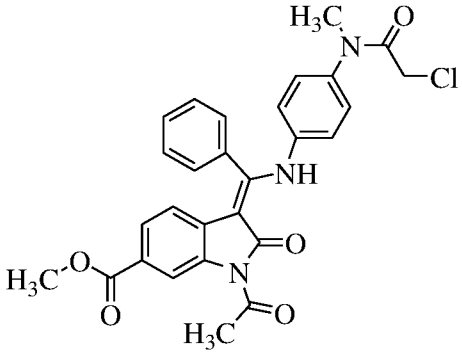
using acetic anhydride,

ii) reacting acetyl derivative of compound of Formula IIa with a compound of Formula IIIa,



Formula IIIa

in a solvent to obtain compound of Formula IVa;



Formula IVa

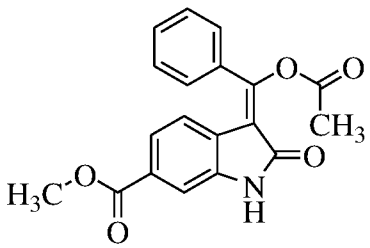
iii) reacting the compound of Formula IVa with 1-methylpiperazine in a solvent to obtain Nintedanib free base of Formula I;

iv) reacting Nintedanib free base with ethane sulfonic acid in a solvent to obtain Nintedanib monoethane sulfonate;

v) optionally recrystallization of Nintedanib ethanesulfonate.

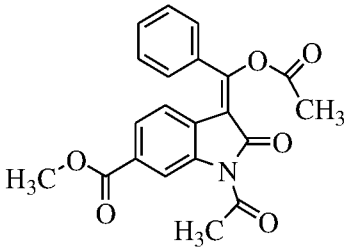
In yet another more preferred embodiment, the present invention provides a novel process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) acetylating the compound of Formula IIb



Formula IIb

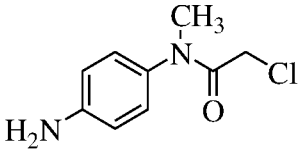
to obtain a compound of Formula IIa



Formula IIa

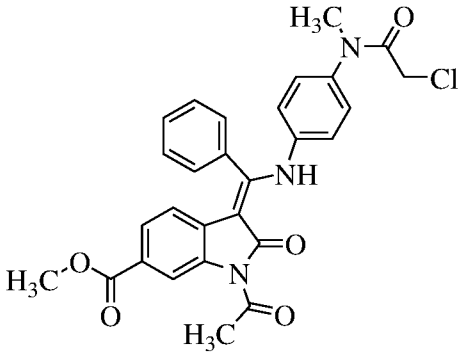
using acetic anhydride,

ii) reacting acetyl derivative of compound of Formula IIa with a compound of Formula IIIa,



Formula IIIa

in a mixture of methanol and DMF to obtain compound of Formula IVa;



Formula IVa

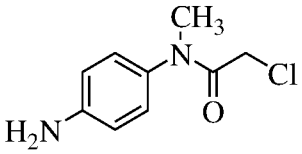
iii) reacting the compound of Formula IVa with 1-methylpiperazine in DMF to obtain Nintedanib free base of Formula I;

iv) reacting Nintedanib free base with ethane sulfonic acid in methanol to obtain Nintedanib monoethane sulfonate;

v) optionally recrystallization of Nintedanib ethanesulfonate.

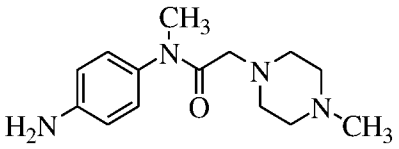
In yet another preferred embodiment, the present invention provides a novel process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) reacting the compound of Formula IIIa



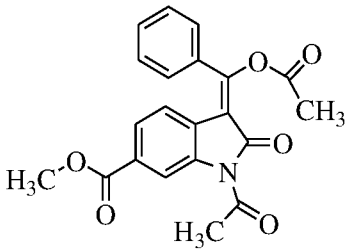
Formula IIIa

with 1-methylpiperazine in a solvent to obtain compound of Formula VII



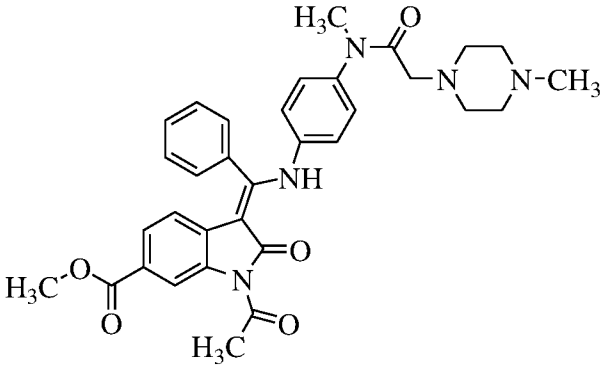
Formula VII

ii) reacting the compound of Formula VII with acetyl derivative of compound of Formula IIa



Formula IIa

in a solvent to obtain compound of Formula VIIIa



Formula VIIIa

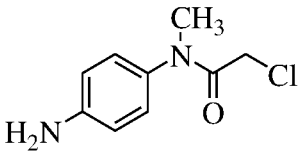
iii) reacting compound of Formula VIIIa with 1-methylpiperazine in a solvent to obtain Nintedanib free base of Formula I;

iv) reacting Nintedanib free base with ethane sulfonic acid in a solvent to obtain Nintedanib monoethane sulfonate;

v) optionally recrystallization of Nintedanib ethanesulfonate.

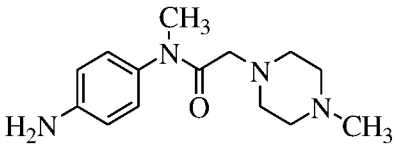
In yet another more preferred embodiment, the present invention provides a novel process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) reacting the compound of Formula IIIa



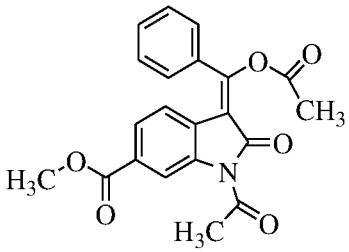
Formula IIIa

with 1-methylpiperazine in toluene to obtain compound of Formula VII



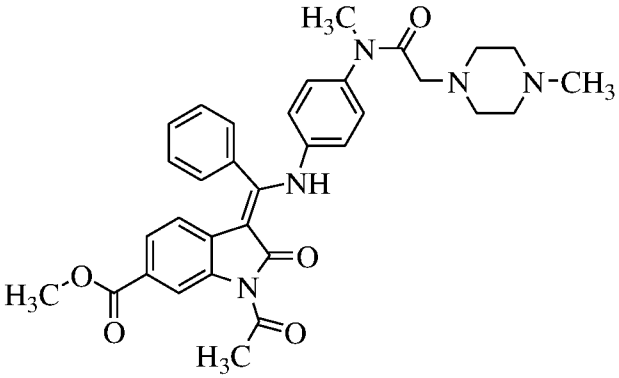
Formula VII

ii) reacting the compound of Formula VII with acetyl derivative of compound of Formula IIa



Formula IIa

in DMF to obtain compound of Formula VIIIa



Formula VIIIa

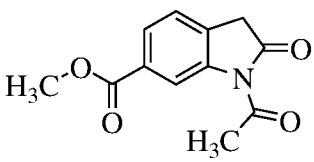
iii) reacting compound of Formula VIIIa with 1-methylpiperazine in a solvent to obtain Nintedanib free base of Formula I;

iv) reacting Nintedanib free base with ethane sulfonic acid in a methanol to obtain Nintedanib monoethane sulfonate;

v) optionally recrystallization of Nintedanib ethanesulfonate.

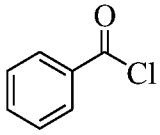
In yet another preferred embodiment, the present invention relates to process for the preparation of novel intermediate of compound of Formula IIa which comprises the steps of:

i) condensing methyl 2-oxoindoline-6-carboxylate of compound of Formula V

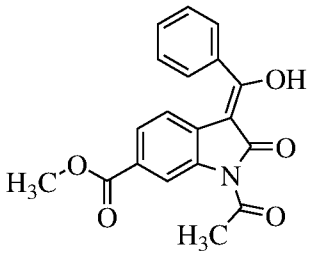


Formula V

with benzoyl chloride



in a solvent in the presence of a base to give compound of Formula VI,

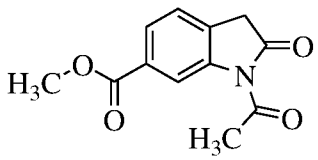


Formula VI

ii) reacting compound of Formula VI with acetic anhydride in the presence of a base to obtain acetyl derivative compound of Formula IIa.

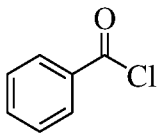
In yet another more preferred embodiment, the present invention relates to process for the preparation of novel intermediate of compound of Formula IIa which comprises the steps of:

i) condensing methyl 2-oxoindoline-6-carboxylate of compound of Formula V

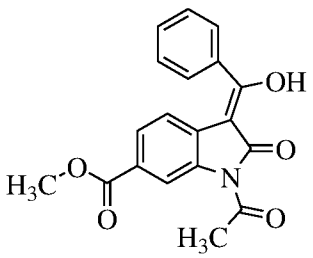


Formula V

with benzoyl chloride



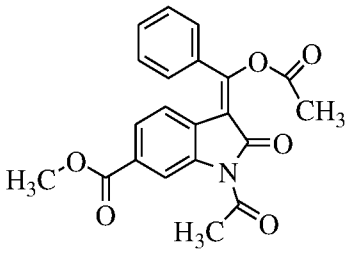
in DMF in the presence of DMAP to give compound of Formula VI



Formula VI

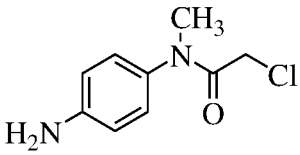
ii) reacting compound of Formula VI with acetic anhydride in the presence of pyridine to obtain acetyl derivative compound of Formula IIa.

In yet another preferred embodiment, the present invention provides a novel process for the preparation of novel intermediate of compound of Formula IVa which comprises the steps of reacting acetyl derivative of compound of Formula IIa



Formula IIa

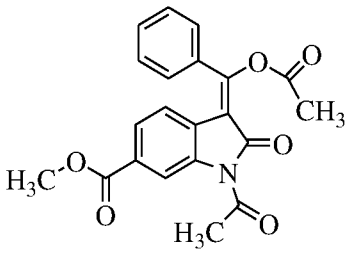
with a compound of Formula IIIa,



Formula IIIa

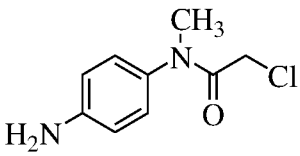
in a solvent to obtain compound of Formula IVa.

In yet another more preferred embodiment, the present invention provides a novel process for the preparation of novel intermediate of compound of Formula IVa which comprises the steps of reacting acetyl derivative of compound of Formula IIa



Formula IIa

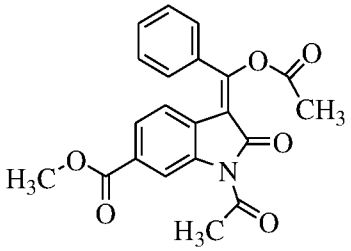
with a compound of Formula IIIa,



Formula IIIa

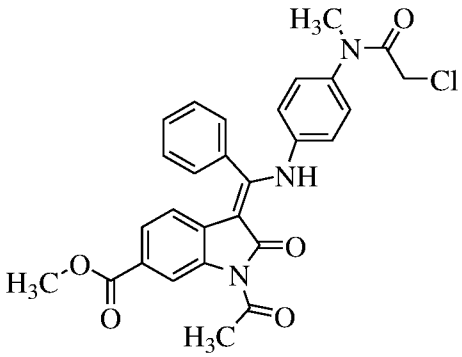
in a mixture of methanol and DMF to obtain compound of Formula IVa.

In yet another more preferred embodiment, the present invention provides a novel intermediate of compound of Formula IIa



Formula IIa

In yet another more preferred embodiment, the present invention provides a novel intermediate of compound of Formula IVa.



Formula IVa

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. The invention is illustrated below with reference to inventive and comparative examples and should not be construed to limit the scope of the invention.

EXAMPLES

Example 1: Process for the preparation of Nintedanib Monoethane Sulfonate:

Step-1: Preparation of methyl-3-(hydroxy(phenyl)methylene)-2-oxoindoline-6-carboxylate:

To the suspension of methyl 2-oxoindoline-6-carboxylate (50 gm, 0.261 mol) in IPA (350 ml) was added slowly SMO-powder (33.8 gm, 0.626 mol) and stirred for about 15 min. Benzyl chloride (44 g, 0.313 mol) was added after completion of the reaction at a reaction temperature of -5 to -10ºC for about 5hrs. The reaction mixture was quenched into ice-water (700 ml) and acidified with Conc. HCl (2.0-2.5 ml). Filtered the reaction mixture, washed with water (2X100 ml) and dried the precipitate to obtain crude product which can be recrystallized from acetonitrile (28 ml) to obtain methyl-3-(hydroxy(phenyl)methylene)-2-

oxoindoline-6-carboxylate pure crystalline solid (32 gm) (61%) (HPLC purity >97%). The filtrate was evaporated in vacuum to give unreacted methyl 2-oxoindoline-6-carboxylate.

MR: 216-223ºC; IR (KBr, cm^{-1}): 3178, 1711, 1651; ^{1}H-NMR (400 MHz, DMSO): δ 3.80 (s, 3H), 7.17 (s, 1H), 7.28-7.31 (m, 2H), 7.46-7.50 (m, 3H), 7.72 (d, 2H, J = 6.0 Hz), 9.52 (s, 1H), 11.53 (s, 1H); ^{13}C-NMR (100 MHz, DMSO): δ 22.12, 52.41, 101.13, 111.13, 119.23, 123.06, 126.65, 127.06, 128.65, 129.21, 132.26, 134.47, 136.99, 166.58, 172.52 and 175.80; MS: m/z 294 $[M]^{-1}$

Step-2: Preparation of methyl-3-(acetoxy(phenyl)methylene)-1-acetyl-2-oxoindoline-6-carboxylate (Acetyl derivative):

To the suspension of methyl-3-(hydroxy(phenyl)methylene)-2-oxoindoline-6-carboxylate (45 gm, 0.1512 mol) in acetic anhydride (300 ml) was added pyridine (4.5g) slowly (drop-wise) and stirred the reaction at temperature of 0-5ºC for about30 min. After completion of the reaction raised the temperature of the reaction mass to 75-80ºC and stirred for about 1hr. Cooled the reaction mass and stirred for about 30 min at 25-28ºC, filtered, washed with hexane (100ml) and dried the precipitate to obtain methyl-3-(acetoxy(phenyl)methylene)-1-acetyl-2-oxoindoline-6-carboxylate.

MR: 226-229ºC; IR (KBr, cm^{-1}): 3413, 1771, 1743, 1717, 1640; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.62 (s, 3H), 3.92 (s, 3H), 7.44 (m, 3H), 7.62 (d, 2H, J = 7.004 Hz), 7.68 (d, 1H, J = 8.12 Hz), 7.91 (d, 1H, J = 8.0 Hz), 8.90 (s, 1H); ^{13}C-NMR (100 MHz, CDCl3): δ 21.08, 21.38, 26.96, 52.25, 52.34, 115.17, 117.18, 121.33, 122.77, 125.82, 126.19, 126.56, 128.15, 128.87, 129.27, 129.34, 130.81, 130.90, 131.47, 131.82, 132.80, 138.55, 160.85, 165.95, 166.38, 166.42, 167.01, 170.67 and 170.76; MS: m/z 380 $[M]^{+1}$.

Step-3: Preparation of methyl-1-acetyl-3-(((4-(2-chloro-N-methylacetamido)phenyl)amino)(phenyl)methylene)-2-oxoindoline-6-carboxylate) (Chloroacetyl derivative):

Suspension of methyl-3-(acetoxy(phenyl)methylene)-1-acetyl-2-oxoindoline-6-carboxylate (Acetyl derivative) (49gm, 0.129mol) and N-(4-aminophenyl)-2-chloro-N-methylacetamide(25.66gm, 0.129 mol) in a mixture of methanol (350 ml) and DMF (88 ml) was heated to 60-65ºC stirred for about 12hr at the same temperature. After completion of the reaction cooled the reaction mass to room temperature and stirred for about 30min. Filtered the reaction mixture, washed with methanol (2X50ml) and dried the precipitate to obtainmethyl-1-acetyl-3-(((4-(2-chloro-N-ethylacetamido)phenyl)amino)(phenyl)methylene)-2-oxoindoline-6-carboxylate).

MR: 247-250ºC; IR (KBr, cm^{-1}): 3432, 1712, 1675, 1591; ^{1}H-NMR (400 MHz, DMSO): δ 2.74 (s, 3H), 3.11 (s, 3H), 3.78(s, 3H), 3.87 (s, 2H), 5.75 (d, 1H, J = 8.08 Hz), 7.01 (d, 2H, J = 7.96 Hz), 7.22 (d, 2H, J = 6.08Hz), 7.36 (d, 1H, J = 8.48 Hz), 7.46 (d, 2H, J = 7.24 Hz), 7.54-7.64 (m, 3H), 8.74 (s, 1H0, 11.92 (s, 1H), ^{13}C-NMR (100MHz, DMSO): δ 27.17, 37.76, 42.48, 52.40, 96.38, 116.17, 117.59, 124.80, 125.33, 125.68, 128.09, 129.00, 130.10, 131.35, 131.97, 134.05, 160.93, 165.63, 166.68, 168.49 and 171.28; MS: m/z 518 $[M]^{+1}$ and 520 $[M]^{+1}$.

Step-4: Preparation of (Z)-methyl-3-(((4-(N-methyl-2-(4-methylpiperazin-1yl)acetamide) phenyl) amino)(phenyl)methylene)-2-oxoindoline-6-carboxylate (Nintedanib free base):

Suspension of methyl-1-acetyl-3-(((4-(2-chloro-N-methylacetamido)phenyl)amino) (phenyl)methylene)-2-oxoindoline-6-carboxylate)(40 gm, 0.077ml) and N-methylpiperidine (23.24 gm, 0.232 mol) in a mixture of DMF (160 ml) was heated to a reaction temperature of 45-50ºC for about 1-2hrs. The reaction mixture was quenched into ice-water (1.6 Lt) and stirred for about 1hr at 15-20ºC. Filtered the reaction mixture mass washed with water and dried the precipitate to obtain crystalline crude solid (36 gm).Purified with acetonitrile to obtain Nintedanib free base (34 gm) as a yellow crystals (93.74%) (HPLC purity: >98%).

MR: 240-246ºC; IR (KBr, cm^{-1}): 3559, 3455, 2940, 2810, 1711, 1657; ^{1}H-NMR (400 MHz, DMSO): δ 2.09 (s, 3H), 2.17 (s, 8H), 2.68 (s, 2H), 3.05 (s, 3H), 3.76 (s, 3H), 5.80 (d, 1H, J = 7.56 Hz), 6.86 (d, 2H, J = 6.72 Hz), 7.11 (d, 1H, J = 6.48 Hz), 7.17 (d, 2H, J = 7.68 Hz), 7.42-7.57 (m, 6H), 10.98 (s, 1H), 12.23 (s, 1H) ; ^{13}C-NMR (100MHz, DMSO): δ 37.17, 46.18, 52.24, 52.79, 55.05, 59.68, 98.10, 109.94, 117.75, 121.96, 124.29, 124.52, 128.06, 128.90, 129.40, 129.92, 130.91, 132.50, 136.72, 140.66, 158.81, 166.84, 169.04 and 170.66; MS: m/z 540 $[M]^{+1}$.

Step-5: Preparation of (Z)-methyl-3-(((4-(N-methyl-2-(4-methylpiperazin-1yl)acetamide) phenyl) amino)(phenyl)methylene)-2-oxoindoline-6-carboxylate ethane sulfonate salt:

Suspension of (Z)-methyl-3-(((4-(N-methyl-2-(4-methylpiperazin-1-yl)acetamide)phenyl) amino)(phenyl)methylene)-2-oxoindoline-6-carboxylate (36 gm, 0.066 mol) in methanol (237 ml) and water (2.88 ml)was heated to 60-65ºC and aq. ethane sulfonic acid was added to the reaction mixture. The resulting solution was cooled to 50ºC, seeds diluted with isopropanol (237 ml) was added. The reaction mixture was cooled at 0ºC for 1hr. Filtered the precipitate, washed with mixture of methanol and isopropanol (50 ml), dried to obtain crude Nintedanib monoethane sulfonate (36.6 gm) and crystallized from methanol (5 Vol) to

obtained pure Nintedanib monoethane sulfonate salt as yellow crystals (33 gm) (80%) (HPLC purity >99%).

DSC: 298ºC; IR (KBr, cm-1): 3321, 3273, 1710, 1652, 1615, 1515, 1435, 1378, 1289, 1209, 1161, 1087; 1H-NMR (400 MHz, DMSO): δ 1.08 (t, 3H, J = 7.31 Hz), 2.41-2.47 (q, 2H), 2.50-3.16 (broad m, 13H), 3.37 (s, 3H), 3.76 (s, 3H), 5.82 (d, 1H, J = 7.88Hz), 6.87 (d, 2H, J = 7.36 Hz), 7.14-7.20 (m, 3H), 7.49 (s, 1H), 7.49 (d, 2H, J = 6.68 Hz), 7.56-7.63 (m, 3H), 9.45 (s, 1H), 10.99 (s, 1H), 12.25 (s, 1H), 13C-NMR (100 MHz, DMSO): δ 37.15, 42.79, 45.65, 49.40, 52.26, 53.10, 58.04, 98.25, 110.01, 117.78, 121.97, 124.32, 124.59, 128.27, 128.90, 129.36, 130.00, 131.00, 132.52, 136.79, 137.93, 140.00, 158.66, 166.85, 168.47 and 170.65; MS: m/z 540$[M]^{+1}$.

Example 2: Process for the preparation of Polymorph Form S of Nintedanib monoethanesulfonate:

Crude Nintedanib monoethane sulfonate was dissolved in methanol and heated to 60-64ºC for about 15 min. After completion of the reaction cooled to room temperature for about 1hr. Filtered the precipitate, washed with mixture of methanol (20ml) and isopropanol (30 ml) and dried to obtain pure crystalline solid (28 gm) (yield: 93.3%) with HPLC purity 99.72% and individual impurities 0.09%, 0.02% and 0.04%.

We Claim:

1. Novel high melting crystalline Form S of Nintedanib ethanesulphonate of Formula I having two characteristic endothermic peaks at 165-180° and at 295-305° in DSC thermogram spectrum.

2. Novel crystalline Form S of Nintedanib ethanesulfonate characterized by X-ray powder diffraction pattern having peaks at 11.47, 17.29, 18.68, 19.64, 19.86 ± 0.2° 2θ values.

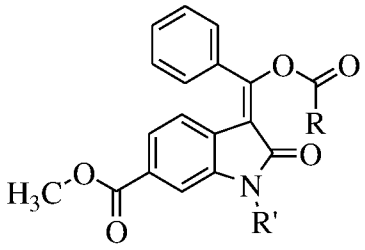
3. Nintedanib ethanesulfonate is further characterized by X-ray powder diffraction pattern having additional peaks at 9.38, 9.69, 13.05, 13.56, 14.03, 16.18, 16.53, 18.26, 18.96, 19.22, 21.82, 22.99, 23.64 and 24.60 ± 0.2° 2θ values.

4. A process for the preparation of novel crystalline Form S of Nintedanib ethanesulfonate of Formula I which comprises the steps:
i) providing a solution of crude Nintedanib ethanesulfonate in a suitable solvent,
ii) crystallizing Nintedanib ethanesulfonate from the solution obtained in step (i) and
iii) isolating crystalline Form S of Nintedanib ethanesulfonate of Formula I.

5. A process for the preparation of novel crystalline Form S of Nintedanib ethanesulfonate of Formula I which comprises the steps:
i) providing a solution of crude Nintedanib ethanesulfonate in a suitable solvent,
ii) adding an anti-solvent to the solution obtained in step (i) and
iii) isolating crystalline Form S of Nintedanib ethanesulfonate of Formula I.

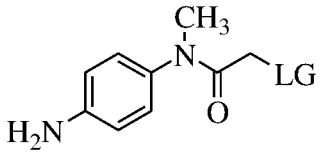
6. A process for the preparation of novel crystalline Form S of Nintedanib ethanesulfonate of Formula I which comprises the steps:
i) suspending crude Nintedanib ethanesulfonate in an alcoholic solvent,
ii) crystallizing Nintedanib ethanesulfonate from the solution obtained in step (i) and
iii) isolating crystalline Form S of Nintedanib ethanesulfonate of Formula I.

7. A process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:
i) reacting acetyl derivative of compound of Formula II



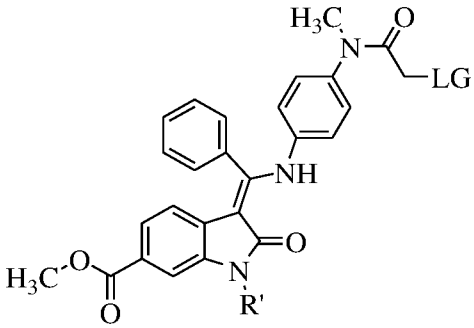
Formula II

wherein R represents alkyl, aryl, halogen and R' is acetyl; with a compound of Formula III,



Formula III

wherein LG is a leaving group in a solvent to obtain compound of Formula IV;



Formula IV

wherein LG is a leaving group and R' is H or acetyl;

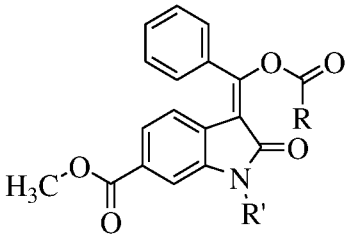
ii) reacting the compound of Formula IV with 1-methylpiperazine in a solvent to obtain Nintedanib free base of Formula I;

iii) reacting Nintedanib free base with ethane sulfonic acid in a solvent to obtain Nintedanib monoethane sulfonate;

iv) optionally recrystallization of Nintedanib ethanesulfonate.

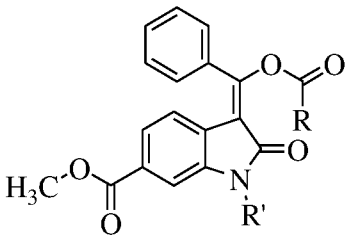
8. A process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) acetylating the compound of Formula II where R' is H to obtain a compound of Formula II where R' is acetyl using acetic anhydride,



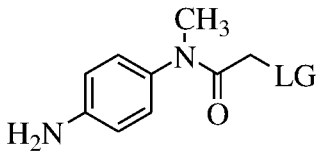
Formula II

ii) reacting acetyl derivative of compound of Formula II



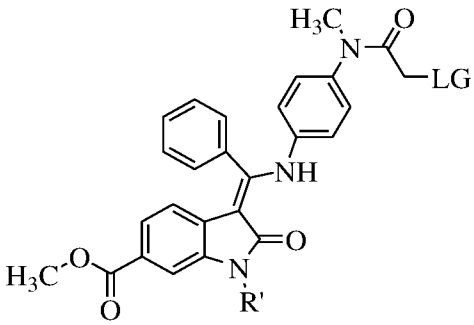
Formula II

wherein R represents alkyl, aryl, halogen and R' is acetyl; with a compound of Formula III,



Formula III

wherein LG is a leaving group in a solvent to obtain compound of Formula IV;



Formula IV

wherein LG and R' are as defined above;

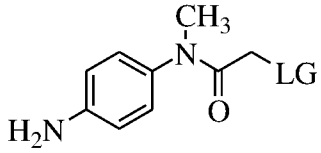
iii) reacting the compound of Formula IV (wherein R' is acetyl group) with 1-methylpiperazine in a solvent to obtain Nintedanib free base of Formula I,

iv) reacting Nintedanib free base with ethane sulfonic acid in a solvent to obtain Nintedanib monoethane sulfonate,

v) optionally recrystallization of Nintedanib ethanesulfonate.

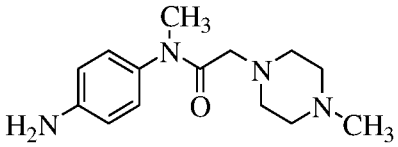
9. A process for the preparation of Nintedanib ethanesulfonate of Formula I which comprises the steps of:

i) reacting the compound of Formula III



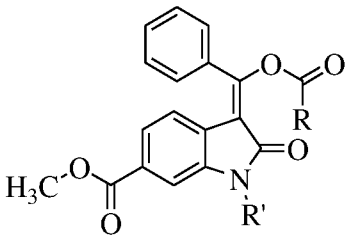
Formula III

wherein LG is a leaving group; with 1-methylpiperazine in a solvent to obtain compound of Formula VII



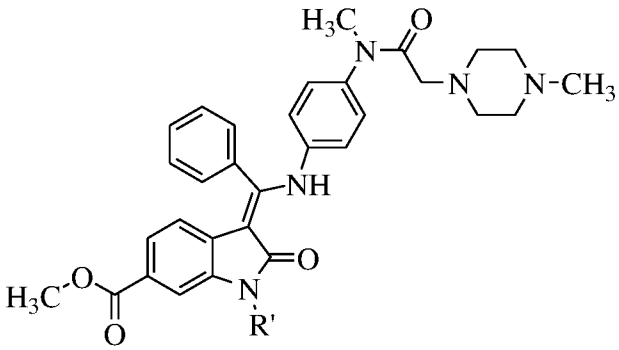
Formula VII

ii) reacting the compound of Formula VII with acetyl derivative of compound of Formula II



Formula II

wherein R represents alkyl, aryl, halogen and R' is acetyl; in a solvent to obtain compound of Formula VIII



Formula VIII

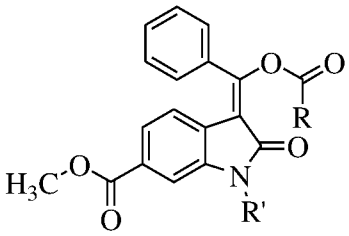
wherein R' is as defined above

iii) reacting compound of Formula VIII with 1-methylpiperazine in a solvent to obtain Nintedanib free base of Formula I,

iv) reacting Nintedanib free base with ethane sulfonic acid in a solvent to obtain Nintedanib monoethane sulfonate,

v) optionally recrystallization of Nintedanib ethanesulfonate.

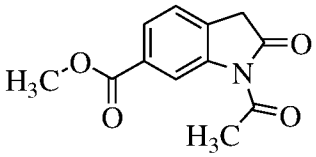
10. A process for the preparation of novel intermediate of acetyl derivative of compound of Formula II



Formula II

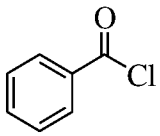
wherein R represents alkyl, aryl, halogen and R' is H or acetyl; which comprises the steps of:

i) condensing methyl 2-oxoindoline-6-carboxylate of compound of Formula V

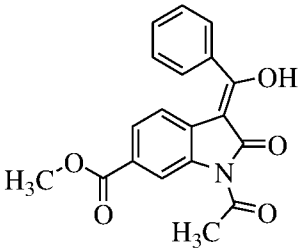


Formula V

with benzoyl chloride



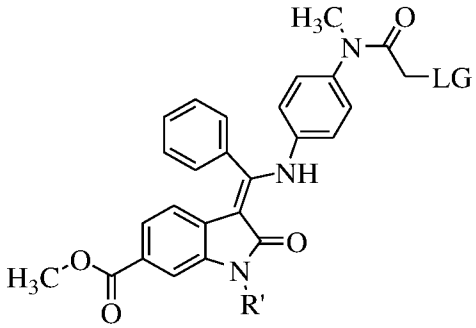
in a solvent in the presence of a base to give compound of Formula VI



Formula VI

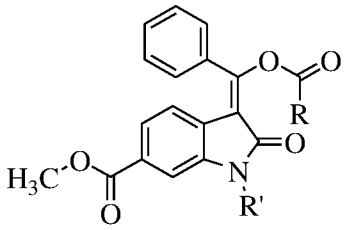
ii) reacting compound of Formula VI with acetic anhydride to obtain acetyl derivative compound of Formula II.

11. A process for the preparation of novel intermediate compound of Formula IV



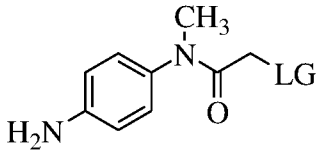
Formula IV

wherein LG is a leaving group and R' is acetyl; which comprises reacting acetyl derivative of compound of Formula II



Formula II

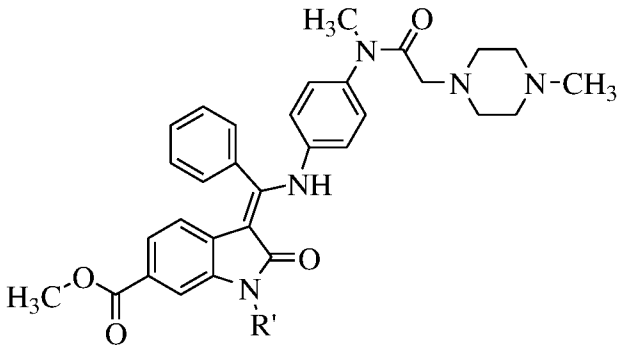
wherein R represents alkyl, aryl, halogen and R' is acetyl; with a compound of Formula III



Formula III

wherein LG is leaving group in a solvent to obtain compound of Formula IV.

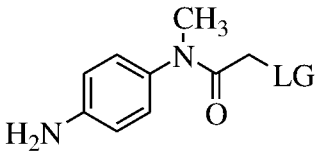
12. A process for the preparation of novel intermediate compound of Formula VIII



Formula VIII

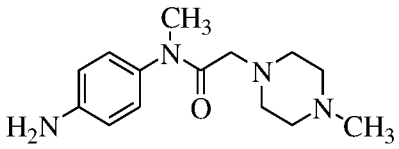
wherein R' is as defined above which comprises the steps of:

i) reacting the compound of Formula III



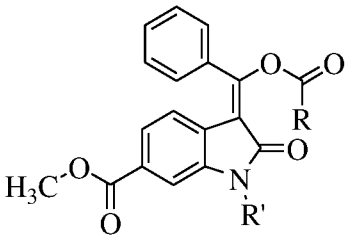
Formula III

wherein LG is a leaving group; with 1-methylpiperazine in a solvent to obtain compound of Formula VII



Formula VII

ii) reacting the compound of Formula VII with acetyl derivative of compound of Formula II



Formula II

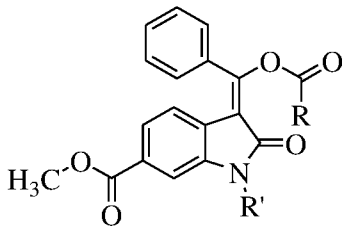
wherein R represents alkyl, aryl, halogen and R' is acetyl; in a solvent to obtain compound of Formula VIII.

13. The process according to any one of the above claims wherein the solvent used is selected from alcohols, esters, ethers, hydrocarbon solvents, chloro solvents, ketones, amides, nitriles or mixtures thereof.

14. The process according to any one of the above claims wherein the base used is selected from ammonia, sodium methoxide, sodium ethoxide, potassium methoxide, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, potassium tert-pentoxide, sodium t-butoxide, potassium tert-butoxide, potassium n-butoxide, sodium hydride, trimethylamine, diisopropylethyl amine (DIPEA), pyridine and Dimethylaminopyridine (DMAP).

15. The process according to claims any one of the above claims wherein the leaving group is selected from halogen tosyl, mesyl.

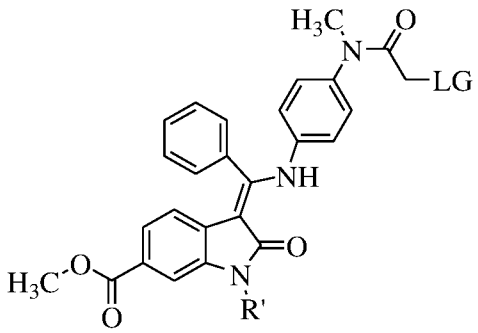
16. Novel intermediate of acetyl derivative of compound of Formula II



Formula II

wherein R represents alkyl, aryl, halogen and R' is acetyl.

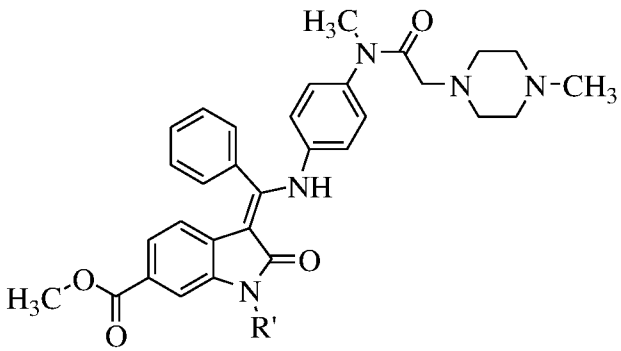
17. Novel intermediate of compound of Formula IV



Formula IV

wherein LG is a leaving group and aryl halide and R' is acetyl.

18. Novel intermediate of compound of Formula VIII



Formula VIII

wherein R' is as defined above.

Figure- 1

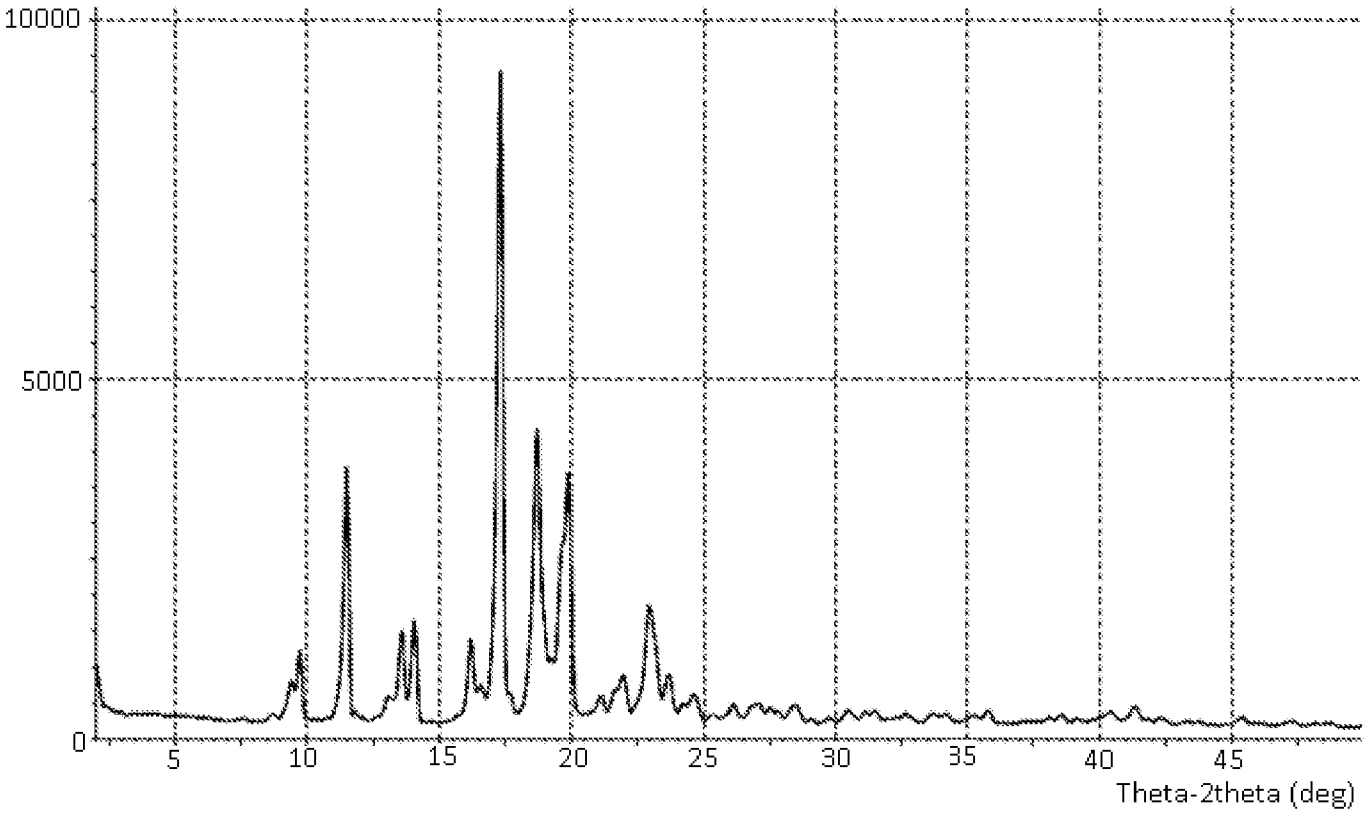
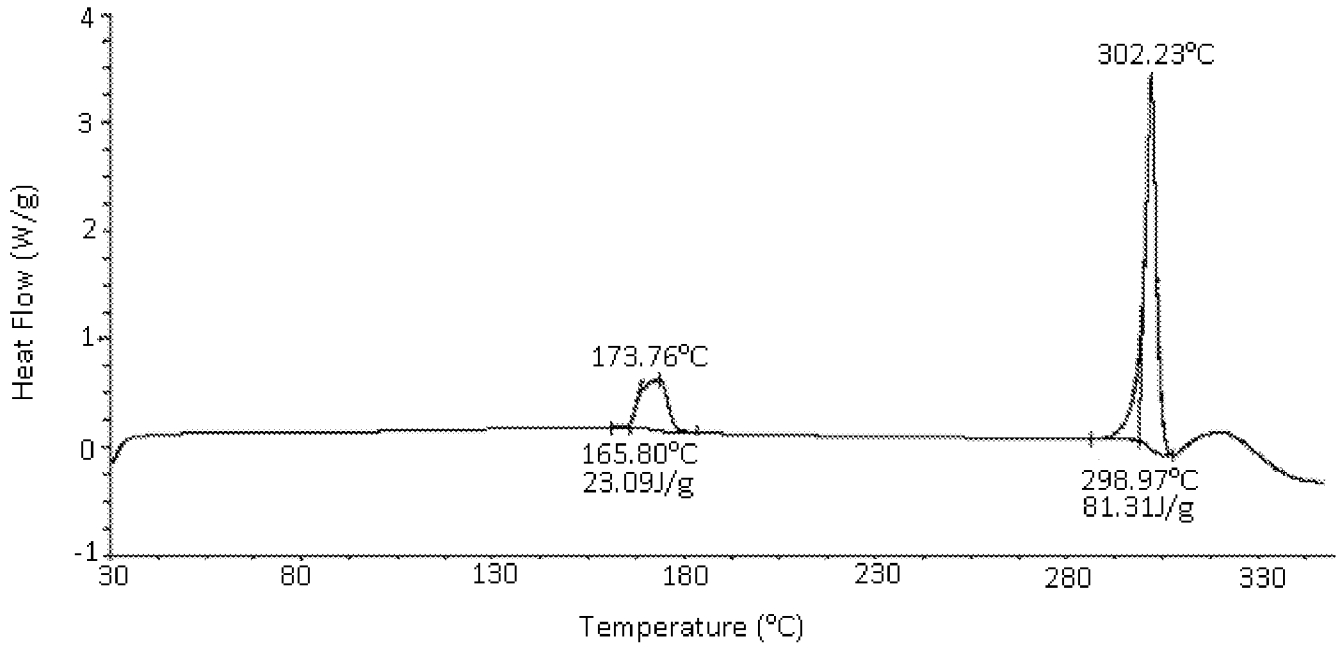


Figure- 2


Heat Flow (W/g)
4
3
2
1
0
-1
30
80
130
180
230
280
330
Temperature (°C)
302.23°C
173.76°C
165.80°C
23.09J/g
298.97°C
81.31J/g

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/054587

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/34 A61K31/404 A61P35/00 A61P11/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/176392 A1 (ROTH GERALD J [DE] ET AL) 9 September 2004 (2004-09-09) cited in the application page 4; example 2 page 2; table 1 figures 1-2 claims 1-9 page 1, paragraphs 2,10-15	1-6
X	WO 2009/071523 A1 (BOEHRINGER INGELHEIM INT [DE]; MERTEN JOERN [DE]; LINZ GUENTER [DE]; S) 11 June 2009 (2009-06-11) pages 25-27; example 8 claims 1-9	1-6

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 August 2015	18/11/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Marzi, Elena

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/054587

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CAIRA: "Crystalline Polymorphism of Organic Compounds", TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP008166276, ISSN: 0340-1022 the whole document -----	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/054587

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6

Form S of Nintedanib ethanesulfonate and processes for its preparation

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2. claims: 7-18

Process for the preparation of Nintedanib ethanesulfonate and intermediates thereof

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/054587

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004176392 A1	09-09-2004	US 2004176392 A1	09-09-2004
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		US 2011201812 A1	18-08-2011
		WO 2009071523 A1	11-06-2009