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(54) **Title:** PROCESS FOR THE PREPARATION OF NINTEDANIB

(57) **Abstract:** The present invention relates to a process for the preparation of nintedanib or salt thereof. The process comprising reacting compound of formula VI with acetic anhydride and triethyl ortho benzoate to obtain a compound of formula V; further reacting the compound of formula V with the compound of formula IV to obtain nintedanib the compound of formula I. The present invention also relates to a process to obtain crystalline compound of formula V.

PROCESS FOR THE PREPARATION OF NINTEDANIB

PRIORITY

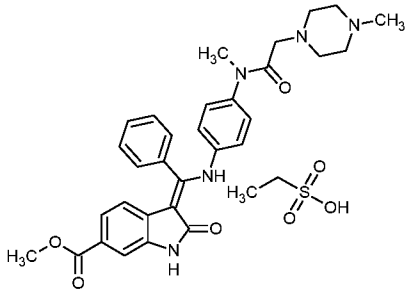
[0001] This application claims the benefit to Indian Provisional Application No. 201721031509, filed on 6 September, 2017, the contents of which are incorporated by reference herein.

FIELD OF THE INVENTION

[0002] The present invention relates to a process for preparation of nintedanib or salt thereof.

BACKGROUND OF THE INVENTION

[0003] Nintedanib ethanesulfonate salt (esylate), also known as *IH*-Indole-6-carboxylic acid,2,3-dihydro-3-[[[4-[methyl[(4-methyl-l-piperazinyl)acetyl]amino] phenyl]amino]phenylmethylene]-2-oxo-, methyl ester, (3Z)-, ethanesulfonate (1:1), is represented by a compound of formula II

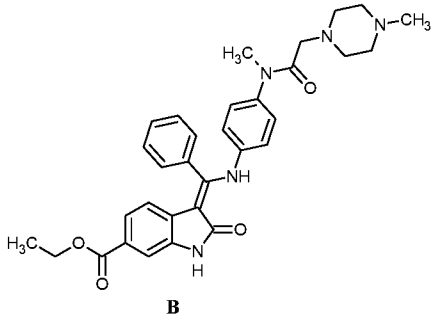


II

[0004] Nintedanib esylate marketed as OFEV ® is a capsule available in multiple strengths for oral administration and is indicated for the treatment of idiopathic pulmonary fibrosis (TPF).

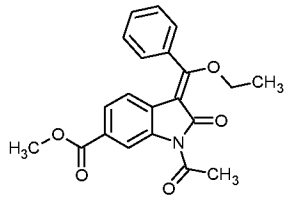
[0005] The present invention provides a process for the preparation of nintedanib or a salt thereof, with a better purity profile without using column chromatography techniques and which can be easily performed on industrial scale.

[0006] Specifically the present invention provides a process for nintedanib or a salt thereof, wherein the level of impurity, the compound of formula B,



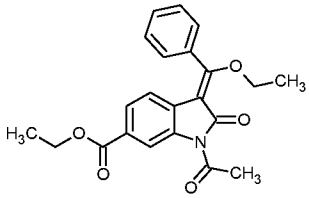
B

is less than 0.15% w/w of nintedanib, the compound of formula I, by a process comprising treating the compound of formula V,



V

with a solvent system to obtain a compound of formula V, wherein the level of transesterification impurity, the compound of formula A,

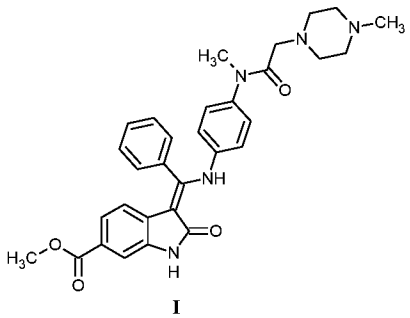


A

is less than 0.15% w/w of the compound of formula V. The compound of formula V thus obtained, when reacted further ensures formation of nintedanib or salt thereof with a purity of at least 99.85% w/w and wherein the level of impurity, the compound of formula B, is less than 0.15%w/w.

SUMMARY OF THE INVENTION

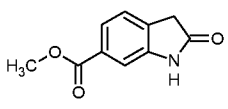
[0007] In one embodiment, the present invention provides a process for the preparation of nintedanib, a compound of formula I,



I

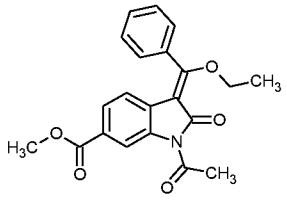
or a salt thereof, comprising the steps of:

reacting a compound of formula VI,



VI

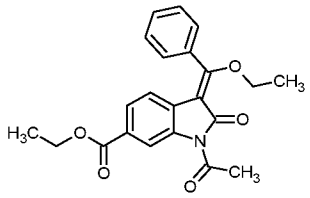
with acetic anhydride and triethyl orthobenzoate to obtain a compound of formula V,



V

; and

b) subjecting the compound of formula V to treatment with a solvent system selected from the group consisting of Ci-C $_6$ amide, Ci-C $_6$ ester, Ci-C $_6$ carboxylic acid, C2-C6 carboxylic anhydride, Ci-C $_6$ aliphatic ether, Ci-C $_6$ haloalkane, C 6-C12 aromatic hydrocarbon, Ci-C $_6$ alcohol or mixtures thereof, to obtain a compound of formula V, wherein the level of impurity, the compound of formula A,



A

is less than 0.15% w/w of the compound of formula V, as determined by HPLC.

BRIEF DESCRIPTION OF THE DRAWINGS

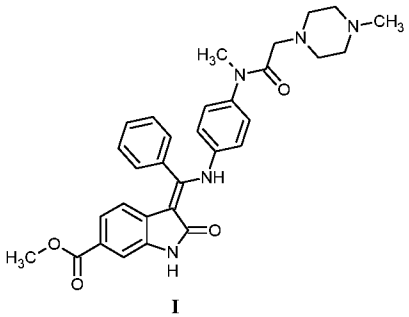
[0008] Figure 1 is a characteristic XRPD of crystalline compound V as obtained in Example 2.

[0009] Figure 2 is a characteristic XRPD of crystalline nintedanib (I) as obtained in Example 7.

[0010] Figure 3 is a characteristic XRPD of crystalline nintedanib esylate hemihydrate as obtained in Example 10.

DETAILED DESCRD7TION OF THE INVENTION

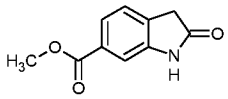
[0011] In one embodiment, the present invention provides a process for the preparation of nintedanib, a compound of formula I,



I

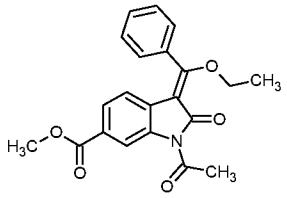
or a salt thereof, comprising the steps of:

a) reacting a compound of formula VI,



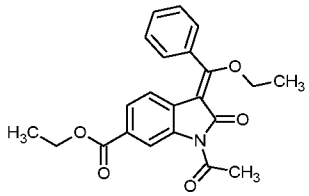
VI

with acetic anhydride and triethyl orthobenzoate to obtain a compound of formula V,



V ; and

b) subjecting the compound of formula V to treatment with a solvent system selected from the group consisting of Ci-C_6 amide, Ci-C_6 ester, Ci-C_6 carboxylic acid, C2-C6 carboxylic anhydride, Ci-C_6 aliphatic ether, Ci-C_6 haloalkane, C6-C12 aromatic hydrocarbon, Ci-C_6 alcohol or mixtures thereof, to obtain a compound of formula V, wherein the level of impurity, the compound of formula A,



A

is less than 0.15% w/w of the compound of formula V, as determined by HPLC.

[0012] In one embodiment, reaction of the compound of formula VI with acetic anhydride and triethyl orthobenzoate in step 'a', is carried out at a temperature in the range of about 80°C to about 150°C.

[0013] In one embodiment, reaction of the compound of formula VI with acetic anhydride and triethyl orthobenzoate in step 'a', is carried out without any solvent.

[0014] In one embodiment, reaction of the compound of formula VI with acetic anhydride and triethyl orthobenzoate in step 'a', is carried out in presence of a solvent selected from hydrocarbon solvent like toluene, xylene and the like

[0015] In one embodiment, in step 'a', the low boiler solvent is distilled out simultaneously at about 100°C to about 140°C.

[0016] In one embodiment, in step 'a', the crude compound of formula V obtained in step 'a', is isolated by any method known in the art. The method, may involve any of the techniques, known in the art, including filtration by gravity or by suction, centrifugation, and the like, evaporation by lyophilisation, freeze-drying technique, spray drying, fluid bed drying, flash drying, spin flash drying, thin-film drying, agitated nutsche filter dryer, complete evaporation in, for example, a rotavapor, a vacuum paddle dryer or in a conventional reactor under vacuum, or concentrating the solution, cooling the solution if required and filtering the obtained solid by gravity or by suction, centrifugation, and the like.

[0017] The compound of formula V thus obtained is subjected to a treatment with solvent system in step 'b'.

[0018] In one embodiment, in step 'b', the treatment with solvent system of the compound of formula V consists of recrystallizing the compound of formula V from a solvent system.

[0019] In one embodiment, in step 'b', the treatment with solvent system of the compound of formula V consists of slurrying the compound of formula V in a solvent system.

[0020] The term slurrying denotes suspending the solid in a solvent system with or without stirring at ambient temperature or at higher temperature.

[0021] In one embodiment, the treatment with solvent system consists of dissolving the compound in a solvent followed by addition of anti-solvent to precipitate the compound.

[0022] In one embodiment, the C_i-C_6 amide solvent is selected from the group consisting of formamide, dimethylformamide (DMF), dimethylacetamide (DMA) or a mixture thereof.

[0023] In one embodiment, the C_i-C_6 ester is selected from the group consisting of methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate or a mixture thereof.

[0024] In one embodiment, the C_i-C_6 carboxylic acid is selected from the group consisting of formic acid, acetic acid, propionic acid or a mixture thereof.

[0025] In one embodiment, the C2-C6 carboxylic anhydride is selected from the group consisting of formic anhydride, acetic anhydride, propionic anhydride or a mixture thereof.

[0026] In one embodiment, the C_i-C_6 aliphatic ether is selected from the group consisting of dimethyl ether, diethyl ether, methyl tert-butyl ether (MTBE) or a mixture thereof.

[0027] In one embodiment, the C1-C4 haloalkane is selected from the group consisting of dichloromethane (DCM), chloroform, 1,1-dichloroethane, 1,2-dichloroethane or a mixture thereof.

[0028] In one embodiment, the C6-C12 aromatic hydrocarbon is selected from the group consisting of toluene, xylene or a mixture thereof.

[0029] In one embodiment, the Ci-C_6 alcohol solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, n-butanol, sec-butanol, 2-butanol, t-butanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-l-butanol, 2-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl-1 -propanol, 1,1,-dimethyl-l-propanol or a mixture thereof.

[0030] In one embodiment, the solvent system maybe a mixture of two or more, same or different solvents.

[0031] In one embodiment, in step 'b', the compound of formula V is subjected to slurrying in a mixture of Ci-C_6 alcohol and C6-C12 aromatic hydrocarbon.

[0032] In one embodiment, in step 'b', the compound of formula V is subjected to slurrying in a mixture of methanol and toluene.

[0033] In one embodiment, in step 'b', the compound of formula V is subjected to slurrying in the mixture of methanol and toluene at the temperature of about 20°C to about 120°C.

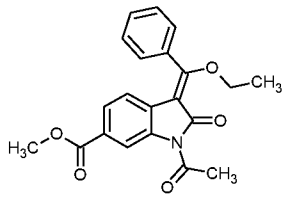
[0034] In one embodiment, in step 'b', the compound of formula V is recrystallized from the mixture of Ci-C_6 alcohol and C6-C12 aromatic hydrocarbon.

[0035] In one embodiment, in step 'b', the compound of formula V is recrystallized from the mixture of methanol and toluene.

[0036] In one embodiment, in step 'b', the compound of formula V is recrystallized from the mixture of methanol and toluene at the temperature of about 20°C to about 120°C.

[0037] In one embodiment, the compound of formula V is obtained in a purity of at least 97.69%, as determined by HPLC (high performance liquid chromatography), without using column chromatographic techniques.

[0038] In one embodiment, the present invention provides a crystalline compound of formula V,



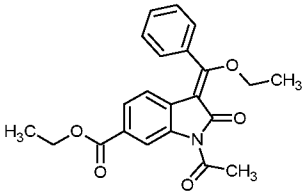
v

.

[0039] In one embodiment, the present invention provides the crystalline compound of formula V, characterized by X-ray powder diffraction (XRPD) spectrum having characteristic peak reflections at about 8.2, 11.2, 16.5 and 25.5 ± 0.2° 2Θ.

[0040] In one embodiment, the present invention provides the compound of formula V in a purity of at least 97.69%, as determined by HPLC.

[0041] In one embodiment, the present invention provides the compound of formula V, wherein the level of impurity, the compound of formula A,



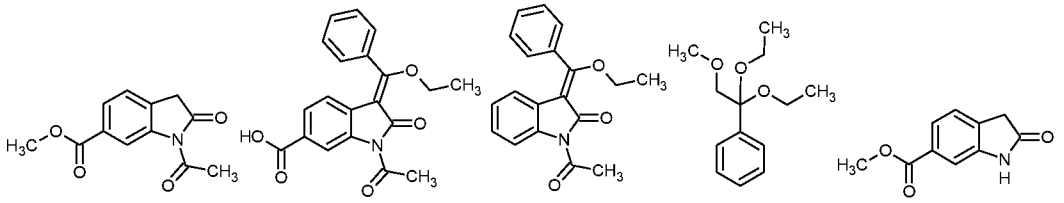
A

,

is less than 0.15% w/w of the compound of formula V, as determined by HPLC.

[0042] In one embodiment, the present invention provides a process for preparing the crystalline compound of formula V, wherein the level of impurity, the compound of formula A is less than 0.15%, as determined by HPLC, the process comprising recrystallizing or slurrying the compound of formula V in a solvent system of mixture of Ci-C_6 alcohol and C_6-Ci2 aromatic hydrocarbon.

[0043] In one embodiment, the present invention provides the compound of formula V, wherein the level of one or more compounds represented by C, D, E, F and VI



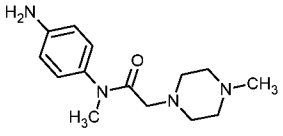
C **D** **E** **F** **VI**

,

is less than 0.15% w/w of the compound of formula V, as determined by HPLC.

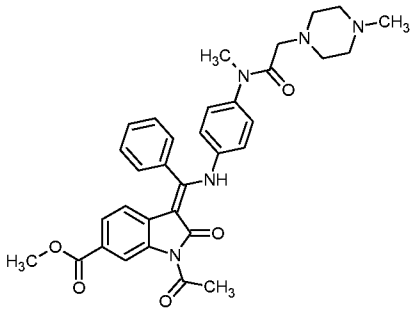
[0044] In one embodiment, the present invention provides a process for the preparation of nintendanib, the compound of formula I, further comprising the steps of:

i) reacting the compound of formula V with a compound of formula IV,



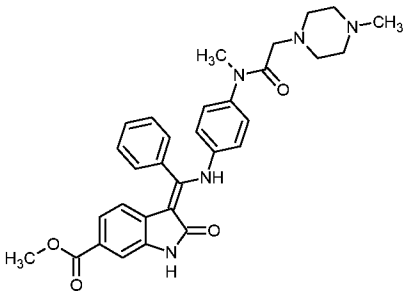
IV

to obtain a compound of formula III;



III

ii) deprotecting the compound of formula III with a base to obtain nintedanib, the compound of formula I,



I

[0045] In one embodiment, the present invention provides reaction of the compound of formula V with the compound of formula IV in step 'i', wherein the compound of formula V is crystalline.

[0046] In one embodiment, in step 'i', the reaction of the compound of formula V with the compound of IV is carried out in a solvent.

[0047] In one embodiment, in step 'i', the reaction of the compound of formula V with the compound of IV is carried out in a solvent selected from the group consisting of C_i-C_6 amide, C_i-C_6 ester, C_i-C_6 carboxylic acid, C_i-C_6 carboxylic anhydride, C_i-C_6 aliphatic ether, C_1-C_4 haloalkane, C_6-C_{12} aromatic hydrocarbon, C_i-C_6 alcohol or mixtures thereof.

[0048] In one embodiment, in step 'i', the reaction of the compound of formula V with the compound of IV is carried out in C_i-C_6 amide solvent selected from the group consisting of formamide, dimethylformamide (DMF), dimethylacetamide (DMA) or a mixture thereof.

[0049] In one embodiment, in step 'i', the reaction of the compound of formula V with the compound of formula IV is carried out at the temperature of about 20°C to about 120°C.

[0050] In one embodiment, the compound of formula III is not isolated and carry forwarded for further reaction.

[0051] In one embodiment, the compound of formula III formed in step 'i', is isolated by filtration.

[0052] In one embodiment, the compound of formula III formed in step 'i', is filtered and wet cake obtained is used in next step.

[0053] In one embodiment, in step 'ii', the deprotection of the compound of formula III maybe carried out using an organic base or an inorganic base.

[0054] In one embodiment, the organic base is selected from the group consisting of amines, organolithiums, metal alkaloids, amides, tetraalkylammonium hydroxides, phosphonium hydroxides and the like.

[0055] In one embodiment, the amine is selected from the group consisting of cyclic aliphatic amine, trialkyl amines and heterocyclic amine.

[0056] In one embodiment, the cyclic aliphatic amine is selected from the group consisting of piperidine and piperazine.

[0057] In one embodiment, the trialkyl amine is selected from the group consisting of triethylamine and diisoporpylethylamine (DIPEA).

[0058] In one embodiment, the heterocyclic amine is selected from the group consisting of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), l,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (Dabco) pyridine, pyrimidine or 4-(dimethylamino)pyridine (DMAP).

[0059] In one embodiment, the inorganic base is selected from the group consisting of metal carbonate, metal bicarbonate and metal hydroxide, wherein the metal is selected from the group consisting of sodium, potassium, lithium, calcium or magnesium.

[0060] In one embodiment, in step 'ii', the deprotection of the compound of formula III is carried out using piperidine as a base.

[0061] In one embodiment, in step 'ii', the deprotection of the compound of formula III is carried out in an amide, Ci-C_6 ester, C1-C4 haloalkane, C_6-C12 aromatic hydrocarbon, Ci-C_6 alcohol, water, or mixtures thereof.

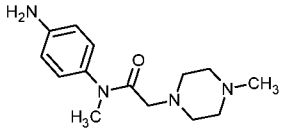
[0062] In one embodiment, in step 'ii', the deprotection of the compound of formula III is carried out in an alcoholic solvent.

[0063] In one embodiment, in step 'ii', the base is added at the temperature of about -10°C to about 20°C.

[0064] In one embodiment, in step 'ii', reaction of compound of formula V with the compound of formula IV is carried out at the temperature of about 0°C to about 80°C.

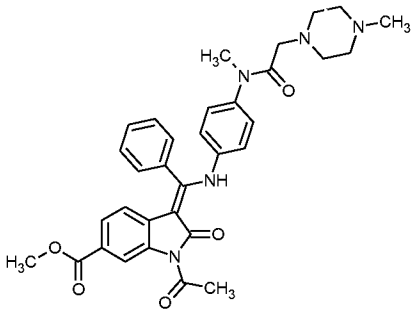
[0065] In one embodiment, the present invention provides a process for the preparation of nintedanib, the compound of formula I, further comprising the steps of:

i) reacting the compound of formula V with a compound of formula IV,



IV

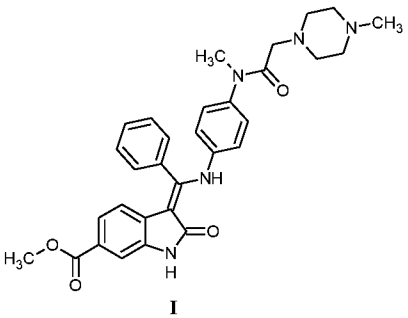
to obtain a compound of formula III,



III

;

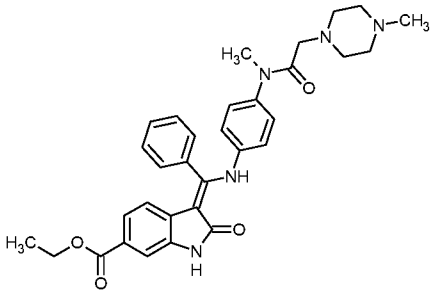
ii) deprotecting the compound of formula III with piperidine in an alcoholic solvent to obtain nintedanib, the compound of formula I,



I

,

wherein the level of impurity, the compound of formula B,

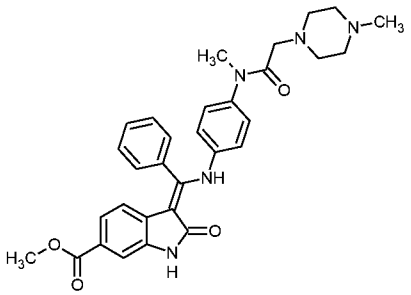


B

is less than 0.15% w/w of nintedanib, the compound of formula I, as determined by HPLC.

[0066] In one embodiment, crude nintedanib, the compound of formula I formed in step ii, is isolated by any method known in the art, as discussed supra.

[0067] In one embodiment, the present invention provides a process further comprising recrystallizing nintedanib, the compound of formula I, in a solvent system selected from the group consisting of Ci-C $_6$ amine, Ci-C $_6$ ester, Ci-C $_6$ carboxylic acid, Ci-C $_6$ carboxylic anhydride, Ci-C $_6$ aliphatic ether, C1-C4 haloalkane, C 6-C12 aromatic hydrocarbon, Ci-C $_6$ alcohol, water or mixtures thereof, to obtain nintedanib, the compound of formula I,



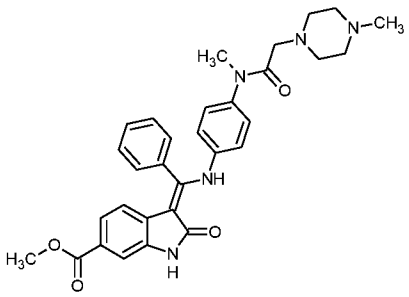
I

.

[0068] In one embodiment, nintedanib, the compound of formula I, is recrystallized from mixture of two or more, same or different solvents.

[0069] In one embodiment, nintedanib the compound of formula I, is recrystallized using methanol: water as solvent.

[0070] In one embodiment, the present invention provides crystalline nintedanib, the compound of formula I.



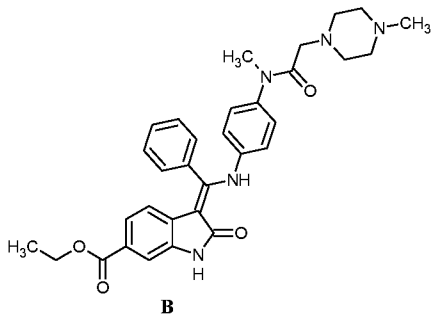
I

.

[0071] In one embodiment, nintedanib, the compound of formula I is characterized by X-ray powder diffraction (XRPD) spectrum having characteristic peak reflections at about 6.5, 10.7, 11.6, 12.2 and 23.2±0.2° 2Θ.

[0072] In one embodiment, the present invention provides nintedanib, the compound of formula I, in a purity of at least 99.98%, as determined by HPLC.

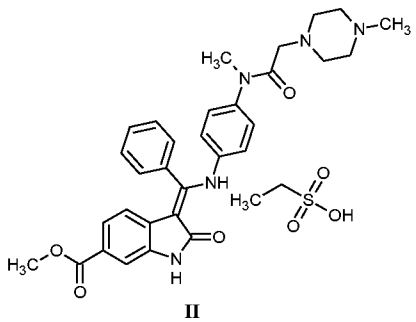
[0073] In one embodiment, the present invention provides nintedanib or salt thereof, the compound of formula I, wherein the level of impurity, the compound of formula B



B

is less than 0.15% w/w of nintedanib, as determined by HPLC.

[0074] In one embodiment, the present invention provides a process, wherein nintedanib, the compound of formula I, is further reacted with ethanesulfonic acid to obtain nintedanib esylate, a compound of formula II.



II

[0075] In one embodiment, nintendanib, the compound of formula I, is further reacted with ethanesulfonic acid in a solvent system.

[0076] In one embodiment, nintendanib, the compound of formula I, is further reacted with ethanesulfonic acid in a solvent system selected from the group consisting of, Ci-C_6 amide, Ci-C_6 ester, Ci-C_6 carboxylic acid, Ci-C_6 carboxylic anhydride, Ci-C_6 aliphatic ether, C1-C4 haloalkane, C_6-C12 aromatic hydrocarbon, Ci-C_6 alcohol, water or mixtures thereof, to obtain nintendanib esylate, the compound of formula II.

[0077] In one embodiment, nintendanib, the compound of formula I, is further reacted with ethanesulfonic acid in an alcoholic solvent to obtain nintendanib esylate, the compound of formula II.

[0078] In one embodiment, nintendanib, the compound of formula I, is further reacted with ethanesulfonic acid to obtain nintedanib esylate, the compound of formula II, wherein nintedanib, the compound of formula I, is crystalline.

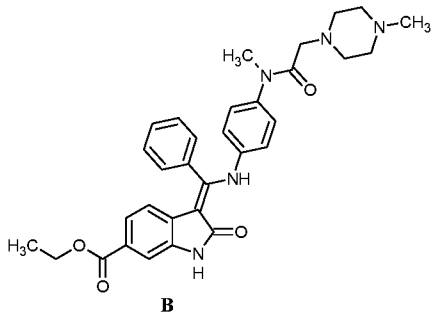
[0079] In one embodiment, the present invention provides nintedanib esylate hemihydrate, the compound of formula II.

[0080] In one embodiment, the present invention provides crystalline nintedanib esylate hemihydrate, the compound of formula II.

[0081] In one embodiment, the present invention provides crystalline nintedanib esylate hemihydrate the compound of formula II, characterized by X-ray powder diffraction (XRPD) spectrum having characteristic peak reflections at about 16.3, 17.4, 18.8, 19.7 and 20.0±0.2° 2Θ.

[0082] In one embodiment, the present invention provides nintedanib esylate hemihydrate, the compound of formula I, in a purity of at least 99.98%, as determined by HPLC.

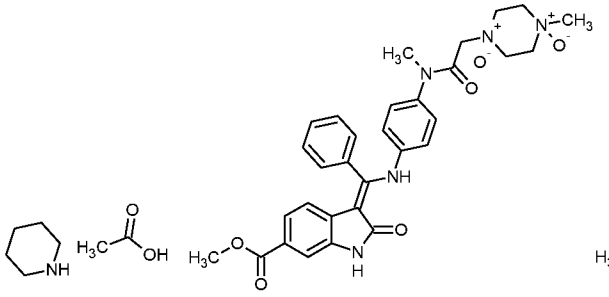
[0083] In one embodiment, the present invention provides nintedanib esylate hemihydrate, the compound of formula II, wherein the level of impurity, the compound of formula B



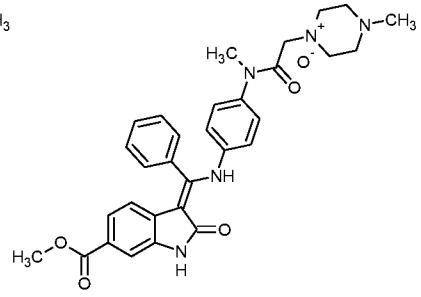
B

is less than 0.15% w/w of nintedanib, as determined by HPLC.

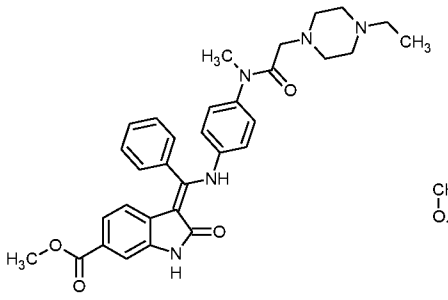
[0084] In one embodiment, the present invention provides nintendanib or nintedanib esylate hemihydrate, wherein the level of one or more impurities represented by G, H, I, J, K and III.



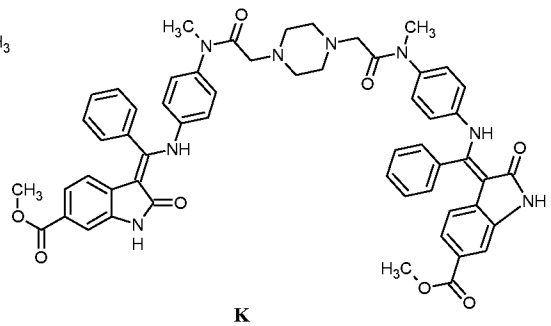
G H



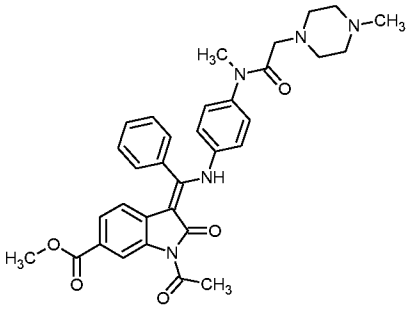
I



J



K



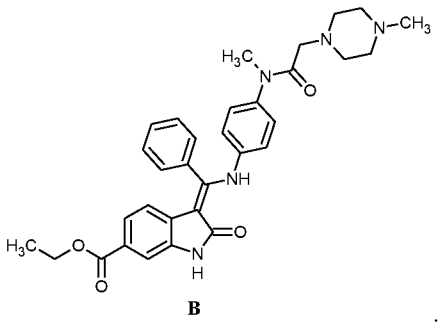
III

is less than 0.15% w/w of nintedanib, as determined by HPLC.

[0085] In one embodiment, the present invention provides nintedanib esylate with purity of at least 99.0%, wherein the level of one or impurities represented by B, G, H, I, J, K and III, is less than 0.15%.

[0086] In one embodiment, the present invention provides a method of assessing the purity of nintedanib or salt thereof or the pharmaceutical composition containing them, by HPLC comprising the steps of:

a) providing a standard solution of the compound of formula B,



B

; and

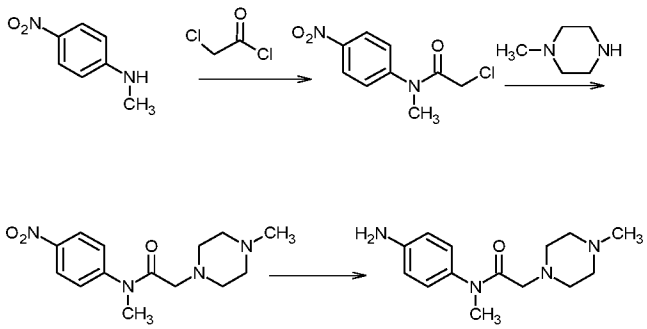
b) using the solution of step 'a', as a reference marker to determine the level of the compound of formula B.

[0087] The determination of the presence of the compound of formula B in the sample of nintedanib or a salt thereof, is effected by comparing the retention of the different components of the sample of nintedanib or a salt thereof, by the chromatographic technique with the retention of the compounds of formula B under the same chromatographic conditions.

[0088] The term "reference marker", as used herein, refers to a compound that may be used in qualitative analysis to identify components of a mixture based on their position, and/or in quantitative analysis to determine the concentration of said compound in a mixture by reference to the concentration of a solution comprising a known amount of said component.

[0089] In one embodiment, according to the present invention a reference marker solution will comprise the compound of formula B, dissolved in an appropriate solvent. Thus, assessing the purity of nintedanib or salt thereof, by using the compound of formula B as reference marker, according to step (b), means determining the concentration of the compound of formula B, respectively. Preferably, the concentration of the compound of formula B is determined by means of conventional methods known in the art for quantifying compounds, such as HPLC.

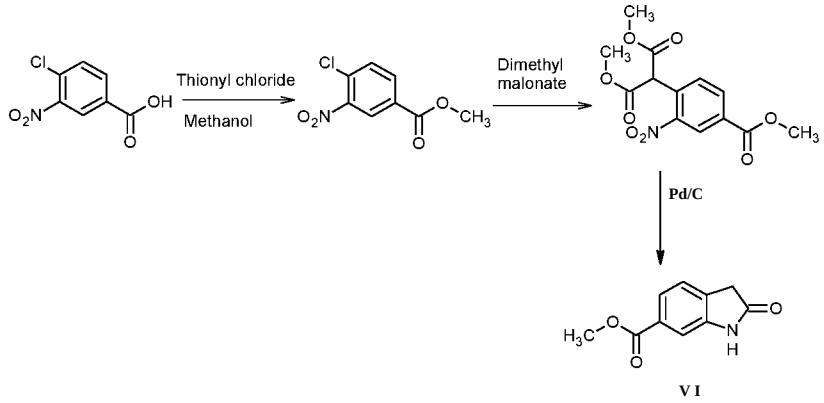
[0090] In one embodiment, the compound of formula IV is synthesized as shown in scheme 1:



IV

Scheme 1

[0091] In one embodiment, the compound of formula VI is synthesized as shown in scheme 2:



VI

Scheme 2

[0092] In one embodiment, the present invention provides solvates of nintedanib.

[0093] The solvates of nintedanib includes solvates with water, methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tert-butanol, ethylene glycol, ethyl acetate, n-butyl acetate, isobutyl acetate, acetonitrile, acetone, butanone, methyl isobutyl ketone, tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, chloroform, dichloromethane (DCM), hexane, n-heptane, toluene, N-methyl pyrrolidone, dimethyl formamide or dimethyl sulfoxide.

[0094] In one embodiment, the present invention provides nintedanib, salt or solvate thereof obtained by the processes herein described, having a D_{10}, D_{50} and D_{90} particle size of less than about 150 microns, preferably less than about 100 microns, more preferably less than about 50 microns, still more preferably less than about 30 microns. The particle size disclosed here can be obtained by, for example, any milling, grinding, micronizing or other particle size reduction method known in the art to bring the solid state nintedanib or salt, solvate thereof into any of the foregoing desired particle size range.

[0095] X-ray powder diffraction profiles were obtained using an X-ray diffractometer (Philips X'Pert Pro, PANalytical). The measurements were carried out with a Pre FIX module programmable divergence slit and anti-scatter Slit (Offset 0.00°) ; target, Cu; filter, Ni; detector, X'Celerator; Scanning Mode; Active length (2Theta) = 2.122°; generator 45KV; tube current 40 mAmp. The samples were scanned in the full 2Θrange of 2-50° with a "time-per-step" optimized to 50 sec.

[0096] HPLC Method: High performance liquid chromatography (HPLC) was performed with the conditions described below for detecting purity:

Column: Kromasil 100-5 C8, 250 x 4.6mm, Column temperature: 30°C, Mobile phase: A= Buffer: 0.01M of Sodium perchlorate monohydrate in water. Adjust to pH 2.2 with diluted perchloric acid, B= acetonitrile: methanol: buffer (750: 150: 100 v/v/v), Diluent: water: acetonitrile (80:20 v/v); Flow Rate: l.OmL/min, Detection wavelength: UV 210nm, Injection volume: 10µL.

Gradient Program:

Time (min)	% Mobile Phase A	% Mobile Phase B
0.01	95	05
05	95	05
19	55	45
55	40	60
78	40	60
80	95	05
0	95	05

[0097] The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention.

Examples

[0098] Example 1: Preparation of methyl l-acetyl-3-[ethoxy(phenyl)methylidene]-2-oxo-2, 3-dihydro-7*H*-indole-6-carboxylate (V)

A mixture of compound VI (lOg) and acetic anhydride (40ml) was stirred at about 110°C-120°C for about 2h. To this reaction mass, triethyl orthobenzoate (35.18gm) was slowly added at about 115-125°C for 3h and distilled out low boiler simultaneously at about 120-125°C. Then the reaction mass was cooled to about 90°C, and concentrated under vacuum to obtain crude compound of formula V.

HPLC Purity: 95%; Imp A: 0.45%.

[0099] Example 2: Purification of compound V in methanol: toluene

The crude compound V from example 1 was diluted with methanol and refluxed for 2h. The Reaction mass was cooled to about 50-55°C, toluene was added and stirred. The reaction mass was then cooled to about 0-5°C and stirred for lh. The reaction mass was filtered and washed with methanol. The obtained solid was slurried in methanol and stirred at about 40-45°C for 30 min. The reaction mass was cooled to about 0-5°C and stirred. The reaction mass was filtered, solid was washed with methanol and dried in vacuum tray drier at about 60-70°C. Yield: 12g; HPLC purity: 97.69%; Imp A: 0.04%.

XRD peaks of compound V:

Pos. [°2θ]	Rel. Int. [%]	Pos. [°2θ]	Rel. Int. [%]	Pos. [°2θ]	Rel. Int. [%]	Pos. [°2θ]	Rel. Int. [%]
2.76	2.53	11.78	1.29	20.36	2.50	31.978	0.94
3.12	7.66	12.41	0.46	21.92	2.83	33.35	0.32
3.47	1.67	13.60	2.90	22.61	1.12	35.91	0.81
3.93	2.65	14.28	1.81	23.69	4.28	36.53	0.71
5.86	0.72	15.01	6.69	24.06	2.44	37.34	0.67
6.90	2.47	15.64	7.71	25.50	24.40	38.56	0.91
7.87	22.67	16.53	15.53	26.23	8.22	41.67	0.83
8.25	100.00	16.84	5.57	27.37	5.39	44.63	0.82
9.34	0.92	17.41	9.34	28.87	2.45	47.64	0.20
9.64	0.68	18.99	0.70	30.08	0.92		
11.24	10.07	19.54	1.24	31.02	0.69		

[0100] Example 3: Purification of compound V in dichloromethane (DCM): methyl t-butyl ether (MTBE)

The crude compound V from example 1 was added in DCM to obtain clear reaction mass. To this solution, MTBE was added at about 25-30°C and stirred for lh. The reaction mass was filtered, solid was washed with MTBE and dried in vacuum tray drier at about 60-70°C Yield: 11.2g; HPLC purity: 99.34%; Imp A: 0.07%.

[0101] Example 4: Purification of compound V in dimethylformamide (DMF): ethyl acetate

The crude compound V from example 1 was added in DMF and heated to get clear reaction mixture. The reaction mass was cooled to about 60°C and ethyl acetate was added. Reaction mass was then cooled to about 0-5°C and stirred for about lh. The reaction mass was filtered, solid was washed with ethyl acetate and dried in vacuum tray drier at about 60-70°C. Yield: 11.5g; HPLC purity: 95.96%; Imp A: 0.03%.

[0102] Example 5: Purification of compound V in methanol: toluene: acetic acid: acetic anhydride

The crude compound V from example 1 was added in methanol, toluene, acetic acid, acetic anhydride and stirred at about 60-65°C. Reaction mass was then cooled to about 0-5°C and stirred for lh. The reaction mass was filtered, solid was washed with methanol and dried in vacuum tray drier at about 60-70°C. Yield: 1lg; HPLC purity: 94.58%; Imp A: 0.12%.

[0103] Example 6: Preparation of nintedanib (I)

A mixture of the compound of formula V (lOg) and N-(4-aminophenyl)-N-methyl-2-(4-methylpiperazin-l-yl)acetamide (formula IV) (7.89g) in DMF (50ml) was stirred at about 65-70°C for 4h. The reaction mass was cooled to about 25-30°C and stirred for lh. Reaction mass was filtered and solid was washed with methanol. The solid wet cake was added in methanol and stirred at about 25-30°C. Reaction mass was cooled to about 0-5°C and piperidine (6.2ml) was added under stirring. The reaction mass was heated to about 25-30°C and stirred for 5h. The reaction mass was cooled to about 0-5°C and stirred for lh. The reaction mass was filtered and solid was washed with cold methanol to obtain crude nintedanib. Yield: 12gm; HPLC purity: 99.96%; Imp B: 0.02%.

[0104] Example 7: Purification of nintedanib in methanol

The crude nintedanib (I) from example 6 was purified with methanol to obtain nintendanib. Yield: lOg; HPLC purity: 99.98%; Imp B: 0.03%.

XRD peaks of nintedanib (I):

Pos. [°2θ]	Rel. Int. [%]	Pos. [°2θ]	Rel. Int. [%]	Pos. [°2θ]	Rel. Int. [%]	Pos. [°2θ]	Rel. Int. [%]
6.50	86.06	16.86	19.41	24.16	22.90	33.41	2.94
9.04	7.90	17.42	86.45	24.52	33.69	35.10	6.37
9.95	1.38	17.70	51.16	24.96	2.80	35.64	4.24
10.72	19.17	17.91	43.01	25.28	2.87	36.23	5.35
11.22	3.20	18.08	19.75	26.40	11.33	37.23	3.72
11.60	28.22	18.79	4.03	26.74	7.59	38.91	6.24
12.20	51.46	19.06	7.98	27.60	5.88	40.27	2.03
12.56	2.91	19.73	85.19	28.71	6.29	41.24	1.12
13.05	10.16	20.03	100.00	29.38	11.64	42.99	3.50
14.11	4.79	21.08	3.90	29.69	6.59	45.38	1.70
15.28	27.85	21.88	8.66	30.64	2.07	46.03	3.26
16.49	55.40	22.57	22.42	31.837	7.17		
16.68	56.55	23.20	85.03	32.73	1.44		

[0105] Example 8: Purification of nintedanib (I) in DMF: Methanol

Crude nintendanib (I) from example 6 was added in DMF methanol mixture and heated to obtain clear solution. The reaction was slowly cooled to about 0-5°C and stirred for lh. The reaction mass was filtered, solid was washed with methanol and dried in trey dryer at 45-50°C Yield: 0.84g; HPLC purity: 99.96%; Imp B: 0.03%.

[0106] Example 9: Purification of nintedanib (I) in DCM: Methanol

Crude nintedanib (I) from example 6 was added to DCM methanol mixture and stirred at about 25-30°C to obtain clear solution. Dichloromethane was distilled out from the reaction mass at about 25-30°C to precipitate the solid. The reaction mass was slowly cooled to about 0-5°C and stirred for lh. The reaction mass was filtered, solid was washed with methanol and dried in tray dryer at 45-50°C Yield: 0.80g; HPLC purity: 99.98%; Imp B: 0.02%.

[0107] Example 10: Preparation of Nintedanib Esylate (Formula II)

A mixture of nintedanib (I) (lOg) in methanol (140ml) was stirred at about 50-55°C for about 30min. 70% aqueous ethanesulfonic acid (3.06gm) was added to above reaction mass at about 50-

55°C and stirred to get clear solution. The reaction mass was filtered through micron filter to remove insoluble particle. MTBE (75ml) was added to clear methanol solution at about 45-50°C. Reaction mass was then cooled to about 25-30°C and stirred for 16h. The reaction mass was cooled 0-5°C and stirred for 2h. Reaction was filtered, solid was washed with MTBE and dried in vacuum trey dryer at about 40-45°C. Yield: lOg; HPLC purity: 99.94%; Imp B : 0.01%.

[0108] Comparative example 1: Preparation of methyl l-acetyl-3-[ethoxy(phenyl)methylidene]-2-oxo-2, 3-dihydro-X*H*-indole-6-carboxylate (V)

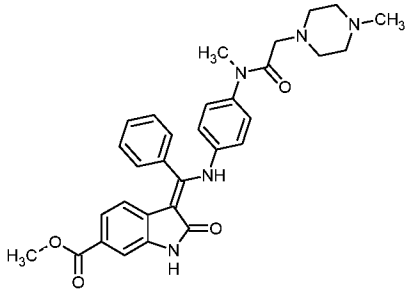
A mixture of compound VI (20g), acetic anhydride (72ml), triethyl ortho benzoate (117.27gm) was stirred at about 120-130°C for about 12h. Low boiler was distilled out and again stirred at about 120°C to about 130°C for about 3h. Reaction was cooled to about 80°C and reaction mass was concentrated under vacuum. MTBE was added to the residue and stirred for 1h at about 20°C-to about 25°C. The reaction mass was filtered, solid was washed with MTBE and dried in vacuum tray dryer at about 40°C to about 50°C. Yield: 18.2g; HPLC purity: 83.67%; Imp A : 0.22%

[0109] Comparative example 2 : Preparation of nintedanib

A mixture of compound V (5g) and N-methyl-2-(4-methyl piperazin-l-yl)-N-(4-nitrophenyl)acetamide (7.54g) in DMF (25ml) was stirred at about 65°C to about 70°C for about 4h. The reaction mixture was cooled to about 25-30°C, piperidine (3.15ml) was added and stirred for about 5h. Water was added to the reaction mass and stirred for lh. The reaction mass was filtered, solid was washed with DMF and dried at about 45°C to about 50°C. Yield: 4.8g; HPLC purity: 91.56%; Imp B : 0.20%.

WE CLAIM:

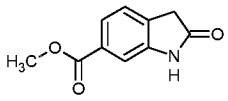
1. A process for the preparation of nintedanib, a compound of formula I,



I

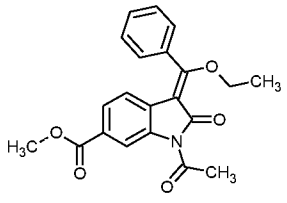
or a salt thereof, comprising the steps of:

a) reacting a compound of formula VI,



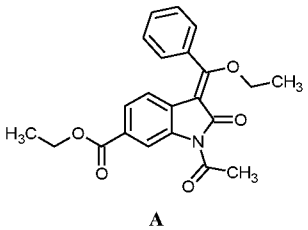
VI

with acetic anhydride and triethyl orthobenzoate to obtain a compound of formula V,



V ; and

b) subjecting the compound of formula V to treatment with a solvent system selected from the group consisting of Ci-C $_6$ amide, Ci-C $_6$ ester, Ci-C $_6$ carboxylic acid, C2-C6 carboxylic anhydride, Ci-C $_6$ aliphatic ether, Ci-C $_6$ haloalkane, C6-C12 aromatic hydrocarbon, Ci-C $_6$ alcohol or mixtures thereof, to obtain a compound of formula V, wherein the level of impurity, the compound of formula A,

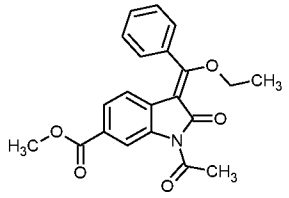


A

is less than 0.15% w/w of the compound of formula V, as determined by HPLC.

2. The process as claimed in claim 1, wherein the compound of formula V is obtained in crystalline form.

3. The process as claimed in claim 2, wherein the compound of formula V,



V

,

is in crystalline form characterized by X-ray powder diffraction (XRPD) spectrum having characteristic peak reflections at about 8.2, 11.2, 16.5 and 25.5±0.2° 2Θ.

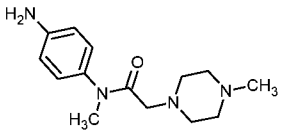
4. The process as claimed in claim 1, wherein treatment with a solvent system comprises recrystallizing from a solvent system or slurrying in a solvent system at ambient temperature or at higher temperature.

5. The process as claimed in claim 1, wherein the solvent system is selected from the group consisting of dimethylformamide (DMF), ethyl acetate, methanol, dichloromethane (DCM), acetic acid, acetic anhydride, toluene, methyl t-butyl ether (MTBE) or mixtures thereof.

6. The process as claimed in claim 5, wherein the solvent system is a mixture of toluene and methanol.

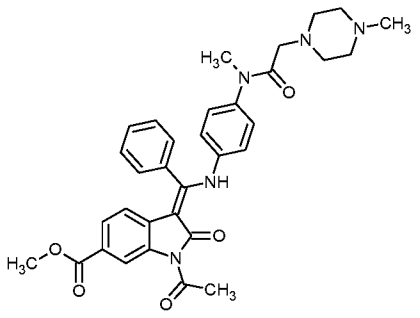
7. The process as claimed in claim 2, further comprising the steps of:

i) reacting the compound of formula V with a compound of formula IV,



IV

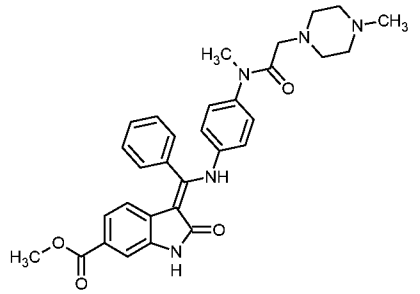
to obtain a compound of formula III,



III

;

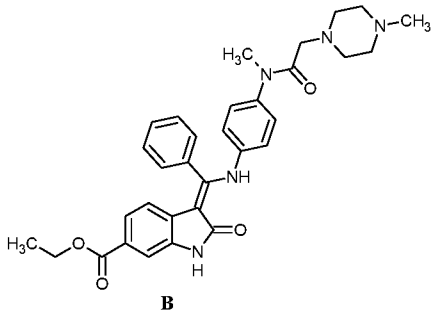
ii) deprotecting the compound of formula III with piperidine in an alcoholic solvent to obtain nintedanib, the compound of formula I,



I

,

wherein the level of impurity, the compound of formula B,



B

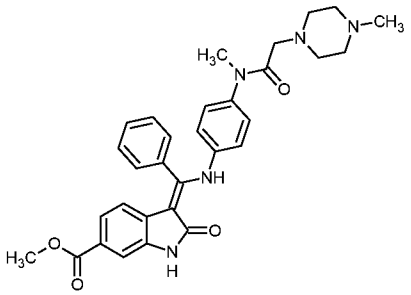
is less than 0.15% w/w of nintedanib, the compound of formula I, as determined by HPLC.

8. The process as claimed in claim 7, wherein the alcoholic solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, n-butanol, sec-butanol, isobutanol, t-butanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-l-butanol, 2-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl-l -propanol, 1,1,-dimethyl-l-propanol or mixture thereof.

9. The process as claimed in claim 8, wherein the alcoholic solvent is methanol.

10. The process as claimed in claim 7, further comprising recrystallizing nintedanib, the compound of formula I, in a solvent system selected from the group consisting of Ci-C_6 amine, Ci-C_6 ester,

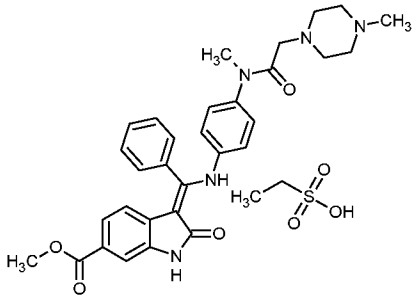
Ci-Ce carboxylic acid, Ci-C_6 carboxylic anhydride, Ci-C_6 aliphatic ether, C1-C4 haloalkane, C_6-C12 aromatic hydrocarbon, Ci-C_6 alcohol, water or mixtures thereof, to obtain nintedanib, the compound of formula I,



I

11. The process as claimed in claim 10, wherein nintedanib, the compound of formula I is recrystallized from the mixture of methanol and water.

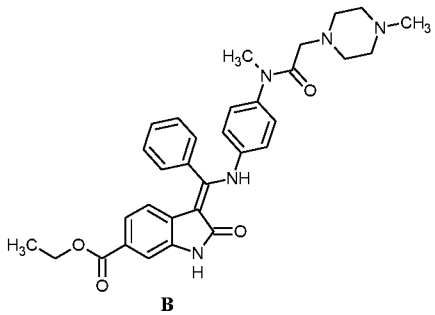
12. The process as claimed in claim 7, wherein nintedanib, the compound of formula I, is further reacted with ethanesulfonic acid to obtain nintedanib esylate hemihydrate, a compound of formula II.



II

13. A method of assessing the purity of nintedanib or a salt thereof or the pharmaceutical composition containing them, by HPLC comprising the steps of:

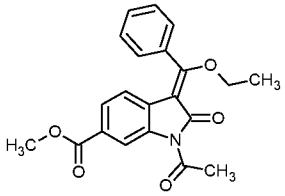
a) providing a standard solution of the compound of formula B; and



B

b) using the solution of step 'a', as a reference marker to determine the level of the compound of formula B.

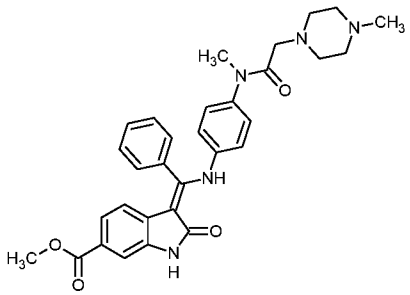
14. A crystalline compound of formula V,



V

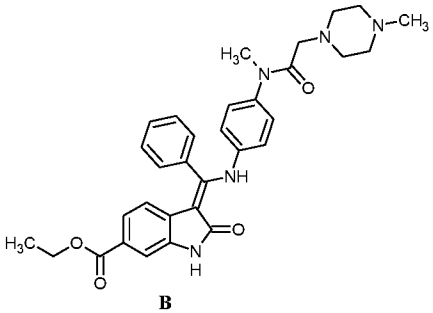
characterized by X-ray powder diffraction (XRPD) spectrum having characteristic peak reflections at about 8.2, 11.2, 16.5 and 25.5±0.2° 2Θ.

15. Nintedanib or a salt thereof, a compound of formula I,



I

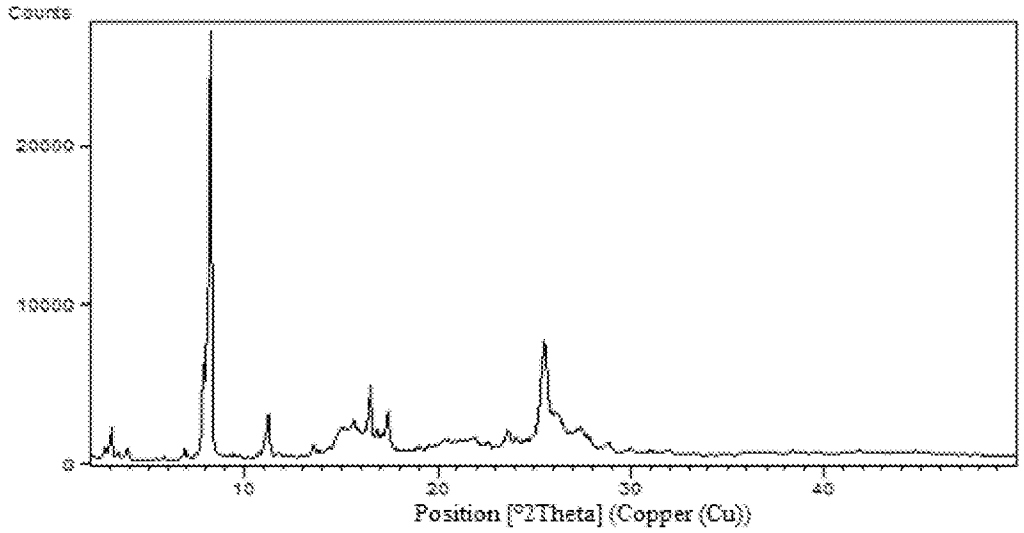
wherein the level of impurity, the compound of formula B,



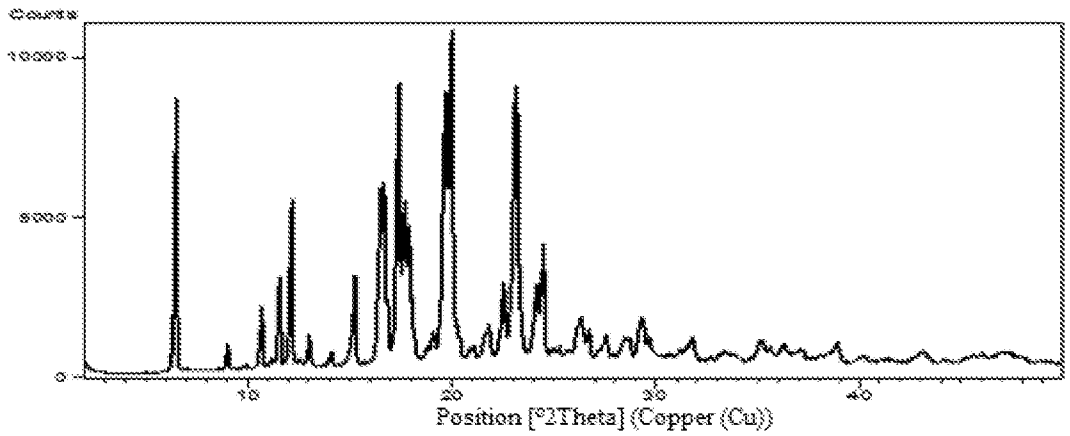
B

is less than 0.15% of nintedanib, as determined by HPLC.

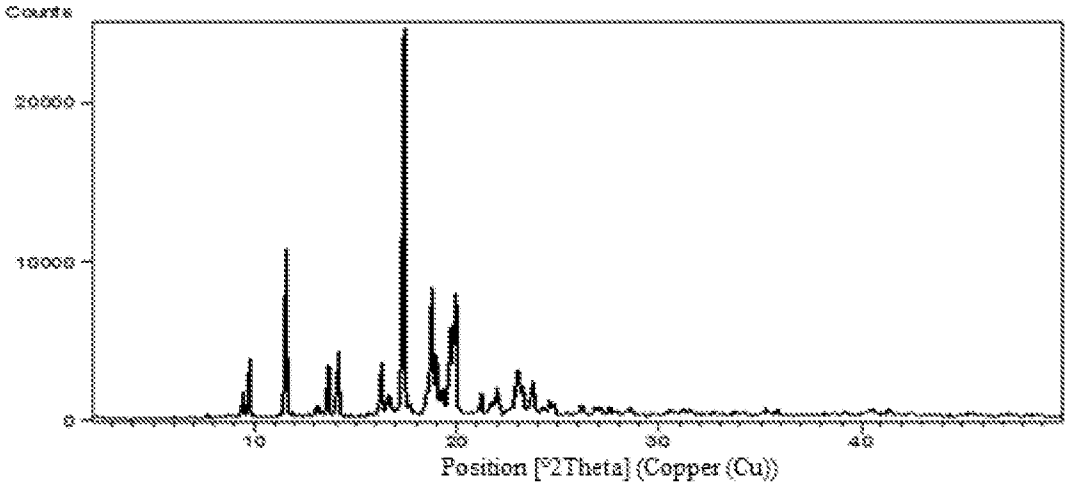
Glenmark Pharmaceuticals Limited **Figure 1**



Glenmark Pharmaceuticals Limited **Figure 2**



Glenmark Pharmaceuticals Limited **Figure 3**



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/056429

A. CLASSIFICATION OF SUBJECT MATTER
C07D209/34 Version=2018.01

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

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)

TotalPatent One, IPO Internal Database

C. DOCUMENTS **CONSIDERED** TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Dl: WO 2017016530 Al (ZENTIVA K.S. [CZ]) (02-02-2017, 2 February 2017) abstract, Examples-2-3, claims-1-3	1-2, 4-9
Y	Examples-4-7	10-13
Y	CN 105461609 A (HANGZHOU SIMBOS PHARM CO LTD) (06-04-2016, 6 April 2016) abstract, page-8, para-0020, claim-1	10-11
X	WO 2004013099 Al (BOEHRINGER INGELHEIM PHARMA et al.) (12-02-2004, 12 February 2004) abstract, page-1, para-10, claim-5	15
Y	page-1, para-10, Example-2, claim-5	12
Y	CN 106841495 A (CHANGZHOU JIADE PHARMACEUTICAL TECH CO LTD) (13-06-2017, 13 June 2017) abstract	13
X	WO 2009071524 A2 (BOEHRINGER INGELHEIM INT et al.) (11-06-2009, 11 June 2009) claims-2, 3, page-17, Example-3, para-10-15	14

☒ Further documents are listed in the continuation of Box C. ☒ 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
16-11-2018	16-11-2018

Name and mailing address of the ISA/	Authorized officer
Indian Patent Office Plot No. 32, Sector 14, Dwarka, New Delhi-110075	Debasish Ghosh
Facsimile No.	Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT / IB2 018/ 056429

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of docmrieut, with indication, where appropriate, of the relevant passages	Relevant to claim No.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT / IB2 018/ 056429

Citation	Pub. Date	Family	Pub. Date
Wo 2017016530 Al	02-02-2017	CN 107820487 A	20-03-2018
		EP 3328831 Al	06-06-2018
		US 2018215735 Al	02-08-2018
		CZ 20150527 A3	08-02-2017
Wo 2004013099 Al	12-02-2004	EP 1527047 Al	04-05-2004
		JP 2005535684 A	24-11-2005
		CN 1671660 A	21-09-2005
		AU 2003254376 Al	23-02-2004
wo 2009071524 A2	11-06-2009	EP 2229360 A2	22-09-2010
		CA 2705490 Al	11-06-2009
		CN 101883755 A	10-11-2010
		AU 2008333287 Al	11-06-2009

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/056429

Box No. II Observations where certain **claims** were foand **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.: 3
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:
The preamble of the claim 3 reveals process while the said claim is being drafted with the only feature of the product. A process claim should emphasize on the process steps rather on the product. Hence, the said claim does not require an international search as per PCT Article 6.

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

Box **No.** Ill 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:
The claims of the alleged invention reveal following groups of invention-

Group (1): Claims 1-12, 14

Group (2): Claim 13

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 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 ihe claims; it is covered by claims Nos.:

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 ihe invitation.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/IB2018/056429

Continuation of Observations where unity of invention is lacking (Box III)

Group (3): Claim 15

Subject-matters of Group (1):

the preparation of nintedanib & crystalline form of the intermediate of the preparation of nintedanib

Subject-matter of Group (2) :

the method of assessing the purity of nintedanib or a salt by HPLC

Subject-matter of Group (3) :

nintedanib or it 's salt form

Observation :

WO 2017016530 Al reveals the compound of formula (1), known under the generic name of nintedanib (claim-1).

The common link among the claims of the present application is nintedanib which is already disclosed in WO 2017016530 Al. Therefore, the common general technical feature present among the claims cannot be considered as a special technical feature.