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HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))

(54) Title: AN IMPROVED METHOD FOR THE SYNTHESIS AND PURIFICATION OF PIRFENIDONE

(57) Abstract: The present invention provides a process for the synthesis of pirferidone by reacting 5-methyl-2-pyridone with a low quantity of bromobenzene in a low quantity of polar aprotic solvent in the presence of a copper catalyst and a base. The present invention also provides a method for purification of pirfenidone by initially synthesizing an acid adduct of pirfenidone from crude pirfenidone and then recovering pirfenidone with increased purity.

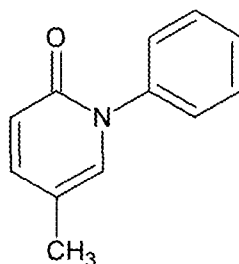


WO 2016/122420 A1

AN IMPROVED METHOD FOR THE SYNTHESIS AND PURIFICATION OF PIRFENIDONE

This invention relates to an improved process for the preparation and purification of pirfenidone.

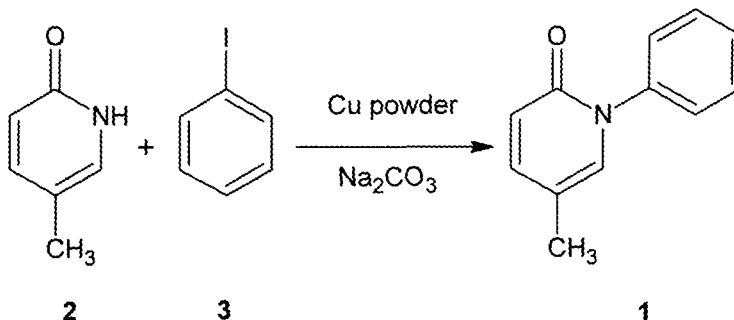
Pirfenidone (1) is a small molecule whose chemical name is 5-methyl-1-phenyl-2-(1H)-pyridone. Its use for the manufacture of a medicament for the preparation and/or prevention of fibrotic lesions is first described in EP0383591.

**1****BRIEF DESCRIPTION OF THE PRIOR ART**

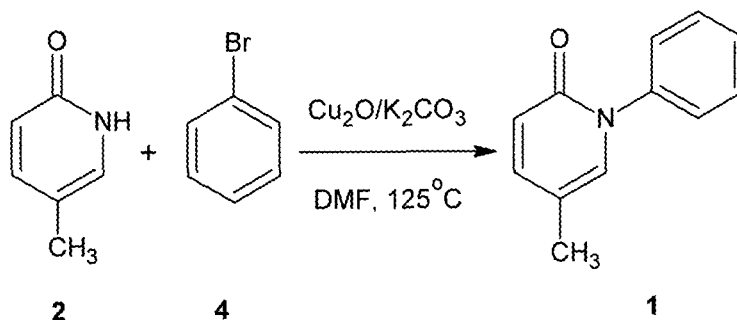
Pirfenidone is typically synthesized by copper catalyzed N-arylation of 5-methyl-2-pyridone with bromobenzene or iodobenzene, generally at elevated temperatures. There are generally two approaches to the copper catalyzed synthesis of pirfenidone starting from 5-methyl-2-pyridone:

- i. The use of iodobenzene or bromobenzene as solvent.
- ii. The use of polar aprotic solvent, such as DMF, in the presence of excess bromobenzene. In this approach, solvent DMF presumably also acts as a supporting ligand for copper catalyst.

US3974281 and US3839346 describe the preparation of pirfenidone (1) starting from 5-methyl-2-pyridone (2) in the presence of anhydrous sodium carbonate, copper powder, iodobenzene (3), under reflux for 18 hours, furnishing crude pirfenidone (1), which after then crystallized in benzene and petroleum ether and obtained in a yield of 85%.



EP2440543 explains the synthesis of pirfenidone (1) from 5-methyl-2-pyridone (2) and excess bromobenzene (1.8 mol eq) (4) with Cu_2O catalysis to obtain crude pirfenidone in 85% yield:



5 Those above mentioned methods have some major drawbacks:

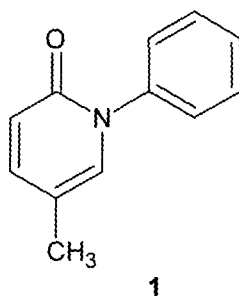
- i. When the iodobenzene or bromobenzene reagent is used as solvent or in excess quantities, their removal from the initially obtained crude product requires the use of large amounts nonpolar solvents; like heptane, hexane, pentane or petroleum ether. These solvents have the proper solubilizing power for iodo- or bromobenzene residues whereas they only poorly dissolve the product pirfenidone. Besides, the use of excess reagents and large amounts of solvents leads to higher manufacturing costs and environmental problems. Thus it would be highly advantageous minimizing the quantities of these reagents and solvents both from economic and environmental point of view.
- 10 ii. When the reaction is run in the presence of polar aprotic solvents like DMF like in EP2440543, the product isolation gets complicated, directly affecting the product yields. In order to prevent the product loss due to the presence of DMF, it must be removed by aqueous washes prior to crude product isolation. Since pirfenidone presents remarkable aqueous solubility, product loss during extractions to the aqueous phases is inevitable unless the aqueous phases are saturated with salts. However, using saturated salt solutions for aqueous extractions would prevent the effective removal of DMF from the organic phase that in turn affects the product isolation yield. In fact, EP244053 teaches that an optimal sodium chloride solution is high enough to minimize the loss of pirfenidone in the aqueous layer, but low enough to allow maximum amount of DMF in the aqueous layer. Thus it would be highly advantageous to have a method that utilizes
20 minimum amount of polar organic solvents like DMF to increase the yields and simplify the manufacturing process.
- 25 iii. Pirfenidone is a small neutral molecule. The absence of acidic or basic sites prevents the isolation and purification of pirfenidone through the formation of salts. As mentioned above, means for isolation or purification of pirfenidone is limited to solvent

precipitations/crystallizations. Thus it would be highly advantageous to have additional means of purification for pirfenidone free from reagents, colored impurities and residual solvents etc.

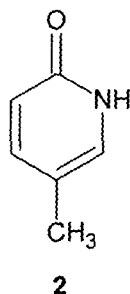
To overcome the disadvantages of the state of art, the present invention provides a process for the synthesis of pirfenidone by reacting 5-methyl-2-pyridone with a low quantity of bromobenzene in a low quantity of polar aprotic solvent in the presence of a copper catalyst and a base. The present invention also provides a method for purification of pirfenidone by initially synthesizing an acid adduct of pirfenidone from crude pirfenidone and then recovering pirfenidone with increased purity.

DETAILED DESCRIPTION OF THE INVENTION

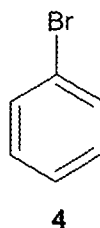
The present invention is a process for the synthesis of pirfenidone (1),



said process comprising the steps of; reacting 5-methyl-2-pyridone (2),



with bromobenzene (4),



in a polar aprotic solvent, in the presence of Cu(I) or Cu(II) salts and a base, wherein bromobenzene (3) is used as 1 to 1,5 mole equivalent of 5-methyl-2-pyridone (2) and the

polar protic solvent is used as 0,1-1 volume equivalent with respect to weight of 5-methyl-2-pyridone (2).

According to the invention, 5-methyl-2-pyridone (2) is reacted with preferably 1,2 - 1,4 mole equivalent of bromobenzene.

- 5 According to the invention the polar aprotic solvent can be selected from dimethylsulfoxide (DMSO), hexamethylphosphoramide (HMPA) and their mixtures thereof. In a preferred embodiment the reaction is carried out in DMSO wherein DMSO is used as 0,1-1 volume equivalent with respect to weight of 5-methyl-2-pyridone (2). In a more preferred embodiment the reaction is carried out in 0,5 volume equivalent DMSO with respect to weight of 5-methyl-
10 2-pyridone (2).

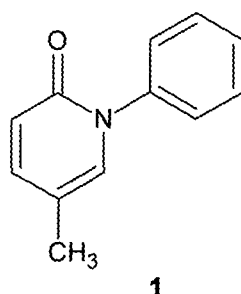
According to the invention the reaction is carried out in the presence of Cu(I) or Cu(II) salts, such as CuCl, CuBr, CuI, Cu₂O, Cu(OAc), Cu(OAc)₂. In a preferred embodiment the reaction is carried out in the presence of Cu₂O or CuBr, wherein the appropriate Cu salt is used in catalytical amount which means that less than stoichiometric amount.

- 15 According to the present invention, the reaction can be carried out in the presence of a base selected from K₂CO₃, Na₂CO₃, Na₃PO₄, K₃PO₄. In a preferred embodiment the reaction is carried out in the presence K₂CO₃. In a more preferred embodiment the reaction is optionally carried out in the presence of an additional base wherein the additional base is 0,05-0,30 mole equivalent of sodium acetate (NaOAc), preferably 0,2 mole equivalent of NaOAc with
20 respect to 5-methyl-2-pyridone (2).

According to the invention the reaction is carried out at temperatures sufficient to form pirfenidone, preferably >100°C, more preferably >120°C or most preferably at 135-140°C.

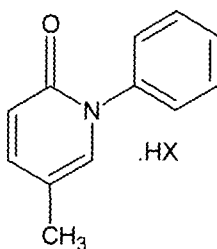
According to the invention pirfenidone can be isolated from the reaction mixture by traditional methods.

- 25 Another embodiment of the present invention is a process for the purification of pirfenidone (1),



wherein said process comprising the steps of;

a) formation of an acid adduct compound (5)



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by reacting pirfenidone or crude pirfenidone with HX, wherein HX is a strong acid with $pK_a < 0$ and,

b) recovering the pirfenidone (1) from acid adduct compound (5).

Crude pirfenidone is unpurified isolated reaction product with any level of purity.

Being a neutral molecule, pirfenidone can only form adducts with strong acids. Acids with $pK_a > 0$ was unable to induce adduct formation. Acids with $pK_a < 0$ are useful acids for adduct formation and isolation. For example, pirfenidone cannot form adducts with acetic acid and phosphoric acid.

According to the invention, suitable acids that may form stable adducts with pirfenidone (1) in step a are acids with $pK_a < 0$. Preferably suitable acids used in adduct formation are selected from the group of sulfuric acid (H_2SO_4), hydrochloric acid (HCl), hydrobromic acid (HBr), hydroiodic acid (HI), and methanesulfonic acid (MsOH).

According to the invention, strong acid that may form stable adducts with pirfenidone (1) in step a is preferably H_2SO_4 .

According to the invention, the acid adduct formation reaction in step a can be carried out in a solvent selected from acetone, tetrahydrofuran (THF), acetic acid, ethyl acetate, dichloromethane and their mixtures or their mixtures with nonpolar solvents, such as toluene. In a preferred embodiment the reaction is carried out in acetone.

According to the invention, recovery of pirfenidone (1) from pirfenidone adduct (5) in step b can be carried out in a solvent in the presence of a base which is basic enough to neutralize the adduct of formula (5). In a preferred embodiment the base is NaOH.

According to the invention, the solvent of step b can be water in which pirfenidone will precipitate after neutralization of the acid adduct form with a suitable base. The solvent can

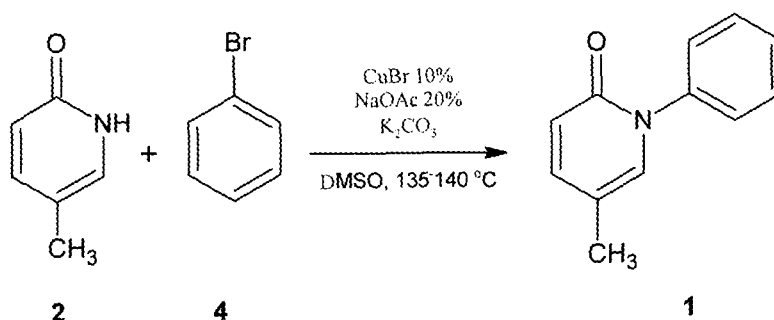
also be an organic solvent such as methanol in which pirfenidone acid adduct can be neutralized.

The present invention provides a process for the synthesis and purification of pirfenidone free of major drawbacks of the processes presented in the prior art:

- 5 a. The use low quantity of bromobenzene (4) is more cost effective and environmentally friendly. The lower quantities of residual bromobenzene (4) in the crude pirfenidone (1) product simplify the isolation and purification process and affect the yields in a positive manner.
 - b. Easy removal of low quantities of DMSO with aqueous washes simplifies the process.
 - 10 c. The lack of considerable quantities of residual DMSO after aqueous washes also simplifies the crude product isolation and has a positive impact on the yields.
 - c. Formation of stable adducts with strong acids provided a strong leverage for the quick and quantitative formation of pirfenidone adduct through which non-polar impurities and residual bromobenzene was removed completely together with colored impurities.
 - 15 Pirfenidone acid adduct compounds are highly soluble in water and soluble in alcohols. Thus, pirfenidone can be recovered easily by dissolving it in a proper media, final filtration followed by neutralization with a base. This process also serves as a final purification of pirfenidone to get the product in a pharmaceutically acceptable purity and form.
- 20 The following examples will illustrate the synthesis, isolation, formation of acid adducts of pirfenidone and recovery of pure pirfenidone from the adduct. These examples should not, however, be construed as limiting the invention:

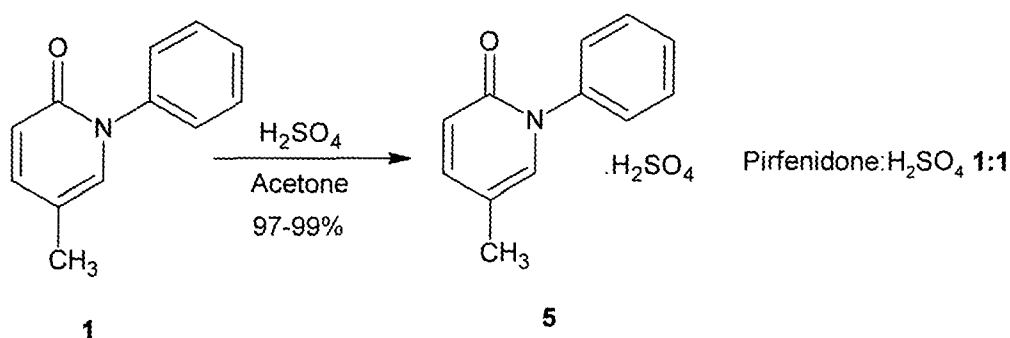
Examples:

A) Synthesis of Crude Pirfenidone:



5-methyl-2-pyridone (2) (20 g, 0,18 mol), K_2CO_3 (30,4 g, 0,22 mol), NaOAc (3 g, 0,036 mol, 0,2 mol eq), CuBr (2,62 g, 0,018 mol, 0.1 mol eq) [or Cu_2O (1,29 g, 0,05 mol eq)], Bromobenzene (4) (40,28 g, 0,26 mol, 1,4 mol eq) and DMSO (10 mL, 0,5 V eq) was placed in a round bottom flask under a nitrogen atmosphere. Flask was heated to 135-140°C and stirred at this temperature for 6-8 h. After the completion of the reaction according to HPLC analysis, reaction medium was cooled down to about 60 °C. Then, 100 mL water was added to the reaction mixture followed by 4 mL NH_4OH and 100 mL toluene. The resulting mixture was stirred for 15 min and the phases were separated. Aqueous phase was extracted with 2x50 mL toluene then organic phases were combined (all extractions were carried out at about 60°C). Combined organic phases were filtered over a bed of celite after treatment with charcoal. After evaporation of toluene to the dryness, 36,3 g crude pirfenidone was obtained. Crude pirfenidone purity is >99,5% (HPLC analysis, UV detector 310 nm).

B) Formation of Pirfenidone: H_2SO_4 adduct:



85 g pirfenidone (1) was placed in round bottom flask followed by 3 volume equivalent of acetone and heated to 40-45°C. After complete dissolution of, 1.0-1.1 mol equivalent of H_2SO_4 was added slowly through a dropping funnel so as to keep the reaction temperature below 50°C. After completion of the addition, an extra 1 volume equivalent of acetone was added to the reaction mixture through the addition funnel. Reaction mixture was stirred for 3-4 hr at room temperature, then cooled to ~-5°C and further stirred for 3-4 hours. Precipitated product was filtered, washed with 1 volume equivalent cold acetone and dried in an oven at 50-60°C to furnish pirfenidone adduct in 97-99% yield based on a 1:1 Pirfenidone: H_2SO_4 .

C) Recovery of Pirfenidone from pirfenidone: H_2SO_4 adduct:

24 g pirfenidone adduct (5) was placed in a round bottom flask together with 2 volume equivalent of MeOH. Mixture was heated to 40-45°C and the starting material was dissolved completely. A separately prepared solution of 2.0-2.2 mol equivalent NaOH dissolved in 4 volume equivalent of MeOH was slowly added during which formation and precipitation of

insoluble inorganic salts was observed. After completion of addition, mixture was further stirred for 15-20 min and filtered to obtain a clear solution of pirfenidone. This resulting clear solution can be evaporated and used for further purification if necessary or can be evaporated to dryness to get a solid product. For example, in our case, to the residue was added 2 volume equivalent water (based on the expected product) and heated to ~80°C to obtain a two phase system or a clear solution based on the amount of residual MeOH in the original residue. Afterwards, solution was cooled to ambient temperature, then to ~-5°C for 4-5h. Then product was filtered, washed with cold water and dried in an oven ~50°C to obtain 14.4-14.7 g white product (90-92% based on the pirfenidone: H₂SO₄ 1:1 adduct).

D) Formation of Pirfenidone: H₂SO₄ adduct from crude Pirfenidone:

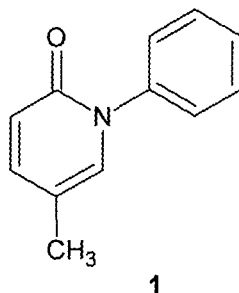
36,3 g crude pirfenidone (from example A) was placed in round bottom flask followed by 3 volume equivalent of acetone and heated to 40-45°C. After complete dissolution, 1.0-1.1 mol equivalent of H₂SO₄ was slowly added through a dropping funnel so as to keep the reaction temperature below 50°C. After the completion of the addition, an extra 1 volume equivalent of acetone was added to the reaction mixture through the addition funnel. Reaction mixture was allowed to cool to room temperature and stirred for 1 hr, then cooled to ~-5°C and further stirred for 4-5 hr at this temperature. Precipitated product was filtered, washed with 1 volume equivalent cold acetone and dried in an oven at 50-60°C to furnish 48 g pirfenidone adduct in 94% overall yield and 99.8% purity starting from 5-methyl-2-pyridone. The obtained product is a white solid completely free from Bromobenzene.

E) Formation of pure Pirfenidone:

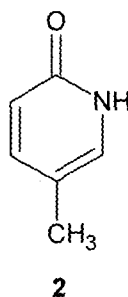
Pirfenidone: H₂SO₄ adduct obtained in example D was treated as described in example C to obtain 29,3 g pure Pirfenidone in 86% overall yield starting from 5-methyl-2-pyridone and >99,9% purity.

CLAIMS

1. A process for the synthesis of pirfenidone (1),

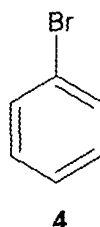


said process comprising the steps of; reacting 5-methyl-2-pyridone (2),



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with bromobenzene (4),



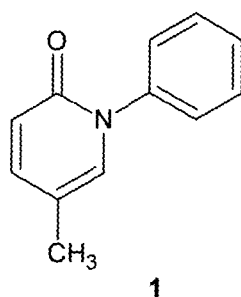
in a polar aprotic solvent, in the presence of Cu(I) or Cu(II) salts and a base, wherein bromobenzene (3) is used as 1 to 1,5 mole equivalent of 5-methyl-2-pyridone (2) and the polar protic solvent is used as 0,1-1 volume equivalent with respect to weight of 5-methyl-2-pyridone (2).

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2. A process according to claim 1, wherein 5-methyl-2-pyridone (2) is reacted with preferably 1,2 - 1,4 mole equivalent of bromobenzene.
3. A process according to claims 1, wherein the polar aprotic solvent is selected from DMSO, HMPA and mixtures thereof.
4. A process according to claim 3, wherein the polar aprotic solvent is DMSO.
5. A process according to claim 1, wherein DMSO is used as 0,5 volume equivalent with respect to weight of 5-methyl-2-pyridone (2).

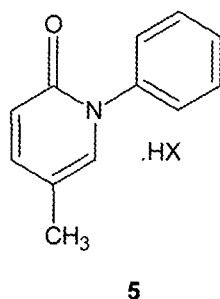
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6. A process according to claim 1, wherein the Cu(I) or Cu(II) salt is selected from CuCl, CuBr, CuI, Cu₂O, Cu(OAc), Cu(OAc)₂, preferably Cu₂O or CuBr.
7. A process according to claim 1, wherein the base is selected from K₂CO₃, Na₂CO₃, Na₃PO₄, K₃PO₄, preferably is K₂CO₃.
8. A process according to claim 7, wherein the reaction is optionally carried out in the presence of an additional base wherein the additional base is 0,05-0,30 mole equivalent of NaOAc, preferably 0,2 mole equivalent with respect to 5-methyl-2-pyridone (2).
9. A process according to claim 1, wherein the reaction is carried out at temperatures sufficient to form pirfenidone, preferably >100°C, more preferably >120°C or at 135-140°C.
10. A process for the purification of pirfenidone (1),



wherein the said process comprising the steps of;

a) formation of an acid adduct compound (5)

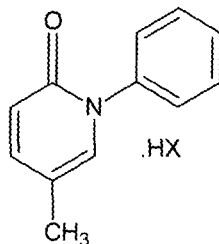


by reacting crude pirfenidone with a strong acid HX, wherein HX is a strong acid with pKa<0 and,

b) recovering the pirfenidone (1) from acid adduct compound (5).

11. A process according to claim 10, wherein the strong acid is selected from the group of H₂SO₄, HCl, HBr, HI, and MsOH.
12. A process according to claim 11, wherein the strong acid HX is H₂SO₄.
13. A process according to claim 10-12, wherein step a is carried out in an organic solvent.
14. A process according to claim 13, wherein the solvent is selected from acetone, THF, acetic acid, ethyl acetate, dichloromethane and their mixtures or their mixtures with nonpolar solvents.

15. A process according to claim 10, wherein step b is carried out in the presence of a base.
16. A process according to claim 15, wherein the base is NaOH.
17. An acid adduct form of pirfenidone of formula (5), wherein HX is a strong acid with $pK_a < 0$.



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18. The use of acid adduct form of pirfenidone of formula (5) for the preparation of pirfenidone.

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INTERNATIONAL SEARCH REPORT

International application No

PCT/TR2015/000030

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D213/64
 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

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, BEILSTEIN Data, BIOSIS, 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.
Y	WO 2010/141600 A2 (INTERMUNE INC [US]; RADHAKRISHNAN RAMACHADRAN [US]; CYR MIKE [US]; BOU) 9 December 2010 (2010-12-09) cited in the application paragraph [0053] - paragraph [0055]; claims	1-9
Y	WO 03/014087 A1 (ASAHI GLASS CO LTD [JP]; TANIGUCHI TOMOKO [JP]; HAYASHI KAZUHIKO [JP];) 20 February 2003 (2003-02-20) page 2, 3rd line from bottom: molar ratio bromobenzole/methylpyridone = 1-50 / 1 page 3, 3rd paragraph: polar aprotic solvents like DMSO ratio solvent/methylpyridone = 0.5-20ml / 1g; example 1	1-9



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

21 April 2015

Date of mailing of the international search report

26/06/2015

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Stroeter, Thomas

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2015/000030

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.:

1-9

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.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ TR2015/ 000030

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-9

Process for the synthesis of pirfenidone by reacting
5-methyl-2-pyridone and bromobenzene

2. claims: 10-18

Process for the purification of pirfenidone via formation of
an acid adduct of pirfenidone as well as said acid adduct
and the use thereof for the preparation of pirfenidone

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/TR2015/000030

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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