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(54) **Title:** PROCESS FOR THE PREPARATION OF ABAMETAPIR AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

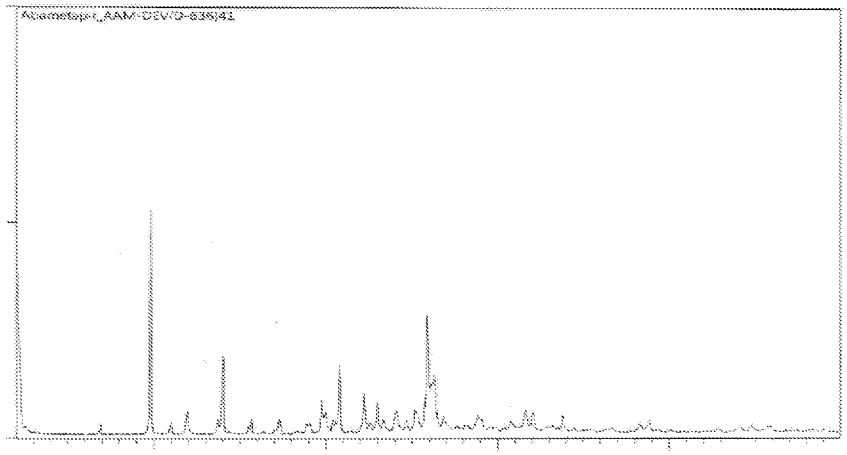

Figure 1

(57) **Abstract:** The present invention relates to process for the preparation of Abametapir. The present 5 invention further relates to Abametapir salts and their preparation thereof.

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[Continued on next page]

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PROCESS FOR THE PREPARATION OF ABAMETAPIR AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

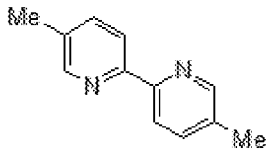
This application claims the benefit of Indian Provisional Patent Application IN201841009214, filed on 13 March 2018, hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to process for the preparation of Abametapir. The present invention further relates to Abametapir salts and their preparation thereof.

BACKGROUND OF THE INVENTION

Abametapir is chemically known as 5-methyl-2-(5-methylpyridin-2-yl)pyridine having the structure shown in formula-I.



Formula-I.

Abametapir is a Metalloprotease inhibitor and chelating agent, targeting proteases essential to insect hatching and survival. It affects multiple proteases essential to insect hatching and survival by chelating heavy metal ions, targeting all stages of the insect life cycle; it is therefore expected to be effective as a single application. The product is in phase III clinical development in the US.

Japanese patent JP1577703 first discloses a process for the preparation of Abametapir.

Tetrahedron Letters Vol.39 Year 1998 Pg 2559 discloses process for the preparation of Abametapir comprising a mixture of 2-Bromo-5-Methyl pyridine, $Pd(OAc)_2$ / nBu_4NBr DMF/H_20, isopropanol and K_2CO_3 it gives final compound.

The journal of Organic Letters Vol. 02 Year 2000 Pg 3373-3376 discloses a process for the preparation of different methyl-substituted 2,2-bipyridines such as monomethyl-substituted, dimethyl-substituted. This process comprising a mixture of 2-tributylstannyl-picoline or 2-tributylstannyl-pyridine, 2-bromo-picoline or 2-bromo-pyridine, and triphenylphosphine-palladium(0) in 65 mL of toluene was refluxed under nitrogen for 48h. The resulting brown mixture was evaporated in vacuum, and the dark, muddy liquid was dissolved in dichloromethane. The organic phase was washed with aqueous HCl. To remove the product from solution the combined aqueous layers were transferred dropwise in aqueous ammonia (10%) under cooling. The resulting oil was extracted with dichloromethane. The organic phases were washed with ammonia and water, and the solvent was removed. The resulting suspension was purified by column chromatography.

J. Hassan et al. : C. R. Acad. Sci. Paris, Se´rie IIc, Chimie : Chemistry 3 (2000) 517–521 discloses process for the preparation of Abametapir comprising a mixture of base, palladium acetate, tetra-n-butylammonium bromide and 2-Bromo-5-Methyl pyridine in a solvent or a mixture of DMF:H_2O was stirred under nitrogen atmosphere for a few minutes at 105 °C in the case of toluene as solvent or at 115 °C in the case of DMF. Isopropanol was added. After cooling to room temperature, water and ether were added. The organic phase was washed with water and dried over MgSO4. The solvent was evaporated under vacuum. The biphenyl product was purified by preparative thin layer chromatography or recrystallization.

Tetrahedron Letters V.44 Year 2003 Pg 2935 discloses process for the preparation of Abametapir comprising a mixture of 2-Bromo-5-Methyl pyridine, $PdCl_2(PPh_3)_2$, DMF, isopropanol and K_3PO_4 it gives final compound.

The present inventors prepared Abametapir by an efficient, economical and industrially feasible process with good yields.

OBJECT AND SUMMARY OF THE INVENTION

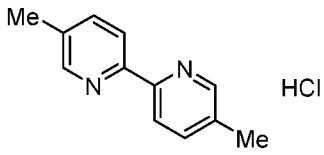
The main aspect of the present invention is to provide a process for the preparation of Abametapir.

In one aspect, the present invention is to provide a process for the preparation of abametapir comprising the steps of:

a) forming a reaction mixture of 2-Bromo-5-methylpyridine, ethylene glycol, a base and a catalyst,
b) optionally adding a second solvent,
c) heating the reaction mixture,
d) extracting the reaction mixture,
e) isolating Abametapir.

In another aspect, the present invention is to provide Abametapir hydrochloride, Abametapir maleate, Abametapir oxalate, Abametapir sulfate and Abametapir tartarate salts from Abametapir and their preparation thereof.

In another aspect, the present invention is to provide a process for the preparation of Abametapir hydrochloride salt of formula (II)

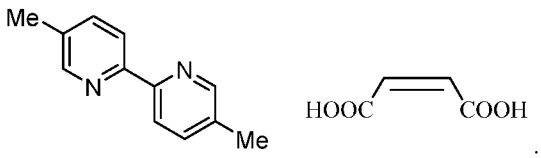


Formula (II)

comprising the steps of:

a) dissolving Abametapir in an organic solvent,
b) purging Hydrogen chloride,
c) isolating Abametapir hydrochloride salt of formula (II).

In yet another aspect, the present invention is to provide a process for the preparation of Abametapir maleate salt of formula (III)



Formula (III)

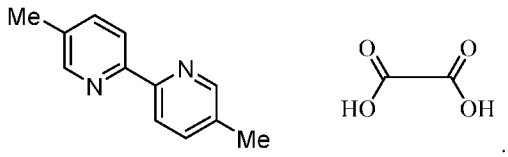
comprising the steps of:

a) dissolving Abametapir in an organic solvent,

b) adding maleic acid,

c) isolating Abametapir maleate salt of formula (III).

In yet another aspect, the present invention is to provide a process for the preparation of Abametapir oxalate salt of formula (IV)



Formula (IV)

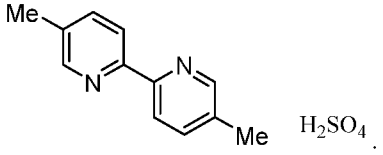
comprising the steps of:

a) dissolving Abametapir in an organic solvent,

b) adding oxalic acid,

c) isolating Abametapir oxalate salt of formula (IV).

In yet another aspect, the present invention is to provide a process for the preparation of Abametapir sulfate salt of formula (V)



Formula (V)

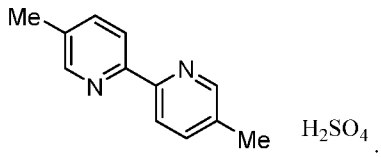
comprising the steps of:

a) dissolving Abametapir in an organic solvent,

b) adding sulfuric acid,

c) isolating Abametapir sulfate salt of formula (V).

In yet another aspect, the present invention is to provide a process for the preparation of Abametapir Tartarate salt of formula (VI)



Formula (VI)

comprising the steps of:

a) dissolving Abametapir in an organic solvent,

b) adding tartaric acid,

c) isolating Abametapir Tartarate salt of formula (VI).

Further aspects of the present invention together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of embodiments which are shown in the accompanying drawing figures wherein:

1. Fig. 1 is an X-ray powder diffractogram of Abametapir HCl salt.
2. Fig. 2 is an X-ray powder diffractogram of Abametapir Maleate salt.
3. Fig. 3 is an X-ray powder diffractogram of Abametapir Oxalate salt.
4. Fig. 4 is an X-ray powder diffractogram of Abametapir Sulfate salt.
5. Fig. 5 is an X-ray powder diffractogram of Abametapir Tartarate salt.
6. Fig. 6 is an X-ray powder diffractogram of Abametapir free base.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for the preparation of Abametapir and its pharmaceutically acceptable salts.

In one embodiment, the present invention relates to a process for the preparation of abametapir comprising the steps of:

a) forming a reaction mixture of 2-Bromo-5-methylpyridine, ethylene glycol, a base and a catalyst,
b) optionally adding a second solvent,
c) heating the reaction mixture,
d) extracting the reaction mixture,
e) isolating Abametapir.

According to the present invention, a mixture of 2-Bromo-5-methylpyridine, ethylene glycol, an inorganic base selected from sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonte, a catalyst such as palladium carbon, optionally a second solvent selected from 1,2-dimethoxy ethane or 1,4-dioxane are heated to about 70 to 110°C. On completion of the reaction, the reaction mixture may be diluted with water and ethyl acetate followed by filteration to remove palladium. The resultant filtrate may be extracted with ethyl acetate and the combined organic layers may be distilled under reduced pressure to obtain abametapir.

According to the present invention, the abametapir obtained above may be recrystallized from aqueous isopropyl alcohol.

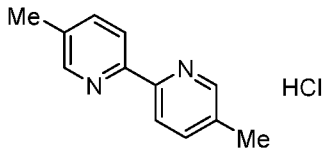
The process according to the present invention has advantages over the prior processes which include but not limited to:

1. Lesser reaction time (~2 h) when compared to use of Palladium acetate process which would approximately takes 65 hours.
2. Heterogenous catalysis, easy and efficient recovery of palladium.
3. Good and improvised yield

4. High productivity

The present invention further relates to Abametapir hydrochloride, Abametapir maleate, Abametapir oxalate, Abametapir sulfate and Abametapir tartarate salts and their preparation thereof.

In one embodiment, the present invention relates to a process for the preparation of Abametapir hydrochloride salt of formula (II)



Formula (II)

comprising the steps of:

a) dissolving Abametapir in an organic solvent

b) purging Hydrogen chloride

c) isolating Abametapir hydrochloride salt of formula (II).

According to the present invention, Abametapir may be dissolved in an organic solvent selected from ester solvents like methyl acetate, ethyl acetate, propyl acetate or butyl acetate, tetrahydrofuran, acetonitrile, dichloromethane, methonal, isopropyl alcohol, Ethonal, methyl ethyl ketone, methyl isobutyl ether, and methyl isopropyl ether and purged with Hydrogen chloride at ambient temperature. The solid obtained may be filtered to obtain Abametapir hydrochloride salt.

In yet another embodiment, Abametapir hydrochloride prepared according to the present invention is characterized by powder X-ray diffraction as depicted in Fig. 1

In yet another embodiment, Abametapir hydrochloride prepared according to the present invention is characterized by powder X-ray diffraction pattern having peaks at 9.82, 14.01, 19.73, 20.79, 22.22, 25.86, 26.30 and 26.83.

In another embodiment, the present invention relates to a process for the preparation of Abametapir maleate salt Formula (III)

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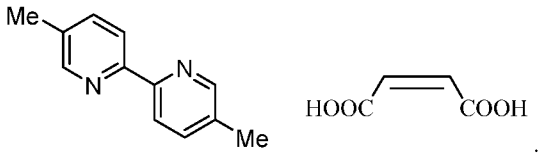


Formula (III)

comprising the steps of:

a) dissolving Abametapir in an organic solvent,

b) adding maleic acid,

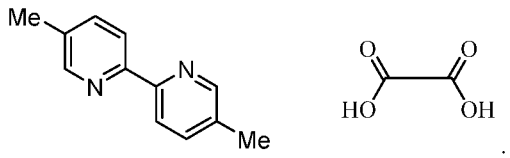
c) isolating Abametapir maleate salt of formula (III).

According to the present invention, Abametapir may be dissolved in an organic solvent selected from ester solvents like methyl acetate, ethyl acetate, propyl acetate or Butyl acetate, tetrahydrofuran, acetonitrile, dichloromethane, methonal, isopropyl alcohol, Ethonal, methyl ethyl ketone, methyl isobutyl ether, and methyl isopropyl ether and added maleic acid. The solid obtained may be filtered to obtain Abametapir maleate salt.

In yet another embodiment, Abametapir maleate prepared according to the present invention is characterized by powder X-ray diffraction as depicted in Fig. 2

In yet another embodiment, Abametapir maleate prepared according to the present invention is characterized by powder X-ray diffraction pattern having peaks at 8.10, 9.31, 13.21, 14.77, 18.67, 20.69, 25.87, 26.73and 28.37.

In another embodiment, the present invention relates to a process for the preparation of Abametapir oxalate salt Formula (IV)



Formula (IV)

comprising the steps of:

a) dissolving Abametapir in an organic solvent,

b) adding oxalic acid,

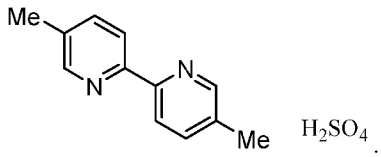
c) isolating Abametapir oxalate salt of formula (IV).

According to the present invention, Abametapir may be dissolved in an organic solvent selected from ester solvents like methyl acetate, ethyl acetate, propyl acetate or Butyl acetate, tetrahydrofuran, acetonitrile, dichloromethane, methonal, isopropyl alcohol, Ethonal, methyl ethyl ketone, methyl isobutyl ether, and methyl isopropyl ether and added oxalic acid. The solid obtained may be filtered to obtain Abametapir oxalate salt.

In yet another embodiment, Abametapir oxalate prepared according to the present invention is characterized by powder X-ray diffraction as depicted in Fig. 3.

In yet another embodiment, Abametapir oxalate prepared according to the present invention is characterized by powder X-ray diffraction pattern having peaks at 8.77, 9.58, 18.36, 19.20, 24.52, 25.28 and 31.68.

In another embodiment, the present invention relates to a process for the preparation of Abametapir sulfate salt Formula (V)



Formula (V)

comprising the steps of:

a) dissolving Abametapir in an organic solvent,

b) adding sulfuric acid,

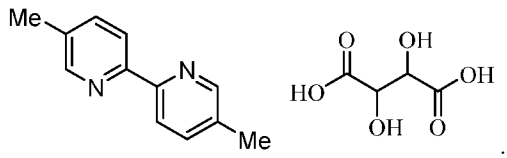
c) isolating Abametapir sulfate salt of formula (V).

According to the present invention, Abametapir may be dissolved in an organic solvent selected from ester solvents like methyl acetate, ethyl acetate, propyl acetate or Butyl acetate, tetrahydrofuran, acetonitrile, dichloromethane, methonal, isopropyl alcohol, Ethonal, methyl ethyl ketone, methyl isobutyl ether, and methyl isopropyl ether and added sulfuric acid. The solid obtained may be filtered to obtain Abametapir sulfate salt.

In yet another embodiment, Abametapir sulfate is is characterized by powder X-ray diffraction as depicted in Fig. 4.

In yet another embodiment, Abametapir sulfate prepared according to the present invention is characterized by powder X-ray diffraction pattern having peaks at 10.23, 16.44, 17.25, 18.02, 20.53, 21.97, 25.70, 26.98 and 28.45.

In another embodiment, the present invention relates to a process for the preparation of Abametapir tartarate salt Formula (VI)



Formula (VI)

comprising the steps of:

a) dissolving Abametapir in an organic solvent,

b) adding tartaric acid,

c) isolating Abametapir tartarate salt of formula (VI).

According to the present invention, Abametapir may be dissolved in an organic solvent selected ester solvents like methyl acetate, ethyl acetate, propyl acetate or Butyl acetate, tetrahydrofuran, acetonitrile, dichloromethane, methonal, isopropyl alcohol, Ethonal, methyl ethyl ketone, methyl isobutyl ether, and methyl isopropyl ether and added tartaric acid. The solid obtained may be filtered to obtain Abametapir Tartarate salt.

In yet another embodiment, Abametapir tartarate is is characterized by powder X-ray diffraction as depicted in Fig. 5.

In yet another embodiment, Abametapir Tartarate prepared according to the present invention is characterized by powder X-ray diffraction pattern having peaks at 9.35, 14.92, 18.80, 21.16, 23.51, 25.22, and 26.38.

According to the present invention, Abametapir salts may be isolated by conventional methods such as filtration, solvent removal by distillation under vacuum etc.

In yet another embodiment, Abametapir is characterized by powder X-ray diffraction as depicted in Fig. 6.

In yet another embodiment, Abametapir prepared according to the present invention is characterized by powder X-ray diffraction pattern having peaks at 12.26, 15.26, 16.05, 20.88, 21.30, 25.05 and 27.74.

Alternately, Abametapir used in the present invention is prepared by the process disclosed in Tetrahedron Letters V.039 Year 1998 Pg 2559.

The following examples should not be considered exhaustive, but merely illustrative of only a few of the many aspects and embodiments contemplated by the present disclosure.

Example

Example 1: Preparation of Abametapir.

Under nitrogen atmosphere, a mixture of 2-Bromo-5-methyl pyridine (8 mmol), potassium carbonate (8 mmol), palladium acetate (0.4 mmol) and tetra-*n*-butylammonium

bromide (4 mmol) in N,N-dimethylformamide (2 volumes, based on 2-Bromo-5-methyl pyridine), water (1 volume, 2-Bromo-5-methyl pyridine) and isopropyl alcohol (0.5volume, based on 2-Bromo-5-methyl pyridine) was heated to 95-100 °C and stirred for 48 hrs. After reaction completion, reaction mass was cooled to room temperature, filtered through hyflo and washed with isopropyl alcohol. Obtained filtrate was concentrated under vacuum and resulted residue was diluted with water, stirred and precipitated solid was filtered. This crude material was further purified by recrystallization in isopropyl alcohol /water to afford Abametapir.

Example 2: Preparation of Abametapir hydrochloride.

To a solution of Abametapir in ethyl acetate (15 volumes), hydrogen chloride gas was purged and stirred the contents at room temperature. The precipitated solid was filtered, washed with ethyl acetate and dried under vacuum to afford Abametapir Hydrochloride.

Example 3: Preparation of Abametapir maleate.

To a solution of Abametapir in ethyl acetate (15 volumes), maleic acid (1 eq.) was added and contents were stirred at room temperature. The precipitated solid was filtered, washed with ethyl acetate and dried under vacuum to get Abametapir maleate.

Example 4: Preparation of Abametapir oxalate:

To a solution of Abametapir in ethyl acetate (15 volumes), oxalic acid (1 eq.) was added and contents were stirred at room temperature. The precipitated solid was filtered, washed with ethyl acetate and dried under vacuum to get Abametapir oxalate.

Example 5: Preparation of Abametapir sulfate:

To a solution of Abametapir in ethyl acetate (15 volumes), sulfuric acid (1 eq.) was added and contents were stirred at room temperature. The precipitated solid was filtered, washed with ethyl acetate and dried under vacuum to get Abametapir sulfate.

Example 6: Preparation of Abametapir Tartarate:

To a solution of Abametapir in methanol (10 volumes), tartaric acid (0.5 eq.) was added and contents were stirred at room temperature. The precipitated solid was filtered, washed with ethyl acetate and dried under vacuum to get Abametapir tartarate.

Example 7: Process Description of 2-Bromo-5-methylpyridine:

2-Amino-5-methylpyridine (100 g, 0.9247 mol.) and), bromine (295.56 g, 1.8495 mol.) and aqueous sodium nitrite solution (127.61 g, 1.8495 mol., in 300 ml water) were added slowly and sequentially to precooled hydrobromic acid (300ml, 5±5°C). Thereafter, stirring was continued at 12±3°C to complete the reaction. After completion, add 25%w/w aqueous sodium hydroxide solution (800 ml) by maintaining same temperature to precipitate the product. After complete precipitation, product was filtered, washed with precooled water (2x100ml, <20 °C) and kept under squeezing to yield 120 g (75%) of 2-Bromo-5-methylpyridine as a white solid

Example 8: Process for the preparation of Abametapir:

Process a: Under inert atmosphere, a mixture of 2-Bromo-5-methylpyridine (100 g, 0.5813 mol.), ethylene glycol (300 ml), 10%w/w palladium on carbon (10 g, 50% w/w, wet) and aqueous sodium hydroxide (46.5 g, 1.1626 mol., in 300 ml water) was heated to 106±3°C and stirred for 2 hrs. After reaction completion, reaction mass was diluted with water (500 ml) and ethyl acetate (1000 ml) and filtered through hyflo to recover palladium on carbon. From the filtrate, organic layer was separated and aqueous layer was extracted with ethyl acetate (300 ml). Thereafter, combined organic layer was treated with activated carbon at room temperature. After filtration, obtained filtrate was concentrated under reduced pressure. Finally, product was crystallized with aqueous isopropyl alcohol and dried to yield Abametapir as a white solid (42 g, 79%).

Process b: Under inert atmosphere, a mixture of 2-Bromo-5-methylpyridine (100 g, 0.5813 mol.), ethylene glycol (36 g, 0.5813 mol.), 10%w/w palladium on carbon (10 g, 50% w/w, wet) and aqueous sodium hydroxide (46.5 g, 1.1626 mol., in 300 ml water) in 1,2-dimethoxy ethane (500 ml) was heated to 77±3°C and stirred for 16 hrs. After

reaction completion, reaction mass was diluted with water (500 ml) and ethyl acetate (1000 ml) and filtered through hyflo to recover palladium on carbon. From the filtrate, organic layer was separated and aqueous layer was extracted with ethyl acetate (300 ml). Thereafter, combined organic layer was treated with activated carbon at room temperature. After filtration, obtained filtrate was concentrated under reduced pressure. Finally, product was crystallized with aqueous isopropyl alcohol and dried to yield Abametapir as a white solid (37 g, 70%).

Process c: Under inert atmosphere, a mixture of 2-Bromo-5-methylpyridine (100 g, 0.5813 mol.), ethylene glycol (36 g, 0.5813 mol.), 10%w/w palladium on carbon (10 g, 50% w/w, wet) and aqueous sodium hydroxide (46.5 g, 1.1626 mol., in 300 ml water) in 1,4-dioxane (500 ml) was heated to 86±3°C and stirred for 16 hrs. After reaction completion, reaction mass was diluted with water (500 ml) and ethyl acetate (1000 ml) and filtered through hyflo to recover palladium on carbon. From the filtrate, organic layer was separated and aqueous layer was extracted with ethyl acetate (300 ml). Thereafter, combined organic layer was treated with activated carbon at room temperature. After filtration, obtained filtrate was concentrated under reduced pressure. Finally, product was crystallized with aqueous isopropyl alcohol and dried to yield Abametapir as a white solid (37 g, 70%).

CLAIMS

1. A process for the preparation of Abametapir comprising the steps of:
   a) forming a reaction mixture of 2-Bromo-5-methylpyridine, ethylene glycol, a base and a catalyst,
   b) optionally adding a second solvent,
   c) heating the reaction mixture,
   d) extracting the reaction mixture,
   e) isolating Abametapir.
2. The process as claimed in claim 1, wherein the catalyst is palladium carbon and the base is selected from inorganic bases like sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonte.
3. The process as claimed in claim 1, wherein the second solvent is selected from 1,2-dimethoxy ethane or 1,4-dioxane.
4. The process as claimed in claim 1, wherein the reaction mass is heated to about 70 to 110°C
5. The process as claimed in claim 1, wherein the reaction mass is diluted with water and ethyl acetate before extraction.
6. The process as claimed in claim 1, wherein extraction is carried by ethyl acetate.
7. The process as claimed in claim 1, wherein the abametapir is recrystallized from aqueous isopropyl alcohol
8. Abametapir hydrochloride salt.
9. Abametapir hydrochloride as claimed in claim 8, is characterized by powder X-ray diffraction as depicted in Fig. 1.
10. Abametapir hydrochloride as claimed in claim 8, is characterized by powder X-ray diffraction pattern having peaks at 9.82, 14.01, 19.73, 20.79, 22.22, 25.86, 26.30 and 26.83.
11. A process for the preparation of abametapir hydrochloride comprising the steps of:
    a) dissolving Abametapir in an organic solvent,
    b) purging Hydrogen chloride,

c) isolating Abametapir hydrochloride salt of formula (II).

12. The process as claimed in claim 11, wherein the organic solvent is selected from methyl acetate, ethyl acetate, propyl acetate or Butyl acetate, tetrahydrofuran, acetonitrile, dichloromethane, methonal, isopropyl alcohol, Ethonal, methyl ethyl ketone, methyl isobutyl ether, and methyl isopropyl ether.

13. Abametapir maleate salt.

14. Abametapir maleate as claimed in claim 13, is characterized by powder X-ray diffraction as depicted in Fig. 2.

15. Abametapir maleate as claimed in claim 13, is characterized by powder X-ray diffraction pattern having peaks at 8.10, 9.31, 13.21, 14.77, 18.67, 20.69, 25.87, 26.73 and 28.37.

16. A process for the preparation of Abametapir maleate comprising the steps of:

a) dissolving Abametapir in an organic solvent,

b) adding maleic acid,

c) isolating Abametapir maleate salt of formula (III).

17. The process as claimed in claim 16, wherein the organic solvent is selected from methyl acetate, ethyl acetate, propyl acetate or Butyl acetate, tetrahydrofuran, acetonitrile, dichloromethane, methonal, isopropyl alcohol, Ethonal, methyl ethyl ketone, methyl isobutyl ether, and methyl isopropyl ether.

18. Abametapir oxalate salt.

19. Abametapir oxalate as claimed in claim 18, is characterized by powder X-ray diffraction as depicted in Fig. 3.

20. Abametapir oxalate as claimed in claim 18, is characterized by powder X-ray diffraction pattern having peaks at 8.77, 9.58, 18.36, 19.20, 24.52, 25.28 and 31.68.

21. A process for the preparation of Abametapir oxalate comprising the steps of:

a) dissolving Abametapir in an organic solvent,

b) adding oxalic acid,

c) isolating Abametapir oxalate salt of formula (IV).

22. The process as claimed in claim 21, wherein the organic solvent is selected from methyl acetate, ethyl acetate, propyl acetate or Butyl acetate, tetrahydrofuran, acetonitrile, dichloromethane, methonal, isopropyl alcohol, Ethonal, methyl ethyl ketone, methyl isobutyl ether, and methyl isopropyl ether.

23. Abametapir sulfate salt.

24. Abametapir sulfate as claimed in claim 23, is characterized by powder X-ray diffraction as depicted in Fig. 4.

25. Abametapir sulfate as claimed in claim 23, is characterized by powder X-ray diffraction pattern having peaks at 10.23, 16.44, 17.25, 18.02, 20.53, 21.97, 25.70, 26.98 and 28.45.

26. A process for the preparation of Abametapir sulfate comprising the steps of:

a) dissolving Abametapir in an organic solvent,

b) adding sulfuric acid,

c) isolating Abametapir sulfate salt of formula (V).

27. The process as claimed in claim 26, wherein the organic solvent is selected from methyl acetate, ethyl acetate, propyl acetate or Butyl acetate, tetrahydrofuran, acetonitrile, dichloromethane, methonal, isopropyl alcohol, Ethonal, methyl ethyl ketone, methyl isobutyl ether, and methyl isopropyl ether.

28. Abametapir Tartarate salt.

29. Abametapir tartarate as claimed in claim 28, is characterized by powder X-ray diffraction as depicted in Fig. 5.

30. Abametapir tartarate as claimed in claim 28, is characterized by powder X-ray diffraction pattern having peaks at 9.35, 14.92, 18.80, 21.16, 23.51, 25.22, and 26.38.

31. A process for the preparation of Abametapir tartarate comprising the steps of:

a) dissolving Abametapir in an organic solvent,

b) adding tartaric acid,

c) isolating Abametapir Tartarate salt of formula (VI).

32. The process as claimed in claim 31, wherein the organic solvent is selected from methyl acetate, ethyl acetate, propyl acetate or Butyl acetate, tetrahydrofuran, acetonitrile, dichloromethane, methonal, isopropyl alcohol, Ethonal, methyl ethyl ketone, methyl isobutyl ether, and methyl isopropyl ether.

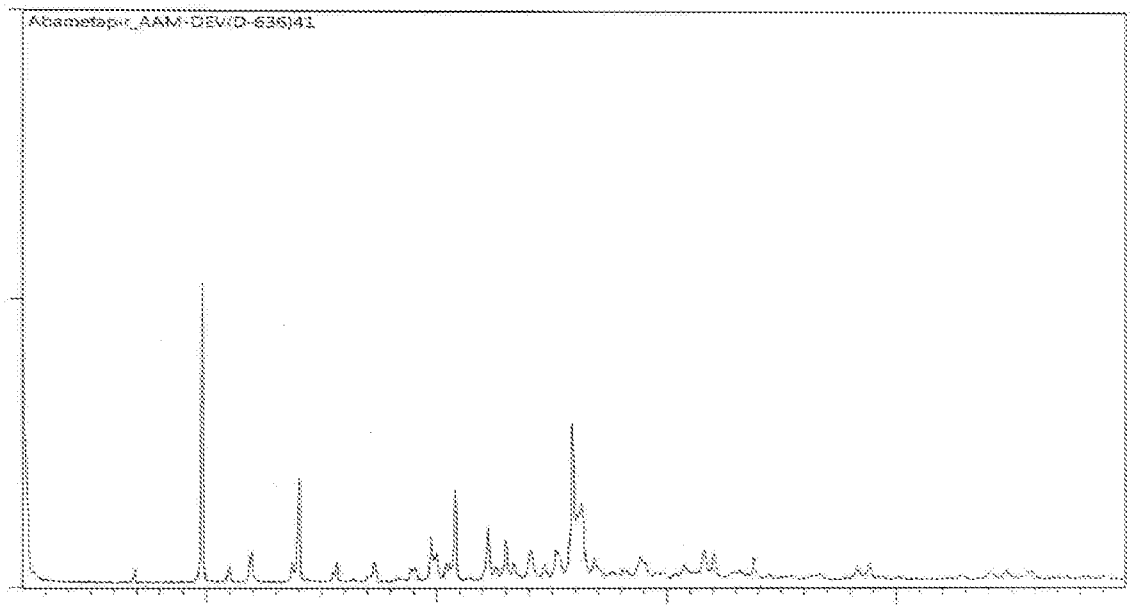


Figure 1

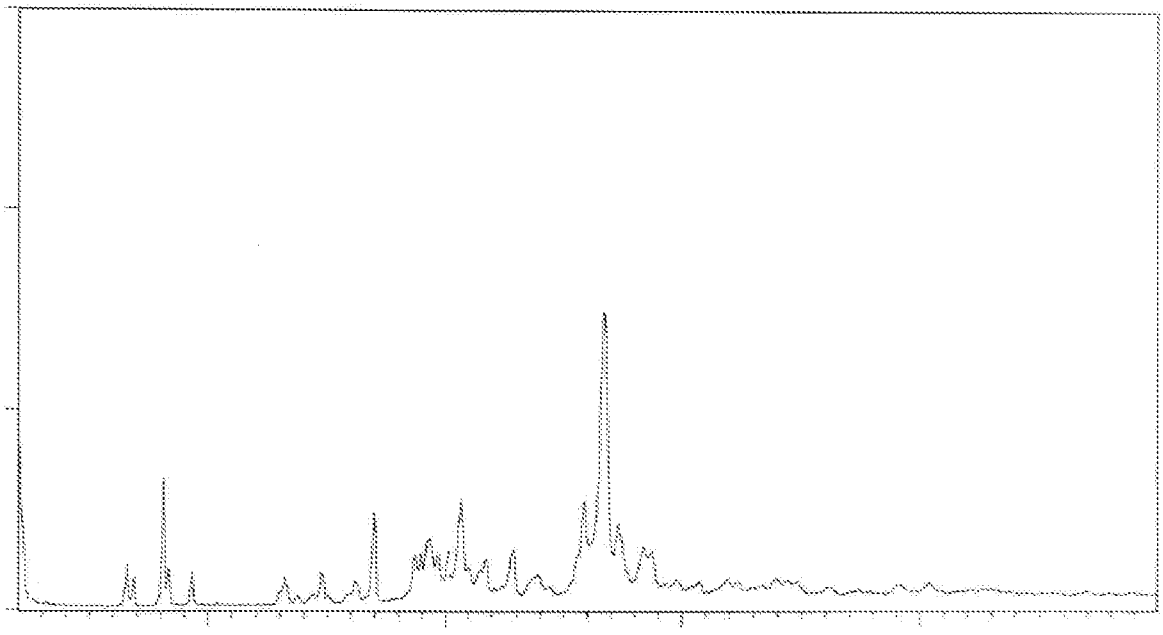


Figure 2

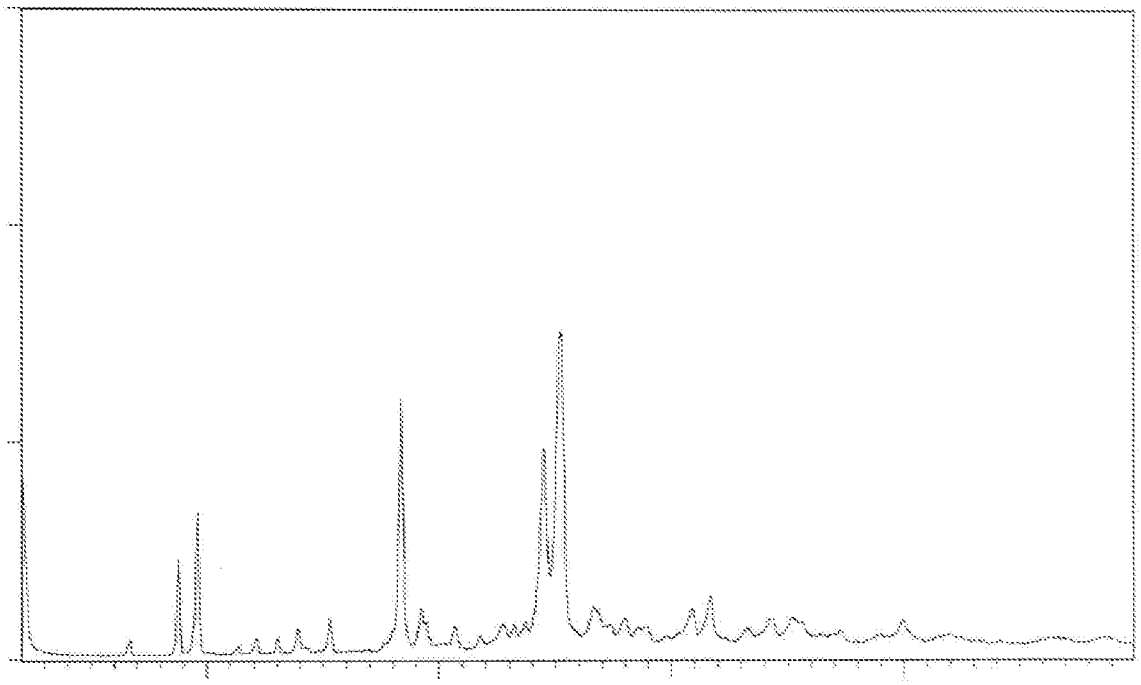


Figure 3

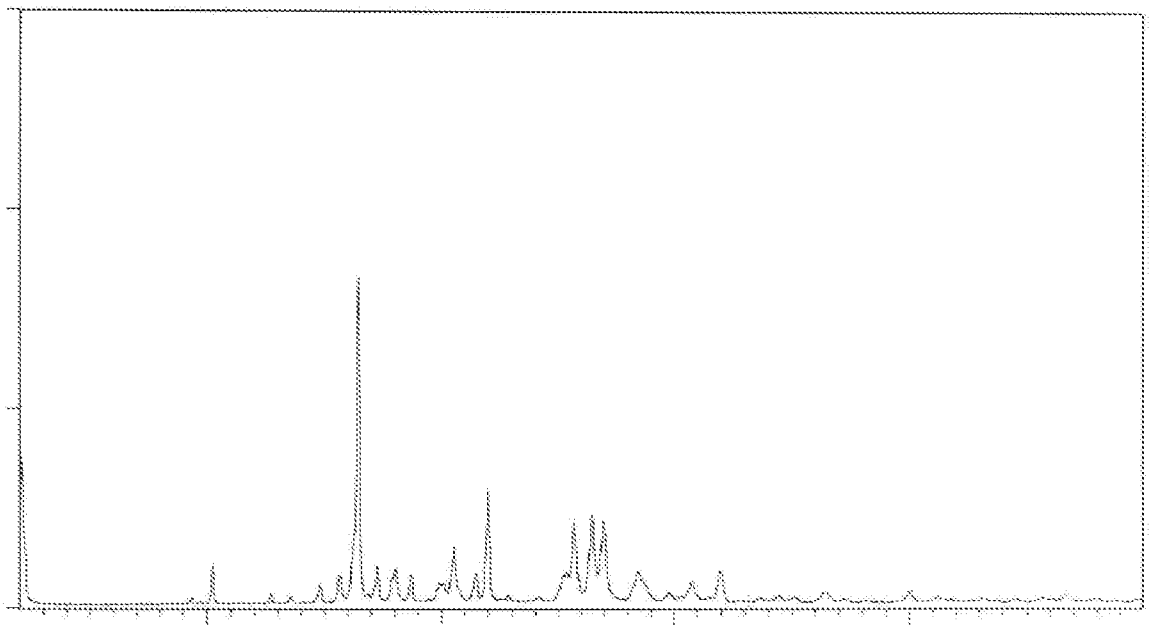


Figure 4

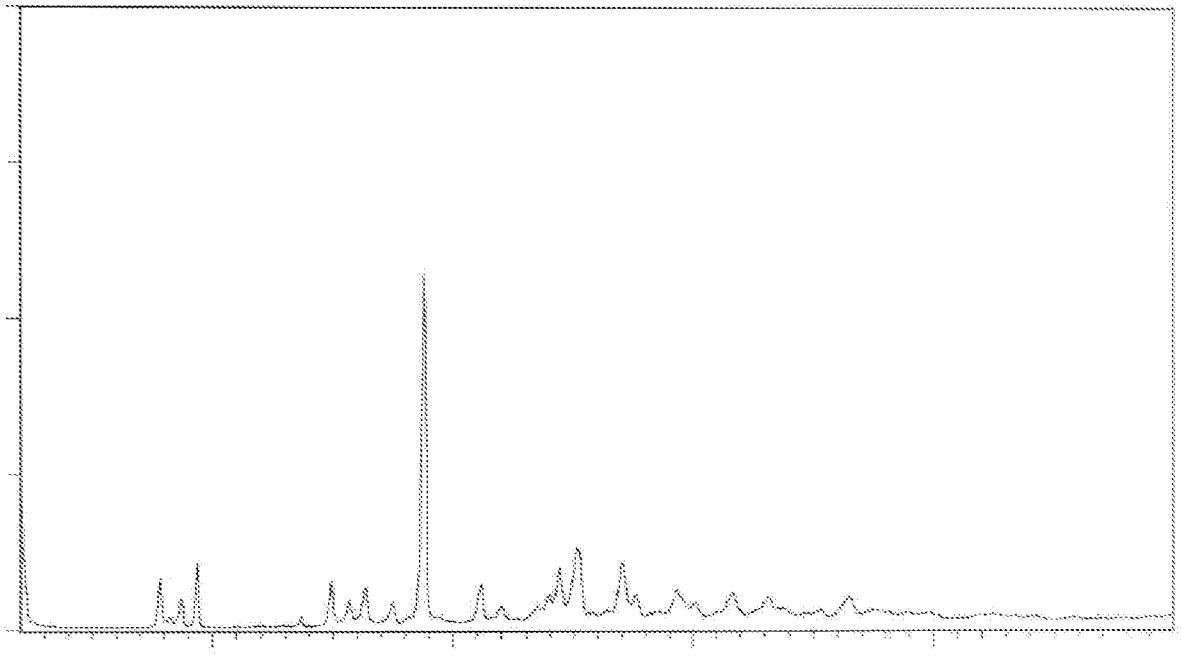


Figure 5

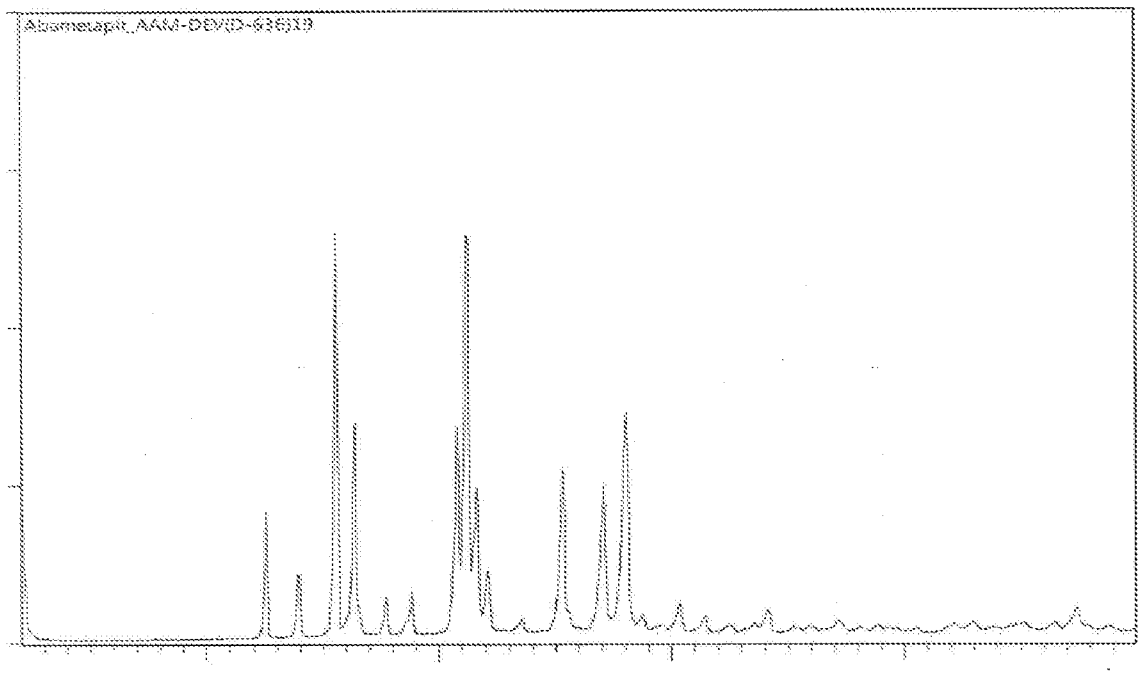


Figure 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/051887

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/53
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PENALVA V ET AL: "Direct Homocoupling of Aryl Halides Catalyzed by Palladium", TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 39, no. 17, 23 April 1998 (1998-04-23), pages 2559-2560, XP004112095, ISSN: 0040-4039, DOI: 10.1016/S0040-4039(98)00196-8 cited in the application preparation of product 2, entry 8 in Table 1 and conditions A ----- -/--	1-7

[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
16 May 2019	06/08/2019

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	Sahagún Krause, H

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/051887

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.:

1-7

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/IB2019/051887

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FULLER A A ET AL: "In situ formation and reaction of 2-pyridylboronic esters", TETRAHEDRON LET, ELSEVIER, AMSTERDAM, NL, vol. 44, no. 14, 31 March 2003 (2003-03-31), pages 2935-2938, XP004414432, ISSN: 0040-4039, DOI: 10.1016/S0040-4039(03)00419-2 cited in the application Scheme 6	1-7
X	HASSAN ET AL: "Catalytic alternative of the Ullmann reaction", TETRAHE, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 54, no. 45, 5 November 1998 (1998-11-05), pages 13793-13804, XP005065954, ISSN: 0040-4020, DOI: 10.1016/S0040-4020(98)00849-7 preparation of product 2, entry 5 in Table 6 and general procedure	1-7
X	WO 98/45265 A1 (COMMW SCIENT IND RES ORG [AU]; MARCUCCIO SEBASTIAN MARIO [AU] ET AL.) 15 October 1998 (1998-10-15) example 30	1-7
A	LIAN-YAN LIAO ET AL: "Reductive Couplings of 2-Halopyridines without External Ligand: Phosphine-Free Nickel-Catalyzed Synthesis of Symmetrical and Unsymmetrical 2,2'-Bipyridines", JOURNAL OF ORGANIC CHEMISTRY, vol. 79, no. 2, 6 January 2014 (2014-01-06), pages 777-782, XP055589286, US ISSN: 0022-3263, DOI: 10.1021/jo402084m entry 4 in Table 1	1-7
A	LEE K ET AL: "Efficient homo-coupling reactions of heterocyclic aromatic bromides catalyzed by Pd(OAc)"2 using indium", TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 49, no. 27, 30 June 2008 (2008-06-30) , pages 4302-4305, XP022695668, ISSN: 0040-4039, DOI: 10.1016/J.TETLET.2008.04.123 [retrieved on 2008-04-24] entry 4 in Table 2	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2019/051887

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9845265 A1	15-10-1998	CA 2285455 A1	15-10-1998
		CN 1255123 A	31-05-2000
		EP 0986541 A1	22-03-2000
		JP 2002505663 A	19-02-2002
		KR 20010006208 A	26-01-2001
		NZ 337951 A	28-02-2000
		US 2002032339 A1	14-03-2002
		US 2002193604 A1	19-12-2002
		WO 9845265 A1	15-10-1998

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-7

process for the preparation of Abametapir.

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2. claims: 8-32

salts of Abametapir and preparations thereof
