

Date: 19th Nov 2019

To,
The Controller of Patents,
Patent Office,
Intellectual Property Office Building
Chennai

Re: Reply to First Examination Report (FER) dated 23 May 2019
Indian Patent Application No.: **38/MUM/2013**
Applicant: VIHITA CHEM PVT. LTD.,
Title: **PROCESS FOR PREPARATION OF (2-BROMO-4,5-DIMETHOXYPHENYL)-METHYL BROMIDE**
Our Ref: PTIN/001596

Thank you very much for the First Examination Report dated 23 May 2019 in respect of the above application. Our observations/submissions are based on the official objections/requirements contained in Part-II (Detailed Technical Report) and in Part-III (Formal Requirements) of the Examination Report. The official objections/requirements include Citations Alleging Lack of Inventive Step; Non-Patentability under Section 3(d); Claim Clarity and Definitiveness.

At the outset, it is submitted that the claims have been amended without prejudice to meet the learned Controller's objections as permitted under Section 57 and in order to comply with the objections raised in the office action. Amended claims are supported by the originally filed claims and specification. It is submitted that revised claims are clear and definitive and the scope of the claims has been limited in order to overcome the objection of insufficiency of disclosure and lack of unity of invention.

Brief of amendments carried out in the claims are as under:

- Amendments in claim 1 included process parameters form claim 1 and 7.
- Previous Claim 9 have been deleted.
- Claim 3 to 10 renumbered

The amended claims are submitted for further prosecution of the subject application.

We now present the following reply on the objections/requirements pointed out/raised in the First Examination Report:

It is respectfully submitted that subject matter of amended Claims 1 to 9 are novel and inventive over D1, D2, D3 & D4. The prior art D1, D2, D3 & D4 does not disclose all the limitations of the invention claimed in Claims 1-8 to establish a prima facie case of Novelty and obviousness. In this respect, the Applicant submits as follows:

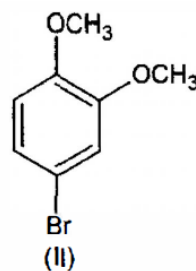
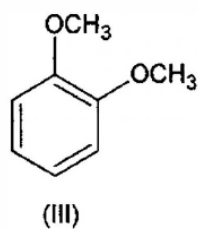
Citations Alleging Lack of Inventive Step:

The Learned Examiner alleges that the claims Inventive Step in view of document D1, D2, D3 & D4 cited above.

We are grateful to the Learned Examiner for assigning reasons and for particularizing specific portion(s) from the cited references in support of his objection. However, none of the references teaches each and every limitation of the claims as amended herein, as explained hereinafter.

The present invention relates to an improved process for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I), which is an intermediate for the preparation of many pharmaceutical compounds like Pinaverium bromide.

The Applicant submits that the process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) is very different from the process disclosed in document D1, D2, D3 & D4 as cited. Further, there is no teaching or suggestion in cited documents, which would have prompted the skilled person to arrive at the claimed matter of process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) comprising: reacting veratrole of formula (III) with a brominating agent in the presence of hydrogen peroxide in a suitable solvent to provide 4-bromo-veratrole of formula (II);



reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent in a suitable solvent to provide (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).

NOVELTY:

The Applicant is pleased to note that the Controller has concluded that the Pending claims are Novel.

INVENTIVE STEP:

Para B (1)

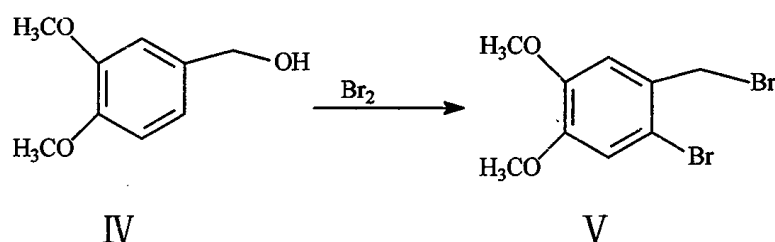
With reference to the objection under section 2(1)(ja) of The Patents Act 1970 claim(s) (1-10) lack(s) Inventive step in view of teachings of cited documents references D1- D4 as being un patentable.

- D1: CN101759666.
- D2: WO 2005/028434.
- D3: Sudip Mukhopadhyay,*;† S. Ananthakrishnan, and Sampatraj B. Chandalia Org. Proc. Res. Dev., 1999, 3 (6), pp 451–454 DOI: 10.1021/op990035n Publication Date (Web): November 2, 1999.
- D4: Minkin, V . I.; Dorofeenko, G. N. Russ. Chem. Rev. 1960, 599 30/11/1960.

Applicants respectfully submit that the claims of the present application have been thoroughly revised and amended accordingly. In this regard, the applicant humbly submits that the novel process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-

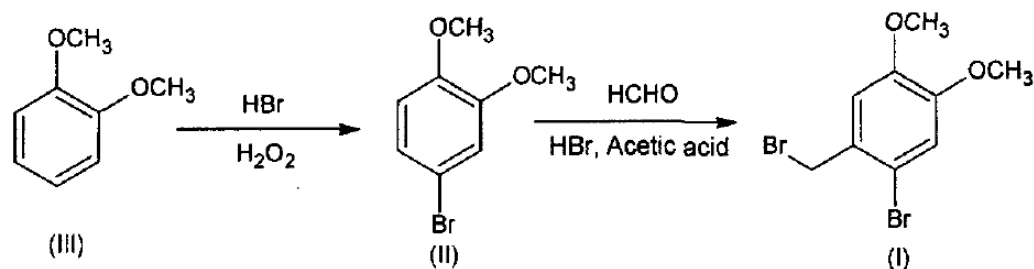
methyl bromide of formula (I) comprising: reacting veratrole of formula (III) with a brominating agent in the presence of hydrogen peroxide in a suitable solvent to provide 4-bromo-veratrole of formula (II); reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent in a suitable solvent to provide (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I), as claimed in claim 1 is a mild reaction conditions, simple operation, less expensive cost effective process.

The cited document D1 (CN101759666) discloses a process of Preparation preparing pinaverium bromide. D1 further teaches process of preparation of 2-bromo-4,5-dimethoxy (intermediate V), by bromination of 3,4- dimethoxybenzyl alcohol (Intermediate IV) with Br₂ to obtain 2-bromo-4,5-dimethoxy - section bromide (intermediate V)



D1 does not teach or suggest about process as claimed in the claimed in the present invention. D1 does not teach or suggest process of preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) reacting veratrole of formula (III) with a brominating agent in the presence of hydrogen peroxide in a suitable solvent to provide 4-bromo-veratrole of formula (II); reacting 4-bromo-veratrole of

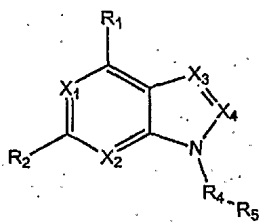
formula (II) with formaldehyde and a brominating agent in a suitable solvent to provide (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).



Further D1 disclose only process of Preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide by bromination of 3,4- dimethoxybenzyl alcohol in presense of Br₂. D1 does not disclose, teach or suggest use or preparation of 4-bromo-veratrole of formula (II) and veratrole of formula (III). Further the D1 does not disclose, teach or suggest preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) by reacting veratrole of formula (III) with a brominating agent and further reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent.

Thus, it is clearly apparent that D1 does not disclose, teach or suggest each and every limitations of the presently claimed process of preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).

The cited **document D2 (WO 2005/028434)** is directed to a compound of Formula A



D2 does not teach or suggest about reacting veratrole of formula (III) with a brominating agent and further reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent for the preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).

Further D2 disclose only heterocyclic compounds and related analogues as specified below in Formulae A, I, IA-E, II, HA-D, III, IIIA-B, and TV an IVA and heterocyclic compounds. Further the D2 does not disclose, teach or suggest use of a 4-bromo-veratrole of formula (II) and veratrole of formula (III) to obtain (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).

Thus, it is clearly apparent that D2 does not disclose, teach or suggest the presently claimed process of reacting veratrole of formula (III) with a brominating agent and further reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent to obtain (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).

The cited **document D3 (Sudip Mukhopadhyay, Org. Proc. Res. Dev., 1999, 3 (6), pp 451–454)** is related to oxidative bromination in a Liquid-Liquid Two-Phase

system to synthesize 2-Bromophenol, 2,6-Dibromophenol, and 2-Bromo-4-methylphenol. The process discloses preparation of a 2-Bromophenol, 2,6-dibromophenol, and 2-bromo-4methyl phenol by Oxidative halogenation by using HCl or HBr and H₂O₂ of a para-blocked substrate followed by deprotection involving desulphonation or decarboxylation is reported..

D3 does not teach or suggest about novel process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) by reacting veratrole of formula (III) with a brominating agent and further reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent.

Consequently, the Applicant does not accept that the skilled person would conceive the claimed matter in light of the disclosure of D3.

The cited **document D4 (Minkin, V . I.; Dorofeenko, G. N. Russ. Chem. Rev. 1960, 599 30/11/1960)** discloses a method of producing veratraldehyde formation from the veratrol using a formylating agent DMF, POCl₃.

D4 does not teach or suggest about novel process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) by reacting veratrole of formula (III) with a brominating agent and further reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent.

Further D4 teaches reacting veratrole formylating agent DMF, POCl₃ to obtain veratraldehyde. D4 does not teach or suggest about reacting veratrole of formula (III) with a brominating agent.

Applicant further states and submits that present invention as claimed in claims does not claims any steps of reacting veratrole formylating agent DMF, POCl₃ to obtain veratraldehyde, further D4 chemical reaction which consequently, does not teach or suggest about novel process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) to the skilled person. Consequently, the Applicant does not accept that the skilled person would conceive the claimed matter in light of the disclosure of D4.

Further the Applicant does not accept that the skilled person would conceive the process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) as claimed matter in light of the disclosure D3 and D4.

It is respectfully submitted that subject matter of Claims 1 to 8 is inventive over D1, D2, D3 and D4. A combined reading of D1, D2, D3 and D4 does not disclose all the limitation the invention claimed in Claims 1-8 to establish a prima facie case of inventive step.

In conclusion, the document D1, D2, D3 and D4 when considered alone or in combination, fail to disclose the presently claimed process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) by reacting veratrole

of formula (III) with a brominating agent and further reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent.

Further, a person skilled in the art could not anticipate process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) comprising: reacting veratrole of formula (III) with a brominating agent in the presence of hydrogen peroxide in a suitable solvent to provide 4-bromo-veratrole of formula (II); reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent in a suitable solvent to provide (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) as claimed in present invention based on cited references. In other words, documents D1, D2, D3 and D4 cited by the Learned Controller does not provide any teaching or motivation to a person skilled in the art to arrive at the present invention without substantial modifications requiring the exercise of inventive skill.

Therefore, the Applicant respectfully submits that the revised / amended claim 1 is inventive over the cited documents. Further, the dependent claim 2-8 are also inventive over the cited documents at least for the reason that the same are directly or indirectly dependent on claim 1 and hence, the scope of these claims should be construed to contain the features of at least independent claim 1.

Hence it cannot be coincided that amended claim 1 to 8 lacks inventive step. It is therefore requested that the learned Controller may please consider these

observation and waive off this objection as the instant invention accordingly
Claims do have inventive step.

In order to anticipate the claimed invention, a reference must teach each and every element of the claim. However, D1, D2, D3 and D4 fails to teach novel process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) comprising: reacting veratrole of formula (III) with a brominating agent in the presence of hydrogen peroxide in a suitable solvent to provide 4-bromo-veratrole of formula (II); reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent in a suitable solvent to provide (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I).

In conclusion, the prior art D1, D2, D3 and D4 does not teach or suggest process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) of the presently claimed. Further none of the documents cited in the FER discloses or suggests a process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) by reacting veratrole of formula (III) with a brominating agent and further reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent as claimed.

Applicant submits that the teachings of D1, D2, D3 and D4 would not motivate the skilled person to produce the claimed compounds.

Applicant submits that the prior art would not have prompted the skilled person to modify D1, D2, D3 and D4 to arrive at the subject matter of the present application. There is no teaching in D1, D2, D3 and D4 that would prompt the skilled person to arrive at the present invention.

Further, a person skilled in the art could not invent the present invention based on any of or any combination of the cited references. In other words, none of the documents cited by the Learned Controller provide any teaching or motivation to a person skilled in the art to arrive at the present invention without substantial modifications requiring the exercise of inventive skill.

For the reasons discussed above, the documents D1, D2, D3 and D4 cited in the Examination Report likewise fail to teach or suggest each and every limitation of the novel process for preparation (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) as claimed. Accordingly, the novelty and inventiveness of the claimed subject matter should be acknowledged.

In view of the foregoing, Applicants believe that the claimed subject matter is inventive over the teachings of D1, D2, D3 and D4.

Therefore, we humbly request you to reconsider the objection favourably.

Para B (2)

NON-PATENTABILITY UNDER SECTION 3(d):

In this context, it is respectfully submitted that the original claims 1-10 are hereby amended. Moreover the novelty of the present invention resided in process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) comprising: reacting veratrole of formula (III) with a brominating agent in the presence of hydrogen peroxide in a suitable solvent to provide 4-bromo-veratrole of formula (II); reacting 4-bromo-veratrole of formula (II) with formaldehyde and a brominating agent in a suitable solvent to provide (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I). The inventors have now found that novel process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) as claimed in amended claim provide mild reaction conditions, simple operation, less expensive cost effective process.

As regards the objection against lack of inventive step and Section 3(d) objections, the applicant, at the outset, submits that none of the prior art documents teach or disclose the currently claimed process. Further, the applicant submits herewith, in order to demonstrate that the claimed process have unexpectedly superior process which has mild reaction conditions, simple operation, less expensive cost effective process against the process of the prior art.

Applicant submits that the prior art D1, D2, D3 and D4 there is no teaching process for preparation of (2-bromo-4,5-dimethoxy-phenyl)-methyl bromide of formula (I) as claimed and have unexpectedly result (example page 9). Applicant further states

and submits that the prior art D1, D2, D3 and D4 would not have prompted the skilled person to arrive at the present invention.

Therefore, the claimed formulation is not merely a mere use of a known process and therefore does not fall under section 3(d) of the Indian Patents Act, 1970. We humbly request you to waive off the objection favorably.

Para B (3)

SUFFICIENCY OF DISCLOSURE:

The applicant herewith submits that amended claims include each and every limitation which is supported by the example in the complete specification automatically addresses objection. Therefore, we humbly request to reconsider the objection to and waive off the said objection.

Para B (4)

SCOPE:

The applicant respectfully submits that the claims include the technical advancement over the prior art as required u/s 2(1)(j) of the Patent's Act are submitted as required u/s 10(4) of the Act.

CLARITY AND CONCISENESS:

The applicant respectfully submits that the amended claims include clarity as required u/s 10(4)(c) and 10(5) of the Act.

DEFINITIVENESS:

The applicant respectfully submits that the claim 3 defined brominating agents which is also disclosed and summarised in specification (Page 6 of specification).

The applicant respectfully submits that the claim 3 is supported by the specification.

The applicant respectfully submits that the solvents of claim 5 are supported by the specification (Page 6 & 7 of specification). Therefore it is respectfully submitted that the claim 5 is supported by the specification.

Therefore, we humbly request to reconsider the objection to and waive off the said objection.

Para B (6)

OTHERS REQUIREMENTS

We respectfully submit that Claim 1-8 has been amended appropriately. The amended claim 1-8 is clear with definite scope and is fully supported by the description. We have also filed Form 13 for require changes in claims and abstract. In view of above, The Learned controller is requested to waive off above objection.

PART-III: FORMAL REQUIREMENTS

Other Deficiencies:

At the time of the filled of application, all the Forms already having a duly signed by the applicant and also available at electronically mode, as well as submit a hard copy at the patent office, so as per learned controller, here submit a Fresh Form 1, Form 3 and Form 5 in a new Format.

Statement and Under Taking (Form-3) Details:

Applicant respectfully submit that they have not made any application for the same or substantially the same invention outside India, so no details are shared with learned controller under section 8(1)(a) and rule 12(1).

Enclosures:

1. Marked and clean copy of the claims amended
2. Marked and clean copy of the abstract amended
3. Form 1, Form 5, Form 3.

To,
The Controller of Patents
The Patent Office
At Mumbai / Delhi / Kolkata / Chennai

Signature:

Name:

Applicant's Agent:



Bhavik Patel

IN/PA-1379

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