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(54) Title: CONTINUOUS FLOW PROCESS FOR THE PREPARATION OF SULPHOXIDE COMPOUNDS

(57) Abstract: A continuous micromixer based process for the synthesis of sulphoxide compounds with a reaction time of less than or equal one minute is disclosed. The process shows selectivity of > 95% towards the sulphoxide compounds.



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"CONTINUOUS FLOW PROCESS FOR THE PREPARATION OF SULPHOXIDE COMPOUNDS"

Technical field of the invention:

The invention relates to a continuous process for the preparation of sulfoxide compounds. Particularly the invention relates to an efficient micromixer based continuous flow process for the synthesis of sulfoxide compounds such as modafinil compounds and proton pump inhibitors, with a high degree of selectivity.

Background and prior art:

Sulfinyl compounds predominantly find use as proton pump inhibitors such as pantaprazole, rabeprazole, lansoprazole, as modafinil compounds and such like. The total world-wide sale of esomprazole, a proton pump inhibitor was over 6 billion in 2006.

Batch processes for the synthesis of these compounds are described in prior art documents.

US 4808596 discloses a process for the synthesis of sulfinyl compounds by reacting the starting compound in chloroform with m-perchlorobenzoic acid at 0 to -5 degree C. The process of the invention is to be carried out at -70 to -30 °C, preferably -20 to 10 °C for a period of time ranging approximately from 1 minute to 24 hours, preferably from 5 minutes to 1 hour.

"Highly selective 30% hydrogen peroxide oxidation of sulfides to sulfoxides using micromixing" by Takuya Noguchi, *Chem. Commun.*, 2008, 3040 - 3042, US2008108122 and "Investigation of Micromixing Efficiency in a Novel High-Throughput Microporous Tube-in-Tube MicroChannel Reactor" by Qi-An Wang, Jie-Xin Wang, et al *Ind. Eng. Chem. Res.*, 2009, 48 (10), pp 5004-5009 present processes for the conversion of sulphides to sulfoxides by various methods.

US 7439367 relates to a batch process for the preparation of a sulfinyl compound involving the oxidation of a sulfide compound in the presence of a catalyst wherein the oxidising agents are aqueous alkali or alkali earth metal hypohalite solution. JP1190682, US2006089376, WO2006024890 and WO2008/087665 also disclose batch processes for the preparation of prazole type compounds.

But the prior art processes suffer from drawbacks such as maintenance of low temperature conditions leading to long processing time. The low temperature maintenance is required to prevent the formation of unnecessary side products and thus improve the specificity of the reaction and its conversion rate. The process of the '367 patent claims about 85% yield of the desired product over a duration of 1 - 4 hours. Therefore there is a need in the art to provide for a more efficient process for the synthesis of sulphinyl compounds.

Further there is a need in the art to have a process for the synthesis of sulphinyl compounds which is quick and does not consume time.

Also, there is a need in the art to provide for a more efficient and quick process for the synthesis of sulphinyl compounds with high selectivity to sulfoxide compounds which in turn results in high yield and purity of the desired product with lower impurities of sulfones.

Further the efficient and quick process for the synthesis of sulphinyl compounds should have high degree of specificity towards the formation of desired sulphoxide compounds.

There is also a need in the industrial level to provide an efficient and quick process for the synthesis of sulphinyl compounds which leads to very low yields of unnecessary side products such as sulfones in a continuous manner as against such features only in batch

processing.

Summary of the invention:

The instant invention discloses a continuous process for the synthesis of sulfoxide compounds wherein the process is conducted in a T-shaped micromixer that results in reaction time of 1 minute. The oxidizing agent of the invention is preferably m-chloroperbenzoic acid. The reaction results in over 90% conversion and > 95% selectivity towards sulfoxide compounds with lesser than 5% formation of undesired sulfones.

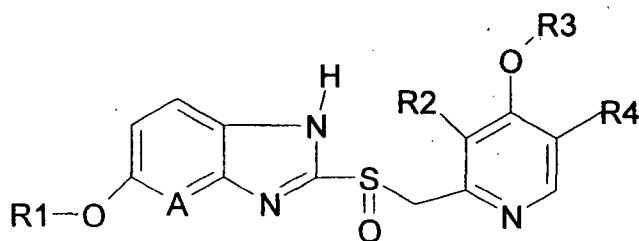
10 Description of drawing:

Figure 1: Schematic of the experimental set-up with the two syringes to inject the two reactants connected to the micromixer followed by a single inlet microreactor.

Figure 2: Schematic presentation of the experimental set-up with the microreactor with spatially discretely located inlets with micromixers at different distances for multipoint injection of one of the reactants.

Detailed description of the invention:

In accordance with the above objectives of the invention, a micromixer based, continuous process for the synthesis of sulfoxide compounds with a high degree of selectivity of > 95% towards sulfoxide compounds at temperature range of -5 - 50 °C, in less than or equal to a minute is disclosed herein. The continuous process for the synthesis of sulfoxide of formula 1

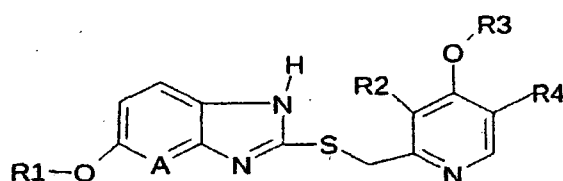


Formula 1

compounds comprises:

- a. mixing imidazo[4,5-b]pyridine compound of formula 2

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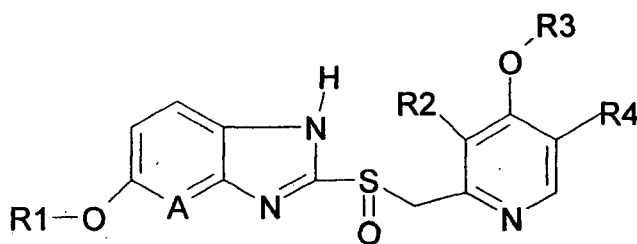
Formula 2

with an oxidizing agent dissolved in a solvent, in a T-shaped micromixer with a reaction tube;

- b. maintaining the temperature of the reaction tube at -5 - 50 °C and specifically in the range of 5 - 25 °C for about a minute and
- c. isolating the product of the process.

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The imidazo[4,5-b]pyridine compound of formula 1 is as shown herein



15

Formula 1

wherein A is carbon or nitrogen and R1, R2, R3, R4 are alkyl groups. In one embodiment of the invention, R1, R2, R3 and R4 are same. In another embodiment of the invention R1, R2, R3 and R4 are different.

The oxidizing agent of the invention is preferably m-chloroperbenzoic acid(m-CPBA). The oxidizing agent is used in the concentration range of 0.5 - 20 equimolar ratio. The solvents are selected from chloroform and methanol, alone or in combinations thereof. In combination, the solvents are used in the ratio of 0 - 0.5, v/v. The concentration of substrate required for the reaction ranges from 0.01 - 0.1 w/v.

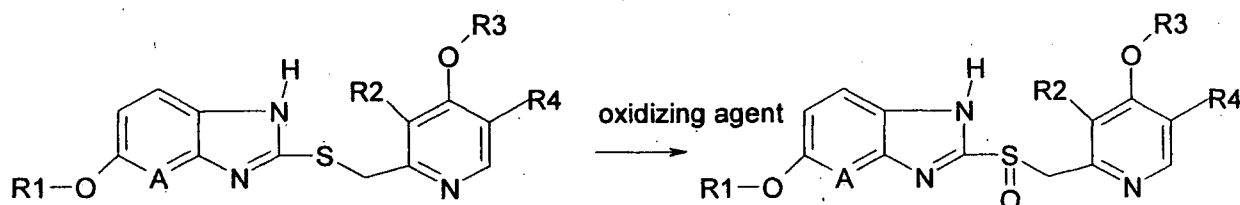
The product obtained from the internally structured T-shaped micromixer with the reaction tube within a reaction time of less than or equal to one minute is with sulfone content not greater than 5% and selectivity of > 95% towards the desired sulphoxide compounds. The process of the invention results in greater than 90% conversion of reactant to respective sulphoxide compound with yield of sulphoxide compound greater than 90%.

With reference to figure 1, depicting the single inlet microreactor for the continuous flow experiments, the experimental set-up consisted of two syringe pumps loaded with glass syringes connected to SS316 tubes [1/16" (1.58mm) o.d.] through an in-house developed and fabricated glass to metal connector made in PTFE. The two metallic tubes were subsequently connected to a micromixer followed by a residence time tube [1/16" (1.58mm) o.d.] which was immersed in a thermostat. The tube can be made of SS316 or Hastelloy. Syringes were filled with each of the reactants and the flow rates were set to achieve the desired residence time in the reaction tube.

In another embodiment of the invention, the continuous process of the invention is carried out by using a 1 m long tube with spatially discretely located multi point inlets. The number of inlets vary in the range of 2 to 6 and the discrete inlets (schematic shown in Figure 2) are maintained at equal spacing. While the imidazo[4,5-b]pyridine compound is injected at the first inlet, the other inlets are used for injecting the oxidizing agent either with equal flow rates or at different flow rates depending up on the need to vary

the residence time and the concentration. In yet another embodiment of the invention, the inlets are maintained at unequal spacing.

The reaction of the invention is schematically represented herein:



Formula 2

Wherein A is carbon or nitrogen and R1, R2, R3, R4 are alkyl groups. In one embodiment of the invention, R1, R2, R3 and R4 are same. In another embodiment of the invention R1, R2, R3 and R4 are different.

The sulfoxide compounds particularly are proton pump inhibitors such as omeprazole, pantoprazole, lansoprazole, tenatoprazole, rabeprazole and modafinil compounds.

The process of the invention has the following advantages:

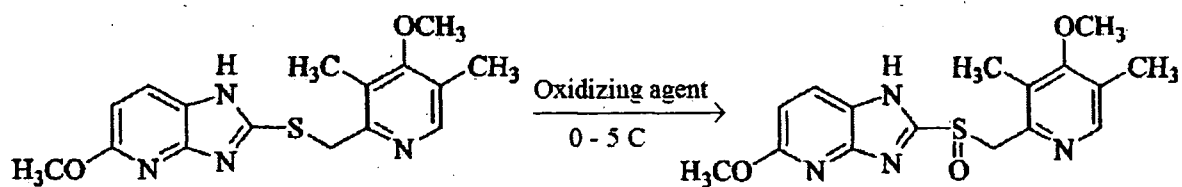
1. It is capable of being easily scaled-up.
2. The process has provided the choice of solvent other than only chloroform, a volatile solvent, since use of chloroform alone changes the concentration of the reaction mass as it evaporates at room temperature.
3. The process is continuous with minimal reaction time of less than or equal to one minute.
4. The sulfone content formation is less than 5%, resulting in high yield of sulfoxide compounds with high selectivity of > 95% towards sulfoxide compounds.
5. The conversion rate is greater than 90%.

Following examples are given by way illustration and should not construed the scope of the present invention.

Examples:

5 Example 1: Experimental set up for examples 1-10

For the continuous flow experiments typically, the experimental set-up involved two syringe pumps (Boading Longer, China) followed by a micromixer, which was then connected to a 1 m long stainless steel (SS316) tube [1/16" (1.58mm) o.d. and 1.38mm i.d.]. The SS tube was immersed in a thermostat (Julabo - ME12, Germany) and the samples were collected at the outlet of the tube. The residence time was varied by changing the flow rates. The samples were collected in alkali solution to quench the reaction at the outlet of the reaction tube. The product was subjected to analysis after further dilution. The general reaction scheme for all examples described is depicted herein. The imidazo[4,5-b]pyridine compound of Formula 3 as shown
 10
 15
 herein was used for the purpose of exemplification of the present invention.



Formula 3

20 Example 2:

100 mg of imidazo[4,5-b]pyridine compound of formula 3 was dissolved in 10 ml chloroform and 80 mg of H₂O₂ in 10 ml solvent chloroform. The two reacting solutions were mixed using a T micro mixer followed by a 1m long retention time tube. The process was carried out at 5 °C. The residence time in the tube was maintained at 60

seconds. The analysis of product formed showed 3% conversion to sulfoxide compound.

Example 3:

5 100 mg of imidazo[4,5-b]pyridine compound of formula 3 was dissolved in 10 ml
chloroform and 80 mg of sodium hypochlorite in 10 ml solvent chloroform. The two
reacting solutions were mixed using a T micro mixer followed by a 1m long retention
time tube. The process was carried out at 5 ° C. The residence time in the tube was
maintained at 60 seconds. The analysis of product formed showed 2% conversion to
10 sulfoxide compound.

Example 4:

100 mg of imidazo[4,5-b]pyridine compound of Formula 3 was dissolved in 10 ml
chloroform and 60 mg of m-CPBA in 10 ml solvent chloroform. The two reacting
solutions were mixed using a T micro mixer followed by a 1m long retention time tube.
15 The process was carried out at 5 ° C. The residence time in the tube was maintained
at 60 seconds. The analysis of product formed showed 82% conversion to sulfoxide
compound. The selectivity towards sulfoxide compound was 94% and 6% sulphone
was formed.

Example 5:

20 100 mg of imidazo[4,5-b]pyridine compound of Formula 3 was dissolved in 10 ml
chloroform and 70 mg of m-CPBA in 10 ml solvent chloroform. The two reacting
solutions were mixed using a T micro mixer followed by a 1m long retention time tube.
The process was carried out at 5 ° C. The residence time in the tube was maintained
at 60 seconds. The analysis of product formed showed 85% conversion to sulfoxide
25 compound. The selectivity towards sulfoxide compound was 93% and 7% sulphone

was formed.

Example 6:

100 mg of imidazo[4,5-b]pyridine compound of Formula 3 was dissolved in 10 ml chloroform and 87 mg of m-CPBA in 10 ml solvent chloroform. The two reacting solutions were mixed using a T micro mixer followed by a 1 m long retention time tube. The process was carried out at 5 ° C. The residence time in the tube was maintained at 60 seconds. The analysis of product formed showed 97% conversion to sulfoxide compound. The selectivity towards sulfoxide compound was 92% and 8 %sulphone was formed.

Example 7:

200 mg of imidazo[4,5-b]pyridine compound of Formula 3 was dissolved in 20 ml chloroform and 160 mg of m-CPBA in 20 ml solvent chloroform. The two reacting solutions were mixed using a T micro mixer followed by a 1 m long retention time tube. The process was carried out at 0 ° C. The residence time in the tube was maintained at 60 seconds. The analysis of product formed showed 96% conversion to sulfoxide compound. The selectivity towards sulfoxide compound was 96% and 4 %sulphone was formed.

Example 8:

200 mg of imidazo[4,5-b]pyridine compound of Formula 3 was dissolved in 20 ml chloroform and 160 mg of m-CPBA in 20 ml solvent chloroform. The two reacting solutions were mixed using a T micro mixer followed by a 1 m long retention time tube. The process was carried out at 5 ° C. The residence time in the tube was maintained at 60 seconds. The analysis of product formed showed 96% conversion to sulfoxide compound. The selectivity towards sulfoxide compound was 96% and 4 %sulphone

was formed.

Example 9:

100 mg of imidazo[4,5-b]pyridine compound of Formula 3 was dissolved in 10 ml chloroform and 100mg of m-CPBA in 10 ml solvent chloroform. The two reacting solutions were mixed using a T micro mixer followed by a 1m long retention time tube. The process was carried out at 5 ° C. The residence time in the tube was maintained at 60 seconds. The analysis of product formed showed 90% conversion to sulfoxide compound. The selectivity towards sulfoxide compound was 95% and 5 %sulphone was formed.

Example 10:

100 mg of imidazo[4,5-b]pyridine compound of Formula 3 was dissolved in 10 ml methanol and 80mg of m-CPBA in 5 ml solvent chloroform. The two reacting solutions were mixed using a T micro mixer followed by a 1m long retention time tube. The process was carried out at 5 ° C. The residence time in the tube was maintained at 60 seconds. The analysis of product formed showed 98% conversion to sulfoxide compound. The selectivity towards sulfoxide compound was 95% and 5 %sulphone was formed.

Example 11:

100 mg of imidazo[4,5-b]pyridine compound of Formula 3 was dissolved in 10 ml of equal volume of chloroform and methanol and 80mg of m-CPBA in 5 ml equal volume of chloroform and methanol. The two reacting solutions were mixed using a T micro mixer followed by a 1m long retention time tube. The process was carried out at 5 °C. The residence time in the tube was maintained at 60 seconds. The analysis of product formed showed 98% conversion to sulfoxide compound. The selectivity towards sulfoxide compound was 95% and 5 %sulphone was formed.

Example 12:

Examples 11-14 were in the multipoint micromixer with spatially discretely located inlets. 100 mg of imidazo[4,5-b]pyridine compound of Formula 3 was dissolved in 10 ml chloroform and 80mg of m-CPBA in 10 ml solvent chloroform. The microreactor was built with multipoint inlets for the m-CPBA. The solution of imidazo[4,5-b]pyridine compound of Formula 3 dissolved in chloroform was injected continuous at the first inlet of the reactor while the solution of m-CPBA was injected continuously at different proportions through the four inlets located discretely along the reactor length for a 1m long retention time tube. At every inlet a T micro mixer was used for inline mixing. The overall residence time of the reaction mixture was maintained at 60 s and at 5 °C reaction temperature. The analysis of product formed showed 85% conversion to sulfoxide compound. The selectivity towards sulfoxide compound was 99% and 0.5 %sulphone was formed.

Example 13:

For the composition of reacting solutions as given in Example 11, experiments with 50 s residence time and at 5 °C reaction temperature yielded 97% conversion to sulfoxide compound. The reduction in residence time was achieved by increasing the flow rate of m-CPBA in all the four inlets along the length of reactor. The selectivity towards sulfoxide compound was 98.5% and 1 %sulphone was formed.

Example 14:

For the composition of reacting solutions as given in Example 11, experiments with 60 s residence time and at 15 °C reaction temperature yielded 90% conversion to sulfoxide compound. The reduction in residence time was achieved by increasing the flow rate of m-CPBA in all the four inlets along the length of reactor. The selectivity towards sulfoxide compound was 99% and 1 %sulphone was formed.

Example 15:

For the reaction conditions given in the Example 12 and at 15 °C reaction temperature, the multipoint reactor yielded 98% conversion to sulfoxide compound. The reduction in residence time was achieved by increasing the flow rate of m-CPBA in all the four inlets along the length of reactor. The selectivity towards sulfoxide compound was 98% and sulphone was formed in the range of less than 1.5%.

We claim:

1. A continuous micromixer based process for the synthesis of sulfoxide compounds of formula 1 with a reaction time of less than or equal to one minute comprising:
 - a) mixing imidazo[4,5-b]pyridine compound of formula 2 with an oxidizing agent dissolved in a solvent in a T-shape micromixer with a reaction tube;
 - b) maintaining the temperature of the reaction tube at - 5 - 50 °C and specifically in the range of 5 - 25 °C and
 - c) isolating the product, wherein the selectivity of the process towards the sulfoxide compounds is > 95%.
2. The process as claimed in claim 1 wherein said oxidizing agent is m-chloroperbenzoic acid in 0.5 - 20 equimolar ratio.
3. The process as claimed in claim 1 wherein said solvent is selected from chloroform, methanol and combinations thereof.
4. The process as claimed in claim 1 wherein said solvents are in the ratio of 0 - 0.5v/v.
5. The process as claimed in claim 1 wherein said imidazo[4,5-b]pyridine compounds are in the range of 0.01 - 0.1 w/v.
6. The process as claimed in claim 1 wherein the micromixer comprises a single point inlet.
7. The process as claimed in claim 1 wherein the micromixer comprises a multi point inlet.

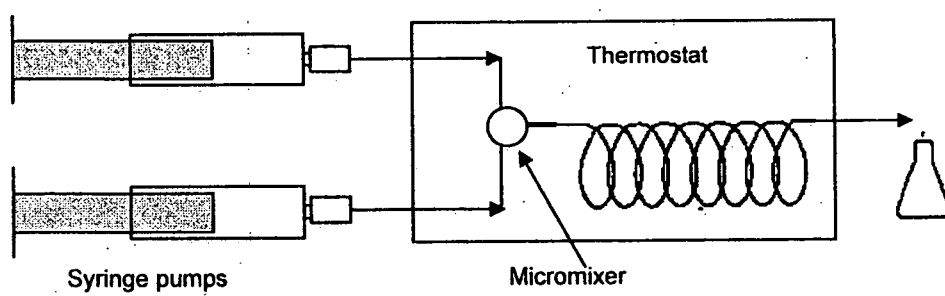


Figure 1

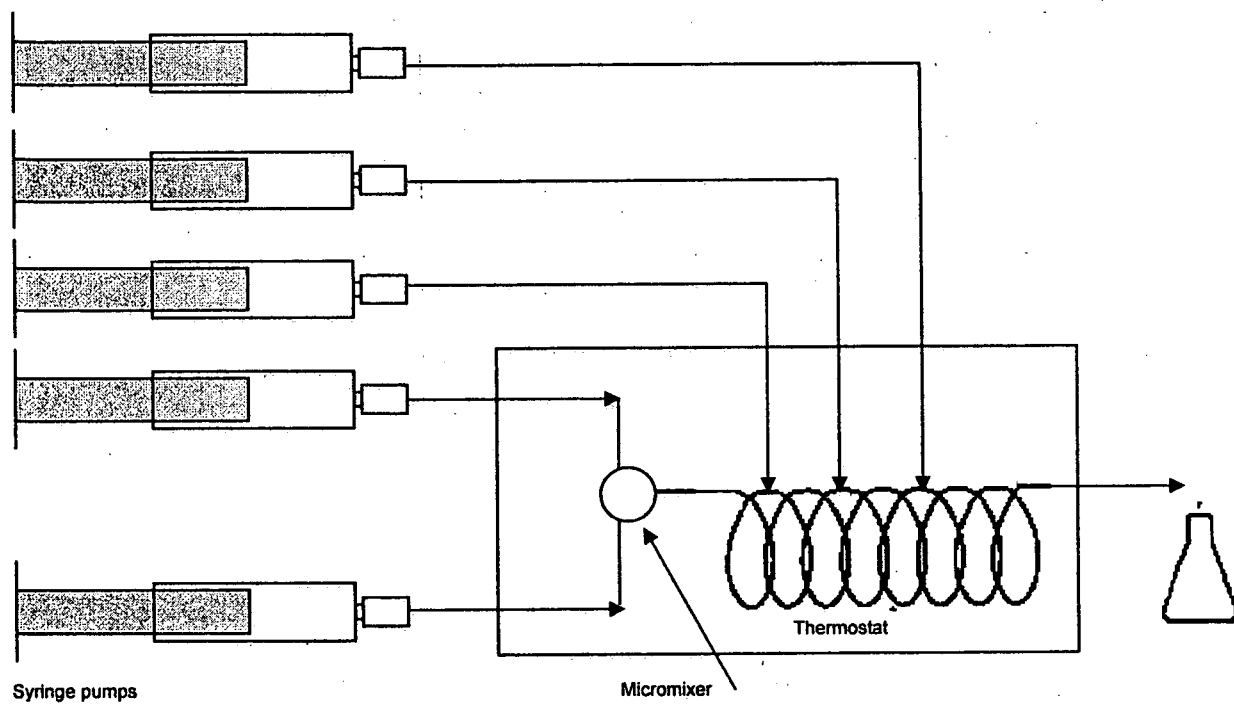


Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2010/000456

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04
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 practical, search terms used)

EPO-Internal , WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/089376 AI (JOSHI RAMESH A [IN] ET AL) 27 April 2006 (2006-04-27) cited in the application examples 1-3 claim 2	1-7
A	TAKUYA NOGUCHI, YOSHIRO HIRAI AND MASAYUKI KIRIHARA: "Highly selective 30% hydrogen peroxideoxidation of sulfides to sulfoxides using micromixing" CHEMICAL COMMUNICATIONS, 2008, pages 3040-3042, XP002602693 DOI : 10.1039/B802502A cited in the application the whole document	1-7

☐ 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 document 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)
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"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
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Date of the actual completion of the international search

29 September 2010

Date of mailing of the international search report

10/11/2010

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Cortes , Jose

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2010/000456

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006089376 AI	27-04-2006	US 2006089377 AI	27-04-2006