

PROCESS FOR PREPARING RETIGABINE & ITS INTERMEDITES

International Patent Application.
PCT/IN2011/000639

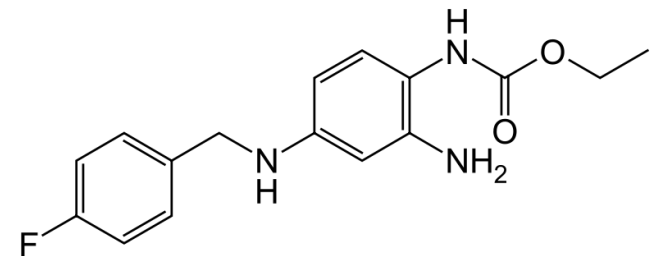
IDENTIFYING OUT-LICENSING PARTNERS



**INSTITUTE OF INTELLECTUAL PROPERTY
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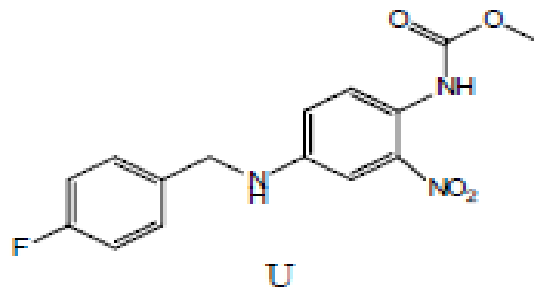
About Retigabine

- Epilepsy is a common and diverse set of chronic neurological disorders characterized by seizures. Definitions of epilepsy require that seizures be recurrent and unprovoked, but others require only a single seizure combined with brain alterations which increase the chance of future seizures.
- Retigabine or ezogabine is an anticonvulsant used as a treatment for partial epilepsies and for muscle relaxing, fever reducing and as peripheral analgesic agent.
- Retigabine works primarily as a potassium channel opener by activating a certain family of voltage gated potassium channels in the brain. This mechanism of action is unique among antiepileptic drugs, and promise for the treatment of other neurologic conditions, including migraine and neuropathic pain.



Advantages Over the Existing Processes:

- Replacement of genotoxic and potentially hazardous hydrazine hydrate as a deprotecting agent by new set of deprotecting agents selected from the set of ammonia, urea, thiourea, alkylamines, and thus avoiding the formation of byproducts like phthaloyl hydrazide, which is difficult to be removed from the product.
- Eliminating the use of catalyst or acid ion exchanger or water separator or azeotropic distillation technique while preparing retigabine intermediates.
- Eliminating the use of methanol as solvent during borohydride reduction of retigabine intermediate of formula S, thus avoiding the formation of transesterified impurity of **formula U**.



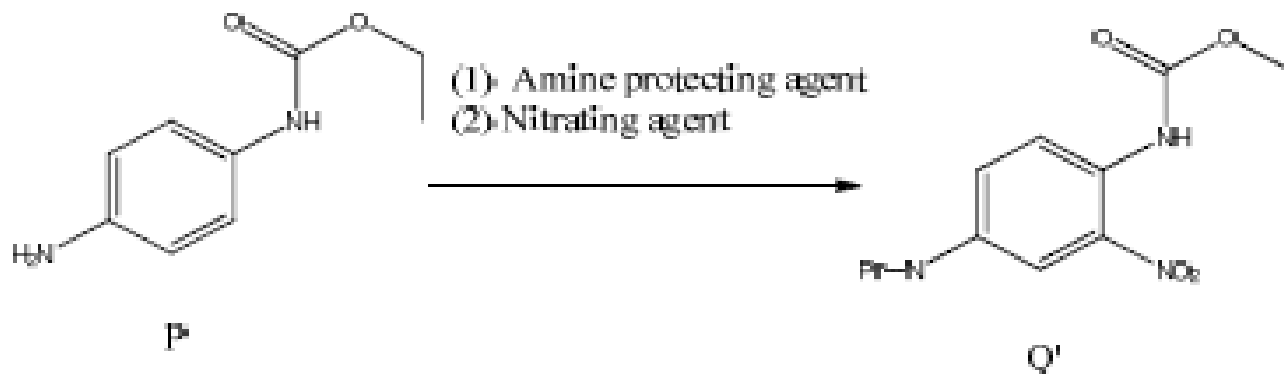
- Direct reductive amination of 5-amino-2-ethoxycarbonylamino-nitrobenzene of formula R or 2-nitrobenzene-1,4-diamine with 4-fluorobenzaldehyde of formula L in presence of borohydrides and aqueous solution, thereby avoiding the formation of hygroscopic and less stable imine compounds.
- Use of catalytic hydrogenation concept in presence of alcohol base combination for simultaneous reduction of double bond and nitro group, thereby eliminating the use of metal borohydride for reduction and thus the number of unit operations are reduced.
- Use of transfer hydrogen reaction technique for the reduction of nitro group comprises ammonium formate in combination with hydrogenation catalyst is advantageous as it avoids pressure reaction and use of external source of hydrogen gas.
- Use of alcohol base combination as a solvent system for the reduction of the intermediates of the formulae S and T through catalytic hydrogenation results in to formation of retigabine base in higher yields and better purity.

Proposed Method

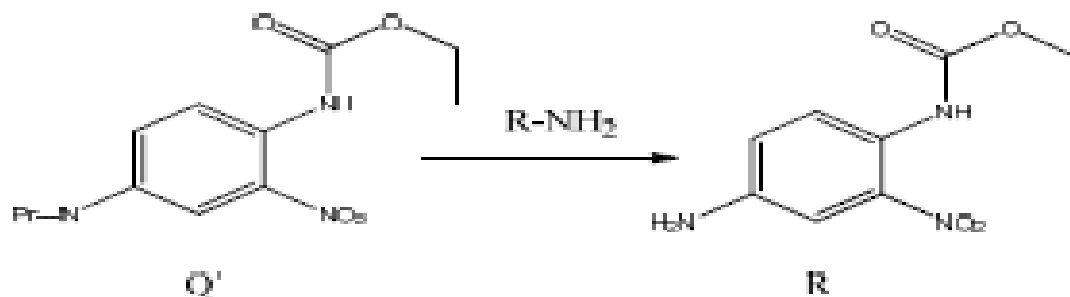
• Present invention relates to a efficient, economical and industrially viable process for the preparation of 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylaminobenzene (Retigabine) of formula (I) with improved yield and purity. Also, claimed new processes for the preparation of retigabine intermediates.

Proposed method for the Preparation of Retigabine(1st method)

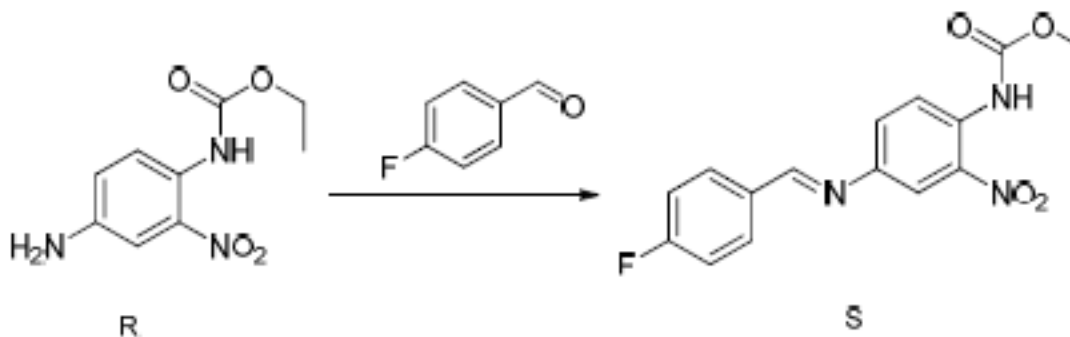
Steps (a). Process of preparation of Retigabine comprises contacting N-ethoxycarbonyl-p-phenylene diamine of **formula (P)** with amine protecting reagent in a solvent and then contacting the reaction mixture with nitrating agent to produce **compound (Q')**.



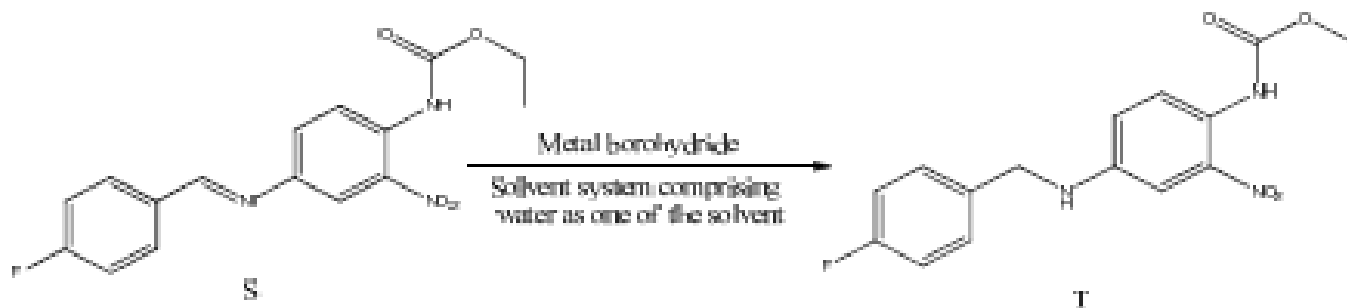
(b). Contacting the compound (Q') with compound of formula R-NH₂ to produce 5-amino-2-ethoxycarbonylamino-nitrobenzene of **formula R**.



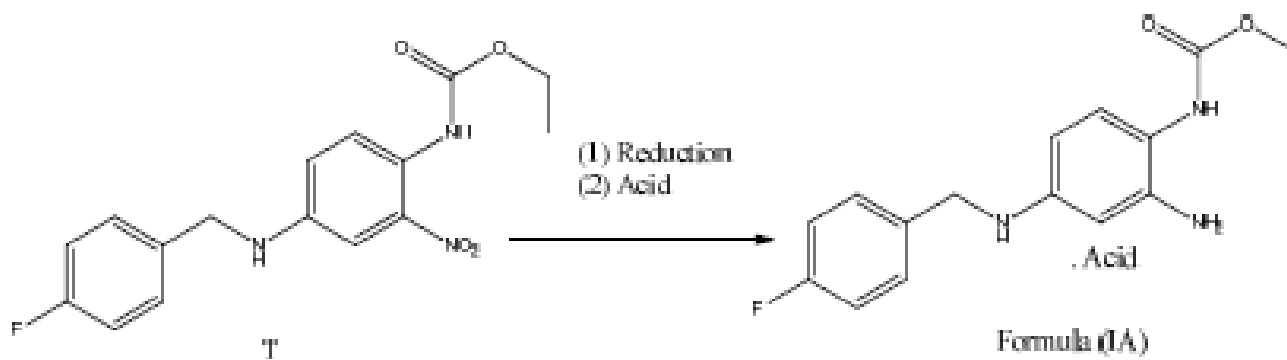
(c). Contacting 5-amino-2-ethoxycarbonylamino-nitrobenzene of formula R obtained with 4-fluorobenzaldehyde in a solvent to produce 2-ethoxycarbonylamino-5-(4-fluorobenzylideneamino)-nitrobenzene of **formula S**



(d). Contacting 2-ethoxycarbonyl-5-(4-fluorobenzylideneamino)-nitrobenzene of formula S obtained in the above step with metalborohydride in a solvent system comprises water as one of the solvent to produce 2-ethoxycarbonylamino-5-(4-fluorobenzylamino)-nitrobenzene of **formula T**

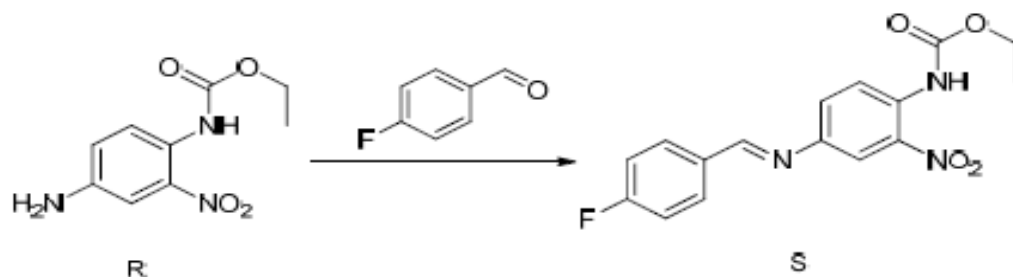


(e). Reducing 2-ethoxycarbonylamino-5-(4-fluorobenzylamino)-nitrobenzene of formula T obtained above by catalytic hydrogenation comprises alcohol-base combination as solvent system or by catalytic transfer hydrogenation reaction in presence of ammonium formate or formic acid in alkaline medium to obtain Retigabine base of **formula (IA)**

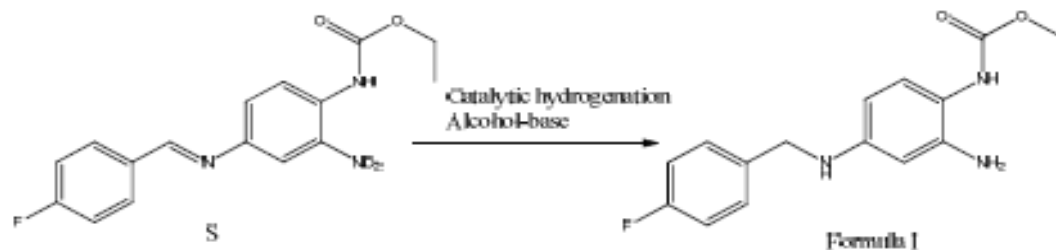


Proposed Retigabine Preparation Process (2nd Method)

Steps (a). Process for preparation of Retigabine of formula (I) comprises contacting 5-amino-2-ethoxycarbonylamino-nitrobenzene of formula R with 4-fluorobenzaldehyde in a solvent to obtain compound of formula S.

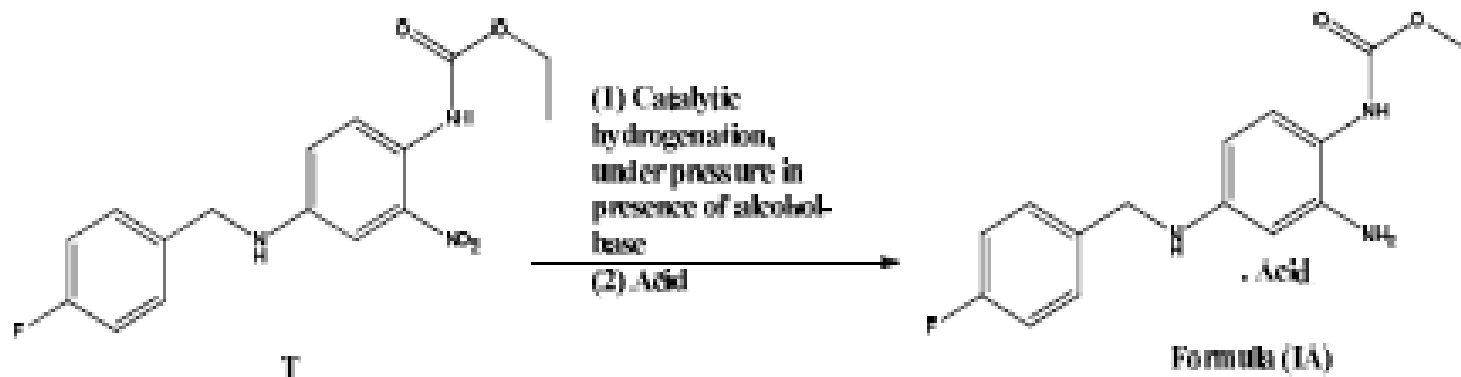


(b). simultaneously reduction of double bond and nitro group comprises catalytic hydrogenation of compound of formula S using alcohol base combination as solvent system to obtain Retigabine of formula(I) and contacting this with acid to obtain Retigabine acid addition salt of formula (IA)



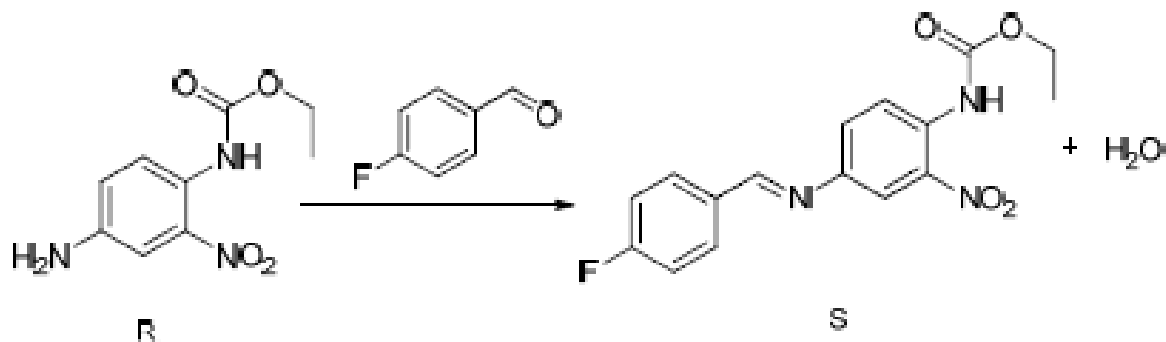
Proposed Retigabine Preparation Process (3rd Method)

(a). Process for preparation of Retigabine and its pharmaceutically acceptable salt comprises catalytic hydrogenation of the compound 2-ethoxycarbonylamino-5-(4-fluorobenzylamino)-nitrobenzene of formula T in presence of alcohol base as solvent system resulting into higher yield and better purity of retigabine which is then converted into its acid addition salt.



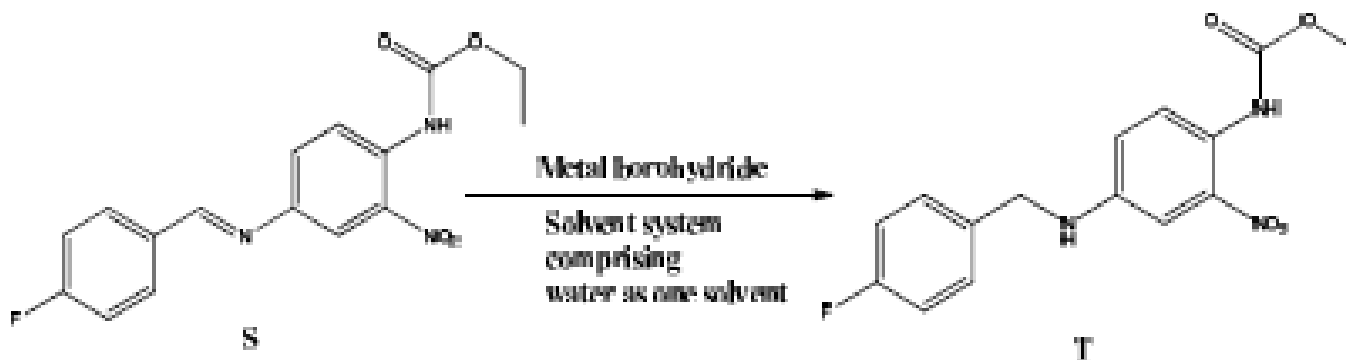
Preparation of Retigabine Intermediate (S):

Process for preparation of 2-ethoxycarbonylamino-5-(4-fluorobenzylideneamino)-nitrobenzene of formula S used as a key intermediate for the preparation of Retigabine of the formula I, comprises contacting 5-amino-2-ethoxycarbonylamino-nitrobenzene of formula R with 4-fluorobenzaldehyde avoiding use of catalyst/ion exchanger or water separator/azeotropic distillation to take the reaction to completion.



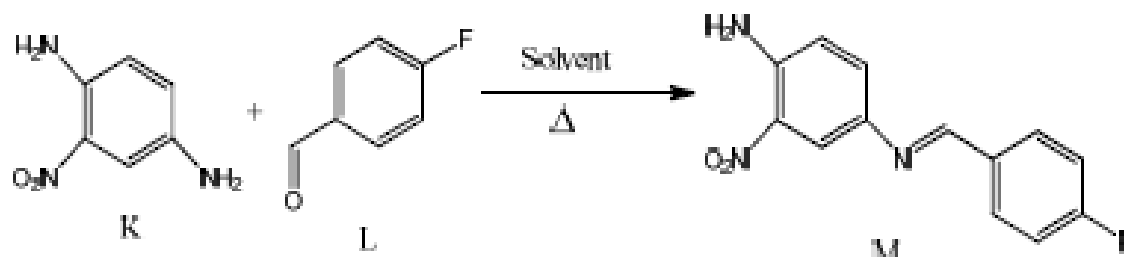
Preparation of Retigabine Intermediate (T)

Process for preparation of 2-ethoxycarbonylamino-5-(4-fluorobenzylamino)-nitrobenzene of **formula T** used as a key intermediate for the preparation of Retigabine of the formula I, comprises contacting 2-ethoxycarbonylamino-5-(4-fluorobenzylideneamino)nitrobenzene of formula S with a metal borohydride in a solvent system.



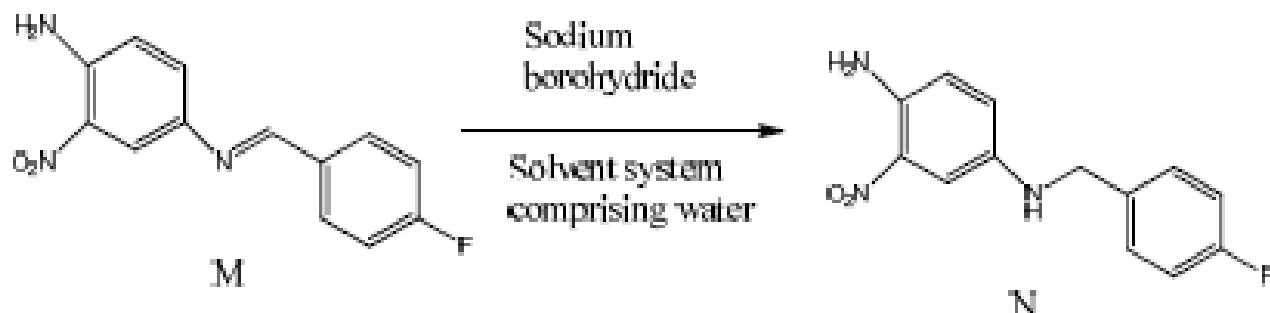
Preparation of Retigabine Intermediate (M)

Process for preparation of (4-fluorobenzylidene)-3-nitrobenzene-1,4-diamine of formula M used as a key intermediate for the preparation of Retigabine of the formula I, comprises contacting 2-nitrobenzene-1,4-diamine of formula K with 4-fluorobenzaldehyde avoiding use of water separator, azeotropic distillation or use of catalyst/ion exchanger to drive the reaction



Preparation of Retigabine Intermediate (N)

Process for preparation of (4-fluorobenzyl)-3-nitrobenzene-1,4-diamine of formula N used as a key intermediate for the preparation of Retigabine of the formula I, comprises contacting (4-fluorobenzylidene)-3-nitrobenzene-1,4-diamine of formula M with metal borohydride in a solvent system.



- Arch Pharma, the applicant of the invention also discloses and claims different process for preparation of Retigabine using intermediate compounds of formula S, T, M, N
- Total of 13 independent claims for Retigabine preparation and its intermediate preparation processes.

PATENT/IP STATUS

- Indian Patent
- International Patent Application No. PCT/IN2011/000639

EXPECTATIONS:

- Applicant seeks to Out-Licensing the Patent Rights on Exclusive or Non-Exclusive Terms.

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