

PROCESS FOR PREPARING OPTICALLY PURE MILNACIPRAN & ITS PHARMACEUTICALLY ACCEPTABLE SALTS

International Patent Application.
PCT/IN2010/000826

IDENTIFYING OUT-LICENSING PARTNERS

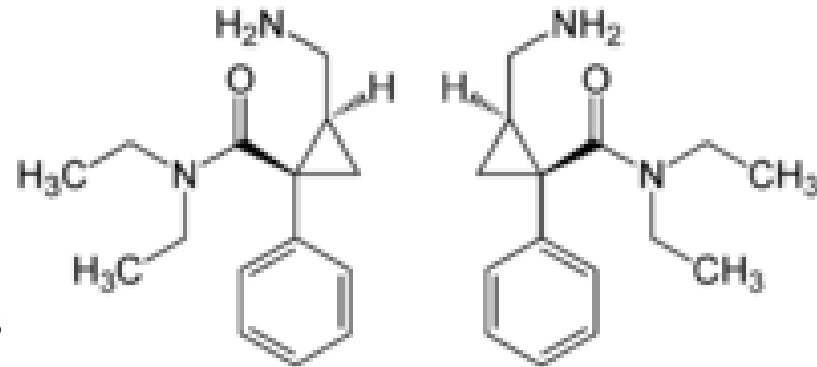


**INSTITUTE OF INTELLECTUAL PROPERTY
RESEARCH & DEVELOPMENT**

About Milnacipran

- Milnacipran (Ixel, Savella, Dalcipran, Toledomin) is a serotonin–norepinephrine reuptake inhibitor (SNRI) used in the clinical treatment of fibromyalgia.
- Racemic milnacipran chemically named as 1-phenyl-2-(aminomethyl) cyclopropane-N, N-diethyl carboxamide) was first approved for the treatment of major depressive episodes in December 1996. It is currently marketed for this indication in over 45 countries worldwide. Invention also claims the a process for preparing optically pure milnacipran.

•Milnacipran inhibits the reuptake of serotonin and norepinephrine in an approximately 1:3 ratio, respectively. Inhibition of both neurotransmitters simultaneously works synergistically to treat both **depression and fibromyalgia**.



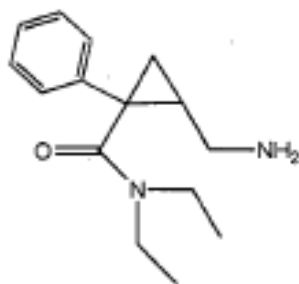
- U.S. Food and Drug Administration (FDA) approved racemic cis milnacipran (under the brand name Savella) for the treatment of fibromyalgia, making it the third medication approved for this purpose in the United States. Fibromyalgia, which is estimated to affect from 2-4% of the population in the US, is a complex syndrome associated with chronic widespread musculoskeletal pain and a reduced pain threshold, with hyperalgesia and allodynia .

IMPORTANCE OF OPTICAL PURITY

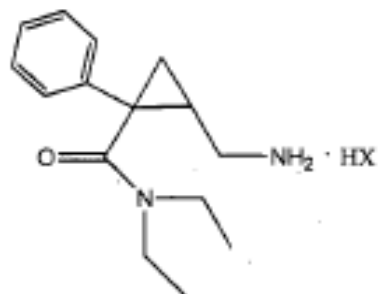
- In 1992, a resolution had been approved by American Food and Drug Administration (FDA) and The European Committee for Proprietary Medicinal Products, which encouraged that drugs with chiral center should be in optically pure form for marketing authorization. In 1996, a project had been proposed by FDA that drugs with chiral center must be in optically pure form when it is applying for marketing authorization.

Present Method

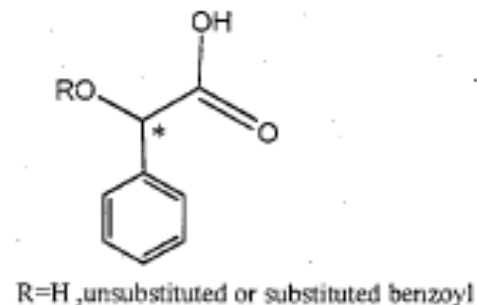
• Present invention comprises using racemic cis milnacipran or its pharmaceutically acceptable salts as starting material, a low cost and commercially available resolving agent of formula III and a industrially safe and economically low cost material such as water as a solvent. The process results into optical isomers of racemic cis milnacipran having excellent optical purity avoiding multiple crystallizations. The present invention uses water as a solvent thereby minimizing the use of any other solvent.



Formula I



Formula II

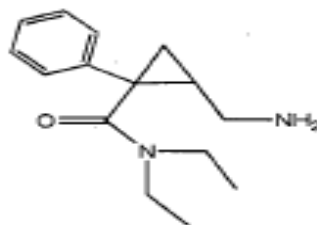


Formula III

• The Process is industrially safe, economic, and simple to practice to obtain two kinds of configurationally optically pure cis Milnacipran.

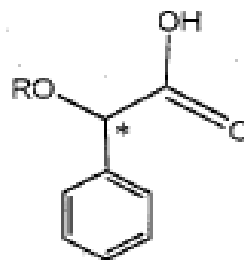
Description :

- A process for preparing optically pure milnacipran and their pharmaceutically acceptable salts comprises
 - Dissolving racemic cis milnacipran of the **formula I** in a solvent.



Formula I

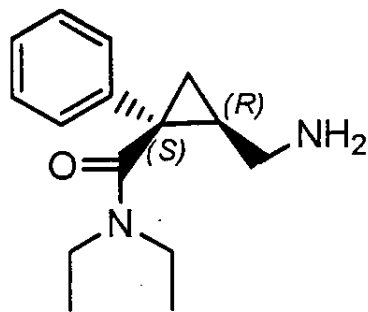
- Adding resolving agent of **formula III** optionally dissolved in a solvent to the solution of racemic cis milnacipran solution obtained in step a comprising optional heating to obtain a clear solution



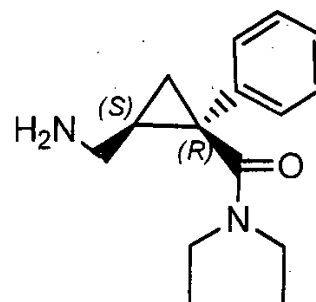
R=H, unsubstituted or substituted benzoyl

Formula III

- Cooling reaction mass of above step to separate optically pure cis- milnacipran resolvable salt which is filtered and washed with solvent.
- Dissolved cis-milnacipran resolvable salt obtained in step c in a solvent and to the said solution about 10% base is added to obtain substantially optically pure cis-milnacipran
- The process for preparation of **optically pure dextrogyral cis-milnacipran and levogyral cis-milnacipran** are claimed using D-mandelic acid and L-mandelic acids as resolving agents respectively.



(1S,2R)-milnacipran



(1R,2S)-cis-milnacipran

Advantages of the Proposed Process :

- Use of simple and low cost commercially available resolving agents thereby reducing overall costing of the product. The earlier processes uses tartaric acid derivatives such as bibenzoyl tartarate as a resolving agent ,these derivatives are very expensive and being of high Mol. Wt more quantity has to be used thus making the process very expensive.
- The alternate to obtain the stereospecificity is the stereoselective synthgesis,which comprises use of very expensive catalysts. Thus, making the process uneconomical.
- Higher yield and higher optical purity.
- Use of water as solvent.
- Avoiding multiple numbers of crystallizations to achieve required purity.
- Avoiding chromatographic separations.
- The process is low cost, easy to operate, suitable for industrial scale production.

PATENT/IP STATUS

- Indian Patent 3054/MUM/2010
- International Patent Publication No. [WO/2012/059933](#)

EXPECTATIONS:

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

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