A Semisynthetic Approach to Production of Keppra
Tech ID: 21546 / UC Case 2009-269-0

SUMMARY

UCLA researchers have designed novel metabolic pathways in E. Coli to easily produce the starting chiral synthons for Keppra synthesis from glucose.

BACKGROUND

Epilepsy is a debilitating disease of the central nervous system, which can cause severe seizures. Affecting around 1% of the population, this disease requires prolonged, and often life-long, drug treatments. Keppra, or Levetiracetam, is an important anti-convulsant drug used to treat seizures in patients with epilepsy. Keppra's patent rights in the US expired in 2009 opening up a large opportunity for generic production of the drug. Drug synthesis can be costly, however, due to laborious and expensive syntheses of starting materials. The ability to renewably produce the chiral-specific starting materials from simple molecules in bacteria could greatly reduce production costs.

INNOVATION

UCLA researchers have constructed novel metabolic pathways in E. Coli to use glucose to produce R-2-hydroxybutyrate or S-2-aminobutyrate, key metabolites for the enantioselective synthesis of Keppra. The researchers have produced R-2-hydroxybutyrate and S-2-aminobutyrate using their engineered strains. In addition, they have successfully completed the chemical synthesis of Keppra using their bacterially-produced S-2-aminobutyrate. Their engineered bacterial strains prove to be an attractive host for the renewable production of key starting metabolites for synthesis of important drug molecules.

APPLICATIONS

▶ Large-scale synthesis of Levetiracetam through large-scale fermentation of R-2-hydroxybutyrate or S-2-aminobutyrate

ADVANTAGES

▶ Cost-effective
▶ Improved efficiency
▶ Renewable starting components through the use of bacterial enzymatic pathway

STATE OF DEVELOPMENT

The researchers have successfully produced both chiral starting molecules using their engineered bacterial strains as well as completed the synthesis of Keppra from one of the starting molecules. They are working to improve the productivity and yield of their metabolites through further metabolic engineering.

PATENT STATUS

<table>
<thead>
<tr>
<th>Country</th>
<th>Type</th>
<th>Number</th>
<th>Dated</th>
<th>Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States Of America</td>
<td>Issued Patent</td>
<td>9,550,980</td>
<td>01/24/2017</td>
<td>2009-269</td>
</tr>
</tbody>
</table>

RELATED MATERIALS

▶ Expanding metabolism for total biosynthesis of the nonnatural amino acid L-homoalanine

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

▶ Novel Enzymes Enabling Microbial Fermentation of Sugar into Long Chain Alcohols
▶ Non-Oxidative Glycolysis For Production Of Acetyl-CoA Derived Compounds
▶ Production of C7 Alcohol (2-Isopropyl-1-Butanol) in Escherichia Coli by Combining Protein Evolution and Metabolic Engineering
▶ Isobutanol Production Using Metabolically Engineered Escherichia Coli
▶ Conversion Of Co2 To Higher Alcohols Using Photosynthetic Microorganisms