

METHOD OF MAKING A BENZYLISOQUINOLINE ALKALOID METABOLITE

Concordia University: UCON 167/180



BACKGROUND

Benzylisoquinoline alkaloids (BIAs) represent a large class of plant secondary metabolites, including pharmaceuticals such as morphine, codeine, sanguinarine and their derivatives. Many pharmaceutical drugs are isolated directly from plants or are semisynthetic derivatives of natural products. Information from New Drug Applications and clinical trials is evidence that the pharmaceutical industry continues to use natural products as a source of new drug leads. However, the pipeline of drug discovery is difficult to sustain, due to technical challenges in isolating new compounds with diverse structures and complex chemistries in sufficient quantities for screening. Indeed, large-scale production of BIA-based pharmaceuticals is limited to extraction and derivatization of alkaloids that accumulate in planta because of their chemically complex structure which renders their synthesis commercially unfeasible.

More recently, molecular and recombinant techniques have enabled the production of certain BIA intermediates like (R,S)-reticuline, (S)-scoulerine, protoberberine intermediates: (S)-tetrahydrocolumbamine, (S)-canadine using the yeast *Saccharomyces cerevisiae*. However, gaps in the biosynthetic pathways and the complexity of multi-gene co-expression in microbial hosts have prevented the production of a more diverse set of BIAs thus far.

TECHNOLOGY

The present invention combines gene discovery with multi-gene heterologous expression in *S. cerevisiae* to reconstitute multiple-gene BIA pathway for the biosynthesis of various BIA including codeine, morphine as well as other BIAs such as dihydro-sanguinarine and sanguinerine.

This reconstitution pathway represents the most complex and longest plant alkaloid biosynthetic pathway ever and hence represents an important advance towards the production of a broader class of alkaloids in a microbial host.

COMPETITIVE ADVANTAGES

- Yield no longer a problem compared to in planta production.
- Simple low-cost operation
- Feasible scaling up for pilot and commercial production

APPLICATIONS

Synthesis of BIA-based pharmaceuticals e.g morphine, codeine and their derivatives.

TECHNOLOGY DEVELOPMENTAL STAGE

Proof of concept completed on biosynthesis of various BIAs including dihydro-sanguinarine, sanguinarine, codeine and morphine.

PATENT STATUS

Title: Method of making a benzylisoquinoline alkaloid (bia) metabolite, enzymes therefore
Status: PCT/CA2015/050021
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Title: Methods of making morphinan alkaloids and enzymes therefore
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BUSINESS OPPORTUNITY

May be licensed on an exclusive basis related to a specific molecule.

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