Title: PROCESS FOR THE PRODUCTION OF AN IMMUNOSUPPRESSANT

Abstract: The present invention discloses process of producing sodium salt of immuno-suppressant of formula I: (I)
TITLE OF INVENTION

PROCESS FOR THE PRODUCTION OF AN IMMUNOSUPPRESSANT

FIELD OF INVENTION

The present invention provides a method for producing the sodium salt of the compound of Formula I.

![Formula I](image)

BACKGROUND OF THE INVENTION

Mycophenolic acid is an immunosuppressive agent that inhibits *de novo* purine nucleotide synthesis via inhibition of IMP dehydrogenase and prevents the formation of XMP and GMP.

Sodium salt of Mycophenolic acid or ERL 080 has been widely discussed in available patent and non-patent literature in treatment of diseases and in transplantation.

Use of Sodium Salt of Mycophenolic acid in treatment of hyperuricaemia has been reported in U.S. patent no. 3,705,946. US Patent Nos. 6,025,391 and 6,172,107 describes an enteric coating composition. In US Patent No. 6025391 the enteric coating composition contains HPMC phthalate and triacetin prepared for capsules containing monosodium mycophenolate; adapted to release mycophenolate in the upper part of the intestinal tract.
South African Patent no. 6814951 relates to the Sodium salt of MPA.

Tolerability profile of sodium mycophenolate and mycophenolate mofetil with and without cyclosporin has been discussed in Toxicology 157(2001) 207-215.

Che journal Acta Crystallographica, Section C: Crystal Structure Communications (2000), C56(4), 432-433 discusses Crystal structure of Sodium mycophenolate.

SUMMARY OF THE INVENTION

The instant invention reveals a process for manufacture of Sodium salt of the compound of formula I, which comprise reacting the compound of formula I with sodium salt of C₂ to C₁₀ carboxylic acid

DETAILED DESCRIPTION OF THE INVENTION

The instant invention describes a Process of manufacturing Sodium salt of the compound of formula I,

\[
\text{Formula I}
\]

by reacting the compound of formula I with a sodium salt of C₂ to C₁₀ carboxylic acid.

Alternately the compound of formula I may be converted to its ammonium or dibenzyl amine form by reacting compound of formula I with a sodium salt of C₂ to C₁₀ carboxylic acid
The compound of formula I is converted to its ammonium salt by treating with ammonia.

The dibenzyl amine salt of the compound of formula I is prepared by reacting with dibenzyl amine.

The sodium salt of C₂ to C₁₀ carboxylic acid is selected from sodium acetate, sodium 2-ethyl hexanoate or sodium caprylate.

The compound of formula I is converted to its ammonium salt by reacting with ammonia. The ammonium salt of formula I is reacted with sodium acetate or sodium 2-ethyl hexanoate or Sodium caprylate to get the sodium salt of the compound of formula I.

The following Examples further illustrate the invention, it being understood that the invention is not intended to be limited by the details disclosed therein.

**EXAMPLE 1**

10g of sodium acetate is dissolved in 55 ml of methanol. To this 74g of mycophenolic acid was added and stirred for half an hour at RT. The contents were chilled to 10°C and filtered. The solid are washed with 50 ml acetone, dried under vacuum at 40 to 50°C. A final yield 90%( 70g) was observed.

**EXAMPLE 2**

To a slurry of mycophenolic acid (25g) in methanol, dicyclohexyl amine was added and stirred at RT. The precipitated solid was then treated with aqueous sodium acetate solution under stirring RT. The reaction mixture was cooled to 10 °C and the precipitated solid was filtered and dried.

**EXAMPLE 3**
25g of sodium 2-ethylcaprylate is dissolved in 175 ml of methanol. To this 250g of mycophenolic acid was added and stirred for half an hour at RT. The contents were chilled to 10°C and filtered. The solid are washed with 50 ml acetone, dried under vacuum at 40 to 50°C. A final yield 90%(22g) was observed.

EXAMPLE 4

25g of sodium 2-ethylhexanoate is dissolved in 175 ml of ethyl acetate. To this 250g of mycophenolic acid was added and stirred for half an hour at RT. The contents were chilled to 10°C and filtered. The solid are washed with 50 ml acetone, dried under vacuum at 40 to 50°C. A final yield 90% (22g) was observed.

EXAMPLE 5

100g of mycophenolic acid was taken in 175 ml of methanol and was stirred for half an hour at RT. Ammonia gas was bubbled for 30 min followed by addition of aqueous sodium acetate. The contents were chilled to 10°C and filtered. The solid are washed with 50 ml acetone, dried under vacuum at 40 to 50°C. A final yield 90% (95g) was observed.
We Claim:

1. A Process of manufacturing sodium salt of the compound of formula I comprising,

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CH3
OCH3
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Formula I

reacting the compound of formula I with a sodium salt of C$_2$ to C$_{10}$ carboxylic acid.

2. A process according to claim 1, wherein the compound of formula I is converted to an ammonium salt or a dibenzyl amine salt before converting it to the sodium salt.

3. A process according to claim 2, wherein the compound of formula I is converted to its ammonium salt by treating with ammonia.

4. A process according to claim 2, wherein the dibenzyl amine salt of the compound of formula I is obtained by reacting with dibenzyl amine.

5. A process according to claim 1, in which sodium salt of C$_2$ to C$_{10}$ carboxylic acid is selected from sodium acetate, sodium 2-ethyl hexanoate or sodium caprylate.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

Int. Cl. 7: C07D 307/88

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)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

STN: CAS online (mycophenolic acid)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>ZA 6804959 (ELI LILLY AND COMPANY) 2 February 1970</td>
<td>1-5</td>
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<td>See Example 3</td>
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<td>X</td>
<td>See page 433 &quot;Experimental&quot;</td>
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☐ Further documents are listed in the continuation of Box C ✗ See patent family annex

"A" Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 20 December 2002

Date of mailing of the international search report 6 JAN 2003

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Form PCT/ISA/210 (second sheet) (July 1998)
This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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