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(54) Title: PREPARATION OF 3,4-DIHYDROISOQUINOLINES FROM AN ACID AND AN AMINE

(57) Abstract: The present invention is directed to processes for the synthesis of morphinans. In particular, a process for coupling a carboxylic acid compound with an amine compound to form an amide product that can then be isolated or the crude amide product can be cyclized to form a 3,4-dihydroisoquinoline. In one embodiment, the carboxylic acid contains a phenol moiety protected with a labile protecting group. The protected phenol reduces reaction times, simplifies work-up of the product, and reduces the amount of cyclizing agent, POCl<sub>3</sub> that is necessary to form the 3,4-dihydroisoquinoline.



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# INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/025263

**A. CLASSIFICATION OF SUBJECT MATTER**

INV . C07C235/34 C07D217/20

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)

C07C C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**EPO-Internal , WPI Data, BEILSTEIN Data, EMBASE**

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
<b>X</b>	<p><b>HUANG W -J ET ALf "Synthesis of (+-)-Glauicine and (+-)-Neospirodienon <math>\theta</math> via an One-Pot Bischler-Napieralski Reaction and Oxidative Coupling by a Hypervalent Iodine Reagent"</b></p> <p><b>HELVETICA CHIMICA ACTA 2004 CH, vol. 87, no. 1, 2004, pages 167-174, XP002476119</b></p> <p><b>ISSN: 0018-019X</b></p> <p><b>precursors of compounds 5a, 5c, 5d, 5f, and 5g; page 173, General Procedure (5a-e and 5f,g)</b></p> <p style="text-align: center;">-----</p> <p style="text-align: center;">-/--</p>	1-11

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents .

"A<sup>1</sup>" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O<sup>1</sup>" 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

11 April 2008

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2007/025263

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>VENKOV A P ET AL: "Synthesis of isoquinolines from 2-phenylethyl amines, amides, nitriles and carboxylic acids in polyphosphoric acid" TETRAHEDRON 19960909 GB, vol. 52, no. 37, 9 September 1996 (1996-09-09), pages 12299-12308, XP002476120 ISSN: 0040-4020 Table 1, compounds 5d, 5f, and 5g; page 12306, Typical procedure (5a-j)</p> <p>-----</p>	1-11
X	<p>DE 922 827 C (KNOLL AG) 27 January 1955 (1955-01-27) claim 1; examples 1,2</p> <p>-----</p>	1-11

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2007/025263

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-11

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-11

a method for preparing compounds of formula 600 from  
compounds of formula 300 and 400

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2. claims: 12-19,28-34

a method for preparing compounds of formula 502 from  
compounds of formula 301 and 400 as well as the compounds of  
formula 502

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3. claims: 20-27

a method for preparing compounds of formula 601 from  
compounds of formula 501

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4. claims: 35-41

the compounds of formula 602

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/025263

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 922827	C	NONE	