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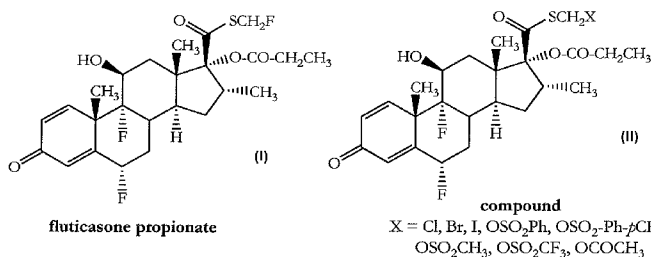
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(54) Title: PROCESS FOR THE PREPARATION OF S-FLUOROMETHYL-6, 9 -DIFLUORO-11 -HYDROXY-16 -METHYL-17-PROPIONYLOXY-3-OXO-ANDROSTA-1,4-DIENE-17 -CARBOTHIOATE AND INTERMEDIATES

(57) Abstract: The present invention relates to a process for the preparation of steroidal 17 $\beta$ -carboxylic thioates. More particularly the present invention relates to a convenient and efficient synthesis of steroidal 17 $\beta$ -carboxylic thioates, such as fluticasone propionate formula (I), using soluble mixed fluorides to introduce fluorine by displacing an appropriate leaving group X in compounds formula (II) resulting in selective and controlled fluorination. The present invention also relates to intermediates formula (II) and their preparation.

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2007/050328

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> INV. C07J31/00 A61K31/56 A61P5/44		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) C07J A61K A61P		
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, CHEM ABS Data		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 088 877 A (GLAXO GROUP LTD) 16 June 1982 (1982-06-16) pages 10,20, lines 28,29; example 18	1-21
X	PHILLIPPS G H ET AL: "SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS IN A SERIES OF ANTIINFLAMMATORY CORTICOSTEROID ANALOGUES, HALOMETHYL ANDROSTANE 17BETA-CARBOETHOATES AND -17BETA-CARBOSELENOATES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, no. 22, 28 October 1994 (1994-10-28), pages 3717-3729, XP002052064 ISSN: 0022-2623 page 3726; tables 1,2; compounds 11E,13E ----- -/--	1-55
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.		
<input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents :		
*A* 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* 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	Date of mailing of the international search report	
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  BOURGHIDA, E	

## INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/052912 A (FARMABIOS S R L [IT]; CAINELLI GIANFRANCO [IT]; UMANI RONCHI ACHILLE [I]) 24 June 2004 (2004-06-24) example 16	1-21
X	EP 1 526 139 A (S N I F F ITALIA S P A [IT]) 27 April 2005 (2005-04-27) example 4	22-30
X	WO 03/066653 A (GLAXO GROUP LTD [GB]; COOTE STEVEN JOHN [GB]; NICE ROSALYN KAY [GB]; W) 14 August 2003 (2003-08-14) example 5	22-30
X	WO 00/38811 A (GLAXO GROUP LTD [GB]; LANCASTER ROBERT WILLIAM [GB]; SINGH HARDEV [GB]) 6 July 2000 (2000-07-06) page 9, lines 5-17; example 1	22-30
X	AIGBIRHIO FRANKLIN I ET AL: "Automated radiosynthesis of no-carrier-added (S-fluoromethyl-18F)fluticasone propionate as a radiotracer for lung deposition studies with PET" JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS, JOHN WILEY, CHICHESTER, GB, vol. 39, no. 7, 1997, pages 567-584, XP002273073 ISSN: 0362-4803 pages 572-573; figure 6	31-55
X	US 4 335 121 A (PHILLIPPS GORDON H ET AL) 15 June 1982 (1982-06-15) column 15	47-55
E	WO 2007/099548 A (SUN PHARMACEUTICAL IND LTD [IN]; PATEL JITEN RANHHODBHAI [IN]; PATEL) 7 September 2007 (2007-09-07) page 56; compound IA27	47-53

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB2007/050328

## 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.:

### 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: 1-21 (fully)

Process of preparing S-fluoromethyl-6 ,9 -difluoro-11  
-hydroxy-16 -methyl-17  
-propionyloxy-3-oxo-androsta-1,4-diene-17 -carbothioate (I)  
from compounds of formula (II) by using soluble mixed  
fluorides and the compound S-fluoromethyl-6 ,9 -difluoro-11  
-hydroxy-16 -methyl-17  
-propionyloxy-3-oxo-androsta-1,4-diene-17 -carbothioate  
obtained by that process.  
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2. claims: 22-30, 47-55 (fully)

Process to purify a compound of formula (II) and compounds  
of formula (II).  
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3. claims: 31-46 (fully)

Process of preparing a compound of formula (II).  
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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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