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Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i)) for all designations*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

[Continued on next page]

(54) Title: CONVENIENT SYNTHESIS OF S-FLUOROMETHYL 6ALPHA, 9ALPHA-DIFLUORO-11BETA-HYDROXY-16ALPHA- METHYL-17ALPHA-PROPIONYLOXY-3-OXOANDROSTA-1, 4-DIENE-17BETA-CARBOTHIOATE

(57) Abstract: The present invention provides a convenient process for the preparation of S-fluoromethyl 6a, 9a-difluoro-11b-hydroxy-16a-methyl-17a-propionyloxy-3-oxoandrosta-1, 4-diene-17b-carbothioate, a compound of formula (1), comprising(a) treating 17b-[(N, N-dimethylcarbamoyl)thio]carbonyl-6a,9a-difluoro-11b-hydroxy-16a-methyl-17a-propionyloxy-3-oxoandrosta-1, 4-diene, a compound of formula (3) with alkali metal carbonate-alcohol system to obtain 6a, 9a-difluoro-11b-hydroxy-16a-methyl-17a-propionyloxy-3-oxoandrosta-1, 4-diene-17b-carbothioic acid, a compound of formula (4); (b) reacting the compound of formula (4) with bromofluoromethane to yield the compound of formula (1).The present invention also provides an improved process for preparation of compound of formula (1) comprising (a) reacting 6a, 9a-difluoro-11b-hydroxy-16a-methyl-3-oxo-17a-(propionyloxy) androsta-1, 4-dien-17b-carboxylic acid, a compound of formula (2), with N,N-dimethylthiocarbamoyl chloride in an inert aprotic solvent in the presence of an iodide catalyst and a base to give a compound of formula (3), (b) reacting the compound of formula (3) with a hydrosulfide reagent and bromofluromethane to obtain a compound of formula (1).

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
8 April 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00219-0

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07J 31/00, 75/00

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)

IPC[7]: C07J

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 practicable, search terms used)

REGISTRY, CASREACT, CAPLUS, WPI, EPODOC, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/62722 A2 (ABBOT LABORATORIES) 30 August 2001 (30.08.01) *the whole document, esp. pages 3-5, page 10 lines 8-9, Scheme 1 on page 12, page 13 line 13 - page 14 line 15, examples 3, 4, 5, 7, 8, claims.*	1-31
A	GB 2088877 A (GLAXO GROUP LIMITED) 16 June 1982 (16.06.82) *the whole document, esp. pages 1-4, preparations.*	1-31
A	IL 109656 A1 (CHEMAGIS LTD.), 22 February 1998 (22.02.98) (abstract) CASREACT [online], Chemical Abstracts online [retrieved on 24.11.2003]. Retrieved from: CASREACT Database, STN-International, Karlsruhe (DE), CASREACT Accession no. 129:276096; *abstract, reaction schemes.* ----	1-31

☐ Further documents are listed in the continuation of Box C. ☒ 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 application or patent 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
24 November 2004 (24.11.2004)	17 February 2004 (17.02.2004)
Name and mailing adress of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535	Authorized officer WENIGER S. Telephone No. 1/53424/341

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00219-0

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

Group I, claims 1-22: a process for the preparation of fluticasone propionate by
a) treating the N,N-dimethylcarbamoylthiocarbonyl derivative of formula 3 with an alkali metal carbonate/alcohol system to obtain the corresponding carbothioic acid derivative 4;
b) reacting compound 4 with bromofluoromethan to obtain fluticasone propionate;

Group II, claims 23-31: a process for the preparation of fluticasone propionate by
a) reacting the androstadien carboxylic acid of formula 2 with N,N-dimethylthiocarbamoyl chloride in an inert aprotic solvent with an iodide catalyst and a base to give the N,N-dimethylcarbamoylthiocarbonyl derivative of formula 3
b)reacting compound 3 with a hydrosulfide reagent and bromofluoromethane to obtain fluticasone propionate;

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Intern: l application No.
PCT/IN 03/00219-0

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB A 2088877		CA A 1205464	1986-06-03
		IE L 862287L	1981-08-15
		IE L 810282L	1981-08-15
		SK B 278140B	1996-02-07
		ES A 8600936	1986-02-16
		ES A 8502447	1985-04-01
IL A 109656	1998-02-22	none	