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(54) Benævnelse: **FREMGANGSMÅDE TIL FREMSTILLING AF ETORICOXIB**

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JP-A- 2003 160 563
DAVIES I W ET AL: "A PRACTICAL SYNTHESIS OF A COX-2-SPECIFIC INHIBITOR" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON.; US LNKD- DOI:10.1021/JO000870Z, vol. 65, 1 January 2000 (2000-01-01), pages 8415-8420, XP002326845 ISSN: 0022-3263
DAVIES, IAN W. ET AL: "Preparation and Novel Reduction Reactions of Vinamidinium Salts" JOURNAL OF ORGANIC CHEMISTRY , 66(1), 251-255 CODEN: JOCEAH; ISSN: 0022-3263, 2001, XP002592388

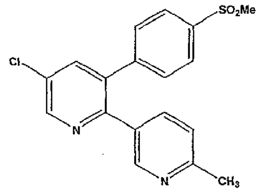
DESCRIPTION

FIELD OF INVENTION

[0001] The present invention relates to an improved process for the preparation of Etoricoxib and also a process for preparing substituted β-chlorovinamidinium salts with cyclic alkyl group (with or without hetero atom), which is one of the intermediate for preparation of Etoricoxib.

BACKGROUND OF THE INVENTION

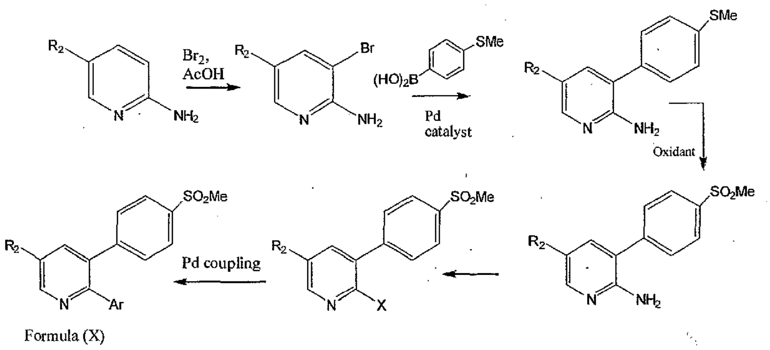
[0002] Etoricoxib is a selective COX-2 inhibitor which has been shown to be as effective as non-selective non-steroidal anti-inflammatory drugs in the management of chronic pain in rheumatoid arthritis, osteoarthritis and other COX-2 mediated disorders. Etoricoxib is 5-chloro-6'-methyl-3-[4-methylsulfonyl)phenyl]-2,3'-bipyridine having structural formula (I).



Etoricoxib [Formula (I)]

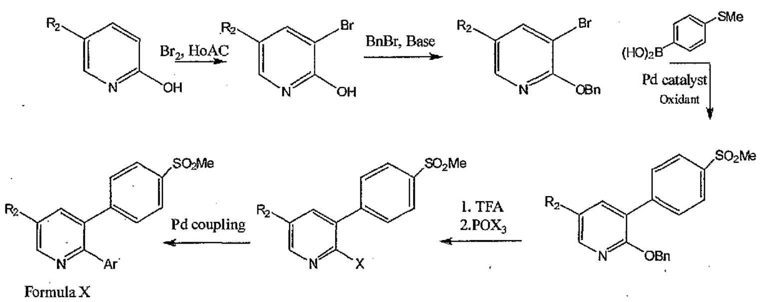
[0003] Etoricoxib belongs to a class of drugs known as COX-2 inhibitors that are used in the treatment of COX-2 mediated disorders. The therapeutic application of Etoricoxib as a COX-2 inhibitor is disclosed in WO 9610012 and WO 9616934.

[0004] Compounds of general formula (X) which includes Etoricoxib are disclosed in WO9803484 (US 5861419). Process for the preparation of Compound of formula (X) involves bromination of 2-amino pyridine derivative with bromine in acetic acid to provide the bromide of 2-amino pyridine derivative. Coupling of this bromide derivative with 4-(methylthio)phenyl-boronic acid is done in presence of a suitable base, which is then oxidized to give the corresponding sulphon. Then the amino group of sulphon is converted to corresponding halide. A second palladium catalyzed coupling of sulphon halide derivative with an appropriately substituted metal containing aromatic give compound of formula (X).



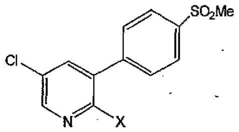
Scheme-I

[0005] WO9803484 application also discloses a second method for the preparation of compound of formula (X), which is as per scheme II.

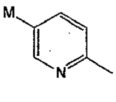


Scheme II

[0006] US 6812346 discloses a method for the preparation of Etoricoxib which comprises reacting a compound of formula B, wherein X is Br or Cl, with compound of formula C, wherein M is $B(OH)_2$ or $SnMe_3$, in the presence of a palladium catalyst to yield Etoricoxib.

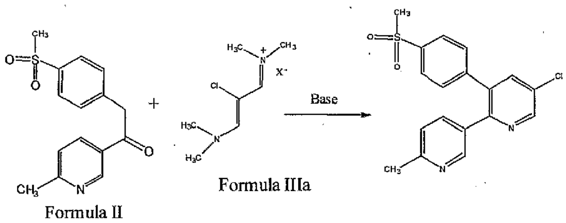


Formula B



Formula C

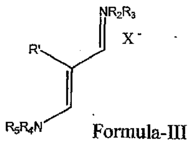
[0007] A process for the preparation of Etoricoxib as described in scheme III, is disclosed in US6040319, wherein X represents phosphates, sulfates, acetates, perchlorate, borates, antimonates, halides, benzoate, napsylate, particularly, hexafluorophosphate, sulfate, mesylate, tosylate, triflate, acetate, trifluoroacetate, tetrafluoroborate, tetraphenyl borate, hexafluoroantimonate, chloride, bromide, fluoride, iodide, benzolate and napsylate. Base used is Na and K hydroxide; Cs carbonate; Li, Na and K C_{1-6} alkoxide; Li, Na and K amides, Li, Na and K hydrides.



Scheme III

[0008] WO 0137833 discloses different polymorphs of Etoricoxib, specifically disclosed are forms II, III and IV, hemihydrate of form IV and sesquihydrate of form I.
WO 0192230 discloses polymorphic form V of Etoricoxib and process for its preparation. WO 0296877 discloses pharmaceutical composition comprising 10-50% of polymorphic form V and remainder of the compound comprising at least one polymorph selected from forms I, II, III and IV.

[0009] WO 2005085199 discloses different other polymorph of Etoricoxib, specifically disclosed forms IX, X, XI, XII, XIII, XIV, XV and XVI.
US 6252116 (divisional of US 6040319) discloses process for preparing intermediate of formula (III), particularly CDTH (2-chloro-1,3-bis(dimethylamino)trimethinium hexafluorophosphate) salt with hexafluorophosphate, tetraphenyl borate, hexafluoroantimonate as it counterion (X^-).



Formula-III

[0010] According to formula (III) R_2 through R_5 each independently represents C_{1-6} alkyl, aryl or aralkyl group.

[0011] Certain heteroatom containing cycloalkyl substituted β-chlorovinamidinium salts are disclosed in J. Org. Chem., Vol. 66, No. 1, p. 251-255, 2001. But a large number of limitations are also reported. The method disclosed for the preparation of substituted β-chlorovinamidinium salt comprises, addition of chloroacetic acid to N-formyl compound containing a cycloalkyl group which optionally contains a hetero atom and the mixture was heated at 70 °C and then to it was added phosphorus oxychloride which after suitable work up gave the substituted β-chlorovinamidinium salt. This document also states that the β-chlorovinamidinium salt using N-formylmorpholine was obtained with very low yield (<10%) and pure sample could not be obtained by using this method. Thus, there exists a need to prepare suitable substituted β-chlorovinamidinium salts containing a cyclic group optionally containing one or more heteroatom, as one of the intermediate for the preparation of Etoricoxib, in a pure form and high yield, and preparing

[0012] Etoricoxib using this intermediate, in a cost effective and industrially scalable way. We herein disclose an improved process for preparation of differently substituted β-chlorovinamidinium salts containing a cyclic group optionally containing one or more heteroatom, and also a process for the preparation Etoricoxib using the substituted β-chlorovinamidinium salts thus obtained.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013]

FIG. 1 is a powder X-ray diffraction (XRPD) pattern of the Etoricoxib obtained according to the process of the present invention.

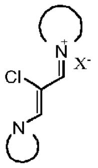
FIG. 2 is a powder X-ray diffraction (XRPD) pattern of form I of 2-chloro 1,3-(bis piperidyl) trimethinium hexafluoro phosphate according to the present invention.

FIG. 3 is a powder X-ray diffraction (XRPD) pattern of form II of 2-chloro 1,3-(bis piperidyl) trimethinium hexafluoro phosphate according to the present invention.

OBJECTS OF THE INVENTION

[0014] The main objective of the present invention is to provide improved process for preparing Etoricoxib.

[0015] In an embodiment is provided an improved process for preparing substituted β-chlorovinamidinium salts of formula (IIIb)



(IIIb)

wherein

represents a cyclic group, optionally containing one or more heteroatom.

[0016] In a preferred embodiment is provided an improved process for preparing substituted β-chlorovinamidinium salts of formula (IIIb).

[0017] In another embodiment is provided a process for preparing Etoricoxib of formula (I) using the intermediate of formula (IIIb).

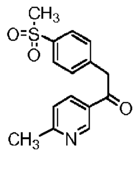
[0018] In one further embodiment is provided a process for the purification of substituted β-chlorovinamidinium salts of formula (IIIb).

[0019] In one of the embodiment of the present invention is disclosed a novel intermediate of formula (IIIc) and use of this intermediate in the process of preparation of Etoricoxib. The above and other embodiments are further described in the following paragraphs.

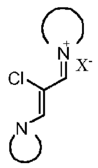
DETAILED DESCRIPTION

[0020] As used herein, the term "THF" refers to tetrahydrofuran, the term "DMF" refers to dimethyl formamide, the term "DIPE" refers to di-isopropyl ether, the term "DMSO" refers to dimethyl sulphoxide, the term "MTBE" refers to methyl t-butyl ether, the term, "MEK" refers to methyl ethyl ketone, the term 'LHMDS' refers to lithium bis (trimethylsilyl)amide, the term 'KHMDS' refers to potassium bis (trimethylsilyl)amide.

[0021] The present invention provides, an improved process for the preparation of Etoricoxib which involves reacting substituted β-chlorovinamidinium salt of formula (IIIb) and a ketosulfone compound of formula (II).



Formula II

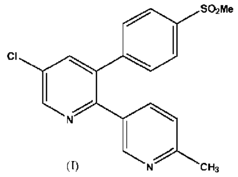


(IIIb)

wherein

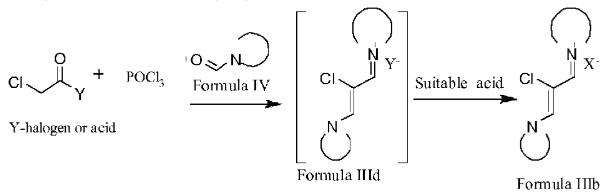
represents a cyclic group, optionally containing one or more heteroatom selected from N, O or S & 'X⁻' represents the suitable counterion.

[0022] Thus, the present invention provides a process for the preparation of Etoricoxib of formula-(I) comprising,



(I)

1. (a) reacting a compound of formula-(IV) with suitable chloroacetyl halide or chloro acetic acid and phosphorous oxychloride to obtain the compound of formula (IIId) & further converting the compound of formula (IIId) into its suitable salt to obtain the compound of formula-(IIIb),



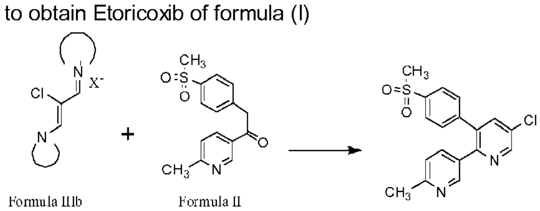
Formula IIId

Formula IIIb

wherein

represents a cyclic group, optionally containing one or more heteroatoms selected from N, O or S & 'X⁻' represents a suitable counter ion.

2. (b) reacting the compound of formula (IIIb) with compound of formula (II) in presence of suitable base and suitable solvent to obtain Etoricoxib of formula (I)



Formula IIIb Formula II Formula I

[0023] Preferably, the groups comprising

may be selected from morpholidinyl, piperidinyl and a pyrolidinyl group.

[0024] Preferably, the suitable salt of compound of formula (IIIb) is prepared by reaction of the compound of formula (IIId) with a suitable salt of an acid to obtain corresponding salt of compound formula (IIIb).

[0025] Preferably, the suitable salt of an acid is selected from the group consisting of phosphate, sulphate, acetates, perchlorate, borates, antimonite, halides, benzoate, napsylate, hexafluorophosphate, tetrafluoro borate, chloride, bromide, fluoride, iodide, benzoate and carbonate.

[0026] Preferably, the suitable salt of acid is hexafluorophosphate.

[0027] Preferably, the suitable solvent is selected from C_1-C_6 alcohols, hydrocarbons selected from benzene, toluene and xylene; halocarbon solvents selected from mono or di halo C_1-C_4 alkyls, nitrogen containing solvents selected from DMF, dimethyl acetamide, N-ethylpyrrolidinone, N-methyl pyrrolidinone and acetonitrile and dioxane and dimethyl sulfoxide.

[0028] Preferably, the solvents are selected from C_1-C_6 alcohol, THF, DMF, dioxane and dimethyl sulfoxide.

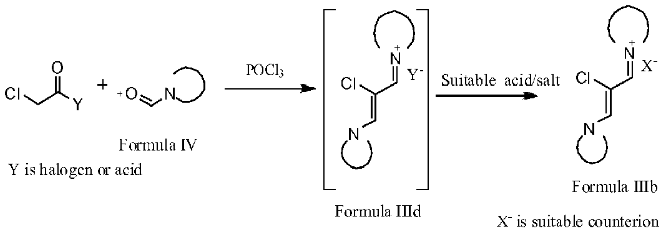
[0029] Preferably, the suitable base used is selected from suitable organic or inorganic bases, wherein the inorganic bases are selected from alkali metal or alkaline earth metal hydroxides, alkali metal or alkaline earth metal carbonates such as $NaHCO_3$, Na_2CO_3, K_2CO_3, alkali metal hydrides, alkali metal alkoxides.

[0030] The present invention further provides a process for the preparation of β-chlorovinamidinium salt of formula (IIIb).

[0031] The present invention also includes a new intermediate of formula (IIIc) for the preparation of Etoricoxib.

[0032] The present invention provides a process for the preparation of substituted β-chlorovinamidinium salt of formula (IIIb) comprising, reacting a compound of formula (IV), wherein

is as defined earlier, with a suitable chloroacetyl halide or chloro acetic acid and phosphorous oxychloride at room temperature or below, and adding the compound of formula (IV) to the combination to obtain the compound of formula (IIId) & further converting the compound of formula (IIId) into its suitable salt of formula-(IIIb).



[0033] Preferably, the temperature is less than 30 °C.

[0034] Preferably, the process comprises combining chloro acetic acid or a sutable chloroacetyl halide and phosphorous oxychloride, and thereafter adding the compound of formula (IV).

[0035] Preferably, the N-formyl compound of formula (IV) is added drop wise to the combination of the chloro aceticacid or chloroacetyl halide and phosphorous oxychloride. Preferably, prior to the addition of N-formyl compound, a cooling step is performed. Preferably, the cooling is to a temperature of -10 °C to 25 °C. More preferably cooling is done to 10 °C to 20 °C and most preferably 0 °C to 10 °C.

[0036] Preferably, after combining chloro acetic acid or suitable chloroacetyl halide, phosphorous oxychloride and N-formyl compound of formula (IV), as above, the reaction mixture was heated to a suitable temperature for suitable period of time.

[0037] Preferably, the suitable temperature during this step may be selected from 50 °C to 150 °C, more preferably from 75 °C to 120 °C and most preferably from 90 °C to 100 °C.

[0038] Preferably, the reaction mixture is maintained at the desired high temperature for 3 hour to 25 hours, more preferably for 5 to 10 and most preferably for 6 to 8 hrs.

Recovery of the β-chlorovinamidinium salt:

[0039] The reaction mixture was cooled to room temperature to obtain a semi solid mass of compound of formula (IIId), which was dissolved in a suitable organic solvent and subsequently added to a suitable acid or a salt of suitable acid at suitable temperature over a suitable period of time. The pH of the reaction mixture was maintained at pH 3-5 using aqueous solution of a suitable base. The β-chlorovinamidinium salt of formula (IIIb) was isolated by adding water. Preferably, the isolation is done by filtration.

[0040] Preferably, the organic solvent used for obtaining the salt may be selected from the group comprising of dimethylformamide (DMF), alcohols like methanol, ethanol, isopropanol, butanol, 1,2-dimethoxy ethanol, 2-methoxy ethanol, 2-ethoxy ethanol, ethylene glycol and the like and their suitable mixtures with water.

[0041] Preferably, the temperature at this step is maintained at 0 °C to 25 °C, more preferably 10 °C to 20 °C and most preferably at 0 °C to 10 °C.

[0042] Preferably, the compound of formula (IIId) is converted to its suitable salt of formula (IIIb) by reacting it with the salt of corresponding acids.

[0043] Preferably, salt of suitable acids may be selected from the group comprising of hexafluorophosphate, phosphate, sulphate, acetates, perchlorate, borates, antimonite, halides, benzoate, napsylate, tetrafluoro borate, chloride, bromide, fluoride, iodide, benzoate, carbonate, hexafluoroantimonate.

[0044] In an embodiment the invention encompasses process for purification of the β-chlorovinamidinium salt of formula (IIIb).

[0045] The process of purification comprises dissolving the β-chlorovinamidinium salt of formula (IIIb) in a mixture of suitable solvent(s) and water and stirring the reaction mixture. Subsequently the reaction mixture was washed with suitable solvent(s) and water to obtain the β-chlorovinamidinium salt with > 95 % purity.

[0046] The suitable solvent used in the purification step may be selected from C_1-C_5 alcohols or their suitable esters or suitable mixtures thereof.

[0047] The β-chlorovinamidinium salt of formula (IIIb) obtained above was further purified (having from 1 to 3 % total impurity) by taking the β-chlorovinamidinium salt of formula (IIIb) in a suitable solvent and adding aqueous solution of a bisulphite or metabisulphite & subsequently washing the solution with water. Suitable solvent for the second purification may be selected from C_1-C_5 alcohols and suitable esters or suitable mixtures thereof. Alcohols are preferred.

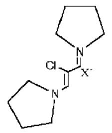
[0048] The present invention also provides a method of producing a compound of formula-(IIIb) as above, wherein the compound of formula (IIIb) is further purified by

1. i) dissolving the compound of formula (IIIb) in C_1-C_5 alcohols or their esters, optionally with water & subsequently isolating the compound of formula (IIIb);
2. ii) treating the compound of formula (IIIb) with suitable alkali bisulphite or metabisulphite, in C_1-C_5 alcohols or their esters and subsequently isolating the pure compound of formula (IIIb).

[0049] The preferred bisulphite or metabisulphite used for the second purification may be selected from sodium or potassium bisulphite or metabisulphite.

[0050] Preferably, the salt of formula (IIIb) is obtained with at least 99 % purity by HPLC.

[0051] The present invention also provides a compound of structural formula-(IIIc), wherein 'X⁻' represents a suitable counter ion.



Formula IIIc

[0052] In one of the embodiment of the invention is disclosed 2-chloro 1,3-(bis piperidyl) trimethinium hexafluoro phosphate and 2-chloro 1,3-(bis pyrolidinyl) trimethinium hexafluoro phosphate salt with at least 99.9 % purity by HPLC.

[0053] It has surprisingly been found according to the invention that 2-chloro 1,3-(bis piperidyl) trimethinium hexafluorophosphate is obtained in two different polymorphic forms, which are designated as Form-I & Form-II respectively.

[0054] Form I of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluorophosphate obtained according to the present invention is characterized by an XPRD pattern substantially in accordance with the pattern disclosed in Fig. 2.

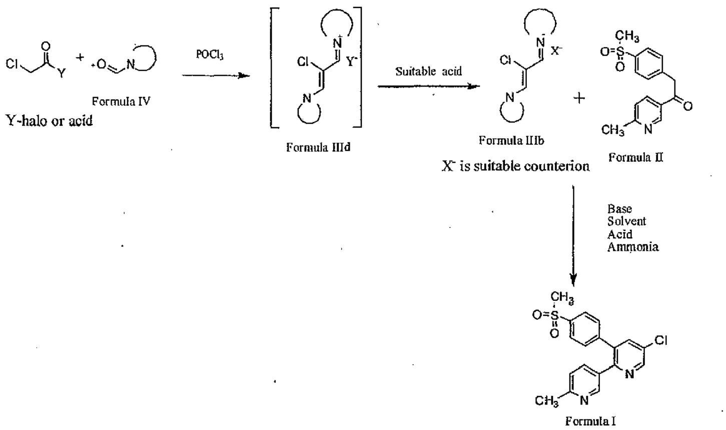
[0055] Form I of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate obtained according to the present invention is also characterized by an XPRD peaks at about 9.06, 11.60, 12.06, 12.89, 13.64, 14.38, 16.022, 16.98, 17.56, 18.16, 19.43, 20.16, 20.46, 21.04, 21.48, 21.98, 22.25, 22.68, 23.35, 23.76, 24.24, 24.64, 25.92, 26.75, 27.42, 28.03, 28.55, 29.04, 29.68, 30.06, 30.52, 31.25, 31.96, 32.36, 33.31, 33.94, 34.30, 35.16, 35.80, 38.14, 39.47 ° ± 0.2 ° degrees (2θ)(Fig. 2) and has melting point in the range of 185-200 °C. (Decomposed)

[0056] Form II of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate obtained according to the present invention is also characterized by an XPRD peaks at about 9.14, 10.142, 12.12, 12.96, 13.71, 17.06, 17.64, 18.24, 19.49, 20.520, 21.10, 21.56, 22.32, 22.74, 23.42, 24.32, 24.72, 26.05, 27.48, 28.10, 29.14, 29.79, 30.12, 30.61, 31.30, 32.06, 32.43, 33.36, 34.02, 34.38° ± 0.2 ° degrees (2θ) (Fig. 3) and has melting point in the range of 190-197 °C.

[0057] The present invention further provides a process for the preparation of Etoricoxib, using the β-chlorovinamidinium salt of formula (IIIb), which comprises of the following steps:

1. (a) reacting a compound of formula-(IV) with suitable chloroacetyl halide or chloro acetic acid and phosphorous oxychloride to obtain the compound of formula (IIId) & further converting the compound of formula (IIId) into its suitable salt to obtain the compound of formula-(IIIb), as described above; and
2. (b) reacting compound of formula (IIIb) with compound of formula (II) in presence of suitable base and suitable solvent to obtain compound of formula (I).

[0058] The above process may be illustrated as per the following Scheme IV:



[0059] Preferably, the groups comprising

may be selected from morpholidinyl, piperidinyl and pyrolidinyl group.

[0060] Preferably, step (a) further comprises the preparation of compound of formula (IIIb) as described above.

[0061] Preferably, the β-chlorovinamidinium salt of formula (IIIb) is as described above. Preferably, step (a) comprises first combining chloroacetyl chloride and phosphorous oxychloride, and thereafter combining the N-formyl compound of formula (IV), to obtain the β-chlorovinamidinium salt of formula (IIIb), by processes as described above. Preferably, the temperature in step (a) is as described above.

[0062] Preferably, the reaction mixture is maintained in step (a) is as described above. Prior to step (b), the β-chlorovinamidinium salt of formula (IIIb) obtained in step (a) is separated. Preferably, the separation is done by filtration as described earlier in the specification.

[0063] The organic solvent in step (b) may be selected from the group comprising of suitable hydrocarbons such as benzene, toluene, xylene, ethyl benzene, trimethyl benzene & the like; suitable halogenated hydrocarbon solvents such as chloroform, dichloromethane, dichloroethane and the like or mixtures thereof; alcohols such as methanol, ethanol, t-butanol and like or mixtures thereof; ketones such as acetone; aprotic solvents such as DMF, dimethyl acetamide; ethers like diethyl ether, 1,4-dioxane, DIPE, MTBE, THF & the like, aprotic polar solvents such as DMF, DMSO, DMA; nitriles like acetonitriles or their suitable mixtures thereof.

[0064] The suitable base used in step (b) may be selected from suitable organic or inorganic bases such as hydroxides selected from NaOH, KOH & the like, carbonates such as $NaHCO_3$, Na_2CO_3, K_2CO_3, hydrides such as NaH and LHMDS, KHMDS and like; alkali metal alkoxides such as sodium, potassium, lithium t-butoxide and like; sodium, potassium, lithium isopropoxide and like.

[0065] Optionally, after completion of step (b) compound formula (I) can be isolated or subjected to insitu purification. Purification of compound formula (I) may be done by using formalin solution and aq. ammonia in suitable solvent. The reaction mixture is stirred at suitable temperature and product is isolated using suitable solvent. Then after recrystallization is carried out using suitable solvent to obtain pure Etoricoxib.

[0066] The suitable solvent used for the purification of Etoricoxib may be selected from C_1-C_5 alcohol; ketones such as acetone and methyl ethyl ketone; ethers such as THF and dioxane or their suitable mixtures.

[0067] The suitable solvent used for the isolation of Etoricoxib may be selected from suitable alcohols or esters. The preferred solvent is isopropyl alcohol.

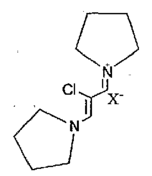
[0068] The suitable solvent used for recrystallization of Etoricoxib may be selected from suitable alcohols, esters, ethers or their suitable mixtures. The preferred solvent for recrystallisation is isopropyl alcohol.

[0069] In one of the embodiment of the invention is disclosed Etoricoxib obtained according to the process of the present invention with at least 99.9 % purity by HPLC.

[0070] Etoricoxib obtained according to the process of the present invention is characterized by an XPRD pattern substantially in accordance with the pattern Fig. 1.

[0071] Etoricoxib obtained according to the present invention is also characterized by an XPRD peaks at 7.00, 8.50, 9.67, 11.72, 12.35, 12.96, 13.24, 15.04, 15.44, 16.51, 17.06, 17.70, 18.07, 18.76, 19.34, 20.00, 20.24, 21.14, 21.50, 22.20, 22.70, 23.28, 24.02, 24.76, 25.73, 26.20, 26.90, 27.37, 28.44, 29.24, 29.83, 30.41, 30.66, 31.22, 33.04, 34.63, 35.76, 37.62, 39.16, 39.65 ° ± 0.2 ° degrees (2θ) (Fig.1) and has melting point in the range of 135-137 °C.

[0072] In one of the embodiment of the present invention is disclosed a novel intermediate of formula (IIIc), and use of this intermediate in the process of preparation of Etoricoxib.



Formula IIIc

X^- is suitable counterion

[0073] The 2-chloro 1,3-(bis pyrolidinyl) trimethinium hexafluoro phosphate salt was isolated and characterized by the following data:

^{1}H NMR (300MHz, DMSO-D6) δ (ppm): 1.82 - 1.95 (8 H, dd), 3.73 (4H, s), 4.01 (4H, s), 7.98 (2H, s);

^{13}C NMR (75MHz, DMSO-D6) δ (ppm): 23.14, 25.50, 49.51, 56.73, 92.70, 156.53

ESI MS = 212.9 m/z (base peak).

[0074] In a further embodiment of the invention is disclosed a pharmaceutical composition of Etoricoxib with a liquid or solid carrier, excipients as is known in the art wherein the Etoricoxib is produced by the above disclosed process.

[0075] The invention is further described by the following examples, which are provided for illustration only and should not be construed to limit the scope of invention.

<u>**Example 1**</u>

Preparation of 2-chloro 1,3-(bis morpholinyl) trimethinium hexafluoro phosphate

[0076] Phosphorous oxychloride (6.6g) was added in to N-formyl morpholine (5g) at -5 to 10 °C and subsequently chloroacetyl chloride (5g) was added at room temperature and the reaction mixture was stirred. Further, N-formyl morpholine (5g) was added to the reaction mixture at room temperature and the reaction mass was heated at 55-110 °C for 3 to 24 hrs. The reaction mixture was then cooled to room temperature to obtain a semi solid mass, which was dissolved in dichloromethane and subsequently a solution of $NaPF_6$ was added at 0-10 °C over a period of one hour. Then into it 50 ml water was added, organic layer was separated, dried and concentrated till dry at less than 50 °C, to give 2-chloro 1,3-(bis morpholinyl) trimethinium hexafluoro phosphate. Yield=(4 g). HPLC purity = 44.63 %.

<u>**Example 2**</u>

Preparation of Etoricoxib

[0077] Potassium tert. butoxide (1.4g) was dissolved in THF and the solution was maintained at 5-25 °C for 10 minutes. Subsequently, a solution containing the 1-(6-methylpyridin-3-yl)-2[4-(methylsulfonyl)phenyl] ethanone (3g) in THF was added and kept this at 25-30 °C for 1 hr. 2-chloro 1,3-(bis morpholinyl) trimethinium hexafluoro phosphate of (formula III) (4g) in THF, obtained above, was added to the previously prepared solution of 1-(6-methylpyridin-3-yl)-2[4-(methylsulfonyl)phenyl] ethanone and the reaction mixture was heated at 30-55 °C for 2-24 hrs. The reaction mixture was dumped into a mixture of trifluoroacetic acid (0.6 g), acetic acid (4.4g) and THF and further heated at 55-60 °C for 6-20 hrs after adding aqueous ammonia solution (30 ml) and ammonium acetate (0.8g). The reaction mixture was dumped into water and extracted with ethyl acetate and washed with 10% aqueous sodium bicarbonate solution. The organic layer was separated, dried & concentrated till dry at temperature less than 50 °C to obtain Etoricoxib. Yield = (3.1 g),
% purity by HPLC = 15.36 % (Etoricoxib), 64.15 % (unreacted ketosulfone compound of formula II

<u>**Example 3 (Reference Example**</u>

Preparation of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluorophosphate

[0078] Chloroacetic acid (4.75g, 0.05 mole) was added to N-formyl piperidine (13.5g, 0.119 mole) and the reaction mixture was heated to 70-75 °C to give a clear solution. Subsequently, phosphorous oxychloride (9.5 ml, 0.1 mole) was added over a period of 1-2 hrs and maintained at 70-75 °C for 3 hrs. The reaction mixture was cooled to room temperature and diluted with absolute alcohol (10 ml) and this reaction mass was added into the solution of $NaPF_6$. The reaction mass was stirred for 30 minutes at 0-10 °C, filtered and washed with water, to obtain 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate (2 g), yield = 10.42 %, HPLC purity- 83.63 %

Example 4

Preparation of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0079] Chloroacetyl chloride (20g) solution was cooled and phosphorous oxychloride (27.2g) was added into it at -10 to 0 °C. Subsequently, N-formyl piperidine (40g) was added over a period of 1 hrs, maintained the reaction mass at 55-110 °C for 6-20 hrs. Then the reaction mixture was cooled to room temperature and diluted with DMF (40 ml). This reaction mass was added into the solution of $NaPF_6$ over a period of 1 hr and the reaction mixture was stirred for 60 minute at 0-10 °C. The reaction mixture was filtered and washed with water to obtain crude 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate (37.2 g), HPLC purity = 83.24 %.

[0080] Crude mass was purified by using methanol: water treatment to obtain 2-chloro 1,3-(bis piperidyl) trimethinium hexafluoro phosphate (18.8 g), yield = 27.48 %, HPLC purity = 99.19 %.

Example-5

Preparation of Etoricoxib

[0081] Potassium tert. butoxide (2.1g) was dissolved in THF (20ml) and the solution was maintained at 5-25 °C for 10 minutes. Subsequently, a solution of 1-(6-methylpyridin-3-yl)-2[4-(methylsulfonyl)phenyl] ethanone (5g) in THF was added and kept the mixture for 1hr at 25-30 °C. 2-chloro 1,3-(bis piperidyl) trimethinium hexafluoro phosphate salt of formula (IIIc) (8g), obtained in Example 4 above, in THF, was added to the previously prepared solution of ketosulfone and the reaction mixture was heated at 30-55 °C for 2-24 hrs. The reaction mixture was dumped into a mixture of trifloroacetic acid (1g), acetic acid (7.5g) and THF. The reaction mixture was further heated to 55-60 °C for 6-20 hrs, after adding ammonia solution (125 ml). Then cooled the reaction mixture to room temperature. The reaction mixture was dumped into water and extracted with ethyl acetate and washed with 10% aqueous sodium bicarbonate solution. The organic layer was separated and concentrated to dryness at less than 50 °C to give Etoricoxib 8.6 g.
HPLC purity- 91.28 % (Etoricoxib).
Crude mass was purified to obtain Etoricoxib (4.7g), yield = 75.9 %; HPLC purity = 96.31 %.

Example-6

Preparation of 2-chloro 1,3-(bis morpholinyl) trimethinium hexafluoro phosphate

[0082] Phosphorous oxychloride (6.6 g) was added in to N-formyl morpholine (5g) at a temperature of -5 to 5 °C. Subsequently chloroacetyl chloride (5g) was added at a temperature of 25-30 °C followed by addition of N-formyl morpholine (5g) at temperature 55 to 60 °C, there after the reaction mass was maintained at temperature 80-90 °C for 5 hr, & then cooled to 25-30 °C. The reaction mixture was diluted with dichloromethane 50 ml and the solution of $NaPF_6$ was added at 0-10 °C over a period of one hour. 50 ml water was added to the reaction mixture and organic layer was separated, dried, and concentrated to dryness at < 50 °C to obtain 2-chloro 1,3-(bis morpholinyl) trimethinium hexafluoro phosphate.
% Yield = 23.13 %, (4 g), HPLC purity = 44.63 %.

Example-7

Preparation of Etoricoxib

[0083] Potassium tert. butoxide (1.4g) was dissolved in THF (7ml) and the solution was maintained at 25-30 °C for 10 minutes and then cooled to 10 °C. Subsequently, solution of 1-(6-methylpyridin-3-yl)-2[4-(methylsulfonyl)phenyl] ethanone (5g) in THF was added and kept the mixture for 1hr at 25-30 °C. Subsequently, 2-chloro 1,3-(bis morpholinyl) trimethinium hexafluoro phosphate (4g) followed by THF (20ml) was added and the reaction mixture was maintained at 25-30 °C for 2 hrs. The reaction mixture was dumped in to the mixture of trifluoroacetic acid (0.6g), acetic acid (4.4g) and THF (10ml) and maintained the reaction mixture at 25-30 °C for 2 hrs. The reaction mixture was stirred at 55-60 °C for 3 hrs and aq. ammonia solution (30ml), and ammonium acetate (0.8g) was added and further stirred at 55-60 °C for 20 hrs. The reaction mixture was cooled to 25-30 °C then after water was added and extract with ethyl acetate (50ml). Organic layer was separated and washed with 10 % sodium bicarbonate solution, dried and concentrated to dryness < 50 °C to obtain Etoricoxib.
Yield = 3.1 g, (12.82 %), HPLC purity = 15.36.% (Etoricoxib), (unreacted 64.15 %-sulfone compound).

<u>**Example-8**</u>

Preparation of 2-chloro 1,3-(bis pyrolidinyl) trimethinium hexafluoro phosphate salt

[0084] Chloroacetyl chloride (5g) was cooled to -10 to 0 °C and phosphorous oxychloride (6.8g) was added in one lot at 0 to 10 °C. Subsequently, N-formyl pyrolidine (8.76g) was added drop wise at 0 to 5 °C and the reaction mixture was maintained at 90-100 °C for 6 hrs. There after the reaction mixture was cooled to 25-30 °C and diluted with DMF (10ml). Subsequently, the reaction mass was added into the solution of $NaPF_6$ within 60 minutes at 0-10 °C and stirred for 60 minutes at 0-10 °C. The solid was precipitated out, which was filtered and washed with water to obtain 2-chloro 1,3-(bis pyrolidinyl) trimethinium hexafluoro phosphate salt. Yield = 8.7 g, HPLC purity = 93.09 %.
Crude mass was purified using Methanol: water. Yield = 5.2 g, (32.9 %), HPLC purity = 98.87 %.

<u>**Example-9**</u>

Preparation of Etoricoxib

[0085] Potassium tert. butoxide (0.426g) was dissolved in THF (40ml) and the solution was maintained at 25-30 °C for 10 minutes and then cooled to 10-15 °C. Subsequently, solution of 1-(6-methylpyridin-3-yl)-2[4-(methylsulfonyl)phenyl] ethanone (1g) in THF was added and kept the mixture for 1hr at 10-15 °C. Subsequently, 2-chloro 1,3-(bis pyrolidinyl) trimethinium hexafluoro phosphate salt (1.3g), in THF (8ml) was added and maintained the reaction mixture for 2 hrs at 25-30 °C. The reaction mixture was dumped in to the mixture of trifloroaceticacid (0.2g), acetic acid (1.5g), and THF (10ml) and maintained for 1 hour at 25-30 °C. Further the reaction mixture was heated at 60-70 °C for 15 hrs after aq. ammonia solution (25ml) was added and the reaction mixture was cooled to 25-30 °C. After then ethyl acetate and water was added, organic layer was separated and washed with water and 10 % sodium bicarbonate solution. Organic layer was separated, dried and concentrated to dryness < 50 °C to give crude Etoricoxib.
Yield = 0.9 g (40.84 %), % HPLC purity = 55.82 % (Etoricoxib), (unreacted sulfone compound = 34.44 %).

<u>**Example-10**</u>

Preparation of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0086] Chloroacetyl chloride (5g) was cooled to -10 to 0 °C and phosphorous oxychloride (6.8g) was added in one lot at 0 to -10

°C. Subsequently, N-formyl piperidine (10g) was added drop wise at 0 to 5 °C and reaction mixture was maintained at 90-100 °C for 16 hrs. Thereafter reaction mixture was cooled to 25-30 °C and diluted with DMF. Subsequently, the reaction mass was added into the solution of $NaPF_6$ within 60 minutes at 0-10 °C and stirred for 60 minutes at 0-10 °C. The solid was precipitated out, which was filtered and washed with water to obtain 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate salt.
% Yield = 15.4 g (61.23 %), HPLC purity = 68.84 %.

Example-11

Preparation of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0087] Phosphorous oxychloride (6.6g) was added in to N-formyl piperidine (6.1g) at temperature 15 to 17 °C. Subsequently chloroacetyl chloride (4.7g) was added drop wise at temperature 0-10 °C followed by addition of N-formyl piperidine (6.1g) in one lot at temperature 5 to 10 °C, then after the reaction mass was maintained at temperature 70-75 °C for 3 hr, cooled to 25-30 °C. The reaction mixture was diluted with DMF and the solution of $NaPF_6$ was added at 0-10 °C over a period of one hour. The reaction mixture was stirred for 60 minutes at 0-10 °C, filtered and washed with water, dried to obtain 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate.
Yield = 3 g, (18.75 %), HPLC purity = 96.95 %

Example-12

Preparation of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0088] N-formyl piperidine (30g) was cooled to 0 to 10 °C and Chloroacetyl chloride (30g) was added drop wise at 0 to 10 °C. Subsequently, phosphorous oxychloride (6.5g) was added drop wise at 0 to 10 °C. Further, N-formyl piperidine (30g) was added drop wise at 0-10 °C and reaction mixture was maintained at 80-90 °C for 16 hrs. Then the reaction mixture was cooled to 25-30 °C and diluted with DMF. Subsequently, the reaction mass was added into the solution of $NaPF_6$ within 60 minutes at 0-10 °C and stirred for 60 minutes at 0-10 °C. The solid was precipitated out, which was filtered and washed with water to obtain 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate salt.
Yield = 55.3 g, (54 %), HPLC purity = 72.74 %.

Example-13

Preparation of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0089] Chloroacetyl chloride (10g) was cooled to 0 to 5 °C and N-formyl piperidine (10g) was added drop wise at 5 to 10 °C and reaction mixture was stirred for 1 hr. Subsequently, phosphorous oxychloride (13.6g) was added drop wise at 0 to 10 °C and further N-formyl piperidine (10g) was added at 0-10 °C, stirred for 1 hrs at 0-5 °C. The reaction mixture was maintained at 75-80 °C for 19 hrs. Then the reaction mixture was cooled to 25-30 °C and diluted with DMF. Subsequently, the reaction mass was added into the solution of $NaPF_6$ within 60 minutes at 0-10 °C and stirred for 60 minutes at 0-10 °C. The solid was precipitated out, which was filtered and washed with water to obtain 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate salt.
Yield = 7.6 g, (22.22 %), HPLC purity = 80.33 %

Example-14

Preparation of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0090] Chloroacetyl chloride (4.9g) was cooled to -5 to 0 °C and phosphorous oxychloride (6.7g) was added in one lot at 0 to -5 °C and stirred for 5minutes. Subsequently, N-formyl piperidine (8g) was added drop wise at 0 to 5 °C and further stirred for 10 minutes at 25-30 °C. The reaction mixture was maintained at 90-100 °C for 6 hrs. Then after reaction mixture was cooled to 25-30 °C and diluted with DMF. Subsequently, the reaction mass was added into the solution of $NaPF_6$ within 60 minutes at 0-10 °C and stirred for 60 minutes at 0-10 °C. The solid was precipitated out, which was filtered and washed with cold methanol: water to obtain 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate salt.
Yield = 10.5 g, (51.19 %), HPLC purity = 83.87 %.

Example-15

Preparation of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0091] N-formyl piperidine (20g) was cooled to 0 to -5 °C and chloroacetyl chloride (10g) was added simultaneously, phosphorous oxychloride (13.4g) was added drop wise at -5 to 5 °C and the reaction mixture was stirred at 25-30 °C for 10 minutes. The reaction mixture was maintained at 90-100 °C for 6 hrs. Then the reaction mixture was cooled to 25-30 °C and diluted with DMF. Subsequently, the reaction mass was added into the solution of $NaPF_6$ within 60 minutes at 0-10 °C and stirred for 60 minutes at 0-10 °C. The solid was precipitated out, which was filtered and washed with water to obtain 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate salt.
Yield = 20 g, (47.39 %), HPLC purity = 81.05 %.

Example-16 (Reference Example)

Preparation of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0092] Chloroacetic acid (4.75 g, 0.05 mole) was added into N-formyl piperidine (13.5 g, 0.119 mole) at 25-30 °C and heat the reaction mixture at 70-75 °C. Subsequently phosphorous oxychloride (9.5 ml, 0.1 mole) was added over a period of 2 hrs at 70-75 °C. The reaction mixture was maintained at 70-80 °C for 3 hrs. Then after reaction mixture was cooled to 25-30 °C and diluted with absolute alcohol (10 ml). Subsequently, the reaction mass was added into the solution of $NaPF_6$ within 60 minutes at 0-10 °C and stirred for 60 minutes at 0-10 °C. The solid was precipitated out, which was filtered and washed with water to obtain 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate salt.
Yield = 2 g, (10.42 %), HPLC purity = 83.63 %.

Example-17

Preparation of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0093] Chloroacetyl chloride (20g) was cooled at -10 to 0 °C and phosphorous oxychloride (27.2g)was added in one lot at -10 to -15 °C and simultaneously N-formyl piperidine (40g) was added drop wise at -8 to -10 °Cover a period of 1 hr. The reaction mixture was maintained at 90-100 °C for 6 hrs. Then after reaction mixture was cooled to 25-30 °C and diluted with absolute alcohol (10 ml). Subsequently, the reaction mass was added into the solution of $NaPF_6$ within 60 minutes at 0-10 °C and stirred for 60 minutes at 0-10 °C. The solid was precipitated out, which was filtered and washed with water to obtain 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate salt.
Yield = (45.27 %), 37.2 g, HPLC purity = 83.24 %.

Example-18

1st Purification of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0094] 2-chloro 1,3-(bis piperidyl) trimethinium hexafluoro phosphate (37g) was dissolved in (185ml) methanol and (18.5ml) water (5:0.5) at 25-30 °C. The reaction mixture was stirred at 70-75 °C for 1 hrs. The reaction mixture was cooled to 0-10 °C and further stirred for 1 hrs, reaction mass was filtered and washed with methanol: water (1:1).
Yield = 23 g, (74.67 %), HPLC purity = 97.25 %.

Example-19

2nd Purification of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0095] 2-chloro 1,3-(bis piperidyl) trimethinium hexafluoro phosphate (11.2g) was dissolved in (55ml) methanol and aq. solution of bisulphate at 25-30 °C. The reaction mixture was stirred at 25-30 °C for 1 hrs, reaction mass was filtered and washed with water to obtain highly pure 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate. Yield = 9.4 g, (83.92 %), HPLC purity = 99.19 %.

Example-20

Preparation of Etoricoxib

[0096] Potassium tert. butoxide (2.1g) was dissolved in THF (20ml) and the solution was maintained at 25-30 °C for 10 minutes and then cooled to 10-15 °C. Subsequently, solution of 1-(6-methylpyridin-3-yl)-2[4-(methylsulfonyl)phenyl] ethanone (5g) in THF was added and kept the mixture for 1hr at 25-30 °C. Subsequently, 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate salt (8g), in THF (40ml) was added and maintained the reaction mixture for 2 hrs at 25-30 °C. The reaction mixture was dumped in to the mixture of trifloroacetic acid (1g), acetic acid (7.5g), and THF (100ml) and maintained for 1 hour at 25-30 °C. Further the reaction mixture was heated at 55-65 °C for 17 hrs after aq. ammonia solution (125 ml) was added and the reaction mixture was cooled to 25-30 °C. After that ethyl acetate and water was added, organic layer was separated and washed with water and 10 % sodium bicarbonate solution. Organic layer was separated, dried and concentrated to dryness at less than 50 °C to give crude Etoricoxib.
Yield = 8.6 g, HPLC purity = 91.28 % (Etoricoxib) (unreacted sulfone compound < 5 %).

Example-21

Preparation of Etoricoxib

[0097] Potassium tert. butoxide (11.6g) was dissolved in THF (90ml) and the solution was maintained at 25-30 °C for 10 minutes and then cooled to 10-15 °C. Subsequently, solution of 1-(6-methylpyridin-3-yl)-2[4-(methylsulfonyl)phenyl] ethanone (27.5g) in THF was added and kept the mixture for 1hr at 15-25 °C. Subsequently, 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate salt (44g), in THF (220ml) was added and maintained the reaction mixture for 3.5 hrs at 25-30 °C. The reaction mixture was dumped in to the mixture of trifloroaceticacid (5.5g), acetic acid (41.2g), and THF (65ml) and maintained for 1 hour at 25-30 °C. Further the reaction mixture was heated at 55-65 °C for 17 hrs after aq. ammonia solution (190ml) was added and the reaction mixture was cooled to 25-30 °C. Then ethyl acetate and water was added, organic layer was separated and washed with water and 10 % sodium bicarbonate solution. Organic layer was separated, dried and concentrated to dryness < 50 °C to give crude Etoricoxib.
Yield = 48.7 g, HPLC purity = 94.45 % (Etoricoxib), (unreacted sulfone compound < 5 %).

Example-22

1st Purification of Etoricoxib

[0098] (48.5 g) crude Etoricoxib (purity = 94.45 %, sulfone compound < 5%) obtained above was dissolved in 200 ml methanol and subsequently, (27.5g) formalin solution (37 %) and (27.5ml) aq. ammonia solution were added at 25-30 °C. The reaction mixture was stirred at 45-55 °C for 2 hrs and then remove the solvent under reduced pressure at < 55 °C. 250 ml ethyl acetate was added and reaction mixture was stirred. Organic layer was separated and washed with water, charcolized with (2.7g) charcoal, filtered and concentrated at < 55 °C, azeotrope with 50 ml isopropyl alcohol to dryness.
Yield = 34.5 g (97.9 %), HPLC purity = 96.49 % (Etoricoxib), (unreacted sulfone compound < 1 %).

Example-23

2nd Purification of Etoricoxib

[0099] (34.4 g) crude Etoricoxib (purity = 96.49 %) was stirred in isopropyl alcohol at 60-65 °C for 1 hr. The reaction mixture was cooled to 25-30 °C and further stirred for 17 hrs. Further (27.5 ml) isopropyl alcohol was added and stirred for 10 minutes at 25-30 °C, filter and washed with isopropyl alcohol, material was dried at 50-55 °C.
Yield = 23.3 g, (69.28 %), HPLC purity > 98 % Etoricoxib.

Example-24

Preparation of Etoricoxib

[0100] Potassium tert. butoxide (0.4g) was dissolved in DMF (4ml) and the solution was maintained at 25-30 °C for 10 minutes and then cooled to 10-15 °C. Subsequently, solution of 1-(6-methylpyridin-3-yl)-2[4-(methylsulfonyl)phenyl] ethanone (1g) in DMF was added and kept the mixture for 1hr at 15-25 °C. Subsequently, 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate salt (1.6g), in DMF (16ml) was added and maintained the reaction mixture for 2 hr at 25-30 °C. The reaction mixture was dumped in to the mixture of trifloroacetic acid (0.2g), acetic acid (1.5g), and DMF (12ml) and maintained for 1 hour at 25-30 °C. Further the reaction mixture was heated at 55-65 °C for 18 hrs after ammonia solution (25ml) was added and the reaction mixture was cooled to 25-30 °C. After then ethyl acetate and water was added, organic layer was separated and washed with water and 10 % sodium bicarbonate solution. Organic layer was separated, dried and concentrated to dryness < 50 °C to give crude Etoricoxib.
Yield = (55.12 %) 1 g, HPLC purity = 67.8 % (Etoricoxib), (unreacted sulfone compound < 5 %).

Example-25

Preparation of Etoricoxib

[0101] 1-(6-methylpyridin-3-yl)-2[4-(methylsulfonyl)phenyl] ethanone (9g) was dissolved in THF and the solution was maintained at 25-30 °C for 10 minutes and then cooled to 10-15 °C. Subsequently, potassium tert. butoxide (4.1 g) was added and reaction mixture was maintained at 10-15 °C for 60 minutes. After then was added 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate (14.8 g), followed by THF. The reaction mixture was maintained for 2 hrs at 10-15 °C and the reaction mixture was dumped into acetic acid (13 g) at 10-15 °C, washed with THF. Subsequently, the reaction mixture was maintained for 2 hour at 10-15 °C, further the reaction mixture was maintained at 60-65 °c for 16 hrs after adding aq. ammonia solution 25 ml and ammonium acetate (2.5 g). The reaction mixture was cooled to 25-30 °C, organic layer was separated and 25g aq. ammonia solution and 2 g formaldehyde solution was added at 25-30 °C. The reaction mixture was maintained at 60-65 °C for 1 hrs, cooled to 40 °C and 2.7 g sodium chloride was added in it & stirred for 30 minutes. Organic layer was separated and distilled till complete solvent removal under reduced pressure. The residue was azeotroped with toluene, and washed with water at 70-75 °C, aqueous

layer was separated and extracted with toluene followed by toluene at 70-75 °C. Combined all the organic layers and washed with 7.5 % sodium bicarbonate solution followed by water. Further organic layer was separated and charcolized with 0.3 g charcoal at 60-65 °C, and separated organic layer was distilled under reduced pressure, residue was azeotroped with IPA at 25-30 °C. The reaction mixture was stirred at 75-80 °C for 30 minutes, cooled to 25-30 °C, further IPA was added at 25-30 °C, cooled to 10-15 °C, stirred for 2 hrs at 10-15 °C, filtered and washed with cold IPA.
Yield = 6.8 g (61 %), HPLC purity = 99.34 % (Etoricoxib), (unreacted sulfone compound < 5 %).

Example-26

Purification of Etoricoxib

[0102] Etoricoxib (5 g) (as obtained in example 25) was dissolved in isopropyl alcohol and stirred at 60-65 °C for 1 hrs after adding 0.17 g charcoal, filtered through hyflow & washed with 2 ml hot IPA. The reaction mixture was cooled to 25-30 °C and stirred for 2 hrs, filtered and washed with isopropyl alcohol, dried the material at 60-65 °C to obtain pure Etoricoxib.
Yield = 3.6 g (72.87 %), HPLC purity 99.83 % Etoricoxib.
Etoricoxib obtained is also characterized by an XPRD peaks at 7.00, 8.50, 9.67, 11.72, 12.35, 12.96, 13.24, 15.04, 15.44, 16.51, 17.06, 17.70, 18.07, 18.76, 19.34, 20.00, 20.24, 21.14, 21.50, 22.20, 22.70, 23.28, 24.02, 24.76, 25.73, 26.20, 26.90, 27.37, 28.44, 29.24, 29.83, 30.41, 30.66, 31.22, 33.04, 34.63, 35.76, 37.62, 39.16, 39.65° ± 0.2° degrees (2θ)(Fig.1) and has melting point in the range of 135-137 °C.

Example-27

Preparation of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0103] Chloroacetyl chloride (200g) was cooled at -10 to 0 °C and phosphorous oxychloride (271.5g) was added in one lot at 0 to -10 °C and simultaneously N-formyl piperidine (400g) was added drop wise at 0 to 10 °C over a period of 1 hr. The reaction mixture was maintained at 90-100 °C for 6 hrs. Then after reaction mixture was cooled to 25-30 °C and diluted with DMF. Subsequently, the reaction mass was added into the solution of $NaPF_6$ within 60 minutes at 0-10 °C and stirred for 60 minutes at 0-10 °C. The solid was precipitated out, which was filtered and washed with water to obtain 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate salt.
Yield = 581.3 g (78.7 %), HPLC purity = 92.81 %.

Example-28

1st Purification of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0104] 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate (580 g) (as obtained in example 27) was dissolved in a mixture of methanol and water (5:0.5) at 25-30 °C. The reaction mixture was stirred at 60-70 °C for 1.5 hrs, cooled to 0-10 °C. Further, the reaction mixture was stirred for 1 hrs, filtered and washed with methanol: water (1:1) to obtain pure 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate.
Yield = 340.5 g (63.28 %), HPLC purity = 99.57 %.

Example-29

2nd Purification of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0105] 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate (340.5g) was dissolved in methanol and aq. solution of bisulphate at 25-30 °C. The reaction mixture was stirred at 25-30 °C for 1 hr, reaction mass was filtered and washed with water to obtain highly pure 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate.
Yield = 305 g, (90.15 %), HPLC purity = 99.65 %.
2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate obtained is also characterized by an XPRD peaks at 9.061, 11.60, 12.06, 12.89, 13.64, 14.38, 16.022, 16.98, 17.56, 18.16, 19.43, 20.16, 20.46, 21.04, 21.48, 21.98, 22.25, 22.68, 23.35, 23.76, 24.24, 24.64, 25.92, 26.75, 27.42, 28.03, 28.55, 29.04, 29.68, 30.06, 30.52, 31.25, 31.96, 32.36, 33.31, 33.94, 34.30, 35.16, 35.80, 38.14, 39.47 ° ± 0.2 ° degrees (2θ)(Fig. 2, Form I) and has melting point in the range of 185-200 °C. (Decomposed).

<u>**Example-30**</u>

Preparation of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0106] Chloroacetyl chloride (100g) was cooled to 0 °C and phosphorous oxychloride (135.7g) was added in one lot at 0 to -10 °C and simultaneously N-formyl piperidine (200g) was added drop wise at 0 to 10 °C over a period of 1 hr. The reaction mixture was maintained at 90-100 °C for 6 hrs. Then the reaction mixture was cooled to 25-30 °C and diluted with DMF. Subsequently, the reaction mass was added into the solution of $NaPF_6$ (prepared by adding 5N aq. NaOH solution in aq. HPF_6 solution) within 60 minutes at 0-10 °C and stirred for 60 minutes at 0-10 °C. The solid was precipitated out, which was filtered and washed with water to obtain 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate salt.
Yield = 189.3 g (45.9 5), HPLC purity: 82.41 %.

<u>**Example-31**</u>

1st Purification of 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0107] 2-chloro 1,3-(bis piperidyl) trimethinium hexafluoro phosphate (180 g) (as obtained in example 30) was dissolved in a mixture of methanol and water (5:0.5) at 25-30 °C. The reaction mixture was stirred at 60-70 °C for 1.5 hrs, cooled to 0-10 °C. Further, the reaction mixture was stirred for 1 hr, filtered and washed with methanol: water (1:1) to obtain pure 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate.
Yield = 110 g (73.36 %), HPLC purity: 99.06 %

<u>**Example-32**</u>

2nd Purification of 2-chloro 1, 3-(bis piperidinyl) trimethinium hexafluoro phosphate

[0108] 2-chloro 1,3-(bis piperidyl) trimethinium hexafluoro phosphate (109.6g; obtained in Example 31) was dissolved in methanol and aq. solution of bisulphate (29.5 g sodium bisulphite dissolved in 109.6 ml water) at 25-30 °C. The reaction mixture was stirred at 25-30 °C for 1 hr, reaction mass was filtered and washed with water to obtain highly pure 2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate.
Yield = 91.9 g (84.65 %), HPLC purity: 99.51 %.
2-chloro 1,3-(bis piperidinyl) trimethinium hexafluoro phosphate obtained is also characterized by an XPRD peaks at 9.14, 10.142, 12.12, 12.96, 13.71, 17.06, 17.64, 18.24, 19.49, 20.520, 21.10, 21.56, 22.32, 22.74, 23.42, 24.32, 24.72, 26.05, 27.48, 28.10, 29.14, 29.79, 30.12, 30.61, 31.30, 32.06, 32.43, 33.36, 34.02, 34.38 ° ± 0.2 ° degrees (2θ)(Fig. 3, Form II) and has melting point in the range of 190-197 °C.

REFERENCES CITED IN THE DESCRIPTION

Patent documents cited in the description

- WO9610012A [0003]
- WO9616934A [0003]
- WO9803484A [0004] [0005]
- US5861419A [0004]
- US6812346B [0006]
- US6040319A [0007] [0009]
- WO0137833A [0008]
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- WO0296877A [0008]
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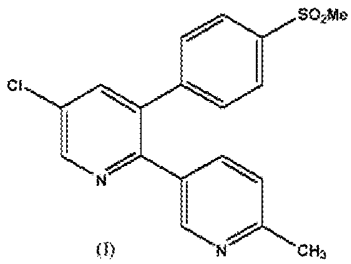
- US6252116B [0009]

Non-patent literature cited in the description

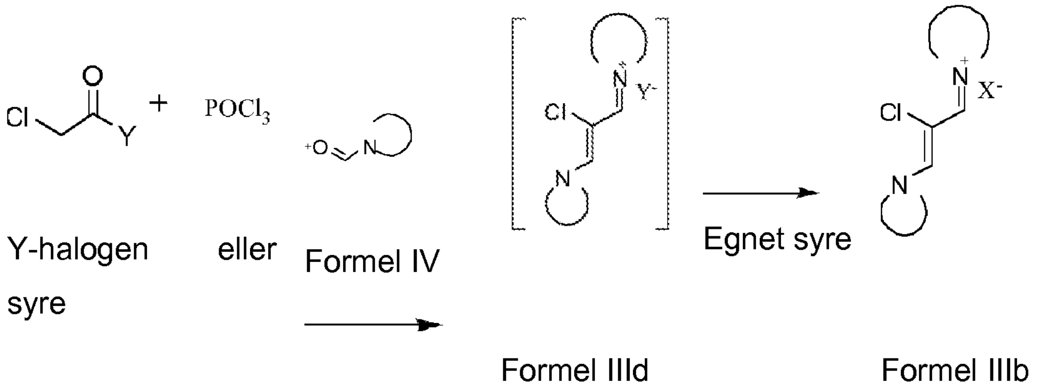
- J. Org. Chem., 2001, vol. 66, 1251-255 [0011]

Patentkrav

1. Fremgangsmåde til fremstilling af Etoricoxib med formlen (I), hvilken fremgangsmåde omfatter

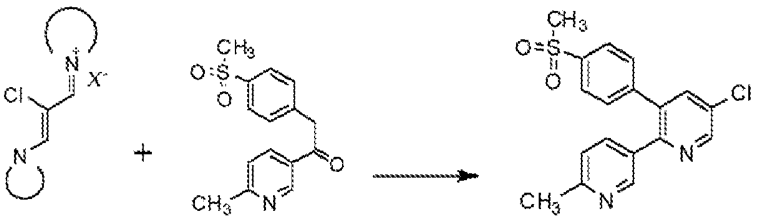


(a) omsætning af en forbindelse med formlen (IV) med egnet chloracetylhalogenid eller chloreddikesyre og phosphoroxychlorid for at opnå forbindelsen med formlen (IIId) og endvidere omdannelse af forbindelsen med formlen (IIId) til dens egnede salt for at opnå forbindelsen med formlen (IIIb),



hvor  repræsenterer en cyklisk gruppe, eventuelt indeholdende ét eller flere heteroatomer udvalgt fra N, O eller S, og 'X-' repræsenterer et egnet modion.

(b) omsætning af forbindelsen med formlen (IIIb) med forbindelsen med formlen (II) i nærvær af en egnet base og et egnet opløsningsmiddel for at opnå Etoricoxib med formlen (I)



Formel IIIb Formel II Formel I

2. Fremgangsmåde ifølge krav 1, hvor  er udvalgt fra en morpholidinyl-, piperidinyl- og pyrolidinylgruppe.

3. Fremgangsmåde ifølge krav 1, hvor det egnede salt af forbindelsen med formlen (IIIb) fremstilles ved omsætning af forbindelsen med formlen (IIId) med et egnet salt af en syre for at opnå det tilsvarende slat af forbindelsen med formlen (IIIb).

4. Fremgangsmåde ifølge krav 3, hvor det egnede salt af en syre er udvalgt fra gruppen bestående af phosphat, sulfat, acetater, perchlorat, borater, antimonit, halogenider, benzoat, napsylat, hexafluorphosphat, tetrafluorborat, chlorid, bromid, fluorid, iodid, benzoat og carbonat.

5. Fremgangsmåde ifølge krav 4, hvor det egnede salt af syre er hexafluorphosphat.

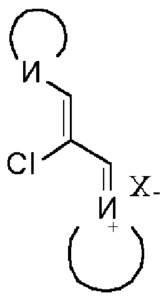
6. Fremgangsmåde ifølge krav 1 i trin (b), hvor det egnede opløsningsmiddel er udvalgt fra C_1-C_6-alkoholer, carbonhydrider udvalgt fra benzen, toluen og xylen; halocarbonopløsningsmidler udvalgt fra mono- eller di-halo C_1-C_4-alkyler, nitrogenholdige opløsningsmidler udvalgt fra DMF, dimethylacetamid, N-ethylpyrrolidinon, N-methylpyrrolidinon og acetonitril og dioxan og dimethylsulfoxid.

7. Fremgangsmåde ifølge krav 6, hvor opløsningsmidlerne er udvalgt fra C_1-C_6-alkohol, THF, DMF, dioxan og dimethylsulfoxid.

8. Fremgangsmåde ifølge krav 1, trin (b), hvor den egnede anvendte base er udvalgt fra organiske eller uorganiske baser, hvor de uorganiske baser er udvalgt fra alkalimetal eller jordalkalimetalhydroxider, alkalimetal eller jordalkalimetalcarbonater, såsom $NaHCO_3$, Na_2CO_3, K_2CO_3, alkalimetalhydrider, alkalimetalalkoxider.

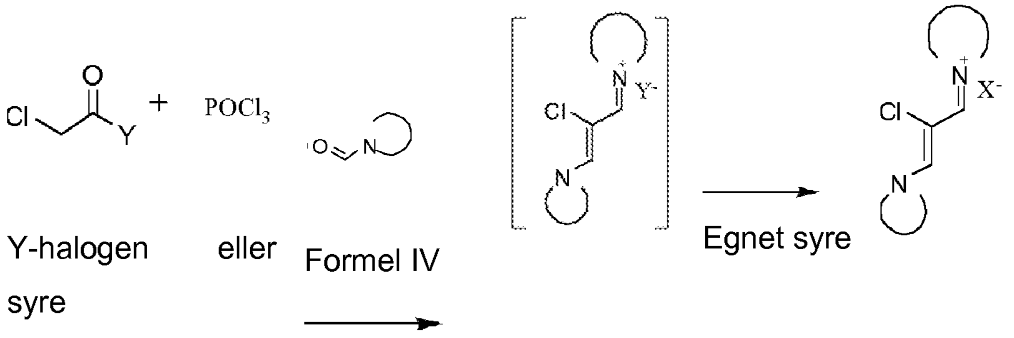
9. Fremgangsmåde til fremstilling af forbindelsen med formlen (IIIb), hvor

repræsenterer en cycloalkylgruppe, eventuelt indeholdende et ekstra heteroatom udvalgt fra N, O eller S, og 'X$^-$' repræsenterer det egnede modion, ifølge krav 1, omfattende



Formel IIIb

omsætning af en forbindelse med formlen (IV) med egnet chloracetylhalogenid eller chloreddikesyre og phosphoroxychlorid ved at kombinere chloracetylhalogenid eller chloreddikesyre og phosphoroxychlorid ved stuetemperatur eller under, og tilsætning af forbindelsen med formlen (IV) til kombinationen for at opnå forbindelsen med formlen (IIId) og endvidere omdannelse af forbindelsen med formlen (IIId) til dens egnede salt med formlen (IIIb),



Formel IIId Formel IIIb

10. Fremgangsmåde ifølge krav 9, hvor temperaturen er mindre end 30 °C.

11. Fremgangsmåde ifølge krav 9, hvor reaktionsblandingen, efter tilsætning af reaktanterne, opvarmes til en temperatur på 50° til 150 °C, mere fortrinsvis 75 °C til 120 °C og mest fortrinsvis, 90 °C til 100 °C, for at opnå forbindelsen med formlen (IIIb).

12. Fremgangsmåde ifølge krav 9, hvor reaktionen udføres i 3 timer til 25 timer, fortrinsvis i6 til 8 timer.

13. Fremgangsmåde ifølge krav 9, hvor forbindelsen med formlen (IIId) omdannes til dens egnede salt med formlen (IIIb) ved omsætning af den med saltet af tilsvarende syrer.

14. Fremgangsmåde ifølge krav 13 hvor, det egnede salt af syre er udvalgt fra gruppen bestående af phosphat, sulphat, acetater, perchlorat, borater, antimonit, halogenider, benzoat, napsylat, såsom hexafluorphosphat, tetrafluorborat, chlorid, bromid, fluorid, iodid, benzoat, carbonat, hexafluorantimonat.

15. Fremgangsmåde ifølge krav 14, hvor det egnede salt af syre er hexafluorphosphat.

16. Fremgangsmåde ifølge krav 9, hvor forbindelsen med formlen (IIIb) endvidere opløses ved

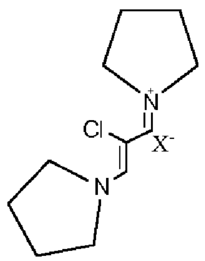
i) opløsning af forbindelsen med formlen (IIIb) i C_1-C_5-alkoholer eller estere deraf, eventuelt med vand og efterfølgende isolering af forbindelsen med formlen (IIIb);

ii) behandling af forbindelsen med formlen (IIIb) med egnet alkalisk bisulfit eller metabisulfit, i C_1-C_5-alkoholer eller estere deraf og efterfølgende isolering af den rene forbindelse med formlen (IIIb).

17. Fremgangsmåde ifølge krav 16, hvor alkalimetalbisulfit eller -metabisulfit er udvalgt fra natrium eller kaliumbisulfit eller -metabisulfit.

18. Fremgangsmåde ifølge krav 16, hvor saltet med formlen (IIIb) opnås med mindst 99 % renhed ved HPLC.

19. Forbindelse med den strukturelle formel (IIIc), hvor 'X^-' repræsenterer et egnet modion.



Formel IIIc

20. Polymorf form I af 2-chlor 1,3-(bispiperidinyl) trimethiniumhexafluorphosphat, kendetegnet ved et PXRD-mønster med spidsværdier ved 9,06, 11,60, 12,06, 12,89, 13,64, 14,38, 16,02, 16,98, 17,56, 18,16, 19,43, 20,16, 20,46, 21,04, 21,48, 21,98, 22,25, 22,68, 23,35, 23,76, 24,24, 24,64, 25,92, 26,75, 27,42, 28,03, 28,55, 29,04, 29,68, 30,06, 30,52, 31,25, 31,96, 32,36, 33,31, 33,94, 34,30, 35,16, 35,80, 38,14, 39,47 ° ± 0,2 ° grader (2θ).

21. Polymorf form II af 2-chlor 1,3-(bispiperidinyl) trimethiniumhexafluorphosphat, kendetegnet ved et PXRD-mønster med spidsværdier ved 9,14, 10,142, 12,12, 12,96, 13,71, 17,06, 17,64, 18,24, 19,49, 20,520, 21,10, 21,56, 22,32, 22,74, 23,42, 24,32, 24,72, 26,05, 27,48, 28,10, 29,14, 29,79, 30,12, 30,61, 31,30, 32,06, 32,43, 33,36, 34,02, 34,38 ° ± 0,2 ° grader (2θ).

DRAWINGS

Fig. 1

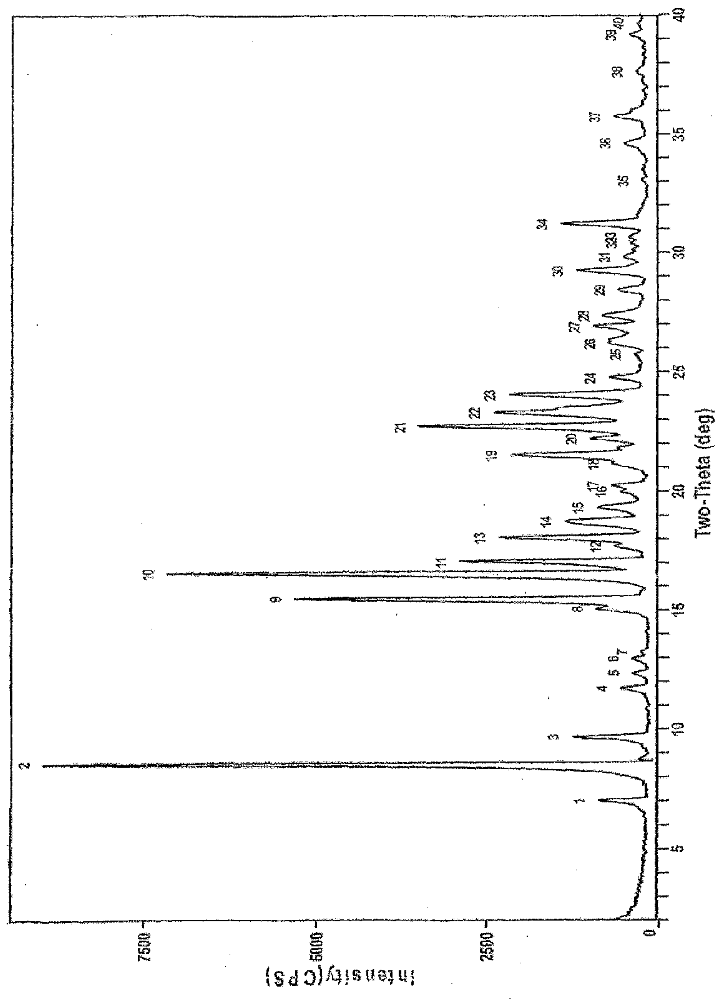


Fig. 2

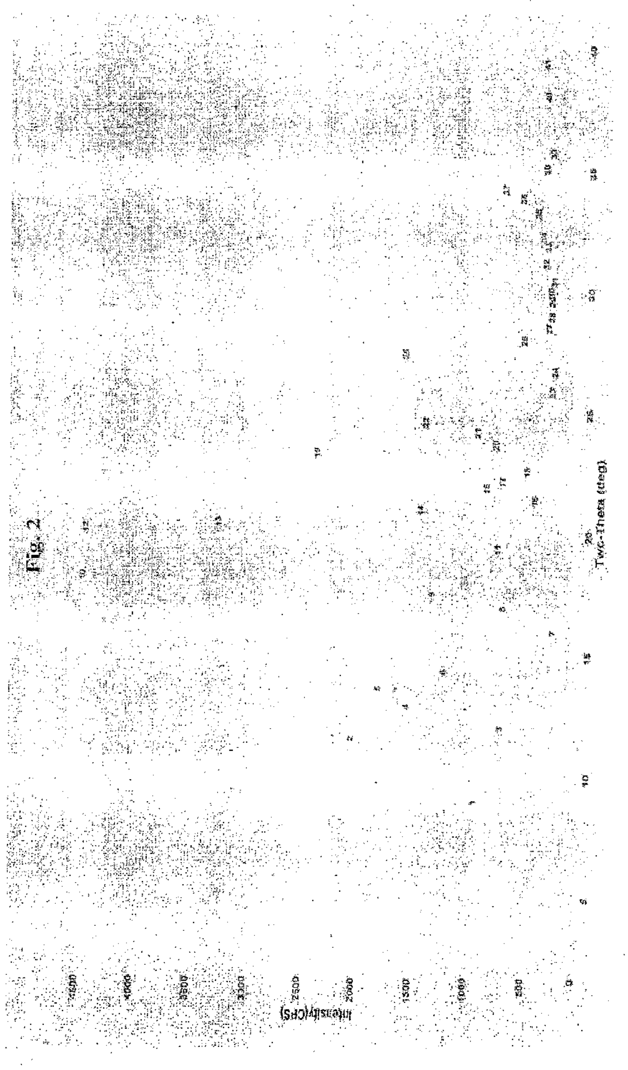


Fig. 3