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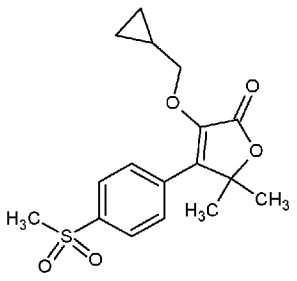
(54) Title: A PROCESS FOR THE PREPARATION OF FIROCOXIB



(I)

(57) Abstract: The present invention provides an improved process for preparation of Firocoxib of Formula I. Further, the present invention relates to novel process for the preparation of crystalline polymorphic form B of Firocoxib of Formula I.

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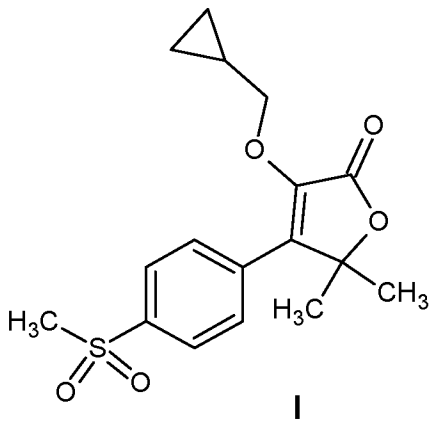
"A PROCESS FOR THE PREPARATION OF FIROCOXIB"

Field of the Invention:

The present invention provides an improved process for the preparation of Firocoxib of Formula I. Further, the present invention also relates to process for the preparation of crystalline polymorphic form B of Firocoxib.

Background of the Invention:

Firocoxib is a coxib-class of non-steroidal anti-inflammatory drug approved as veterinary medicine for the treatment of equine osteoarthritis, chronic pain and inflammation caused by the clinical surgery. COX-2 is a subtype of cyclooxygenase, responsible for prostaglandin synthesis, regulation of pain, inflammation and fever. Selective inhibition of COX-2 can effectively relieve osteoarthritis pain. Firocoxib is highly effective than other non-steroidal anti-inflammatory drugs because of highly selective inhibition of COX-2, upon oral administration it is rapidly absorbed. Firocoxib have chemical name 3-(cyclopropylmethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-(5H)-furan-2-one as represented by Formula I.



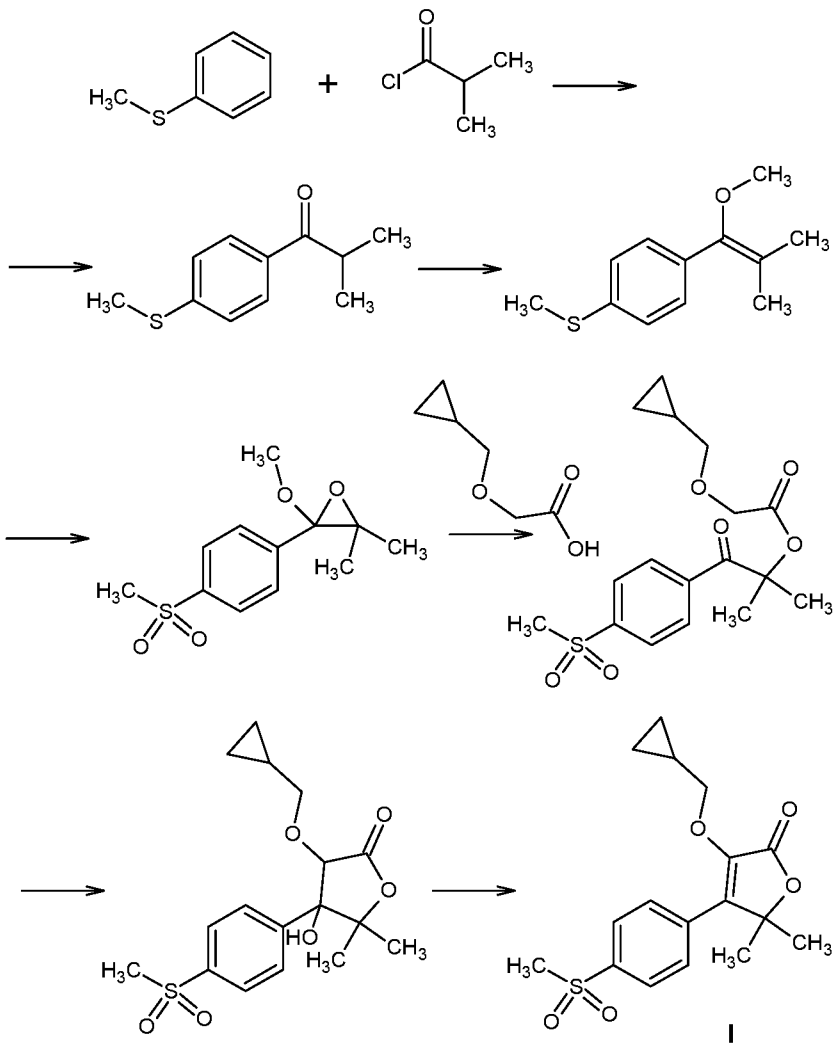
I

US patent 5981576A reports Firocoxib. A number of synthetic routes are provided therein. This patent describes a process for the preparation of Firocoxib, by treating cyclopropylmethanol with haloacetic acid in presence of 95% sodium hydride as a

base to give (cyclopropylmethoxy)acetic acid, which on further reactions gives Firocoxib. Usage of sodium hydride as base in large scale production is very dangerous because it ignites in air especially in contact with water to release hydrogen and also it is highly flammable. Hence it is not advisable to use sodium hydride as a base in large commercial scale. High volume of solvent used in the synthetic examples given.

US6541646B2 process patent from Merial provides the preparation of Firocoxib using the following reaction scheme A. The work up procedures provided are complex.

Scheme A

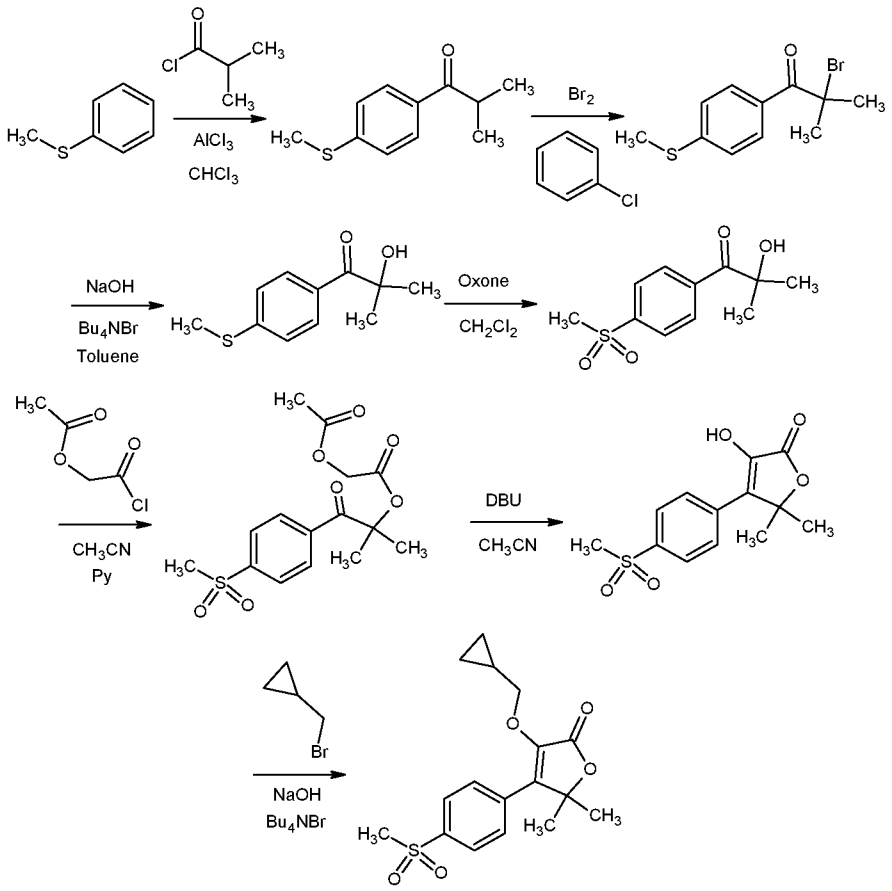


US6677373B2 describes a process for preparation of crystalline polymorph B of Firocoxib. Polymorph B of Firocoxib was prepared from polymorph A, either by conversion of polymorph A to polymorph B or by recrystallization of Form A in methylcyclohexane and tetrahydrofuran mixture along with seeding with polymorph B.

US6787342B2 provided veterinary paste formulation of Firocoxib polymorph B. The examples used polymorph A for the preparation of polymorph B along with seeding.

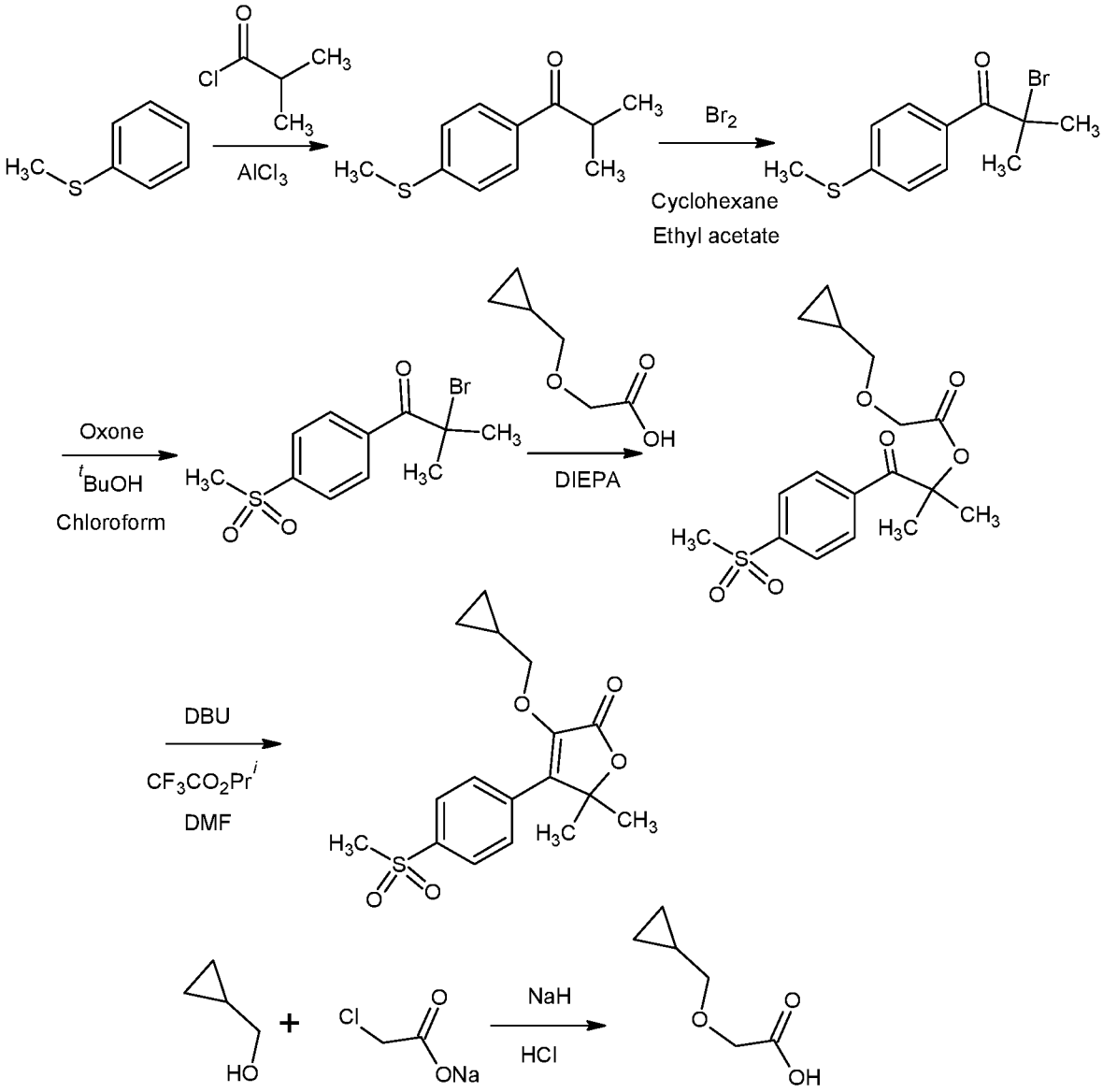
CN104803956A describes a process for preparation of Firocoxib using phase transfer catalysts as shown in below reaction scheme B. Hazardous solvents such as chloroform, chlorobenzene and pyridine were used that are not preferred industrially.

Scheme B



CN105859664A provides a process for the preparation of Firocoxib as shown in below synthetic scheme C. The reaction steps take very long duration for completion. The drawback is the use of solvent like chloroform, which is hazardous to health and environmentally unfriendly, also recovery or recycle of solvent is very difficult.

Scheme C



Thus it is highly desirable to develop a process which overcomes the drawbacks of the prior art. The present inventors have developed a cost effective simple process

for the preparation of crystalline polymorphic Form B of Firocoxib, without the necessity for seeding with polymorphic Form B of Firocoxib, with better purity, better yield, easy handling in bulk and avoided formation of unwanted impurities.

Summary of the Invention:

The principal aspect of the present invention is to provide a process for the preparation of Firocoxib of formula I, which comprises:

a) condensing thioanisole of formula VII with isobutyryl chloride of formula VIII in presence of aluminum chloride and solvent to obtain 2-methyl-1-[4-(methylsulfanyl) phenyl]propan-1-one of formula VI;

b) brominating 2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula VI with liquid bromine in presence of solvent or mixture thereof to give 2-bromo-2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula V;

c) oxidizing 2-bromo-2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula V with oxidizing agent to give 2-bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one of formula III;

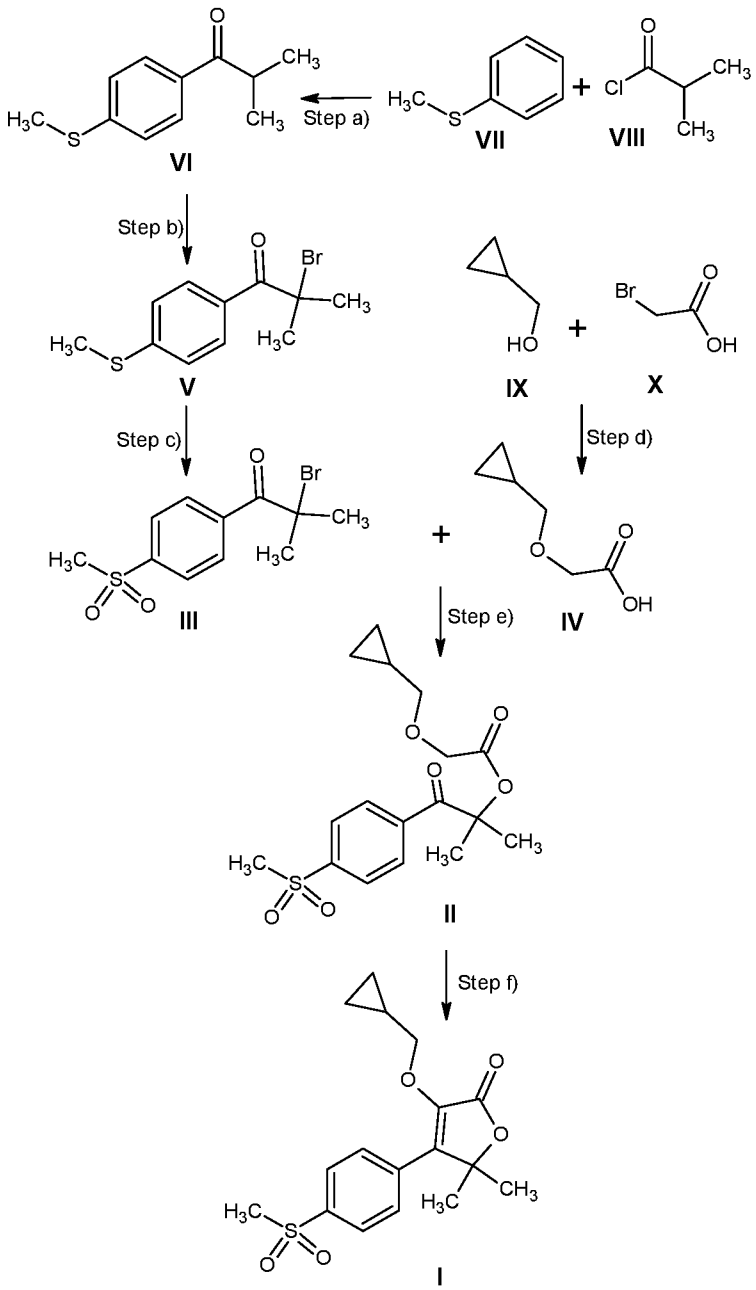
d) condensing cyclopropylmethanol of formula IX with bromoacetic acid of formula X in presence of base and solvent to give (cyclopropylmethoxy)acetic acid of formula IV;

e) condensing 2-bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one of formula III with (cyclopropylmethoxy)acetic acid of formula IV in the presence of base and solvent to give 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate of formula II; and

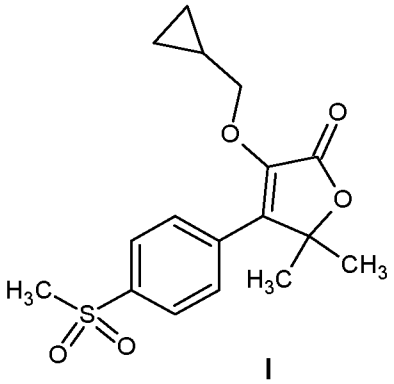
f) cyclizing 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate of formula II with isopropyl trifluoroacetate in the presence of base and solvent to give Firocoxib of formula I.

The process of the present invention may be illustrated as shown in the below scheme I.

Scheme I

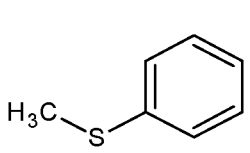


In one aspect, described herein is a process for the preparation of Firocoxib of formula I, which comprises the steps of:

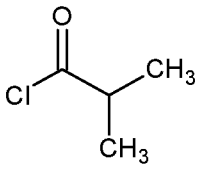


I

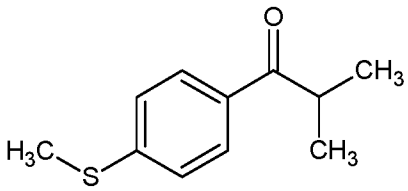
a) condensing thioanisole of formula VII with isobutyryl chloride of formula VIII in dichloromethane in presence of aluminum chloride to obtain 2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula VI;



VII

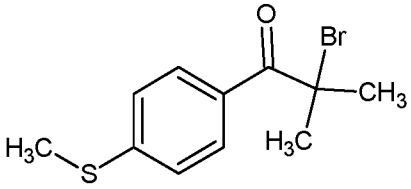


VIII



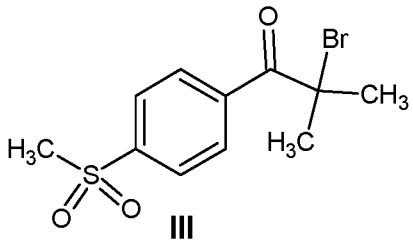
VI

b) brominating 2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula VI with liquid bromine in cyclohexane and ethyl acetate to give 2-bromo-2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula V;



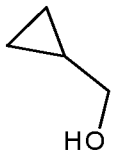
V

c) oxidizing 2-bromo-2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula V with hydrogen peroxide to give 2-bromo-2-methyl-1-[4-(methylsulfonyl) phenyl]propan-1-one of formula III;

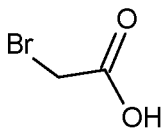


III

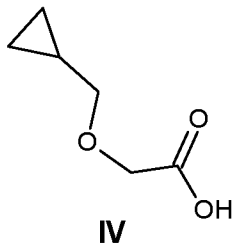
d) condensing cyclopropylmethanol of formula IX with bromoacetic acid of formula X in presence of potassium *tert*-butoxide and THF or DMF as solvent to give (cyclopropylmethoxy)acetic acid of formula IV;



IX

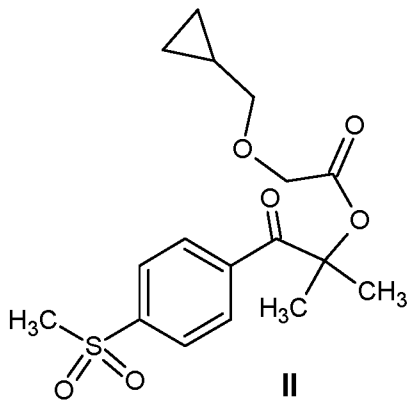


X



IV

e) condensing 2-bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one of formula III with (cyclopropylmethoxy)acetic acid of formula IV in presence of N,N-diisopropylethylamine (DIPEA) and methanol as solvent to give 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate of formula II; and



II

f) cyclizing 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate of formula II using isopropyl trifluoroacetate in

presence of 1,8-diazabicycloundec-7-ene (DBU) and acetonitrile as solvent to give Firocoxib of formula I,

wherein the improvement consists of:

1. using potassium *tert*-butoxide in the preparation of (cyclopropylmethoxy)acetic acid of formula IV in step d);
2. obtaining form B from the cyclization in step f);
3. crystalline compound of formula (II), among others.

In another aspect, provided herein is a process for preparing polymorphic form B of Firocoxib from cyclisation reaction of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate. The cyclisation is carried out using DBU, acetonitrile and isopropyl trifluoroacetate followed by adjusting pH to 3.5 to 4.5 with dilute hydrochloric acid.

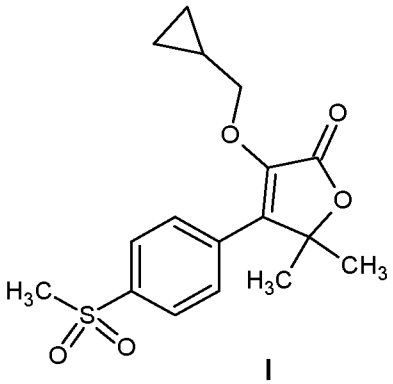
In a further aspect, the present invention provides a process for preparing crystalline Polymorphic Form B of Firocoxib, which comprises:

a) treating Firocoxib in a solvent;
b) heating the mass to 50 °C to reflux temperature;
c) optionally treating with carbon followed by filtration;
d) optionally seeding with polymorph B;
e) cooling to 0 to 20 °C; and
f) isolating polymorph B of Firocoxib.

In still another aspect, disclosed herein is a process for the preparation of (cyclopropylmethoxy)acetic acid by the reaction of cyclopropylmethanol with haloacetic acid or salts thereof comprising bromoacetic acid, chloroacetic acid, sodium chloroacetate, potassium chloroacetate preferably bromoacetic acid using potassium *tert*-butoxide. The (cyclopropylmethoxy)acetic acid thus prepared using potassium *tert*-butoxide was used further in the preparation of Firocoxib.

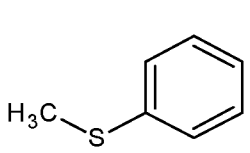
In yet another aspect, the invention relates to the preparation of crystalline 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate of formula II.

In one more aspect, described herein is a process for the preparation of Firocoxib of formula I, which comprises the steps of:

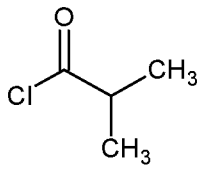


I

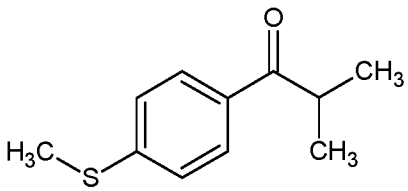
a) condensing thioanisole of formula VII with isobutyryl chloride of formula VIII in presence of aluminum chloride to obtain 2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula VI;



VII

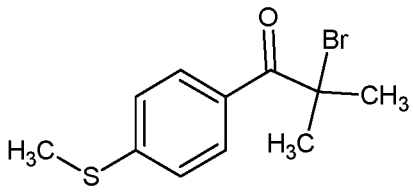


VIII



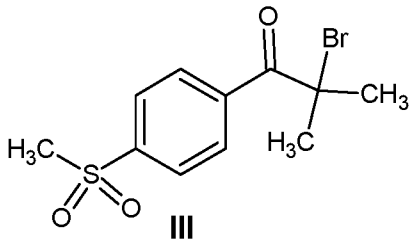
VI

b) brominating 2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula VI with bromine to give 2-bromo-2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula V;



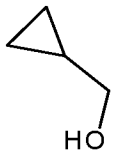
V

c) oxidizing 2-bromo-2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula V with hydrogen peroxide to give 2-bromo-2-methyl-1-[4-(methylsulfonyl) phenyl]propan-1-one of formula III;

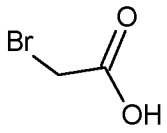


III

d) condensing cyclopropylmethanol of formula IX with bromoacetic acid of formula X in presence of potassium *tert*-butoxide to give (cyclopropylmethoxy)acetic acid of formula IV;



IX



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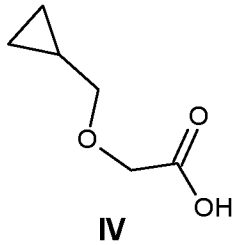
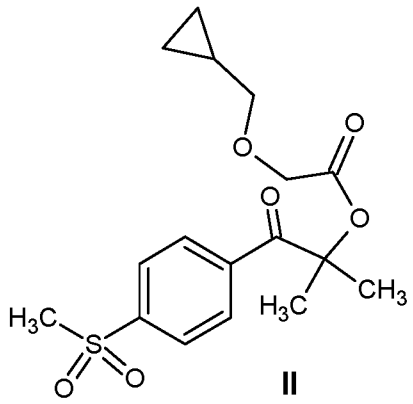


IV

e) condensing 2-bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one of formula III with (cyclopropylmethoxy)acetic acid of formula IV in presence of N,N-diisopropylethylamine (DIPEA) to give 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate of formula II; and



II

f) cyclizing 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate of formula II using isopropyl trifluoroacetate in presence of 1,8-diazabicycloundec-7-ene (DBU) to give Firocoxib of formula I.

These aspects and advantages of the present invention will be apparent to those skilled in the art from the following description.

Brief description of the figures:

Figure 1 shows PXRD pattern of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate (Compound of formula II).

Figure 2 shows DSC of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate (Compound of formula II).

Figure 3 shows Infrared (IR) spectrum of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate (Compound of formula II).

Figure 4 shows TGA of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate (Compound of formula II).

Detailed Description of the Invention:

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated. However, any skilled person will appreciate the extent to which such embodiments could be extrapolated in practice.

Accordingly in an embodiment of the invention, the condensation of thioanisole of formula VII with isobutyryl chloride of formula VIII in step a) is carried out in presence of aluminum chloride (Lewis acid) in chlorinated solvent preferably dichloromethane (MDC) to obtain 2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula VI.

In another embodiment of the invention, bromination of 2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula VI in step b) is carried out using bromine solution in presence of solvent selected from cyclohexane, ethyl acetate, dichloromethane or mixture thereof preferably cyclohexane and ethyl acetate mixture to give 2-bromo-2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula V.

In another embodiment of the invention, oxidation of 2-bromo-2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula V in step c) is carried out using oxidizing agent selected from hydrogen peroxide or peracetic acid preferably hydrogen peroxide, at the temperature range 30 to 50 °C, preferably at 40 to 45 °C to give 2-bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one of formula III.

In another embodiment of the invention, condensation of cyclopropylmethanol of formula IX with bromoacetic acid of formula X in step d) is carried out in presence of a base preferably potassium tertiary butoxide and a solvent selected from tetrahydrofuran (THF) or dimethylformamide (DMF) or acetonitrile preferably tetrahydrofuran at a temperature 20 to 70 °C preferably 30 to 35 °C to give (cyclopropylmethoxy)acetic acid of formula IV.

In one embodiment, potassium *tert*-butoxide used was about 2 to 2.5 mole equivalent to cyclopropylmethanol. Preferably 2.2 equivalent was used. Potassium *tert*-butoxide and cyclopropylmethanol were used in the mole ratio of 2:1 to 2.5:1. Preferred mole ratio of potassium *tert*-butoxide : cyclopropylmethanol is 2.2:1.

In another embodiment of the invention, condensation of 2-bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one of formula III with (cyclopropylmethoxy)acetic acid of formula IV in step e) is carried out using a solvent selected from methanol or ethanol or isopropanol preferably methanol and base preferably N,N-diisopropylethylamine (DIPEA) to give 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate of formula II.

In another embodiment of the invention, 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate of formula II is obtained in step e) is in crystalline form.

In another embodiment of the invention, the cyclization of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate of formula II in step f) is carried out using isopropyl trifluoroacetate in presence of a base preferably 1,8-diazabicycloundec-7-ene (DBU) and solvent selected from acetonitrile or dimethylformamide (DMF) preferably acetonitrile, to obtain Firocoxib of formula I. Optimum quantity of solvent was used in cyclization reaction. Minimum volume of acetonitrile used.

In another embodiment of the invention, compounds of formulae VI and V were not isolated, avoiding any further purification and used as such *in situ* for next stages thus making the instant process easy and viable for scale up.

In one embodiment of the invention, polymorphic B of Firocoxib was prepared directly from cyclisation reaction of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate. The cyclisation process is carried out using DBU, acetonitrile and isopropyl trifluoroacetate.

In one embodiment of the invention, polymorphic B of Firocoxib was prepared from cyclisation reaction of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-

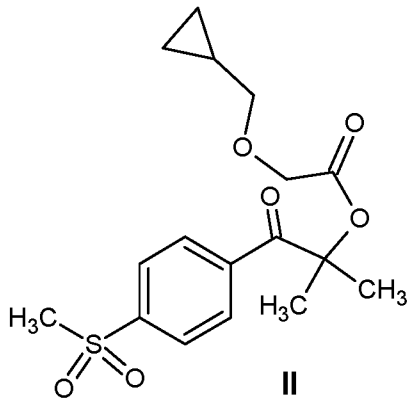
2-yl (cyclopropylmethoxy)acetate. The cyclisation process is carried out using DBU, acetonitrile and isopropyl trifluoroacetate followed by adjusting pH to 3 to 5 with dilute hydrochloric acid.

In one embodiment of the invention, polymorphic B of Firocoxib was prepared from cyclisation reaction of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate. The cyclisation process is carried out using DBU, acetonitrile and isopropyl trifluoroacetate followed by adjusting pH to 3.5 to 4.5 with dilute hydrochloric acid.

In another embodiment of the invention, the process for the preparation of polymorph B does not proceed via using polymorph A. Form B was isolated after completion of the reaction. The use of polymorph A as starting compound in the preparation of polymorph B as described in prior art is avoided in the instant invention.

In yet another embodiment of the invention, recrystallization of Firocoxib of formula I is carried out by treating Firocoxib of formula I using a solvent selected from ethanol or methanol preferably methanol at the temperature range 40 to 70 °C preferably at 50 to 55 °C. Further, the reaction mass was treated with activated carbon, followed by filtration and finally the Firocoxib polymorph B obtained was filtered and dried to get Firocoxib of formula I. The Firocoxib obtained was highly pure with the purity of 99.9%.

In another embodiment, provided herein is a crystalline compound of formula II.



II

The crystalline compound of formula II is used in the preparation of Firocoxib of compound of formula I.

Provided herein below is the powder X-ray diffraction (PXRD) pattern of formula II with the characteristic peaks expressed in degrees 2θ (Theta) along with the corresponding % intensity values.

PXRD pattern of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate				
2θ (±0.2) °	Intensity %		2θ (±0.2) °	Intensity %
7.37	100		23.08	15
11.27	45		24.50	12
18.14	11		25.48	22
19.39	85		29.20	26
22.15	46		29.66	78
37.32	30			

In yet another embodiment, crystalline 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate or compound of formula II exhibits characteristic 2θ ° PXRD peaks (±0.2) at 7.37, 11.27, 19.39, 22.15, 37.32, and 29.66. Preferably, 7.37, 19.39, and 29.66. Most preferably, 7.37 and 19.39.

In one embodiment, the present invention provides a process for preparing crystalline polymorphic Form B of Firocoxib, which comprises:

a) treating Firocoxib in a solvent;

b) heating the mass to 50 °C to reflux temperature;

c) cooling to 0 to 20 °C; and

d) isolating polymorph B of Firocoxib.

In another embodiment, the present invention provides a process for preparing crystalline polymorphic Form B of Firocoxib, which comprises:

a) treating Firocoxib in a solvent;

b) heating the mass to 50 °C to reflux temperature;

c) treating with carbon followed by filtration;

d) cooling to 0 to 20 °C; and

e) isolating polymorph B of Firocoxib.

In a further embodiment, the present invention provides a process for preparing crystalline polymorphic Form B of Firocoxib, which comprises:

a) treating Firocoxib in a solvent;

b) heating the mass to 50 °C to reflux temperature;

c) seeding with polymorph B;

d) cooling to 0 to 20 °C; and

e) isolating polymorph B of Firocoxib.

In yet another embodiment, the present invention provides a process for preparing polymorph B of Firocoxib, which comprises:

a) treating Firocoxib in a solvent;

b) heating;

c) optionally treating with carbon;

d) optionally seeding with suitable seeding material;

e) cooling; and

f) isolating Firocoxib.

In another embodiment, the present invention provides a process for preparing polymorph B of Firocoxib, which comprises:

a) treating Firocoxib in methanol;
b) heating the mass to 50 °C to reflux temperature;
c) optionally treating with carbon followed by filtration;
d) optionally seeding with polymorph B;
e) cooling to 0 to 20 °C; and
f) isolating polymorph B of Firocoxib.

In one embodiment, Firocoxib is micronized, where necessary, to desired particle size range using appropriate micronization techniques known in the prior art.

Within the context of the present invention and as used herein, the terms, 'crystalline polymorphic form B' or 'polymorph B' or 'Form B' refers to Firocoxib crystalline polymorph B as characterized with the melting point around 120 °C.
The process of the present invention is advantageous over prior art, some of them are stated below:

1. Polymorphic Form B is obtained without the need of going via polymorph A.
2. Use of sodium hydride is avoided.
3. Column chromatography is totally avoided throughout the process making the process viable for easy scale up.
4. Duration of reactions of the instant invention is lesser than the duration reported in the prior art processes.
5. Use of chloroform is removed.
6. Smaller volume of solvent used throughout the process.
7. The process of the present invention provides preparation of polymorph Form B of Firocoxib without the necessity of seeding with polymorph B.
8. The process of the present invention is very user friendly avoids the lengthy workup and in turn minimizes the generation of hazardous effluent.
9. Compound of formula III was prepared without isolating compounds of formulae VI and V.
10. Step b) and step c) reactions were carried out using same solvent system, cyclohexane and ethyl acetate mixture.

US6677373B2 indicates that polymorph B of Firocoxib possesses better flow characteristics and therefore easy to handle than polymorph A. The examples 1-4 provided in US6677373B2 use Firocoxib polymorph A in the preparation of polymorph B. Inventors of the instant invention arrived at preparing Firocoxib polymorph B directly from the reaction, avoiding using polymorph A. Therefore the process of the instant invention is simple with the ease of handling polymorph B and easy for scale up.

The following abbreviations and terms are used herein.

List of abbreviations				
DMF	N,N-Dimethylformamide		g	Gram
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene		L	Litre
PXRD	Powder X-Ray Diffraction		mL	Millilitre
DSC	Differential Scanning Calorimetry		THF	Tetrahydrofuran
DIPEA	Diisopropylethylamine		MDC	Dichloromethane
TGA	Thermogravimetric analysis		HCl	Hydrochloric acid

The following examples, which fully illustrate the practice of the preferred embodiments of the present invention, are intended to be for illustrative purpose only and should not be considered in any way to limit the scope of the present invention.

Example-1: Preparation of 2-bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one (Compound of formula III)

Aluminum chloride (129 g; 0.97 mol) and dichloromethane (1000 mL) were added into a flask under stirring at 25 to 35 °C, cooled to -5 °C to 5 °C. Isobutyryl chloride (113 g; 1.06 mol; compound of formula VIII) was slowly added dropwise through dropping funnel at -5 to 5 °C for 1 hour. Thioanisole (100 g; 0.81 mol; compound of formula VII) was added to reaction mass at -5 to 5°C under stirring for 30 to 45

minutes. The reaction mass was heated to 25 to 35 °C and stirred for 2 hours. Water (500 mL) was added to reaction mass under stirring at 10 to 20 °C for 15 minutes and allowed to settle for 30 minutes. The organic layer was separated out, washed with saturated sodium bicarbonate (500 mL) solution and washed with saturated sodium chloride solution. Dichloromethane was distilled out under vacuum at below 50 °C and cooled to 25 to 35 °C. Residual mass of 2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of compound of formula VI obtained was dissolved in cyclohexane and ethyl acetate mixture (1:1, 400 mL:400 mL) under stirring at 25 to 35 °C for 10 to 15 minutes. Bromine (142 g; 0.89 mol) was added to reaction mass under stirring for 1 hour at 25 to 35 °C. Water (500 mL) was added to reaction mass under stirring at 10 to 20 °C for 15 minutes and allowed to settle for 15 minutes. Organic layer was separated. Water (72 mL) was added to the organic layer containing compound 2-bromo-2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula V under stirring at 25 to 35 °C. Sodium tungstate (2.7 g) and aliquate 336 (9.6 g) were added to reaction mass under stirring at 25 to 35 °C. A mixture of 48% hydrogen peroxide solution (175 mL) and water (60 mL) was added and stirred at 40 to 45 °C for two hours. After completion of reaction, the reaction mass was cooled to 0 to 5 °C and stirred for an hour. The solid obtained was filtered off, washed with cold ethyl acetate: cyclohexane mixture (1:1) and dried under vacuum to obtain the title compound. Yield: 210 g; 86%.

Example-1a: Preparation of 2-bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one

Aluminum chloride (113 g; 0.84 mol) and dichloromethane (1000 mL) were added into a flask under stirring at room temperature, cooled to 10 to 20 °C. Isobutyryl chloride (95 g; 0.89 mol) was slowly added dropwise through dropping funnel at 10 to 20 °C. Thioanisole (100 g) was added to reaction mass at 10 to 20 °C and stirred for 4 hours. Water (500 mL) was added to reaction mass at 10 to 20 °C for 15 minutes and allowed to settle for 30 minutes. The organic layer was separated out, washed with saturated sodium bicarbonate (500 mL) solution and washed with saturated sodium chloride solution. Dichloromethane was distilled out under

vacuum at below 50 °C and cooled to 25-35°C. Acetone (500 mL) was added and the solid of (2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one) was isolated. The solid thus obtained was dissolved in ethyl acetate (400 mL). Bromine (129 g; 0.81 mol) was added to reaction mass under stirring for 1 hour. Water (500 mL) was added to reaction mass at 10 to 20 °C for 15 minutes and allowed to settle for 15 minutes. Organic layer was separated, water (72 mL) was added to the organic layer under stirring at 25 to 35 °C. Sodium tungstate (2.5 g) and aliquate 336 (9.0 g) was added to reaction mass. A mixture of 48% hydrogen peroxide solution (160 mL) and water (60 mL) was added and stirred at 40 to 45 °C for two hours. After completion of reaction, the reaction mass was cooled to 0 to 5 °C and stirred for an hour. The solid obtained was filtered off, washed with cold ethyl acetate:cyclohexane mixture (1:1) and dried under vacuum to obtain the title compound. Yield: 220 g; 90%.

Example-2: Preparation of (cyclopropylmethoxy)acetic acid (Compound of formula IV)

Potassium *tert*-butoxide (390 g; 3.48 mol) and THF (800 mL) were added into a flask at 25 to 35 °C, cooled to -5 to 5 °C. Cyclopropylcarbinol (100 g; 1.39 mol; compound of formula IX) was slowly added, bromoacetic acid (212 g; 1.53 mol; compound of formula X) in THF was added slowly and stirred for 12 hours at reflux temperature. After completion of reaction, the reaction mass was cooled to 25 to 35 °C. Water (1000 mL), MDC (500 mL) and concentrated hydrochloric acid were added. The organic layer was separated and MDC was distilled out to obtain the title compound. Yield: 135 g; 75%.

Example-2a: Preparation of (cyclopropylmethoxy)acetic acid

Potassium *tert*-butoxide (343 g; 3.06 mol) and THF (800 mL) were added into a flask, cooled to -5 to 5 °C. Cyclopropylcarbinol (100 g; 1.39 mol) was slowly added, chloroacetic acid (144 g; 1.53 mol) in THF was added slowly and stirring continued for 10 hours at reflux temperature. After cooling, water (1000 mL) and MDC (500 mL) were added. Then concentrated hydrochloric acid was added. The

organic layer was separated and MDC was distilled out to obtain the title compound. Yield: 142 g; 79%.

Example-2b: Preparation of (cyclopropylmethoxy)acetic acid

Potassium *tert*-butoxide (390 g; 3.48 mol) and DMF (800 mL) at 25 to 35 °C were added into a flask, cooled to -5 to 5 °C. Cyclopropylcarbinol (100 g; 1.39 mol) was slowly added, bromoacetic acid (212 g; 1.53 mol) in THF was added slowly and stirring continued for 12 hours at reflux temperature. After the reaction was completed, the reaction mass was cooled to 25 to 35 °C. Water (1000 mL), MDC (500 mL) and concentrated hydrochloric acid were added. The organic layer was separated and MDC was distilled out to obtain the title compound. Yield: 133 g; 74%.

Example-2c: Preparation of (cyclopropylmethoxy)acetic acid

Potassium *tert*-butoxide (343 g; 3.06 mol) and THF (800 mL) were added into a flask, cooled to -5 to 5 °C. Cyclopropylcarbinol (100 g; 1.39 mol) was slowly added, bromoacetic acid (212 g; 1.53 mol) in THF was added slowly and stirring continued for 18 hours. Water (1000 mL) and MDC (500 mL) were added. Then con.HCl was added. The organic layer was separated and MDC was distilled out to obtain the title compound. Yield: 150 g; 83%.

Example-2d: Preparation of (cyclopropylmethoxy)acetic acid

Potassium *tert*-butoxide (312 g; 2.78 mol) and THF (800 mL) were added into a flask, cooled to -5 to 5 °C. Cyclopropylcarbinol (100 g; 1.39 mol) was slowly added, bromoacetic acid (144 g; 1.53 mol) in THF was added slowly and stirring continued for 18 hours. Water (1000 mL) and MDC (500 mL) were added. Then con.HCl was added. The organic layer was separated and MDC was distilled out to obtain the title compound. Yield: 162.5 g; 90%.

Example-3: Preparation of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2- yl (cyclopropylmethoxy)acetate (Compound of formula II)

2-Bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one (100 g; 0.33 mol), (cyclopropylmethoxy)acetic acid (64 g; 0.49 mol) and methanol (400 mL) were added into a flask. DIPEA (63.5 g; 0.49 mol) was slowly added, stirred for 10 hours at reflux temperature and cooled to 25 to 35 °C. After completion of reaction, water (100 mL) was added and stirred for an hour. The reaction mass was cooled to 0 to 5 °C and stirred for one hour. The solid obtained was filtered, washed with 50% aqueous methanol and dried under vacuum. 2-Methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate thus obtained is crystalline and characterized using PXRD, DSC, IR and TGA as shown in figures 1, 2, 3 and 4, respectively. Yield: 70 g; 60%. Melting point 114 °C.

Example-3a: Preparation of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate

2-Bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one (100 g; 0.33 mol), (cyclopropylmethoxy)acetic acid (72.5 g; 0.55 mol) and methanol (400 mL) were added into a flask. DIPEA (63.5 g; 0.49 mol) was slowly added, stirred for 6 hours at reflux temperature and cooled to 25 to 35 °C. After completion of reaction, water (100 mL) was added and stirred for an hour. The reaction mass was cooled to 0 to 5 °C and stirred for one hour. The solid obtained was filtered, washed with 50% aqueous methanol and dried under vacuum. Yield: 75 g; 65%.

Example-3b: Preparation of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2- yl (cyclopropylmethoxy)acetate

2-Bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one (100 g; 0.33 mol), (cyclopropylmethoxy)acetic acid (64 g; 0.49 mol) and methanol (400 mL) were added into a flask. DIPEA (63.5 g; 0.49 mol) was slowly added, stirred for 6 hours at reflux temperature and cooled to 25 to 35 °C. The reaction mass was further

cooled to 0 to 5 °C and stirred for one hour. The solid obtained was filtered, washed with methanol and dried under vacuum. Yield: 60 g; 52%.

Example-4: Preparation of Firocoxib (Compound of formula I)

2-Methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl(cyclopropylmethoxy) acetate (100 g; 0.28 mol) and acetonitrile (100 mL) at 25 to 35 °C were added into flask. Isopropyl trifluoroacetate (44 g; 0.28 mol) was then added and stirred. DBU (64 g; 0.42 mol) was added, stirred, heated to reflux temperature and stirred for 10 hours. After completion of the reaction, reaction mass was cooled to 25 to 35 °C, pH of the reaction mass was adjusted to 3.5 to 4.5 using 0.2 N dilute HCl. The solid obtained was filtered and washed with hot water (100 mL) then dried under vacuum to obtain Firocoxib. The Firocoxib obtained was characterized to be polymorph B. Yield: 85 g; 90%. Purity: 99%.

Example-4a: Preparation of Firocoxib

2-Methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl(cyclopropylmethoxy) acetate (100 g; 0.28 mol) and acetonitrile (500 mL) were added into a flask. Isopropyl trifluoroacetate (44 g; 0.28 mol) was then added and stirred. DBU (47 g; 0.31 mol) was added, stirred, heated to reflux temperature and stirred for 12 hours. After completion of the reaction, reaction mass was cooled to 25 to 35 °C, pH of the reaction mass was adjusted to 3 to 5 using dilute HCl. The solid obtained was filtered and washed with water (100 mL) then dried under vacuum to obtain Firocoxib polymorph B. Yield: 89 g; 94%. Purity: 99.1%.

Example-5: Recrystallization of Firocoxib

Firocoxib (100 g) and methanol (500 mL) were added into a flask at 25 to 35 °C and reaction mass was refluxed to get clear solution. Firocoxib Form B was seeded at 50 to 55 °C. After cooling, the solid obtained was filtered and washed with cold methanol (100 mL). The solid was dried under vacuum. The recrystallization is optional to further improve the purity. Yield: 95 g; 95%. Purity: 99.8%.

Example-5a: Recrystallisation of Firocoxib

Firocoxib (100 g) and methanol (1500 mL) were added into a flask at 25 to 35°C and reaction mass was heated to 50 to 55 °C to get clear solution. Carbon was added, stirred for 30 minutes. The solution was filtered through hyflow bed and washed with hot methanol (100 mL). The filtrate was concentrated by distilling out methanol. Seeding material of Form B was added at 50 to 55 °C. The reaction mass was cooled to 25 to 30 °C, stirred for one hour and further cooled to 0 to 5°C and further stirred for one hour. The solid obtained was filtered and washed with cold methanol (100 mL). The solid was dried under vacuum. Solids was isolated. The results on the polymorphic form were confirmed by powder X-Ray diffraction and DSC to be crystalline polymorphic Form B of Firocoxib. Yield: 94 g; 94%. Purity: 99.9%.

Example-5b: Recrystallisation of Firocoxib

Firocoxib (100 g) and methanol (1500 mL) were added into a flask at 25 to 35°C and reaction mass was heated to 50 to 55 °C to get clear solution. Carbon was added, stirred for 30 minutes. The solution was filtered through hyflow bed and washed with hot methanol (100 mL). The filtrate was concentrated by distilling out methanol. The reaction mass was cooled to 25 to 30 °C, stirred for one hour, cooled to 0 to 5 °C and further stirred for one hour. The solid obtained was filtered and washed with cold methanol (100 mL). The solid was dried under vacuum and isolated. The results on the polymorphic form were confirmed by powder X-Ray diffraction to be crystalline polymorphic Form B of Firocoxib. Yield: 92 g; 92%. Purity: 99.9%.

Example-5c: Recrystallisation of Firocoxib

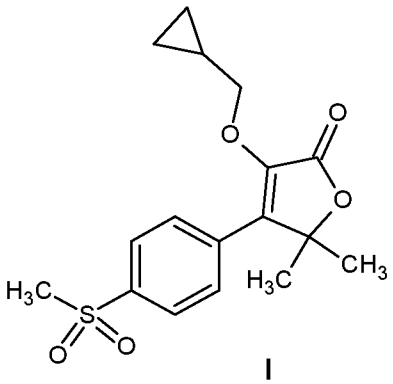
Firocoxib (100 g) and methanol (500 mL) were added into a flask at 25 to 35 °C and reaction mass was refluxed to get clear solution and cooled. The solid obtained was filtered at 0 to 5 °C and washed with cold methanol (100 mL). The solid was then dried under vacuum. Yield: 95 g; 95%. Purity: 99.9%.

Example-5d: Recrystallization of Firocoxib

Firocoxib (100 g) and dichloromethane (200 mL) were added into a flask, stirred for 15 minutes to get clear solution. Carbon was added, stirred for 30 minutes. The solution was filtered through hyflow bed and washed with dichloromethane (100 mL). The filtrate was concentrated by distilling out dichloromethane. Methanol (500 mL) was added and refluxed to get clear solution. After cooling, the solid obtained was filtered and washed with cold methanol (100 mL). The solid was dried under vacuum. Yield: 94 g; 94%. Purity: 99.8%.

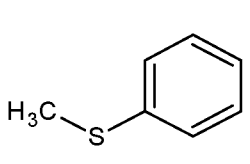
We claim:

1. A process for the preparation of Firocoxib of formula I, which comprises:

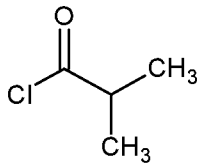


I

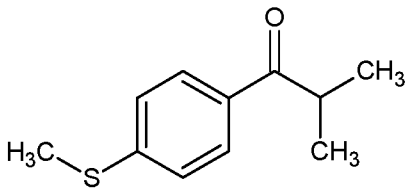
a) condensing thioanisole of formula VII with isobutyryl chloride of formula VIII in presence of aluminum chloride to obtain 2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula VI;



VII

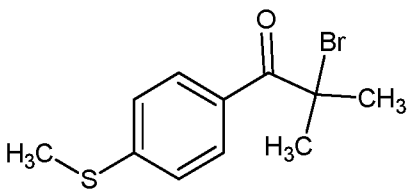


VIII



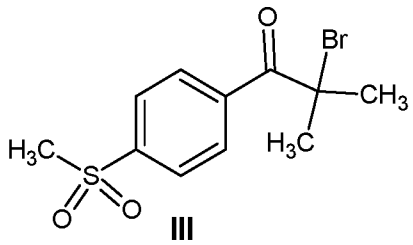
VI

b) brominating 2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula VI with bromine to give 2-bromo-2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula V;



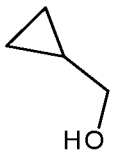
V

c) oxidizing 2-bromo-2-methyl-1-[4-(methylsulfanyl)phenyl]propan-1-one of formula V with hydrogen peroxide to give 2-bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one of formula III;

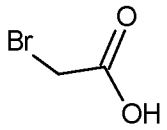


III

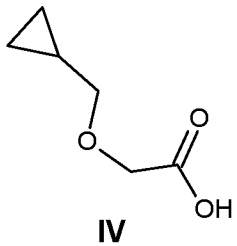
d) condensing cyclopropylmethanol of formula IX with bromoacetic acid of formula X in presence of potassium *tert*-butoxide to give (cyclopropylmethoxy)acetic acid of formula IV;



IX

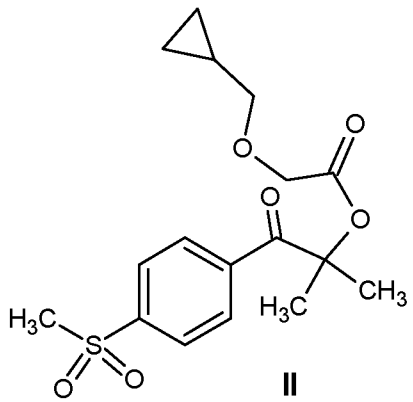


X



IV

e) condensing 2-bromo-2-methyl-1-[4-(methylsulfonyl)phenyl]propan-1-one of formula III with (cyclopropylmethoxy)acetic acid of formula IV in presence of N,N-diisopropylethylamine (DIPEA) to give 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate of formula II; and



II

f) cyclizing 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl(cyclopropylmethoxy)acetate of formula II using isopropyl trifluoroacetate in presence of 1,8-diazabicycloundec-7-ene (DBU) to give Firocoxib of formula I.

2. The process according to claim 1 wherein Firocoxib obtained in step f) is polymorph B.

3. The process according to claim 1 wherein 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate of formula II obtained in step e) is having PXRD as provided in figure 1.

4. A process for preparing polymorph B of Firocoxib from cyclisation reaction of 2-methyl-1-[4-(methylsulfonyl)phenyl]-1-oxopropan-2-yl (cyclopropylmethoxy)acetate.

5. The process according to claim 4 wherein the cyclisation reaction is carried out using DBU, acetonitrile and isopropyl trifluoroacetate.

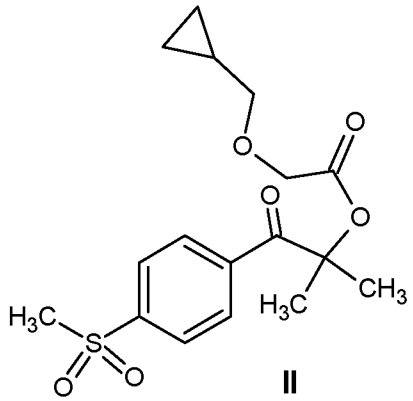
6. A process for recrystallization of Firocoxib comprising the steps of:

a) treating Firocoxib in methanol;
b) heating the mass to 50 °C to reflux temperature;
c) optionally treating with carbon followed by filtration;
d) optionally seeding with polymorph B;
e) cooling to 0 to 20 °C; and
f) isolating polymorph B of Firocoxib.

7. A process for the preparation of (cyclopropylmethoxy)acetic acid by the reaction of cyclopropylmethanol with haloacetic acid or salts thereof comprising bromoacetic acid, chloroacetic acid, sodium chloroacetate preferably bromoacetic acid using potassium *tert*-butoxide.

8. The process according to claim 7 wherein (cyclopropylmethoxy)acetic acid prepared was used in the preparation of Firocoxib.

9. Crystalline compound of formula II,



II

10. Crystalline compound of formula II as claimed in claim 9 for use in the preparation of Firocoxib of compound of formula I.

Figure 1

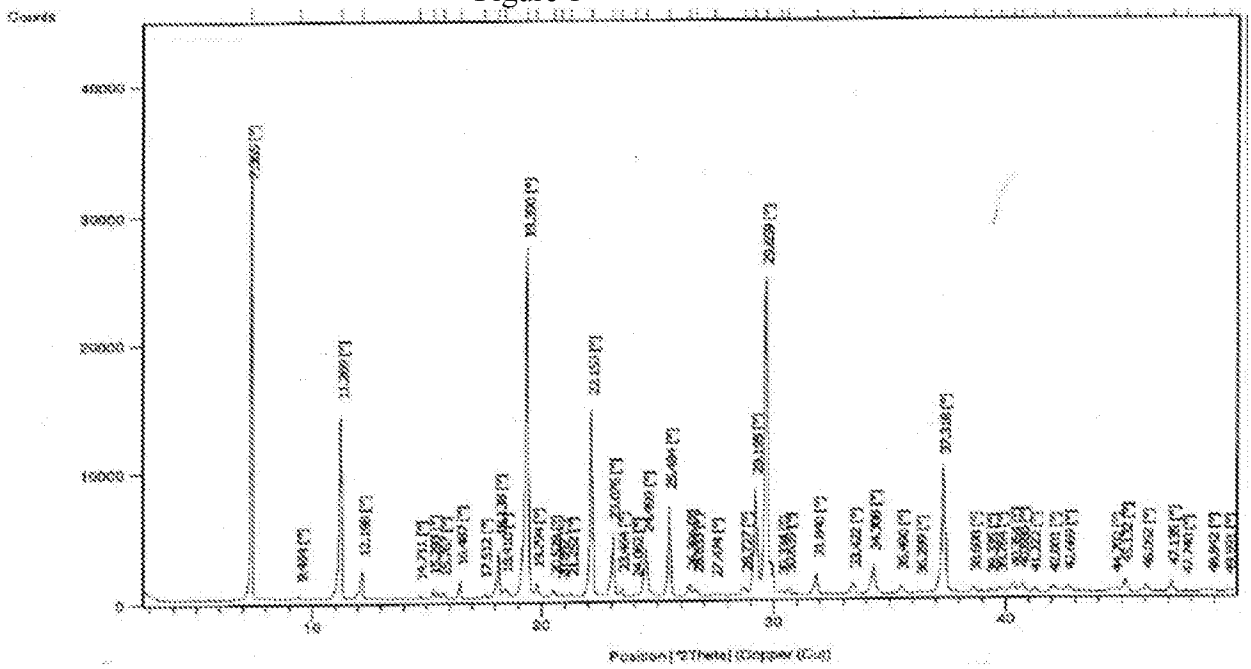


Figure 2

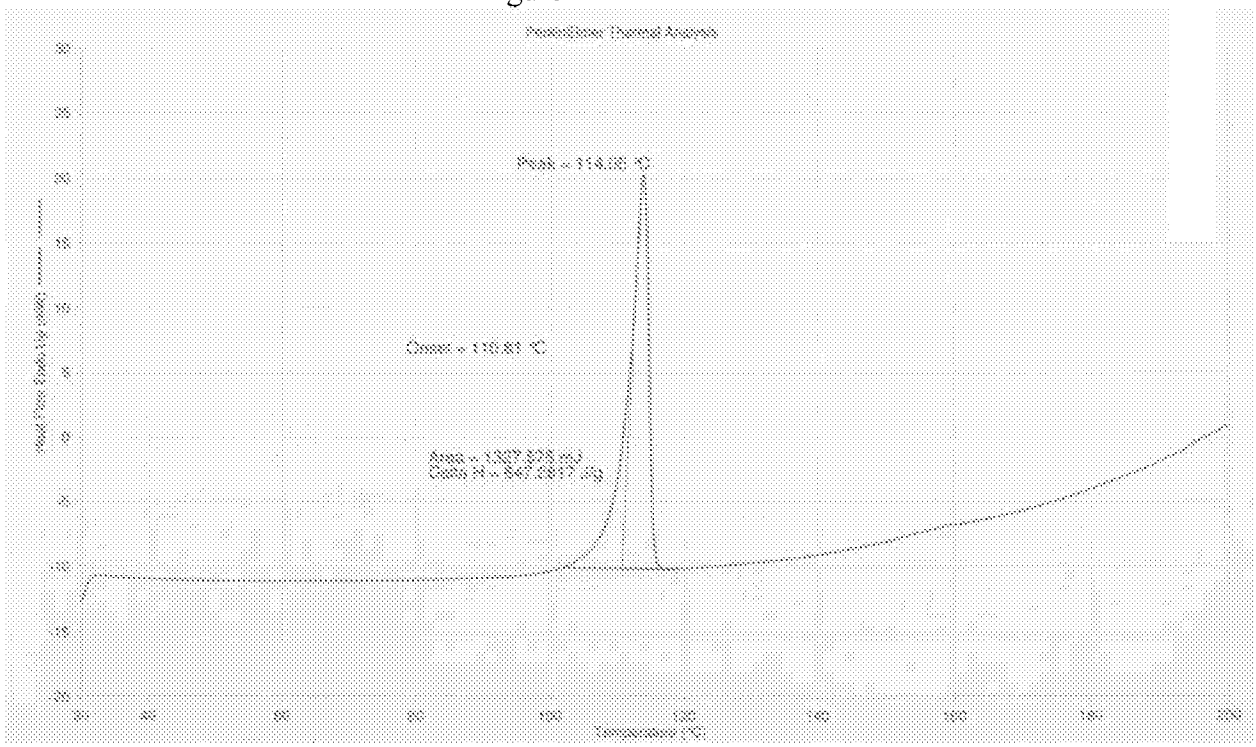


Figure 3

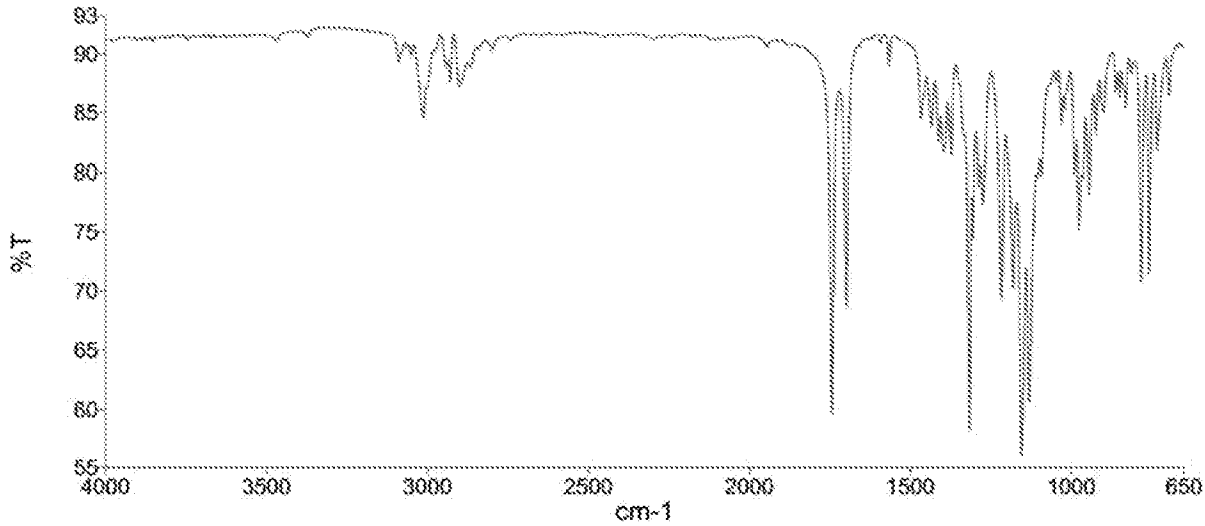
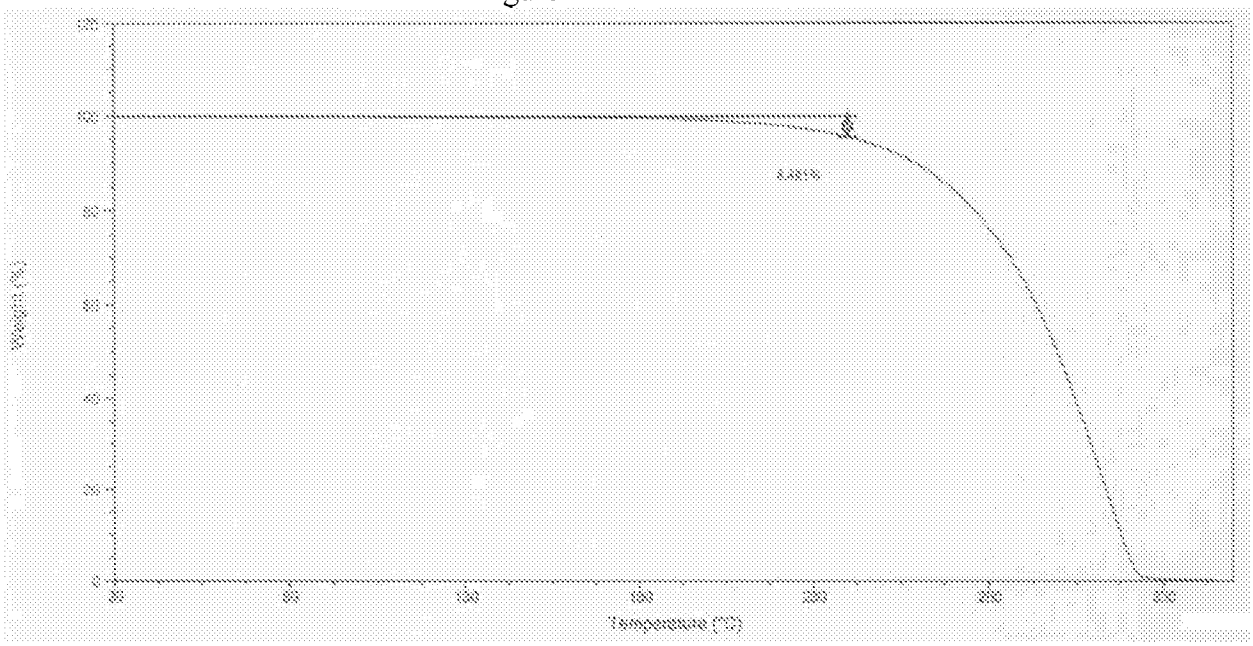


Figure 4



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/050572

A. CLASSIFICATION OF SUBJECT MATTER
C07D307/60 Version=2018.01

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)

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 practicable, search terms used)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN104803956A (UNIV CHINA PHARMA) 17 August 2016 (17/08/2016),(Cited in the application) The whole Document specifically claim 1	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22-03-2018	22-03-2018

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