(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 June 2017 (08.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/094031 A2

(51) International Patent Classification:
C07D 209/48 (2006.01)

(21) International Application Number:
PCT/IN2016/050434

(22) International Filing Date:
5 December 2016 (05.12.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
4599/MUM/2015 4 December 2015 (04.12.2015) IN
201621007579 3 March 2016 (03.03.2016) IN

(71) Applicant: **SUN PHARMACEUTICAL INDUSTRIES LIMITED** [IN/IN]; Sun House,201 B/1, Western Express Highway, Goregoan (E), Maharashtra, Mumbai 400063 (IN).

(72) Inventors: **THENNATI, Rajamannar**; Sun Pharmaceutical Industries Limited,nima Compound, Near Pratham Enclave, Tandalja Road,gujarat, Baroda 390020 (IN). **DWIVEDI, Shriprakash Dhar**; Sun Pharmaceutical Industries Limited,nima Compound, Near Pratham Enclave, Tandalja Road,gujarat, Baroda 390020 (IN). **JADAV, Kanaksinh Jesingbhai**; Sun Pharmaceutical Industries Limited,nima Compound, Near Pratham Enclave, Tandalja Road,gujarat, Baroda 390020 (IN). **KAMBHAMPATI, Sudhakar**; Sun Pharmaceutical Industries Limited,nima Compound, Near Pratham Enclave, Tandalja Road,gujarat, Baroda 390020 (IN). **GIRI, Rajesh Lalmani**; Sun Pharmaceutical Industries Limited,nima Compound, Near Pratham Enclave, Tandalja Road,gujarat, Baroda 390020 (IN). **PATEL, Mehulkumar Maheshbhai**; Sun Pharmaceutical Industries Limited,nima Compound, Near Pratham Enclave, Tandalja Road,gujarat, Baroda 390020 (IN). **MOHITE, Vishal Diliprao**; Sun Pharmaceutical Industries Limited,nima Compound, Near Pratham Enclave, Tandalja Road,gujarat, Baroda 390020 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

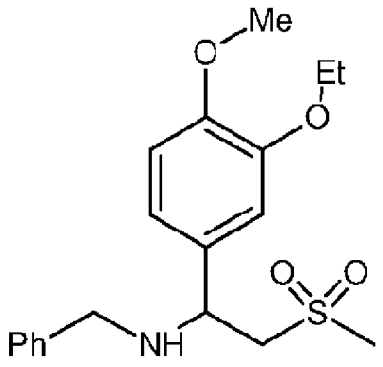
Declarations under Rule 4.17:

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

— *of inventorship (Rule 4.17(iv))*

[Continued on next page]

(54) **Title**: NOVEL PROCESS FOR PREPARATION OF APREMILAST



Formula II

(57) **Abstract**: The present invention related to a novel compound of Formula II, its enantiomers or acid addition salts thereof and process for its preparation. The compound of Formula II can be used for preparation of *N*-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-*1H*-isoindol-4-yl]acetamide also known as apremilast.

WO 2017/094031 A2

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

NOVEL PROCESS FOR PREPARATION OF APREMILAST

RELATED APPLICATIONS

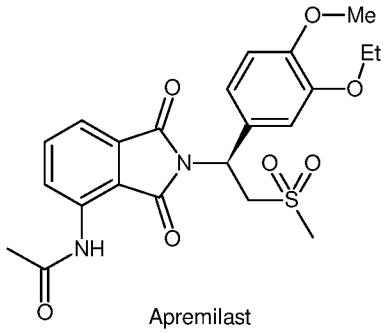
This application claims the benefit of Indian Patent Application no. 4599/MUM/2015 filed on December 04, 2015 and IN201621007579 filed on March 03, 2016; which is hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to a novel process for the preparation of apremilast and a novel intermediate for the preparation of apremilast.

BACKGROUND OF THE INVENTION

Apremilast or *N*-[2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-*1H*-isoindol-4-yl]acetamide having following structure



Apremilast

was first disclosed in U.S. Patent. No. 7,427,638 and was approved by the USFDA in March 2014 for treatment of adults with active psoriatic arthritis.

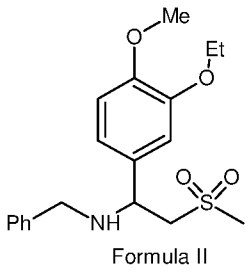
Many processes for the preparation of isoindoline compound *N*-[2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-*1H*-isoindol-4-yl]acetamide are reported. Generally, racemic 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione can be prepared using the methods described in U.S. Pat. No. 6,020,358. The corresponding *S* enantiomer can be isolated from the racemic compound by techniques known in the art.

U.S. Pat. No.7,427,638 discloses a process for preparation of *S* enantiomer of 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione wherein it is synthesized from 3-acetamidophthalic anhydride and a chiral amino acid salt of (*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethylamine.

US20130217918 patent application discloses the processes for preparation of (*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethylamine, an intermediate which is used for preparation of apremilast by using chiral auxillary namely (*R*)-*tert*-butylsulfinamide or (*S*)-*α*-methylbenzylamine.

SUMMARY OF THE INVENTION

The present invention provides a novel compound of Formula II



Formula II ,

its enantiomers or acid addition salts thereof and process for its preparation.

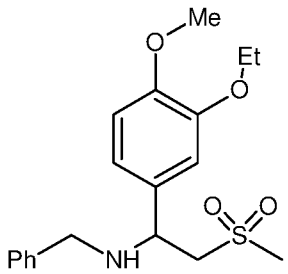
The present invention also provides a process for preparation of *N*-[2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-*1H*-isoindol-4-yl]acetamide or apremilast which comprises converting the compound of Formula II to apremilast.

The process of the present invention is economical and involves use of reagents which are easy to handle in commercial scale thus making the process plant friendly.

DETAILED DESCRIPTION OF THE INVENTION

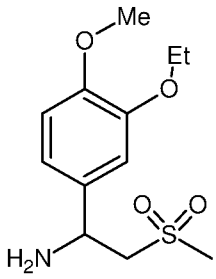
In one aspect the present invention provides a process for the preparation of *N*-[2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-*1H*-isoindol-4-yl]acetamide (apremilast) wherein the process comprises:

a) debenzylating the compound of Formula II



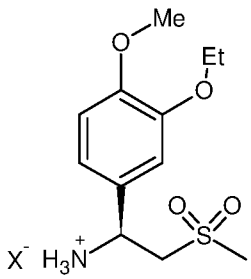
Formula II

to obtain a compound of Formula III



Formula III

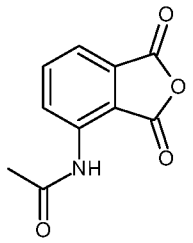
b) reacting the compound of Formula III with a chiral acid HX, to form an acid addition salt of following formula



Acid addition salt

and isolating the acid addition salt thereof, and

c) reacting the acid addition salt with a compound of Formula IV



Formula IV

Step "a" can be carried out by well-known process for debenzylation such as hydrogenation by using palladium on carbon and hydrogen gas. Step "a" can be carried out in presence of a suitable solvent. The suitable solvent for the purpose may be selected from aqueous hydrochloric acid, acetic acid, methanol, ethanol, isopropyl alcohol, tetrahydrofuran, 1,4-dioxane, dichloromethane and the like. In a preferred embodiment the solvent is aqueous hydrochloric acid or acetic acid. The reaction may be carried out at a temperature of about 25 °C to reflux temperature of the solvent used for a time sufficient for completion of the reaction. The free amino intermediate of Formula III may be isolated from the reaction mixture by any of the processes under common knowledge of a person skilled in the art like filtration or extraction.

In step "b" of the reaction, the compound of Formula III is reacted with a chiral acid HX wherein X represents the carboxylate part of the acid and H is hydrogen. The chiral acid is selected from amino acids or their derivatives. A preferred chiral acid is *N*-acetyl-*L*-leucine. The reaction can be conveniently carried out in presence of a solvent selected from C_{1-4} alcohols like methanol, ethanol; acetone and other equivalent ketones, halogenated solvents like dichloromethane and chloroform. In an embodiment the preferred solvent is methanol. The reaction may be heated to a temperature of 25 °C to reflux temperature of the solvent. The salt may be separated from the reaction mass by the processes known to a person skilled in the art.

In step "c", the acid addition salt obtained in step "b" is reacted with a compound of Formula IV in presence of a suitable solvent. The solvent may be selected from acetone and other equivalent ketones, halogenated solvents like dichloromethane and chloroform, ethers like tetrahydrofuran and 1,4-dioxane or acids like acetic acid or formic acid. In a preferred embodiment the solvent is acetic acid. When the solvent is other than acid, an acid like acetic acid or dilute hydrochloric acid may be added to the reaction mixture. The reaction may be carried out at temperature of about 25 °C to reflux temperature of the solvent used for a time sufficient for completion of the reaction.

The present invention also provides a process for isolation and purification of apremilast by recrystallization comprising:

i) after carrying out step "c", the reaction mixture is concentrated to give a residue,

ii) the residue of step i is dissolved in a solvent to obtain a solution,

iii) cooling the solution and

iv) filtering the solution to obtain pure apremilast and a filtrate.

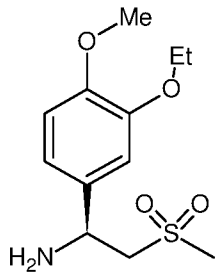
Step i is carried out by concentrating the reaction mixture obtained after carrying out step "c", by the process such as evaporating the solvent to obtain a residue. Optionally, the obtained residue may be dissolved in an organic solvent and washed with water and/or a base like sodium bicarbonate, sodium carbonate and concentrated to obtain the residue. A suitable organic solvent can be selected from water immiscible solvents like dichloromethane, ethyl acetate and the like.

The residue of step i can be dissolved in a suitable solvent selected from C_{1-4} alcohols like methanol, ethanol or isopropyl alcohol; ketones like acetone, ethyl methyl ketone, diethyl ketone; or mixtures thereof. The solution can be heated to temperature of about 40 °C to the reflux temperature of the solvent to facilitate the dissolution. The solution can be cooled to temperature necessary for crystallization for example 0 °C to 25 °C. In step iv, the crystallized apremilast may be isolated by filtration to give pure apremilast and filtrate.

It was found that the recovery of apremilast by the above process of isolation was about 70 % to about 85 %. About 15 % to 30 % apremilast was getting lost in the filtrate. Thus in another aspect, the present invention provides a process for recovering apremilast lost in the filtrate during step iv of the process for isolation and purification described above. Accordingly, the process for recovery of apremilast from the filtrate obtained during step iv of the above process comprises:

I) concentrating the filtrate to obtain a residue,

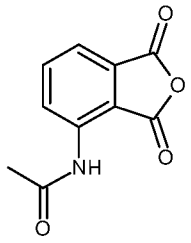
II) treating the residue with hydrazine hydrate to obtain a compound of Formula V



Formula V

,

III) reacting the compound of Formula V with a compound of Formula IV



Formula IV

to obtain apremilast,

IV) optionally, purifying the apremilast obtained in step III to obtain pure apremilast and a filtrate,

V) optionally, repeating the step I to III with the filtrate of step IV.

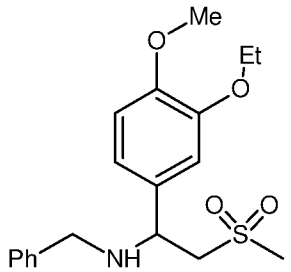
In step I, the filtrate obtained in step iv during isolation and purification process is concentrated by evaporating the solvent to obtain a residue. The filtrate of more than one batch may be clubbed together and the combined filtrate can be subjected to recovery process as described herein.

In step II, the residue is treated with hydrazine hydrate which may be carried out in a suitable solvent selected from the group comprising of ethanol, methanol, isopropyl alcohol, 1,4-dioxane, tetrahydrofuran, dichloromethane or a mixture thereof. Preferably, the solvent is ethanol. The reaction may be carried out at a temperature of about 25 °C to reflux temperature of the solvent used for a time sufficient for completion of the reaction. The compound of Formula V may be isolated from the reaction mixture by any of the processes under common knowledge of a person skilled in the art like filtration or extraction. Hydrazine hydrate may be used in molar equivalent of 3 to 15 equivalents with respect to apremilast in the residue. The quantity of apremilast in the residue can be determined by analysing sample of the residue by techniques like High Pressure Liquid Chromatography (HPLC). Preferably, hydrazine hydrate is 8 to 12 equivalent with respect to apremilast in the residue; more preferably hydrazine hydrate is 10 equivalent with respect to apremilast in the residue. Applicant has found that reaction did not go to completion when less than 3 equivalent of hydrazine hydrate with respect to apremilast in the residue was used in the reaction. Further applicant when tried other reagents instead of hydrazine hydrate such as methane sulfonic acid, hydrochloric acid or sodium hydroxide, reaction did not work out as monitored by TLC.

Step III involves reacting the compound of Formula V with compound of Formula IV in presence of a suitable solvent. In another embodiment, the solvent is selected from acetone and other equivalent ketones, halogenated solvents like dichloromethane and chloroform, ethers like tetrahydrofuran and 1,4-dioxane or acids like acetic acid or formic acid. In a preferred embodiment the solvent is acetic acid. When the solvent is other than acid, an acid like acetic acid or dilute hydrochloric acid may be added to the reaction mixture. The reaction may be carried out at temperature of about 25 °C to reflux temperature of the solvent used for a time sufficient for completion of the reaction.

Apremilast obtained in step III can be further purified by purification process as described earlier in the specification. The filtrate obtained during purification may again be subjected to recovery process as described above. The recycling steps can be repeated as many times as required to obtain desired yield of apremilast.

In another aspect, the present invention provides a compound of Formula II



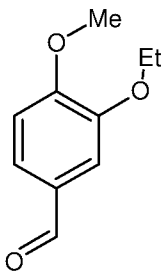
Formula II

,

its enantiomers or acid addition salts thereof.

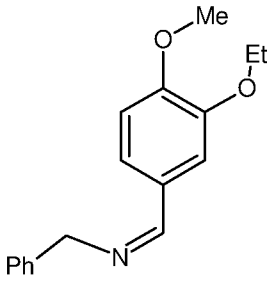
The compound of Formula II can be prepared by a process comprising:

aa) reacting a compound of Formula I



Formula I

with benzylamine to form an imine of Formula IIa



Formula IIa

ab) reacting the imine of Formula IIa with boron trifluoride etherate to form a complex,

ac) adding the boron trifluoride etherate complex into a mixture of dimethylsulfone and n-butyl lithium in a solvent,

ad) isolating the compound of Formula II.

Step "aa" involve reaction of aldehyde of Formula I with benzylamine to form imine of Formula IIa. The reaction can be carried out in presence of a suitable solvent selected from aromatic hydrocarbons like toluene, xylene, chlorobenzene; ether like tetrahydrofuran, 1,4-dioxane; chlorinated solvents like dichloromethane; alcoholic solvents like methanol or a mixture thereof. The preferred solvent is toluene. The reaction can be carried out at a temperature ranging from room temperature to reflux temperature of solvent; more preferably at a temperature of about 70 °C to 90 °C for a time sufficient for completion of the reaction. The imine may be isolated or can be taken into the next step without isolation.

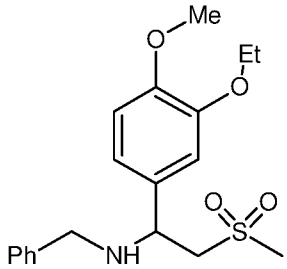
In step "ab" the imine is reacted with boron trifluoride etherate to form a complex. Suitable solvent for the reaction may be selected from toluene, tetrahydrofuran, 1,4-dioxane, dichloromethane, xylene, chlorobenzene or a mixture thereof. The preferred solvent is toluene or tetrahydrofuran. The reaction can be carried out by dissolving the imine of Formula IIa in the solvent and reacting it with boron trifluoride etherate (BF_3 etherate) at temperatures of about -5 °C to about 5 °C for a time sufficient for the reaction to complete like 1 to 3 hours. The whole reaction mixture of step "ab" is considered as Imine-BF_3 complex. The complex can be taken directly to step "ac" without isolation.

In step "ac", the Imine-BF_3 complex is reacted with a mixture prepared separately by reacting dimethylsulfone with n-butyl lithium (n-BuLi) in a solvent. The suitable solvent for the purpose can be selected from tetrahydrofuran, toluene, 2-methyltetrahydrofuran, diethylether

or a mixture thereof. The preferred solvent is tetrahydrofuran. The reaction of dimethylsulfone with n-BuLi can be carried out at a temperature of about -80 °C to about -50 °C. The Imine-BF_3 complex of step "ab" is added to this mixture at a temperature of -80 °C to -50 °C. The resultant reaction mixture can be stirred at this temperature and then at room temperature for a time sufficient for the completion of reaction to form the compound of Formula II.

In step "ad", the compound of Formula II can be isolated from reaction mass as per the known processes under the purview of a skilled artisan for instance by concentrating the reaction mass or by extracting with a suitable solvent & evaporating the solvent to obtain the compound of Formula II. The compound of Formula II can be purified either by acid-base treatment or by crystallization in a suitable solvent such as toluene or methanol. Alternatively, the compound of Formula II can be purified by multiple crystallization. For instance, the compound of Formula II can be purified by first crystallization in toluene and further recrystallization in methanol to obtain the pure compound of Formula II.

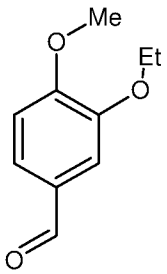
In another embodiment the present invention provides a process for preparation of compound of Formula II



Formula II

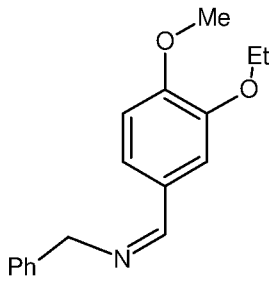
or acid addition salts thereof comprising:

Aa) reacting a compound of Formula I



Formula I

with benzylamine to form an imine of Formula IIa



Formula IIa

Ab) reacting the imine of Formula IIa with boron trifluoride etherate to form a complex,

Ac) adding the boron trifluoride etherate complex into a solution prepared by reacting dimethylsulfone with a base in presence of dimethyl sulfoxide and a solvent,

Ad) isolating the compound of Formula II.

Step "Aa" involve reaction of aldehyde of Formula I with benzylamine to form imine of Formula IIa. The reaction can be carried out in presence of a suitable solvent selected from aromatic hydrocarbons like toluene, xylene, chlorobenzene; ether like tetrahydrofuran, 1,4-dioxane; chlorinated solvents like dichloromethane; alcoholic solvents like methanol or a mixture thereof. The preferred solvent is toluene. The reaction can be carried out at a temperature ranging from room temperature to reflux temperature of solvent; more preferably at a temperature of about 70 °C to 90 °C for a time sufficient for completion of the reaction. The imine may be isolated or can be taken into the next step without isolation.

In step "Ab" the imine is reacted with boron trifluoride etherate to form a complex. Suitable solvent for the reaction may be selected from toluene, tetrahydrofuran, 1,4-dioxane, dichloromethane, xylene, chlorobenzene or a mixture thereof. The preferred solvent is toluene. The reaction can be carried out by dissolving the imine of Formula IIa in the solvent and reacting it with boron trifluoride etherate (BF_3 etherate) at temperatures of about -5 °C to about 5 °C for a time sufficient for the reaction to complete like 1 to 3 hours. The whole reaction mixture of step "Ab" is considered as Imine-BF_3 complex. The complex can be taken directly to step "Ac" without isolation.

In step "Ac", the Imine-BF_3 complex is reacted with a solution prepared separately by reacting dimethylsulfone with a base in presence of dimethyl sulfoxide and a solvent. A suitable base for the purpose can be selected from sodium hydride (NaH), lithium hydride (LiH), potassium hydride (KH), sodium *tert*-butoxide, potassium *tert*-butoxide and their equivalents. The preferred base is sodium hydride. The reaction can be carried out in presence of a suitable solvent selected from aromatic hydrocarbons like toluene and xylene and ethers like tetrahydrofuran, dimethoxyethane, 1,4-dioxane, 2-methyltetrahydrofuran, diglym or mixtures thereof. The preferred solvent is toluene. The reaction can be carried out at a temperature of about 50 °C to about 80 °C; more preferably at a temperature of about 65 °C to about 75 °C, for a time sufficient for the completion of reaction, for instance about 1 to 3 hours. The Imine-BF_3 complex of step "Ab" can be added to this solution at a temperature of about -10 °C to about 30 °C; more preferably at a temperature of about -5 °C to about 10 °C. The resultant reaction mixture can be stirred at this temperature for a time sufficient for the completion of reaction to form the compound of Formula II.

The reaction involves base to abstract a proton from dimethylsulfone to generate an anion which then reacts with the complex prepared in step "Ab". The prior art uses a strong base n-butyl lithium (n-BuLi) for the purpose of anion generation which is highly inflammable compound and require special techniques to handle. The difficulty further increases during commercial manufacturing requiring handling of large quantities and maintaining the sub-zero temperature required by the reagent. Another disadvantage of n-BuLi is its cost. The cost of overall process increases due to costly n-BuLi reagent.

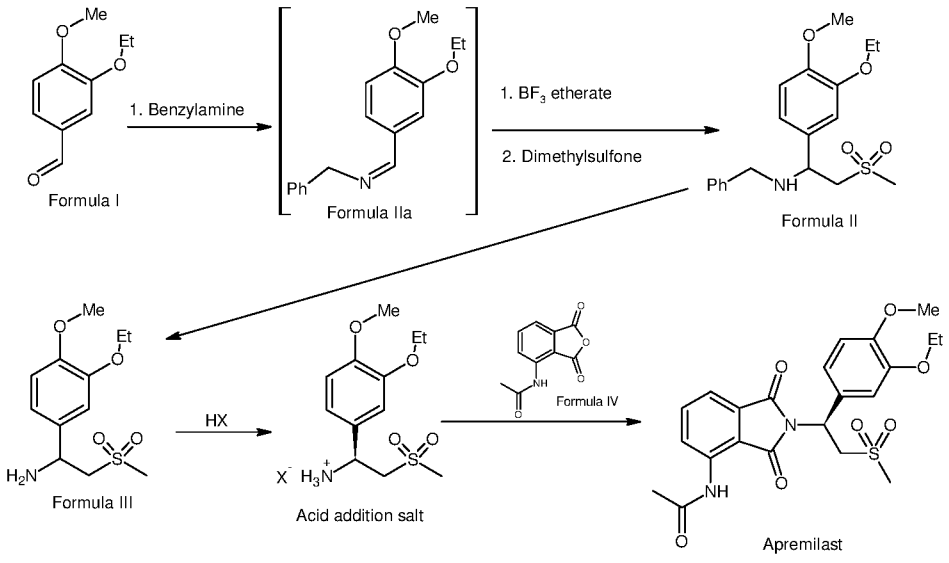
The present inventors when working on improving the process, tried to replace n-BuLi with other bases like NaH, LiH and KH which are easy to handle and less expensive than n-BuLi. However, the results were discouraging as the reaction did not go to completion. For instance, when NaH was used as a base and reacted with dimethylsulfone for about 10 to 15 hours at a temperature ranging from 50 °C to more than 100 °C, followed by the reaction with the Imine-BF_3 complex, only up to 10 % of the reaction got completed. Moreover, the inventors were unable to or found very difficult to isolate the product from the reaction mass.

Addition of dimethyl sulfoxide (DMSO) in the reaction gave surprising results as the reaction got completed in a short time of about 1 to 3 hours; requiring lower temperature. Without being bound to any theory, it is assumed that during the reaction, DMSO first react with the

base and forms an anion (sodium methylsulfinylmethylide or dimsyl sodium) which in turn reacts with dimethylsulfone and generate the required anion of dimethylsulfone which further reacts with the complex of step "Ab" to give the product. Dimethylsulfone when reacted with NaH directly requires longer reaction time and more drastic conditions like high temperature at which the dimethylsulfone anion may get decomposed. Whereas, dimsyl sodium is formed at lower temperatures and once formed it readily reacts with dimethylsulfone to generate the required anion.

In step "Ad", the compound of Formula II can be isolated from reaction mass as per the known processes under the purview of a skilled artisan for instance by concentrating the reaction mass or by extracting with a suitable solvent & evaporating the solvent to obtain the compound of Formula II. The compound of Formula II can be purified either by acid-base treatment or by crystallization in a suitable solvent such as toluene or methanol. Alternatively, the compound of Formula II can be purified by multiple crystallization. For instance, the compound of Formula II can be purified by first crystallization in toluene and further recrystallization in methanol to obtain the pure compound of Formula II.

The complete process for preparation of apremilast from the compound of Formula I can be depicted as in Scheme below:



The present invention is further illustrated in detail with reference to the following examples. It is desired that the examples be considered in all respect as illustrative and are not intended to limit the scope of the claimed invention.

EXAMPLES

Example 1: 1-(3-Ethoxy-4-methoxy-phenyl)-2-methylsulfonyl-*N*-[1-phenylmethyl]-ethanamine

In a 1.0 liter RBF equipped with dean stark apparatus, 3-ethoxy-4-methoxy benzaldehyde (125 g; 0.6944 moles), benzylamine (78 g; 0.7285 moles) and toluene (375 mL) was charged, the clear solution was stirred at 105 °C to 110 °C till no more water come out azeotropically. Toluene was distilled out and THF (625 mL) was charged to the residue. The solution was cooled to 0 °C to 5 °C. Boron trifluoetherate (BF_3 etherate) (100 mL; 0.6944 moles) was charged to the above solution maintaining the temperature at 0 °C to 5 °C for 1.0 hour (Imine-BF3 complex-Solution A).

Meanwhile in separate RBF, THF (1620 mL) and dimethylsulfone (162 g; 1.7361 moles) was charged under nitrogen atmosphere and the suspension was cooled to -70 °C. n-Butyl lithium 1.6M (1000 mL; 1.5685 moles) was charged at -70 °C to -55 °C during 30 min to the above suspension and the suspension was maintained for 1 hour at -70 °C to -55 °C (Solution B).

Solution A was added into Solution B at -70 °C to -55 °C and maintained for 1 hour at -70 °C to -55 °C followed by stirring at room temperature for one hour. After completion of the reaction, THF was distilled completely. The residue was quenched in aqueous sodium hydroxide solution and extracted product in dichloromethane. Dichloromethane layer was distilled off and crude product was isolated from diisopropylether at room temperature to give 200 g off white color powder.

^{1}H NMR (400MHZ, $CDCl_3$) δ 1.45 (t, *J*=6.98 Hz, 3H), 2.24 (s, 1H), 2.79 (s, 3H), 3.19 (dd, *J*=3.80 & 14.45 Hz, 1H), 3.35 (dd, *J*=9.15 & 14.40 Hz, 1H), 3.61 (dd, *J*= 13.23 & 53.89 Hz, 2 H), 3.86 (s, 3H), 4.10 (q, *J*= 6.99 Hz, 2H), 4.23 (dd, *J*= 3.85 & 9.15, 1H), 6.85-6.92 (m, 3H), 7.19-7.32 (m, 5H).

Example 2: 1-(3-Ethoxy-4-methoxy-phenyl)-2-methylsulfonyl-*N*-[1-phenylmethyl]-ethanamine

In a 1.0 liter RBF, 3-ethoxy-4-methoxy benzaldehyde (100 g; 0.556 moles), benzylamine (63.6 g; 0.594 moles) and toluene (200 mL) were charged. The clear solution thus obtained was stirred at 78 °C to 82 °C for 2 hours. Toluene was distilled out from the reaction mixture and toluene (500 mL) was charged to the residue. The resultant solution was cooled to -5 °C to 5 °C. Boron trifluoride etherate (BF_3 etherate) (92 g; 0.679 moles) was charged to the above solution and the resultant solution was maintained at 0 °C to 6 °C for 2.0 hours (Imine-BF3 complex-**Solution A**).

Meanwhile in separate 2.0 liter RBF, toluene (1.0 liter), dimethyl sulfoxide (400 mL) and dimethylsulfone (240 g, 2.55 moles) were charged under N_2 atmosphere at room temperature. The resultant suspension was cooled to -3 °C to 3 °C and sodium hydride (60 % suspension)(100 g , 2.5 moles) was added at -3 °C to 3 °C . The resultant suspension was stirred at 70 °C to 75 °C for 120 minutes **(Solution B).**

Solution B was cooled to -5 °C to 10 °C and Solution A was added to it. The resultant reaction mixture was stirred at -5 °C to 10 °C for 30 minutes. After completion of reaction, methanol (100 mL) was added to above reaction mixture and temperature of reaction mixture was raised to 22 °C to 28 °C and stirred for 10 hours at this temperature. Water (800 mL) was added to above reaction mixture and stirred at 22 °C to 28 °C for 15 minutes. The temperature was raised to 66 °C to 70 °C. The organic layer was separated and washed with water. Concentrated hydrochloric acid (80 mL) and water (920 mL) was added to above organic layer. Aqueous layer was separated and washed with toluene at 66 °C to 70 °C. Aqueous layer was cooled to 5 °C to 10 °C and diisopropyl ether (800 mL) was added to it. The resultant biphasic suspension was stirred at 5 °C to 10 °C for 3 hours and hydrochloride salt of title compound was isolated by filtration. The HCl salt was converted to free base by adding aq. sodium hydroxide and diisopropyl ether, followed by filtration to afford 160 g of title compound as an off white powder.

Example 3: 2-(3-Ethoxy-4-methoxy-phenyl)-2-(methylsulfonyl)-eth-2-ylamine

The product of example 1 or example 2 (170 g), aqueous hydrochloric acid (0.7N) (2040 mL) and 10 % palladium on carbon (50 % wet) (34 g) were charged in an RBF and stirred under hydrogen purging for 10 hours at room temperature. Palladium carbon was filtered and washed with DM Water (demineralized water) & diisopropylether. Caustic lye was added to the filtrate to achieve pH between 11.5 to 13.0 and the product was extracted with dichloromethane. Dichloromethane was distilled off completely and product was isolated with isopropyl alcohol to give 75 g off white powder.

Example 4: 2-(3-Ethoxy-4-methoxy-phenyl)-2-(methylsulfonyl)-eth-2-ylamine

A mixture of product of example 1 or example 2 (170 g), aqueous hydrochloric acid (0.5N) (1360 mL) and 10 % palladium on carbon (50 % wet) (34 g) were hydrogenated at 60 °C to 65 °C for 6 hours under hydrogen gas pressure 0.1 to 0.2 kg/cm^2. After completion of reaction, palladium carbon was filtered off and washed it with DM water & diisopropylether. Caustic lye was added to the filtrate to achieve pH between 11.5 to 13.0 and the product was

extracted with dichloromethane. Organic layer was distilled off completely and product was isolated with isopropyl alcohol to give 102 g of title compound as an off white powder.

Example 5: (*S*)-2-(3-Ethoxy-4-methoxy-phenyl)-2-(methylsulfonyl)-eth-2-ylamine-*N*-acetyl-*L*-leucine salt

To 1 liter RBF the product of example 3 or 4 (75 g; 0.2743 moles), *N*-acetyl-*L*-leucine (47.5 g ; 0.2743) and methanol (545 mL) were charged and the suspension was stirred at 60 °C to 65 °C for 1 hour, the suspension was cooled to room temperature and stirred for another 3 hours. The solid was filtered and dried under reduced pressure to obtain 60 g of title compound with chiral purity of 85% desired isomer.

It was further purified by methanol to give 35 g of pure title compound having chiral purity 99.5%.

Example 6: Apremilast

To a 500 mL RBF the product of example 5 (70 g; 0.1280 moles), 3-acetamidophthalic anhydride (27.6 g; 0.1345 moles) and acetic acid (350 mL) were charged and stirred at 110 °C to 115 °C for 1 hour and the solution was cooled to 60-65 °C. Acetic acid was distilled off completely and the residue was dissolved in dichloromethane. The dichloromethane layer was washed with DM water followed by sodium bicarbonate solution and distilled off completely and the product isolated by recrystallization in acetone:ethanol mixture to give 40 g of apremilast as a light yellow solid with chiral purity of 99.9 % and HPLC purity of 99.8 %.

Example 7: 1-(3-Ethoxy-4-methoxy-phenyl)-2-methylsulfonyl-*N*-[(*1S*)-1-phenylethyl]-ethanamine

The filtrate remained after the isolation of apremilast by recrystallization (from example 6) was concentrated to give crude apremilast (48 g). A mixture of crude apremilast (48 g; 0.1042 moles), hydrazine hydrate (26.08 g; 0.5211 moles) and ethanol (480 mL) was heated at 75 °C to 80 °C for 2 hours. After completion of reaction, ethanol was distilled out completely. Water was added to the residue, basified it with ~10 mL of caustic lye to adjust the pH greater than 12.5 and extracted with dichloromethane. Organic layer was distilled out completely and the product was isolated by recrystallization in isopropyl alcohol to yield the title compound.

Example 8: 3-Acetamidophthalic acid

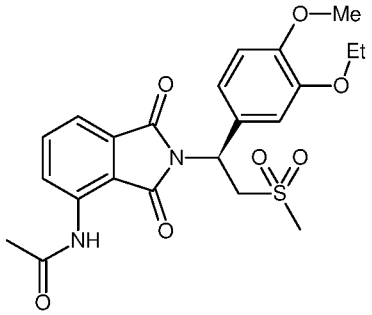
3-Nitrophthalic acid (100 g, 0.4736 moles) was added to a solution of sodium hydroxide (38.83 g, 0.9709 moles) in water (500 mL). 10 % Palladium on carbon (1.0 g, 50% wet) was added to this solution and the resultant mixture was hydrogenated at room temperature under 2 kg/cm^2 hydrogen pressure. After completion of reaction, the reaction mixture was filtered to remove Pd/C and the bed was washed with water (100 mL). The washing and the filtrate were combined and to this solution was added acetic anhydride (58.2 mL, 0.6157 moles) at 15 °C to 20 °C. The reaction mixture was stirred at room temperature for 2.0 hours. After completion of reaction, the reaction mixture was cooled to 0 °C to 5 °C and acidified with aqueous hydrochloric acid solution (6N, 170 mL). The formed solid was filtered and dried under vacuum to get 93.0 g of title compound.

Example 9: Apremilast

To a 500 mL RBF the product of example 5 (5 g; 0.01119 moles), 3-acetamidophthalic acid (2.62 g; 0.011756 moles) and acetic acid (50 mL) were charged and stirred at 110 °C to 115 °C for 1 hour and the solution was cooled to 60-65 °C. Acetic acid was distilled off completely and the residue was dissolved in dichloromethane. The dichloromethane layer was washed with DM water followed by washing with aq. sodium bicarbonate solution. The dichloromethane layer was separated and distilled off completely. The product was isolated by recrystallization in acetone:ethanol mixture to give 3.4 g of apremilast as a light yellow solid with HPLC purity of 99.9 %.

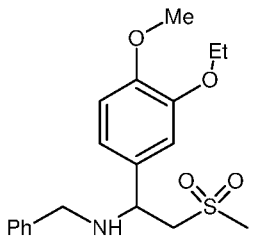
CLAIMS:

1. A process for preparation of apremilast having following Formula



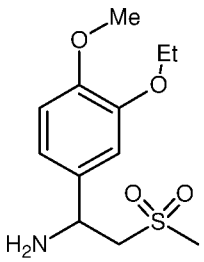
comprising:

a) debenzylating the compound of Formula II



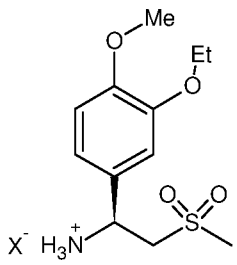
Formula II

to obtain a compound of Formula III



Formula III

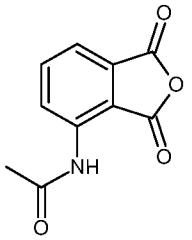
b) reacting the compound of Formula III with a chiral acid HX, to form an acid addition salt of following formula



Acid addition salt

and isolating the acid addition salt thereof, and

c) reacting the acid addition salt with a compound of Formula IV

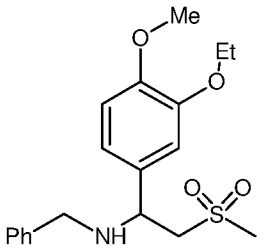


Formula IV

2. The process as in claim 1, wherein the chiral acid HX is *N*-acetyl-*L*-leucine.

3. The process as in claim 1, wherein in step "c" the acid addition salt is reacted with compound of Formula IV in acetic acid as solvent.

4. A compound of Formula II

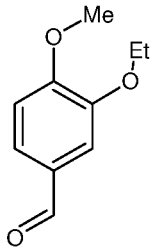


Formula II

its enantiomers or acid addition salts thereof.

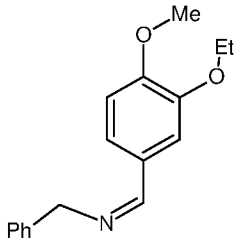
5. The process of claim 1, wherein the compound of Formula II is prepared by a process comprising:

aa) reacting a compound of Formula I



Formula I

with benzylamine to form an imine of Formula IIa



Formula IIa

,

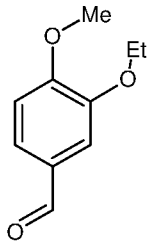
ab) reacting the imine of Formula IIa with boron trifluoride etherate to form a complex,

ac) adding the boron trifluoride etherate complex into a mixture of dimethylsulfone and n-butyl lithium in a solvent,

ad) isolating the compound of Formula II.

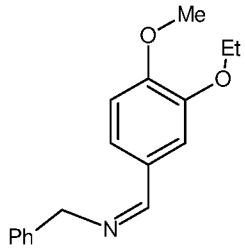
6. The process of claim 1, wherein the compound of Formula II is prepared by a process comprising:

Aa) reacting a compound of Formula I



Formula I

with benzylamine to form an imine of Formula IIa



Formula IIa

,

Ab) reacting the imine of Formula IIa with boron trifluoride etherate to form a complex,

Ac) adding the boron trifluoride etherate complex into a solution prepared by reacting dimethylsulfone with a base in presence of dimethyl sulfoxide and a solvent,

Ad) isolating the compound of Formula II.

7. The process as in claim 6, wherein the solvent is toluene.

8. The process as in claim 6, wherein the base is sodium hydride (NaH), potassium hydride (KH), sodium *tert*-butoxide or potassium *tert*-butoxide.

9. The process as in claim 8, wherein the base is sodium hydride.