ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 6, 366-374

Chemistry & Biology Interface

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Research Paper

Identification, Synthesis and Characterization of Potential Impurities of Dexlansoprazole

Manne Nagaraju[a*], Rakeshwar Bandichhor[a], Kagga Mukkanti[b]

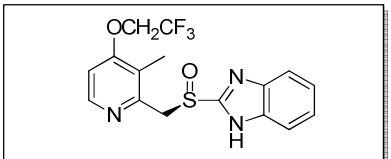
[a]*Research and Development, API-PDT-03, Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd, Bachupally, Qutubullapur, R.R.Dist-500072, A.P., India*
[b]*Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad 500072, A.P., India*
[#]*DRL-IPD Communication number: IPDO-IPM-00288*
Received 27 September 2013; Accepted 21 November 2013

Keywords: HR-MS, impurities, Levo, dextro, characterization, synthesis.

Abstract: Research work featured in this article describes the synthesis and characterization of related substance of Dexlansoprazole ((*R*)-(+)-**1**); the successor and (*R*)-enantiomer of Lansoprazole with an enantiomeric excess of >99.8% and ICH grade quality of final API. During the laboratory development and scale up, we have observed six possible potential impurities in the selected synthetic sequence Viz., Nitro sulfone, Levo Nitro sulfoxide, lansoprazole sulfide, Lansoprazole sulfone, Spiro compound and Levo Dexlansoprazole.

Introduction

(*R*)-(+)-2-[3-Methyl-4-(2,2,2-trifluoro-ethoxy)-pyridin-2-ylmethanesulfinyl]-1*H*-benzoimidazole, which has the generic name Dexlansoprazole, is the prototypical compound of a class of highly gastric secretion inhibitor.[1] Lansoprazole, a racemic mixture, is successfully used for the treatment of duodenal and gastric ulcers, reflux esophasitis, and Zollinger-Ellison syndrome. [2,3] However, the dexlansoprazole is introduced for the treatment of acid-related disorders and the treatment and maintenance of patients with reflux erosive oesophagitis and non-erosive reflux disease, i.e. gastro-oesophageal disease (GERD or GORD), under the brand name of DEXILANT.[4].



(*R*)-(+)-**1**

Figure 1. Structure of Dexlansoprazole

The presence of impurities in an active pharmaceutical ingredient (API) can have a significant impact on the quality and safety of the drug product. Therefore, it is necessary to study the impact of impurity profile of the API to be used in the

Corresponding Author* Telephone: +91 4044346145, Fax: +91 4044346285 E-mail: nagarm@drreddys.com

ISSN: 2249 –4820

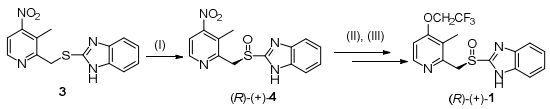
Chemistry & Biology Interface, 2013, 3, 6, 366-374

manufacturing of a drug product. International Conference on Harmonization (ICH) guidelines recommends indentifying and characterizing all impurities that are present at a level of ≥0.10%.[5] In this context, a comprehensive study was undertaken to synthesize and characterize the following six impurities:[6] 2-(((3-methyl-4-nitropyridin-2-yl)methyl)sulfonyl)-1*H*-benzo[d]imidazole (**5**), 2-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)sulfonyl)-1*H*-benzimidazole (**6**), (S)-2-(((3-methyl-4-nitropyridin-2-yl)methyl)sulfinyl)-1*H*-benzimidazole (**7**), (S)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)sulfinyl)-1*H*-benzimidazole (**8**), 2-(((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)methyl)thio)-1*H*-beimidazole (**9**), 12-((1*H*-benzimidazol-2-yl)thio)-1-methyl-2-(2,2,2-trifluoroethoxy)benzo[4',5']imidazo[2',1':2,3]imidazo[1,5-a]pyridine (**10**).

Several analytical methods were reported for the determination of lansoprazole and pantoprazole in biological fluids and pharmaceutical formulations.[7] Two of the lansoprazole impurities, lansoprazole sulfide **9** and sulfone **6**, were earlier reported as metabolites.[8] Among these six, impurities **5**, **7**, **8** and **10** impurities are reported here for the first time and also alternative synthetic procedures were reported for **9** and **6**.

Results and discussion

Our approach began with enantioselective oxidation of prochiral nitrosulfide intermediate **3** under modified Kagan's oxidative conditions to obtain either enantiopure or enantiomerically enriched nitrosulfoxide intermediate (*R*)-(+)-**4** that can be easily converted to Dexlansoprazole ((*R*)-(+)-**1**) in the subsequent step.[9] Our optimized route consists of two steps involving asymmetric oxidation of **3** with cumene hydroperoxide[10] (CHP) in the presence of titanium derived chiral complex prepared in situ from L-(+)-Diethyl tartarate (L-(+)-DET), $Ti(O^iPr)_4$ and water applied in the molar ratio of 2.2:1.1:0.6 to obtain (*R*)-(+)-**4** with >90% ee. The enantiomerically enriched (*R*)-(+)-**4** as a resultant was subjected to acetone mediated preferential crystallization to yield enantiopure (*R*)-(+)-**4** (>97% ee). The structure and absolute configuration of (*R*)-(+)-**4** has been unambiguously confirmed report by single crystal analysis,[11] which on further treatment with potassium salt of 2,2,2-triflouroethanol in dimethylformamide (DMF) to afford Dexlansoprazole (after necessary aqueous work up) with ICH quality having >99.8 % ee.



Scheme 1. Dexlansoprazole synthesis *via* nitrosulphide **3** asymmetric oxidation[a]

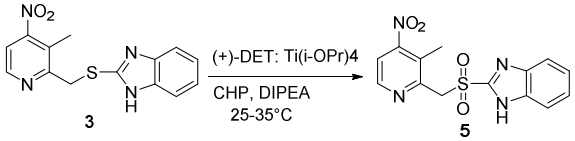
[a]**Reagents and Conditions**: (i) $Ti(O\text{-}Pr)_4$/ (*R*, *R*)-DET/ H_2O, $PhCH_3$, $(^iPr)_2NEt$, $PhC(CH_3)_2OOH$; 0-5°C, 4-5 hrs, Aq. NH_3 and Piperidine, Acetonitrile, Acetic acid; (II) Acetone, 45-50°C; (III) K_2CO_3, DMF, CF_3CH_2OH, Acetonitrile, Acetic acid, water

Nitro sulfone (**5**) is one of the most potential impurity can be form in stage 1 process of dexlansoprazole ((*R*)-(+)-**1**), due to over oxidation of nitro sulfoxide intermediate ((*R*)-(+)-**4)** with cumene hydroperoxide. The washability of nitro sulfone (**5**) impurity is difficult because of structural similarity with (*R*)-(+)-**4.** Hence, preparation and characterization of nitro sulfone impurity is essential. Nitro sulfone (**5**) was prepared by controlled oxidation of nitro sulfide intermediate (**3**), using excess equivalent (2.5eq) of **CHP** (Scheme 2). The protonated molecular ion appeared at 332.9 and a sodium with methanol adduct appeared at 387 in the ESI mass spectrum. HRMS (EI), m/z calcd. For $C_{14}H_{12}N_4S$ $[M+H]^+$: 333; found: 333; IR stretching frequencies:

ISSN: 2249 –4820

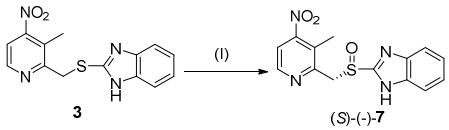
Chemistry & Biology Interface, 2013, 3, 6, 366-374

O=S=O stretching (1339 cm^{-1}), NO_2 stretching (1538 cm^{-1}). The ^{1}HNMR spectral data of compound **5** is similar to that of compound (*R*)-(+)-**4.**



Scheme 2. Synthesis of Nitro sulfone (**5**)

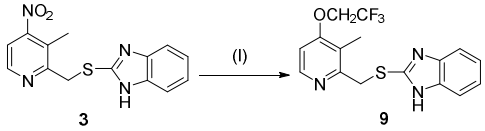
The modified Kagan's enantioselelctive asymmetric sulfoxidation conditions were applied on prochiral nitro sulphide intermediate (**3**) to accomplish corresponding either enantiopure or enriched nitro sulfoxide intermediate (*R*)-(+)-**4** that will be taken further for Dexlansoprazole (*R*)-(+)-**1** synthesis. Hence, more possibility for the formation of opposite isomer (i.e. S-isomer of (*R*)-(+)-**4)** during the synthesis of required isomer of (*R*)-(+)-**4**, which was prepared and well characterized first time. S-isomer (*S*)-(-)-**7** of (*R*)-(+)-**4** was prepared by employing titanium mediated asymmetric oxidation on nitro sulfide (**3**) using (-)-Diethyl tartrate in place of (+)-Diethyl tartrate with CHP in toluene solvent medium at 0-5°C for 3-4 h, resulted pure form of S-isomer (*S*)-(-)-**7** (Scheme 3). The protonated molecular ion of (S)-(-)-**7** at 316.9, and the sodium adduct appeared as base peak at 338.9 in ESI spectrum. HRMS *m/z* calcd. For $C_{14}H_{12}N_4O_2S$ $[M+H]^+$: 316.9; found: 316.9; this is consistent with the assigned structure of (*S*)-(-)-**7** and confirmed by Chiral HPLC comparing with (*R*)-(+)- (S)-(-)-**7**. **IR** stretching frequencies of (*S*)-(-)-**7** showed the presence of O=S=O stretching (1371 cm^{-1}), C-N stretching (1165 cm^{-1}), NO_2 stretching (1544 cm^{-1}). The ^{1}HNMR spectral data of compound (*S*)-(-)-**7** is similar to that of (*R*)-(+)-**4**.



Scheme 3. Synthesis of S-Isomer of (*R*)-(+)-**4**

[a]Reagents and Conditions: (i) $Ti(O\text{-}^iPr)_4$/ (*S, S*)-DET/ H_2O, $PhCH_3$, $(^iPr)_2NEt$, $PhC(CH_3)_2OOH$; 0-5°C, 4-5 hrs, Aq. NH_3 and Piperidine, Acetonitrile, Acetic acid;

Sulfide **9** of (*R*)-Lansoprazole is one of the potential impurity which is forming due to left over compound of nitro sulfide starting material during asymmetric sulfoxidation in step 1 of synthetic sequence followed for Dxalnsoprazole, followed by aromatic nucleophilic substitution with potassium salt of 2,2,2-triflouroethanol in DMF solvent medium at 85-95 °C to afford desired compound **9** (Scheme **4**). The resulted sulfide impurity was well characterized Viz., IR, ^{1}HNMR, mass and HRMS m/z calcd. For $C_{16}H_{15}N_3OF_3S$ $[M+H]^+$: 354.08; found: 354.08; m/z calcd. for $C_{16}H_{14}N_3OF_3SNa$ $[M+Na]^+$: 376.1; found: 376.1. The spectral data of **5** is identical with data represented in reference example. [12]



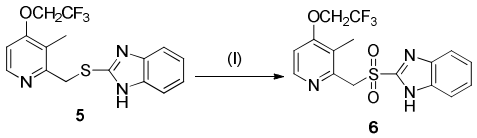
Scheme 4. Synthesis of Sulfide **9** of (*R*)-Lansoprazole

[a]Reagents and Conditions: (i) 2,2,2,-triflouroethanol, K_2CO_3, DMF, 85-90 °C, 6-8 h,Acetonitrile, DM Water and 10% acetic acid,

Sulfone **6** of (*R*)-Lansoprazole is a typical impurity, which is forming due to over oxidation during the synthesis of Nitro sulfoxide intermediate (*R*)-(+)-**4**. The intended impurity was prepared by employing the controlled oxidation of lansoprazole sulfide **9**; using titanium mediated chiral oxidation using 5.0 mol equivalent of cumene hydroperoxide at ambient temperature to yield desired compound with >96% purity (Scheme **5**). The protonated molecular ion appeared at 386 in the EI spectrum. HRMS (EI), *m/z* calcd. for $C_{16}H_{15}N_3O_3F_3S$ $[M+H]^+$: 386.07; found: 386.07;

ISSN: 2249 –4820

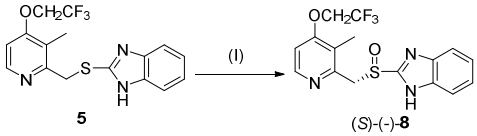
Chemistry & Biology Interface, 2013, 3, 6, 366-374



Scheme 5. Synthesis of Sulfone **6** of R-Lansoprazole (*R*)-(+)-**1**

[a]**Reagents and Conditions**: (i) $Ti(O\text{-}^{i}Pr)_4$/ (*R*, *R*)-DET/ H_2O, $PhCH_3$, $(^{i}Pr)_2NEt$, $PhC(CH_3)_2OOH$; 25-35 °C, 10-12 hrs,

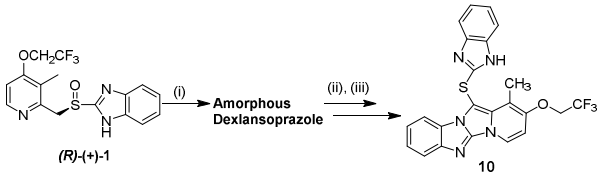
Dexlansoprazole has been synthesized via asymmetric oxidation strategy on prochiral nitro sulfide **3** intermediate. Hence, further chances for the formation of LevoLanaoprazole (***S***)-(-)-**8** in the final API is more and showing less than 0.15% is also challenging activity. The Levo Lanaoprazole (***S***)-(-)-**8** impurity has been synthesized according to the scheme sequence shown in scheme **6**. Subjecting prochiral nitrosulfide to titanium mediated asymmetric oxidation using (*S, S*)-(-)-DET instead of (*R, R*)-(+)-DET with cumene hydro peroxide at 0-5 °C to afford Levo Lansoprazole (***S***)-(-)-**8** (Scheme **6**). Structure of Levo Lansoprazole (***S***)-(-)-**8** was confirmed by standard spectral analysis.



Scheme 6. Synthesis of Levo Lansoprazole (*S*)-(-)-**8**

[a]**Reagents and Conditions**: (i) $Ti(O\text{-}^{i}Pr)_4$/ (*S, S*)-DET/ H_2O, $PhCH_3$, $(^{i}Pr)_2NEt$, $PhC(CH_3)_2OOH$; 0-5°C, 4-5 hrs, Aq. NH_3 and Piperidine, Acetonitrile, Acetic acid;

Upon subjecting the Dexlansoprazole (***R***)-(+)-**1** to spray drying technique in acetone solvent medium at 40-45 °C for the preparation of stable amorphous Dexlansoprazole (***R***)-(+)-**1**, encountered one unknown impurity with molecular ion peak at 467 $[M+H]^+$ in mass as well as LC-MS spectral data. Started our efforts to make it known impurity to meet the ICH quality of final API. Subjected final amorphous Dexlansoprazole to thermal degradation at 90 °C for 6-8 days in the air tray drier. After it has been suspended in toluene solvent medium at 25-35 °C for 60-120 min, collected the solid material by filter and thoroughly washed with toluene. Wet quake was again suspended in acetonitrile at 25-35 °C for 60-120 min, finally collected the yellow coloured solid by filtration and washed with acetonitrile to yield >99% pure compound of spiro compound. The spiro impurity was confirmed by elucidating the structure with standard spectral data.



Scheme 7. Synthesis of **10**[a]

[a]**Reagents and Conditions:** (i) Spary drying in Acetone at 40-45°C. (ii) Degradation at 90°C under ATD for 6-8 days. (iii) Toluene and Acetonitrile.

Conclusion

To have a thorough understanding of impurity formation pathway of the anti ulcerative drug Dexlansoprazole, it is essential to have detailed information about the various possible impurities, metabolites, and their synthetic approach. In view of reguralatory importance of the impurities in the final API, a detailed study on various impurities in Dexlansoprazole was conducted. Different process related impurities, degradation products, and metabolites in Dexlansoprazole API were indentified, synthesized, and characterized by using various spectroscopic techniques Viz., LC-MS, mass, ^{1}HNMR and IR.

Acknowledgements

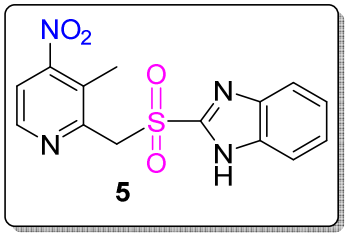
The authors are grateful to colleagues in the Analytical Research Development Department of Integrated Product Development Organization and the management for Dr. reddy's Laboratories Ltd. for providing the necessary support.

ISSN: 2249 –4820
Chemistry & Biology Interface, 2013, 3, 6, 366-374

Experimental Section

^{1}HNMR spectra's were measured in DMSO-d6 and $CDCl_3$ on a Varian Gemini 2000 (400 MHz) FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra's were recorded in the solid state as a KBr dispersion using Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on an HP-5989A LC/MS spectrometer. The melting points were determined by using the capillary method on a POLOMON (model MP-96) melting point apparatus. The solvents and reagents were used without further purification.

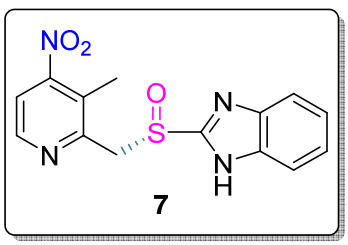
2-(4-Nitro-3-methyl-pyridin-2-ylmethylsulfonyl)-1*H*-benzoimidazole (Nitro Sulphone, 5)



5

A mixture of Nitro sulphide (**3**, 5.0 g, 0.016 mol), (*R*, *R*)-(+)-DET (6.86 g, 0.032 mol) and toluene (150.0 mL) were heated to 65-70 °C under N_2-atmosphere and stirred at the same temperature for 30-45 min. Ti(O-^{i}Pr)$_4$ (Assay 91%, 5.48 mL, 0.016 mol) was added to the resulted clear solution at 65-70 °C and stirred at the same temperature for 50-60 min. Reaction mass was slowly cooled to 25-35 °C, added *N*, *N*-EDIPA (2.86 mL, 0.016 mol) followed by drop wise addition of cumene hydroperoxide (Assay, 73%, 8.69 mL, 0.04 mol) at the same temperature over a period of 15-30 min and then continued stirring at same temperature (25-35 °C) for 3-4 h under N_2-atmosphere for reaction completion. After reaction completion, reaction mass was quenched by slowly adding 12.5% aqueous ammonia solution (50.0 mL) at below 5 °C, allowed the reaction mass temperature to raise 25-35 °C and then stirred at 25-35 °C for 10-15 min. The resulting organic layer was separated and extracted once with same aqueous piperidine solution (50.0 mL). All the aqueous extracts were combined, washed with toluene (50.0 mL). The separated final aqueous layer was cooled to 10-15 °C and then adjusted pH of the solution between 8.1-8.8 using 10% acetic acid. The resulting slurry mass was stirred at 10-15 °C for 2-3 h. The solid obtained was filtered, washed with water (50.0 mL) and then dried at 45-50 °C under vacuum for 6-8 hrs to afford Nitro sulphone, 2-(4-Nitro-3-methyl-pyridin-2-ylmethylsulfonyl)-1*H*-benzoimidazole (**4**). Yield 3.19 gm (57.69%); Purity by HPLC 96.3%; MS (m/z): 332.9 $[M+H]^+$; IR (KBr, cm^{-1}): 3567 (N-H), 3072 (Ar-CH), 2930, 2875 C-H), 1584, 1436 (C=C), 1408, 1376 (C-H, bending) 1538, 1566, 1338 (NO_2 stretching), 1304, 1275 (C-N), 1072 (S=O stretching), 852, 749 (Ar-CH bending); ^{1}HNMR (400 MHz, DMSO-d6) 13.5 (br, NH), 8.45 (d, *J* = 5.2, 1H), 7.81 (d, *J* = 5.6, 1H), 7.40 (d, *J* = 3.6, 2H), 7.38 (m, 2H), 5.32 (s, 2H), 2.08 (s, 3H); ^{13}CNMR (DMSO-d6, 400 MHz, δ ppm): 156.8, 148.3, 142.5, 125.3, 123.4, 116.0, 112.5, 59.6, 13.68; HRMS (MS ES+): *m/z* calcd. for $[M+H]^+$ $C_{14}H_{13}N_4O_4S$: 333.0658; found: 333.0646 (ppm: -3.6)

(*S*)-2-[[[3-methyl-4-nitro-2-pyridyl] methyl] sulfinyl]-1*H*-benzimidazole (Levo Nitro sulfoxide, (*S*)-(-)-7))



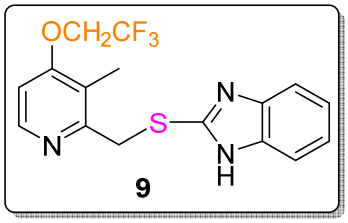
7

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 6, 366-374

A mixture of Nitro sulphide (**3**, 10.0 g, 0.033 mol), (*S, S*)-(-)-DET (13.73 g, 0.066 mol), Ti(O-^{i}Pr)$_4$ (91% assay, 10.97 mL, 0.033 mol), DM Water (0.1 mL, 0.019 mol) and toluene (300.0 mL) were heated to 65-70 °C under N_2-atmosphere and stirred at the same temperature for 50-60 min. Reaction mass was slowly cooled to 15-25 °C, added *N*, *N*-EDIPA (4.3 g, 0.033 mol) and further cooled to 0-5 °C. A solution of cumene hydroperoxide (Assay 74.4%, 10.86 mL, 0.049 mol) was added slowly by drop wise to the above reaction mass at below 5 °C over a period of 30-45 min and then continued stirring at same temperature (0-5 °C) for 3-4 hrs under N_2-atmosphere for reaction completion. After reaction completion, reaction mass was quenched by slowly adding 12.5% aqueous piperidine solution (100.0 mL) at below 5 °C, allowed the reaction mass temperature to raise 25-35 °C and then stirred at 25-35 °C for 10-15 min. The resulting organic layer was separated and extracted trice with aqueous piperidine solution (3 x 50.0 mL) at 25-35 °C. All the aqueous extracts were combined, washed with toluene (50.0 mL). Resulting aqueous layer cooled to 5-10 °C and then adjusted pH of the solution between 8.1-8.8 using 10% acetic acid. The resulting slurry was stirred at 5-10 °C for 2-3 h. The solid obtained was filtered, washed with water (50.0 mL) and then dried at 45-50 °C under vacuum for 6-8 h to afford enantiomerically enriched (*S*)-(-)-2-(3-Methyl-4-nitro-pyridin-2-ylmethansulfinyl)-1*H*-benzimidazole (*S*-(-)-**4**). Yield 5.9 g (56.0%); Purity by HPLC 96.03%; Chiral Purity by HPLC 96.62%; MS (m/z): 316.9 $[M+H]^+$ and 338.9 $[M+Na+NH_3]^+$; IR (KBr, cm^{-1}): 3422 (N-H), 3067, 3028 (Ar-CH), 2949, 2811 (C-H), 1564, 1439 (C=C), 1411 (C-H, bending) 1544, 1371 (NO_2), 1297, 1274 (C-N), 1039 (S=O), 843, 744 (Ar-CH bending); ^{1}HNMR (400 MHz, DMSO-d6): 13.4 (NH), 8.58 (d, *J* = 5.2, 1H), 7.79 (d, *J* = 5.6, 1H), 7.64 (d, *J* = 3.6, 2H), 7.31 (m, 2H), 4.9 (q, *J* = 13.8, 2H), 2.08 (s, 3H); ^{13}CNMR (DMSO-d6, 400 MHz, δ ppm): 156.8, 148.9, 143.5, 124.4, 123.1, 116.6, 112.9, 60.2, 14.1; HRMS (MS ES+): *m/z* calcd. for $[M+H]^+$ $C_{14}H_{13}N_4O_3S$: 317.0708; found: 317.0707 (ppm: -0.3); SOR: $[\alpha]_D^{23}$ = 238º (*c* = 1, $CHCl_3$, 97% *ee* from HPLC); Source of chirality: Ti(O^{i}Pr)$_4$: (*R, R*)-DET: H_2O.

2-({(3-methyl-4-(2, 2, 2-trifluoroethoxy) pyridin-2-yl) methyl} sulfanyl)-1*H*-benzimidazole (Lansoprazole Sulfide, 9)



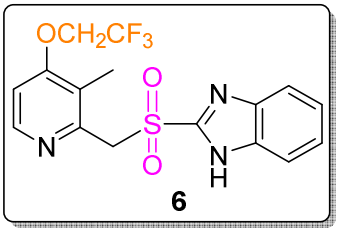
9

N,*N*-dimethyl formamide (60.0 mL) was charged in dry clean and dry RB flask at 25-35 °C, cooled to 15-20 °C and then added 2,2,2-trifluoroethanol (23.33 g, 0.233 mol) at below 20 °C under stirring. Potassium carbonate (32.2 g, 0.233 mol) was charged to the resulting reaction mass at below 20 °C and then heated to 50-55 °C for 30-45 min to form the potassium salt of 2,2,2-trifluoroethanol. Reaction mass was cooled to 25-35 °C, added solution of **3** (10.0 g, 0.033 mol) in DMF (40.0 mL) at 25-35 °C and then heated to 85-95 °C for 4-6 h. The resulting reaction mass was cooled to 25-35 °C, filtered to remove all the inorganic byproducts present in the reaction mass and then filtered cake was washed with acetonitrile (40.0 mL). To the combined filtrate, DM Water (200.0 mL) and activated carbon (0.3 g) was charged and stirred at 60-70 °C for 20-30 min. Again, reaction mass was filtered over hyflow bed to remove carbon and then washed the bed with DM Water (100.0 mL). The resulting filtrate was cooled to 5-10 °C and then adjusted pH of the solution to 8.0-8.7 using 10% Acetic

ISSN: 2249 –4820
Chemistry & Biology Interface, 2013, 3, 6, 366-374

acid solution. The resulting heterogeneous mass was stirred at 5-10°C for 2-3 hrs to ensure the total solid ejection. The solid obtained was filtered, washed with DM Water (50.0 mL) and then dried at 45-50 °C under vacuum for 10-12 hrs to afford Sulfide of Lansoprazole (**9**) in 8.26 g with Yield 70%; mp 111-116 °C; MS (m/z): 354.1 $[M+H]^+$ and 376.1 $[M+Na]^+$; IR (KBr, cm^{-1}): 3545 (N-H), 3068, 3053 (Ar-CH), 2976, 2897 (C-H), 1590, 1473 (C=C), 1305 (C-N), 1256, 1162, 1110 (C-O), 1444 (C-H bending), 857, 745 (Ar-CH bending); ^{1}HNMR (DMSO-d_6, 400 MHz, δ ppm): 12.6 (br, NH), 8.31 (d, J = 5.6, 1H), 7.39 (d, J = 3.6, 2H), 7.11 (m, 2H), 7.08 (d, J = 6.0, 1H), 4.88 (dd, J = 8.4, 2H), 4.73 (s, 2H), 2.09 (s, 3H); ^{13}CNMR (DMSO-d6, 400 MHz, δ ppm): 161.1, 155.5, 150.0, 147.7, 125.1, 122.4, 121.4, 119.9, 106.8, 64.8, 64.4, 10.2; HRMS (MS ES+): *m/z* calcd. for $[M+H]^+$ $C_{16}H_{15}N_3OF_3S$: 354.0888; found 354.0894 (ppm: 1.7).

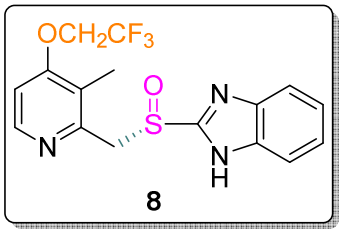
2-({(3-methyl-4-(2, 2, 2-trifluoroethoxy) pyridin-2-yl) methyl} sulfonyl)-1*H*-benzimidazole (Lansoprazole Sulfone, 6)



6

To a solution of 2-({(3-methyl-4-(2, 2, 2-trifluoroethoxy) pyridin-2-yl) methyl} sulfanyl)-1*H*-benzimidazole (**9**, 10.0 g, 0.028 mol) in $CHCl_3$ (50.0 mL) was added another solution of m-CPBA (9.77 g, 0.056 mol) in $CHCl_3$ (60.0 mL) at –10 to –15 °C over a period of 1-1.5 h and stirred for 20-30 min at –10 to –15 °C. Reaction mass is slowly quenched with a solution of NaOH (5.0 g) in water (100.0 mL); the aqueous layer was separated and adjusted pH of the aqueous layer to 7.5-8.0 with acetic acid in presence of acetonitrile at below 5-10 °C. The resulting solid reaction mass was stirred at 5-10 °C for 1.0-1.5 h for the complete solid ejection. The crystalline solid obtained was filtered, washed with chilled acetonitrile (15 mL), and dried at 60-65 °C to yield 7.6 g (70% of yiled) of desired compound of Lansoprazole sulfone impurity **6**. MS (m/z): 385.9 $[M+H]^+$; IR (KBr, cm-1): 3367 (N-H), 3090 (Ar-CH), 2964, 2892 (C-H), 1585, 1441 (C=C), 1375, 1384 (C-H, bending), 1303, 1276 (C-N), 1268, 1164, 1109, 1085 (C-O), 1143 (C-F), 1057 (S=O), 832, 743 (Ar-CH bending); ^{1}HNMR (DMSO-d_6, 400 MHz, δ ppm): 13.74 (br, 1H), 8.11 (d, J = 5.6, 1H), 7.78 (d, J = 3.6, 2H), 7.39 (m, 2H), 7.07 (d, J = 5.2, 1H), 4.86 (dd, J = 8.8, 2H), 4.79 (dd, J = 14, 2H), 2.08 (s, 3H); ^{13}CNMR (DMSO-d6, 400 MHz, δ ppm): 161.4, 154, 148, 147.8, 123.7, 123.3, 123.2, 117, 107.4, 64.4, 60.4, 10.9.; HRMS (MS ES+): m/z calcd. for [M+H]+ $C_{16}H_{15}F_3N_3O_3S$: 386.0786; found: 386.07. 386.0786.

(*S*)-2-(4-(2,2,2-triflouroethoxy)-3-methyl-pyridin-2-ylmethylsulfinyl)-*1H*-benzimidazole (Levo Lansoprazole, (*S*)-(-)-8)



8

A mixture of 2-({(3-methyl-4-(2, 2, 2-trifluoroethoxy) pyridin-2-yl) methyl} sulfanyl)-1*H*-benzimidazole (**9**, 15.0 g, 0.042 mol), (*S*, *S*)-(-)-DET (35.01 g, 0.169 mol) in toluene (450.0 mL) were stirred at 55-60 °C for 30 min. Ti(O-^{i}Pr)$_4$ (90% assay, 26.57 mL, 0.084 mol) was slowly added drop wise to the resulted reaction mixture at 55-60°C and stirred the contents were for 50-60 min at the same temperature. Reaction mass was slowly cooled to 15-25 °C, added *N*, *N*-EDIPA (5.48 g, 0.042 mol) and further

ISSN: 2249 –4820
Chemistry & Biology Interface, 2013, 3, 6, 366-374

cooled to 0-5 °C. A solution of cumene hydroperoxide (Assay 70%, 13.84 mL, 0.063 mol) was added slowly by drop wise to the above reaction mass at below 5 °C over a period of 30-45 min and then continued stirring at same temperature (0-5 °C) for 3-4 hrs under N_2-atmosphere for reaction completion. After reaction completion, reaction mass was quenched by slowly adding 12.5% aqueous pyrrolidine solution (125.0 mL) at below 5 °C, allowed the reaction mass temperature to raise 25-35 °C and then stirred at 25-35 °C for 10-15 min. The resulting organic layer was separated and extracted twice with 12.5% aqueous pyrrolidine solution (2 x 125.0 mL) at 25-35 °C. All the aqueous extracts were combined, washed with toluene (75.0 mL). Resulting aqueous layer cooled to 10-15 °C and then adjusted pH of the solution 8.5-9.0 using acetic acid. The resulting slurry was stirred at 25-35 °C for 2-3 h. The solid obtained was filtered, washed with DM Water (50.0 mL) and then dried at 45-50 °C under vacuum for 6-8 h to afford enantiomerically enriched (*S*)-2-(4-(2,2,2-triflouroethoxy)-3-methyl-pyridin-2-ylmethylsulfinyl)-*1H*-benzoimidazole (Levo Lansoprazole, (*S*)-(-)-**1**) with 67.3% (10.5 g); Purity by HPLC 99.0%; Chiral Purity by HPLC 98.8%; MS (m/z): 369.9 $[M+H]^+$; IR (KBr, cm^{-1}): 3391 (N-H), 3070 (Ar-CH), 2976, 2881 (C-H), 1583, 1481 (C=C), 1441, 1381 (C-H, bending), 1313 (C-N), 1262, 1166, 1023 (C-O), 1110 (C-F), 857, 743 (Ar-CH bending); ^{1}HNMR (DMSO-d_6, 400 MHz, δ ppm): 8.29 (d, *J* = 5.6, 1H), 7.65 (d, *J* = 3.6, 2H), 7.40 (m, 2H), 7.09 (d, *J* = 5.2, 1H), 4.89 (dd, *J* = 8.8, 2H), 4.79 (dd, *J* = 13.6, 2H), 2.18 (s, 3H); ^{13}CNMR (DMSO-d6, 400 MHz, δ ppm): 161.8, 154.6, 151.4, 143.5, 125.6, 123.1, 122.9, 112.9, 107.5, 64.9, 60.4, 11.0; HRMS [MS ES]+: m/z calcd. for $[M+H]^+$ $C_{16}H_{15}F_3N_3O_2S$: 370.0837; found: 370.07831 (ppm: -1.6).

12-((1*H*-benzo[d]imidazol-2-yl)thio)-1-methyl-2-(2,2,2-trifluoroethoxy)benzo [4',5']imidazo[2',1':2,3]imidazo[1,5-a] pyridine (10)

Dexlansoprazole (**1,** 20.0 g) amorphous was dried in air tray drier at 60-90 °C for 8-10 days for thermal degradation. Further it was suspended in toluene (100.0 mL) at 25-35°C for 15-30 min. Collected the precipitated solid by filtration and thoroughly washed twice with toluene (2 X 25.0 mL) and suck dried under vacuum for 40-60 min. The resulted wet compound was suspended in acetonitrile (100.0 mL) at 25-35 °C for 25-30 min. Filtered the solid and washed twice with acetonitrile (2 X 25.0 mL) and dried to a constant weight at 25-35 °C under vaccum to yield **7**. Yiled 0.82 g, purity by HPLC 99.6%; ^{1}HNMR (400 MHz, DMSO, δ ppm): 12.70 (s, NH), 8.57 (d, *J* = 7.5, 1H), 7.99 (d, *J* = 8.0, 1H), 7.75 (d, *J* = 8.0, 1H), 7.56 (d, *J* = 8.0, 1H), 7.32 (t, *J* = 8.0, 1H), 7.20 (d, *J* = 8.0, 1H), 7.15 (m, 1H), 7.13 (m, 1H), 7.08 (m, 2H), 2.60 (s, 3H), 5.05 (q, *J* = 8.5, 2H, OCH_2CF_3, the coupling is due to ^{1}H-^{19}F); ^{13}CNMR (DMSO-d6, 400 MHz, δ ppm): 152.22, 136.94, 124.18, 122.81, 122.01, 121.61, 119.36, 118.85, 117.87, 111.32, 111.29, 110.62, 103.57, 66.43; HRMS (MS ES+): *m/z* calcd. for $[M+H]^+$ $C_{23}H_{17}N_5F_3OS$: 468.11; found: 468.11 (4.1 ppm); HRMS (MS ES-): *m/z* calcd. for $[M-H]^-$ $C_{23}H_{15}N_5F_3OS$: 466.09; found: 466.09 (-1.3 ppm).

References

[1] (a) Fujishima, A.; Aoki, I.; Kamiyama, K. US 6462058 B1, **2002**; (b) "KAPIDEX (dexlansoprazole) Renamed DEXILANT in U.S. to Avoid Name Confusion". Takeda. 4 March **2010**. http://www.takeda.com/press/article_35868.html.

[2] Barradell, L. B.; Faulds, D.; McTavish, D. A review of its paharmacodynamic and pharmacokinetic properties and its therapeutic efficacy in acid related disorders. *Drugs 44*, (**1992**), 225–250.

[3] Hatlebakk, J. G.; Berstad, A.; Carling, L.; Svedberg, L. E.; Unge, P.;Ekstrom, P.; Halvorsen, L.; Stallemo, A.; Hovdenak, N.; Trondstad, R.; Kittang, E.; Lange,

ISSN: 2249 –4820

Chemistry & Biology Interface, 2013, 3, 6, 366-374

O. J. Lansoprazole versus omeprazole in short term treatment of reflux oesophagitis: Results of scandinavian multicentre trial. *Scand.J. Gastroenterol*. (**1993**), *28*, 224–228.

[4] FDA Approves KAPIDEX (dexlansoprazole) delayed release capsules for the Treatment of GERD., http://www.takeda.com/press/article_32521.html and http://www.allbusiness.com/medicine-health/diseases-disorders/14048741-1.html

[5] ICH Guideline Q3A (R), Impurities in New Drug Substances, June, **2008**.

[6] The impurity levels in the final API of Dexlansoprazole were estimated by HPLC with the use of YMC-PRO C18, 100 x 4.6 mm, 3µ, or equivalent; Mobile phase (MP): MP-A, 100% Water degas. MP-B, filtered and degassed mixture of buffer and acetonitrile, water and triethylamine in the ratio of 160: 40: 1 (v/v), then adjust the pH to 6.2 with dilute ortho phosphoric acid. Gradient program:

Time (Min)	0.01	4.0	25	40	45	55	57	65
MP-A %	70	70	50	30	20	20	70	70
MP-B %	30	30	50	70	80	80	30	30

[7] (a) El-Sherif, Z. A.; Mohamed, A. O.; El-Bardicy, M. G.; El-Tarras, M. F.Reversed-phase high performance liquid chromatographic method for the determination of lansoprazole, omeprazole and pantoprazole sodium sesquihydrate in the presence of their acid-induced degradation products. *Chem. Pharm. Bull*. **2006**, *54*, 814–818; (b) Ekpe, A.; Jacobsen, T. Effect of various salts on stability of lansoprazole, omeprazole and pantoprazole has determined by high performance liquid chromatography. *Drug Dev. Ind. Pharm*. **1999**, *25*, 1057–1065; (c) Peres, O.; Oliveira, C. H.; Barrientos-Astigarraga, R. E.; Rezende, V. M.; Mendes, G. P.; De Nucci, G. Determination of pantoprazole in human plasma by LC-MS-MS using lansoprazole as a internal standared. Arzneim.-Forsch. *Drug Res*. **2004**, *54*, 314–319; (d) Basavaiah, K.; Ramakrishna, V.; Anilkumar, U. R. Sensitive spectrophotometric determination of lansoprazole in pharmaceutical using ceric ammonium sulphate based on redox and complex formation reactions. *Eclet. Quim*. **2006**, *31* (3), 67–74; (e) Aydogmus, Z. Spectrophotometric methods for the determination of lansoprazole in capsules. *Acta Pharm. Sci*. **2006**, *48*(1), 45–54; (f) Prasada Rao, K. V. S. P.; Vijaya Kumar, G.; Vijaya Kumari, K.; Srinivas, L. D.; Prabhakar, G. Reversed phase HPLC estimation of lansoprazole in pure and pharmaceutical formulations. *Asian J. Chem*. **2006**, *18*(2), 798–802.

[8] (a) Karol, M. D.; Granneman, G. R.; Alexander, K. Determination of lansoprazole and five metabolites in plasma by high performance liquid chromatography. J. Chrom. B: *Biomed. Sci. Appl*. **1995**, *668*(1), 182–186; (b) Nannan, C.; Weili, C.; Hongrong, X.; Mi, Z.; Xuening L. LC-MS-MS determination of lansoprazole and its metabolites in human plasma. *Yaowu Fenxi Zazhi* **2006**, *26*(1), 35–39.

[9] (a) Kumar, K. N.; Nagaraju, M.; Srinivas, G.; Kumar, N. U.; Anitha, N.; Reddy, B. S.; Vishwasrao, P. S.; Kumar, T. A.; Reddy, P. S.; Gulabrao, S. S.; Ashok, S.; Varma, M. S. PCT 114789 A1, **2009**; (b) Nagaraju M.; Udaykumar N.; Sudhakar Reddy B.; Anitha N.; Srinivas G.; Bhattacharya A.; Mukkanti K.; Naveenkumar K.; Rakeshwar B.; *Tetrahedron Lett.* **2011**, *53*, 5464-5466.

[10] The commercially available ~75% cumenehydroperoxide (CHP) has been used for present asymmetric oxidation by applying correction for raw material calculation.

[11] Nagaraju M.; Udaykumar N.; Mukkanti K.; Naveenkumar K.; Rakeshwar B.; Vishweshwar P.; *Act Cryst*. **2011**, *E67*, o2190.

[12] Kubo, K.; Oda, K.; Kaneko, T.; Satoh, H.; Nohara, A. Synthesis of 2-[[(4-flouroalkoxy-2-pyridyl)methyl]sulfinyl]-1*H* benzimidazoles as antiulecer agents. *Chem. Pharm. Bull*. **1990**, *38*, 2853–2858.