Novel Synthesis and Pharmaceutical Impurities of Anti-Hypertensive Drugs: A Review

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Abstract: Hypertension is the disease which mainly occurred due to the lifestyle which is very abnormal adopted by today’s human beings. Therapy to this disease led to the prevention disease such as myocardial infarction and stroke which is very common. The motive behind the study is to gain the interest of the reviewer to understand the novel impurities of the hypertensive drugs and the intermediate that occur during the synthesis which will to understand the purity of the API formation which will conclude through the impurities formation.

Key words: Anti-Hypertensive drugs, Synthesis, Pharmaceutical Impurities.

Introduction

Nowadays hypertension is the disease which mainly occurred due to the lifestyle which is very abnormal adopted by today’s human beings. Therapy to this disease led to the prevention disease such as myocardial infarction and stroke which is very common. Hypertensive drugs like telmisartan, losartan, valsartan, irbesartan and Olmesartanmedoxomil mainly used to treat the blood pressure. There are many drugs based on different mechanism lower the blood pressure through different means of actions. Though there are various synthetic methods that were discussed during recent years. During following of various synthetic procedure impurities are also synthesised as by-product, microbial and chemical. According to the ICH guidelines the chance of impurities formation is ≥ 0.10% that identified during API synthesized and characterization.

Olmesartanmedoxomil, the latest receptor of angiotensin through FDA approved for the hypertension treatment. The four impurities of Olmesartanmedoxomil were synthesized. Barnidipine hydrochloride chemically known as (3'S,4'S) -1-benzyl-3-pyrrolidinyl-methyl-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride. The other class hypertensive drug like Terazosin chemical known as hydrochloride (1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(tetrahydro-2-furoyl) piperazinemonohydrochloride) acting as quinazoline type of derivative that mainly acts on by blocking the selective alpha-1 adrenergic receptor. The potency of alpha1 adrenergic receptor is selectively high and chemically similar to the structure of prazosin but mainly effective by relation the arteries and vein for the treatment of symptomatic in the obstruction of urinary and relaxing the bladder and the prostate gland.

The motive behind the study is to gain the interest of the reviewer to understand the novel impurities of the hypertensive drugs and the intermediate that occur during the synthesis which will to understand the purity of the API formation which will conclude through the impurities formation.


DOI= http://dx.doi.org/10.20902/IJCTR.2019.130203
2 Synthesis of Hypertensive impurities

2.1 Synthesis of Olmesartan

![Chemical structure diagram]

2.1.1 Isopropyl Impurity of Olmesartan Medoxomil

The solution of 4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-ethylcarboxylate (2) was reacted with 4-((2-trityltetrazol-5-yl)-phenyl)-benzyl bromide 3 with a solvent of acetone to the ambient temperature then tetrabutylammonium bromide and potassium carbonate was added in appropriate mole quantity and refluxing done for 22 hours. After completion the reaction mixture cooled and then filtration was done. the layer was then separated between ethyl acetate and water and then Ethyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-((2-((1-trityl-1H-tetrazol-5-yl) biphenyl)-4-yl)methyl)-1H-imidazole-5-carboxylate 4 was formed. Isopropyl alcohol IPA was added to 4 with the saturated solution of potassium hydroxide by maintain the ambient temperature for 22 hours. when reaction was completed IPA was removed through distillation. On the continuous stirring the acetone and potassium carbonate then continuous stirring for 20 minutes. 2-bromo propane was added slowly maintain ambient temperature for 24 hours and washed with acetone filtration using Hyflowbed. The acetone layer was then combined and the solution was in concentrated form and then portioned with the help of ethyl acetate. at last sodium sulfate was added to remove the moisture and then purified with the help of column chromatography using ethyl acetate and hexane as the mobile phase e to get viscous oily like substance 13 1-(4-(2-Hydroxypropan-2-yl)-2-propyl-1-((2-((1-trityl-1H-tetrazol-5-yl) biphenyl-4-yl) methyl)-1H-imidazol-5-yl)-3-methylbutan-1-one.
Compound 13 was added with the solution of formic acid and methanolacetonitrile at cooled temperature and solvent was removed under reduced pressure. To the residue the filtrate the residue was extracted with ethyl acetate that combined with organic layer and then washed with sodium bicarbonate solution and then dried under anhydrous condition with sodium sulfate and purification done with column under hexane and heptane that will give pure white solid compound 12.

2.2 Preparation of dibiphenyl impurity (17)

The solution of Ethyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-((2-(1-trityl-1H-tetrazol-5-yl) biphenyl-4-y1)methyl)-1H-imidazole-5-carboxylate 4 was added with isopropyl alcohol with potassium hydroxide as a saturated solution to its ambient temperature. The reaction mixture was continue on the stirring by maintaining the ambient temperature. The ipa was distilled off after the completion of the reaction and then acetone was added with potassium carbonate and continue stirred for 10 minutes. 5-(4-(bromomethyl) biphenyl-2-y1)-1-trityl-1H-tetrazole 3 was added with continuime stirring for 4 hours by maintain temperature OF 45-50 °C. after the completion of the reaction it was then filtered through the hydrofl ow bed and washed with the help of acetone the layer was formed between the ethyl acetate and acetone the ethyl acetate layer was dired off and the crude was purified with the help of column in methanol and ethyl acetate as a mobile phased to give 18 as the colored browned compound. The compound 18 solution of prepartedin methanol-acetonitrile following by the addion of formic acid to the solution and continue heated for 4 hour by maintaining the temperature of 50°C. THE Solution was cooled and dried and cooled room temperature. The residue is then extracted with the help of ethyl acetate. The organic layer was then washed with saturated solution of sodium bicarbonate solution and dried with sodium sulfate. The evaporation was done under reduced pressure to get the (2-(1H-Tetrazol-5-yl) biphenyl-4-y1)methyl 1-((2-(1H-tetrazol-5-yl) biphenyl-4-y1)methyl)-4-(2-hydroxypropan-2-y1)-2-propyl-1H-imidazole-5-carboxylate compound 17 which was then purified with the help of column and recrystallization done with the help of white solid.
2.3 Preparation of Dimedoxomil Impurity (19)

Saturate solution of potassium hydroxide was added slowly to the solution of compound 4 in ipa by maintain the ambient temperature and continue stirring for 22 hours. The completion of reaction was then distilled off and the crude mass was then dissolve in in the appropriate ratio of dichloromethane and methanol. Formic acid was then heated and maintaing temperature 0-5°C. After completion of the reaction the solution was cooled off at the room temperature and then solvent was distilled off under the reduced pressure. The crude obtained 8 was then purifed with the help of column chromatography to afford solid and recrystallized with acetone to get white solid 8-1-((2-((1H-Tetrazol-5-yl) biphenyl-4-yl)methyl)-4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylic acid. The compound 8-1-((2-((1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylic acid 8 was prepared with acetone with the addition of 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one and then potassium carbonate with tetrabutylammonium bromide was continue heated and reflux for 12 hours. The reaction cooled at room temperature and washed with acetone. The filtrate residue was partitioned with the layer of ethyl acetate under anhydrous condition with the addition of sodium sulfate under the reduced pressure which was then purified by column chromatography to five solid residue when recrysllized with acetone to yield off- white coloured solid compound. (5-Methyl-2-oxo-1,3-dioxol-4-yl) methyl4-(2-hydroxypropan-2-yl)-1-((2-((1-(5-methyl-2-oxo-1,3-dioxol-4-yl) methyl)-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-2-propyl-1H-imidazole-5-carboxylate.
2.4 Synthesis of barnidipine hydrochloride

The compound 2-cyanoethyl 3-oxobutanoate (6) reacted with 3-nitrobenzaldehyde (7) at the room temperature for 15 hour to give the intermediate 2-cyanoethyl 2-(3-nitrobenzylidene)-3-oxobutanoate (8). The cyclization of compound 8 was done through methyl 3-aminobut-2-enoate (9) after refluxing for 2 hour to give 3-(2-cyanoethyl) 5-methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (10), compound 10 is then hydrolysed with sodium hydroxide and hydrochloric acid to give 5-(methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid 11. After the resolution of compound 11. To compound were yield (R)-5-(methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid (12), and (S)-5-(methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid 13, which is an isomer of compound 12 when using cinchonine as the resolving agent. barnidipine (15 and in the presence of methyl chloride and ethanol give barnidipine hydrochloride 1.27

2.4.1 Synthesis of impurity

The isomer of the 12 compound (S)-5-(methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid 13 which is a resolution product formed the impurity of barnidipine hydrochloride in the presence of methyl chloride, phosphorous pentachloride and S)-1-benzylpyrrolidin-3-ol (14) to give impurity 228
2.4.2 Synthesis of impurity 3

Barnidipine degradation product is the formation of the impurity 3. Compound 15 react in the presence of magnesium oxide and methyl chloride that leads to the formation of compound 3.

2.4.3 Synthesis of impurity 4

The derivative of compound 12 is the synthesis of compound 4. The reaction occurs in the presence of phosphorus pentachloride and methyl chloride yield the product which was characterized by 13C-NMR, 1H-NMR, MS data, and HPLC retention time.

2.4.4 Synthesis of impurity 5

Compound 8 was reacted in the presence of Ethyl 3-aminobut-2-enoate (16) to give 3-(2-Cyanoethyl) 5-ethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-pyridine-3,5-dicarboxylate17. In the presence of 3.8% NaOH solution, 1,2-dimethoxyethane and acidification done with the help of 10% HCl give 5-(Ethoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid(18). To the solution of 18 chinchonine and N,N-dimethylformamide was added and heated by maintaining temperature of 80 °C which give clear solution. The solution cooled at 20 °C temperature and continue stirred for 12 hours. The filterate is then washed and filtered with N,N-dimethylformamide. The filtered was dissolved in sodium hydroxide 35% solution and extraction was done with dichloromethane. The aqueous portion acidified with concentrated hydrochloric acid by maintaining pH 2.0. The precipate was washed and collected and dried at the temperature of 100°C to provide (R)-5-(Ethoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid 19.

Compound 19 was reacted in the presence of Phosphorus pentachloride solution with Dichloromethane solution by maintaining temperature 0 °C. Stirred for 1 hour, when the reaction mixture cooled to -20 °C the solution of (S)-1-benzylpyrrolidin-3-ol (14) was then added. The saturated solution was added to the reaction mixture and extraction was done in the presence of dichloromethane. The organic phase washed with magnesium sulfate then the residue was purified with the help of flash chromatograph taking ethyl acetate and petroleum ether in 3:2 ratio as a mobile phase that give yellow light coloured solid compound(3'S,4S)-1-Benzyl-3-pyrrolidinyl ethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5pyridinedicarboxylate(5).
2.5 Synthesis of terazocin impurity A

2-Chloro-6,7-dimethoxyquinazoline- 4-amino WAS reacting in the presence of piperazine and isoamyl alcohol in the presence of temperature less than 115°C. in an round bottom flask that was fitted with the condenser, stirrer, and thermostat in which whole process of reaction was going on. The reaction was continued for 4 hour maintain temperature 120°C then it was colld to 70 0C. The precipitaed of white solid was appeared which is then filtered and washed with hot isoamyl alcohol and then dried. Then in other round bottom vessel methanol and IAT was charged with strong hydrochloric acicd and reflux for 1 hour by maintain temperature 60°C. THE reation mixture was evaporated under vaccum and the residue was washed with filtered. The filtrate was concentrated to give residue under reduced pressure which was the product of IAT (impurity A of terazosin) hydrochloride was synthesised.

2.6 Intermediate of hypertensive drug which can also be acting a impurities

2.6.1 Synthesis of Irbesartan Intermediate

The reaction occur with 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one 12 and 4-bromomethyl-2’-cyanobiphenyl 13 containing acetone as an solvent as an ambient temperature for 30 minutes. after the completion of 30 minutes the reaction mass was heated for 4 hour for reflux . charging Hydrotalcite for three times slotwise at 4 hour during reflux condition. After the completion of the reaction the acetonitrile was distilled off under reduced pressure mainating temperature below 45°C so that solid residue can be obtained which is then was treated with methylene chloride at room temperature so that slurry can be obtained , the hydrotalcite catalyst again can be used as catalyst for further. After the filtration the filterate was washed with sodium sulfate to get the dried product at last under the reduced pressure the oily residue was obtained. the oily product was then treated with cyclohexane and acetone so that crystal can be obtained which is then
dried under oven at 50°C to get 2-butyl-3-((4-[2-cyanophenyl]phenyl)methyl)-1, 3-diazaspiro-[4.4]-non-1-en-4-one as an Irbesartan intermediate. 39, 40, 41

2.6.2 Synthesis of Telmisartan Intermediate

The reaction started with the 2-n-propyl-4-methyl-6-(1′-methylbenzimidazol-2′-yl) benzimidazole16 and methyl 4′-(bromomethyl)biphenyl-2-carboxylate 17 with acetone as a solvent at ambient temperature. 42 The reaction mass continued to stir for 10 min maintaining temperature at 25–30°C and charged hydrotalcite as a base to Digest by maintaining temperature for 8 h. The reaction can be monitored on the bases of TLC. After the completion of the reaction the reaction mass was filtered and dried under vacuum maintaining temperature 25-30 °C so that to get solid residue. 43 The telmisartan intermediate was filtered and dried under vacuum to get the solid residue and recrystallized with the help of acetonitrile to get free crystals as a precipitate which is then dried under oven at 60 °C. To get 4′-((1,4′-dimethyl-2′-propyl(2,6′-bi-benzimidazole)-1′-yl)methyl)-1′-biphenyl-2-carbonitrile 18

2.6.3 Synthesis of valsartan intermediate

In an reaction mixture (S)-methyl 2-((2′-cyanobiphenyl-4-yl)methylamino)-3-methylbutanoate 20 was reacting with tetra butyl ammonium bromide, With the toluene as a solvent with water, charging hydrotalcite as an solvent at the same time at the room temperature mainating temperature 25-30°C. THE reaction was checked on TLC. After the completion of the reaction the hydrotalcite was filtered and dried. 45 The dried hydrotalcite was further get reused and after the filterartion the filterate was separated with both by organic and aqueous layer, out of which the aqueous layer was dried to give the product in the organic layer which filtered through m distilled and maintaing vacuum 60°C to get the residue. Residue get dissolved in the ethylacetate and continue stirred for 15 minutes which on further washed with sodium bicarbonate solution by maintain temperature 25-30 °C. 46 THE layer of organic was distilled and u=dried under vacuum at temperature 50°C to give (S)-methyl 2-(N-((2′-cyanobiphenyl-4-yl)methyl)pentanamido)-3-methylbutanoate as an oily substance.

2.6.4 Intermediate of hydrochloride thiazide

The reaction was done with the reactant 5-chloro-2, 4-disulfamyl aniline 24 ( with Para formaldehyde which was allowed to stirred for 15 min by maintain at ambient temperature which followed by hydrotalcite
addition to the reaction mass. And refluxing the solvent for 6 to 8 hour tlc parameter used to monitored the reaction. After the completion to the reaction it was colled that give crystalline structure of Hydrochlorothiazide 23 that further which was dissolved in Ammonia solution to get turbid mass. After the filtration Hydrochlorothiazide recovering process was done to get the clear filtrate that decolonized through charcoal. It was then dried and clear solution further treated with aqueous acetic acid solution by maintain pH 9-9.5 at the room temperature. The dried slurry give the product 6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide (as an pure compound.

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