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# 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. [13]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 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. [1]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.[2]Olmesartanmedoxomil , the latest receptor of angiotensin through FDA appoved for the hypertension treatment.[3,4]The four impurities of Olmesartanmedoxomil were synthesized.[5,6]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.[7-10]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 adrenoreceptor. The potency of alpha1 adrenoreceptor 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.[11-13]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 of the API formation which will conclude through the impurities formation.



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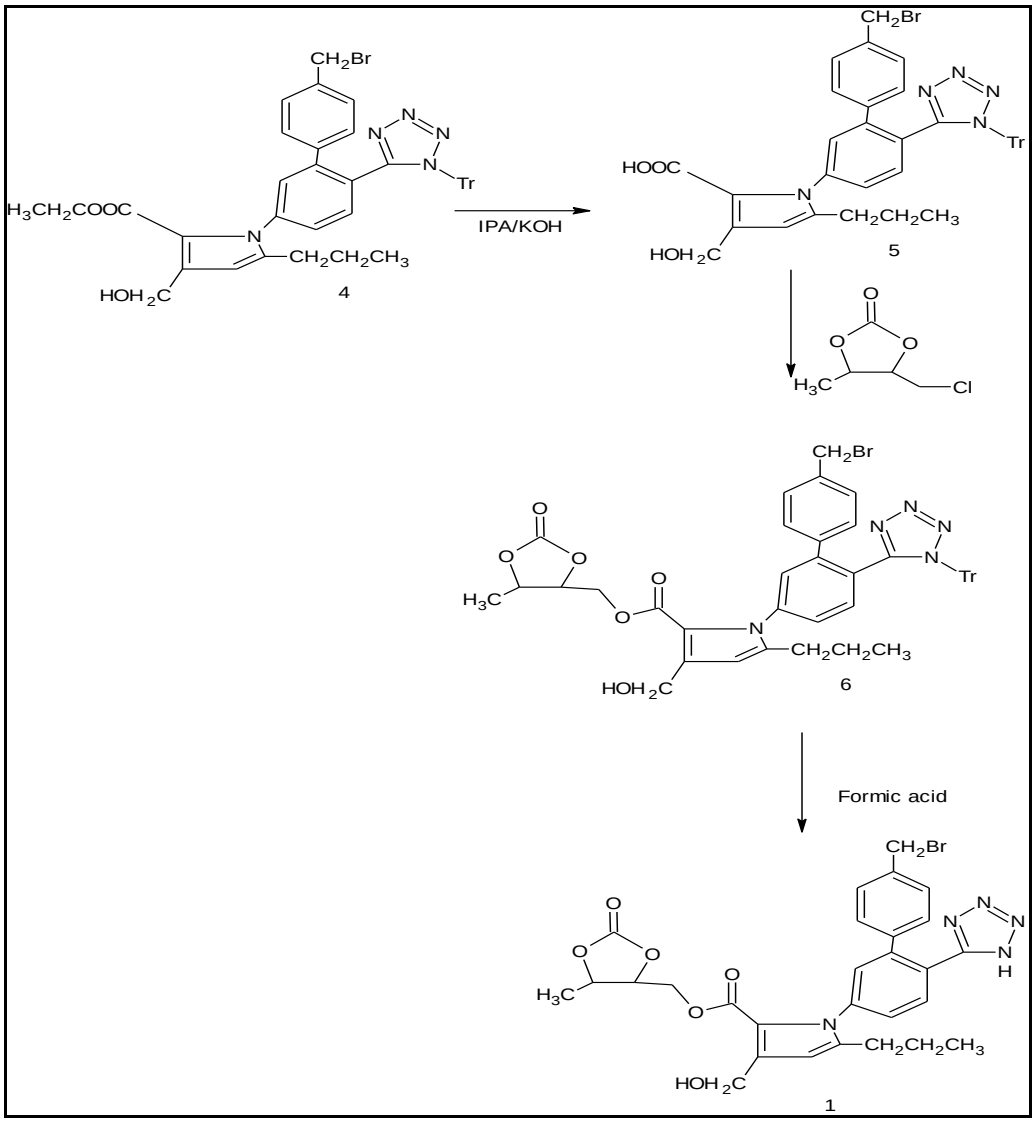
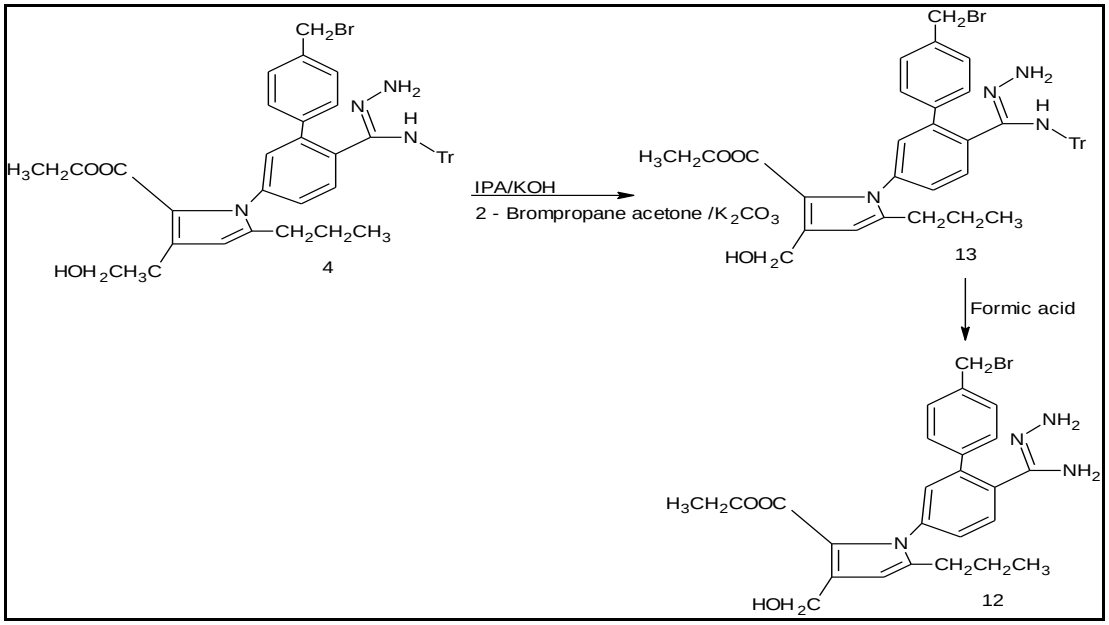
## 2 Synthesis of Hypertensive impurities

### 2.1 Synthesis of Olmesartan




### 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.[14] After complection the reaction mixture cooled and then filteration was done . the layer was then separated between ethyl aceateand 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. [15]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 filteration 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 chromatographusing 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.[16]

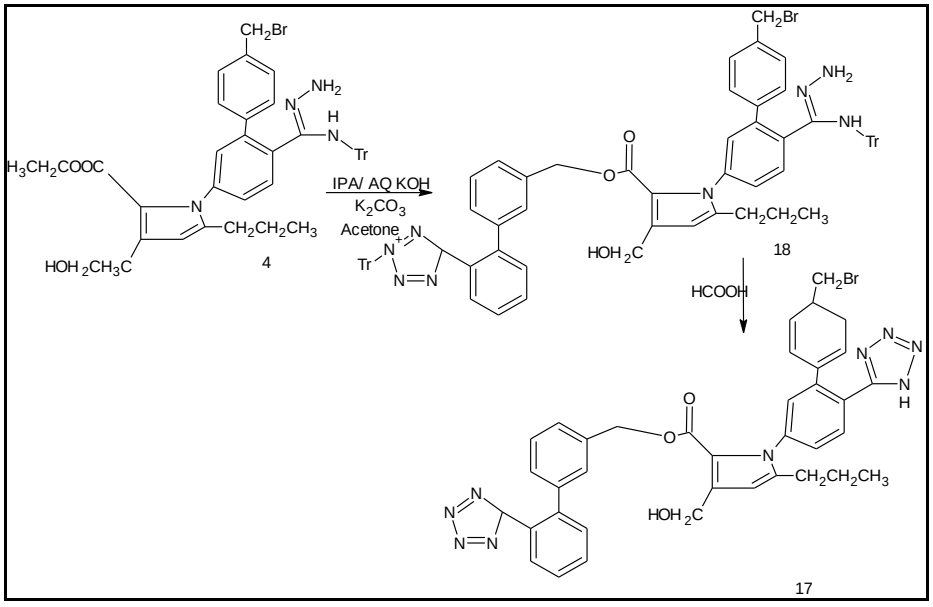



Compound 13 was added with the solution of formic acid and methanolacetonitrile at cooled temperature and solvent was removed under reduced pressure. To the residue the filterate the residue was estracted with ethyl acetate that combined with organic layer and then washed with sodium bicarbonate solution and then dried under anhydrous conditionwith sodium sulfate and purification done with column under hexane and heptane that will give pure white solid compound 12[17]

**2.2 Preparation of dibiphenyl impurity (17)**

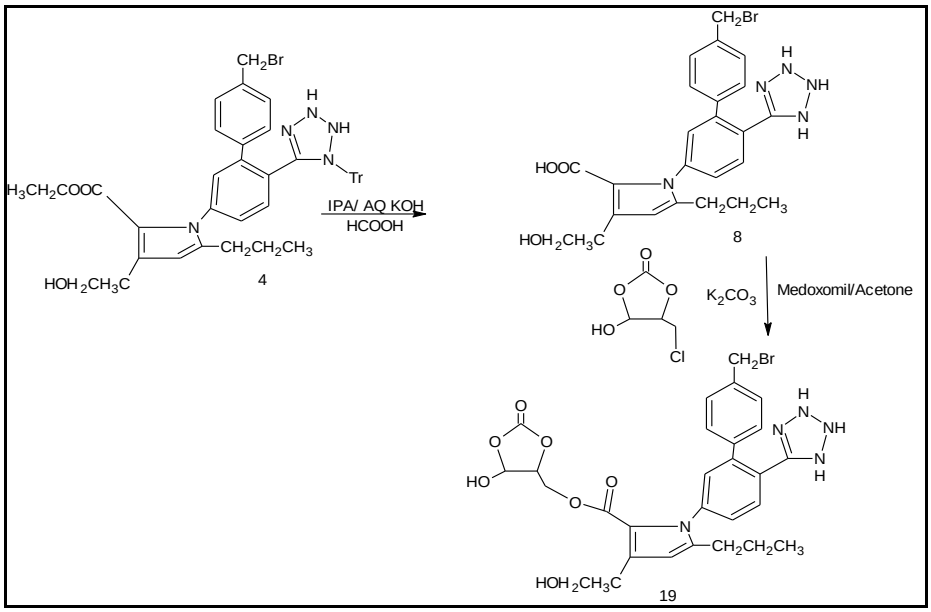
The solution of Ethyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-((2□-(1-trityl-1H-tetrazol-5-yl) biphenyl-4-yl)methyl)-1H-imidazole-5-carboxylate 4 was added with isopropyl alcohol with potassium hydroxide as a saturated solution to its ambient temperature. The reaction mixture was continue on the stirring by maintaining the ambient temperature. [18]The ipa was distilled off after the completion of the reaction and then acetone was adeed with potassium carbonate and continue stirred for 10 minutes. 5-(4-(bromomethyl) biphenyl-2-yl)-1-trityl-1H-tetrazole 3 was added with contuinues stirring for 4 hours by maintain temperature OF 45-50 $^0$ C. after the completion of the reaction it was then filtered through the hyflowbed and washed with the help of acetone the layer was formed between the ethyl acetate and acetone the aethyl acetate layer was dired off and the crude was purified with the help of coloumn in methanol and ethyl acetate as a mobile phased to give 18 as the colored browned compound.[19,20](2□-(1-Trityl-1H-tetrazol-5-yl) biphenyl-4-yl) methyl 4-(2-hydroxy propan-2-yl)-2-propyl-1-((2□-(1-trityl-1H-tetrazol-5-yl) biphenyl-4-yl) methyl)-1H-imidazole-5-carboxylate1 (18).

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$^0$C . THE Solution was cooled and dried and cooled room temperature. The residue is then extracted with the help of ethyl acetate. [21]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-yl)methyl 1-((2□-(1H-tetrazol-5-yl) biphenyl-4-yl) methyl)-4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylatecompound 17 which was then purified with the help of coloumn and recrystallization done with the help of white solid.[22]



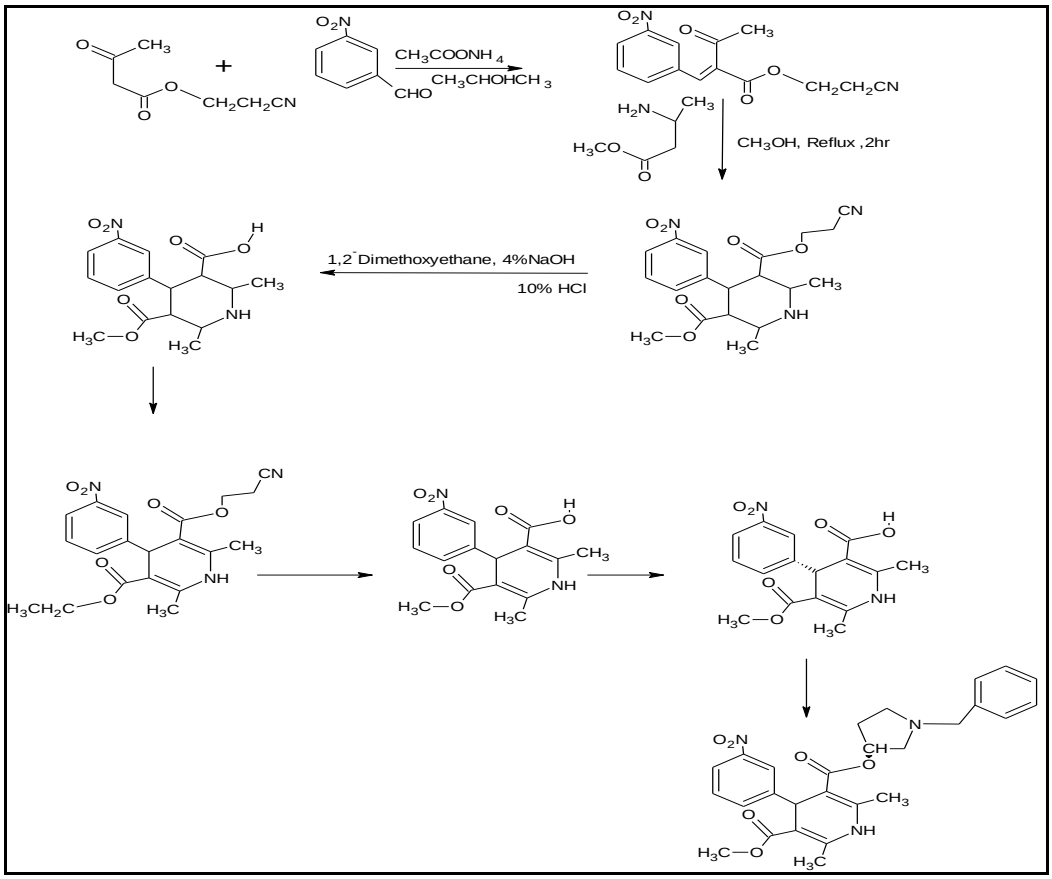

## 2.3 Preparation of Dimedoxomil Impurity (19)

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 naintaing temperature 0-5$^0$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. [23]The crude obtained 8 was then purified with the help of coloumnchromatographyto afford solid and recrystallized with acetone to get white solid 8 1-((2□-(1H-Tetrazol-5-yl) biphenyl-4-yl)methyl)-4-(2-hydroxy propan-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. [24]The reaction cooled at room temperature and washed with acetone. The filtrate residue was patitioned with the layer of ethyl acetate under anhydrous condition with the addition of sodium sulfate under the reduced pressure which was then purified by coloumn chromatography to five solid residue when recryrsllized 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.19[25]



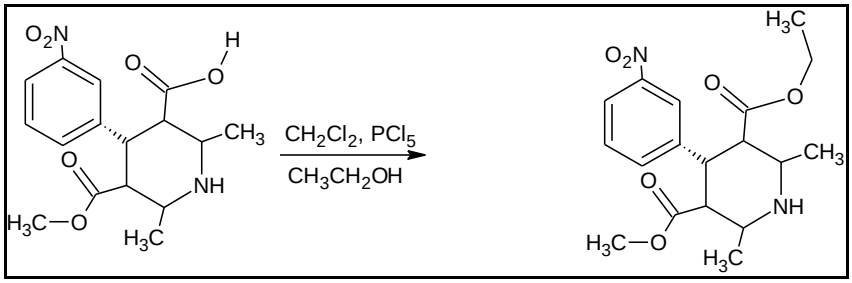
### 2.4 Synthesis of barnidipine hydrochloride

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 for2 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. [26]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]



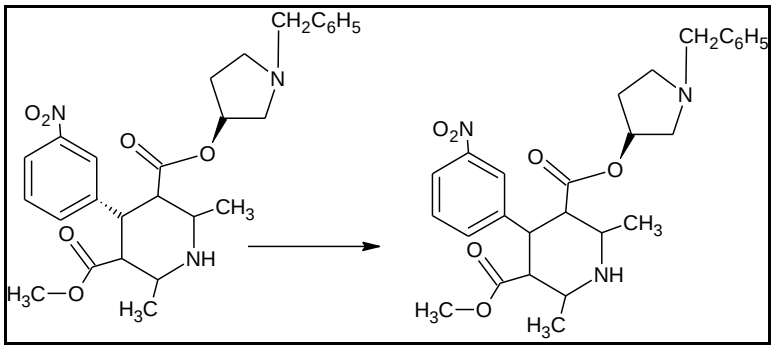

### 2.4.1 Synthesis of impurity

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 2[28]



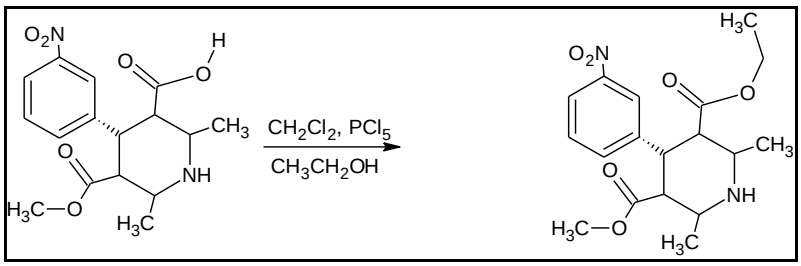
### 2.4.2 Synthesis of impurity 3

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




### 2.4.3 Synthesis of impurity 4

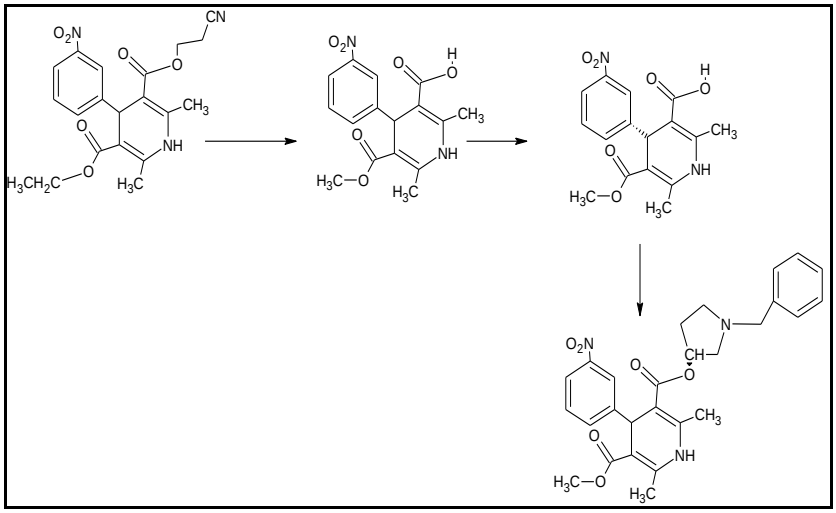
The derivative of compound 12 is the synthesis of compound 4 . The reaction occurs in the presence of phosphorous pentachloride and methyl chloride yield the product which was characterized by13C-NMR, ,1H-NMR, MS data, and HPLC retention time.[29]




### 2.4.4 Synthesis of impurity 5

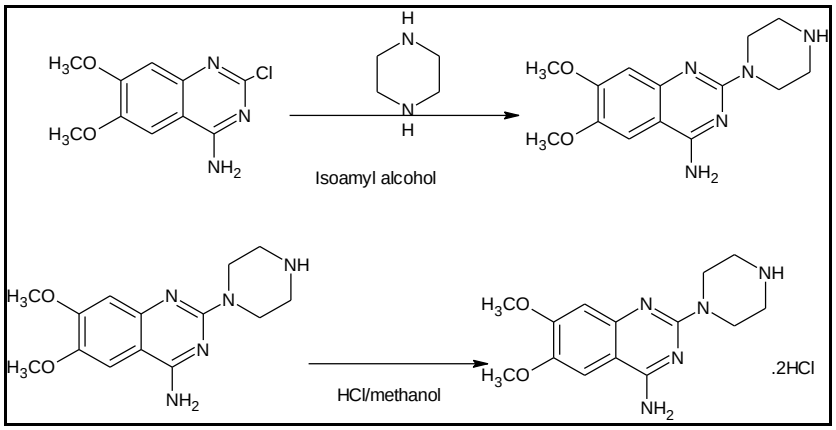
Compound 8 was reacted in the presence of Ethyl 3-aminobut-2-enoate (16) to give 3-(2-Cyanoethyl) 5-ethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-pyridine-3,5-dicarboxylate17. In the presence of 3.8% NaOH solution ,1,2-dimethoxyethane and acidification done with the help of 10 % HCl give 5-(Ethoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid(18. . to the solution of 18 chinchonine and N,N-dimethylformamide was added and heated by maintaing temperature of 80 °C which give clear solution. The solution cooled at 20 $^{0}$ C temperature and continue stirred for 12 hours. The filterate is then washed and filtered with t *N*,*N*-dimethylformamide. The filtered was dissolved in sodium hydroxide 35% solution and extraction was done with dichlormethane. [30]The aqueous portion acidified with concentrated hydrochloric acid by mainating pH 2.0 . the precipate was washed and collected and dried at the temperature of 100$^{0}$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 Dichloromethaane solution by maintain temperature 0 $^{0}$C .Stirred for 1 hours , when the reaction mixture cooled to -20 $^{0}$ 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. [31]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).[32]



### 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 $115^0$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 $120^0$C then it was colled to 70 $^0$C. The precipitaed of white solid was appeared which is then filteredand washed with hot isoamyl alcohol and then dried. [33]Then in other round bottom vessel methanol and IAT was charged with strong hydrochloric acicd and reflux for 1 hour by maintain temperature $60^0$C. THE reation mixture was evaporated under vaccum and the residue was washed with filtered . [34] The filtrate was concentrated to give residue under reduced pressure which was the product of IAT (impurity A of terazosin) hydrochloride was synthesised.[35]

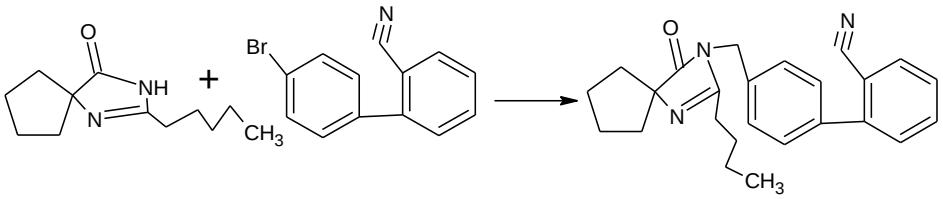



### 2.6 Intermediate of hypertensive drug which can also be acting a impurities

#### 2.6.1 Synthesis of Irbesartan Intermediate

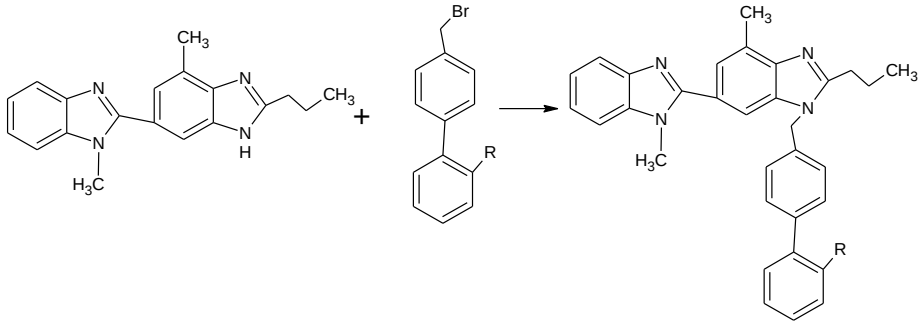
The reaction occur with 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one 12 and 4-bromomethyl-2'-cyanobiphenyl 13 contaning acetone as an solvent as an ambient temperature for 30 minutes . [36]after the completion of 30 minutes the reaction mass was heated for 4 hour for reflux . charging Hydrotalcite for three times slotwise at 4 hour during reflux condition. After the completion of the reactionthe acetonitrile was distilled off under reduced pressure mainating temperature below $45^0$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. [37] After the filteration the filterate was washed with sodium sulfate to get the dried product at last under the reduced pressure the oily residue was obtained .[38] the oily product was then treated with cyclohexane and acetone so that crystal can be obtained which is then

dried under oven at 50$^0$C to get 2-butyl-3-({4-[2cyanophenyl]phenyl}methyl)-1, 3-diazaspiro- [4.4]-non-1-en-4-one as an Irbesartan intermediate. [39.40.41]



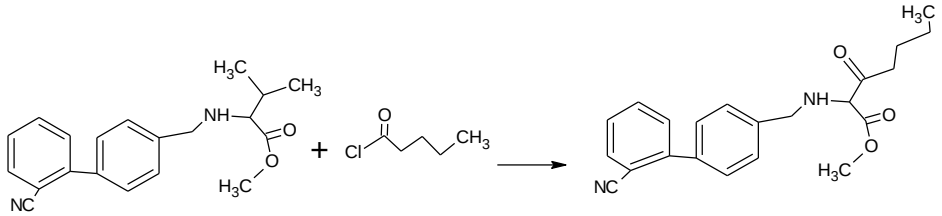
**2.6.2 Synthesis of Telmisartan Intermediate**

The reaction strated 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 mss continue to stir for 10 min maintain temperature at 25 – 30°C and charged hydrotalcite as a base to Digest by mainating 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 vaccum maintain temperature 25-30 0C so that to get solid residue. [43]The telmisartan intermediate was filtered and dried under vaccum to get the solid resdidue and recrystallized with the help of acetonitrile to get free crystals as an precipitatewhich is then dried under oven at 60 $^0$C. To get 4'-((1,4'-dimethyl-2'-propyl(2,6'-bi-1hbenzimidazole)-1'-yl)methyl)-1,1'-biphenyl-2-carbonitrile 18 [44]



**2.6.3 Synthesis of valsartan intermediate**

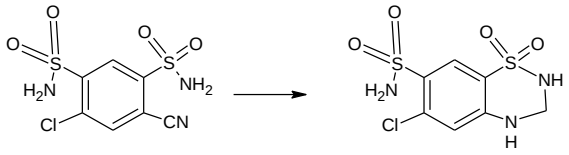
In an reaction mixture (S)-methyl 2-((2'-cyanobiphenyl-4-yl)methylamino)-3-methylbutanoate 20was reacting with tetra butyl ammonium bromide,With the toluene as a solvent with water. charging hydrotalciteas an solvent at the same time at the room temperature mainating temperature 25-30$^0$C · THE reaction was checked on TLC . after the completion of the reaction the hydrotalcitewas filtered and dried.[45] The dried hydrotalcite was further get reused and after the filterartion the filterate was separetd with both by organic and aqueous layer .out of which the aqueous layer was dried to gib=ve the product in the organic layer which filtered through m distilled and maitaingvaccum 60$^0$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 temperastureb25-30 $^0$C .[46]THE layer of organic was distilled and u=dried under vaccum at temperature 50$^0$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 reasction.[47] 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 flteration Hydrotalcite 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 slury give the product 6-chloro-1,1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide (as an pure compound.[48]




## References


1. "International conference on harmonization (ich) guidelines,"q3a (r) impurities in new drug substances, february 2002.
2. Venkanna, G., Madhusudhan, G., Mukkanti, K., Sankar, A., Sampath Kumar, Y., & Venakata Narayana, G. (2012). Synthesis and characterization of process-related impurities of antihypertensive drug olmesartan medoxomil. *Journal of Chemistry*, *2013*.
3. Yanagisawa, h., amemiya, y., kanazaki, t., shimoji, y., fujimoto, k., kitahara, y., ... & furukawa, y. Nonpeptide angiotensin ii receptor antagonists: synthesis, biological activities, and structure– activity relationships of imidazole-5-carboxylic acids bearing alkyl, alkenyl, and hydroxyalkyl substituents at the 4-position and their related compounds. *Journal of medicinal chemistry*, (1996). *39*(1), 323-338.
4. Gardner, s. F., & franks, a. M. Olmesartan medoxomil: the seventh angiotensin receptor antagonist. *Annals of pharmacotherapy*, (2003). *37*(1), 99-105.
5. Huh, w. S., kim, y. S., han, j. S., kim, s. G., kim, s. B., park, j. S., & yamamoto, m. , antihypertensive efficacy and tolerability of barnidipine hydrochloride in patients with renal parenchymal hypertension. *Current therapeutic research*, (2000). *61*(7), 395-405.
6. Imai, y., abe, k., nishiyama, a., sekino, m., & yoshinaga, k.,. Evaluation of the antihypertensive effect of barnidipine, a dihydropyridine calcium entry blocker, as determined by the ambulatory blood pressure level averaged for 24 h, daytime, and nighttime. *American journal of hypertension*, (1997). *10*(12), 1415-1419.
7. Tamazawa, k., arima, h., kojima, t., isomura, y., okada, m., fujita, s., ... & terai, m., stereoselectivity of a potent calcium antagonist, 1-benzyl-3-pyrrolidinyl methyl 2, 6-dimethyl-4-(m-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate. *Journal of medicinal chemistry*, (1986). *29*(12), 2504-2511.
8. Kojima, t., & takenaka, t. (1980). *U.s. Patent no. 4,220,649*. Washington, dc: u.s. Patent and trademark office.
9. Oh, e. Y., bae, s. K., kwon, j. W., you, m., lee, d. C., & lee, m. G. (2007). Pharmacokinetic and pharmacodynamic consequences of inhibition of terazosin metabolism via cyp3a1 and/or 3a2 by da-8159, an erectogenic, in rats. *British journal of pharmacology*, *151*(1), 24-34.
10. Tehranchi, a., rezaei, y., khalkhali, h., & rezaei, m. (2013). Effects of terazosin and tolterodine on ureteral stent related symptoms: a double-blind placebo-controlled randomized clinical trial. *International braz j urol*, *39*(6), 832-840.
11. Yong, y., zhao, x. F., li, h. Z., wei, w. A. N. G., zhang, y., he, x. I. A. O., & zhang, x. (2007). Efficacy and safety of combined therapy with terazosin and tolteradine for patients with lower urinary tract symptoms associated with benign prostatic hyperplasia: a prospective study. *Chinese medical journal*, *120*(5), 370-374.
12. Argentine, m. D., owens, p. K., & olsen, b. A. (2007). Strategies for the investigation and control of process-related impurities in drug substances. *Advanced drug delivery reviews*, *59*(1), 12-28.
13. Fukuda, m., yamanaka, t., mizuno, m., motokawa, m., shirasawa, y., miyagi, s., ... & kimura, g. (2008). Angiotensin ii type 1 receptor blocker, olmesartan, restores nocturnal blood pressure decline by enhancing daytime natriuresis. *Journal of hypertension*, *26*(3), 583-588.
14. Kurikawa, n., suga, m., kuroda, s., yamada, k., & ishikawa, h. (2003). An angiotensin ii type 1 receptor antagonist, olmesartan medoxomil, improves experimental liver fibrosis by suppression of proliferation

and collagen synthesis in activated hepatic stellate cells. *British journal of pharmacology*, *139*(6), 1085-1094.

15. Yanagisawa, h., amemiya, y., kanazaki, t., shimoji, y., fujimoto, k., kitahara, y.,& furukawa, y. (1996). Nonpeptide angiotensin ii receptor antagonists: synthesis, biological activities, and structure− activity relationships of imidazole-5-carboxylic acids bearing alkyl, alkenyl, and hydroxyalkyl substituents at the 4-position and their related compounds. *Journal of medicinal chemistry*, *39*(1), 323-338.
16. Gardner, s. F., & franks, a. M. (2003). Olmesartan medoxomil: the seventh angiotensin receptor antagonist. *Annals of pharmacotherapy*, *37*(1), 99-105.
17. Teng, j., fukuda, n., suzuki, r., takagi, h., ikeda, y., tahira, y., & kanmatsuse, k. (2002). Inhibitory effect of a novel angiotensin ii type 1 receptor antagonist rnh-6270 on growth of vascular smooth muscle cells from spontaneously hypertensive rats: different anti-proliferative effect to angiotensin-converting enzyme inhibitor. *Journal of cardiovascular pharmacology*, *39*(2), 161-171.
18. Venkanna, g., madhusudhan, g., mukkanti, k., sankar, a., sampath kumar, y., & venakata narayana, g. (2012). Synthesis and characterization of process-related impurities of antihypertensive drug olmesartan medoxomil. *Journal of chemistry*, *2013*.
19. Srimurugan, s., suresh, p., babu, b., hiriyanna, s. G., & pati, h. N. (2008). Unusual detritylation of tritylated tetrazole in sartan molecules. *Chemical and pharmaceutical bulletin*, *56*(3), 383-384.
20. Pati, h. N., lahiri, s., sabbam, r. K., vangala, v. B., ramalingam, b., hiriyanna, s. G., & bose, p. (2008). A convenient and practical synthesis of olmesartan medoxomil methyl ether. *Journal of heterocyclic chemistry*, *45*(3), 917-920.
21. Babu, k. S., tagore, a. R., reddy, g. S., venkateswarlu, g., reddy, p. P., & anand, r. V. (2010). Synthesis of related substances of olmesartan medoxomil, antihypertensive drug. *Arkivoc*, *2*, 292-302.
22. Tamazawa, k., arima, h., kojima, t., isomura, y., okada, m., fujita, s., ... & terai, m. (1986). Stereoselectivity of a potent calcium antagonist, 1-benzyl-3-pyrrolidinyl methyl 2, 6-dimethyl-4-(m-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate. *Journal of medicinal chemistry*, *29*(12), 2504-2511.
23. Kojima, t., & takenaka, t. (1980). *U.s. Patent no. 4,220,649*. Washington, dc: u.s. Patent and trademark office.
24. Guideline, i. H. T. (2006, october). Impurities in new drug substances q3a (r2). In *proceedings of the international conference on harmonization of technical requirements for registration of pharmaceuticals for human use, geneva, switzerland* (vol. 25).
25. Inagaki, o., asano, m., & takenaka, t. (1999). In vitro and in vivo vasodilatory activity of barnidipine and its enantiomers. *Biological and pharmaceutical bulletin*, *22*(2), 151-156.
26. Pawula, m., watson, d., teramura, t., watanabe, t., higuchi, s., & cheng, k. N. (1998). Sensitive and specific liquid chromatographic–tandem mass spectrometric assay for barnidipine in human plasma. *Journal of chromatography b: biomedical sciences and applications*, *719*(1-2), 113-123.
27. Ioele, g., oliverio, f., andreu, i., de luca, m., miranda, m. A., & ragno, g. (2010). Different photodegradation behavior of barnidipine under natural and forced irradiation. *Journal of photochemistry and photobiology a: chemistry*, *215*(2-3), 205-213.
28. Li, l., cheng, z., li, x., gao, j., su, c., & ma, x. (2010). Synthesis process of barnidipine hydrochloride. *Cn patent*, *101643469*.
29. Bernhart, c. A., perreaut, p. M., ferrari, b. P., muneaux, y. A., assens, j. L. A., clement, j., ... & gougat, j. (1993). A new series of imidazolones: highly specific and potent nonpeptide at1 angiotensin ii receptor antagonists. *Journal of medicinal chemistry*, *36*(22), 3371-3380.
30. Caron, a., chantreux, d., & bouloumie, c. (1997). *U.s. Patent no. 5,629,331*. Washington, dc: u.s. Patent and trademark office.
31. Arora s, kumar y. Processes for the preparation of highly pure irbesartan. *Wo pat*. 2005051943 a1, 2004.
32. Edgar m, cornelis v. A method for preparing irbesartan and intermediates thereof. *Wo pat*. 2006023889 a3, 2005.
33. Reddy b, sunkari s, rao n. Process for preparing irbesartan.*wo pat*. 2005113518 a1, 2005. 27. Telmisartan - wikipedia, the free encyclopedia -http://en.wikipedia.org/wiki/telmisartan. 2014
34. Benson, s. C., pershadsingh, h. A., ho, c. I., chittiboyina, a., desai, p., pravenec, m., ... & kurtz, t. W. (2004). Identification of telmisartan as a unique angiotensin ii receptor antagonist with selective pparγ–modulating activity. *Hypertension*, *43*(5), 993-1002.
35. Bessa j. Process for preparing an angiotensin ii receptor antagonist. *Us pat*. 20080281097 a1, 2006.

36. Reddy, k. S., srinivasan, n., reddy, c. R., kolla, n., anjaneyulu, y., venkatraman, s., ... & mathad, v. T. (2007). An efficient and impurity-free process for telmisartan: an antihypertensive drug. *Organic process research & development*, *11*(1), 81-85.
37. Hauel, n., dach, r., heitger, h., & meyer, o. (2007). *U.s. Patent no. 7,193,089*. Washington, dc: u.s. Patent and trademark office.
38. Ray p, pandey a, patil p. A new process for the preparation of pure telmisartan. *Wo pat.*, 2011077444, 2011.
39. Brand, m., salman, a., gafni, y., noiman, m., weisman, a., & kaspi, j. (2006). *U.s. Patent application no. 11/449,087*.
40. Chava, s., gorantla, s. R., & ginjupalli, s. P. B. L. (2011). *U.s. Patent no. 7,884,214*. Washington, dc: u.s. Patent and trademark office.
41. Patil p.b, pandey anand, shinde d. B, chaudhari b. R. An improved, scalable and cost effective one-pot synthesis of telmisartan *ijrpbs*, 2013, 4, 293 – 295.
42. Perlman, n., & gilboa, e. (2009). *U.s. Patent application no. 12/319,834*.
43. Marshall, t. G. (2014). *U.s. Patent no. 8,865,749*. Washington, dc: u.s. Patent and trademark office.
44. Buhlmayer p, ostermayer f, schmidlin t. Acyl compounds.*us pat.*, 5399578 a, 1995.
45. Aminul i, reddy s, reddy r. An improved process for the preparation of valsartan. *Wo pat.*, 2012001484 a2, 2011.
46. Penikelapati h, ambati s, ambat n. New and improved synthesis of valsartan: an antihypertensive drug *researchjournal of pharmaceutical, biological and chemical sciences.* 2011, 2(4), 632
47. Duarte, j. D., & cooper-dehoff, r. M. (2010). Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics. *Expert review of cardiovascular therapy*, *8*(6), 793-802.
48. De, s. G., & harvey, w. L. (1964). *U.s. Patent no. 3,163,645*. Washington, dc: u.s. Patent and trademark office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