A Review on Synthesis of Antihypertensive Sartan Drugs

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ABSTRACT
Elevated blood pressure or hypertension is the chronic medical condition which is mainly responsible for cardiovascular diseases today. Renin-Angiotensin-Aldosterone System (RAAS) is the basic system in humans which is used to regulate the blood pressure as well as related values such as sodium levels and fluid volumes. Targeting the AT_1 receptors of Angiotensin-II with non-peptide based drugs which are otherwise called as Angiotensin Receptor Blockers (ARB's), led to the control of hypertension, ultimately controlling its associated heart related ailments such as coronary heart disease and stroke. The non-peptide imidazole derivatives also called as Sartans, are the latest family of drugs which stop the activity of angiotensin II by blocking its AT_1 receptors. These drugs control blood pressure by dilating blood vessels, increase release of water and salt to urine, ultimately controlling the blood pressure. There are about six ARB's approved by US-FDA which are superior to its alternative class of drugs called Angiotensin Converting Enzyme (ACE) inhibitors which block the conversion of Angiotensin I to Angiotensin II. ARB's can be used to treat coronary heart disease in the people who cannot tolerate certain side effects caused due to the ACE inhibitors such as common ACE cough and patients with kidney ailments and diabetes. This review gives a brief account of the synthetic routes which were employed in the synthesis of presently marketed ARB's or Sartan drugs.

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INTRODUCTION

Pharmacological agents which target RAAS (Renin-Angiotensin-Aldosterone System) are one of the most significant therapeutic interventions available in curing the cardiovascular disease today. Renin-Angiotensin-Aldosterone System (RAAS) is the basic system in humans which is used to regulate the blood pressure as well as related values such as sodium levels and fluid volumes. Low blood pressure or loss of sodium levels in the body stimulates kidneys to release a proteolytic enzyme called Renin. Renin acts on angiotensinogen, a circulating protein, to angiotensin-I, which is further converted to angiotensin-II by angiotensin converting enzyme (ACE). Angiotensin-II executes multiple functions in the body, primarily smooth muscle contraction of vascular cells (vasoconstriction) thereby causing an increase in blood pressure and next, triggering the release of adrenaline, noradrenaline, biosynthesis of aldosterone and secretion of Vasopressin (Anti Diuretic Hormone-ADH), leading to an influence in Na^+ retention and decrease in urine production from kidneys, along with increase in fluid volume in the body, resulting into the elevation of blood pressure levels [1]. Although, Angiotensin's effect is transitory in nature, they play a major role in maintaining homeostasis of the body.

Sartans are a new series of non-peptide based drugs which can competitively block angiotensin-II receptors and regulate blood pressure. It was discovered in early 1970's that, Saralasin, an oligopeptide, competitively inhibited the angiotensin-II receptors acting as ARB. Because of its poor oral bioavailability and partial agonist activity, Sartan drugs were developed which physiologically played the same role as Saralasin.

Mechanistically, Sartans (Angiotensin-II antagonists) exhibit the blood pressure lowering ability by inhibiting the Angiotensin-II to bind to the integral membrane protein receptor subtype AT_1 on blood vessels and other tissues [2]. These blood pressure lowering drugs, can be given as active compounds, as prodrugs, or in combination with other drugs, which are generally prescribed for those who are sensitive to ACE inhibitors. Compared to ACE inhibitors, Sartans exhibit less 1st dose hypotension, less renal dysfunction (kidney damage due to diabetes – diabetic nephropathy)[3], congestive heart failure and are devoid of ACE cough, a side effect caused due to ACE inhibitors [2].
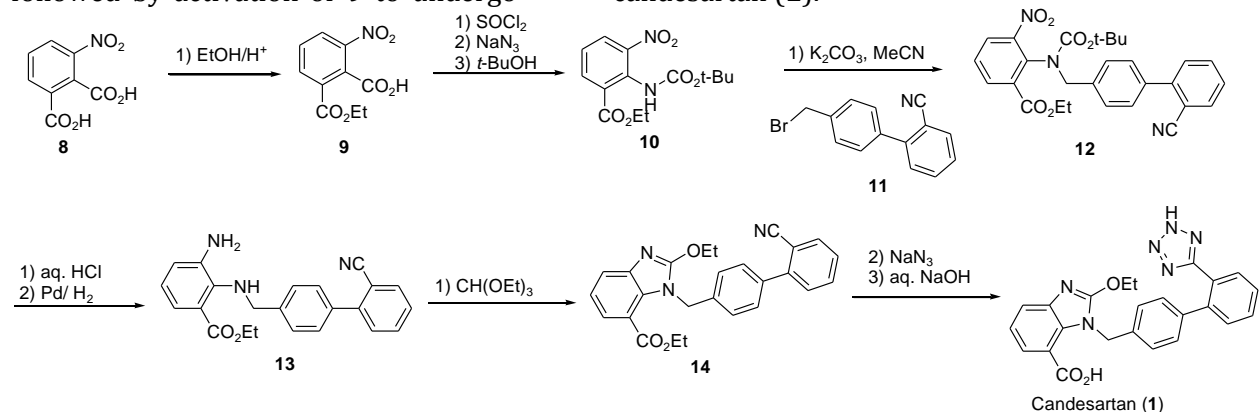
Drugs ending with –sartan are invariably ARB's. All ARB's are more or less similar in action and mostly they can be differentiated by the extent to which they are distributed throughout the body and how they are eliminated from the body. There are about seven sartan drugs approved by U.S. Food and Drug Administration (FDA) (Figure-1) e.g.: Candesartan (**1**) (Atacand), Eprosartan (**2**) (Teveten), Irbisartan (**3**) (Avapro), Losartan (**4**) (Cozaar), Olmesartan (**5**) (Benicar), Telmisartan (**6**) (Micardis) and Valsartan (**7**) (Diovan). As our ongoing research was involved in the isolation and synthesis of Olemesartan impurities [4], it interested us to review briefly about the syntheses and manufacture of Sartan drugs followed by academia and some major pharmaceutical industries, respectively. To the best of our knowledge so far no recent reviews are available in the literature towards the synthesis of Sartan drugs. Therefore, a simple and brief account of Sartan drug syntheses is described in alphabetical order in this review article.

Candesartan (1)   Eprosartan (2)   Irbesartan (3)   Losartan (4)   Olmesartan medoxomil (5)   Telmisartan (6)   Valsartan (7)
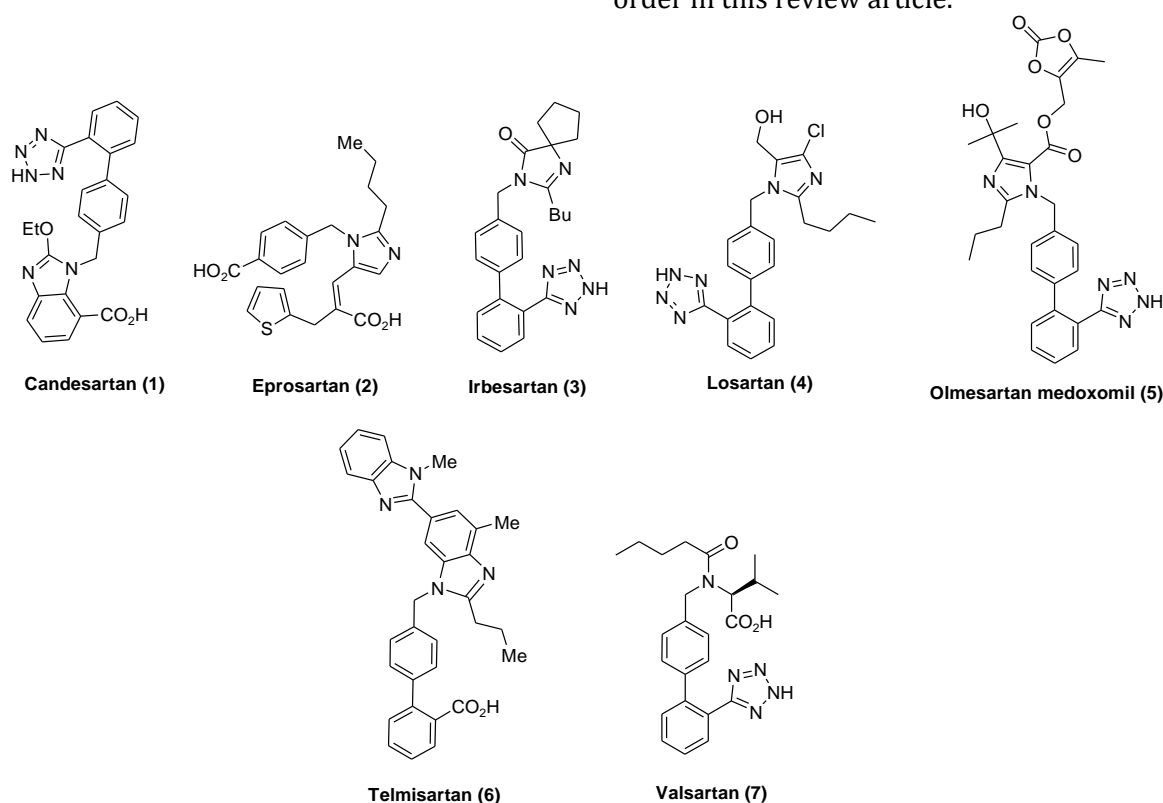
Figure1: Structures of Sartan drugs

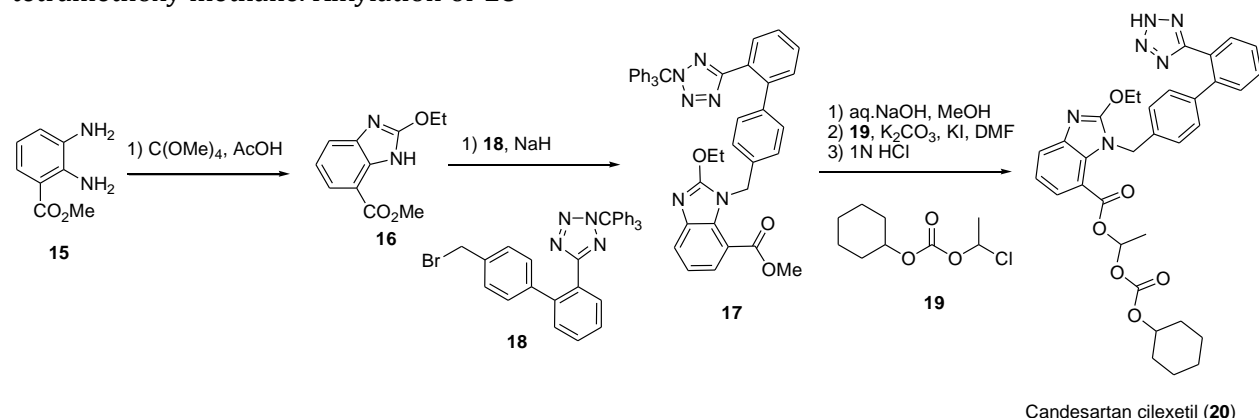## Synthesis of Candesartan (1):

Candesartan (**1**) is marketed as a prodrug Candesartan cilexetil ester, owing to its poor oral absorption. It is metabolized on intestinal walls by esterases to active drug which is absorbed into the blood as its active molecule **1**. Husain *et al*, recently reviewed its pharmacological and pharmaceutical profile [5].The synthesis of Candesartan reported by Kubo *et al* [6, 7] is summarized in Scheme-1 & 2. Selective monoesterification of **8** followed by activation of **9** to undergo

rearrangement in the presence of sodium azide furnished **10**. The major molecular frame work of candesartan (**1**) was achieved after alkylation of **10** with bromo benzyl biphenyl nitrile **11** which provided **12**. Deprotection of Boc protecting group and reduction of nitro group produced **13**, which was treated with triethyl ortho formate yielded ethoxy benzimidazole **14**. Finally, tetrazole ring was incorporated by treating **14** with sodium azide followed by ester hydrolysis produced candesartan (**1**).

Scheme 1: Synthesis of Candesartan (1)

In an alternate concise and convergent approach for the synthesis of **1** (Scheme-2) reported by the same authors, ethoxy benzimidazole intermediate **16** was made by reacting 2,3-diamino methyl benzoate **15** with tetramethoxy methane. Alkylation of **16**
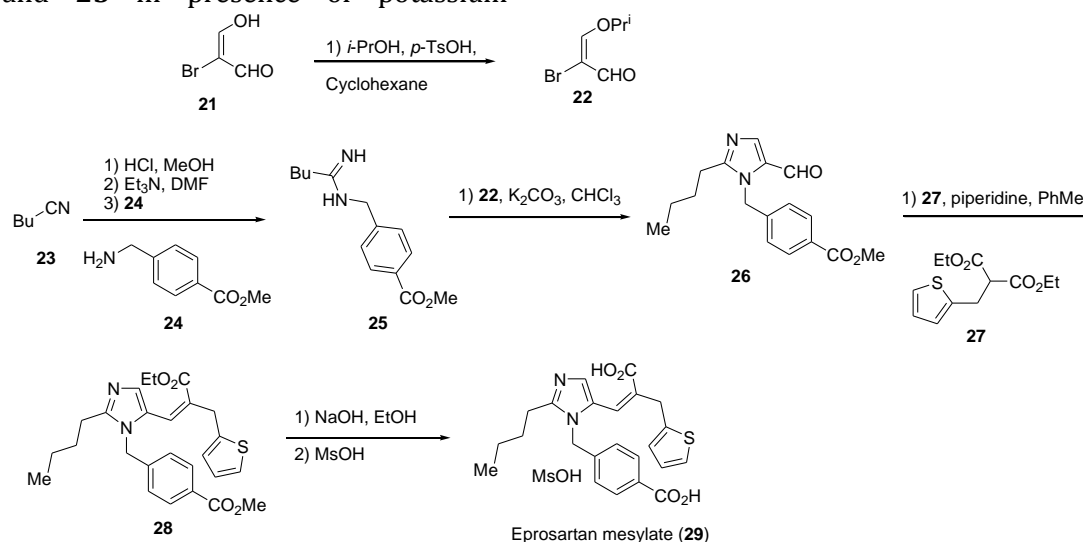
with tetrazole biphenyl benzyl bromide **18** provided **17** which was hydrolyzed and esterified with cyclo hexyl 1-chloroethyl carbonate **19** provided trityl protected candesartan cilexetil. Finally, deprotection of trityl group in the presence of dilute hydrochloric acid afforded Candesartan cilexetil **20**.

Candesartan cilexetil (**20**)

Scheme 2: Synthesis of Candesartan cilexetil (20)

Synthesis of Eprosartan (2):

Eprosartan (**2**) is the non-biphenyl tetrazole containing sartan drug available as its mesylate salt (**29**). A convergent approach followed by
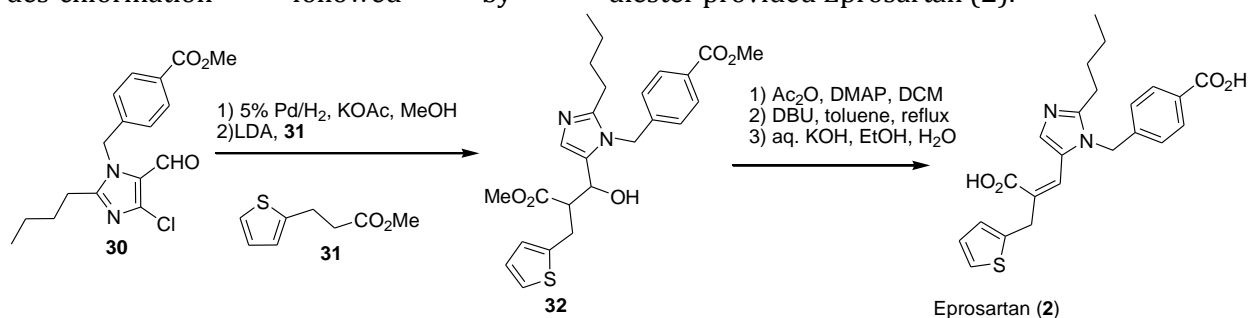
Keenan *et al* [8, 9] is outlined in Scheme-3. The key fragment **25** was prepared by treatment of benzyl amine (**24**) with imide salt, which was made by passing dry hydrogen chloride gas in

solution of valeronitrile (**23**) in methanol. The enol ether of bromo malonaldehyde (**22**) was prepared by refluxing **21** in propanol-cyclohexane in the presence of PTSA. Imidazole ring was further synthesized by reacting **22** and **25** in presence of potassium

carbonate. Finally, condensation of aldehyde **26** with thiophene diester (**27**) produced **28**, followed by hydrolysis of diester and making into its diacid to its mesylate salt completed the synthesis of Eprosartanmesylate (**29**).

Scheme 3: A convergent approach to Eprosartan mesylate (29)

In an alternate approach employed by same authors (Scheme-4), the benzylated imidazole aldehyde (**30**) was subjected to palladium catalyzed des-chlorination followed by

condensation with **31** produced aldol condensation product **32**. Finally, DBU induced elimination of acetylated aldol product followed by the hydrolysis of diester provided Eprosartan (**2**).

Scheme 4: An alternate approach to Eprosartan (2)

Synthesis of Irbesartan (**3**):

Irbesartan, unlike the other sartan drugs, does not depend on the formation of active metabolite for complete expression of potency and it shows almost complete bioavailability when administered orally. A concise route developed by Bernhart *et al* [10, 11] is summarized in Scheme-5. 1-Amino-cyclopentane ethyl carboxylate (**33**) is reacted with salt of ethyl pentanimidate (**34**) which provided dihydroimidazolone (**35**). Finally,

alkylation of **35** with **11** followed by the incorporation of tetrazole ring by reacting **35** with tributyl tin azide afforded Irbesartan (**3**).

In a convergent approach, one of the key intermediate **38**, synthesized by the alkylation of **35** with bromobenzyl bromide (**37**), was coupled with **39** under Suzuki conditions provided **35**, which was finally subjected to trityl group deprotection in the presence of hydrochloric acid afforded Irbesartan (**3**) (Scheme-6).
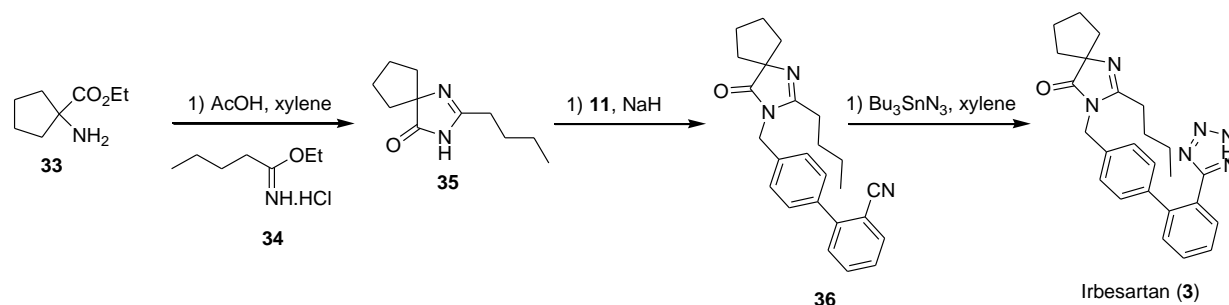
Scheme 5: Synthetic route to Irbesartan (3)
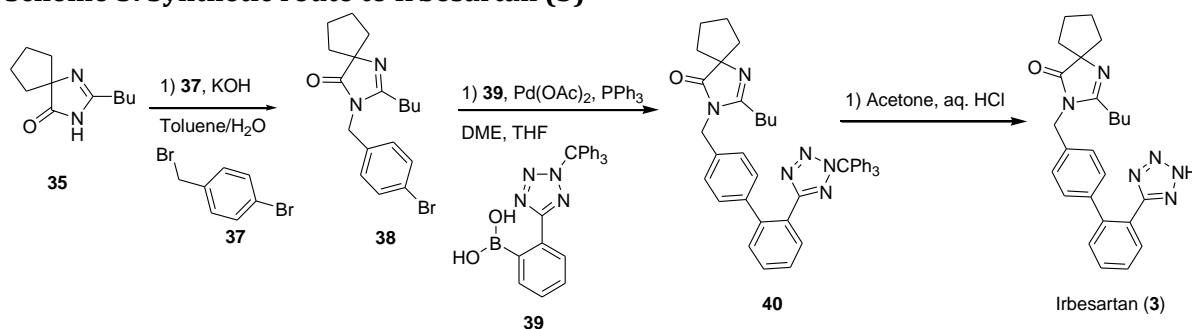
Scheme 6: A convergent approach to Irbesartan (3)

Recently, a new improved and efficient process suitable for large scale production of the Irbesartan (**3**) was reported by Rao *et al* [12]. In their approach one of the key intermediate benzyl group protected bromo biphenyl tetrazole prepared from its corresponding precursor 4'-methyl-biphenyl-2-carboxylic acid, was alkylated with HCl salt of **35**, produced a benzylated Irbesartan which was subjected to debenzylation afforded Irbesartan (**3**).
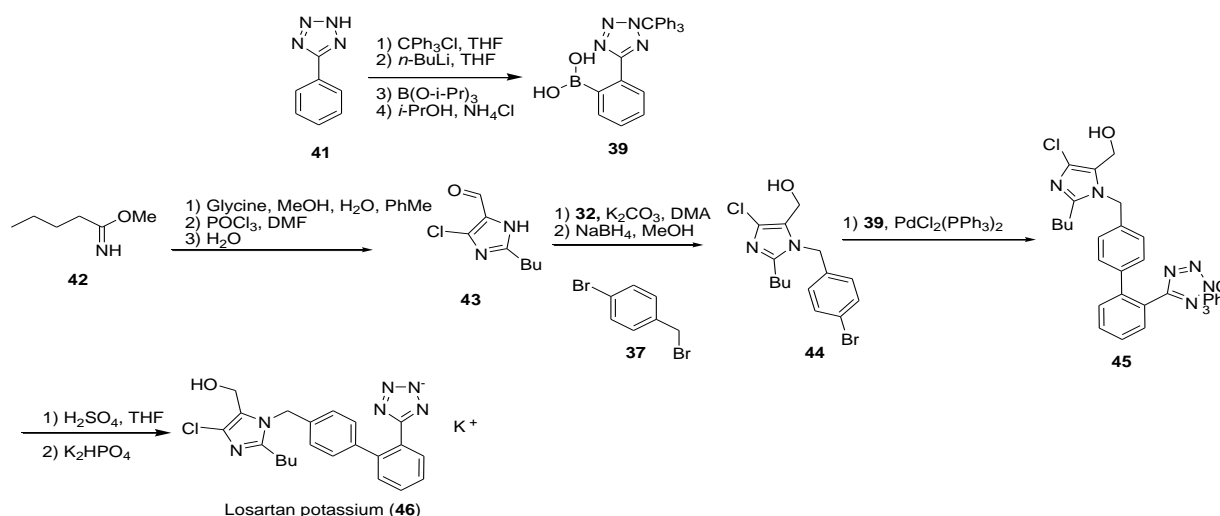
Synthesis of Losartan (4):

Losartan (**4**) is the first orally active and selective non-peptide AT_1 receptor antagonist from a series of 1-benzylimidazole-5-acetic acid derivatives developed by Takeda Pharma. It is the first ARB drug among seven sartan drugs approved for clinical use in United States. It can be administered orally as its mono potassium salt (**46**) (Cozaar: Merk) or as co-active ingredient with hydrochlorothiazide (Hyzaar: Merk).

A variety of synthetic approaches were employed in the synthesis of **4**[13] while most of them involve trityl losartan (**45**) as key penultimate product. In a convergent approach developed by Merk laboratories

(Scheme-7), trityl protected phenyl tetrazole was ortho litihated with n-butyl lithium followed by quenching it with tri isopropyl borate and treatment with ammonium chloride produced **39**[14]. Reaction with glycine and methyl pentanimidate (**42**) in methanol/water produced (pentanimidoylamino) acetic acid, which on Vilsmeir reaction yielded imidazole carbaldehyde (**43**). The carbaldehyde derivative was alkylated with 4-benzyl bromide (**37**) in the presence of potassium carbonate followed by immediate reduction with sodium borohydride produced imidazole alcohol **44** which was made to undergo Suzuki cross coupling with **34** to yield **45**. Finally, the trityl losartan **45** was deprotected in dilute sulfuric acid followed by making of its potassium salt with potassium hydroxide or potassium tertiary butoxide completed the synthesis of Losartan potassium (**46**).

In an alternative synthetic process detailed by David *et al*[15] (Scheme-8), intermediate **47** derived from imidazole alcohol and intermediate **11,** was made to undergo cyclo addition between trimethyl tin azide and tethered nitrile group of **47**, afforded **48**, a core

molecular frame work of Losartan (**4**). Finally, replacing trimethyl stannyl group with trityl group by reacting with trityl chloride followed by the cleavage of trityl group in dilute HCl and adjusting pH with NaOH produced Losartan (**4**).

Scheme 7: Convergent synthesis toward Losartan potassium (46)
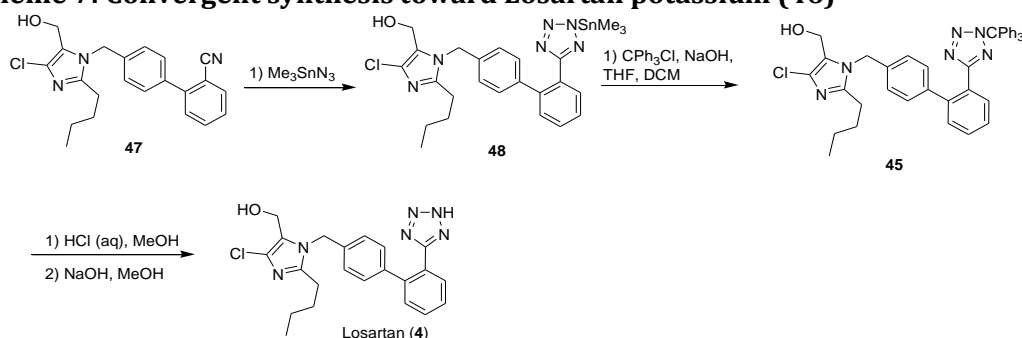
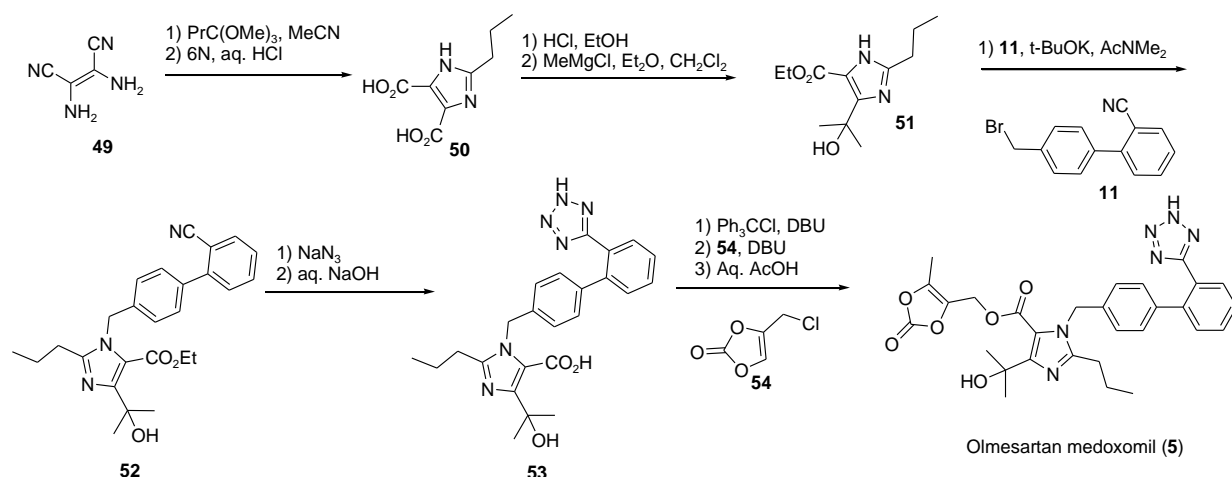**Scheme 8: Synthetic route to Losartan (4)**

Synthesis of Olmesartan medoxomil (5):

Olmesartan medoxomil is an ester prodrug developed by Sankyo Pharma which is hydrolysed to its biologically active metabolite olmesartan (**5**) in the gastro intestinal tract during absorption. A practical approach followed in industrial production of olmesartan (**5**) reported by Yanagisawa *et al* [16, 17] is outlined in the Scheme-9. 2-Propyl imidazole (**50**) prepared by condensation of diaminomaleonitrile (**49**) and trimetyl orthobutyrate, was hydrolyzed to its corresponding dicarboxylic acid **50**, which was esterified to its diester and selectively reacted with methyl magnesium chloride to give its corresponding tertiary alcohol **51**. Benzylation of **51** with **11** produced **52**, which on

treatment with sodium azide and hydrolysis of ethyl ester produced olmesartan (**53**). Finally, the prodrug was synthesized by tritylation of **53** with trityl chloride, followed by esterification with side chain **54** and deprotection of trityl group afforded Olmesartan medoxomil (**5**).

A scalable route to **5** was reported by Babu *et al* [18, 19] is outlined in Scheme-10. A selective Grignard addition with methyl magnesium chloride over a diester **56** which was derived from the alkylation of **55** with tetrazoylbiphenyl bromide (**18**) produced imidazole alcohol (**57**). Synthesis of Olmesartan medoxomil (**5**) was completed by hydrolysis of **57**, alkylation with **54** followed by deprotection of trityl group in **58** under

acidic conditions afforded Olmesartan medoxomil (**5**).

**Scheme 9: Synthetic route to Olmesartan medoxomil (5)**
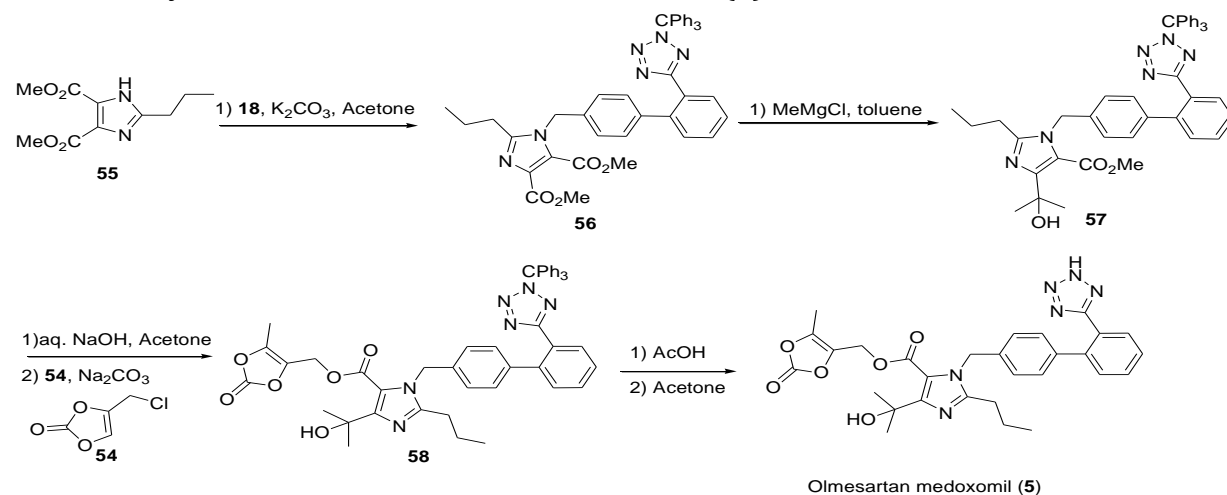
Scheme 10: Alternative scalable route to Olmesartan medoxomil (5)

Synthesis of Telmisartan (6):

Telmisartan (**6**) is an angiotensin II receptor antagonist marketed under the trade name Micardis by Bhoringer Ingelheim Pharma. Synthesis of Telmisartan (**6**) is outlined in Scheme-11[20, 21]. Acylation of 4-Amino-3-methylbenzoate (**59**) followed by nitration of corresponding amide produced **60**, which was subjected to palladium catalyzed reduction and cyclization in acetic acid under reflux condition afforded **61**. Bis-benzimidazole (**63**) was synthesized by cyclization of hydrolysis productof **61** with N-methyl phenylene diamine (**62**) in the presence of PPA. Finally, alkylation of **63** with biphenyl benzyl bromide (**64**) followed by hydrolysis of *tert*-butyl ester furnished Telmisartan(**6**).

Valsartan (7):

A non-heterocyclic derivative of Losartan (**4**) with acylated valine methyl ester in place of imidazole ring is, Valsartan (**7**). The synthesis of **7** by Novartis/Ciba-Giegy laboratories is summarized in Scheme-12[22, 23]. Biphenyl benzyl alcohol derived from its corresponding bromo derivative **11**, is oxidised under Swern oxidation conditions to yield aldehyde **65**. Carrying out reductive amination on imine derived from **65** and L-valine methyl ester by sodium cyano borohydride followed by acylation of corresponding amine with valeryl chloride afforded nitrile intermediate **66**. Finally, incorporation of tetrazole ring followed by ester hydrolysis and acidification of **66** produced Valsartan (**7**).
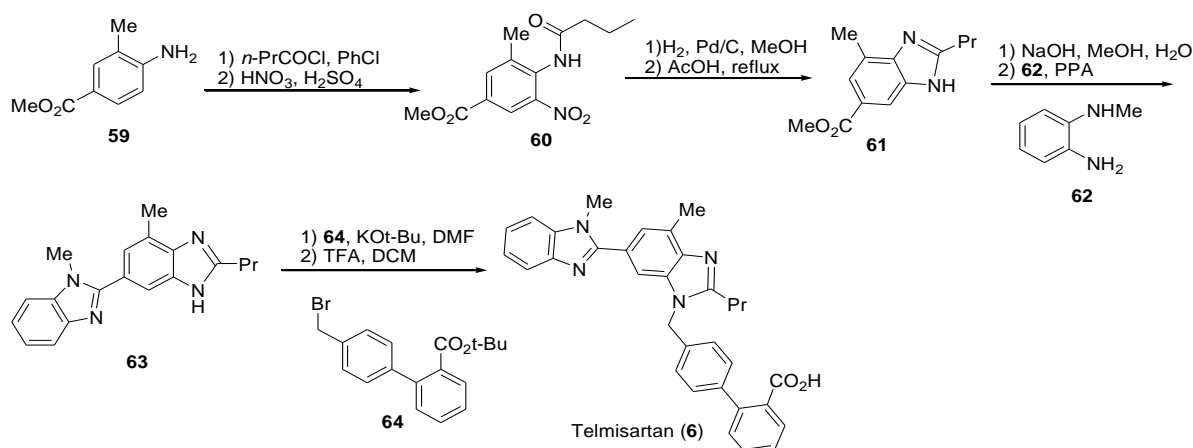
Scheme 11: Synthetic route to Telmisartan (6)
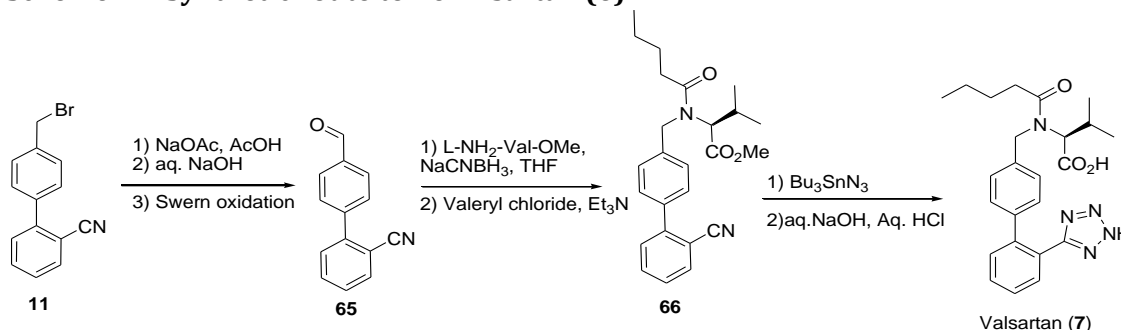
Scheme 12: Synthetic route to Valsartan (7)

In an alternate approach reported by Buhlmayer *et al* (Scheme-13)[24], the tetrazole is previously incorporated as its trityl protected bromo biphenyl derivative **18**. The intermediate **18** was reacted with L-valine benzyl ester provided **67**, which was acylated with valeryl chloride afforded **68**. Finally, deprotecting trityl group using HCl in dioxane gave **69**, followed by palladium catalyzed debenzylation of benzyl ester completed Valsartan (**7**) synthesis.
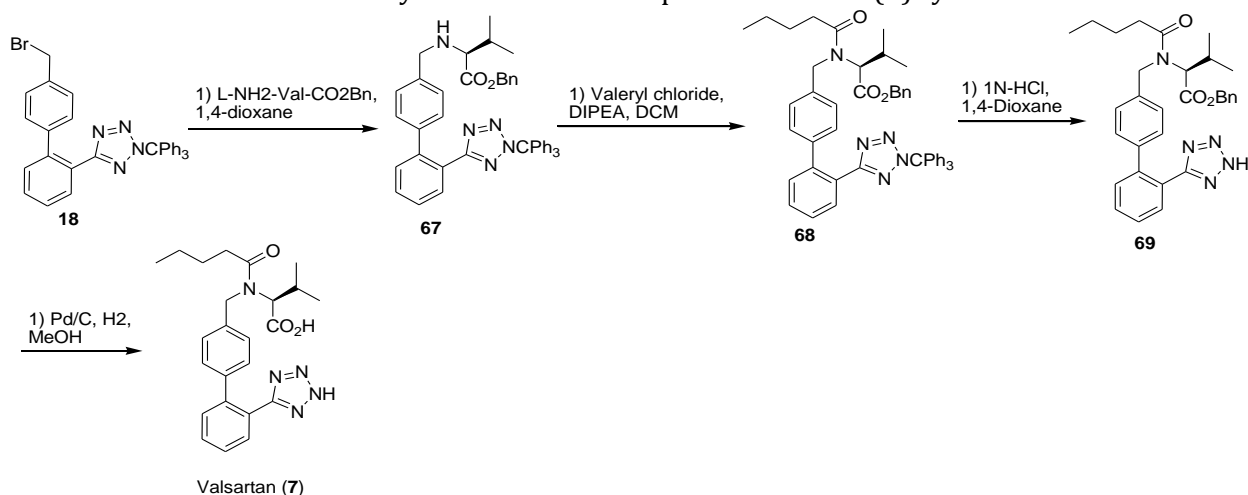
Scheme 13: Alternate approach to Valsartan (7)

In another approach reported by Bessa *et al* (Scheme-14)[25], **37** was made to react with HCl salt of valine methyl ester to provide **70** which was hydrolyzed with potassium hydroxide and the corresponding amino acid intermediate was acylated with valeryl chloride to afford **71**. Finally, coupling

71 with tetrazole phenyl boronic acid (**72**) under Suzuki conditions provided
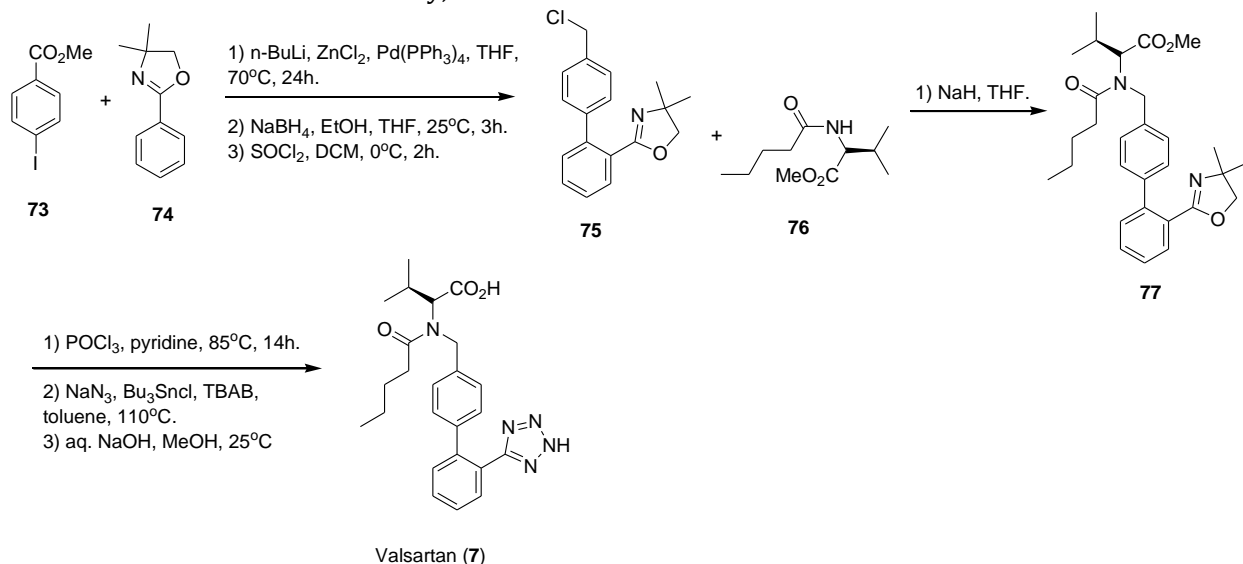
Valsartan (**7**).
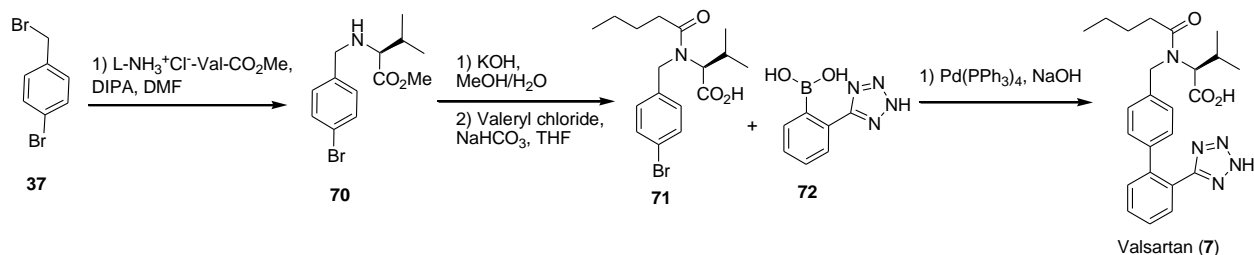
Scheme 14: Synthetic approach toward Valsartan (7)

An efficient synthetic approach toward Valsartan was reported by Penikelapati *et al* (Scheme-15) [26]. Intermediate **75** prepared from iodo compound **73** and dihydro oxazole **74** was N-alkylated with methyl-N-pentanoyl-L-valinate to afford intermediate **77**. Finally, the

synthesis was completed by conversion of dihydro oxazole in **77** to its corresponding nitrile followed by incorporation of tetrazole with sodium azide and hydrolysis of its ester produced Valsartan (**7**).

Scheme 15: An efficient synthetic approach toward Valsartan (7)

CONCLUSION

Although Sartans originated as lifesaving drugs by reducing the risk of heart diseases, they are also known to produce minor side effects such as hyperkalemia, renal failure, dizziness and hypotension. The research efforts are being carried out in the discovery and development of few new non-peptide ARB's and some of them are also undergoing clinical trials or at preclinical stages namely Embusartan, Fonsartan, Pratosartan, etc [27]. The present review article emphasizes broadly over several scalable approaches carried out toward the syntheses of various Sartan drugs which

are commercially available in the market and this should serve the purpose for those who aspire to come out with cost effective, ecofriendly and robust alternative approaches towards synthesis of existing Sartan drugs. This article also provides a way forward for new insights in design and development of new upcoming Sartan drugs. There also a broad scope in the development of Sartan drugs and further research is needed to come out with new Sartan drug hybrids which can reduce the risk of hypertension related heart diseases with minimal or zero side effects, caused with their intake.

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