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A Quick, Simple, and Specific Stability Indicating RP-HPLC technique for Determining Valsartan in Pharmaceuticals was developed and the validated.

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ABSTRACT:

The aim of this paper is to define and improve the technique of (HPLC), which is the high-performance liquid chromatography, technique for estimating Valsartan in pharmaceuticals. Methodologies: The results of the reversed-phase HPLC (RP-HPLC) process were used to evaluate the type of Valsartan. Chromatographic analysis was carried out using an HPLC-UV method along with an Ion Pac column (Arcus EP-C18; 5 m, 4.6 mm, 250 mm) and a mobile phase of Methanol: chloroform (25:75) and 1 mM acetic acid, pH 3.3, at a flow rate of 1.0 ml/min. At 400 nm, UV detection was employed in the HPLC method. Exactness, precision, particularity, linearity, and affectability were all accepted for the technique. The Valsartan had a maintenance time of (3.55-4.35) minutes. The Valsartan alignment plots were right over the target ranges of 1–5 g/L. The quantitation limit was 0.85 g/ml, with a detection limit of 0.33 g/ml. The precision of the proposed procedure, which ranged from 96.0 percent to 100 percent, was determined through recovery experiments. Conclusion: The modern HPLC-UV approach was used to analyze generic drug products under the Iraqi Ministry of Health's registered trademark, and the planned technique's efficiency was confirmed. The study's findings show that precision, accuracy, and efficiency are all within reasonable limits, so there is no substantial difference between the values obtained using the proposed methodology and those obtained using the traditional method.

Keywords: Valsartan chromatographic, Valsartan Degradation, Valsartan Crud**.**

1- INTRODUCTION:

The chemical name AUPIC for Valsartan: [N-((2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-N-pentanoyl-L-valine], $C_{24}H_{29}N_5O_3$, Mol.Wt.435.519 g/mol).

Valsartan is a light white crystalline powder that is odorless and soluble in water, ethanol, chloroform, and soluble acetone. It has a melting point of 684.9°C and a structural structure as shown in Figure 1.

Valsartan (brand name: Diovan) is a drug in the group of angiotensin II receptor antagonists (usually called ARB, or angiotensin receptor blocker), and valsartan is a selective type (AT1) of Angiotensin-converting enzyme inhibitor that is employed in general to treat high blood pressure, heart failure, and diabetic neuropathy. Produced by the Swiss company Novartis.

Valsartan is being utilized in general to treat elevated blood pressure, congestive heart failure, and to lower mortality rates in patients who have had a heart attack and have left ventricular dysfunction. Valsartan is employed also to treat high blood pressure, and vasartan has a special mechanism of action that blocks angiotensin 2 receptors.

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Angiotensin II is a substance in the body that promotes constriction of blood vessels. Restricting the activity of this substance enables blood vessels to dilate.

Valsartan is also effective for treating heart failure, and is given to patients who cannot tolerate drugs that are part of the ACE inhibitor family of angiotensin converting enzyme (ACE) inhibitors)converting enzyme inhibitors Angiotensin: ACE -I) such as enalapril and Captopril due to side effects such as coughing or angioedema.

A stronger antihypertensive effect can be achieved when a low dose of the diuretics (Diuretics) is added to valsartan. Valsartan is also available in combination with hydrochlorothiazide.

Valsartan is an orally administered antagonist that works on the ATI receptor subtype. The drug valsartan, as previously mentioned, is being employed in particular to treat high blood pressure. Any use of valsartan for the treatment of diabetes-related hypertension is covered by U.S. Pat. No. 6,395,728. The patents 6,465,502 and 6,485,745 are for the use of valsartan to treat lung cancer. U.S. Pat. No. 6,294,197 is about solid oral dosage forms of valsartan. This paper incorporates those patents explicitly.

1.1- synthesis of valsartan

United States Patent No. 5,399,578, which is adopted herein in its totality by reference, discusses the synthesis of valsartan, among other things. The last synthetic step (excluding work-up and purification) in the synthesis disclosed therein is the reaction of a cyano group on the biphenyl ring with an azide, such as tributyl tin azide. The '578 patent's reaction scheme is as follows**:**
2- The current study aim was to establish and validate an RP-HPLC system with an ultraviolet (UV) detector for quantitative Valsartan determination in pharmaceuticals.

3- Experiment:

Tools:

Completely automatic digitalcomputer control is standard on the LC-100 series S-HPLC. Its electronic circuit design, internal mechanical construction techniques, processing technology, cinematography workstation functions, and technical requirements make it one of the most stable and reliable instruments availableA double-beam optical spectrometer (Angstrom Advanced Inc.USA), a sort UV-100 PC with a 1 cm light frequency quartz cell, and an IBM compatible PC make up the LC100-style HPLC-UV. The replica was made out of UPVC. PLS Toolbox for Matlab R2003b, VP pumps, and a UV indicator with variable frequency programming, as well as PLS Toolbox for Matlab R2003b, chemometric techniques, and the halfway least squares process, were all great (PLS). An Angstrom Developed Inc. LCsolution programming tool was used to coordinate peakareas. An Ion Pac segment and an ArcusEP-C18 analyticalcolumn were used to conduct the chromatographic separation and measurement at room temperature (250 mm 4.6 mm; molecule size 5 m). Before being injected into the HPLC device, drug standard and tablet test arrangements were processed via a millipore layer channel in the portable stage [10-12].

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CHEMICALS AND REAGENTS

3.2.1-Pure Standard

Valsartan with a quality assertion of 99 percent, granted by Industries Pharma SamarraAlfayhaa®Iraq under the number DH02821114, for medical devices and pharmaceuticals, depending on the company's factory certificate. Valsartan- TAJ pharma-tablets, INDIA.

3.2.2-Market Sample

Valsartan- TAJ pharma-tablets, INDIA, contains 40 mg per TAJ pharma-tablets ® tablet.

3.2.3. Set up the Samples for Measuring

• Sigma-Aldrich® HPLC grade solution

• To prepare a concentration of 1 mg/ml from Valsartan, stock standard solutions were prepared in Methanol: chloroform (25:75) and 1 mM acetic acid at pH 3.3.

• Valsartan (standard solution) concentrations of 1.0, 2.0, 3.0, 4.0, and 5.0 g/ml were prepared in Methanol: chloroform (25:75) and 1 mM acetic acid at pH 3.3.

3.2.4-Modernization example

To conduct sample Modernization, various examples of Valsartan -Samarra® tablets containing known amounts from standard Valsartan -25mg tablets developed by Samarra® were added to the streamlined PLS alignment package. One known emphasis on three oblique convergences of measures, each of which was divided into different groupings, was included as a justification for performing the fundamental modification and the updated example's precognitive capacity was assessed using outer approval tests, then figure out how to conduct test refreshing for each section using the produced strategy. In the RP-HPLC, three centralizations of additional refreshing examples were used.

4- Procedure:

4.1. Standard Drug Remedy

In traditional setups, the mobile phase is commonly used as a solvent. Dissolving a clearly specified quantity of Valsartan (50 mg) in 100 ml of flexible stage in a 250 ml volumetric flagon yielded a normal stock arrangement of Valsartan (500 g/ml). The cup was therefore made suitable using the portable stage. Valsartan working standard arrangements (1, 2, 3, 4, and 5 g/ml) were created after the stock arrangement was adequately undermined with the changed number.

4.2- Chromatographic Parameters

Table 1 shows the critical parameter values acquired by utulizing reverse-phase chromatography process. (High-performance liquid chromatography, or RP-HPLC).

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4.3- The proposed strategy's Calibration Curve

Alignment bends were prepared over a focus range of 1–5 g/ml for Valsartan. The three-fold arrangement was prepared, and 20 l of each arrangement was injected onto the section. At 400 nm, the pinnacles were resolved. Valsartan's adjustment bend was created by plotting the pinnacle zone versus concentration.

4.4- Exercising Degeneration Research [13-20]

Different ICH-recommended pressure conditions, such as acidic, basic, oxidative, wet, and photolytic effort, were used in the effort degeneration studies.

4.4.1. Acid degeneration (section 4.4.1)

In a 100 ml volumetric cup, 60 mg of Valsartan tablet powder was taken. The jar being loaded with 5 mL 0.1 N HCl and held at 70–80 oC in a reflux state for 2–3 hours. The arrangement was killed with 0.1 N NaOH after the strain was reached, and the flexible stage was used to finish the job. Hydrochloric acid can be used to break down Valsartan. Hydrolysis, or water splitting, is one such reaction. ”Any acid or base stimulates amine hydrolysis. [Figure 2].

4.4.2- Base degeneration

By using sources to suppress amine, such as NaOH or potassium hydroxide, the product is amine salt. In a 100 ml volumetric carafe, 60 mg of Valsartan tablet powder was taken. The jar being loaded with 5 mL 0.1 N NaOH and held at 70–80°C in a reflux state for 2–3 hours. A dynamic stage was used to complete the structure after it was killed with 0.1 N HCl and after the pressure was completed [Figure 3].

4.4.3- Oxidative degeneration

In a 100 ml volumetric flask, 60 mg of Valsartan tablet powder and 5 ml of 20% H2O2 were combined. For 2–3 hours, the flask was held at 70–80°C in a reflux state. The jar was finished sufficiently with the portable stage after the pressure culmination [Figure 4].

4.4.4. Degeneration due to photolysis

For the photolytic degeneration analysis, 60 mg of Valsartan e tablet powder is being put in a glass Petri dish and exposed to direct sunlight for 2–3 hours. The tablet powder is being moved to a 100 mL volumetric cup and formed suitable with the portable amount after applying pressure. The solution's infrared spectrum is then examined. Figure 5 shows how the HPLC-UV peaks are unstable and often overlap, this decomposition process results in partial disintegration of the Valsartan compound and uncontrolled interaction with pharmaceutical additives.

4.4.5. Thermal degeneration

60 mg Valsartan tablet powder was baked for 2–3 hours at 105°C in a glass Petri dish. In a 100 ml volumetric flask, the tablet powder was dissolved and a solution was composed. to the stain after a given time with the handheld portion. Controlling the Valsartan's synthetic structure and thus achieving complete thermal dissolution of the compound becomes difficult as the temperature of the Valsartan solution rises above 100 oC, as it is appeared in Figure 6.

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4.5-Valsartan Infrared Spectrophotometer [21-25]

In the shape of a potassium bromide plate, the compounds are prepared. KBr's infrared measurements were performed at Basra University / College of Education for Pure Sciences in the area (4000500 cm-1) at room temperature with a system of the type FTIR-84005-SHIMADZU, made in Germany. The active groups can be seen in the FT-IR spectrum of the compound valisartan (Fig. 7).

4.5.1- For Valsartan-Standard

Valsartan -Standard's infrared spectrum, important peaks for stretching and bending vibrations can be seen in [Figure 8, Table 2], which are compatible with the structure. Standard-FT-IR Valsartan's spectrum appears to be small, with peaks at 3415 cm-1 (M)for (OH) Carboxylic acids and 1604 cm^{-1} (S) for (C=O) Carboxylic acids, the 1730 cm^{-1}(S) for (C=O) Keton, the 1205 cm^{-1}(M) and 759cm^{-1}(M) for (C−N), the 1467cm^{-1} (M) for(C=N), the 3415cm^{-1}(m) for (N−H), Aromatic stretching of C-H is allocated to 3062 cm-1(W), while aliphatic stretching of C-H is allocated to 2962 cm-1(M). Aromatic C=C peaks occur in the range 1411 cm-1 (M).

4.5.2- For Valsartan -Sample

The Valsartan sample's infrared spectrum [Fig. 9, Table 2] displays peaks that correspond to the standard model's peaks, with vibrations that lead to the structure's extension and curvature Standard-FT-IR Valsartan's spectrum seems to be small, with peaks at 3460 cm-1 (M) for (OH) Carboxylic acids and 1604 cm^{-1} (S) for (C=O) Carboxylic acids, the 1732 cm^{-1}(S) for (C=O) Keton, the 1205 cm^{-1}(m) and 759cm^{-1}(M) for (C‑N), the 1471cm^{-1} (M) for (C=N), the 3419 cm^{-1}(m) for (N−H), Aromatic stretching of C-H can be assigned to 3059 cm-1(W) and aliphatic stretching of C-H to 2962 cm-1(M). Aromatic C=C peaks occur in the range 1409 cm-1 (M).

5-Debate on the Findings:

5.1- Improvements to HPLC conditions

To isolate all of the degradation products from the Valsartan peaks, chromatographic conditions were established. The Ion Pac Arcus EP-C18 has a length of 5 meters, a diameter of 4.5 millimeters, and a diameter of 250 millimeters, as well as the requisite organic step. Methanol, was used in several trials, during the process of HPLC technique optimization: chloroform(25:75) and 1 mM acetic acid at pH 3.3 and 1 ml/min flow rate during the process of HPLC technique optimization: chloroform(25:75) and 1 mM acetic acid at pH 3.3 and 1 ml The wavelength was measured to be 400 nanometers [26]. Valsartan had a retention time of 3.55-3.78 minutes. The new analyticcal method produced a good peak shape [Figure 10].

5.2- Suitability of the System

The HPLC-UV device was subjected to research in order to adapt it. Three replicas of the same concentration were repeated using the ideal method using the normal Valsartan (3 g/mL). The machine suitability is shown in Table 3. These findings follow the separation method's criteria as well as Valsartan estimates in different pharmaceuticals[27].

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5.3. The Validation of Methods and Assays

Specificity, linearity range, and sensitivity, as well as regression, precision, accuracy, and rigidity, were employed specifically in order to validate the new chromatographic technique HPLC-UV in accordance with ICH: To determine process validity, the impact of experimental conditions on the peak areas of the analytes was investigated. At a Valsartan concentration of 3 g/ml, the technique's validity was checked. Table 4 listed all of the research results. The results showed that minor changes in flow rate, mobile phase work of art, temperature, and detection wavelength had no impact on the drug peak areas, indicating that the method was valid.

5.4-The Specificity

Forced deprivation was used to investigate the specificity of the proposed plan. The research was carried out to ensure that During the forced degradation analysis, Valsartan could be distinguished from the potential degradation products using the proposed process. The tablet sample was tested using acid, base, oxidation, photolysis, and heat at a concentration of 3 g/ml Valsartan. The outcomes of forced decomposition are shown in Table 5. The shapes of chromatograms are depicted in Figures 2-6. The drug's alkaline conditions resulted in the highest percentage of degradation [29]. The lowest percentage of Valsartan degradation occurred when it was exposed to heat and when it was exposed to photosynthesis. Decomposition goods showed a single peak of degradation. Other stress-related degradation products do not interfere with Valsartan identification, so the tool can be used as a stability indicator.

5.5- The Linearity Range and Sensitivity

A solid relationship was formed when the pinnacle regions for the drug were plotted against the medication fixation (g/ml) under ideal test conditions. The target range of valsartan was discovered to be (1–5) g/ml. The following conditions were obtained from the straight relapse investigation of the information:

$y = 0.6x$ ($R^2 = 1.0$) for Valsartan

On the basis of the following assumptions: y = peak area, x = drug convergence (g/mL), and R2 = regression coefficient[30]. The high relapse coefficient estimations with a small catch illustrate the adjustment bend's great linearity, as shown in Figure 11.

5.6-The Regression

Calculating the limit of quantitation (LLOQ) and edge of detection helped determine the proposed process's comprehension (LLOD). The following equations were used to measure the LOD and LLOQ [31]:

LLOD=3.3SD/S; LLOQ=10SD/S

Where SD denotes the drug rejoinder's standard deviation and S denotes the calibration curve's slope. The LLOQ values were found to be 0.85 g/ml, while the LLOD values were 0.33 g/ml. These figures show that the sensitivity of the predicted technique for studying the chosen drug is adequate. The regression statistics of the anticipated method are shown in Table 6 [32].

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5.7- The Precision

Three separate quantities of a recognized volume of standard solution were put to the pre-analysis tablet sample solutions, 10 percent, 20 percent, and 30 percent. The predicted methodology was used to re-analyze the solutions. With a percentage of RSD of 0.3 percent, the percentage recovery was between 96 and 100 percent. The results show that the procedure is very accurate. The non-interference of the excipients was determined by analyzing the analytes to determine the process' selectivity [33]. Table 7 shows a summary of the findings.

5.8- The Precision

Valsartan was analyzed at a concentration of 3 g/ml to determine precision. The precision of the method was checked by using the established technique for estimating Valsartan in pure standard Valsartan three times (n = 3). The method's precision was checked by repeating the Valsartan investigation in tablet samples three times (n = 3). Table 8 shows a summary of the findings. System and method precision percentage RSD values were both less than 0.3 percent, suggesting that the proposed Valsartan investigation strategy is extremely precise [34,35].

5.9- The Applications of Method:

Examining commercially available Valsartan-40 mg tablets was used to test the analytical process (TAJ pharma-tablets, INDIA, claiming to contain 40 mg of Valsartan). The proportion of Standard-Valsartan was discovered to be 100 0.216 percent, while the ratio of Valsartan in Valsartan-40 (Limited TAJ pharma) was discovered to be 99 0.212 percent. This result indicates that the proposed approach was reliable and precise in analyzing Valsartan in dosage types, as shown by the percentage recovery and RSD percent values. The results of the applications were presented in Table 9.

6- CONCLUSION

The presence of Valsartan in two commercial pharmaceutical products was determined using an HPLC system (LC100 Angstrom advanced) with a UV detector in this analysis. This tried-and-true approach is easy to use, low-cost, and only needs a small amount of sample. It also employs an ultraviolet detector, which, due to a single peak in the chromatogram, makes this system extremely sensitive. Since pharmaceutical drugs have such low concentrations, high sensitivity is not needed in this application. The method was validated using HPLC-UV guidelines, and the established technique meets Beer's law for drug fixation in the range of 1.0–5.0 g/mL.

This study shows the critical analytical approach used to determine the existence of Valsartan in the measurements structure in the light of the findings. Easy, accurate, exact, delicate, explicit, rough, and hearty describes the established and authorized HPLC-UV safety showing technique for Valsartan measurement. In this way, the proposed technique can be used on a routine basis to analyze Valsartan in the tablet dose structure.

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8- Efforts of the Researchers

The research was conducted in the College of Pharmacy at the University of Basrah and Southern Technical University. This research took three months to complete with significant and consistent effort, and the results were excellent in terms of evaluating a clear and sensitive method for estimating the DPH.

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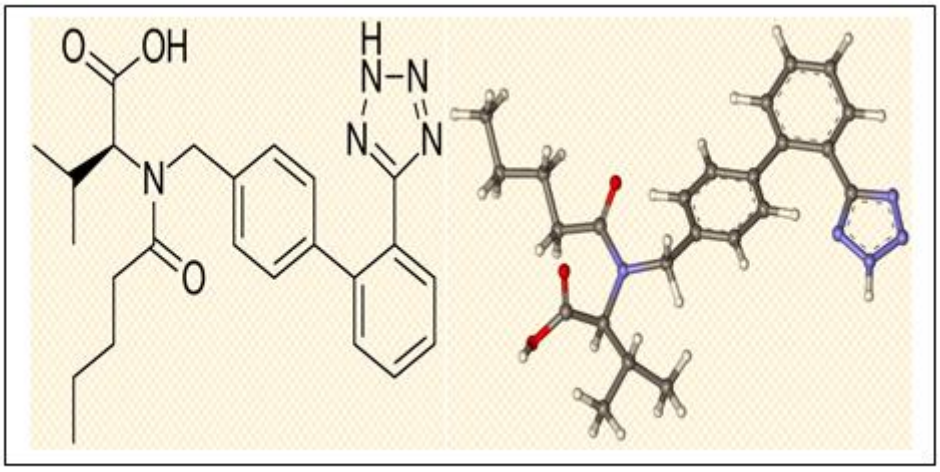
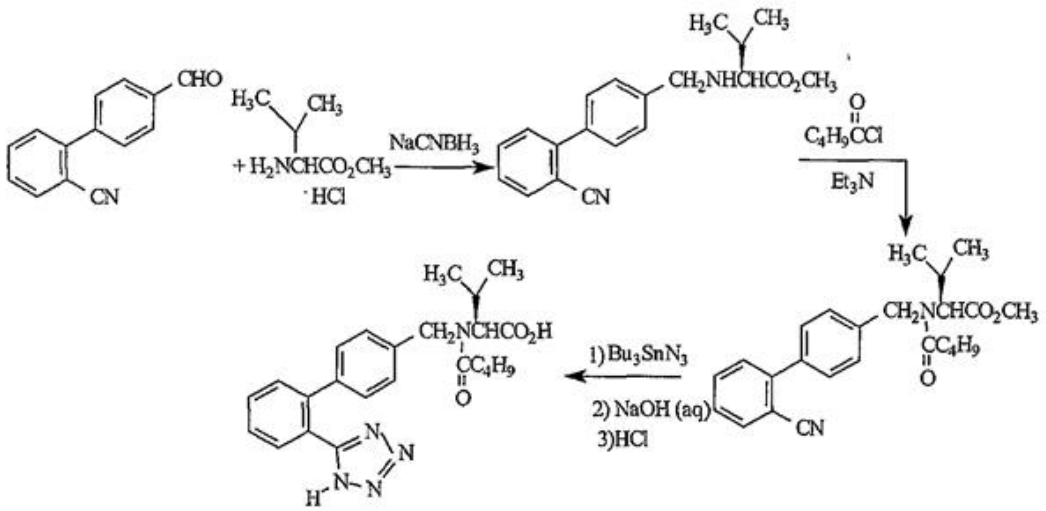


Figure 1: chemical stracture of Valsartan



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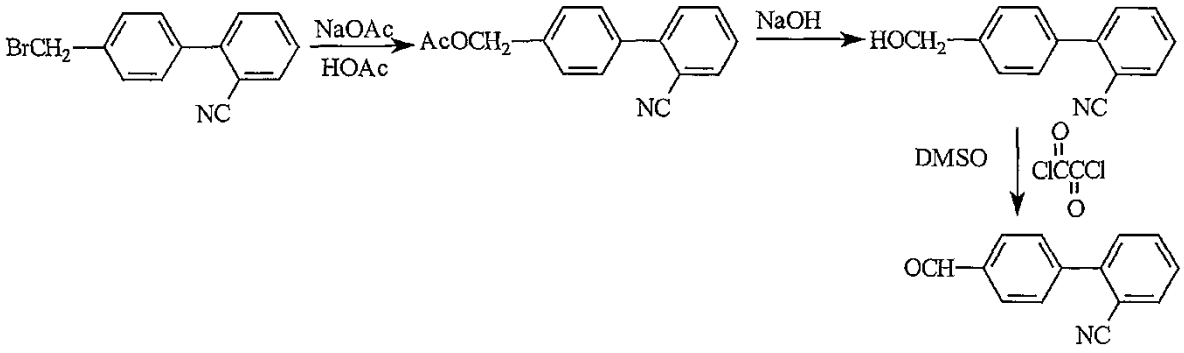
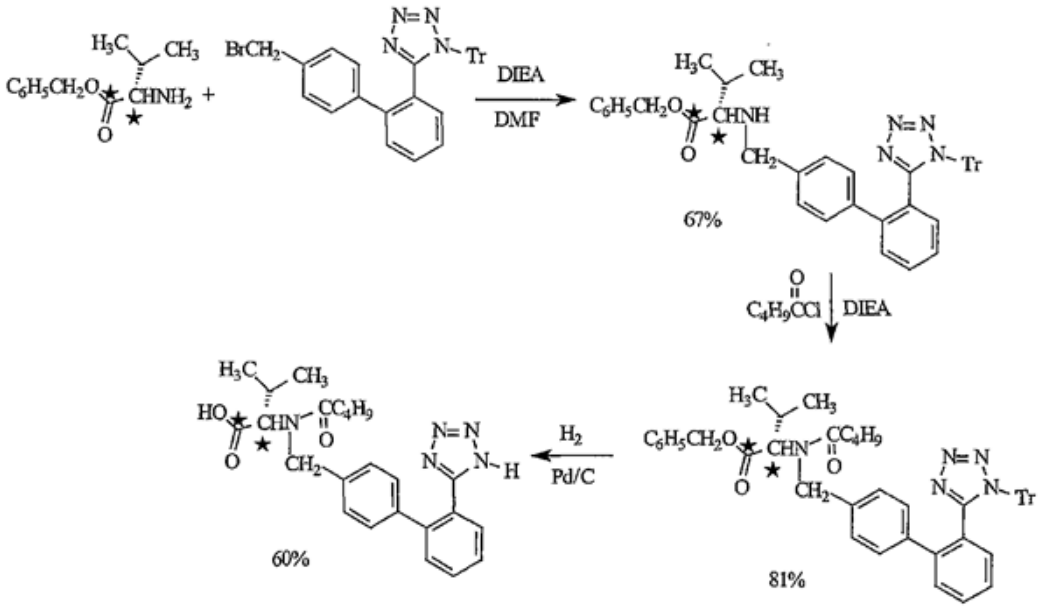
The following is how the '578 patent's starting compound is formed:



Peter Böhlmayer, et. al, Bioorgan. & Med. Chem. Let., 4(1) 29-34 (1994), In Moenius, et. al., J. Labelled Cpd. Radiopharm., 43(13) 1245 - 1252 (2000), various schemes for synthesis of valsartan are provided, with one being:



Another paper, Qingzhong Jia, et. al., Zhongguo Yiyao Gongye Zazhi, 32(9) 385- 387 (2001), discloses a synthesis scheme for valsartan as follows:

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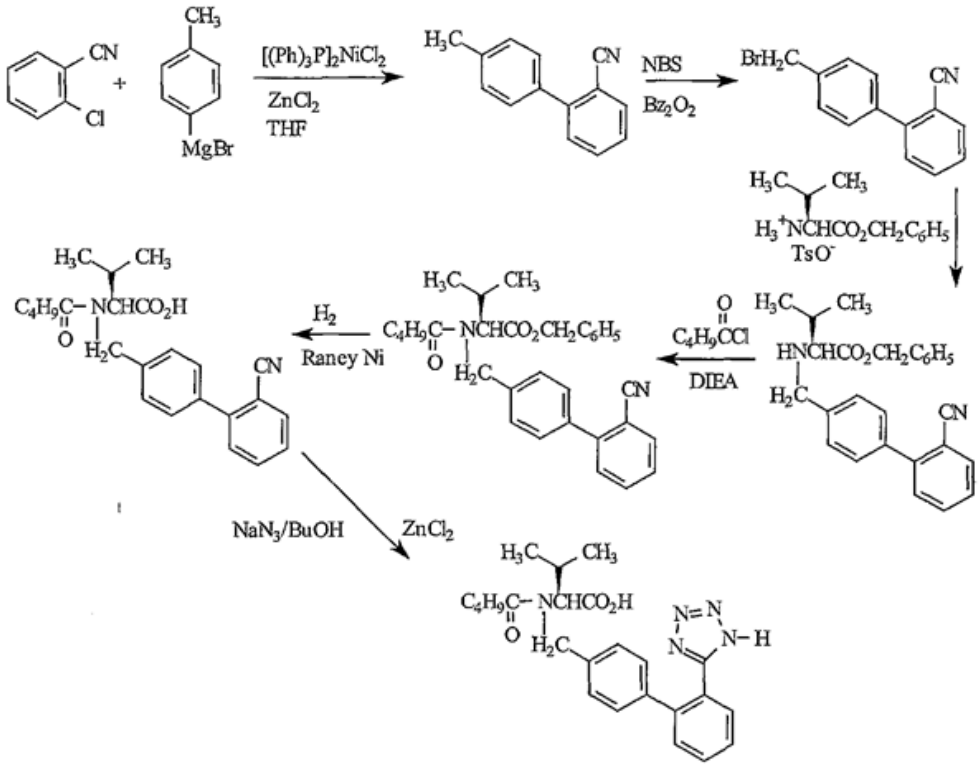

Scheme 1: Synthesis of Valsartan

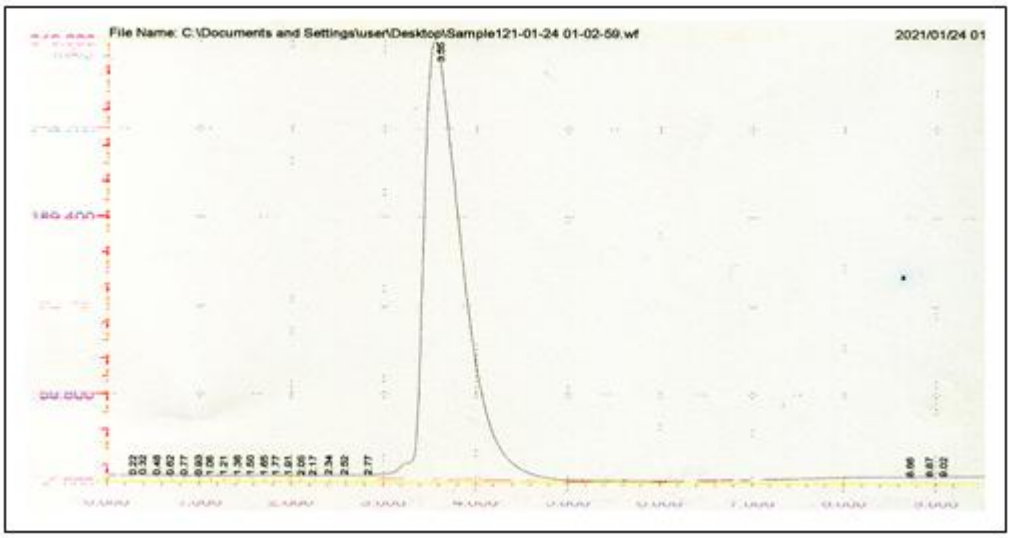

Figure 2: RP‑HPLC Chromatogram of acid degeneration

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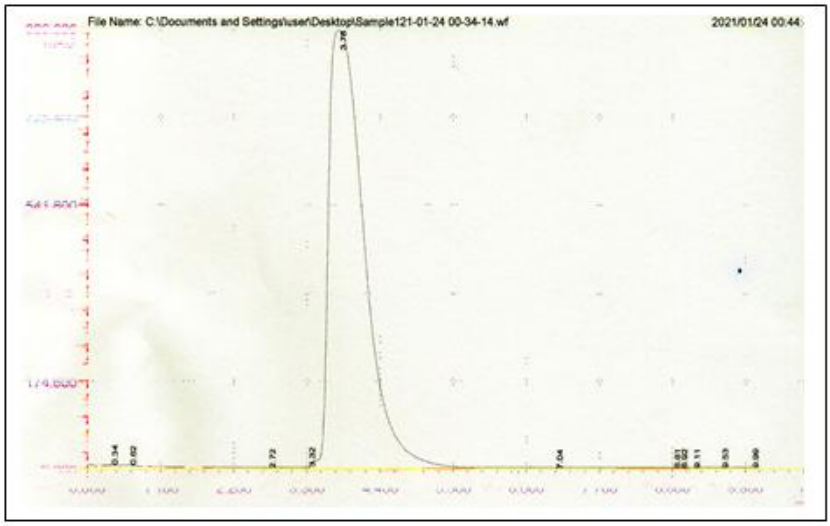

Figure 3: RP‑HPLC Chromatogram of Base degeneration

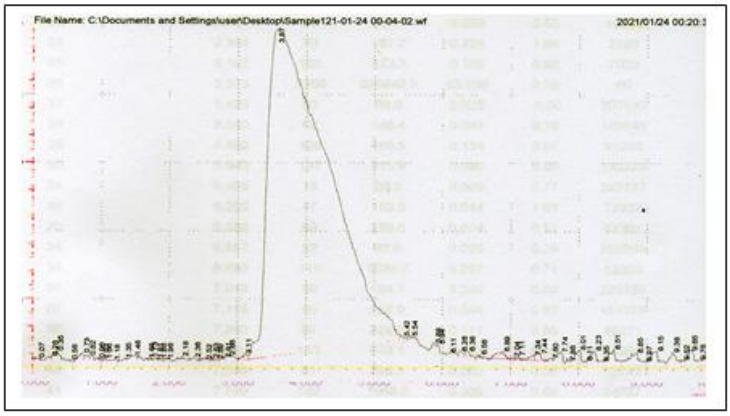

Figure 4: RP‑HPLC Chromatogram of oxidative degradation

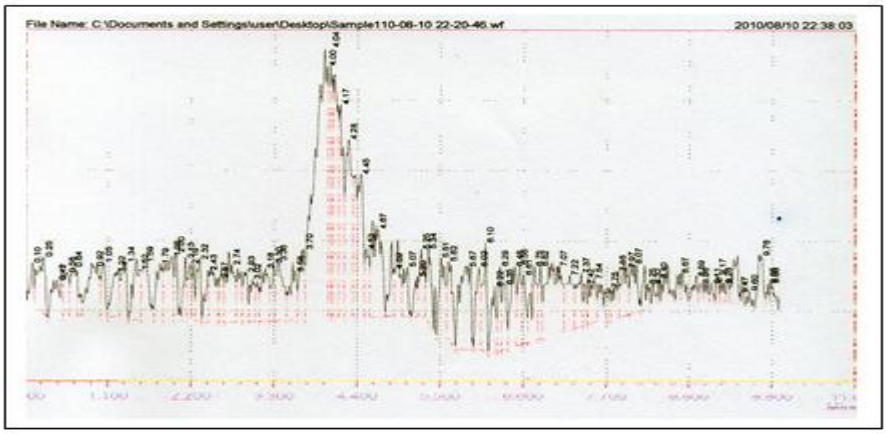

Figure 5: Photolytic degeneration RPHPLC Chromatogram

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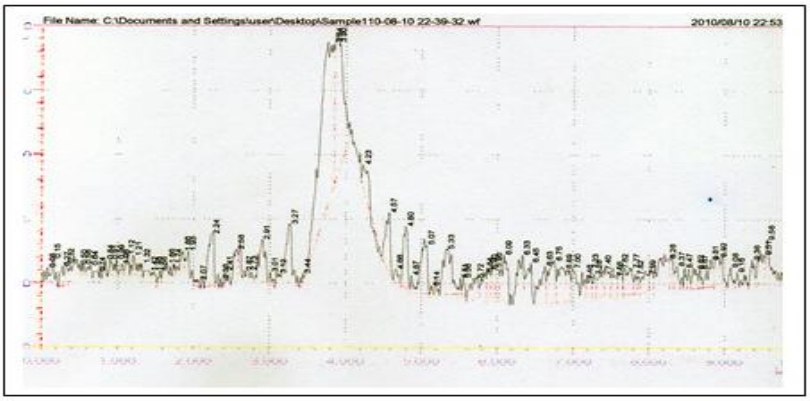


Figure 6: RP‑HPLC Chromatogram of thermal degeneration

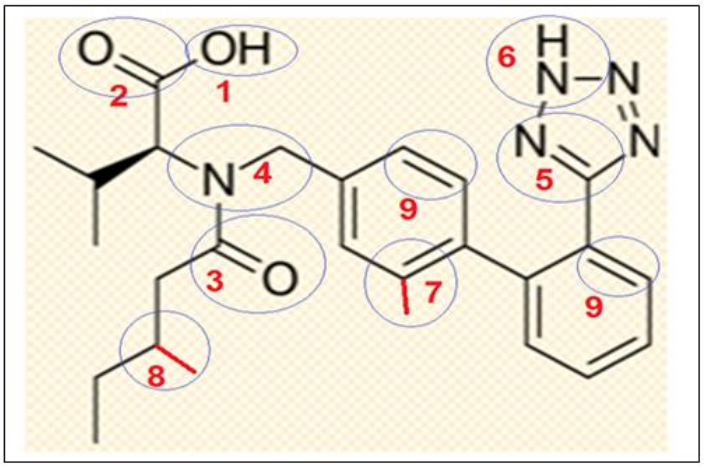
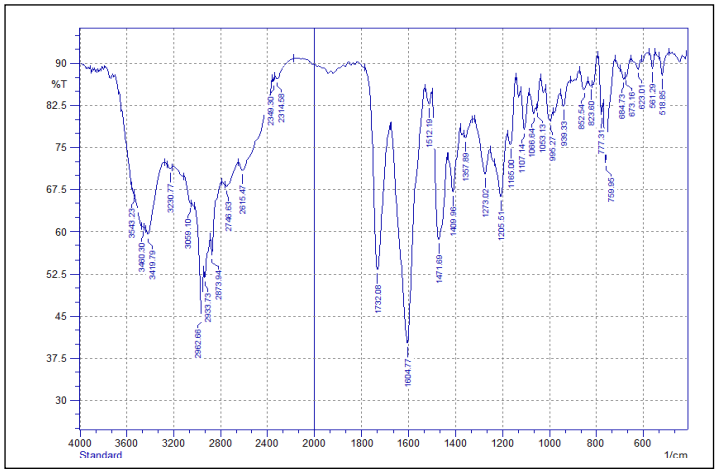


Figure 7: FT-IR spectrum of Valsartan



Notes :- S = strong, M = middle, W = weak

Figure 8: FT-IR spectrum of Valsartan standard

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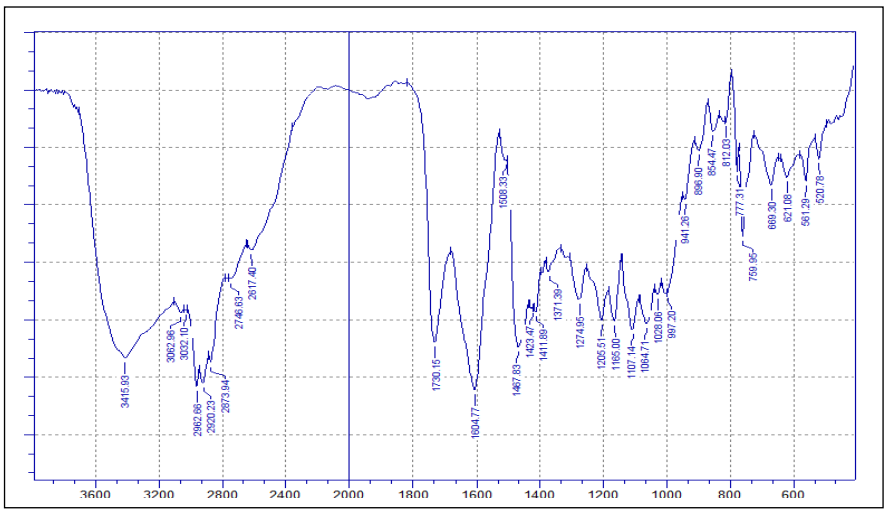


Figure 9: FT-IR spectrum of Valsartan -Sample

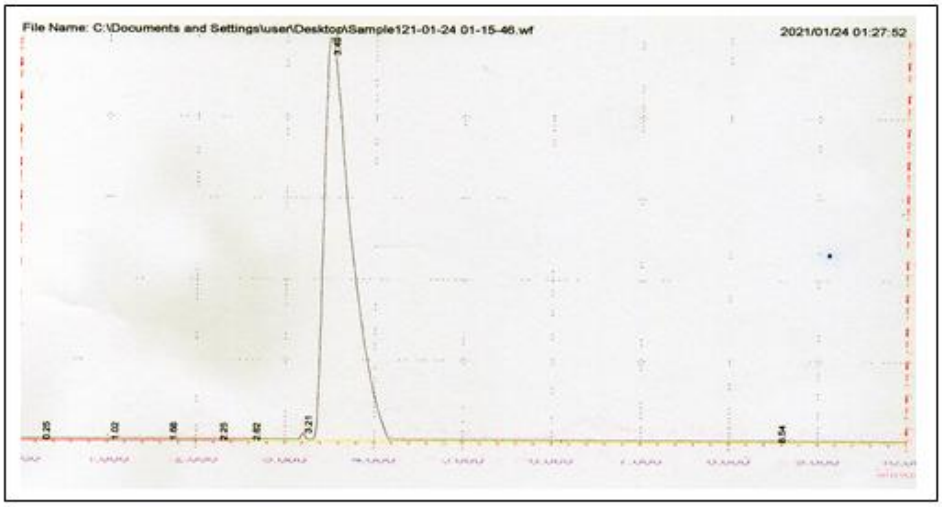
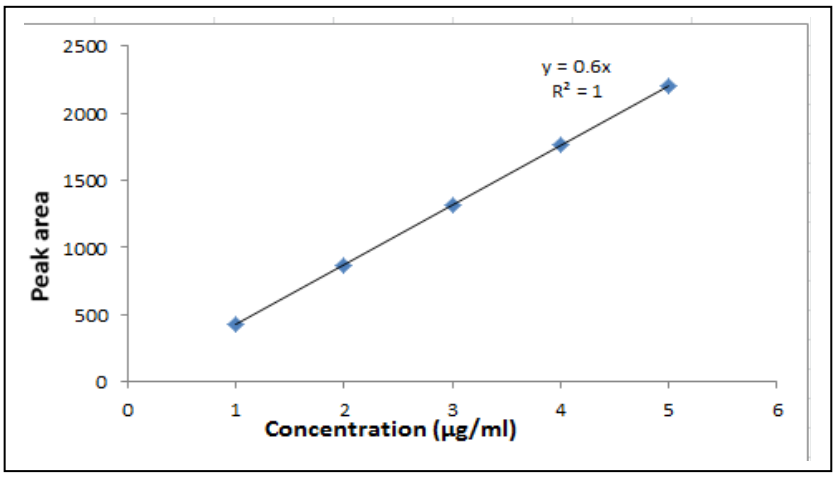


Figure 10: RP‑HPLC Chromatogram obtained after method optimization



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Mobile phase	**Methanol: chloroform (25:75) and 1 mM acetic acid, at pH 3.3**
Flow rate	1.0 ml/minute
Detection wavelength	400 nm
Column temperature	Room temperature
Injection volume	20 µL
Run time	10 min

Table 2: Absorption bands in the infrared spectrum that are characteristic of valsartan

	Functional groups	**Valsartan-sample(cm^{-1})**	**Valsartan‑Standard (cm^{-1})**
1	(OH) Carboxylic acids	3460 m	3415 m
2	(C=O) Carboxylic acids	1604 S	1604 S
3	(C=O) Keton	1732 S	1730 S
4	(C‑N)	1205 m 759 m	1205 m 759 m
5	(C=N)	1471 m	1467 m
6	(N ‑H)	3419 m	3415 m
7	(C‑H) aromatic	3059 w	3062 w
8	(C‑H) aliphatic	2962 m	2962 m
9	(C=C) aromatic	1409 m	1411 m

Table 3: adequacy of the system

Parameters	**Value of Valsartan**	**Recommended limits**
Retention time	2.815 (%RSD 0.289)	RSD≈ 0.101
Peak area	577,025.2 (%RSD 0.223)	RSD≤ 1
USP plate count	1980	≥2000−2500
USP tailing factor	2.14	≤1.9−2.5
Resolution	3.55-3.78 min	≥5

Table 4: Results of method robustness

Parameter	**DPH (3 µg/ml)**		
	Found (µg/ml)	**%Recovery**	**%RSD**
Analyst	3.0	100.0	0.201
System	3.0	100.0	0.992

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Table 5 shows the results of research on forced degradation.

Type of degradation	**Valsartan (60 µg/ml)**	
	%Recovery	**%Degradation**
Undegraded	100	0.090
Acid	98.323	1.241
Base	96.021	4.082
Oxidative	92.944	3.832
Photolytic	90.102	1.666
Thermal	95.541	1.001

Table 6 shows the proposed scheme's regression statistics.

R^2	1.0
Standard error	0.00
Standard error estimate	0.00
Intercept	0.00
Slope	0.6
LLOD (µg/ml)	0.33
LLOQ (µg/ml)	0.85

Table 7 summarizes the accuracy results.

Claimed conc. (µg ml^{-1})	**Found conc. (µg ml^{-1})**	**Recovery±RSD**
1	1.0	100±0.222
2	2	100±0.276
3	2.9	96.6±0.211
3.0 µg ml^{-1} for drugs (Valsartan ‑Samarra® tablets)	3.0	100±0.295

Table 8 shows the findings of precision studies.

Claimed conc. (µg ml^{-1})	**Intraday**		**Interday**	
	Found (µg ml^{-1})	Recovery±RSD%	Found (µg/ml)	Recovery±RSD%
1	1	100±0.222	1	100±0.200
2	2	100±0.276	2.1	110±0.233
3	2.9	96.6±0.211	2.87	95.6±0.201
4	3.88	97.6±0.281	4.1	102±0.204
5	5	100±0.295	4.9	97.4±0.244
3.0 µg/ml drug (Valsartan	3	100±0.295	2.9	96.6±0.283

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-Samarra® tablets)				

Table 9 shows the results of a Valsartan tablet assay.

Analyte	**Labeled claim (mg)**	**Found (mg)**	**Mean (mg)**	**%Recovery**	**%RSD**
Standard - Valsartan	40	40	40	100	±0.216
Valsartan-40	40	39.5	39.75	99	±0.212