

A COMPUTATIONAL AND THEORETICAL APPROACH TO AZILSARTAN: A NOVEL ANGIOTENSIN II RECEPTOR BLOCKERShazia Parveen¹, Najmussehar², Sharique Ahmed³, Nadeem Siddiqui*¹, Vivek Kumar⁴ and Shagufi Nazar¹¹ Department of Pharmaceutical Chemistry, School of Pharmaceutical Education and Research (Formerly Faculty of Pharmacy), Jamia Hamdard, Hamdard Nagar, New Delhi, India.² College of Business, British University of Bahrain, Bahrain.³ Allied Health Department, College of Health and Sports Sciences, University of Bahrain, Kingdom of Bahrain.⁴ Department of Cardiology, Fortis Heart Institute, New Delhi, 110025, India.***Corresponding Author: Nadeem Siddiqui**

Department of Pharmaceutical Chemistry, School of Pharmaceutical Education and Research (Formerly Faculty of Pharmacy), Jamia Hamdard, Hamdard Nagar, New Delhi, India.

Article Received on 09/10/2021

Article Revised on 29/10/2021

Article Accepted on 19/11/2021

ABSTRACT

Hypertension is a global health issue. Azilsartan belongs to a class of drugs known as angiotensin receptor blockers (ARBs) and is used to treat hypertension. Among all ARBs, azilsartan is proven to be more potent till date. Azilsartan is the latest ARB approved for hypertension with greater potency and minimal side effects. The present report is a summary on this class of antihypertensive azilsartan with emphasis on its computational study and spectral prediction.

KEYWORDS: Azilsartan, Antihypertensive, computational, spectral prediction.**INTRODUCTION**

Hypertension is a global health pandemic, if uncontrolled it is leading risk factor for cardiovascular diseases and stroke death.^[1,2] In due course two or more drugs are required for majority of patient to maintain normal blood pressure. In the present era more potent antihypertensive is a favourable sign of treatment. Angiotensin receptor blocker (ARBs) are known to be keystones for management of hypertension. Due to their beneficial profile most practitioners prescribe ARB over ACE as first line treatment.^[3] Azilsartan is a new generation ARB proved to be most potent with minimal side effects. It has strong pharmacological and pharmacodynamic properties as compared to other ARBs in similar doses.^[4,5] Preclinical and clinical studies have shown azilsartan in reducing blood pressure more drastically as compared precursors to it, valsartan and olmesartan.^[6] Azilsartan works by relaxing blood vessels so that blood can flow more easily.

Losartan was one of the first ARB approved for hypertension in 1996. Since then various ARBs were developed. Azilsartan is the latest 8th edition to this armamentarium.^[3] The chronological development order of ARBs are listed in Table 1.

Table 1: Chronological development of ARBs.

NAME OF ARBs	YEAR
Losartan	1986
Valsartan, Candesartan, and Irbesartan	1990
Telmisartan	1991
Eprosartan	1992
Olmesartan	1995
Azilsartan	2011

Drug Profile**Iupac Name:** 2-Ethoxy-3-[[4-[2-(5-oxo-4H-1,2,4-oxadiazole-3-yl)phenyl]phenyl]methyl]benzimidazole-4-carboxylic acid.**Molecular Formula:** C₂₅H₂₀N₄O₅**Molecular Weight:** 456.4 g/mol

The 2D and 3D structure of azilsartan is shown in [Fig.1,2].

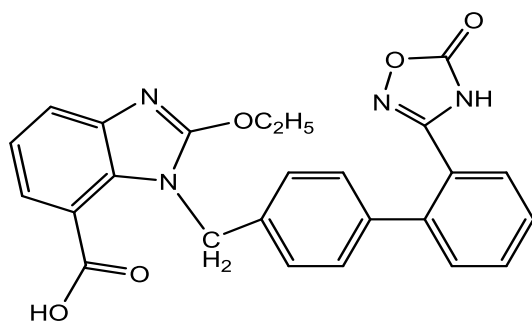


Fig. 1: 2D structure.

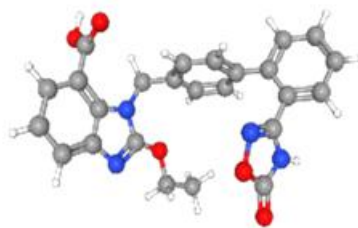
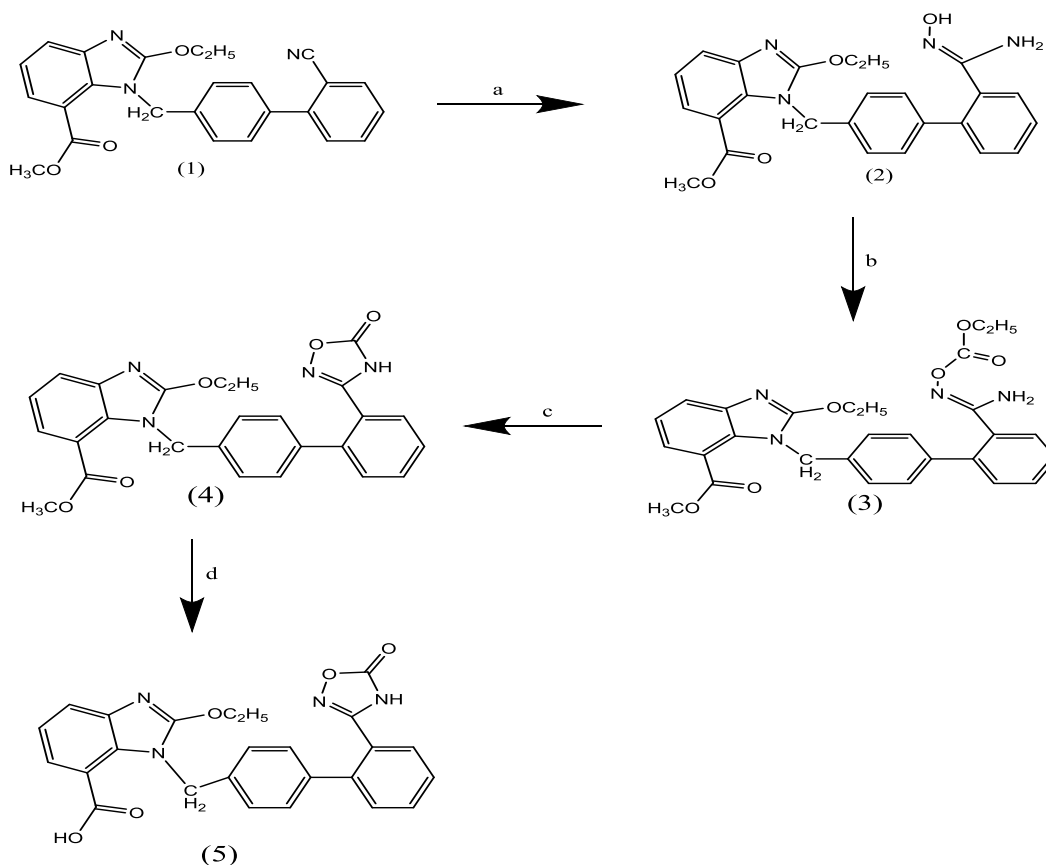


Fig. 2: 3D structure.

Table 2: Azilsartan brands in India.

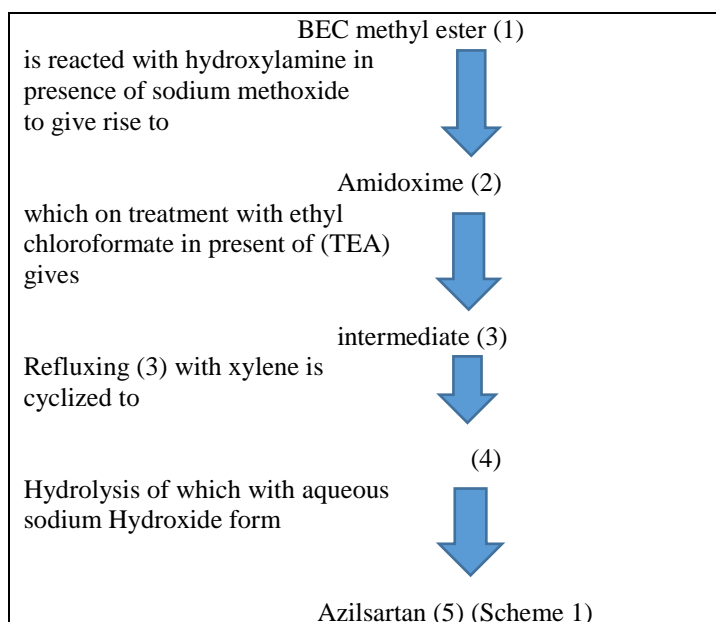
S. NO.	BRAND	MANUFACTURER
1.	AZTRIC	Intas Pharmaceuticals Ltd.
2.	ABEL	Lupin Ltd.
3.	ASAR	Glenmark Pharmaceuticals Ltd.
4.	ALTORAN	Alembic Pharmaceuticals Ltd.
5.	AZARBI	Dr. Reddy's Laboratories Ltd.
6.	ARBAZEAL	Eris Life Sciences Ltd.
7.	AZILDIC	Zydus Pharmaceuticals Pvt. Ltd.
8.	AZILURA	MSN Laboratories Pvt. Ltd.
9.	NEXSART	Macleods Pharmaceuticals Pvt. Ltd.
10.	ZILARBI	Emcure Pharmaceuticals Ltd.
11.	ZILSAR	Torrent Pharmaceuticals Ltd.
12.	ZILOKEM	Alkem Pharmaceuticals Ltd.
13.	ZOLAHART	Mankind Pharm Ltd.
14.	ZILARTA	Micro Labs Ltd.
15.	ZILPRESS	Aristo Pharmaceuticals Ltd.

Synthesis



Scheme 1: Synthetic route for Azilsartan.^[7,8]

Reagent and Conditions: a) $\text{NH}_2\text{OH}\cdot\text{HCl}$, NaOCH_3 , DMSO 55%; b) $\text{ClCOOC}_2\text{H}_5$, TEA, DCM; c) Xylene, reflux, 50%; d) aq. NaOH, 90%



Pharmacodynamic

Recent introduction of azilsartan medoxomil as an eight ARB as a prodrug has achieved approval by FDA in 2011 for the treatment of hypertension. Azilsartan medoxomil an angiotensin II receptor type 1 antagonist is hydrolysed in the gastrointestinal tract after oral administration to the bioactive moiety azilsartan, before systemic absorption.

The renin-angiotensin-aldosterone system is responsible for the regulation of blood pressure and the main pressor agent in it is a peptide hormone, Angiotensin II. This strong vasoconstrictor on binding to angiotensin II type 1 (AT1) results in the synthesis and release of aldosterone raising cardiac stimulus.

The antihypertensive effect of azilsartan medoxomil is produced selectively by blocking the binding of angiotensin II to the angiotensin type 1 (AT1) receptor, thereby antagonizing the pressor response activity of angiotensin II. The mechanism of action is illustrated in [Fig.3]. Azilsartan has minor effects on the levels of potassium and sodium, nor does it bind to any ion channels which are involved in regulating Cardiovascular system.^[9]

Recent literature has also shown that elevated BP was completely antagonized by Angiotensin II with azilsartan resulting prevention of cardiac hypertrophy and reduced renal damage.^[3,9]

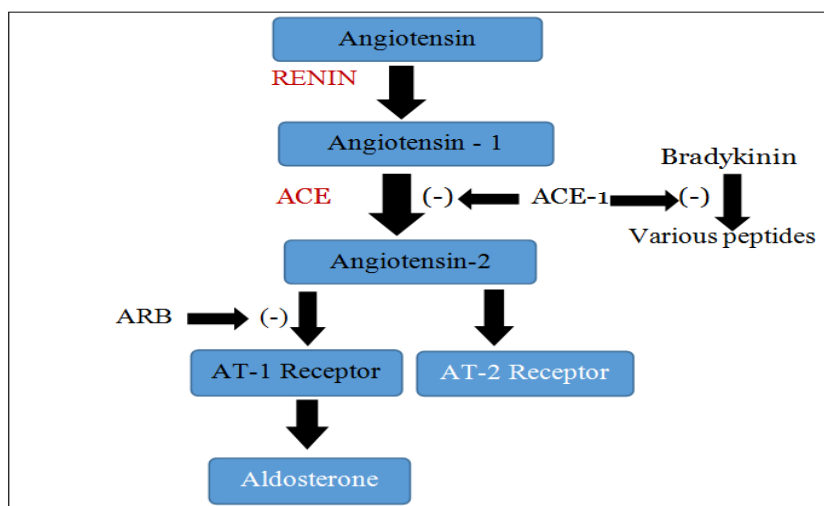


Fig. 3: Mechanism of action of ARB.

Pharmacokinetic

Azilsartan medoxomil is a prodrug which on oral absorption is rapidly hydrolyzed to the active moiety azilsartan in gastrointestinal tract. The bioavailability of the active moiety is approximately 60% which is not affected by intake of food. The peak plasma level (T_{max}) reaches within 1.5 to 3 hours. The drug is highly bound to plasma protein (>99%) mainly albumin and has volume of distribution approximately 16 L. After hydrolysis of azilsartan medoxomil to its active metabolite, it undergoes metabolism to two pharmacological inactive metabolites (M-II and M-I) [Fig. 4].

1. **M-II (Major metabolite):** Formed by O-dealkylation mediated by enzyme CYP2C9 has approximately 50% systemic exposure of azilsartan.
2. **M-I (Minor metabolite):** Formed by decarboxylation mediated by CPYP2C8 and CYP2B6 has systemic exposure of azilsartan less than 1%.

The drug is eliminated approximately 55% in faeces and 42% in urine. Renal clearance of the administered dose is approximately 2.3 ml/min and the half life of elimination after orally administered dose is approximately 11 hours.^[9]

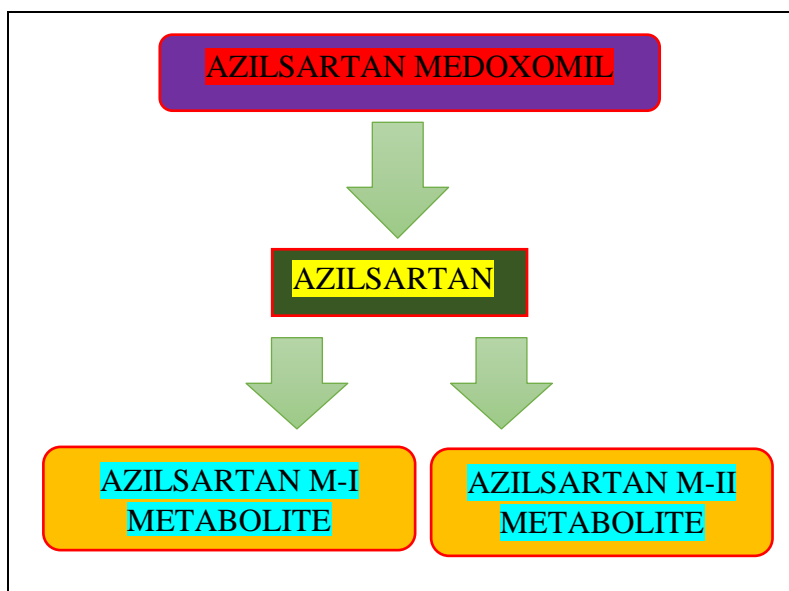


Fig. 4: Metabolism of Azilsartan

Computed and Physiochemical properties

Computed and Physiochemical properties are represented in Table 3,4.

Table 3: Computed Properties.

PROPERTIES	VALUES
Molecular weight	456.458 g/mol
XLogP3	4.4
Hydrogen Bond Donor Count	2
Hydrogen Bond Acceptor Count	7
Rotatable Bond Count	7
Exact Mass	456.143 g/mol
Monoisotopic Mass	456.143 g/mol
Topological Polar Surface Area	115Å ²
Heavy Atom Count	34
Formal Charge	0
Complexity	786
Isotope Atom Count	0
Defined Atom Stereocenter Count	0
Undefined Atom Stereocenter Count	0
Covalently Bonded Unit Count	1
Compound is Canonicalized	Yes

Data obtained from king draw chemical structure editor / PubChem.

Table 4: Physicochemical Parameters.

PROPERTIES	VALUES
Color/Form	Colorless Prism from ethanol
Melting point	212-214 deg C
Solubility	In Water 4.28×10^{-3} mg/L at 25 deg C (est)
Vapor pressure	1.45×10^{-20} mm Hg at 25 deg C (est)
Octanol/Water Partition Coefficient	Log Kow = 6.44 (est)
Stability/Shelf Life	Stable under recommended storage conditions.
Decomposition	Hazardous decomposition products formed under fire condition. – Carbon oxides, nitrogen oxides (NOx). Henry's law constant = 5.45×10^{-20} atm-cu m/mol at 25 deg C (est).
Other experimental properties	Hydroxyl radical reaction rate constant = 5.38×10^{-10} cu cm/mole-sec at 25 deg C (est).

Data obtained from king draw chemical structure editor / PubChem.

Spectral Prediction

The IR value for Azilsartan were theoretically determined from its structure. The predicted ^1H NMR and ^{13}C NMR data was estimated by Chem Draw

professional 16.0 (Fig. 5,6). Mass Spectrometry (MS) obtained by King Draw chemical structure editor version 2.5.4.

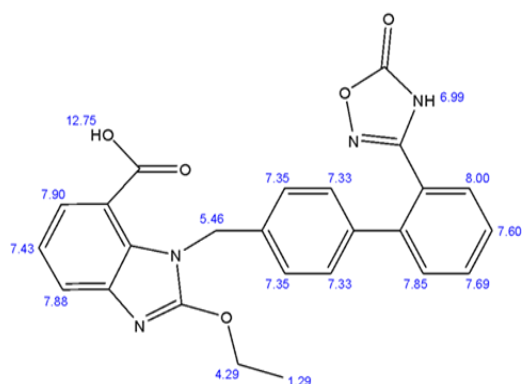


Fig. 5: Chem NMR ^1H estimation.

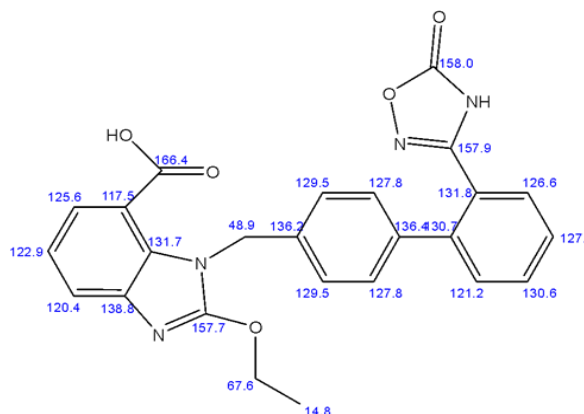


Fig. 6: Chem NMR ^{13}C estimation.

IR (KBr, Cm^{-1}): 3410(NH), 3110(CH-Ar), 2800(CH-Alip), 2700(OH, COOH), 1700(C=O, Oxadiazole), 1620(C=N), 1200(C-N), 1085(C-O, Alip), 1000(C-O, Oxadiazole); ^1H NMR (300MHz, $\text{DMSO}-d_6$, δ ppm): 1.29(s,3H,CH₃), 4.29(q,2H,CH₂), 5.46(s,2H, N-CH₂-Ar), 6.99(s,1H,NH), 7.33-8.00(m,11H,Ar-H), 12.75(s,1H,OH); ^{13}C NMR (75MHz, δ ppm): 14.8,48.9,67.6,117.6,120.4,121.2,122.9, 125.6,126.6,127.7,127.8,127.8,129.5,129.5,130.6,130.7,1 31.7,131.8,136.2,136.4,138.8,157.7,157.9,158.0,166.4;L C-MS(m/z):457.15[M+H]⁺.

Current Prospects

Azilsartan is approved worldwide either alone as a primary or azilsartan medoxomil, a prodrug for the treatment of hypertension. An oxo-oxadiazole ring present in the molecule enhances its lipophilicity and reduces its acidic character than the other ARBs. Apart from control of BP, the efficacy of azilsartan includes cardiac hypertrophy, fibrosis, insulin resistance and stabilization of coronary plaques. Clinical trials have

demonstrated to have more potency on clinical systolic and diastolic blood pressure. Treatment with azilsartan have shown to improve arterial stiffness and also endothelial dysfunction. The drug is prescribed when combination therapy with ARBs fail to control BP. In such instance shifting to azilsartan therapy is admissible stratagem. The plethora of available data on azilsartan is an evidence of its being unique in controlling BP. The drug has now been of first choice by physicians due to its evolution as a potential agent.^[3,10]

CONCLUSION

The surplus evidence on azilsartan reveals its superiority to other angiotensin receptor blockers in management of hypertension. Treatment with AzL-M is the safest and effectual option now a days for lowering of blood pressure. The computative review will be of further utility for QSAR analysis.

REFERENCES

1. Lewington S, Clarke R, Qizilbash Net al, "Age-specific relevance of usual blood pressure to vascular mortality: a meta- analysis of individual data for one million adults in 61 prospective studies," *The Lancet*, 2002; 360: 1903-13.
2. Lim S. S., Vos T, Flaxman AD et al, "A comparative risk assessment of burden of disease and injury attributable to 67 risk factor clusters in 21 regions, 1990-2010," a systemic analysis for the global burden of disease study 2010," *The Lancet*, 2010; 380: 2224-60.
3. Pradhan A, Tiwari A, Sethi R. Azilsartan: Current evidence and perspectives in management of hypertension. *Int. J.Hypertens*, 2019. <http://doi.org10.1155/2019/1824621>.
4. Zaiken CJW. Azilsartanmedoxomil: a new angiotensin receptor blocker. *Clin Ther*, 2011; 33(11): 1577-89.
5. Bakris GL, Sica D, Weber M et al. The comparative effect of azilsartanmedoxomil and olmesartan an ambulatory and clinic blood pressure. *J Clin Hypertens (green wire)*, 2011; 13(2): 81-83.
6. Hjerimitslev M, Grimm DG, Wehland M, Simonson U, Kruger M. Azilsartanmedoxomil an angiotensin II receptor antagonist for treatment of hypertension. *Basic Clin Pharmacol Toxicol*, 2017; 121(4): 225-33.
7. Reddy AVR, Garag S, Takshinamoorthy C, Gupta B, Naidu A. Improved synthesis of azilsartan: Development and control of process related impurities. *Indo-Am J Pharm Res.*, 2015; 5(6): 2208-2216.
8. Kohara Y, Kubo I, Wada T, Inad Y, Naka T. Synthesis and angiotensin II receptor. Activities of benzimidazole derivatives bearing acidic heterocycles as novel tetrazolebioesters: *J Med Chem*, 1996; 39(26): 5228-35.
9. Azilsartanmedoxomil; Uses; Interaction; Mechanism of action. Available from: <https://go.drugbank.com/drugs/DB08822>.
10. Hiremath J S, Hajare AL, Chinchansur SR, Dey A, Jain R. Azilsartan: The novel ARB with unique mechanism of action. *Int JBasic & Clin pharmacol. (IJBPCP)*, 2017; 6(3): 482-86.