CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1035249

Available online at: http://www.iajps.com *Review Article*

RECENT ADVANCES AND APPLICATIONS OF TELMISARTAN

Premchand Patil[1], Deepak V. Nagarale[1,2] and Bhata R. Chaudhari[*2]

[1]Dept. of Chemistry, JET's Z.B. Patil College, Dhule (MS), India

[1,2*]S.S.V.P.S.'s ACS College, Shindkheda, Dist: Dhule(MS), India

Abstract:

Telmisartan is pharmacologically active molecule, Here we reviewed some synthetic methods and their application like angiotensin II receptor, quantitative determination for the biological activity using NMR, restrict NFAT nuclear translocation and etc..

Corresponding author:

Bhata R. Chaudhari,

S.S.V.P.S.'s ACS College,

Shindkheda, Dist: Dhule(MS),

India

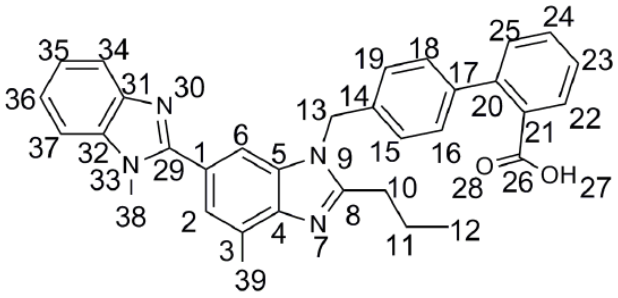
E-mail: brc155@gmail.com, brc15@rediffmail.com

QR code

*Please cite this article in press as Bhata R. Chaudhari et al , **Recent Advances and Applications of Telmisartan** , Indo Am. J. P. Sci, 2017; 4(10).*

INTRODUCTION:

Chemical Nomenclature of Telmisartan (TEL) 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl][1,1'-biphenyl]-2-carboxylic acid (144701-48-4) (Fig. 1). It is an angiotensin II receptor antagonist of PPARγ, influence the expression of PPARγ target genes involved in the regulation of carbohydrate and lipid metabolism and reduces glucose, insulin and triglyceride levels and widely used in hypertensive[1] and non-competitive inhibition [2]. Since TEL has high pharmacologically active with respect to other antihypertensive molecule, it is necessary to identify, characterize and quantify it as an active pharmaceutical ingredient. Several high-performance liquid chromatography (HPLC) and some reverse phase HPLC methods have been reported for a single drug in bulk, pharmaceutical formulation and in combination.[3-7] Ultra performance liquid chromatography (UPLC) and liquid chromatography-mass spectrometry method have also been reported for the quantitative and qualitative analysis for TEL.[8-9]



(a)

Fig-1 Telmisartan (TEL)

Nowadays NMR spectroscopy has found new tool for quantitative for the determination of pharmaceutical potent biologically active molecules in bulk drug and its tablet formulation than the other analytical techniques. Jadeja Y. et al gave Herein, qNMR method was developed for an anti-hypertensive drug, telmisartan in bulk drug and its tablet formulation. The developed method by ^{1}H NMR spectroscopy is comparatively easy and more precise with respect to the other analytical tools. [10]

Telmisartan was known as angiotensin receptor blocker and PPAR-γ agonist with potential anti-inflammatory and metabolic benefits. Catherine N. Le and it's co-workers assessed how telmisartan's produce effect on urine eicosanoids among HIV+ adults with central adiposity on suppressive antiretroviral therapy enrolled in a prospective clinical trial.[11]

Jordan E. Lake et al made a pilot study and they demonstrated that 12 weeks of standard dose telmisartan therapy was related with improved EPC count and EPC commitment to endothelial lineage in grown-up HIV-1-infected individuals with conventional CVD hazard. This study is the first to assess telmisartan's effects on EPCs in HIV infection, and suggests that vascular reparative ability can be modulated in unremitting, treated HIV infection**.[12]**

Telmisartan also restrict NFAT nuclear translocation and ANP/BNP expression. NFAT is an important nuclear transcriptional factor to take part in cardiac hypertrophy [13] Thus, Pu WT et al were investigated whether telmisartan inhibited NFAT nuclear translocation. There are five subtypes of NFAT in cardiomyocytes, however, it is thought that NFATc3 and NFATc4 are the majority expressed in cardiomyocytes, and therefore NFATc3 and NFATc4 may be the two most important subtypes [14].

The study done by Xiurong Li et al demonstrated that telmisartan suppressed cardiomyocyte hypertrophy in vivo and in vitro, effectively by suppressing cardiomyocyte ANP/BNP expression and apoptosis, which may be lie on the inhibition of NFAT nuclear translocation. These results may provide a unique insight into the mechanism of telmisartan- induced cardiomyocyte hypertrophy inhibition [15]

It was also seen that the Telmisartan suppresses the development of endometriotic lesions. but, the drug furthermore up-regulates the expression of cyclooxygenase (COX)-2, which has been suggested to promote the progression of endometriosis. Accordingly, we herein analyzed whether a combination therapy with telmisartan and a COX-2 inhibitor may be more effective in the treatment of endometriotic lesions than application of telmisartan alone. Telmisartan-treated lesions exhibited a extensively minimized lesion volume when compared to vehicle-treated controls and parecoxib-treated lesions. This inhibitory effect of telmisartan was even more pronounced in combination with parecoxib. The combination therapy resulted in a reduced microvessel density as well as lower numbers of proliferating Ki67-positive cells and higher numbers of apoptotic cleaved caspase-3-positive stromal cells within the lesions. This was associated with a lower expression of COX-2, matrix metalloproteinase (MMP)-9 and p-AKT/AKT when compared to controls. The application of the two drugs further inhibited the in growth of nerve fibers into the lesions[16]

J. Zhang and co-workers utilized computational techniques for the sake of details on the binding interactions and conformational stability. In past

angiotensin II receptor blockers not only antagonize angiotensin II type 1 receptor (AT1R), but also exert stimulation in peroxisome proliferator-activated receptor γ (PPARγ) partial start, among which telmisartan showed the finest. Telmisartan has been tested as a bifunctional ligand with antihypertensive and hypoglycemic activity. Aiming at more potent leads with selective AT1R antagonism and PPARγ partial agonism, the three parts of telmisartan including the distal benzimidazole ring, the biphenyl moiety, and the carboxylic acid group experienced modification. Standard precision docking analysis and absorption, distribution, metabolism, excretion, and toxicity prediction received 10 molecules with higher Glide scores, similar interactions, and improved pharmacokinetic profiles compared to telmisartan as shown in fig.2 [17]

Anjali Sharma et al were studied S-TEL-PEG-CNPs which shown promising consequences in preliminary investigations for the treatment of cervical cancer through non-invasive intravaginal route. S-TEL-PEG-CNPs have shown promising consequences in preliminary investigations for the treatment of cervical cancer through non-invasive intravaginal route.[18]

M. Kaur et al investigated soluble telmisartan [19] was encapsulated in poly (ethylene glycol) grafted chitosan nanoparticles (S-TEL-PEGCNPs) by ionic gelation method [20]. In addition, telmisartan loaded poly (ethylene glycol) conjugated chitosan nanoparticles (TEL-PEGCNPs) and blank chitosan nanoparticles (PEG-CNPs and CNPs) were also formulated for comparative studies. Initially, acetic acid functionalized poly (ethylene glycol) (mPEG-CH2COOH) was conjugated to primary amine group of chitosan by activating the carboxylic acid terminus [21]. The conjugation reaction was confirmed by FT-IR spectroscopy.

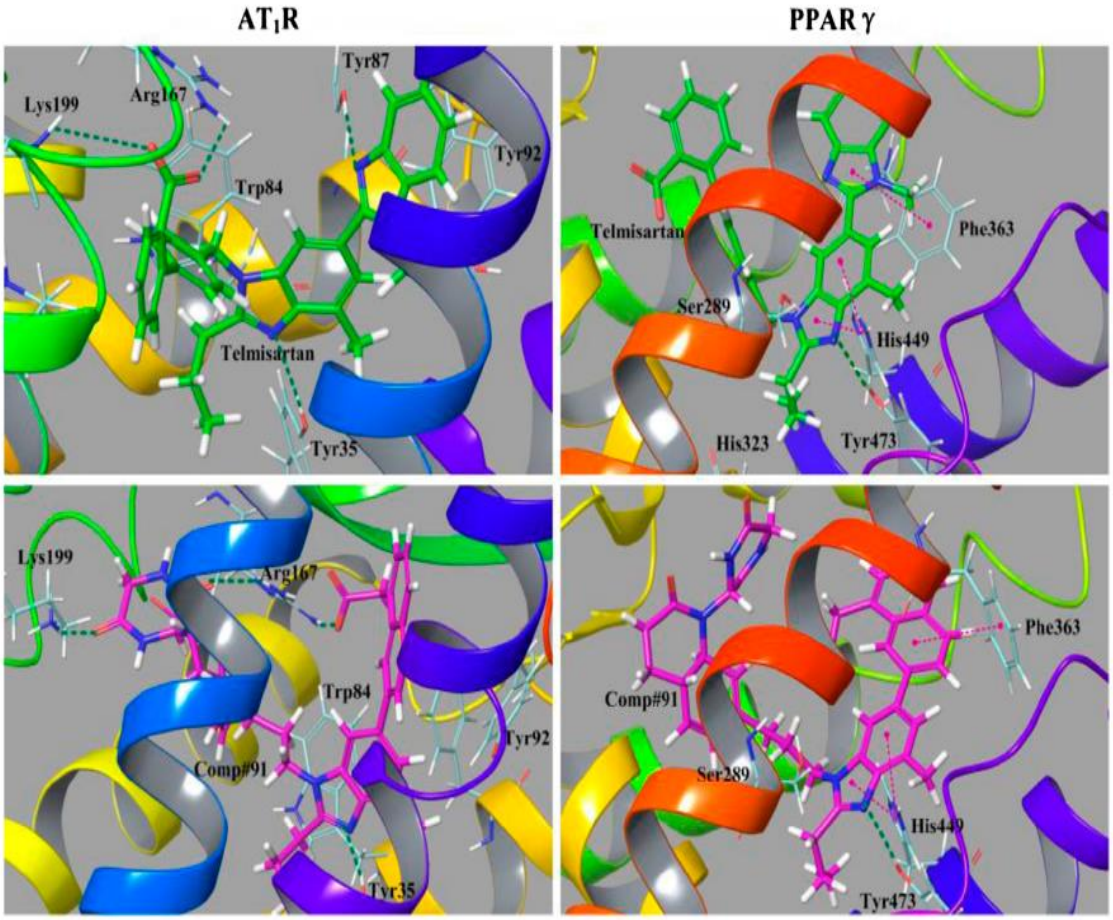


Fig-2: The interactions of telmisartan AT1R (left) and PPARγ (right) ligand-binding pockets

Table 1
Fourier-transforms infrared (FT-IR) spectroscopy of tailored samples measured in the range of 4000–500 cm^{-1}.

Sample	Peaks	Assignment
Chitosan	3460 cm^{-1}	(–NH_2 and –OH stretching)
	1602 cm^{-1}	(–NH bending)
mPEG-CH_2COOH	2884 cm^{-1}	(–CH_3/–CH_2 group)
	1740 cm^{-1}	(–COOH group)
mPEG-CH_2CONH-Chitosan	3467 cm^{-1}	(–CONH stretch)
	1660 cm^{-1}	(–CONH bond)
S-TEL	3058 cm^{-1}	(Aromatic C–H stretching)
	1652 cm^{-1}	(H–O–H bonding)
	1014 cm^{-1}	(C–O–C bonding)
PEG-CNPs	2976 cm^{-1}	(CH_3–stretching)
	1655 cm^{-1}	(–$CONH_2$)
Physical mixture	3401 cm^{-1}	(OH–stretching)
	2972 cm^{-1}	(CH_3–stretching)
	1010 cm^{-1}	(C–O–C bending)
S-TEL-PEG-CNPs	3335 cm^{-1}	(OH–stretching)
	2891 cm^{-1}	(CH_3–stretching)
	1009 cm^{-1}	(C–O–C bending)

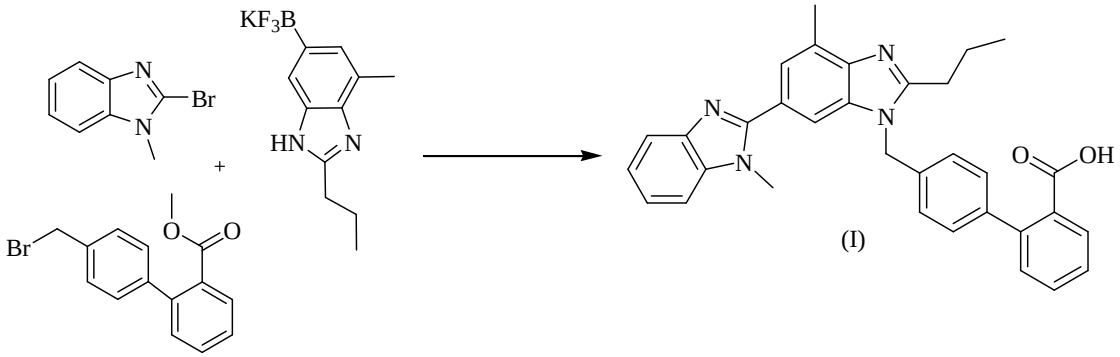
Note: S-TEL: soluble telmisartan; PEG-CNPs: poly (ethylene glycol) grafted chitosan nanoparticles; S-TEL-PEG-CNPs: soluble telmisartan loaded poly (ethylene glycol) grafted chitosan nanoparticles.

Pinaki Sengupta et al developed and validated a high throughput LC-MS/MS method for simultaneous quantitation of pioglitazone and telmisartan in rat plasma. This developed method is more sensitive and able to quantitate the analytes in relatively shorter period of time compared to the previously reported methods for their individual quantification. Moreover, till date, there is no bioanalytical method available to simultaneously quantitate pioglitazone and telmisartan in a single run. The method has been validated according to the USFDA guidelines for bioanalytical method validation.[22]

Telmisartan (TLM), an angiotensin type 1 receptor blocker (ARB) antihypertensive has been shown to have significant PPAR-γ receptor activation capacity [23-25]. Amongst all the tested antihypertensive agents, the binding affinity for TLM to PPAR-γ has been reported to be the highest. Due to this 3 uniqueness, TLM shows beneficial antidiabetic effects in diabetic patient independent of their antihypertensive effects [26-27].

Telmisartan although reduces glucose levels and improves beta cell mass but the effect is statistically non-significant as compared to pioglitazone. In hypertensive type 2 diabetics a combination of these two drugs may help in reducing the dose of pioglitazone and consequently the cardiovascular adverse effects of pioglitazone[28].

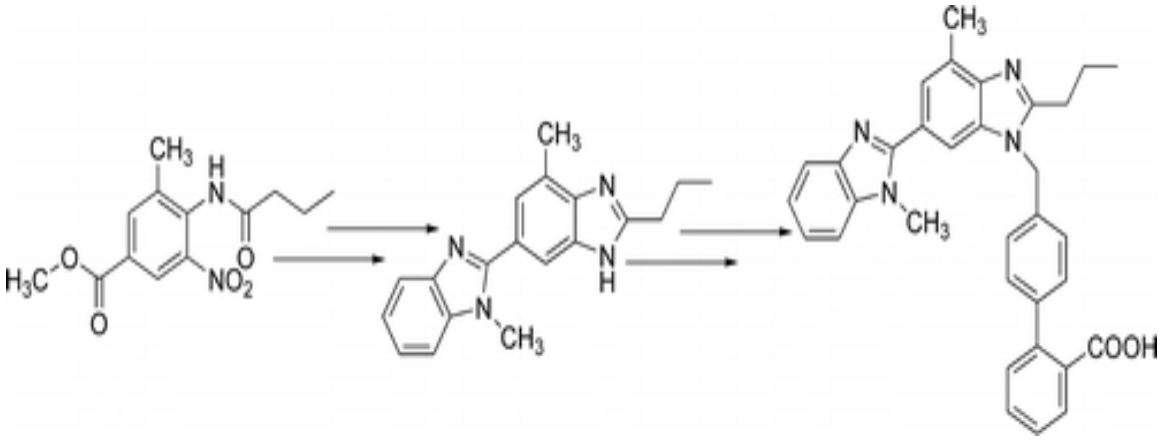
Suzuki reaction catalyzed by either a homogeneous palladium source or graphene-supported palladium nanoparticles. The cross-coupling reaction was facilitated by the regio-controlled preparation of the 2-bromo-1-methylbenzimidazole precursor. This convergent approach provides telmisartan shown in scheme 1 [29]



Scheme-1

K. Reddy et al gave dibenzimidazole derivative of Telmisartan, shows antihypertensive drug, essentially used to control blood pressure shown in scheme 2 [30].

C. Chunxia and Co-workers has been described method for the synthesis of the benzimidazole ring system through a carbon-nitrogen cross-coupling reaction. In the presence of K_2CO_3 in water at 100 °C, the intramolecular ring formation of N-(2-iodoaryl) benzamidine to gets benzimidazole derivatives. The procedure occurs exclusively in water and doesn't require the use of any additional reagent/catalyst, rendering the methodology highly valuable from both environmental and economical points of view shown in fig 3. [31]



Scheme 2

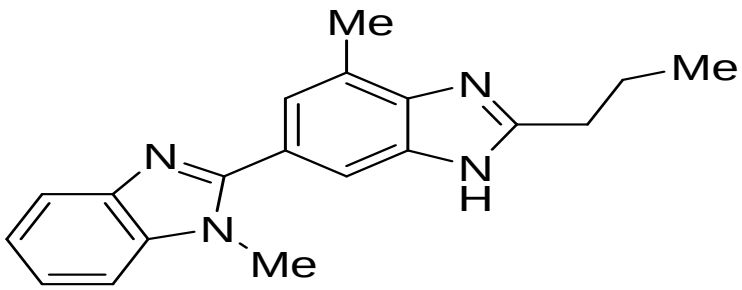
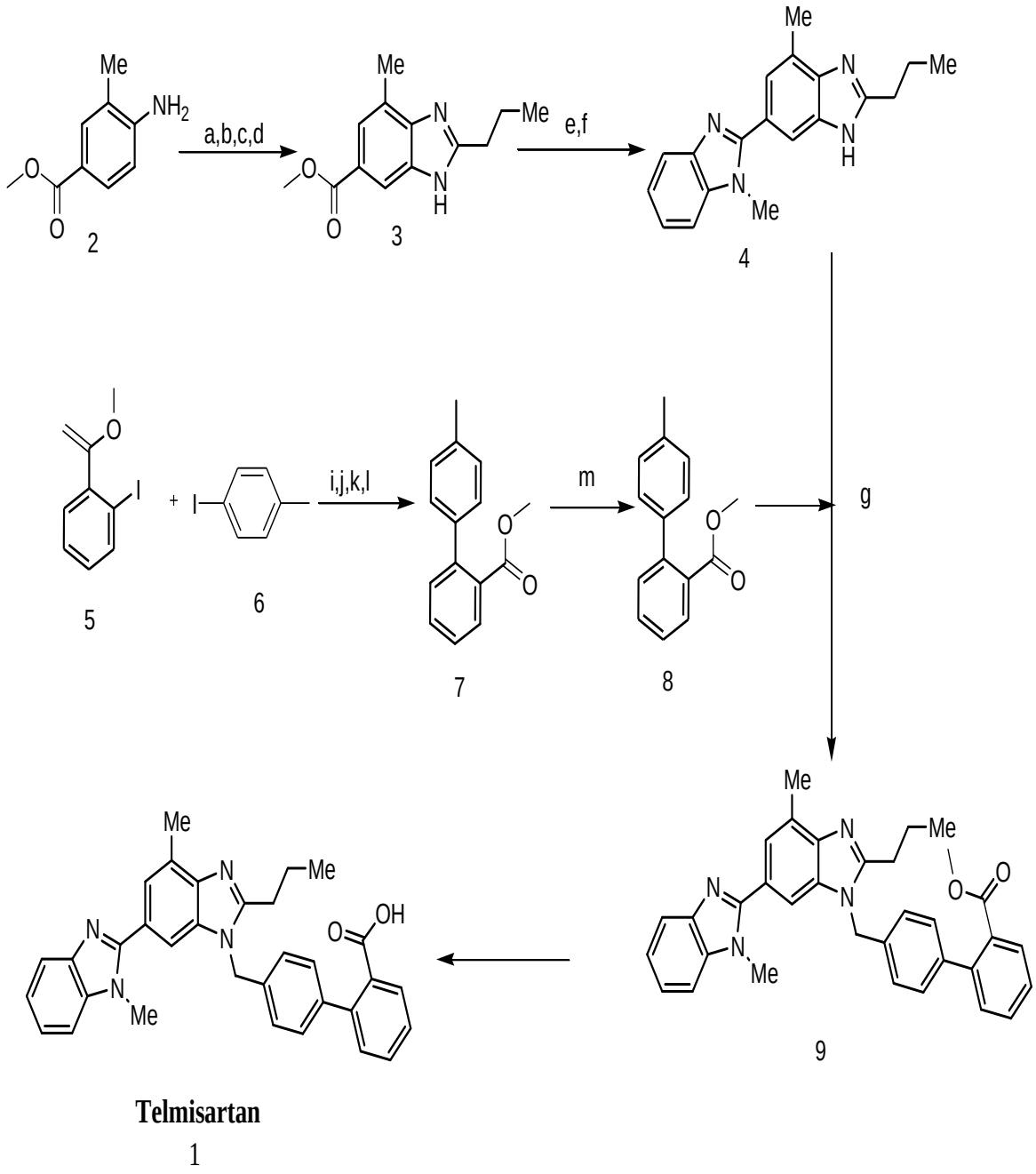


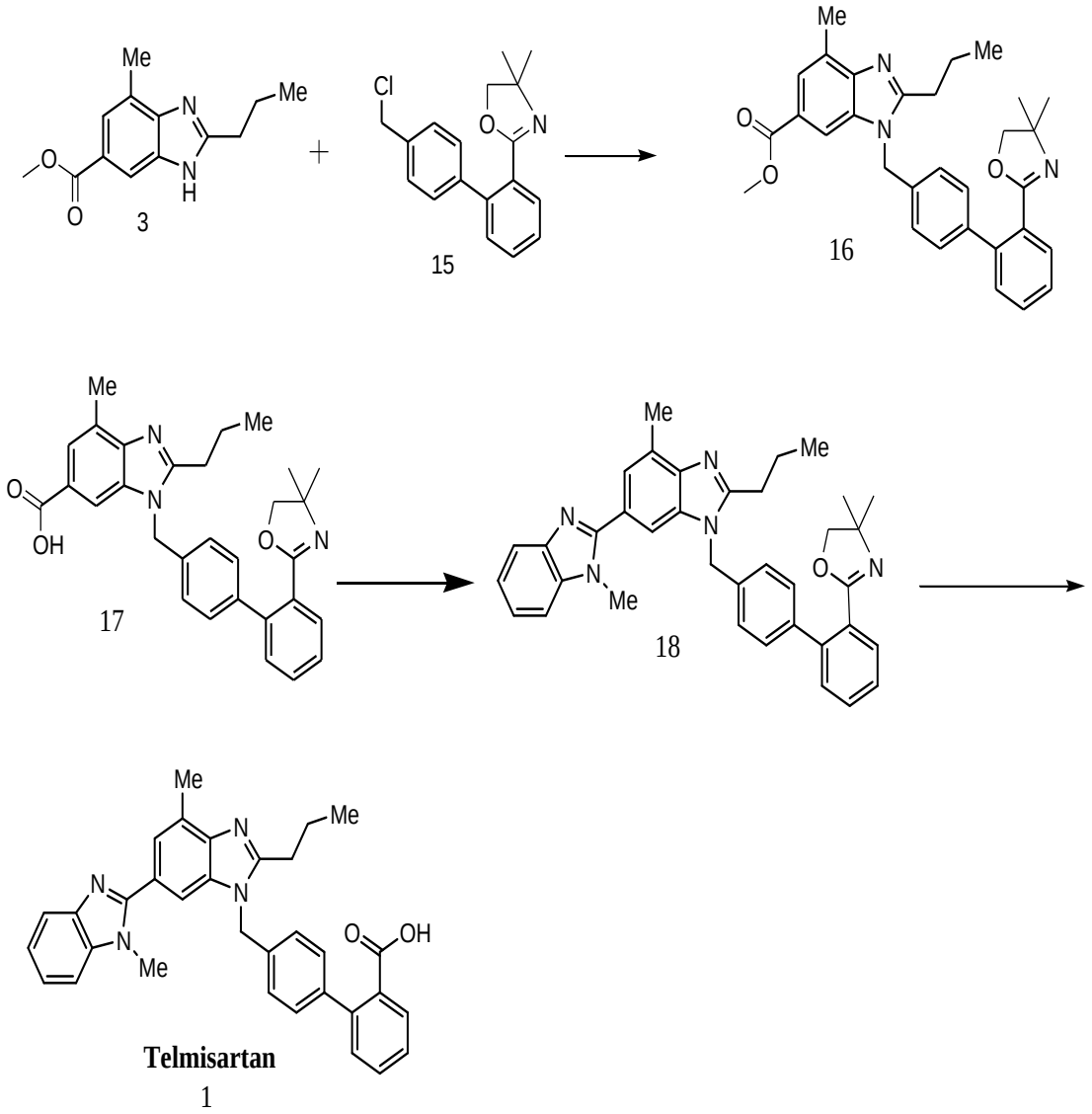
Fig-3

T V Maruthikumar et al gave a synthesis of the angiotensin II receptor antagonist telmisartan is described. It involves Suzuki coupling of 4-formylphenylboronic acid with 2-(2-bromophenyl)-4,4-dimethyl-2- oxazoline followed by construction of benzimidazole moiety regioselectively though a reductive amination-condensation sequence, replacing the earlier alkylation of the preformed benzimidazole route. This methodology overcomes many drawbacks of the reported synthesis shown in scheme 3.[32]



Scheme 3

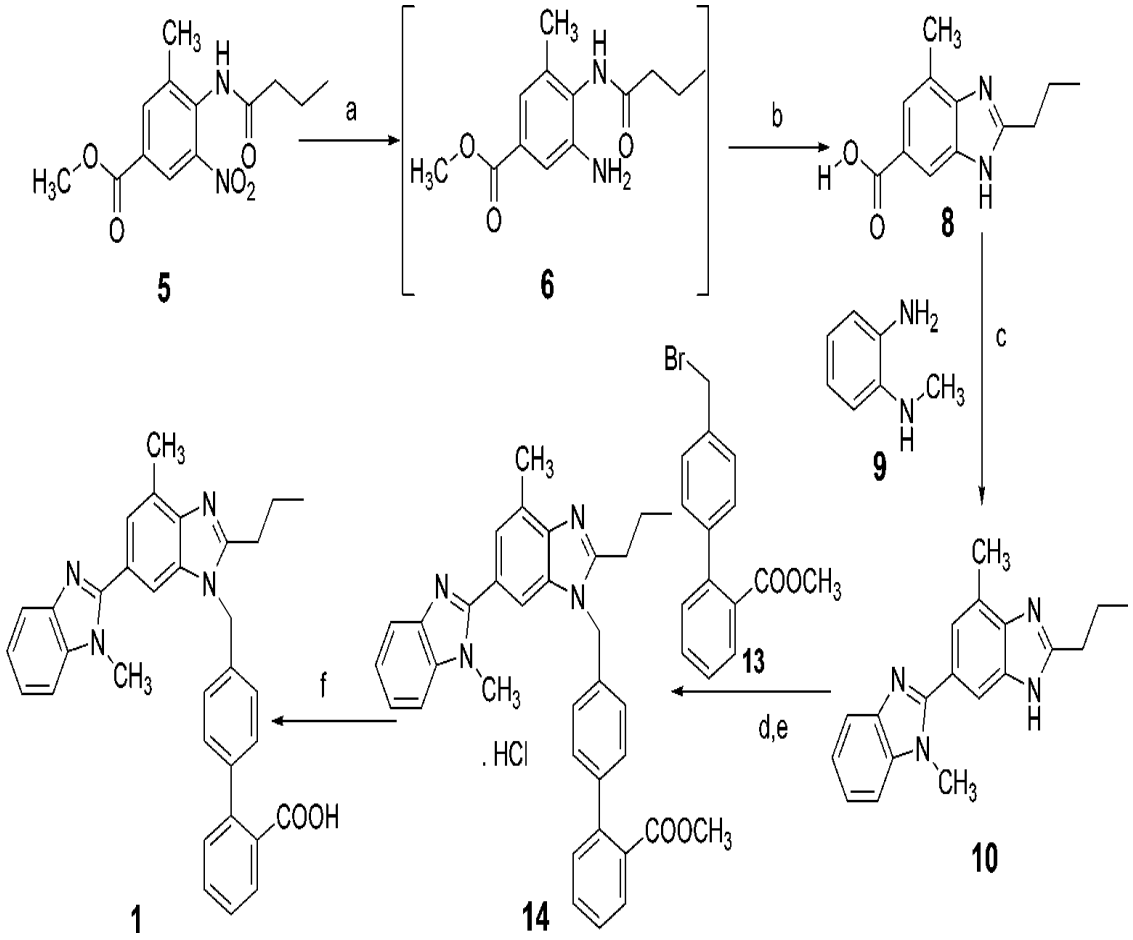
A. S. Kumar et al studied a highly efficient, convergent approach to the synthesis of the angiotensin II receptor antagonist telmisartan (1) is described. Involving a Suzuki coupling of 4-(hydroxymethyl)phenylboronic acid with 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline as the key step. The bisbenzimidazole moiety is constructed alternatively via an N-alkylation-condensation sequence, this convergent synthesis with the sequence consisting of six steps shown in scheme 4[33] .



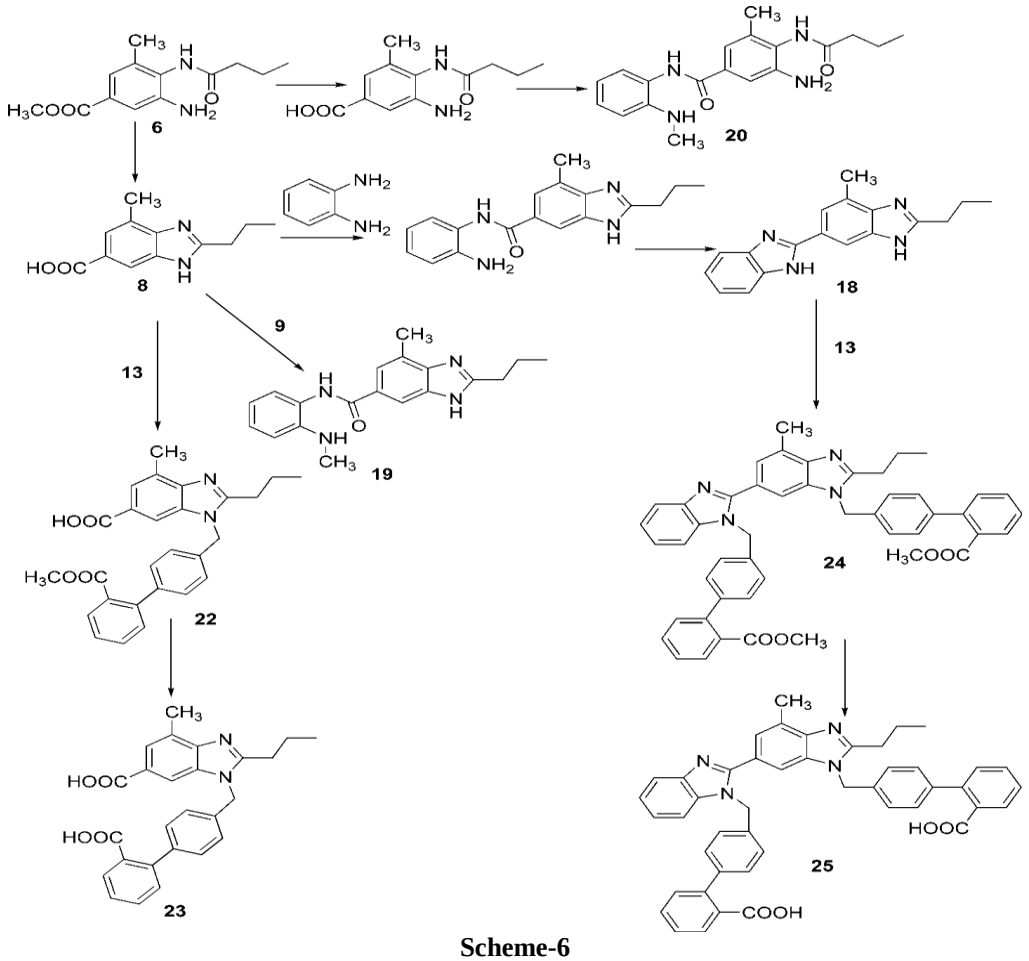
Scheme 4

The reduction of nitro compound 5 to obtain amine 6, the resulting reaction mass was filtered to remove Pd-C catalyst and the filtrate was concentrated to a thick syrup which was directly react with aqueous sodium hydroxide to get benzimidazole intermediate 8 after adjusting pH between 4.5 and 5.0 with concd HCl in a one step Fig 1 .

Reddy, Kikkuru S and coworkers studied further intermediate 8 was then condensed with N-methyl-benzene-1,2-found in 10 were desmethyl dibenzimidazole (18) which may be due to the presence of traces of benzene-1,2-diamine in 9, 7-methyl-2-propyl-3H-benzoimidazole-5-carboxylic acid (2-methylaminophenyl)amide (19), and 3-amino-4-butyrylamino- 5-methyl-N-(2-methylaminophenyl)benzamide (20) [34].

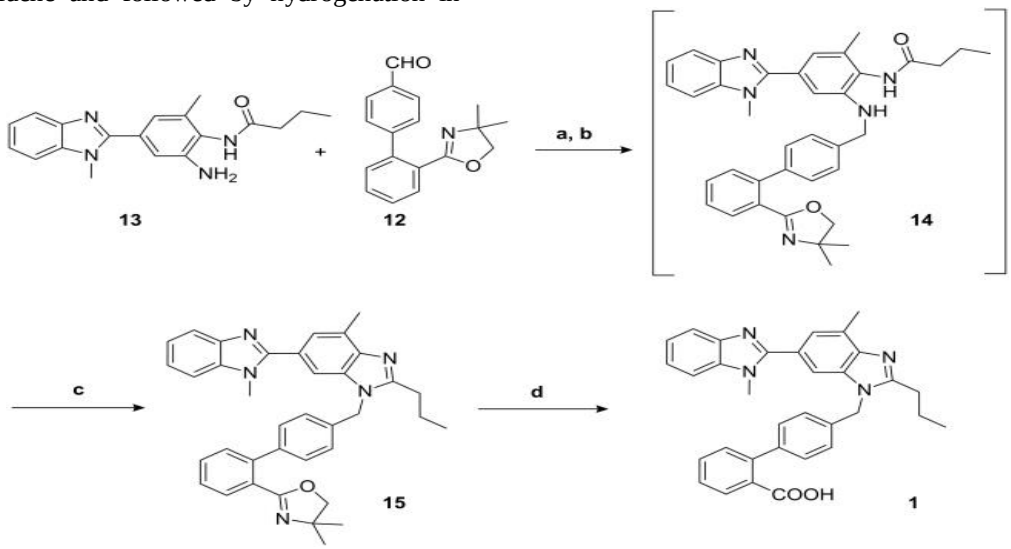


Scheme-5

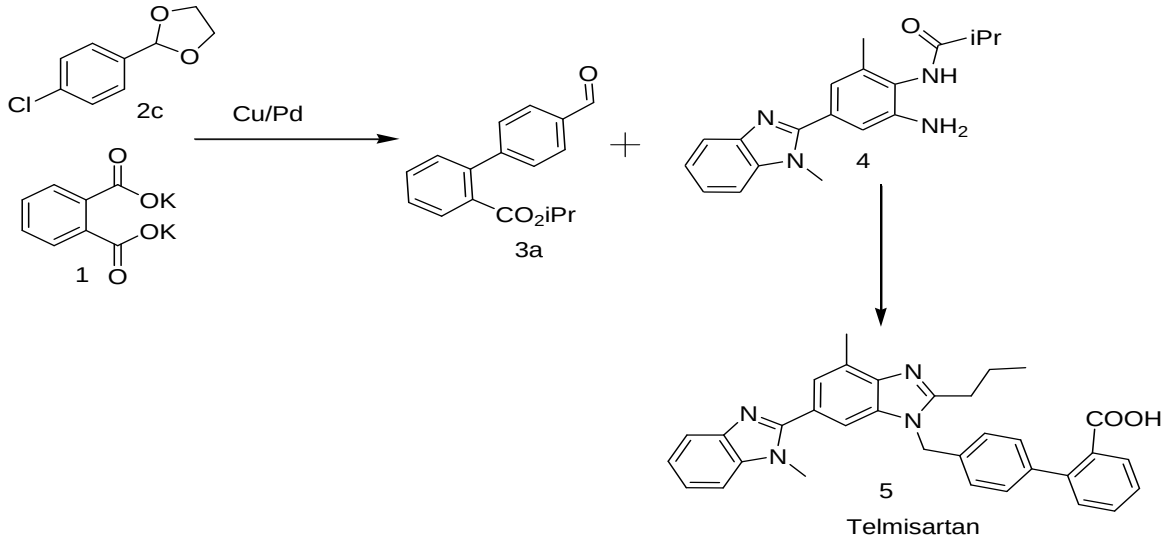


Scheme-6

In another findings by Sanjeev Kumar, shows the synthesis of the angiotensin II receptor antagonist Telmisartan (**1**) is presented involving The reductive amination of the biaryl aldehyde **12** with amine **13** was carried out in the presence of p-toluenesulfonic acid in toluene and followed by hydrogenation in methyl alcohol. The resulting amine **14** was not isolated but cyclized in situ to the n-propyl benzimidazole **15** in refluxing glacial acetic acid. Finally, cleavage of the oxazoline moiety in **15** by acid afforded Telmisartan (**1**) shown in scheme 7 **[35]**



Scheme-7



Scheme-8

Goossen, Lukas J et al examined an efficient synthesis of the angiotensin II receptor antagonist telmisartan is described decarboxylative cross-coupling of isopropyl phthalate (**1**) with 2-(4-chlorophenyl)-1,3-dioxolane (**2c**) as the key step. The benzimidazole moiety is constructed regioselectively via a reductive amination−condensation sequence, replacing the previously published route via alkylation of the preformed benzimidazole shown in scheme 8[36].

And some heterocyclic drugs synthesis via several name reactions [37-41].

CONCLUSION:

The current review article emphasizes broadly over several scalable approaches carried out toward the syntheses of Telmisartan drug 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 Telmisartan drugs.

ACKNOWLEDGEMENTS:

The author is thankful to Hon'ble Principal and Head of Department of Chemistry, JET's Z. B. Patil College, Dhule for providing the laboratory facilities.

REFERENCES:

1.S. C. Benson, H. A. Pershadsingh, C. I. Ho, A. Chittiboyina, P. Desai, M. Pravenec, N. Qi, J. Wang, M. A. Avery, T. W. Kurtz. Hypertension 2004; 43: 993-1002.

2.W. Wienen, N. Hauel, J. v. Meel, B. Narr, U. Ries, M. Entzeroth. British journal of pharmacology 1993;110: 245-252.

3.V. Rane, J. Sangshetti, D. Shinde. Journal of chromatographic science 2008; 46: 887-891.

4.S. Nandipati, V. K. Reddy, T. R. Reddy. Int. Res J Pharm. App Sci 2012; 2:39-43.

5.R. N. Rao, S. Sen, P. Nagaraju, V. S. Reddy, P. R. Krishnamurthy, S. U. Bhaskar. Asian Journal of Chemistry 2006; 18: 775-782

6.M. Palled, P. Rajesh, M. Chatter, A. Bhat. Indian journal of pharmaceutical sciences 2005;67:108-110.

7.H. Zhang, Y. Jiang, J. Wen, T. Zhou, G. Fan, Y. Wu. Journal of Chromatography B 2009; 877: 3729-3733.

8.B. R. Patra, S. Mohan, N. Gowda. International Journal of Pharmaceutical Sciences and Research 2016; 7:2031

9.N. H. Dhekale, K. H. Bindu, K. Kirankumar, A. H. Gore, P. V. Anbhule, G. B. Kolekar. Analytical Methods 2014; 6:5168-5182.

10.Yashwantsinh Jadeja, Bhagyawanti Chomal, Madhavi Patel, Hetal Jebaliya, Ranjan Khunt and Anamik Shah, 2016;55(7);634-638

11.Le CN, Hulgan T, Tseng C-H, Milne GL, Lake JE (2017) Urine Eicosanoids in the Metabolic Abnormalities, Telmisartan, and HIV Infection (MATH) Trial. PLoS ONE 12(1): e0170515. doi:10.1371/journal.pone.0170515.

12.Jordan E. Lake, Sophie Seang, Theodoros Kelesidis, Judith S. Currier & Otto O. Yang, HIV Clinical Trials, 2016;17(6):225-232.

13.Molkentin JD: Calcineurin-NFAT signaling regulates the cardiac hypertrophic response in coordination with the MAPKs. Cardiovasc Res ,2004;63: 467-475.

14.Pu WT, Ma Q and Izumo S: NFAT transcription factors are critical survival factors that inhibit

cardiomyocyte apoptosis during phenylephrine stimulation in vitro. Circ Res 2003;92: 725-731.

15.Xiurong Li, Yuhuai Lan, Yan Wang, Minghao Nie, Yanhong Lu And Eryang Zhao, Molecular Medicine Reports 2017; 15: 2574-2582

16.Anca Nenicu, Yuan Gu, Christina Körbel, Michael D. Menger and Matthias W. Laschke, Br. J. Pharmacol , August 2017; 174(16): 2623–2635

17.Jun Zhang, Xin Liu, Shu-Qing Wang, Gui-You Liu, Wei-Ren Xu, Xian-Chao Cheng and Run-Ling Wang, Journal of Biomolecular Structure and Dynamics, 2017;35(12): 2665-2680

18.Anjali Sharma a, Kiran Jyoti a, Vikas Bansal a, Upendra Kumar Jain a, Bharat Bhushanb, JitenderMadan, Materials Science and Engineering C 2017;72: 69–76

19.M. Kaur, R.K. Bhatia, R.R. Pissurlenkar, E.C. Coutinho, U.K. Jain, O.P. Katare, R. Chandra, J. Madan, Telmisartan complex augments solubility, dissolution and drug delivery in prostate cancer cells, Carbohydr. Polym. 2014;101:614–622.

20.N. Emmanuel, A. Koukaras, S.A. Papadimitriou, D.N. Bikiaris, G.E. Froudakis, Insight on the formation of chitosan nanoparticles through ionotropic gelation with tripolyphosphate, Mol. Pharm.2012; 9: 2856–2862

21.T. Yadavalli, S. Ramasamy, G. Chandrasekaran, I. Michael, H.A. Therese, R. Chennakesavulu, Dual responsive PNIPAM–chitosan targeted magnetic nanopolymers for targeted drug delivery, J. Magn. Magn. Mater. 2015;380: 315–320.

22.Pinaki Senguptaa*, Bappaditya Chatterjeea, Uttam Kumar Mandala, Bapi Gorainb, Tapan Kumar Pal, J Pharm Biomed Anal. 2017 Sep 10;144:

23.Y.M. Attia, E.F. Elalkamy, O.A. Hammam, et al., Parasit. Vectors. 6 (2013) 199-211

24.A. Fujimura, K. Ushijima, H. Ando, Hyperten. Res. 36 (2013) 183.

25.T. Pang, J. Benicky, J. Wang, et al., , J. Hypertens. 2012;30 : 87-96.

26.P. Vipula, L. Yalin, R. Sima, et al.,, FASEB. J. 25 (2011) lb545.

27.W. Hsueh, G. Davidai, R. Henry, et al., J. Clin. Hypertens. 2010;12:746–752.

28.Asma Khan, Bushra Tayyaba Khan, Aisha Qayyum, Pak Armed Forces Med J 2017; 67 (1):31-36.

29.Martin, Alex D., Ali R. Siamaki, Katherine Belecki, and B. F. Gupton. The Journal of Organic Chemistry80.3 (2015): 1915-1919.

30.KikkuruSrirami Reddy, NetiSrinivasan, ChintaRaveendra Reddy, NaveenkumarKolla, etc Organic Process Research & Development 2007; 11: 81-85.

31.Chen, Chunxia, Chen Chen, Bin Li, Jingwei Tao, and Jinsong Peng. "Aqueous Synthesis of 1-H-2-Substituted Benzimidazoles via Transition-Metal-Free Intramolecular Amination of Aryl Iodides." Molecules 17.12 (2012): 2506-2520.

32.T V Maruthikumar et al . " An Improved Synthesis of Telmisartan: An Antihypertensive Drug" Der Chemica Sinica, 2011;2(6):151-157.

33.A Sanjeev Kumar, Samir Ghosh, GN Mehta "Efficient And Convergent Synthesis Of Telmisartan" Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2010; 1, (3): 461.

34.Reddy, Kikkuru S., Neti Srinivasan, Chinta R. Reddy, Naveenkumar Kolla, Yerremilli Anjaneyulu, Sundaram Venkatraman, Apurba Bhattacharya, and Vijayavitthal T. Mathad. "An Efficient and Impurity-Free Process for Telmisartan: An Antihypertensive Drug§." Organic Process Research & Development 11.1 (2007): 81-85.

35.Sanjeev Kumar, A., Samir Ghosh, and G. N. Mehta. "Efficient and improved synthesis of Telmisartan." Beilstein Journal of Organic Chemistry 6 (2010): 25.

36.Goossen, Lukas J., and Thomas Knauber. "Concise Synthesis of Telmisartan via Decarboxylative Cross-Coupling." The Journal of Organic Chemistry 2008;73(21): 8631-8634.

37.A.P. Rajput, D.V. Nagarale, International Journal of Pharmaceutical Chemistry, 2016; 06 (07),181-185

38.A.P. Rajput, D.V. Nagarale, Journal of Chemical Pharmaceutical Research ,2016; 8(7):557-575

39.A.P. Rajput, D.V. Nagarale, Journal of Chemical, Pharmaceutical Research, 2016; 8(6):213-217

40.A.P. Rajput, D.V. Nagarale, Der Pharma Chemica, 2016;8(8):182-186.

41.A.P. Rajput, D.V. Nagarale, Chemical Science Transactions, 2016;5(4):912-917.