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SYNTHESIS OF OLMESARTAN ACID IMPURITY OF OLMESARTAN MEDOXOMIL, ANTI-HYPERTENSIVE DRUG

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ABSTRACT
Olmesartan medoxomil is the latest angiotensin receptor antagonist approved by FDA for the treatment of hypertension. During the process development of olmesartan medoxomil[6-9], one of the related substances (impurity) was observed along with the final API. This impurity was identified as olmesartan acid[6-9]. Present work describes the synthesis and characterization of this impurity[2-4]
Keywords: API, angiotensin receptor, olmesartan medoxomil impurity, synthesis

INTRODUCTION

Drugs have become an important part of human life to combat with various diseases. Unlike ancient days, most of the drugs in recent years are purely synthetically made. Unambiguously, the synthetic drugs certainly contain various impurities such as chemical or microbial[1]. But of course most of the impurities are chemical only. The presence of impurities, also called as, related substances in an active pharmaceutical ingredient (API) can have a significant impact on the quality and safety of the drug products[1]. Therefore, it is necessary to study the impurity profile of any API and control it during the manufacturing of a drug product[1]. As per the ICH guidelines for any impurities[1], which are forming at a level of $\geq 0.10\%$ with respect to the API should be identified, synthesized and characterized thoroughly. Olmesartan medoxomil [Benicar®, Sankyo pharma] is the latest angiotensin receptor antagonist[2-7] approved by the FDA for the treatment of hypertension. Refer Figure 1 for Molecular framework of olmesartan medoxomil. Among the various health problems, high blood pressure is one of the critical one and of course most of the times itself doesn't harm much, but it leads to various chronic and panic health disorders such as cardio diseases, cerebral haemorrhage and others[2-7]. Olmesartan medoxomil [Benicar®, Sankyo pharma] is the latest angiotensin receptor antagonist approved by the FDA for the treatment of hypertension (Figure-1). The drug works by inhibiting the effects of angiotensin II, a potent vasoconstrictor and one of the key contributors to cardiovascular and renal disease[2-7]. Herein, we wished to discuss identification, synthesis and characterization of Olmesartan acid impurity of Olmesartan medoxomil

EXPERIMENTAL

Materials and reagents

Pure samples of Olmesartan medoxomil were obtained from Glenmark Pharmaceutical Limited as a gift. For synthesis of impurity, sample of Trityl olmesartan was obtained from Vivan Life Sciences Ltd. Synthesis grade acetic acid and toluene was also used. For Analysis by HPLC; acetonitrile HPLC grade and Sodium dihydrogen phosphate, AR grade, Triethylamine HPLC grade & Orthophosphoric acid AR grade were used. Highly pure water was prepared by double distillation and filtration through a 0.45 μm membrane filter

High performance liquid chromatography (analytical)

Shimadzu LC 2010 system equipped with a low pressure quaternary gradient pump along with a photo diode array detector and auto sampler injector was used. The data was collected and processed using LC

Solution software. A Kromasil C18, 5 µm (150 mm x 4.6 mm) column was employed for the separation of impurity from olmesartan medoxomil. The column eluent was monitored at 225 nm. The sample diluent was a mixture of buffer and Acetonitrile in the ratio of 6:4 (v/v), filtered through a 0.2 µm or finer porosity membrane filter. The mobile phase was mixture of buffer and Acetonitrile in the ratio of 6:4 (v/v), filtered through a 0.2 µm or finer porosity membrane filter

Mass spectrometry (LC/MS)
Initial LC/MS analysis was performed on a Varian Inc. (USA) 410 Prostar Binary LC with 500 MS IT PDA detectors. The analysis was performed in positive ionization mode with turbo ion spray interface. The parameters for ion source voltage, IS = 5500V, declustering potential, DP = 70V, focusing potential, FP = 400V, entrance potential, EP = 10V were set with nebulizer gas as air at a pressure of 40 psi and nitrogen gas at a pressure of 25 psi in mass spectrometer. Further, to get accurate mass, analysis was performed on a high resolution mass spectrometer using electrospray ionization. The accurate mass obtained from the instrument, theoretical mass and mass error was calculated

NMR Spectroscopy
The 1H experiment was carried out for unknown impurity at processional frequencies 400.1328 MHz at 25ºC on a Cona Bruker Avance-300FT NMR spectrometer. 1H chemical shift was recorded on the δ scale in ppm, relative to tetramethylsilane (TMS) δ 0.00 in ppm

FT IR Spectroscopy
The IR spectra were obtained using Shimadzu, FT IR spectrophotometer, with substances being pressed in a KBr pellet

Chromatographic condition
The mobile phase A consisted of 4.7 g of Sodium Dihydrogen Phosphate and 1 ml of triethylamine in 1000 ml buffer, adjusted pH 4.0 ± 0.05 with Orthophosphoric acid and mobile phase B consisted of acetonitrile flow in ratio 60:40. A Kromasil C18 column (150mm x 4.6 mm, 5-Micron) was found to resolve olmesartan medoxomil. The mobile phase was filtered through a 0.2 µm membrane filter and then sonicated for 10 min. The flow rate was set at 1.0 ml/min. The drug showed good absorbance at 225 nm, which was selected as the wavelength for further analysis. All determinations were performed at 30ºC column temperature. Mobile phases as buffer and acetonitrile in the ratio of 60:40 v/v, were used as sample diluents

Preparation of stock solution and standard solution
Accurately weighed 25 mg of Olmesartan medoxomil WS, was dissolved in a 50 ml volumetric flask with diluent (stock solution). The stock solution was further diluted by using the mobile phase to get the concentration of 5 µg/ml of Olmesartan medoxomil

Preparation of sample solution
Accurately weighed 25 mg of Olmesartan medoxomil, was dissolved in a 25 ml volumetric flask with diluent to get the concentration of 1000 µg/ml of Olmesartan medoxomil

Preparation of System Suitability Solution
Accurately weighed each of 25 mg of Olmesartan medoxomil WS and olmesartan acid impurity, was dissolved in a 50 ml volumetric flask with diluent (stock solution). The stock solution was further diluted by using the mobile phase to get the concentration of 5 µg/ml of each of Olmesartan medoxomil and Olmesartan acid impurity

Detection of impurities by HPLC
Refer Figure 2 for typical HPLC chromatograms of Olmesartan medoxomil and its impurity, observed in drug substance obtained by using the HPLC method

The Synthesis root of Olmesartan medoxomil
Refer Figure-3. It shows Synthesis of Olmesartan medoxomil.

Preparation of Olmesartan Acid Impurity
Preparation of (4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(tetrazol-5-yl)phenyl]phenyl}methyl imidazole-5-carboxylic Acid.)

Procedure-1
Charged 375 ml acetic acid in reaction assembly and then charged 125 ml process water at RT, stirred for 5-10 minutes. Charged Trityl Olmesartan 50 gm in one lot and raised temperature to 30-35^{0}C. Maintained the mass at 60–70^{0}C till completion of the reaction (approx. 16–17 hrs). After reaction was over, cooled to 25^{0}C and charged 500 ml water and stirred for 10 min. Cooled reaction mass to 10–15^{0}C, Trityl Alcohol precipitated out. Filtered the reaction mass and washed with 50 ml of 50% aq. Acetic acid. Charged filtrate in RBF & washed with 250 ml Toluene. Separated Toluene layer and charged 400 ml Ethyl Acetate in aq. Reaction mass, stirred and charged 202.5 gm NaCl. Stirred for 20–25 mins. Separated Ethyl Acetate layer and re-extracted aqueous layer with 100 ml of Ethyl Acetate. Combined the Ethyl Acetate layers and distilled out the Ethyl Acetate containing Acetic Acid under reduced pressure to maximum temp of 45^{0}C completely to get oil. Charge 1 L Ethyl Acetate and 1.25 L water to the oil, cool reaction mass to 10–15^{0}C and adjust pH to 6.5-6.7 by using solid sodium bicarbonate. Raised the temperature to RT and the ethyl acetate layer got separated. Re-extracted the aqueous layer with 250 ml of ethyl acetate. Combined the ethyl acetate layers and washed with 500 ml DM water. Charged 2.5 gm charcoal and 100 gm sodium sulphate to ethyl acetate layer and stirred for 15–20 min. Filtered and washed with 50 ml ethyl acetate. Distilled out ethyl acetate under reduced pressure till approx. 650 ml was left in the reaction assembly at 40–45^{0}C. Cooled to RT and stirred for 12 hours at 25–30^{0}C. Filtered the reaction mass and washed with 50 ml of ethyl acetate. Sucked & dried for 15–20 min and unloaded. Dried in air oven at 75–85^{0}C for 3–4 hrs till LOD was NMT 0.30%
Unloaded and checked the purity. Refer Figure-4. It shows the Synthesis of Olmesartan acid impurity.
Result: Dry Weight =18.0 gm; Yield =65 %

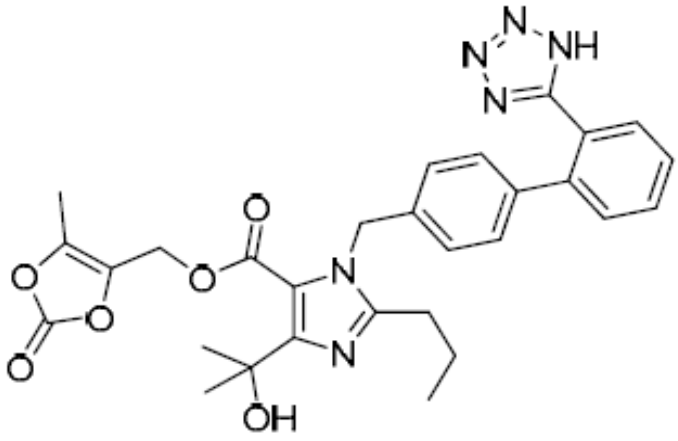

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Fig.-1: Molecular framework of olmesartan medoxomil

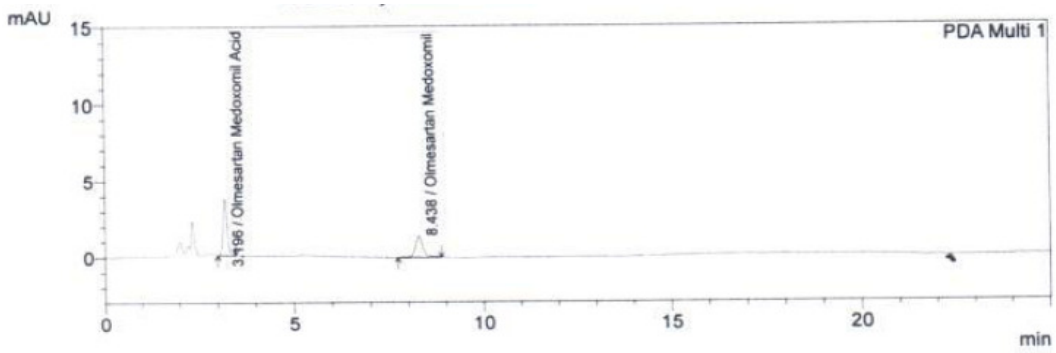
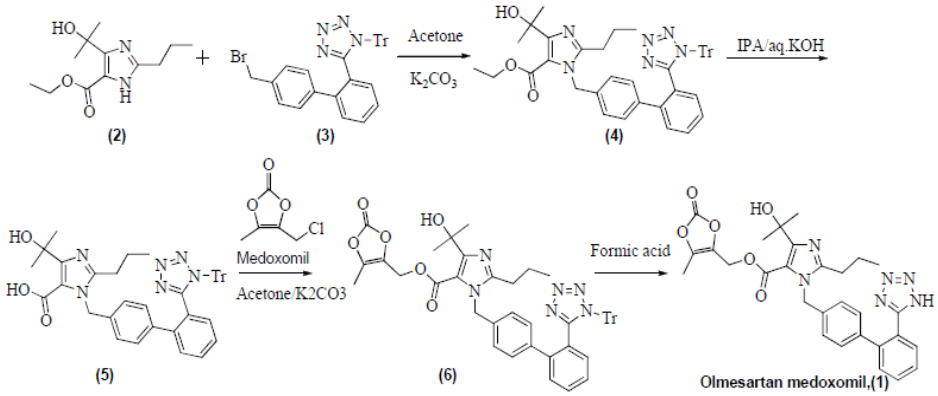


Fig.-2: Typical HPLC chromatograms of olmesartan medoxomil and its impurity, observed in drug substance obtained by using the HPLC method



Scheme-1: Synthesis of Olmesartan medoxomil,(**1**)

Fig.-3

RESULTS AND DISCUSSION

During the API process development of Olmesartan medoxomil various process-related impurities have been identified. The one known impurity was prepared by procedure-1 and characterized and confirmed. The structural data of the known impurities were confirmed with literature reported values.

A comprehensive study was undertaken to identify the unknown impurities by LC-MS followed by confirming through synthesis of this unknown impurity, followed by characterization based on spectroscopic techniques such as 1H NMR, IR Mass spectroscopy

Presence of this unknown impurity was detected by HPLC in synthesized Olmesartan Medoxomil. Also Olmesartan medoxomil Impurity A as per BP is also used to compare with our synthesised impurity by using HPLC analysis and it was found comparable

Characterisation of Impurity

The structure of impurity was confirmed by spectral analysis

Peak purity index by HPLC 99%; FT IR (KBr) 3407, 2930, 1678 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) 0.84 (t, 3H), 1.6 (s, 6H), 1.51 (m, 8H), 2.58 (t, 2H), 5.66 (s, 2H), 6.95-7.66 (m, 8H), 13.03 (s, 1H); MS (EI) m/z 447.4 (M^+ + 1); CHN Analysis: calcd. for $C_{24}H_{26}N_6O_3$: C, 64.56; H, 5.87; N, 18.82; Found: C, 64.78; H, 5.98; N, 18.91

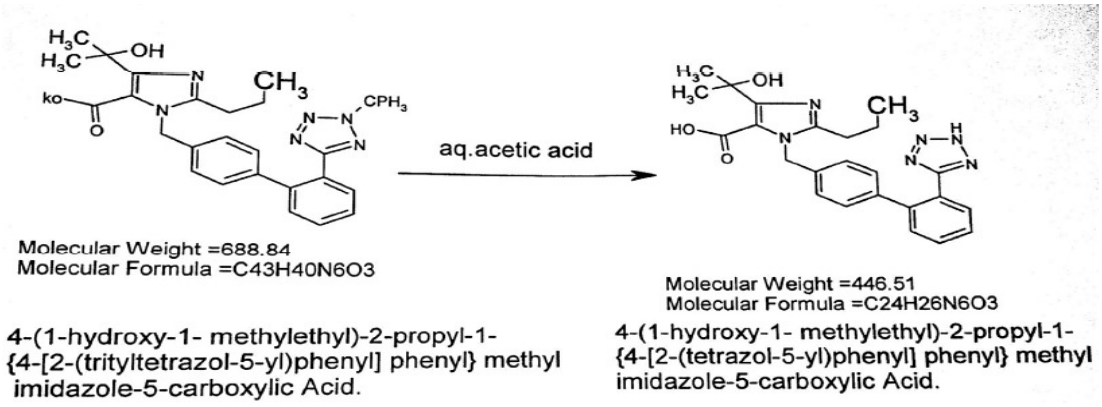


Fig.-4: The Synthesis of Olmesartan Acid impurity

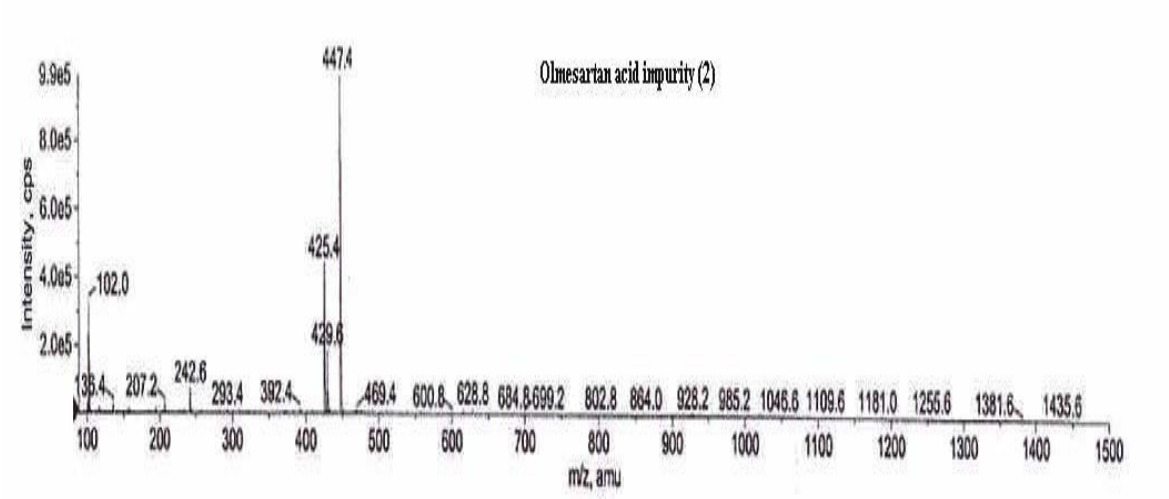


Fig.-5: LC-MS Spectrum of olmesartan acid impurity

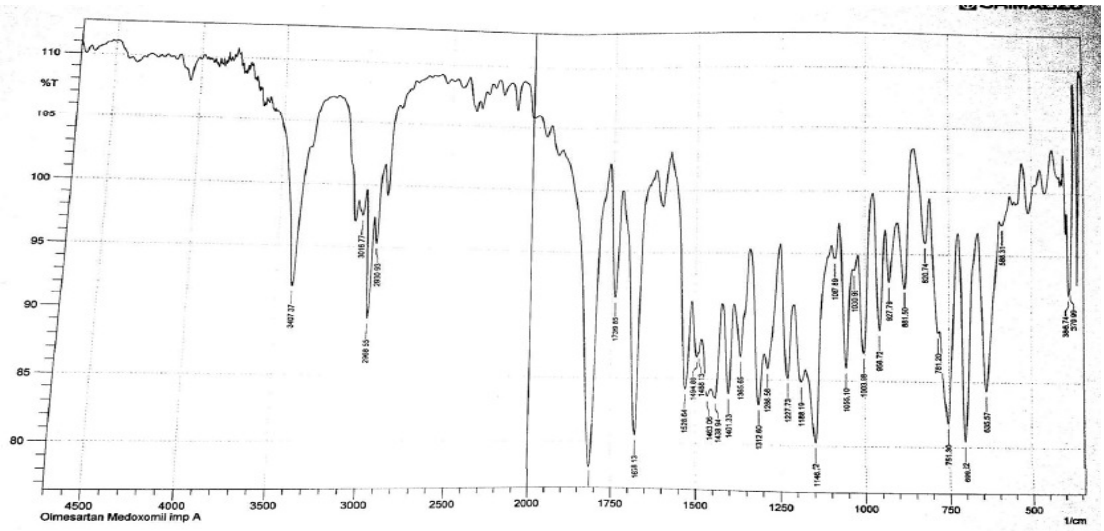


Fig.-6: FTIR Spectrum of olmesartan acid impurity

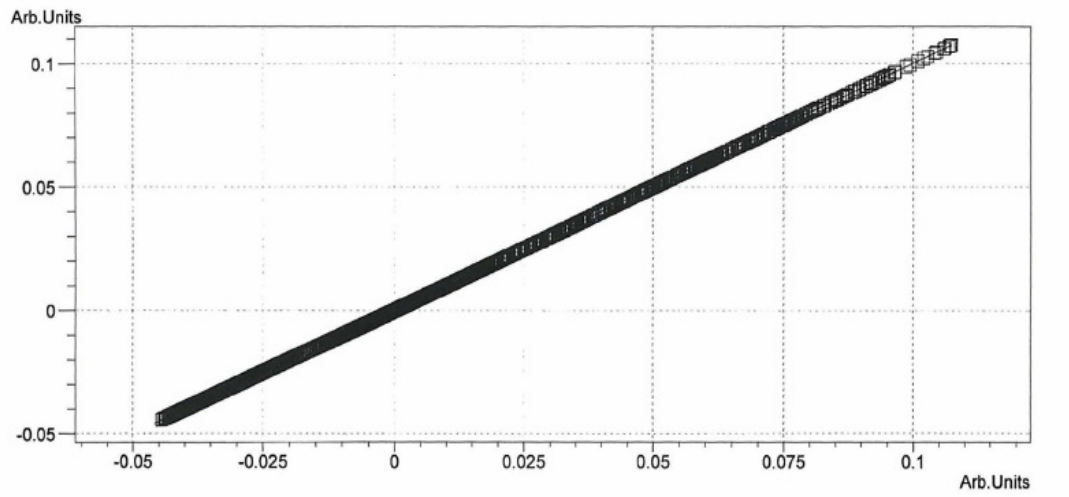


Fig.-7: FTIR Purity Index graph of olmesartan acid impurity

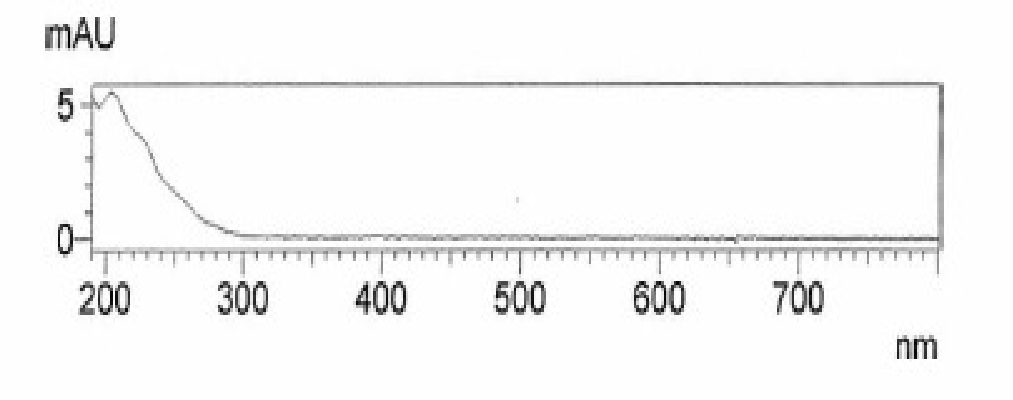


Fig.-8: UV Spectrum Index of olmesartan acid impurity

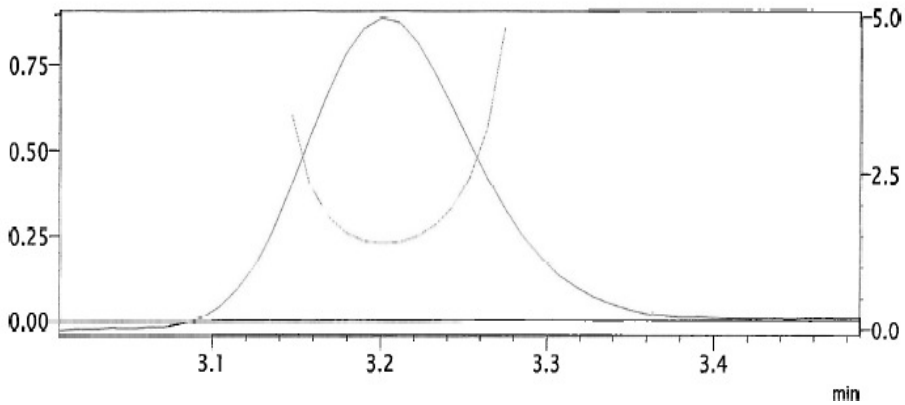


Fig.-9: HPLC Purity Graph of olmesartan acid impurity

Finally, Olmesartan acid impurity was individually injected with the Olmesartan Medoxomil API in the HPLC and the HPLC data was compared with that of the Olmesartan impurity A as per BP by using

spectral purity graph. As expected, by using FTIR purity graph (Figure-7), synthesised impurity was matching with the BP impurity purity graph

CONCLUSIONS

We have demonstrated the synthesis and complete characterization of one of the critical impurity Olmesartan acid impurity of Olmesartan medoxomil. This investigation helped us to establish the impurity profile of Olmesartan medoxomil

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REFERENCES

1. International conference on harmonization (ICH) Guidelines, Q_3A (R) Impurities in New Drug Substances, February (2002)
2. M.Fukuda, T. Yamanaka, M. Mizuno, M. Motokawa, Y. Shirasawa, S. Miyagi, T. Nishio, A. Yoshida, G. Kimura, *J. Hypertens.*, **26,** 583(2008)
3. K. Nobuya, S. Miwa, K. Shoko, Y. Keisuke, I. Hirokazu, *Br. J. Pharmacol.*, **139,** 1085(2003)
4. H. Yanagisawa, Y. Amemiya, T. Kanazaki, Y. Shimoji, K. Fujimoto, Y. Kitahara, T. Sada, M. Mizuno, M. Ikeda, S. Miyamoto, Y. Furukawa, H. Koike, *J. Med. Chem.,* **39,** 323(1996)
5. S.F. Gardner, A.M. Franks, *Ann. Pharmacother.,* **37,** 99(2003)
6. K.S. Babu, M.S. Reddy, A. R. Tagore, G.S. Reddy, S.Sebastian, WO **047838 A2**, (2007)
7. K.S. Babu, M.S. Reddy, A.R. Tagore, G.S. Reddy, S. Sebastian, M.S. Varma, R.V. Anand*, Syn. Commun.*, **39,** 291(2009)
8. J. Teng, N. Fukuda, R. Suzuki, H. Takagi, *J. Cardiovas. Pharmacol.,* **39,** 161(2002)
9. M.A.H.Ismail, S. Barker, D.A. Abou El Ella, K.A.M. Abouzid, R.A. Toubar, M.H. Todd, J. *Med. Chem.,* **49,** 1526(2006)

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