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SYNTHESIS OF THE ANTI-HYPERTENSIVE DRUG OLMESARTAN MEDOXOMIL IN GREENER APPROACH

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Abstract: Proton and metal ion-exchanged Montmorillonite and Copper–Aluminium Hydroxyapatite (Cu-HAP) catalysts were effectively used in the esterifiaction, C-N bond formation and Detritylation in methanol efford Olmesartan Medoxomil in good yields. The catalysts were quantitatively recovered from reaction mixture by simple filtration and reused for four cycles with consistent activity.

Key words: Montmorillonites, Copper–Aluminium Hydroxyapatite (Cu-HAP), C-N coupling, Detritylation, Green chemistry, Reusable catalyst, Olmesartan Medoxomil.

1. Introduction:

Olmesartan medoxomil (trade names: Benicar in the US, Olmetec in EU, Canada and Japan, WinBP, Golme in India, Erastapex in Egypt) is an angiotensin II receptor antagonist used to treat high blood pressure. Elevated blood pressure is one of the most important causes of death and disability worldwide, accounting for 7.6 million premature deaths and 92 million disability-adjusted life years annually[1]. Controlling blood pressure and prevention of its complications such as coronary heart disease, stroke, renal failure and eye damage are the main objectives for the treatment of hypertension.[2,3]

Angiotensin-II receptor antagonists should be used with caution in renal artery stenosis. Monitoring of plasma-potassium concentration is advised, particularly in the elderly and in patients with renal impairment; lower initial doses may be appropriate in these patients. Angiotensin-II receptor antagonists should be used with caution in aortic or mitral valve stenosis and in hypertrophic cardiomyopathy. Olmesartan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. [4] The U.S. Food and Drug Administration (FDA) has determined that the benefits of Benicar continue to outweigh its potential risks when used for the treatment of patients with high blood pressure according to the drug label.[5] the drug works by inhibiting effects potent vasoconstrictor cardiovascular and renal disease.[6-8] There are about seven sartans in clinical practice, of which five of them possess a tetrazole moiety in their structure. The protection and de protection of the N-atom of the tetrazole moiety becomes essential during the synthesis of the sartan drugs.

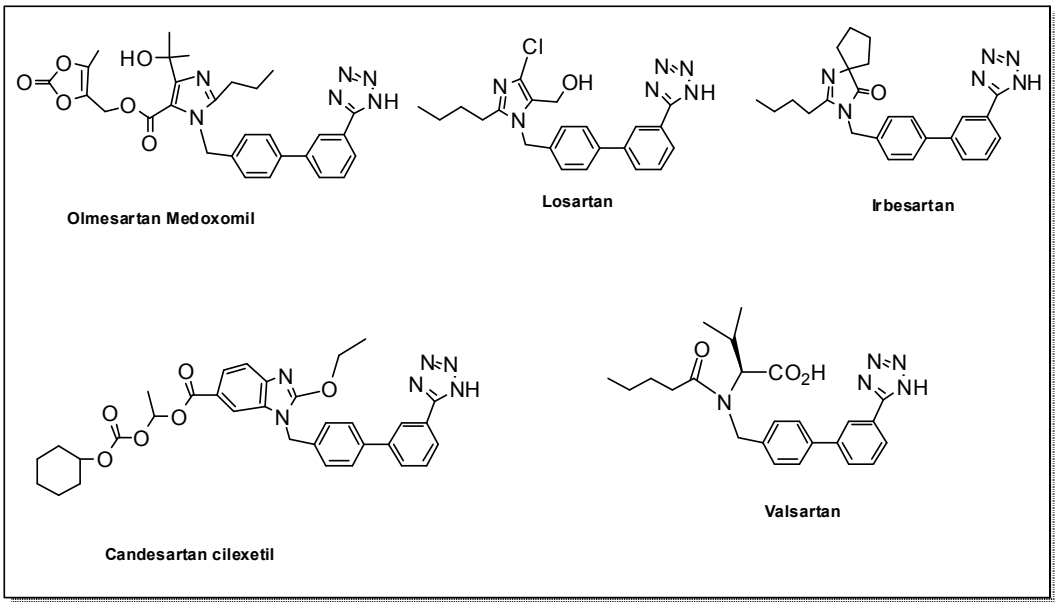


Figure1: Structure of angiotension II receptor blockers used in the treatment of hypertension

Structure: Olmesartan is a prodrug containing an ester moiety, which is active absorption the gastrointestinal tract. The olmesartan molecule includes one tetrazole group (a 5-member heterocyclic ring of four nitrogen and one carbon atom) and one imidazole group (a 5-membered planar heterocyclic aromatic ring of two nitrogen and three carbon atoms, classified as an alkaloid). Apart from olmesartan five other sartans used in clinical practice i.e. losratan, valsartan, irbesartan candesartan and Azilsartan are 5-(biphenyl-2-yl)tetrazole derivatives [2′-(N-Triphenylmethyltetrazol-5-yl)biphenyl-4-yl]methyl bromide (2) is a common intermediate used in the synthesis of these sartan drugs.

The development of heterogeneous catalysts for the fine chemical and process development synthesis has become major area of research recently in pharmaceutical industry, as the potential advantages of these solid materials (simplified recovery and reusability) over homogeneous system can make a major impact on the environmental performance of synthesis. Recently, we have developed an improved, scalable, cost-effective and environment-friendly technology for the industrial-scale synthesis of olmesartan based on the general route.

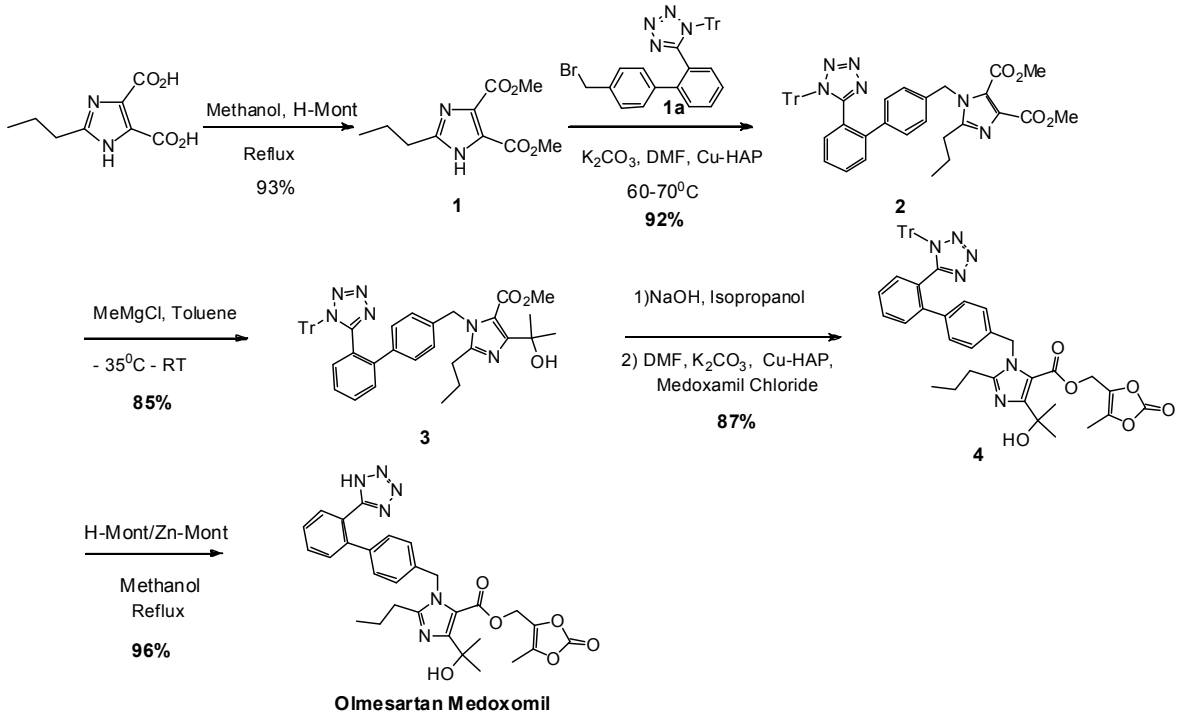
2. RESULTS AND DISCUSSION

Esterfication on 2-propyl-1H-imidazole-4,5-dicarboxylic acid explored in a greener approach in presence of Lewis Acid catalyst i.e. H-Montmorillonite in methanol at reflux temperature efford 93% yiled. Compound dimethyl 2-propyl-1H-imidazole-4,5-dicarboxylate **1** was coupled[7] with 4-{(2-trityltetrazol-5-yl)- phenyl}-benzyl bromide [8] (TTBB) **1a** using potassium carbonate in Dimethylformaide (DMF) in presence of green solid catalyst Cu-HAP,[9] and the product was crystallized to give **2** in 92 % yield.[10] This method has advantages over the reported methods where the product was isolated by column chromatography with low yield.

Compound **2** subjected with methyl magnesium chloride at -35° C (MMC) in toluene efford compound **3** with 85 % yield. Base hydrolysis of **3** subjected with Sodium hydroxide in

Isopropanol below 40^{O}C to minimize the unusual detritylation compound, after completion of reaction distill off the solvent and followed by the medoximil chloride coupling in presence of Green catalyst Cu-HAP, catalytic amount of base like K_2CO_3 in Acetone : DMF mixture (4:1) efford the compound **4** in 87 % yield.

Scheme:



Detritylation of of compound **4** subjected with Ion-exchanged Montmorillonite i.e. Zn-mont. in methanol as solvent at 45° C yield 96% of Olmesartan Medoxomil. The Catalyst was reusable without any appreciable loss in its catalytic activity, high yields of products, operational simplicity, inexpensive recyclable and the use of an environmentally friendly green Lewis acid catalyst. Detritylation method has advantages over the reported methods.[11-12] where the product was isolated by column chromatography, long reaction times, low yields and use of hazardous reagents and the inability to recycle.

Green catalysts: Apatites are metal basic phosphates for example calcium hydroxy apatites, $Ca_{10}(PO_4)_6(OH)_2$ (CaHAP). CaHAP attracted wide attention because of its versatile applications in the field of bioceramics, acid base catalysis. Hydroxyapatites(HAPs) posses Ca^{2+} sites surrounded by PO_4^{3-} tetrahedral parallel to the hexagonal axis, which are of considerable interest in many areas owing to their multiple functionalities. The chemical composition of HAPs can be modified from the stoichiometric form, $Ca_{10}(PO_4)_6(OH)_2$ (Ca/P = 1.67), to the non-stoichiometric Ca-deficient form, Ca_{10}-z(HPO_4)z$(PO_4)_6$-z$(OH)_2$-z ($0 < z < 1$, $1.5 < Ca/P < 1.67$). Thus the empirical formula which represents apatite like materials can be expressed as follows. $M_{10}(PO_4)(X)_2$ [M = divalent metal, X = monovalent anion] and various kinds of cations and anions can be readily introduced into their frameworks due to their large ion exchange ability and such exchanged apatites are already in use in several organic transformations.

Montmorillonites, referred to as monts, are hydrophilic clays with a layered structure. They are of considerable interest as environmentally benign and reusable catalysts. Owing to

their ion-exchange properties, various types of metal cations can be introduced readily into their expansible interlayer spaces.[13-14] The mont lattice is composed of a sheet of gibbsite ($Al_2(OH)_6$) Sand witched between two sheets of tetrahedral co-ordinated silicate $(SiO_4)^{-4}$-sheets. An important and useful properties of mont stems from its high degree of efficiency for M^+ cation exchange. The various metal cations are successfully introduced within the interlayer's via a simple ion-exchange method to afford metal ion species in unique structures as efficient solid acid catalysts.[15]

3. Conclusion

In summary, we have described a simple, convenient and efficient protocol for the synthesis of Olmesartan Medoxomil. using Montmorillonites, Copper–Aluminium Hydroxyapatite (Cu-HAP), as a cost-effective reusable and heterogeneous catalysts. The notable features of this method are simplicity in operation, cleaner reaction profiles and reusability of the catalyst, which make it an attractive and very useful process for the synthesis of naphthoxazinones of biological importance.

4. Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Varian-unity 300 spectrometer in DMSO-d_6 using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

Synthesis of Olmesartan Medoxomil:

H-Mont (0.1 g) was added to a suspension of compound **4** (1 g, 1.25 mmol) in methanol at room temperature and stirred at 40°C about 3-4 hours. The completion of the reaction was monitored by TLC, after completion of reaction catalyst is separated by simple filtration, washed with methanol and reused for several cycles. The reaction was cooled to 25°C until trityl methyl ether crystallized, separate it by filtration then filtrate methanol was evaporated in vaccuo to give compound ***Olmesartan Medoxomil*** in 96% yield.

Mp: 175-179^o C; ^{1}H NMR(300 MHz, $CDCl_3$): δ 0.91(t, 3H, *J* = 8.3Hz, CH_3), 1.62 (d, 6H, *J* = 9.3Hz, CH_3), 1.68 (t, 2H, *J* = 8.3Hz, CH_2), 2.18 (s, 3H, CH_3), 2.54 (t, 2H, *J* = 8.3Hz, CH_2), 4.96 (s, 1H, NCH_2), 5.40 (s, 2H, OCH_2), 6.77 (d, 2H, *J* = 8.6Hz ArH) ,7.06 (d, 2H, *J* = 8.6Hz ,ArH), 7.42-7.62 (m, 3H, ArH), 7.80 (d, 1H, *J* = 8.3Hz, ArH); ^{13}C NMR(200 MHz, $CDCl_3$); δ 13.7, 16.2, 24.1, 31.3, 32.7, 48.4, 62.7, 74.2, 116.2, 121.8, 127.8, 128.0, 128.2, 128.4, 129.3, 129.5, 133.4, 135.1, 135.4, 144.2, 147.5, 152.4, 163.5, 167.9; MS (ESI): M=558, found 559 $[M+H]^+$.

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