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Theoretical Study of Angiotensin Receptor Blockers Losartan Candesartan and Olmesartan and Their Suggested Metabolites

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Abstract: The activity of most Angiotensin Receptor Blockers (ARBs) is associated with the stability of their metabolites via a process termed bio-activation. A process called biotransformation forms these stable metabolites. The reactivity of these metabolite intermediates makes it difficult to observe and describe them directly. This work employed computational chemistry to investigate certain (ARBs) and their metabolites, as well as to forecast the most stable parent drugs. HOMO values show that the Losartan metabolite (Losa.M) product is the lowest energy value for the HOMO values, the thermodynamic energy, and the zero-point energy, in addition to having the lowest value of entropy associated with the rest of the other compounds. Losa. metabolism or biotransformation occurred via the oxidation of methanol moiety at position 5 of imidazole heterocyclic ring which produces the more stable carboxylic acid metabolite Losa M., this chemical reaction does not occur in the case of Olme and Cande. Olme and Cande undergo metabolism in another mechanism which is ester hydrolysis process, this reaction occurs rapidly and completely by GI esterases, the HOMO of these two drugs has low energy, (their HOMOs are not filled), and they are highly susceptible to reduction. and thus, this potential hydrolysis increased the drug metabolism and thus excretion.

Keywords: ARBs, Losartan, Candesartan, Olmesartan, Computational Chemistry, AM1, PM3.

Introduction:

Antihypertensive medications known as angiotensin receptor blockers (ARBs), also known as angiotensin (AT1) receptor antagonists, work by blocking the effects of the hormone angiotensin II (Ang II) in the body, decreasing blood pressure (Block and Beale, 2004). Because their structures are similar to those of Ang II, they bind to receptors as inhibitors. These agents considered as an excellent tolerability profiles since 1995 (Sipahi *et al*, 2010). Both professionals and the Food and Drug Administration have largely discounted these concerns (FDA), (Pasternak *et al*, 2011).

Ang II, which was isolated in the 1930s are naturally occurring hormone that is a portion of the renin-angiotensin system, which results in powerful systemic vasoconstriction (Brown *et al*, 2013).

This hormone activates two types of angiotensin II receptors: the first (ATR1) receptors, which are abundant in the vessels, brain, heart, kidney, adrenal gland, and nerves, and the second (ATR2) receptors, which are only found in small amounts in the adult kidney, adrenal gland, heart, brain, uterus, and ovary (Appel and Appel, 2004).

The activation of (ATR1) causes an increase in inositol triphosphate and various arachidonic acid metabolites, as well as a decrease in cyclic adenosine monophosphate. Therefore, this results in vascular smooth muscle constriction, aldosterone and sodium reabsorption in the proximal tubule, and cell growth in the arteries and heart (Block, and Beale, 2004; Sipahi *et al*, 2010; Pasternak *et al*, 2011; Brown *et al*, 2013; Appel and Appel, 2004; Brenner and Stevens, 2013).

Because it stimulates catecholamine release from the adrenal medulla and nerve terminals, angiotensin II also causes sympathetic nervous system hyperactivity (Weir and Dzau, 1999).

To decrease the cardiac afterload and preload, ATR1 must be antagonized (Brenner and Stevens, 2013).

By using molecular modelling, it was seen in the 1980s that two agents namely S-8307 & S-8308 Non-peptide Ang II receptors and their structures would have to closely resemble the pharmacophore of Ang II to be particularly, selective, and promising (Goodman and Gilman's, 2006).

Losartan, an orally active, potent, and selective non-peptide AT1 receptor blocker, created after modifying its structure.

Since 1995, approval obtained for the use of Lorestan as a treatment product in the United States of America, after which six additional blockers were approved (Goodman and Gilman's, 2006; Farsang and Fisher, 2006). These medicines are recognized for having great side-effect profiles that have been demonstrated in clinical studies to be comparable to placebos (inert tablets with no therapeutic value) (Arnstein *et al*, 2011), these ARBs employ their antihypertension properties mainly by a drop of peripheral vascular resistance (Israili, 2000). Candesartan (Cande.), scheme (1a), as AT1 receptor antagonists bind to and inhibit the angiotensin II receptor type 1 (AT1), blocking the renin-angiotensin system's arteriolar contraction and Na element retention effects (Bakris *et al*, 2001).

These ARBs have differed in their binding characteristics to the ATR1 subtype of angiotensin II receptor, Preclinical studies have established that candesartan is different in its binding properties to the ATR1 than other ARBs by its highly selective and has an in vitro affinity for this receptor 80 times greater than that of losartan (Cernes *et al*, 2011). Losartan (Losa.), an ATRII receptor antagonist, is the first of a new class of agents to be introduced for the treatment of hypertension (McIntyrea *et al*,1997). Losartan's mode of action includes perfections in vascular structure and endothelial function with decreases in vascular oxidative stress and reductions in left ventricular hypertrophy and myocardial fibrosis (Timmermans *et al*,1999). All these with modulation of atherosclerotic disease progression and lower serum uric acid levels (a proposed independent risk factor for cardiovascular disease) appear to be a molecule-specific effect (Díez, 2006). Losartan (Losa.) is effective with once-daily dosing and has an excellent safety profile. This agent is a useful first-line or add-on treatment option in patients with hypertension (Conlin, 2001). Olmesartan (Olme.) is the final ATRII receptor antagonist in this study. It is a hypotension agent and used to treat heart failure patients with diabetic kidney disease. It is a reasonable first-line treatment for high blood pressure, and it should take by mouth. It comes in two versions: olmesartan/hydrochlorothiazide and olmesartan/amlodipine (Fischer *et al*, 2006). Bioactivation is a process that links the activity of most (ARBs) to the stability of their metabolites. A process known as biotransformation produces these stable metabolites. The reactivity of these metabolite intermediates makes it difficult to observe and describe them directly.

The aim:

The goal of this work is to investigate the stability of some (ARBs) metabolites and to forecast the most stable parent drugs using computational chemistry.

Computational Chemistry:

Computational chemistry has proven to be a valuable tool for researching materials that are either impossible to obtain or prohibitively costly.

It also aids chemists in making forecasts before to doing real experiments, allowing them to be more qualified to make observations. The bases for most computational chemistry theory and computer applications are in quantum and classical mechanics, as well as mathematical physics and thermodynamics. This is how they use geometry to model atoms and molecules**.** The most important computational techniques are ab-initio, semi-empirical and molecular mechanics (Young, 2001). Therefore, used to study the Angiotensin Receptor Blockers (ARB): Losartan (Losa.), Candesartan (Cande.), Olmesartan (Olme.) and their Metabolites, as shown in Fig (1):

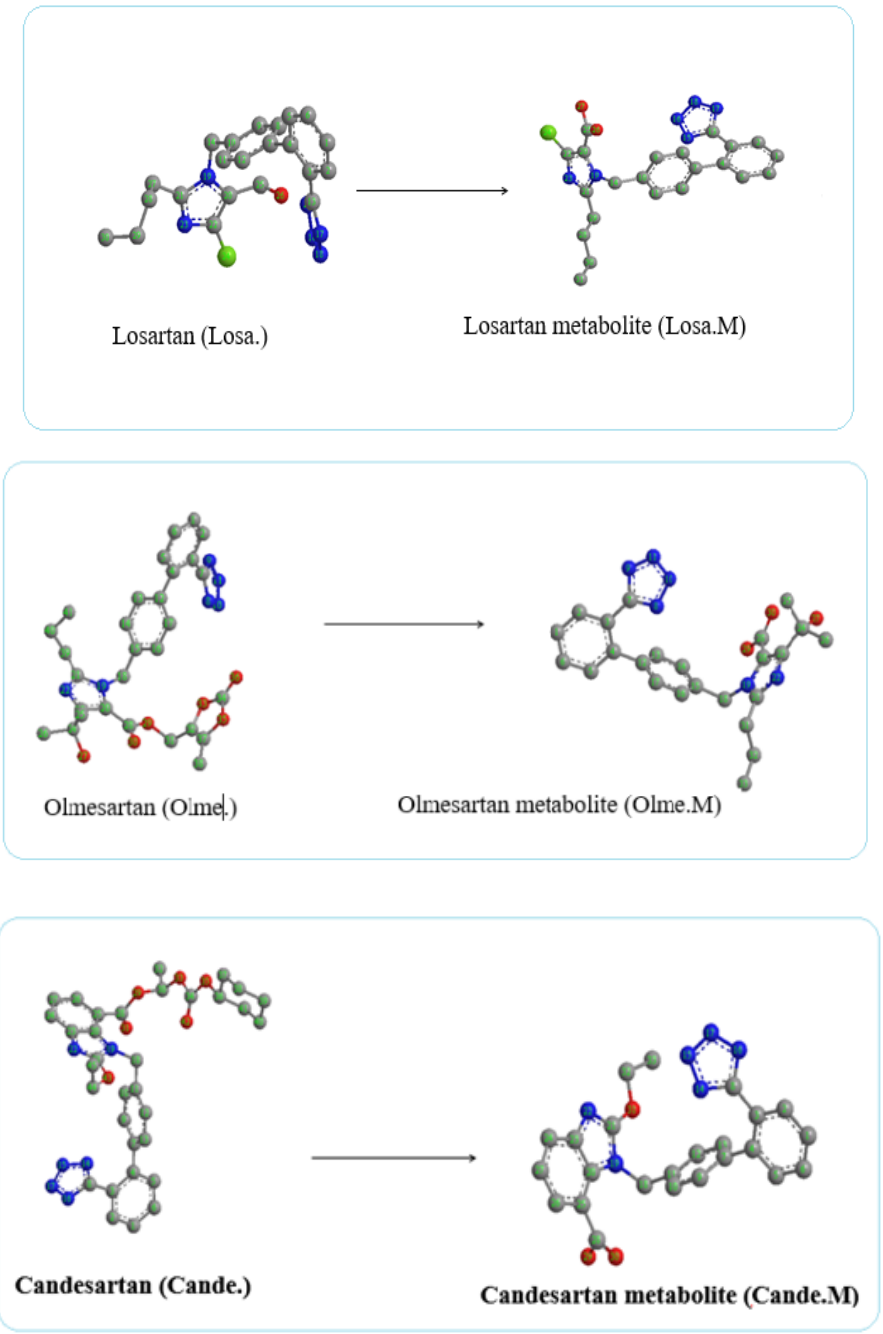


Fig (1): A schematic illustration of (Losa., Cande. And Olme.) conformations and their metabolites (Losa.M, Cande.M and Olem.M)

Computational Detail:

Angiotensin receptor blockers (ARBs): (Cande., Losa. and Olem.) and their metabolites) were theoretically treated using the Chem Office 3D program. At first, the compounds were drawn using Chem. Draw.2D, version 16, and after checking the correct structures, then converted to Chem. 3D and a series of theoretical calculations were done. The minimization has done by using molecular mechanics (MM2) and molecular dynamics until the molecule reached its lowest energy state (Zgarbova *et al*, 2010).

The minimization process repeated using quantum mechanics, the Austin Model1 **(**AM1) system, and then Parametric Method 3(PM3), a semi-empirical approach for quantum molecular electronic structure calculations, to reach the lowest energy level of each molecule.

After having the globe state, different properties and parameters for each molecule had calculated by using the Gaussian Interface version 09 program (Frisch, 2009).

The HOMO and LUMO energy values calculated, and were the basic values for calculating many descriptors such as chemical hardness (η), electronic chemical potential (μ) and electrophilicity (ω). Chemical hardness measures the resistance to change in the electron distribution or charge transfer of a chemical system (Peters *et al*, 1998).

Chemical hardness corresponds to the gap between the HOMO and LUMO, chemical hardness (η) is approximated using equation (1).

$\eta = (E_{LUMO} - E_{HOMO}) / 2$ – – – – 1

E_{LUMO} and E_{HOMO} are the LUMO and HOMO energies. Electronic chemical potential has defined as the negative electronegativity (μ) of a molecule and it had calculated by using equation (2).

$\mu = (E_{HOMO} + E_{LUMO}) / 2$ – – – – 2

While the electrophilicity index (ω) is calculated using the electronic chemical potential and chemical hardness (ω) as shown in equation (3).

$\omega = \mu 2 / 2\eta$ – – – – 3

In addition to the previously computed descriptions, the thermodynamic energy and the energy of the molecule were calculated the zero-point energy, and the entropy of the particles was calculated.

Results and Discussion:

As shown in Table (1), the important descriptors that have been computationally calculated for angiotensin receptor blockers (ARBs): Losartan (Losa.), Candesartan (Cande.) and Olmesartan (Olme.) and their suggested metabolites (Losartan. M.), (Cande.M.) and (Olme.M.)**,** these were depending in their calculation on the energy of HOMO and LUMO, the direct relationship to the stability of the compounds and their physical properties. The lower the energy of the HOMO, the more stable the compound might become. The HOMO alone is insufficient to predict its reaction. The relative occupancy of the HOMO and the LUMO, as well as the LUMO's electricity, plays a part. Thus, when the HOMO has low energy, (the HOMO did not fill), the compound is highly susceptible to reduction. These HOMO values, which obtained from AM1 and PM3, show that the (Losa.M) metabolite product is the lowest energy value for the HOMO values, the thermodynamic energy, and the zero-point energy, in addition to having the lowest value of entropy associated with the rest of the other compounds. Each angiotensin receptor blocker (ARB), which compared with its metabolite, shows that the metabolite molecule more stable compared with the parent drug molecule. However, this was done through the energy values in addition to the entropy value of the molecules, but angiotensin receptor blocker (Cande) molecule is the lowest stable, and these metabolites arranged from the least to the most stable as Cande.M, Olem.M, and Losa.M respectively, and these results indicated that angiotensin receptor blocker (Losa) is the most active one.

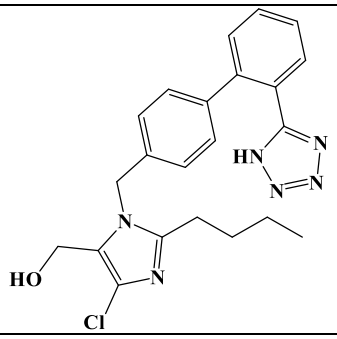
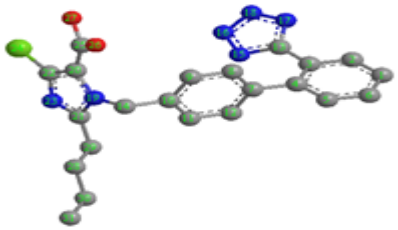
Table (1): Theoretical descriptors of (ARBs): (Cande.) , (Losa), (Olem), and their metabolites.

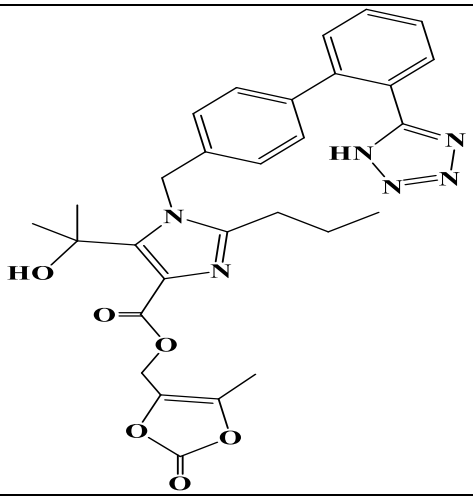
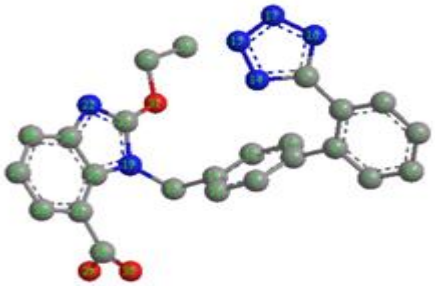
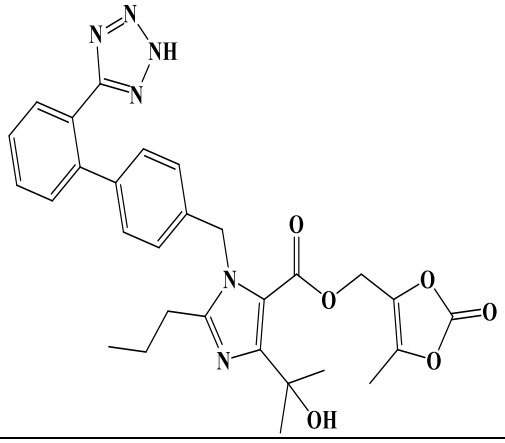
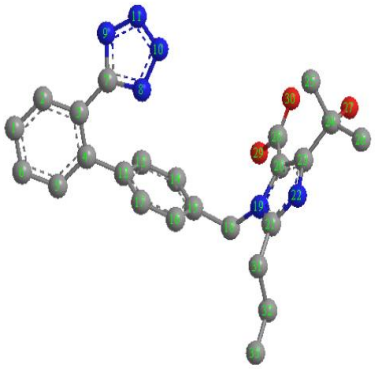
Parameters \ Compounds	Cande	Cande.M	Losa	Losa.M	Olem	Olem.M
HOMO (AM1)	-0.3312	-0.33612	-0.33968	-0.35969	-0.35523	-0.35627
HOMO (PM3)	-0.33486	-0.33677	-0.33336	-0.35458	-0.35621	-0.36008
LUMO (AM1)	-0.02547	-0.02879	-0.02559	-0.02628	-0.03367	-0.03191
LUMO (PM3)	-0.03384	-0.03585	-0.03558	-0.0386	-0.04066	-0.03959
HOMO–LUMO gap 1	0.30573	0.30733	0.30733	0.33341	0.32156	0.32436
HOMO-LUMO gap 2	0.30102	0.30092	0.30092	0.31598	0.31555	0.32049
Hardness η (a.u)	0.152865	0.153665	0.153665	0.157045	0.160780	0.162180
Hardness η(Kcal/Mol)	95.924	96.426	96.426	104.609	100.891	101.769
Chemical potential μ (ev)	-0.178335	-0.182455	-0.182455	-0.192985	-0.194450	-0.194090
Electrophilicity index ω (ev)	0.104024	0.108319	0.106197	0.111704	0.117586	0.116139
RMS (Kcal/Mol)	0.0008	0.0033	0.0037	0.0014	0.0015	0.0012
Finished Energy (Kcal/Mol)	-87.65	-55.12	-87.96	-46.55	-87.61	-54.1
Entropy S (Cal/Mol-Kelvin	207.609	161.165	154.558	152.96	204.698	162.84
Thermodynamic Energy (Kcal/Mol)	446.482	291.232	300.234	287.999	400.547	336.912
Zero-point Energy (Kcal/Mol)	425.830	276.876	286.990	274.624	380.433	321.894
No. of H-Bond Acceptors	9	8	7	7	9	8
No. of H-Bond Donors	1	2	2	2	2	3

Chemistry:

The chemical structures of angiotensin receptor blockers (ARBs): Losartan (Losa.), Candesartan (Cande.) and Olmesartan (Olme.) and their suggested metabolites (Losartan. M.), (Cande.M.) and (Olme.M.) were listed in Table (2).

Table (2): The chemical structures of angiotensin receptor blockers (ARBs): Losartan (Losa.), Candesartan (Cande.) and Olmesartan (Olme.) and their suggested metabolites (Losartan. M.), (Cande.M.) and (Olme.M.)

ARBs	ARBs Structure	ARBs metabolite Structure
Losa.		

Cande.		
Olme.		

Experimental and Methods:

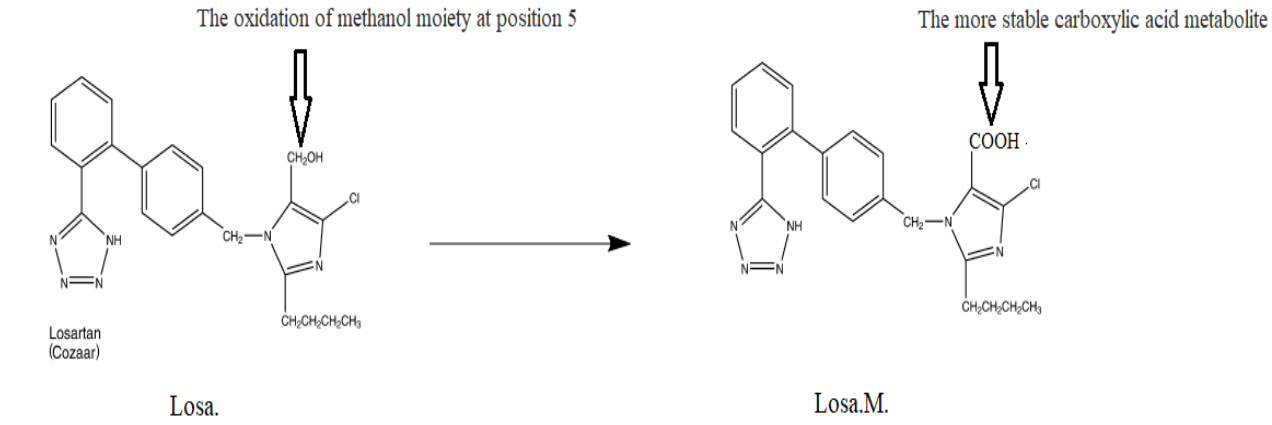
The CS Chem Office (version 16) software package was applied for theoretical calculations, the Semi-empirical approach (Gaussian) was employed, whereas, for energy value calculations, the Semi-empirical method was utilized. In addition, the (MM2) method was used to calculate the steric energy (S.E) of a molecule that required calculations. The molecule was drawn using CS Chem Office Draws, then transformed to a three-dimensional structure (3D-structure), and calculations were performed on it.

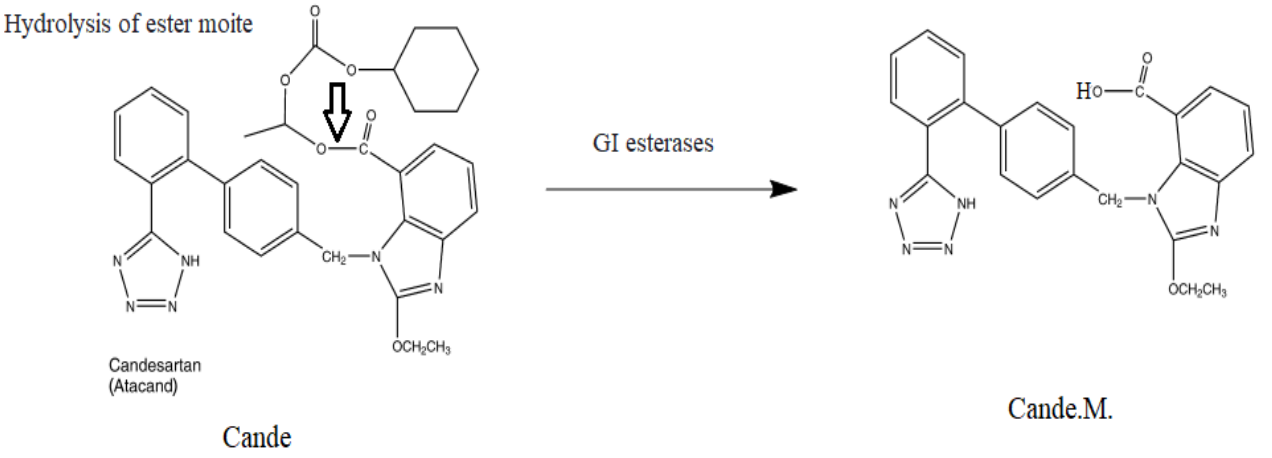
AM1 was used for semi-empirical calculations, and MM2 was used for molecular mechanic calculations. Bond length and energy were used as variables in spreadsheets and graphs. The independent variable was a bond length, whereas the dependent variable was bond energy.

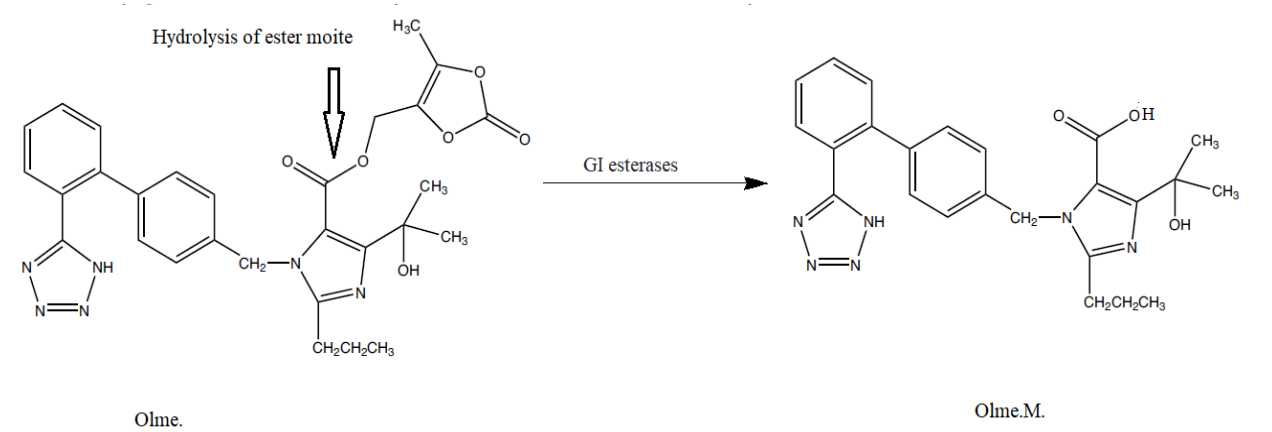
All the results of, Computational calculations data of angiotensin receptor blockers (ARBs):

Losartan (Losa.), Canesartan (Cande.) and Olmesartan (Olme.)

and their suggested metabolites (Losartan.M.), Cande.M.) and (Olme.M.) were listed in Table (1), and their chemical structures were listed in Table (2).







Conclusion:

Losa M. is the most stable metabolite, which means that its parent medication Losa is the most effective hypotension power followed by Olem. and Cand.

To predict the activity of drugs via the computational study of their metabolites stability which is produced by biotransformations which are known as phase 1 metabolism or (functionalization), this enzymatic reaction involved one or more sequential reactions like oxidation, reduction or, hydrolysis (Bachmann, 2009). HOMO values show that

the (Losa.M) metabolite product is the lowest energy value for the HOMO values, the thermodynamic energy, and the zero-point energy, in addition to having the lowest value of entropy associated with the rest of the other compounds. Losa. metabolism or biotransformation has occurred via the oxidation of methanol moiety at position 5 of the imidazole heterocyclic ring which produces the more stable carboxylic acid metabolite Losa M. This chemical reaction does not occur in the case of Olme and Cande. Therefore, Olme. and Cande. Undergoes metabolism in another mechanism which is the ester hydrolysis process, this reaction occurs rapidly and completely by GI esterase, the HOMO of these two drugs has low energy, (their HOMOs are not filled), and they are highly susceptible to reduction. Thus, this potential hydrolysis increased the drug metabolism and thus excretion (Ferreirósab *et al*, 2007)

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