DOCKING STUDIES OF A NEW HETEROCYCLIC METHYLTHIOMORPHOLIN PHENOLS DERIVATIVES AS ANTIHYPERTENSIVE DRUGS WITH ACE TARGET.

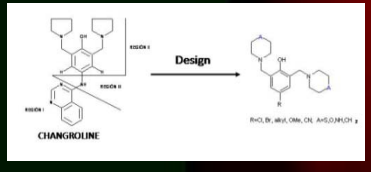
CASE FESCDIPINE II

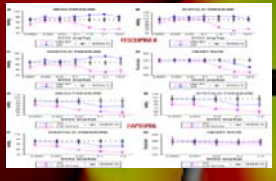
[1]V. Vázquez,[1]O. Vázquez, [1,2]M.A.Balboa, [1]A. Ma. Velázquez, [1]V.H. Abrego, [1]B.Camacho, [1]L. Martínez, [1]L.A. Torres, [1]A. Ramírez, [1]I.Martínez, [3]R.López-Castañares, [1]S.Díaz-Barriga, [4]J. Bocanegra, [4]Froylan Gómez-Laguna, [1]F. Olvera, [1]E.Angeles.

1) Departamento de C. Químicas FESC, UNAM, 2) Facultad de C. Química UNACH, 3) Facultad de Química, UAEM, 4) Facultad de Medicina UNAM email:angeles@servidor.unam.mx

•In the last twenty years, cardiovascular diseases have become the world's leading cause of death. In 1983, Stout and his research group, studied the structure of changrolin for its dissimilarity with currently marketed antiarrhythmics; there are also other recent studies about the biological structure activity relationships. In our experience, methylmorpholinphenol and methylpiperidinylphenol derivatives show cardiovascular effects and, in the literature, there is only one report about the cardiovascular effects of methylmorpholinphenols. We now report, as part of the Drug Design in Medicinal Chemistry Program of the UNAM, new methylthiomorpholinphenol compounds with cardiovascular effects, considering that the development of new antihypertensive drugs is justified as there is a need to search for medicines that promote blood pressure decrease, such as monotherapy, to achieve a good protection for most hypertensive patients and a reduction in adverse reactions. In this case FESCDIPINE II, was an excellent antihypertensive drug, that has low toxicity and preliminary studies indicate that the Angiotensin-converting enzyme (ACE) system is the biological target of this compound. Through this data we can conclude that the thiomorpholinic compounds have the higher affinity to the ACE active site that we computed, and that the 319 (FESCDIPINE II), 318 and 322 compounds have the optimal energy value range than all over the other compounds, thiomorpholinic and morpholinic. So we can say that the Angiotensin-Converter Enzyme could be the target for the compounds of the LQM 300's.

• In this research, some of these compounds were compared with captopril (ACE inhibitors), in normotensive and hypertensive rat. The results obtained in the dose effect curves in the arterial pressure model show two important candidate compounds as LQM319, since these have a lower ED50 than the other synthesized compounds. In addition, we determined that some compounds exist that not only reduce arterial pressure but also reduce heart rate. This could be relevant because, in these compounds, we can find the groups that influence the decrease in cardiac rhythm and then test them in a cardiac arrhythmia model. On account of their characteristics, they are prime candidates to exert possible anti-arrhythmic activity.





• Methods

•We modelled the members of the LQM-300 family with the *sybyl* program and using a conformational analysis we obtained the lowest energy conformer for each compound. After that we obtained the ACE through the Cambridge Protein Data Bank. The enzyme has a resolution of 1.8 angstroms, this resolution value gets between the optimal range of 1.6-2.0 angstroms of resolution. With the modelling interface of *sybyl* we clean up the ACE of any other molecules, and using the *what if check* program the enzyme was optimized. Using the *fast ms channel* model the ACE cavity was measured and through this we compute the Active site of the enzyme. We compared the compounds of the LQM-300 family through their biological activity *in silico* against the ACE (Angiotensin-Converter Enzyme) using the Sybyl *Docking* method and computing their complexes energies.

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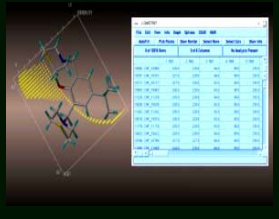
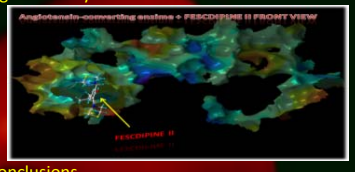
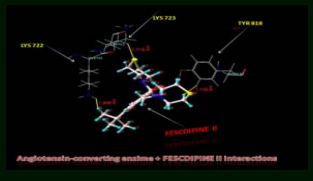


•Results

•We determined that the ACE is a possible target for the compounds of the LQM 300 family but the most relevant results are from LQM 319 (FESCDIPINE II), LQM318 and LQM322 which has the most optimal energy value. All the energy values results are shown on the table 1. And as it can be observed the thiomorpholinic compounds are those who have the higher affinity with the ACE.





•Conclusions

•Through this data we can conclude that the thiomorpholinic compounds have the higher affinity to the ACE active site that we computed, and that the 319 (FESCDIPINE II), 318 and 322 compounds have the optimal energy value range than all over the other compounds, thiomorpholinic and morpholinic. So we can say that the Angiotensin-Converter Enzyme could be the target for the compounds of the LQM 300's.

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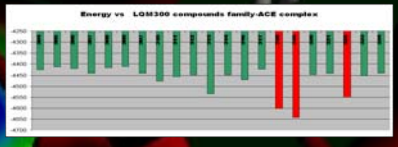

•We can say that the development of new antihypertensive drugs is justified because it is necessary to search for drugs that are able to reduce blood pressure, like monotherapy, in order to achieve good protection for the majority of hypertensive patients and a reduction of adverse reactions. As shown, the compound that exhibited the highest antihypertensive activity in the conscious spontaneous hypertensive rat model was LQM319 (FESCDIPINE II), confirming what has been observed in the anesthetized rat model. Finally, we observed that of the studied compounds, LQM319 (FESCDIPINE II) exhibits the best decreasing effect in both systolic and diastolic pressure; it also exhibits the best heart rate decreasing effect. The results obtained suggest that LQM compounds have a hypotensive effect and could be used for chronic patients and previous studies of toxicity and genotoxicity show that FESCDIPINE II is less toxic that captopril

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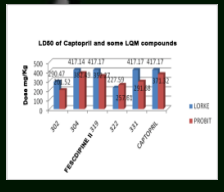

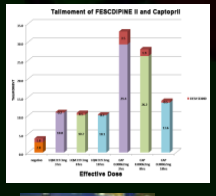

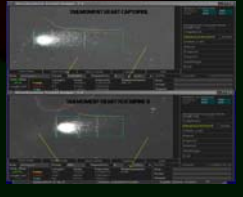

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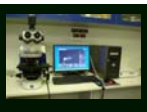

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•References:

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