The Development of New Molecules Having Antiemetic Activity Using Molecular Modeling

1Khalil Errahmane Kanouni* and 2Yacine Benguerba

1Department of Process Engineering, Faculty of Technology, Laboratory of Chemical Process Engineering, Sétif-1-University, 19000 Sétif, Algeria
2Centre de Recherche en Biotechnologie (CRBt), Constantine, Algeria

Abstract: The solubility of a drug in water or in the blood represents the most desired parameter in medicine. Our aim is to obtain molecules with properties more effective than those of metoclopramide. In this work, two molecules with high solubility are constructed. Metoclopramide (a benzamide derivative) is a dopamine receptor antagonist used as an antiemetic drug. Its solubility in water is 200 mg/L at 25°C. In this work, we will develop two other molecules that have the same therapeutic activity of metoclopramide with a higher solubility in water, therefore in the blood, without affecting the other properties. The two molecules developed by molecular modeling with a chemical modification of the OH group of metoclopramide have a high solubility: approximately 3 times and 8 times that of metoclopramide. For the other physicochemical properties, there is a great similarity between the molecules. Thus, the two proposed molecules will have antiemetic activity, the second molecule will be more favorable because of its higher solubility and the number of HBA and HBD.

Keywords: Solubility, Drug, Metoclopramide, Antiemetic, Molecular Modeling

Introduction

Computers have become indispensable tools in modern pharmaceutical chemistry (Lewars, 2019). The role of the latter has become very essential, both in the discovery of new drugs and the development of them (Cui, 2011). Rapid advances in software and hardware have meant that most of the operations that could be done by experienced computer scientists can now be performed by pharmaco-chemists, with computers commonly used in laboratories, provided they possess the elementary notions of quantum mechanics and other equations that relate to molecules (Stellmach, 2009).

Molecular modeling (Zhang et al., 2019a) is an application of theoretical and computational methods to solve problems involving molecular structure and chemical reactivity. Molecular modeling is the investigation of molecular structures, (Baran, 2019) using computational computer chemistry (Jolfaei et al., 2020) and graphical visualization techniques (Zhu et al., 2018) to give a plausible three-dimensional representation in defined circumstances and to determine the physico-chemical properties.

Molecular modeling involves the use of theoretical calculation methods (Bošnjaković-Pavlović et al., 2019) (molecular mechanics, molecular dynamics, ab-initio or semi-empirical quantum mechanics (Wormald and Hawari, 2017), ...) to determine the graphical representation of the geometry or the configuration of the molecule atoms (Barabas et al., 2019) and to evaluate the physicochemical properties of the studied molecule (Lecerf et al., 2019). Molecular modeling associated with an infographic representation of stereochemistry makes it possible to interpret physico-chemical phenomena (Rasmussen et al., 2018), to suggest new experiments and thus to analyze results in a more critical way than the experiments conventionally used (Zeng et al., 2018), but these two purely theoretical approaches or experimental are complementary.

An antiemetic is a drug that can relieve preventatively or curative vomiting and nausea (Li et al., 2016), metoclopramide is the most commonly used antiemetic medication and is administered orally (Umar, 2018).

The majority of oral medications have a high solubility (Ferguson et al., 2019), but that of metoclopramide is very low (0.986 mg/L) (Kanouni et al., 2019). For this reason, we will seek in this work to develop another drug that has the same therapeutic activity of metoclopramide and a higher solubility, without influencing on the other physicochemical properties.
Problematic

✓ Most antiemetic drugs have a low solubility
✓ We must develop a new drug with the same effect and higher solubility

Objectives

✓ We will develop a drug that binds to the receptor site of metoclopramide and gives the same therapeutic activity
✓ This medicine must have better properties (solubility) than metoclopramide

Methods and Computational Details

Using the molecular modeling and the application of the different theoretical methods we can calculate some properties: $\xi_{\text{HOMO}}$, $\xi_{\text{LUMO}}$, (Santos et al., 2019) the Dipole Moment (Lindic et al., 2019), Log (P) (Caron et al., 2018), the solubility... of three bioactive molecules.

In this work we will study the affinity of molecules (Lan et al., 2019) to the receptor sites to confirm that all molecules are attached to the same receptor site (Zeng and Gifford, 2019), a comparative study of the bonds between each molecule with the receptor site helps us to know the molecule that has a great affinity so a better effect (Aviño et al., 2019).

Then we will calculate the energies $\xi_{\text{HOMO}}$ and $\xi_{\text{LUMO}}$, the electronic chemical potential, the global hardness (Arab et al., 2016) and electrophilicity index for each molecule, in order to explain that the three molecules can belong to the same therapeutic class so they can have the same therapeutic effect (Qian et al., 2019).

In this work the chosen method is the DFT (Chanana et al., 2019) because it is the best in the electronic description of the molecule and associated properties, as well as it is widespread for the analysis of molecules for the purpose to obtain information on their structures and chemical environments. Calculations were made with TmoleX and COSMOtherm programs (Klamt and Eckert, 2004).

Results and Discussion

The two proposed molecules have a structure similar to that of metoclopramide, the only difference being the substitution of the atom "Cl" with "F" in the molecule_1 and the "OH" in the molecule_2, the structures of metoclopramide. and both molecules are shown in Fig. 1 to 3.

When applying the Structure/Activity relationship (Ghawanmeh et al., 2020) to these molecules, we can assume that the three molecules have the same therapeutic effect (Thirumaran et al., 2019).

To validate this proposition, we will calculate the affinity of these three molecules to the different proteins (receptor sites).

The receptor sites are:

✓ **GPCR ligand:** G protein-coupled receptors, also includes Dopamine D3 (So et al., 2020)
✓ **Ion channel modulator:** Ion channel modulator, is a type of drug that can modulates ion channels (Churchill et al., 2019)
✓ **Kinase inhibitor:** Represent a type of enzyme inhibitor that can block the action of a protein kinases. Protein kinases are enzymes that add a Phosphate (PO₄) group to a protein and can modulate its function (Xie et al., 2020)
✓ **Nuclear receptor ligands:** Are active proteins in the nucleus of cells (Guan et al., 2019)
✓ **Enzyme inhibitor:** Is a substance that binds to an enzyme to decrease its activity
✓ **Protease inhibitors:** Are a class of antiviral drugs used in the treatment of HIV (Zhang et al., 2019b)
From the affinity values towards the 6 protein receptors represented in Fig. 4 we remark that the fixation of the two molecules is directed towards the GPCR protein ligand: The G-protein coupled receptors, also includes Dopamine D3 like metoclopramide (Gurevich et al., 2016).

The most important remark in Fig. 5 is the equality of the number of rotatable bonds because there is no big difference between the three structures and also the most necessary remark is that the number of HBA and HBD of molecule_2 are greater than those of metoclopramide and molecule_1, this difference is due to the presence of the (OH) group (Palomba et al., 2018), this difference also improves the affinity of the molecule towards the receptor site.

Frontier orbitals are two types of particular molecular orbitals: the HOMO: Energy of the highest occupied molecular orbital by at least one electron and the LUMO: Energy of the lowest unoccupied molecular orbital by an electron (Zhao et al., 2019).

**Fig. 4:** Affinity of the molecules for the different receptor sites

**Fig. 5:** Bonds made by molecules
It has been observed in Fig. 6 that the three molecules have very close values for $\xi_{\text{HOMO}}$ and also for $\xi_{\text{LUMO}}$ so they have a very close reactivity, that expresses the proximity of the pharmacological effect (Mary et al., 2015) of these molecules towards the receptor site.

The electronic chemical potential $\mu$ and the global hardness $\eta$ (Zohdy et al., 2019) can be calculated from the energies of the molecular orbitals boundaries $\xi_{\text{HOMO}}$ et $\xi_{\text{LUMO}}$ as following:

$$\mu = (\xi_{\text{HOMO}} + \xi_{\text{LUMO}})/2$$



$$\eta = (\xi_{\text{LUMO}} - \xi_{\text{HOMO}})$$

The electrophilicity index is defined as the energy stabilization due to the charge transfer it is noted $\omega$ (Wei et al., 2019):

$$\omega = \mu^2 / 2 \eta$$

From the values of electronic chemical potential $\mu$, represented in Fig. 7 it is noted that they are almost similar (approximately -0.12 au). The same remark is also observed for the electrophilicity index $\omega$ (about 0.07 au).

The global hardness $\eta$ represents the strongest index to confirm the therapeutic class of a series of drugs, we note that the values of $\eta$ are very close for the 3 molecules for that we can confirm that they belong to the same therapeutic class (Noureddine et al., 2019).

The results given in Table 1 show that the values of the HOMO-LUMO energies are very close between the three molecules (about 3 eV), the same remark is also observed for the Molecular Weight (MW), the volume and the Total Polar Area Surface (TPSA), as well as the Log(P) which makes it possible to apprehend the hydrophilic or lipophilic character of the molecule (Zhang and Jiao, 2019) and since the three molecules have a Log (P) between (0 <Log (P)<+5) we can say that they have both hydrophilic and lipophilic characters (Finat, 2016).

According to the solubility values of the two molecules represented in Fig. 8 we note that they are higher than that of metoclopramide in terms of solubility, so they will be more soluble in the blood (Loonen et al., 2019).

Table 1: Different properties of the three molecules

| Log (P) | TPSA (Å²) | Volume (Å³) | MW (g/mol) | HOMO-LUMO (eV) | Molecule          |
|--------|-----------|-------------|------------|----------------|------------------|
| 2.54   | 67.59     | 278.91      | 299.80     | 2.98           | Métoclopramide   |
| 2.02   | 67.59     | 270.31      | 283.35     | 2.82           | Molecule_1       |
| 2      | 88        | 273         | 281        | 3.18           | Molecule_2       |

Fig. 6: Molecular orbital energies: HOMO_LUMO
Conclusion

Using the molecular modeling we have built two molecules whose structure is close to that of metoclopramide having similar therapeutic effect because they are fixed on the same receptor site, these molecules have a great solubility:

- $S_{\text{molecule}_1} = 3 \times S_{\text{metoclopramide}}$
- $S_{\text{molecule}_2} = 8 \times S_{\text{metoclopramide}}$

So they have no problems of dissolution (Dong and Yang, 2020).

For the other physico-chemical properties there is a great similarity between the molecules. Thus, it can be concluded that the two proposed molecules may have antiemetic activity and the molecule_2 is the best because it has a higher solubility and also the number of HBD and HBA (Salehi et al., 2019).

This work is carried out by molecular modeling software and it will soon require in-vitro and in-vivo experiments for the confirmation of the results.
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Author’s Contributions
Khalil Errahmane Kanouni participated in:
✓ Contribution and design of data
✓ Analysis and interpretation of results
✓ Drafting the article
✓ Read and approved the manuscript.

Yacine Benguerba participated in:
✓ Contribution and design of data
✓ Analysis and interpretation of results
✓ Reviewing the article
✓ Read and approved the manuscript.

Ethics
This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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