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PHYSICO-CHEMICAL PROPERTIES OF SOME ANTIBIOTICS WITH TUBERCULOSTATIC ACTIVITY

BY

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Abstract. Tuberculosis is an infectious disease which affects, usually, the lungs but it can also spread to other parts of the body. The treatment consists in administration of antibiotics for several months. The goal of this paper is to analyze some of these pharmaceutical compounds and to calculate main physico-chemical parameters, using molecular modeling methods.

Keywords: antibiotics; tuberculosis; electro-optical parameters.

1. Introduction

Antibiotics are pharmaceutical compounds acting against micro-organisms, *e.g*. bacteria, being used to treat several types of infections.

Tuberculosis is a spreadable disease caused by Gram positive bacteria called *Mycobacterium tuberculosis.* The infection can arise in the lungs, when

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the disease is known as pulmonary tuberculosis, or it can be developed in other organs, mainly in pleura, central nervous, lymphatic and genitourinary systems, known as extra-pulmonary tuberculosis.

Tuberculosis causes a high number of deaths worldwide, even exceeding the ones caused by HIV infections. It is a disease sustained by poverty with a cure rate of only 1.5% due to the more and more frequently development of multi-drug resistant tuberculosis (Patil, 2018).

The anti-tuberculosis drugs are those natural, semisynthetic or synthetic compounds that are effective in the pulmonary and extra-pulmonary infections caused by *M. tuberculosis* (Cristea, 2006).

By their use in the treatment of tuberculosis, they can be classified in:

1. Major anti-tuberculosis drugs, "first line" choice: isoniazid, rifampicin, pyrazinamide, ethambutol.

2. Minor anti-tuberculosis drugs, "back-up" choice: ethionamide, prothionamide, aminosalicylic acid, cycloserine, ofloxacin, moxifloxacin and levofloxacin (Caminero, 2015).

From the major anti-tuberculosis drugs class, the first three of them are considered the core molecules, while ethambutol is a companion drug. A standard therapy for tuberculosis consists from a combination between these four compounds.

Isoniazid

Isoniazid is a very effective anti-tuberculosis drug that can be used with good results in monotherapy or for tuberculosis prevention. Unfortunately, it brings along a series of toxic effects such as severe hepatotoxicity, fact that limited it's use (Wang, 2016).

Pyrazinamide

Pyrazinamide is a drug with a very good tissue distribution, including the cerebrospinal fluid, fact that makes it active even in the central nervous system tuberculosis. Drug resistance occurs very rapidly when used as monotherapy, which is why this molecule is always associated with other drugs in therapy. As for side effects, hepatotoxicity expressed by hepatitis and hepatic necrosis represents a major drawback.)

Ethambutol

Ethambutol is a compound with bacteriostatic action on *M. tuberculosis* that is found in the multiplication phase. In the tuberculosis treatment, this drug is recommended to be associated with others chemotherapeutical agents, being utilised especially for elderly patients. The main side effect is the optical damage, fact that requires an attentive examination of the ocular function before, meanwhile and after treatment.

2. Computational Method

Isoniazid, Pyrazinamide and Ethambutol were studied using HYPERCHEM and semi-empirical method PM3 developed by J.J.P. Stewart and published for the first time in 1989 (Stewart, 1989). Semi-empirical methods have an advantage over ab-initio methods in studying medium and large molecules. PM3 quantum chemical calculations were carried out with HyperChem 8.0 Molecular Modeling program (www.hyper.com) with root mean square (RMS) gradient 0.1 kcal/ mol using Polak–Ribiere algorithm. All the parameters were allowed to relax and all the calculation converged to an optimized geometry, which corresponds to a true energy minimum.

3. Results and Discussions

The structural formulas for the studied compounds are represented in Fig. 1.

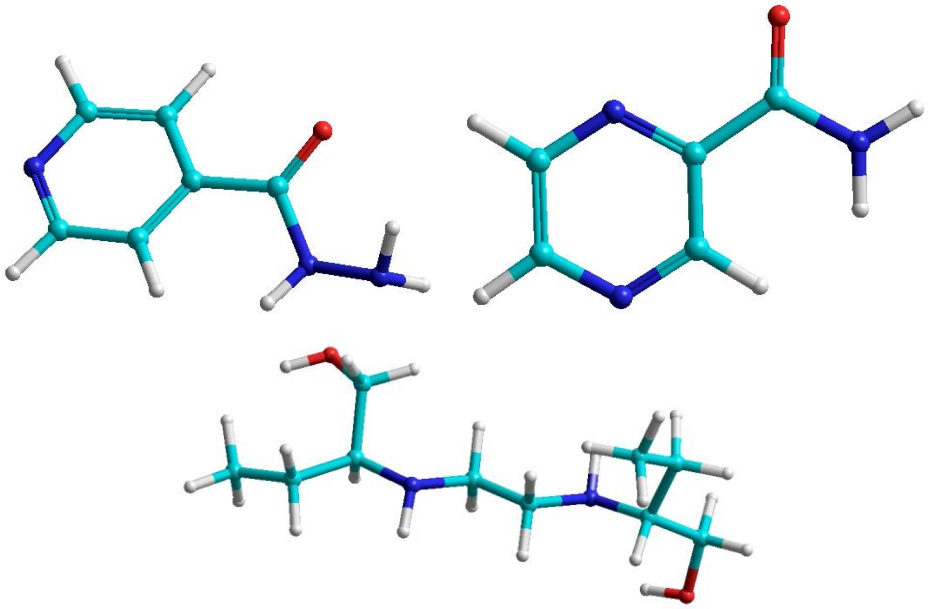

Fig. 1− Isoniazid, Pyrazinamide and Ethambutol molecules
(green-carbon, white-hydrogen, blue-nitrogen and red-oxygen).

The energies of the frontier molecular orbital, HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital), can be used to calculate the energy gap and the wavenumber in the maximum of the electronic absorption band.

HOMO and LUMO orbitals of the studied drugs are plotted in Fig. 2.

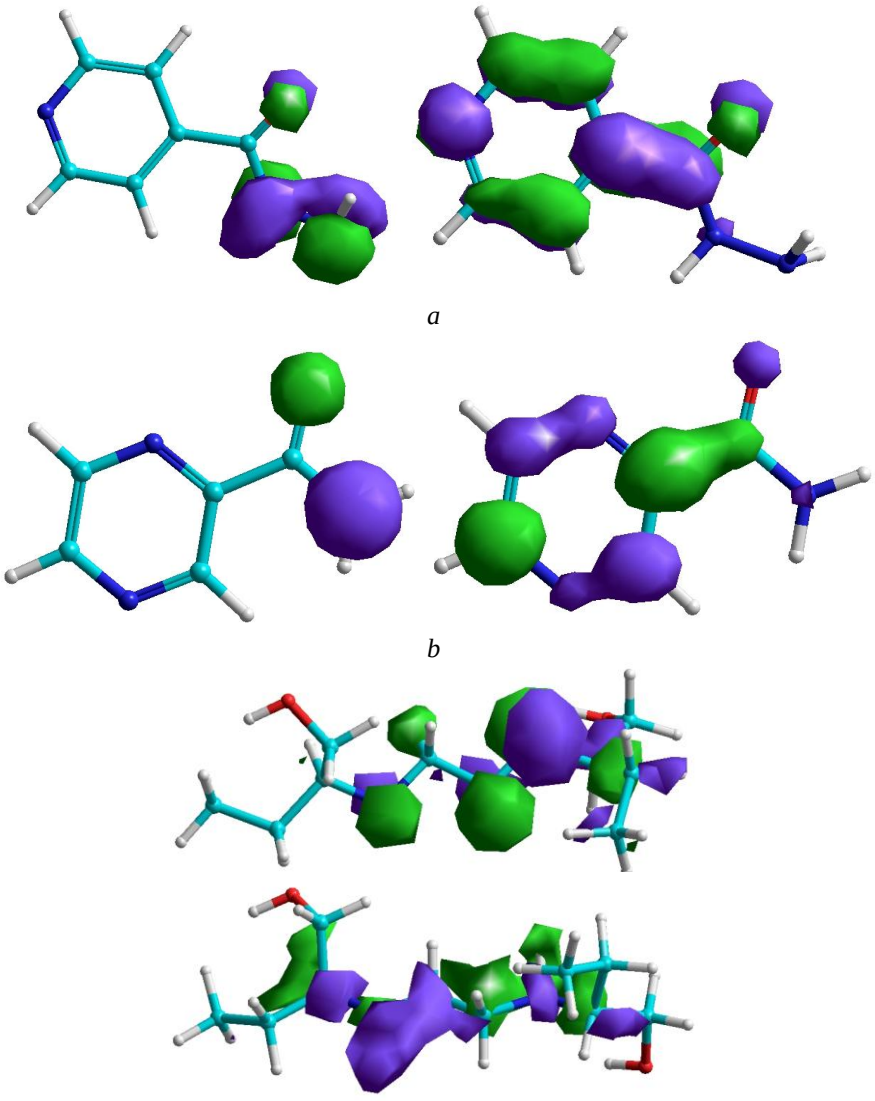

Fig. 2 – HOMO and LUMO orbitals for every compound:
a – HOMO and LUMO orbitals of Isoniazid; *b* – HOMO and LUMO orbitals of Pirazinamide; *c* – HOMO and LUMO orbitals for Ethambutol.

The PM3 semi-empirical method gives the energetic parameters, as can be seen in Table 1. From these data, the highest total energy corresponds to Ethambutol meaning that it is the most stable compound of our study.

Table 1
Energetic Parameters of Isoniazid, Pyrazinamide and Ethambutol

Studied compounds / Electro-optical parameters	Isoniazid	Pyrazinamide	Ethambutol
Total energy (kcal/mol)	- 36848.8	- 33418	-56930.2
Heat of formation (kcal/mol)	17.294	4.967	-125
Binding energy (kcal/mol)	-1771.318	-1508.55	-3429.46
E_{HOMO} (eV)	-9.98	-9.34	-9.43
E_{LUMO} (eV)	-0.88	-1.07	2.11

Administration of biologically active compounds involves several stages until its removal from the body. As a result, QSAR models have appeared necessary to be done because they can give important information on the relationship between the structure and biological activity of the studied compound (Table 2). As it can be observed from Table 2, the Ethambutol has positive value of logP (logP > 0) which means that its solubility in water is very low which is explained by its low polarity (being as an aliphatic compound).

Table 2
QSAR Parameters of Isoniazid, Pyrazinamide and Ethambuthol

QSAR parameters	Isoniazid	Pirazinamida	Ethambutol
Surface area ($Å^2$)	303.83	274.6	465.59
Volume ($Å^3$)	446.08	394.62	737.34
logP	-1.37	-1.08	0.29
Refractivity ($Å^3$)	39.69	32.06	57.89
Polarizability ($Å^3$)	14.35	12.29	23.10

4. Conclusions

1. Tuberculosis is a very serious disease killing every year more than 10 million people around the world that's way researchers in the pharmaceutical field try to develop more efficient compounds to help combat this disease

2. Molecular modeling is a real help in finding certain parameters of the molecules that are in draft stage, before chemical synthesis.

3. Worldwide, continuous research is being conducted for the discovery of new molecules used to treat serious diseases, incurable or not. The new molecules are, usually, synthesized starting from the moiety of already existing compounds, with efficient and known pharmacological action. These derivatives exhibit the same properties with the initial molecule. Knowing the features of the main molecule helps understand better the action of the new compounds.

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PROPRIETĂȚILE FIZICO-CHIMICE ALE UNOR ANTIBIOTICE AVÂND ACTIVITATE ANTI-TUBERCULOASĂ

(Rezumat)

Tuberculoza este o boală infecțioasă ce afectează, de obicei, plămânii, dar se poate extinde şi spre alte părți ale corpului. Tratamentul constă în administrarea unor antibiotice timp de câteva luni. Scopul acestui articol este acela de a analiza unii dintre aceşti compuşi farmaceutici şi de a le calcula principalii parametri fizico-chimici utilizând metodele modelării moleculare.