Original Paper

Theoretical study of chlorpromazine Drug and its metabolites: DFT calculation and QSAR toolbox investigation

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Abstract

Introduction: Pharmaceutical compounds are among the most important products for the treatment and prevention of various problems. However, their excess or incompatibility with other compounds can harm human health. These compounds include, in particular, psychological and neurological effects, which have recently become widely used to treat schizophrenia and behavioraldisorders.

Methods: This work aims to study chlorpromazine, a pharmaceutical compound used as an antipsychotic in psychological and neurological conditions, as well as its characteristics, chemical and biological properties, and interactions with other compounds. The drug and its metabolites induce the human body to avoid them, as well as the resulting hot flashes. This theoretical study was carried out using molecular modelling with Gaussian program. Density functional theory (DFT) was used to identify the geometric, energetic, and reactivity properties of the systems studied. To study the biological activity and toxicity of our compounds, we used the QSAR-Toxtree program.

Results: Our results allowed us to determine the most biologically active compound and conclude that the resulting compounds are likely to produce more or less toxic compounds. In light of these results, it can be stated that: the compound chlorpromazine is more biologically stable compared to its metabolites, which confirms that it is an active substance in medical applications. In general, we found that all the compounds studied have chemical and biological activity and are combined with each other in the resulting potential toxicity.

Keywords: chlorpromazine, metabolites, DFT, QSAR Model

Introduction

Psychotropic drugs are a relatively old class of drugs since the first discoveries, dating back to the mid-fifties, especially antipsychotics. However, it has steadily developed throughout the half. The second from the twentieth century to the twentieth century. Their discovery dramatically changed the way I was treated Psychiatric diseases, their primary significance despite their significant side effects, including neurological effects. In fact, the treatments have so far lacked effective means.

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Chlorpromazine (CPZ) is a phenothiazine derivative (Amaral et al., 2001; Karlsson et al., 1993; Molnár et al., 1976; Smith et al., 1963). It has antipsychotic, sedative, and antiemetic properties and is used in the form of its hydrochloride, $C_{17}H_{19}ClN_2S{\cdot}HCl$, specifically to manage the symptoms of psychotic disorders. This compound is primarily used to treat the symptoms of schizophrenia, mania, and other conditions associated with severe, aggressive conduct disorders that require sedation (*Antipsychotic Agents in the Treatment of Bipolar Mania - Tohen - 2009 - Bipolar Disorders - Wiley Online Library*, n.d.; *Chlorpromazine-Induced Increase in Dipalmitoylphosphatidylserine Surface Area in Monolayers at Room Temperature - PubMed*, n.d.; Liu and De Haan, 2009; Morak-Młodawska and Jeleń, 2007; Vinken, 2018). CPZ has been considered one of the most effective antipsychotics, as it plays an important role in a range of biological processes, well known for its intensive use in psychotherapy (Ww et al., 1958). It is also used to treat nausea and vomiting, especially those caused by drug or radiation treatments or as a result of general anesthesia for surgery. CPZ is shown to act as an efflux pump inhibitor, playing an important role in combating acquired antibiotic resistance in bacteria (Martins et al., 2008).

As an amphiphilic compound, CPZ can easily incorporate into the lipid bilayer, change the physicochemical properties of bio-membranes, and change the activities of different membrane proteins (*Effects of Chlorpromazine Drug on DPPC Lipid: Density Functional Theory Study: International Journal of Environmental Analytical Chemistry: Vol 101 , No 12 - Get Access*, n.d.). CPZ binds to serotonin, dopamine and GABAB receptors but its exact mechanism of actions is not known (Gómez-Jeria & Iberti-Arancibia, 2021; Hannon et al., 2021; Hirjak et al., 2021; Iwata et al., 2021; Kim et al., 2018; Robichon et al., 2021).Several derivatives of CPZ have been synthesized and tested (Capuano et al., 2008, 2010; Garipelli et al., 2009; McRobb et al., 2012). Despite its high efficacy, CPZ remains underutilized because of the required frequent and invasive blood draws to monitor adverse side effects such as agranulocytosis (decrease in the amount of white blood cells) (Ben-Yoav et al., 2014).

Drug metabolism and pharmacokinetic parameters should be thoroughly investigated during drug development and toxicity studies of chemical entities (Park et al., 2011). Overall, the identification of metabolites, especially reactive metabolites, helps distinguish potential drug candidates and supports future drug development. The formation of reactive or unwanted metabolites can lead to further chemical modifications, which bypass or limit some drug metabolic reactions (Bussy et al., 2015). Chlorpromazine clearance is an enzymatic process and occurs extensively in the liver. Hence, most of the metabolites exhibit biological activity and may contribute to the side effects of the parent drug (Abernathy et al., 1977; Tavoloni & Boyer, 1980). The metabolic mechanisms of chlorpromazine remain elusive up to now, but are thought to result in the formation of some reactive metabolites having side effects on the parent drug (Xue et al., 2016).

Actually, many previous studies have devoted to find out the particular metabolic processes of chlorpromazine (Abernathy et al., 1977; Ben-Yoav et al., 2014; Bussy et al., 2015; Capuano et al., 2008, 2010; Garipelli et al., 2009; Kim et al., 2018; McRobb et al., 2012; Park et al., 2011; Tavoloni and Boyer, 1980; Xue et al., 2016). But these studies did not conduct a study of the toxicity and interactions of chlorpromazine metabolites. In this context, we have studied this compound and the resulting metabolites in order to know the extent of its effect and interaction in order to reduce and limit its side effects. In this part of the work, we applied molecular modeling to study the various geometric, energetic, spectral and reactive properties of chlorpromazine and its metabolites. Our main objective of this study is to discuss the obtained results and identify the most chemically and biologically active compound, of the parent molecule (the main compound) and the resulting metabolites.

Computational details

The density functional theory (DFT) study

The theoretical calculations of the energetic properties and the geometric parameters are carried out using the density functional theory (DFT), at the level of the functional B3LYP (Becke 1993) and the 6-311g+(d, p) basis set (Hariharan & and Pople, 1974). All calculations are performed using the software Gaussian 09 (*Gaussian 09 Citation | Gaussian.Com*, n.d.). The frontier molecular orbitals are realized using the Gauss View program. The different global descriptors of reactivity: the energy gap (E_{GAP}), the dipole moment, the chemical potential (μ), the ionization potential (I), the electron affinity (A), the softness (S), the electronegativity (χ), chemical hardness (η), electrophilicity (φ), and net electrophilicity ($\Delta\omega\pm$) as well as donor and acceptor power are calculated by applying these formulas:

$E_{GAP} = \mid E_{LUMO} - E_{HOMO}$	**(1)**
$\mu = (E_{LUMO} + E_{HOMO})/2$	(2)
$I = -E_{HOMO}$	(3)
$A = -E_{LUMO}$	(4)
$S = 1/(2\eta)$	(5)
$\varphi = \mu^2/(2\eta)$	(6)
$\chi = -\mu$	(7)
$\eta = E_{GAP}$	(8)
$\omega^- = (3I+A)^2/16(I-A)$	(9)
$\omega^+ = (I+3A)^2/16(I-A)$	(10)
$\Delta\omega^{\pm} = \omega^+ + \omega^-$	(11)

Quantitative Structure Activity Relationship (QSAR)

Is theoretical model that relate a quantitative measure of chemical structure to a physical property, or a biological activity. Principle: Structurally similar chemicals are likely to have similar. Physicochemical and biological properties. The QSAR method consists in using a data analysis method, linking microscopic molecular properties to an experimental effect (biological activity, toxicity, affinity for a receptor). Toxtree is a free QSAR tool (Patlewicz et al., 2008) that can be used to determine the Cramer class (Committee et al., 2019) of a chemical substance and estimate its relative toxic hazard. It is jointly developed by Idea consult Ltd (Sofia, Bulgaria) and the Join Research Centre (JRC) of the European Commission.

Results

In this context, we have been interested by the study of CPZ compound and its metabolites (we have chosen five Metabolites), in order to know the extent of its effect and its interaction in sequence to minimize and limit its side effects. Fig 1 represents the steric structure of chlorpromazine (the parent compound), the steric structure and abbreviation of the resulting compounds are represented in Fig 2.

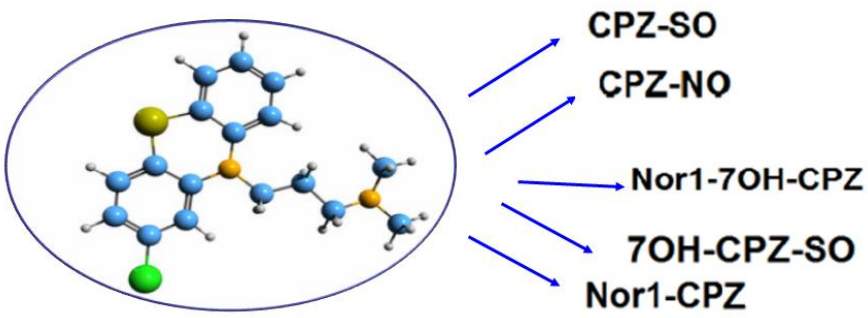
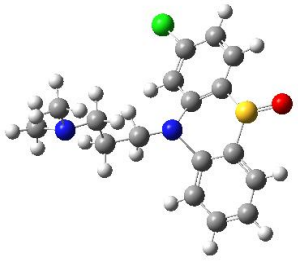
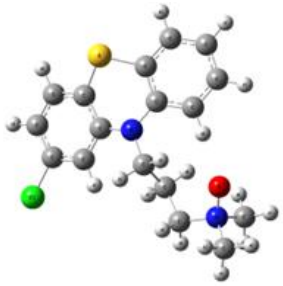


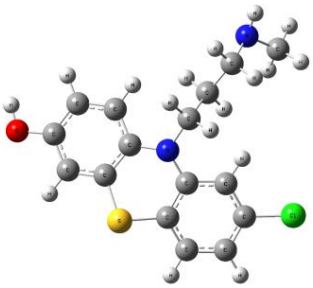
Figure 1: The parent compound and its metabolites.



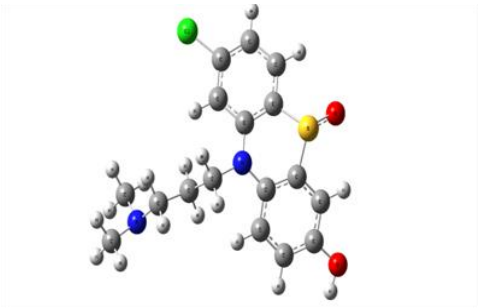
Compound 1 CPZ-SO



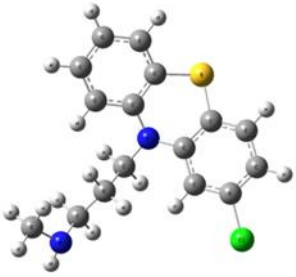
Compound 2 CPZ-NO



Compound 3 Nor1-7OH-CPZ



Compound 4 7OH-CPZ-SO



Compound 5 Nor1-CPZ

Figure 2: The metabolites of CPZ.

DFT Results:

We studied the geometric structure of chlorpromazine and the resulting compounds (new metabolites), where we extracted some bond lengths and some angles as shown in the Tables 1 and 2.

Table 1: Some bond length (A°) of the parent compound and its metabolites.

Bond Length (A°)	The parent Compound	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
C=C	1.397	1.406	1.395	1.395	1.409	1.413
S=O	/	1.515	/	/	1.515	/
C-O	/	/	/	/	1.369	/
N-C	1.420	1.413	1.423	1.407	1.405	1.410
C-Cl	1.762	1.760	1.764	1.763	1.760	1.762
S-C	1.784	1.811	1.780	1.778	1.808	1.777
C-H	1.087	1.086	1.085	1.085	1.086	1.085
N-O	/	/	1.366	/	/	/
O-H	/	/	/	0.964	0.964	/

Table 2: Some angles (°) of the parent compound and its metabolites.

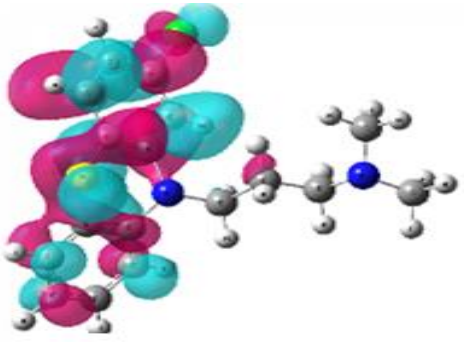
	The parent Compound	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5
N-C-C	117.4	116.6	121.1	112.4	110.7	121.4
C-C-Cl	118.6	118.4	118.3	118.4	118.2	118.4
C-C-C	120.5	119.5	117.6	119.2	116.27	117.5
C-N-O	/	/	109.6	/	/	/
C-S-C	97.7	93.5	99.2	99.2	94.7	99.1
N-C-H	110.8	111.2	107.2	112.1	/	109.4
C-O-H	/	/	/	109.5	/	/

The reactivity descriptors are mentioned in the Table 3.

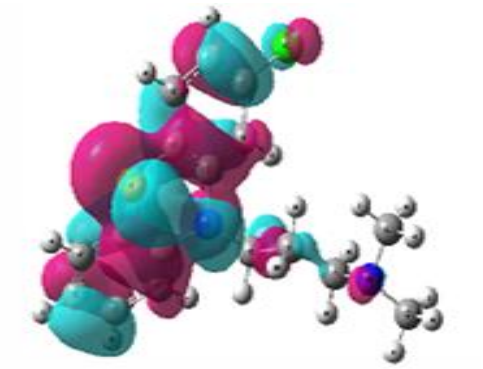
Table 3: Values of reactivity descriptors.

Reactivity descriptors	**The parent Compound**	**Compound 1**	**Compound 2**	**Compound 3**	**Compound 4**	**Compound 5**
E_{HOMO} (eV)	-6.0890	-5.5127	-5.0789	-5.1780	-5.7435	-5.2883
E_{LUMO} (eV)	-1.3088	-0.9033	-0.8279	-0.9089	-1.3730	-0.9864
E_{HOMO}'(eV)	-12.88	-12.30	-11.97	-11.97	-12.07	-12.53
M(Debye)	2.04	5.09	5.91	3.75	6.68	3.27
E_{Gap} (ev)	4.7807	4.6084	4.2510	4.2701	4.3704	4.3019
η(eV)	4.7807	4.6084	4.2510	4.2701	4.3704	4.3019
S (eV-1)	0.045	0.1084	0.1176	0.1171	0.1144	0.1162
I (eV)	6.0890	5.5127	5.0779	5.1780	5.7434	5.2882
A (eV)	1.3083	0.9033	0.8269	0.9079	0.3730	0.9863
μ (eV)	-3.6991	-3.2080	-2.9524	-3.0430	-3.5582	-3.1373
χ(eV)	3.6991	3.2080	2.9524	3.0430	3.5582	3.1373
N (eV)	6.7910	6.7880	6.8921	6.7919	6.3265	6.2418
ω (eV)	1.4311	1.1163	1.0252	1.0843	1.4485	1.1439
ω^+ (eV)	1.3109	0.9167	0.8399	0.9139	0.8543	0.6775
ω^- (eV)	5.0096	4.1247	3.7924	3.9570	3.0395	2.8285
Δω (eV)	6.3205	5.0414	4.6323	4.8709	3.8938	3.506

We show through the Fig 3 the distribution of the electronic density of the valence orbitals for CPZ (the parent compound).



LUMO



HOMO

Figure 3: The HOMO and LUMO shape of CPZ.

QSAR Results

Using the QSAR program, we were able to obtain nine compounds from the oxidation reactions of the parent compound, seven of which correspond to the empirical structural formulas found in bibliographic research, except for compounds 2 and 5, which were not obtained. We have clarified the compounds derived from the program, which have not undergone a significant change and are represented as follows:

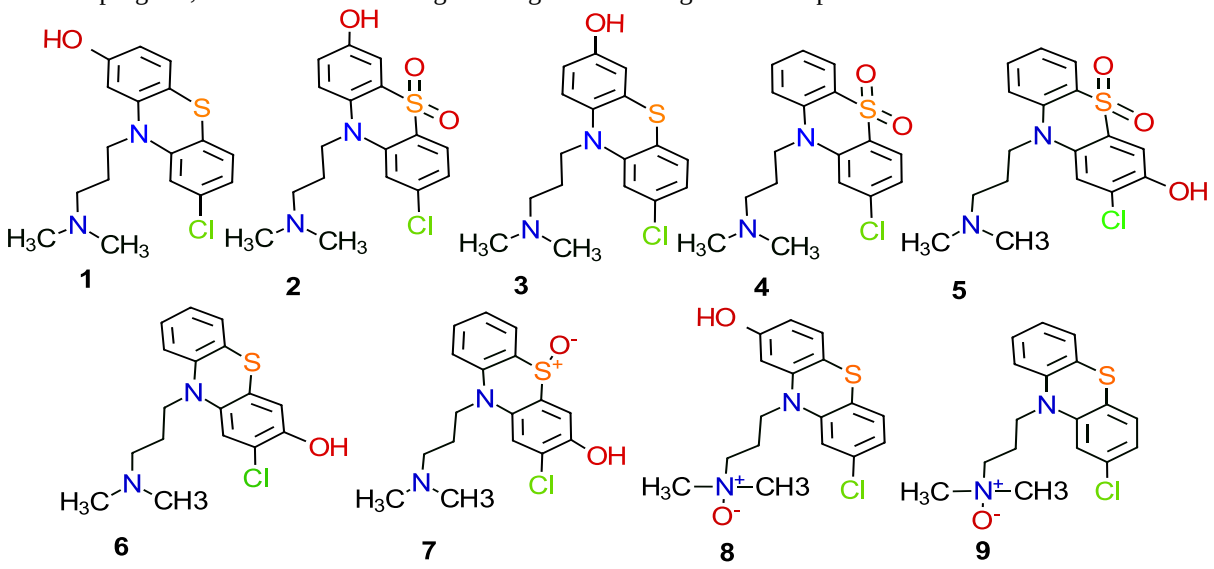


Figure 4: The compounds from QSAR Calculation.

Through the completed calculations, we were able to derive several conclusions that will be discussed separately.

Discussions

Geometric parameters

By analyzing the Tables 1 and 2, we note that the bond lengths and bond angles change according to the chemical environment of the atoms in the molecule, as:
The bond length (C = C) changes from one compound to another according to its link in the molecule. The compound 3 (CPZ-NO) and the compound 4 Nor-7-OH-CPZ) give the same value for this bond, which is very close to that of the parent molecule.

Regarding the length of the bond (C-Cl), all the resulting compounds have bond lengths very close to the value recorded for the parent compound. The same previous notes apply to the rest of the link lengths.

Concerning the angles, we generally notice that their values decrease with the increase of the bond length. The angle (N-C-C) with respect to the parent molecule equals 117.4°, and we note that the values of the angles for the compounds obtained range from (112.4° to 121.4°.). With regard to the angle measure (C-C-Cl), we record that the values are closely related to the parent compound and the resulting compounds.

Chemical reactivity

From reactivity descriptors values (Table 3),We note that the parent molecule has a small dipole moment compared to the molecules which present its metabolites, and this indicates its stability and effectiveness in microbiological resistance (Das et al., 2021).
The order of moments is given in descending order as follows:

$$Mparent < M_5 < M_3 < M_1 < M_2 < M_4$$

Compound 4 has the highest dipole moment. This shows that it has great chemical activity. If there are side effects, it is the most dangerous (Uetrecht, 2022).

We note that the Energy of the HOMO of compound 2 is the most valuable among the compounds obtained, so it is capable of participating in nucleophilic reactions, as it is able to give its electrons more easily. From this point of view, we must commit ourselves not to include substances that interact with the compound 2 to avoid the appearance of side effects.

We note that the Energy of LUMO of compound 4 has the smallest value, and therefore it has the ability to receive electrons and enter into electrophilic reactions.

We note that the Energy gap of the parent compound has the largest value compared to the values of the resulting compounds, which confirms the stability of the latter.

Also, the parent compound has the largest value of hardness and the smallest value of softness, which indicates that it is chemically stable (Kaya and Putz, 2022) and biologically active, as we have obtained from previous results. The chemical potential values of all compounds are negative, which indicates that the reactions of their formation are spontaneous (Adnanhatem et al., 2016).

Compound 4 has the largest electrophilic value, and this explains its ability to receive electrons. The nucleophilic value of compound 2 is the largest compared to other compounds, and this proves its chemical activity. Regarding the electronegativity values, we note that compound 4 is the one that gives the highest value. Concerning the binary electrophilic descriptor, we note that compounds 1 and 3 give the highest values.

From Fig 3, We note that the parent compound is characterized by a high electron density distributed over most of the molecule in the cases of higher and lower orbital fullness. This confirms that the parent compound does not have good charge transfers, which confirm its stability as we previously confirmed.

QSAR

The QSAR program has allowed us to obtain 9 highly toxic compounds according to Cramer's classification showed in the Fig 4. The principle of work was carried out using simulation on the rat organism (in vivo) at the level of the nucleus, which allowed us to obtain the following results:

Interaction with DNA

We recorded in the first interphase that the parent molecule is not associated with DNA, while the resulting molecules (there are seven) are bound with it, because they contain the triple amine radical that is linked to it according to the nucleophilic interaction of type SN1, and is included in the composition of the amino acid chain.

Toxicity

As for the toxicity in the first intermediate stage, according to Cramer's classification, we noted that the program classified the nine compounds in the third class of high toxicity. That would be the result:

Compounds with structural warnings: they are hydrogen-receptive, because they contain Oxygen-O, which is highly electronegative and negative. However, it is not possible to determine the exact proportion of the

toxicity of the compounds, and it remains only possibilities as a result of the difference in their interaction from one body to another and its ability to resist.

Genotoxicity

When the first compounds react and enter the second interphase, 9 compounds are produced:

- 6 of them do not provide structural alerts.
- 3 of them present structural warnings: with the triple amine root: the compound is a hydrogen acceptor at the triple amine level. We know that each gene at the level of DNA is responsible for a precise and clear action, so this structural alarm leads to a dysfunction of these genes and makes completely different proteins and is toxic in the long run average.

structural alert in this case:

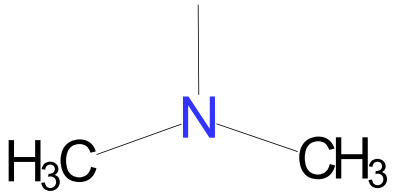


Figure 5: Structural alert forgenotoxic interactions.

Squeamishness

There are 6 compounds that present structural alarms: the latter cause skin sensitivity, resulting in itching and abrasion. This is due to the phenolic ring, resulting from the interaction of the aromatic ring with the OH function.

structural alert in this case:

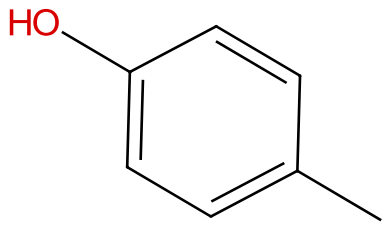


Figure 6: Structural alert for Squeamishness interactions.

Hepatotoxicity

The result of taking repeated doses of chlorpromazine appears which leads to the bioaccumulation of this drug in the organ starting from the 28th day of taking repeated doses, which is estimated at 15mg/day, so we can say that this drug is short-lived. Vehicles with structural alarms given are similar to those studied experimentally.

Nephrotoxicity

The latter occurs in the form of kidney failure as a result of dealing with general medicines (or what is also known as quasi-drugs), which have a similarity rate between them and the parent molecule estimated at 50%. Among these medicines, we mention:

- Imipramine
- Thiocarbonate
- Promethazine
- Sulfide
- Tianeptine
- Metamizole

We recall that the above was recorded in the category of general cases, because the effect of the drug varies from one body to another.

Primary classifications of cancer

The same previously highly toxic compounds may be carcinogenic, as the possibility or prediction has been made:

- The structural alarm is in the middle aromatic ring, which gives a heterogeneous ring.
  Carcinogenic Toxicity

When the first compounds react and enter the second interphase, 21 compounds are produced:

- 16 of them do not provide structural alerts.
- 3 of them provide structural warnings: they are the result of the movement of the OH group from the ring to the linear chain and its association with the triple amine.
- 2 of them provide structural alarms: with aldehydic functions.

Conclusion

After analyzing the results of the reactivity descriptor's, we have deduced that all compounds have chemical or biological activity, and this is what confirms that chlorpromazine is an active substance in pharmaceutical and medical applications, we have determined the type of reactions that the resulting compounds can conduct according to their chemical properties. Therefore, the medium and the dimensions of the materials that cause its interaction must be known.

Using QSAR we obtained that all studied metabolites of CPZ are in the third degree of high toxicity and their interaction differ from one body to another, as it is likely to produce other compounds of different degree of toxicity, depending on bioaccumulation. The resulting compounds can affect the DNA and cause several types of toxicity to the body Human (liver, cancerous, cutaneous and genetic).

We concluded by determining the type of reactions that the resulting compounds can carry out according to their chemical properties. Therefore, the medium and the dimensions of the materials that cause its interaction must be known.

Conflict of interest

There is no conflict of interest to be declared.

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