Incidence of penile neoplasia associated with the use of pesticides in the Irrigated Perimeter Jaguaribe Apodi - Ceará, Brazil: An *in silico* approach

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Abstract
The insertion of irrigated perimeters and the intensive use of pesticides made the Baixo Jaguaribe region one of the most critical areas of agribusiness in Ceará. However, the excessive use of pesticides has been associated with increased cases of premature births, congenital malformations and mainly neoplasms, especially penile cancer. Objective: To characterize in silico the pesticides of the triazine group used in the Jaguaribe-Apodi Irrigated Perimeter in the Baixo Jaguaribe region to investigate the relationship between penile cancer associated with the use of pesticides. Methodology: It was given through molecular modeling using Classical Force Field (MMF94) to obtain more stable structures and physicochemical properties and molecular docking to elucidate the possible inhibition between ligand (triazine)-protein (p53). Results: The electronic and structural characterization established that the pesticides of the triazine group are soluble and have no rotation, their double bonds are derived from the heterocyclic ring in their conformations and the stability energies are relatively high. Conclusions: Regarding molecular docking, ametryn and atrazine are likely to initiate a carcinogenic response to workers in the Jaguaribe-Apodi Irrigated Perimeter, i.e., penile cancer, while cyromazine ligand shows no interactions with p53 protein; thus, it does not act with inhibitory potency.
Keywords: Pesticides; Molecular modeling; Molecular docking; Penile cancer; Public health; Baixo jaguaribe.

Resumo
A inserção de perímetros irrigados e o uso intensivo de agrotóxicos fizeram da região do Baixo Jaguaribe uma das áreas mais críticas do agronegócio cearense. No entanto, o uso excessivo de agrotóxicos tem sido associado ao aumento de casos de partos prematuros, malformações congênitas e principalmente neoplasias, especialmente câncer peniano. Objetivo: Caracterizar in silico os agrotóxicos do grupo triazina utilizados no Perímetro Irrigado Jaguaribe-Apodi na região do Baixo Jaguaribe para investigar a relação entre câncer peniano associado ao uso de agrotóxicos. Metodologia: Foi dado através de modelagem molecular utilizando o Campo de Força Clássico (MMF94) para obter

estruturas mais estáveis e propriedades físico-químicas e docking molecular para elucidar a possível inibição entre a proteína-ligante (triazinas) (p53). Resultados: A caracterização eletrônica e estrutural estabeleceu que os pesticidas do grupo triazina são solúveis e não têm rotação, suas ligações duplas são derivadas do anel heterocíclico em suas conformações e as energias de estabilidade são relativamente altas. Conclusões: Em relação ao acoplamento molecular, a ametrina e a atrazina são susceptíveis de iniciar uma resposta carcinogênica aos trabalhadores no perímetro irrigado de Jaguaribe-Apodi, isto é, câncer peniano, enquanto o ligante de ciromazina não apresenta interações com a proteína p53; assim não atua com potência inibitória.

Palavras-chave: Agrotóxicos; Modelagem molecular; Docking molecular; Câncer de pênis; Saúde pública; Baixo jaguaribe.

Resumen

La inserción de perímetros irrigados y el uso intensivo de agrotóxicos hicieron de la región del Bajo Jaguaribe una de las áreas más críticas del agronegocio cearense. Sin embargo, el uso excesivo de agrotóxicos ha sido asociado al aumento de casos de partos prematuros, malformaciones congénitas y principalmente neoplasias, especialmente cáncer peniano. Objetivo: Caracterizar in silico los agrotóxicos del grupo triazina utilizados en el Perímetro Irrigado Jaguaribe-Apodi en la región del Bajo Jaguaribe para investigar la relación entre cáncer peniano asociado al uso de agrotóxicos. Metodología: Fue dado a través de modelado molecular utilizando el Campo de Fuerza Clásico (MMF94) para obtener estructuras más estables y propiedades fisicoquímicas y docking molecular para dilucidar la posible inhibición entre la proteína ligante (triazinas) (p53). Resultados: La caracterización electrónica y estructural estableció que los pesticidas del grupo triazina son solubles y no tienen rotación, sus enlaces dobles se derivan del anillo heterocíclico en sus conformaciones y las energías de estabilidad son relativamente altas. Conclusiones: En relación al acoplamiento molecular, la ametrina y la atrazina son susceptibles de iniciar una respuesta carcinogénica a los trabajadores en el perímetro irrigado de Jaguaribe-Apodi, es decir, cáncer peniano, mientras que el ligando de ciromazina no presenta interacciones con la proteína p53; así no actúa con potencia inhibitoria.

Palabras clave: Agrotóxicos; Modelado molecular; Acoplamiento molecular; Cáncer de pene; Salud pública; Bajo jaguaribe.

1. Introduction

According to Borsoi et al., (2014), pesticides are all chemicals that have attraction, repulsion, prevention, and elimination effects on biological beings: microbes, fungi, insects, bacteria, and weeds, among others, and are harmful to crop monocultures and their products.

However, the expansion and encouragement of pesticides in Brazil have been occurring gradually since the Second World War, marked by the synthesis of DDT (Dichloro-Diphenyl-Trichloroethane) (Salomão; et al., 2020). The factors: increased agricultural commodities, instrumentalization in the field and political easing have made Brazil one of the largest importers of pesticides in the world (Borsoi et al., 2014).

This production model is called the "green revolution" or agribusiness, which makes possible the high dependence on pesticides, mechanization of crops, genetic selection of domestic animals with high production potential and the selection of agricultural cultivars with high potential, widespread use of irrigation and drainage systems, as well as dependence on economic and fiscal incentive policies for the promotion and development of contemporary agriculture (Ramos; et al., 2018; Simon et al., 2022).

This model has several negative impacts on environmental and socioeconomic relations: a) rural exodus of tenant family producers, households, partners and others from the rural environment to the cities; b) condition of the quality of life of the expelled workers; c) ecological imbalance, loss of biological diversity; d) acute and/or chronic poisoning of rural workers and adjacent areas by the intensive use of pesticides (Carneiro; et al., 2012; Barbosa et al., 2020). Although the increase in pesticide use does not cause drastic reductions in production, on the other hand, environmental problems, food contamination and public health have increased significantly (Campanhola & Bettiol, 2003).

The manifestation of agribusiness in northeastern Brazil began with the creation of irrigation programs to meet the socio-economic demands of the water crises in Ceará, generation of employment in urban activities rural, aiming to increase and improve the distribution of income and high food production, enabling investments in the production sectors in the

countryside. From the popularization of this model, the irrigated perimeters became promising in the economy of Ceará (Gama; et al., 2013; Pontes et al., 2013).

Thus, the irrigated perimeters are areas delimited by the State for the implementation of public projects of irrigated agriculture that, in general, have significant agricultural potentials, characterized by fertile soils, water presence, climate and abundant labor (Dantas et al., 2012; Pontes et al., 2013).

With emphasis on the Jaguaribe-Apodi Irrigated Perimeter (PIJA) located in the Lower Jaguaribe region which is composed of the municipalities of Morada Nova, Limoeiro do Norte, Jaguaruana, Palhano, Alto Santo, Quixeré, Russas, São João do Jaguaribe, Ibicuitinga and Tabuleiro do Norte located east of Ceará and belonging to the Jaguaribe Valley (Freitas & Bombardi, 2018). It has climatic characteristics such as: average annual temperature 28.5ºC and precipitation of 772mm, recording irregular rainfall during the years (Milhome et al., 2009).

Specifically, the Jaguaribe-Apodi Irrigated Perimeter represents one of the main monoculture areas of the region located in Chapada do Apodi and encompassing the municipalities of Limoeiro do Norte and Quixeré. The primary soils found in the region are podzolic, cambisol and litholic eutrophic. With a water supply provided by the Jaguaribe River with a capacity of 2,100,000,000 m3, it also has many drinking water wells for rural and urban communities in the region. Where mango, grape, acerola, melon, pineapple, passion fruit, cashew, cotton, banana, lemon, sorghum, beans, corn and tomatoes are grown (Rigotto et al., 2010).

However, the risks related to exposure to pesticides can occur from different routes (dermal, oral, inhalation or ingestion) and interactions, as they do not only reflect on rural workers but, in the areas adjacent to the planting areas, factory workers, sellers and consumers of urban food sprayers among others (Porto & Soares, 2012; Ródio; et al., 2021). Between 2007 and 2014, there were 34,000 notifications of cases of pesticide poisoning for each notified event, and another 50 were not reported (Freitas & Bombardi, 2018).

According to Rigotto et al., (2010), the effects caused by chronic intoxication can produce neurobehavioral changes such as encephalopathies, respiratory diseases such as asthma and pulmonary fibrosis, chronic toxic hepatopathies, among others, as well as an increase in brain cancers, prostate, melanomas, sarcomas, lung and testicles (Ballestreri, 2017; Pereira et al., 2017; Pessoa & Rigotto, 2012). Other alterations may be congenital malformations, male infertility, low birth weight, and premature deliveries. The highest cancer rates are in testicles (5.77%), leukemias (6.35%) and penises (6.44%) (Rigotto, 2011; Rigotto et al., 2013; Silva et al., 2005).

Regarding environmental aspects, pesticides cause imbalances in terrestrial and aquatic systems. They alter the natural biological process performed by organisms and consequently change the function of ecosystems (Avelino et al., 2013). The impacts caused depend on the concentration of contaminating load and the fate of pesticides in the environment. These affect the surface waters and can reach the groundwater, whose decontamination is very difficult, thus interfering with the breathing of the soil, killing fish and/or birds, nutrient cycling mainly the reduction of populations, among other effects (Dantas et al., 2012; Dos Santos & Da Silva, 2007).

In this context, the study aims at: 1) structural electronic characterization and 2) molecular docking of pesticides of the triazine group found by Avelino et al., (2013) in water bodies in the Jaguaribe-Apodi Irrigated Perimeter with tumor immunosuppressive protein (p53) associated with penile cancer. Seeking to investigate the association of triazines to penile cancer, which has a higher incidence in the Baixo Jaguaribe region.

2. Theoretical frameworks

2.1 Penile cancer

Penile cancer is a rare neoplasm that, although it affects a portion of the population (1/100.000), has high mortality rates due to late treatment and/or the disease itself that proves to impact the psychological health of patients (Costa et al., 2013).

In Brazil, this type of carcinoma is high in the northern (5.7%) and northeastern (5.3%) regions, especially in older men, regardless of their ethnic classification. It should be noted that the young population can also be affected. About 22% of the cases recorded patients are below the age of forty years (Bleeker et al., 2009; Reis et al., 2010).

Despite the unknown etiology, studies point to the relationship of penile carcinogens to HPV (human papillomavirus), mainly in lesions with verrucous or basal pattern. Patients infected with the oncogenic viral types 16, 18, 31 and 33 are predisposed to the development of squamous carcinoma (SCC) of the penis. HPV causes changes in the cell cycle by the expression of the viral proteins E6 and E7 in the deactivation and elimination of the products of tumor suppressor genes (p53 - inhibited by E6 and Rb - inhibited by E7) that contribute to the initiation and progression of neoplasia (Favorito et al., 2008; Micali et al., 2006).

Specifically, the state of Ceará concentrates about 12.87% of penile cancer case rates in the Northeast. The factors that contribute to this disorder in public health are: 1) the regionality in which the propensity of the disease is related to the patient's residence rather than its origin; 2) the presence of phimosis and low hygiene conditions, and the workers of the Jaguaribe/Apodi Irrigated Perimeter the factors involve 3) the poisoning of pesticides by direct routes (chronic poisoning) caused by the worker's exposure time and absence of Epis (Personal Protective Equipment) and indirect (acute poisoning via food, meat, vegetables and cereals) caused by the physical-chemical characteristics that make pesticides resistant to biotic and abiotic degradation (Jobim et al., 2010; Leite et al., 2015).

2.2 Chemical group: Triazines

Herbicides and insecticides in the triazine group account for about 30% of the annual production of pesticides. The s-triazines have a six-membered heterocyclic ring in their structure, whose atoms can be -C or –N, in which they are symmetrically bound. The nomenclature and properties of s-triazines are determined by the substituents present in the 2nd, 4th and 6th position of the heterocyclic ring, with -Cl being the most common (Name ending in -azine), -SCH3 (-trin) and -OCH3 (-tona) (Coutinho et al., 2005).

In the present study, ametryn, atrazine and cyromazine were used. The ametryn (Figure 1A) is a systemic herbicide used in banana, coffee, pineapple, and Citrus corn. It has a half-life of 20 to 100 days and is highly persistent in water and soil. In addition, it is related to human health problems such as neurological, behavioral diseases and neoplasms (Cabral et al., 2003).

Atrazine (Figure 1B) is a compound used for weed control in corn and sugarcane plantations. However, its biodegradation in the water-based system soil may vary depending on the content of organic matter, influencing its detection on the surface and underground and human health interferes with the nervous and endocrine systems (Carmo et al., 2014; Coutinho et al., 2005).

Figure 1. Pesticides of the triazine group.

Source: Elaborated from < https://pubchem.ncbi.nlm.nih.gov/>.
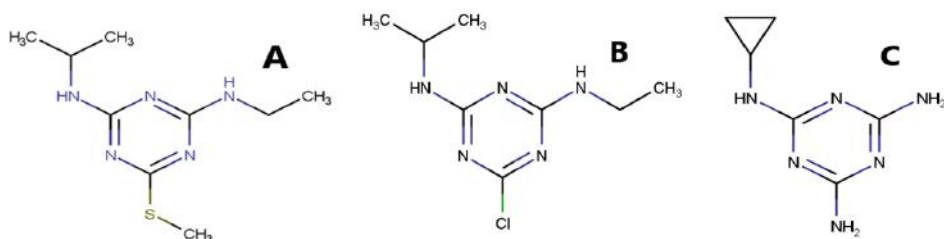
The cyromazine (Figure 1C) is an insect growth regulator, specifically immature flies, altering morphophysiological functions, causing the elimination of insects, and acts on monoculture melon, lettuce, and banana, among others. It has a persistent character in the aquatic environment and interferes with endocrine dysfunctions, such as human health (Crespo; Lecuona and Hogsette, 2002).

3. Methodology

3.1 Ligand preparation

The two-dimensional structures of the compounds were obtained in the PubChem® (https://pubchem.ncbi.nlm.nih.gov/) virtual repository to which some physicochemical characteristics were described and were delineated in MarvinSketch© (http://www.chemaxon.com) being saved in .mol2 format. The structures were optimized using the Avogadro© (http://avogadro.cc/) configured to use the force field of Merck Molecular Force Field 94 – (MMFF94) with the descending steepest algorithm, configured to perform cycles of 500 interactions generating the smaller structure potential energy (O'Boyle et al., 2011; Sant'anna, 2009).

3.2 Protein preparation

The three-dimensional structure of the p53 protein (PDB ID: 4MZI) was obtained from the Protein Data Bank (PDB) virtual repository (https://www.rcsb.org/) deposited with the resolution of 1.25Å, determined from X-ray diffraction, with R-Value Free: 0.201, R-Value Work: 0.198 and R-Value Observed: 0.198 (Emamzadah et al., 2014). In the preparation of target enzymes, the residues present in the structures were removed , and the polar hydrogens were added.

3.3 Molecular docking

The AutoDock Vina© (version 1.1.2) was used (Morris et al., 2009). The grid box was defined with parameters of 120Å x 106Å x 126Å, centered on the whole protein with the dimensions Center (x, y, z) = (-20.180, -5.187, 8.609), Size (x, y, z) = (106, 126, 126) spacing = 0.397 e exhaustiveness = 8. Independent simulations were carried out, obtaining 10 poses each. For the selection of simulations with better poses, the simulations that presented RMSD (Root Mean Square Deviation) value less than 2Å and free bonding energy (DG) ΔG below 6.0 kcal/mol were used as criteria (Yusuf et al., 2008). The results were analyzed and visualized using the codes Discovery Studio Visualizer and UCSF Chimera© (Pettersen et al., 2004).

4. Results and Discussion

4.1 Geometric optimization and structural properties

The structural optimization of the molecule was removed from the canonical address of the molecule from an online repository since it is not in its most stable conformation. Thus, to obtain more accurate calculations on the molecule, a geometric optimization was carried out using the energy minimization process that allows each of the atoms that make up the structure to occupy its place of least energy in the system.

In this context, two-dimensional structures denote that ametryn after geometric optimization leaves it stable (Figure 2A. Supplementary). The compound acquired the most stable structure of value of $5.123.256KJ/mol^{-1}$, and in the generation of five conformers of lower energy, there is a variation in the order of -399.69 to $-390.76KJ/mol^{-1}$.

With the optimized molecule, it was possible to calculate the dipole momentum vector module (μ), i.e., the resulting value calculated from the dipolar momentum vectors of the individual chemical bonds of the molecule. Therefore, the higher the dipole moment, the greater the affinity of molecules with polar environments and as a consequence, the melting and boiling point increased. The dipole moment is measured in debyes (D) with the relationship between the distance of the most electronegative ends of the molecule and the partial charges. Ametryn has dipole moment equal to 1.837D and vector directions -0.65 (x), 2.35 (y) and -1.48 (z). Furthermore, (Figure 2B, Supplementary) represents the Van Der Walls surfaces depicting the molar volume of the compound.

In this case, it can be established that each atom occupies a lower energy stationary state enabling a more stable three-dimensional structure. Thus, it was possible to calculate the valences of each atom coming from the ametryn with prominence to the highest C3 (4 valences) and lowest H (1 valence). Concerning the formal charges, all had a value equal to 0, configuring the most stable neutral characteristic structure and the partial charges detaching less partial charge -0.314 (atom 3: N N3) and the most significant partial charge 0.221 (atom 10: C C3) (Table 1, Supplementary). Next, it was analyzed the second-order bonds, that is, double bonds located between (Atom 8: N3-C5), (Atom 9: N4-C4) and (Atom 12: N5-C7). As a result, the compound ametryn does not have rotation (Table 2, Supplementary).

Based on the conformational analysis, all angles between the links and the torsion angles formed from the intersection between two planes and called dihedral angles were calculated. Taking smaller and larger angles of links as descriptors in the compound, it can be established that the smallest angle is located at 13 (NCH) with a value of 83845Å and the largest is 16 (CCH) with a value of 179.974Å. While the lowest torsion was in atom 36 (CNCS), measuring -179.540Å, and the largest torsion was 54 (HCCH), measuring 180.000Å.

Atrazine acquired a stable conformation of $3.523.590KJ/mol^{-1}$, and in the generation of five lower energy conformers, a variation of -387.06 to $-376.64KJ/mol^{-1}$ (Figure 2C, Supplementary) is observed. Atrazine has a dipole moment of 2.431D and vector directions of 0.56 (x), -5.32 (y) and -0.08 (z). Furthermore, (Figure 2D, Supplementary) represents the Van Der Walls surfaces depicting the molar volume of the compound.

The valence calculations of each atom from atrazine reveal the atom C3 (4 valences) and H (1 valence). From the analyses of the formal charges, the compound is stable, and the partial charges indicate a lower partial charge of -0.314 (atom 3: N N3) and the most significant partial charge of 0.229 (atom 14: C C3) (Table 3, Supplementary). Next, it was analyzed the second-order bonds, that is, double bonds located between (Atom 7: N3-C6), (Atom 8: N4-C4) and (Atom 11: N5-C8). The compound atrazine does not have rotation (Table 4, Supplementary).

Concerning the linkage angle descriptors in the compound, it can be established that the lowest angle is located at 27 (HCH) with a value of 84.058Å and the largest is 15 (CCH) with a value of 179.974Å. Furthermore, respectively, the lowest torsion was in atom 23 (CNCN), measuring -177.305 Å, and the highest torsion was 49 (HCCH), measuring 180.000Å.

Cyromazine, in turn, has a stable conformation with a minimum energy of -1.185.330 KJ/mol-1 and its conformers can range from -450.45 to 449.30 KJ/mol-1 (Figure 4E, Supplementary). The observed dipole moment was 0.626D with vector directions -0.52 (x), 0.07 (y) and 0.01 (z). A (Figure 4F, Supplementary) represents the Van Der Walls surfaces depicting the molar volume of the compound.

The valences of each cyromazine atom emphasize the atom C3 (4 valences) and H (1 valence). According to the partial charges, the minor partial charge -0.327 (atom 5: N N3) and the most significant partial charge 0.221 (atom 10: C C3) (Table 5, Supplementary) are indicated. Second-order bonds are located between (Atom 3: N2-C4), (Atom 6: N3-C6) and (Atom 7: N4-C5). The cyromazine compound does not rotate, as indicated in (Table 6, Supplementary).

For the angles of connections in the compound, it can be established that the smallest angle is located in the 16 (CCC) with a value of 59.900Å and the largest is the 37 (NCN) with a value of 125.281Å. Moreover, respectively, the lowest torsion was in atom 20 (CNCN), measuring -179,878Å, and the largest torsion was 49 (CNCN), measuring 179,865Å.

4.2 Molecular docking

Calculations of the distances between the amino acid residues of protein (p53) and ligands (ametryn, atrazine and cyromazine) have shown that the enzyme p53 has at its binding site five amino acids Arg-280, Ala-276, Cys-277, Lys120, Gly-122 and Phe121, these are important in the strong interactions with Human DNA (Emamzadah et al., 2014).

It was observed that the ametryn and atrazine molecules remained in the region of the active protein site, as they had distances close to the amino acids of the active protein site with emphasis on Phe121, which may be related to intermolecular interactions. However, cyromazine does not present good results concerning the active protein site because it remains distant and thus does not exert any interaction with the highlighted amino acids Table 1).

Table 1. Amino acid and ligand distances A, B and C.

Amino acids	Ametryn (A)	Atrazine (B)	Cyromazine (C)
ARG280	12.9Å	8.4Å	18.6Å
ALA276	13.2Å	11.4Å	21.4Å
CYS277	11.9Å	9.8Å	17.9Å
LYS120	7.2Å	6.0Å	20.3Å
GLY122	7.5Å	8.4Å	22.5Å
PHE121	4.4Å	3.2Å	16.6Å

Source: Author himself.

In molecular Docking, it is essential to emphasize and analyze the affinity and HDMR, representing the potential energy between the ligand and the protein. The lower the potential energy, the more stable the interaction between ligand and protein is, and (Root-Mean-square deviation of atomic positions) the mean quadratic deviation of a structure X from it (Yusuf et al., 2008). Soon affinity and RMSD of the ligands were: ametryn was -4.1 and 1.867Å; atrazine -3.9 and 1.861Å; and cyromazine -4.3 and 0.175Å (Figure 2).

Figure 2. Binder affinity and RMSD.
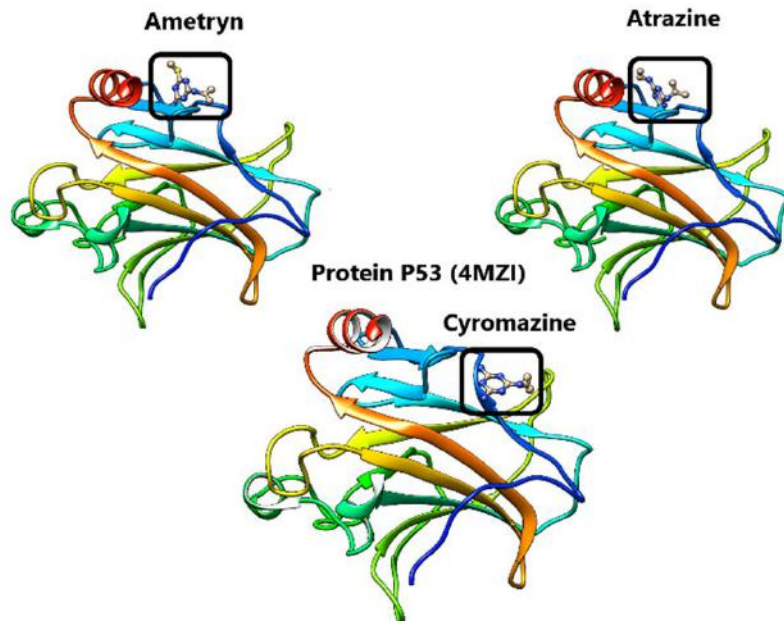
Source: Elaborated from UCSF Chimera©.

When analyzing the interactions between the ligands and the amino acids of the enzyme 4MZI, it can be seen that the ligand atrazine contains a pi-alkyl interaction with the amino acid phenylalanine 121, pi-alkyl interactions correspond to alkyl bonds with the electronic cloud of the amino acid aromatic ring (Figure 3).

Figure 3. 2D interaction map.
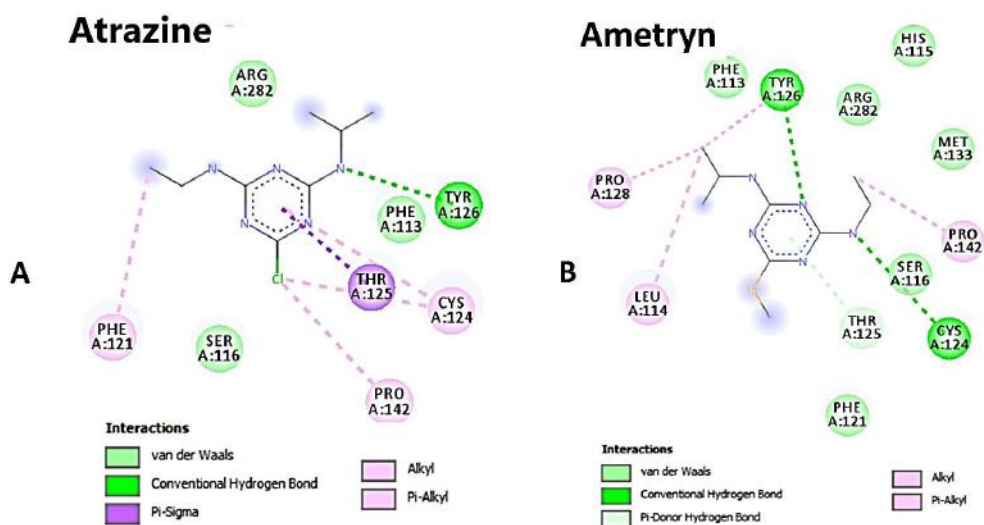
Source: Elaborated from Discovery Studio©.

The ametryn ligand shows only one interaction of Van Der Waals with phenylalanine 121, a weak interaction, but

evidence that the ligand is near the site. However, as seen in the table and the comparison images of ligands, cyromazine, had no interaction with the amino acids of the active site, having no probable inhibition.

5. Conclusion

The electronic and structural approach by MMFF94 demonstrated that ametryn, atrazine and cyromazine have the most stable structures in the values (5.123.256KJ/mol^{-1}; 3,523,590KJ/mol^{-1} and -1.185.330 KJ/mol^{-1}) in which there is variation in the formation of their conformers. Furthermore, the dipole moment was (1.837D; 2.431D, and 0.626D), establishing that each atom occupies a lower energy stationary state enabling a more stable three-dimensional structure; all compounds are polar. Moreover, with the Van der Waals surface, the molar volume is analyzed throughout the length of the molecule for future molecular dynamics assays. In addition, it should be mentioned that the compounds have no second-order bonds and no rotation.

The molecular docking of the pesticides of the triazine group: ametryn and atrazine showed that these are inhibitors of the enzyme P53 (4MZI). They are likely to initiate a carcinogenic response to workers of the Jaguaribe-Apodi Irrigated Perimeter, i.e., penile cancer, while cyromazine ligand does not interact with the enzyme p53. Therefore, it does not act as an inhibitor.

Since the region of the Jaguaribe Apodi Irrigated Perimeter has great relevance for the agro-industry sector, as well as impacts on human health. It is suggested the expansion and development of research that acts in the investigation of interactions of pesticides used in the region with receptors indicators of neoplasia which present higher incidence in the region in order to demonstrate the danger of these inputs to the health of workers and surrounding populations.

Acknowledgments

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