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ANALYSIS OF IVERMECTIN AND THE RELATIONSHIP WITH NEUROTRANSMITTERS USING QUANTUM CHEMISTRY

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ABSTRACT

Ivermectin (IVM) is currently the most successful drug in the avermectin family and was approved by the FDA for use in humans. Hyperchem software was used as a quantum chemistry simulator. The theory of the electron transfer coefficient (ETC) was the fundamental basis of quantum calculations. As a result, the ETC is lower when the IVM acts as an oxidant. This result confirms the role of IVM as an excellent oxidant of adrenaline. This finding opens intriguing possibilities for future research and possible applications in pharmacology and neurochemistry and sparks curiosity about the possible implications of this interaction. On the other hand, and with other neurotransmitters, it is concluded that IVM is a better oxidant than antioxidant of several neurotransmitters.

KEYWORDS: Ivermectin, GABA, Quantum Chemistry, Glycine, Anthelmintics.

INTRODUCTION

Ivermectin (Generalities)

Ivermectin (IVM) is currently the most successful drug in the avermectin family and was approved by the FDA for use in humans in 1978. IVM is a macrolide antiparasitic drug with a

16-membered ring derived from avermectin that is composed of 80% 22,23-dihydro avermectin-B1a and 20% 22,23-dihydro avermectin-B1b. In addition to IVM, current members of the avermectin family include selamectin, doramectin, and moxidectin.[1,2]

Mechanism of action of the IVM

IVM activates glutamate-gated chloride channels in the parasite, causing a large amount of chloride ion influx and neuronal hyperpolarization, leading to the release of gamma-aminobutyric acid (GABA) to destroy nerves and Nerve transmission from muscle cells, inducing paralysis of somatic muscles to kill parasites.[2]

IVM related to other diseases

IVM has demonstrated beneficial effects against a variety of parasitic diseases, such as malaria, trypanosomiasis, schistosomiasis, trichinosis, and leishmaniasis. Its potential antiviral effects are also noteworthy, including the ability to inhibit flavivirus replication by targeting the NS3 helicase, block nuclear transport of viral proteins through α/-mediated nuclear transport, and exert antiviral activity against HIV-1 and dengue viruses. The promising inhibitory effect of IVM on the SARS-CoV-2 virus, which caused a global outbreak in 2020, further highlights its potential. Equally significant is IVM's potential for clinical application in asthma and neurological diseases. However, what sets IVM apart is its strong anticancer effect, which makes it a potentially safe drug.[2]

Neurotransmitters and Antiparasitic

Neurotransmitters, the focus of ongoing and dynamic research, are the molecules that amplify, transmit, and convert signals in cells. Their role in the transmission of information through the nervous system is nothing short of essential. Over the last century, hundreds of these chemicals have been discovered, with more being identified and studied. These substances have a profound influence on a myriad of functions, including emotions, thoughts, memories, learning, and movements.[14]

Many anthelmintics interfere with part of the acetylcholine neurotransmitter system, blocking the worm's neuromuscular system. Levamisole and pyrantel interact with the acetylcholine receptor; organophosphate components (bromophos, metrifonate) inhibit the enzyme acetylcholinesterase; piperazine and diethylcarbamazine have a curative effect on the motor plate, so the muscle is paralyzed; Oxamniquin also appears to have action on the neuromuscular system. IVM and praziquantel increase membrane permeability by creating

chloride channels, although the former also appears to be an agonist of the neurotransmitter (GABA).[15]

Relationship of IVM and the neurotransmitter GABA

GABA is quantitatively one of the most important inhibitory transmitters in the CNS, and mediates transmission from interneurons to motoneurons in nematodes and from motoneurons to muscle cells in arthropods. IVM, with its unique mechanism, stimulates the discharge of (GABA) in the nerve endings of endoparasites (nematodes), and increases the fixation of GASA in special receptors at nerve junctions. This accumulated GAS interrupts nerve impulses in a fascinating way, paralyzing and killing parasites. The main peripheral neurotransmitter in man, acetylcholine, is not altered by IVM. IVM does not easily penetrate the central nervous system of mammals where GABA functions as a neurotransmitter, for this reason it is safe for human use.[1]

MATERIAL AND METHODS

Hyperchem software was used as a quantum chemistry simulator. The ETC theory was the fundamental basis of quantum calculations. Tables 1-2 specify the parameters used in this simulation. The electrostatic potential (EP) was calculated using the Plot Molecular Graph method in three dimensions. Finally, the ETC was calculated by dividing the bandgap by the EP. There are too many calculations, so only the oxidation-reduction tables and diagrams are presented in this article.

Table 1. Parameters used for quantum computing molecular orbitals-HOMO and LUMO

Parameter	Value	Parameter	Value
Total charge	0	Polarizability	Not
Spin Multiplicity	1	Geometry Optimization algorithm	Polak-Ribiere (Conjugate Gradient)
Spin Pairing	RHF	Termination condition RMS gradeint of	0.1 Kcal/Amol
State Lowest Convergent Limit	0.01	Termination condition or	1000 maximum cycles
Interaction Limit	50	Termination condition or	In vacuo
Accelerate Convergence	Yes	Screen refresh period	1 cycle

Table 2. Parameters used for visualizing the map of the electrostatic potential of the molecules

Parameter	Value	Parameter	Value
Molecular Property	Property Electrostatic Potential	Contour Grid increment	0.05
Representation	3D Mapped Isosurface	Mapped Function Options	Default
Isosurface Grid: Grid Mesh Size	Coarse	Transparency level	A criteria
Isosurface Grid: Grid Layout	Default	Isosurface Rendering: Total charge density contour value.	0.015
Contour Grid: Starting Value	Default	Rendering Wire Mesh	

Interpretation of the quantum well

Fig. 1 presents the quantum well of interactions through its ETC. On the left side are shown the antioxidant or reducing interactions, and on the right side are the oxidative interactions. The well is divided into four quadrants, ordered from lowest to highest, from bottom to top. Interactions deeper in the well have a greater chemical affinity and probability of occurring.

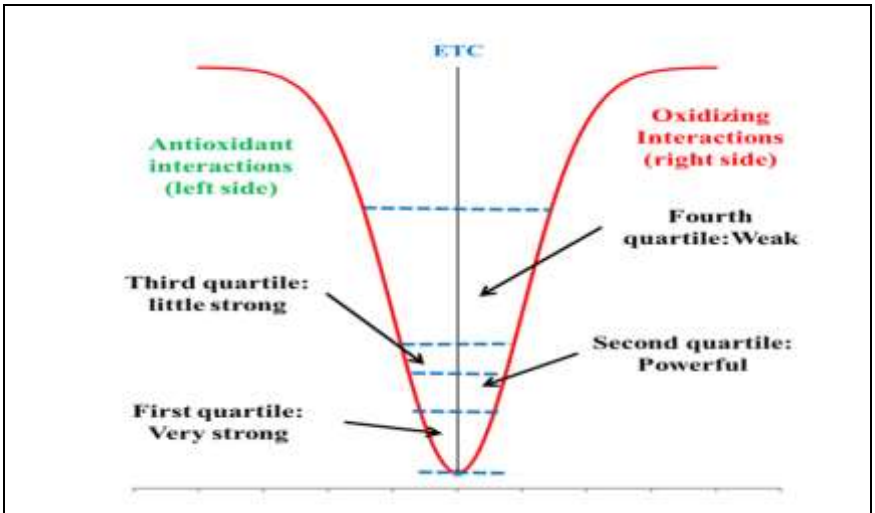


Fig. 1: Quantum well. Interpretation of interactions in the four statistical quadrants.

RESULTS AND DISCUSSIONS

Classic characterization

Figs. 2 and 3 show the results of the simulated Nuclear Magnetic Resonance H^1 characterization and the IVM's common name.

In the figure, you can see protons more unprotected than 6 ppm. These protons can suffer nucleophilic attacks more easily.

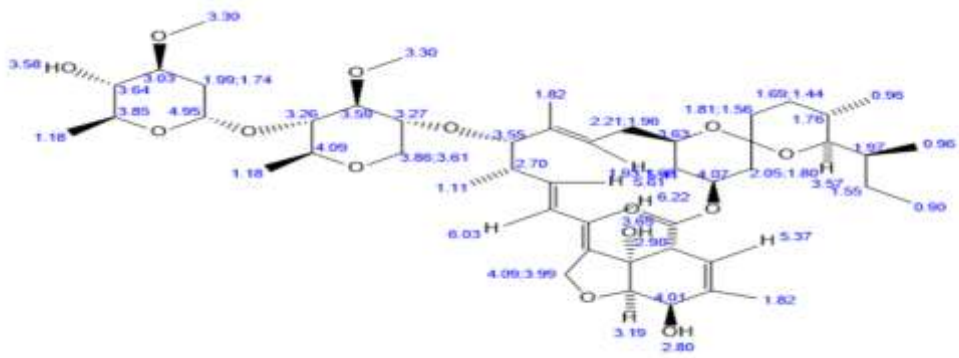


Fig. 2: Nuclear Magnetic Resonance of H^1, with its protons quantized.

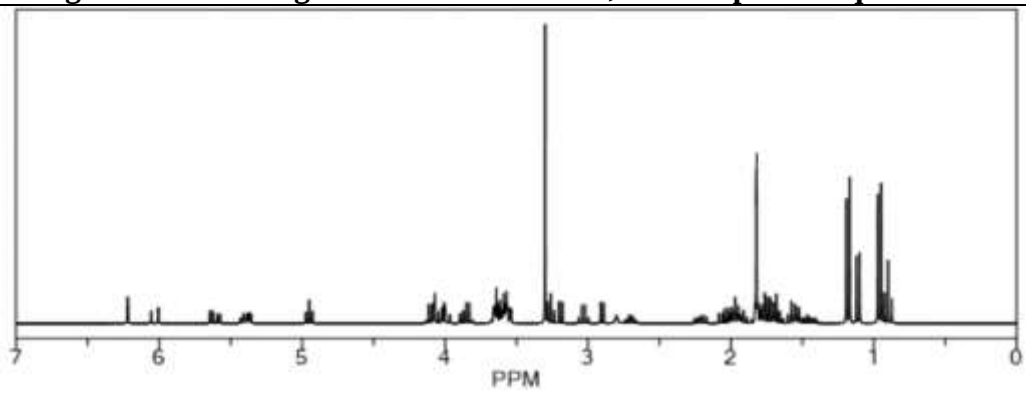


Fig. 3: Proton multiplicity diagram.

Fig. 4 and 5 show the results of the simulated characterization of C^{13} Nuclear Magnetic Resonance and the scientific name according to the UIPAC of the IVM.

In the figure, you can see carbons more unprotected than 138 ppm. These carons can suffer nucleophilic attacks more easily.

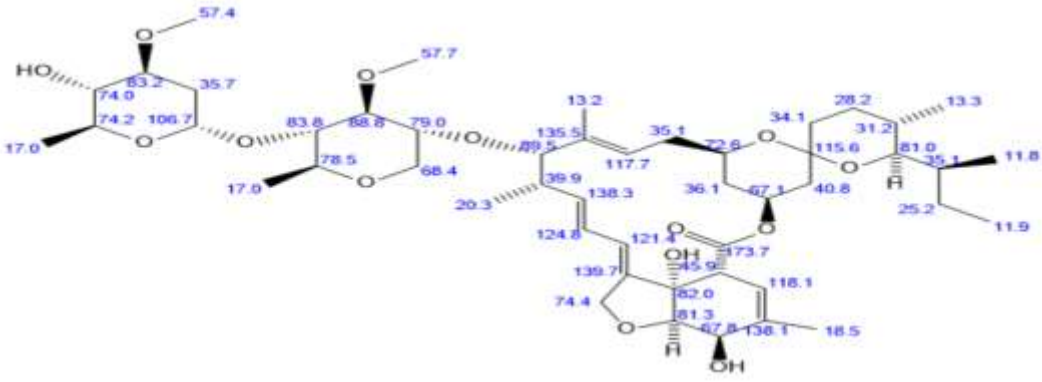


Fig. 4: C13 nuclear magnetic resonance. The molecule is shown with its quantification.

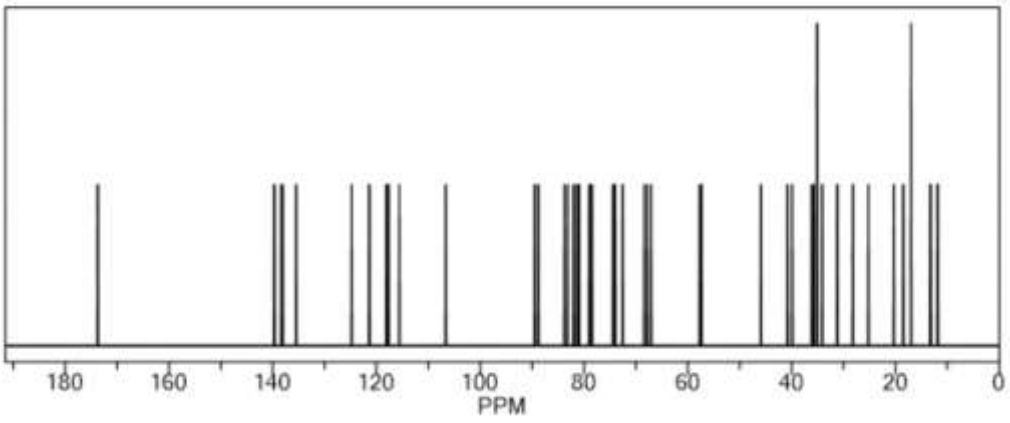
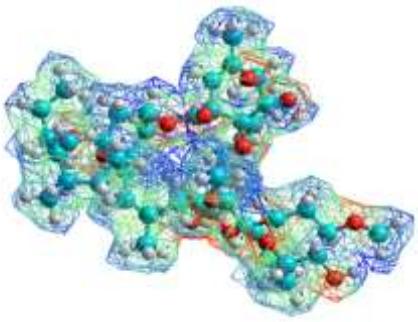


Fig. 5: C^{13} multiplicity diagram.

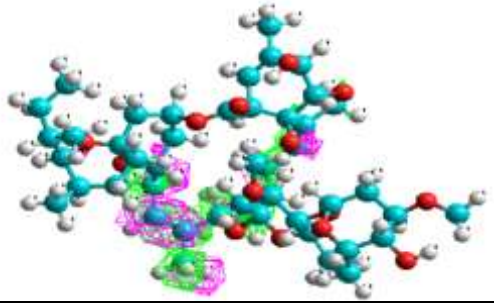
Quantum characterization

Fig. 6 shows us the IVM molecule characterized by its different quantum concepts. This molecule presents a quantum superposition of HOMO and LUMO. This quantum property infers that it has spheres or micelles.

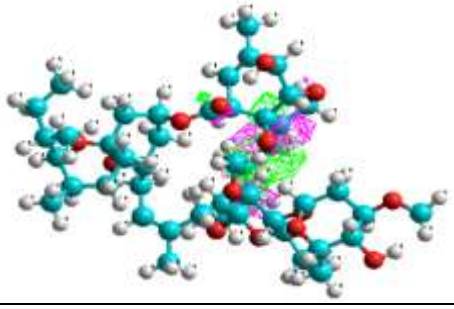
IVM. HyperChem



IVM. Electrostatic potential. -E= -0.103 eV/a°; +E = 0.152 eV/a°



IVM. HOMO. -9.722151 eV



IVM. LUMO. -0.4688011 eV

Fig. 6: Quantum characterization. A) Cyan = C; White = H; Blue = N; Red = O; B) Electrostatic Potential; C) HOMO; D) LUMO

IVM and Interaction with adrenaline

Adrenaline, also called epinephrine, is a chemical compound that the body secretes through the adrenal glands to react quickly to dangerous situations that require alertness and activity.

It is clear that in both cases of the HOMO-LUMO gap, there is a notable difference in values. The ETC is lower when the IVM acts as an oxidant. This lower oxidation value (31.708 a°) than the reduction value (32.604 a°) confirms the role of IVM as an excellent oxidant of adrenaline. This finding opens up intriguing possibilities for future research and possible applications in pharmacology and neurochemistry, raising curiosity about the possible implications of this interaction.

Table 3: IVM – adrenaline interaction. Oxidation-reduction table.

Data	Name	Reducing agent	Oxidizing agent	Homo	Lumo	Bg	E-	E+	EP	ETC
436	IVM	IVM	IVM	-9.722	-0.469	9.253	-0.103	0.152	0.255	36.288
437	Adrenalin	ADR	ADR	-8.998	0.092	9.090	-0.117	0.198	0.315	28.858
Option 1	IVM vs. Adrenalin	IVM	ADR	-9.722	0.092	9.814	-0.103	0.198	0.301	32.604
Option 2	Adrenalin vs. IVM	ADR	IVM	-8.998	-0.469	8.529	-0.117	0.152	0.269	31.708

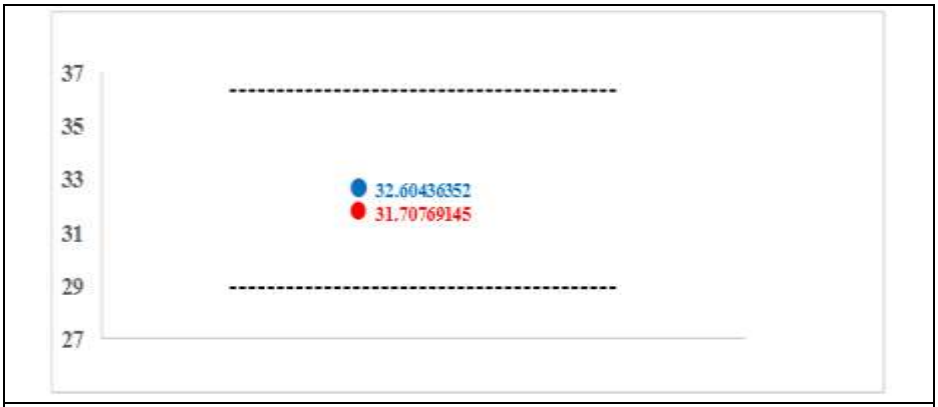


Fig. 7: Oxide-Reduction Graph adrenalin vs. IVM.

IVM and interaction with the neurotransmitter serotonin

Serotonin sends signals between nerve cells and regulates their intensity. Scientists believe it plays a role in mood and the central nervous system and affects functions throughout the body.

In both options of the HOMO-LUMO gap, there is a notable difference in values. The ETC is lower when IVM acts as an oxidant; with this, we confirm that IVM is an excellent oxidant of serotonin.

Table 4: IVM – serotonin interaction. Oxide-Reduction Table.

Data	Name	Reducing agent	Oxidizing agent	Homo	Lumo	Bg	E-	E+	EP	ETC
436	IVM	IVM	IVM	-9.722	-0.469	9.253	-0.103	0.152	0.255	36.288

438	Serotonin	SER	SER	-8.948	-0.129	8.818	-0.145	0.141	0.286	30.835
Option 1	IVM vs. Serotonin	IVM	SER	-9.722	-0.129	9.593	-0.103	0.141	0.244	39.314
Option 2	Serotonin vs. IVM	SER	IVM	-8.948	-0.469	8.479	-0.145	0.152	0.297	28.550

Fig. 8: Oxide-Reduction Graph serotonin vs. IVM.

IVM and Interaction with the neurotransmitter dopamine

Dopamine is a neurotransmitter, a molecule responsible for carrying a message from the neurons that produce it to other cells.

There is a notable difference in values between the HOMO-LUMO gap options. The ETC is lower when IVM acts as an oxidant, which confirms that IVM is an excellent oxidant of dopamine.

Table 5: IVM – Dopamine interaction. Oxide-Reduction Table.

Data	Name	Reducing agent	Oxidizing agen	Homo	Lumo	Bg	E-	E+	EP	ETC
436	IVM	IVM	IVM	-9.722	-0.469	9.253	-0.103	0.152	0.255	36.288
439	Dopamine	DOP	DOP	-8.867	0.198	9.066	-0.098	0.189	0.287	31.591
Option 1	IVM vs. Dopamine	IVM	DOP	-9.722	0.199	9.921	-0.103	0.189	0.292	33.976
Option2	Dopamine vs. IVM	DOP	IVM	-8.868	-0.469	8.399	-0.098	0.152	0.250	33.595

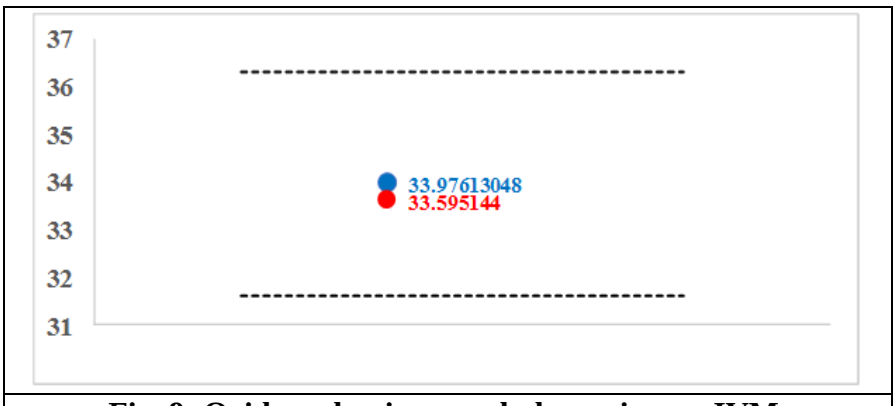


Fig. 9: Oxide-reduction graph dopamine vs. IVM.

IVM and Interaction with the neurotransmitter GABA

Gamma-aminobutyric acid (γ-aminobutyric acid, or GABA) is a non-protein amino acid found in high concentrations in the central nervous system of mammals. Its primary function is to act as an inhibitory neurotransmitter.

It's reassuring to see that both options for the HOMO-LUMO gap have similar values, around -9.5 eV. ETC is lower when IVM acts as an oxidant, providing strong confirmation that IVM is indeed an excellent oxidant of GABA.

Table 6: IVM – GABA interaction. Oxide-Reduction Table.

Data	Name	Reducing agent	Oxidizing agen	Homo	Lumo	Bg	E-	E+	EP	ETC
436	IVM	IVM	IVM	-9.722	-0.469	9.253	-0.103	0.152	0.255	36.288
440	GABA	GAB	GAB	-9.561	0.938	10.500	-0.14	0.18	0.32	32.812
Option1	IVM vs. Gaba	IVM	GAB	-9.722	0.939	10.661	-0.103	0.180	0.283	37.670
Option 2	Gaba vs. IVM	GAB	IVM	-9.562	-0.469	9.093	-0.140	0.152	0.292	31.139

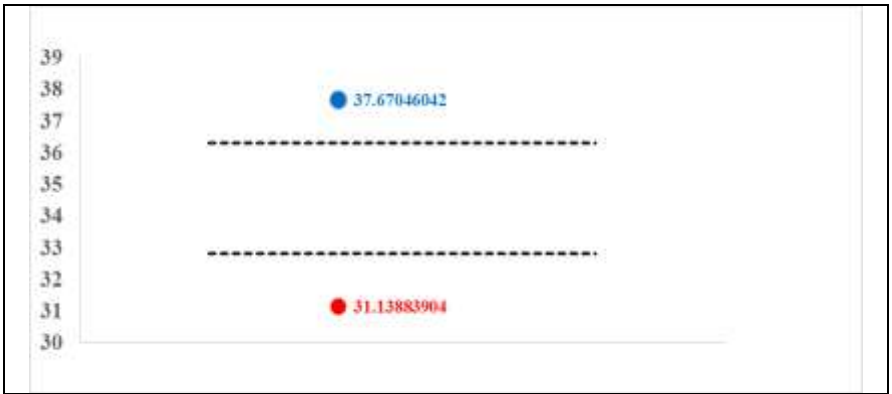


Fig. 10: Oxide-reduction graph gaba vs. IVM.

IVM and Interaction with the neurotransmitter glutamic acid

Glutamic acid can help the nerve exchange (send and receive) information with other cells. It is being studied for its ability to reduce or prevent nerve damage caused by some anti-cancer drugs.

Notably, there is a significant difference in the HOMO-LUMO gap values in both scenarios. This intriguing finding piques our interest and underscores the importance of our research. The lower electron transfer coefficient (ETC) when IVM acts as an oxidant further confirms its excellent oxidizing potential on GLUTAMIC ACID.

Table 7: IVM – GLUTAMIC ACID interaction. Oxide-Reduction Table.										
Data	**Name**	**Reducing agent**	**Oxidizing agen**	**Homo**	**Lumo**	**Bg**	**E-**	**E+**	**EP**	**ETC**
436	IVM	IVM	IVM	-9.722	-0.469	9.253	-0.103	0.152	0.255	36.288
441	Glutamic acid	AGT	AGT	-10.144	0.505	10.650	-0.136	0.161	0.297	35.861
Option 1	IVM vs. Glutamic acid	IVM	AGT	-9.722	0.506	10.228	-0.103	0.161	0.264	38.743
Option2	Glutamic acid vs. IVM	AGT	IVM	-10.145	-0.469	9.676	-0.136	0.152	0.288	33.596

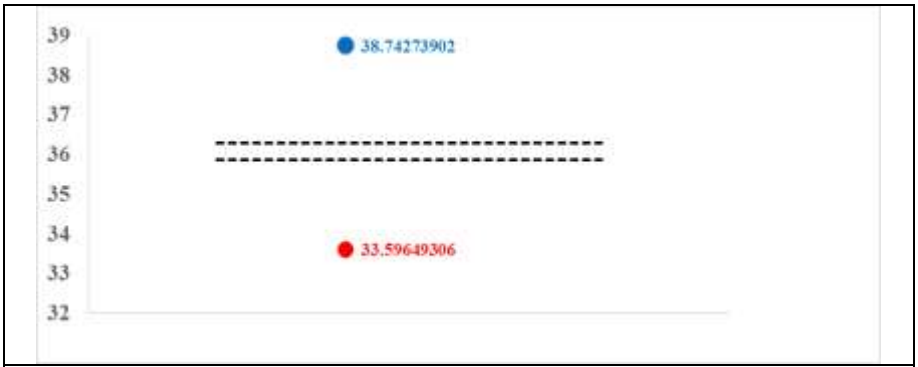


Fig. 11: Oxide-reduction graph glutamic acid vs. IVM.

IVM and Interaction with the neurotransmitter glycine

Glycine is an amino acid, specifically the smallest and one of the so-called "non-essentials." It helps form our body's proteins. In addition, it acts as an inhibitory neurotransmitter in the central nervous system, especially in the retina, brain stem, and spinal cord.

It is reassuring to see that both options of the HOMO-LUMO gap share similar values, around -9.7 eV. The electron transfer coefficient (ETC) is lower when IVM acts as an oxidant, confirming IVM's role as an excellent oxidant of GLYCINE.

Table 8: IVM – Glycine interaction. Oxide-Reduction Table.										
Data	**Name**	**Reducing agent**	**Oxidizing agen**	**Homo**	**Lumo**	**Bg**	**E-**	**E+**	**EP**	**ETC**
436	IVM	IVM	IVM	-9.722	-0.469	9.253	-0.103	0.152	0.255	36.288
442	GLYCINE	GLY	GLY	-9.853	0.874	10.727	-0.126	0.188	0.314	34.163
Option 1	IVM vs. Glycine	IVM	GLY	-9.722	0.874	10.597	-0.103	0.188	0.291	36.414
Option 2	Glycine vs. IVM	GLY	IVM	-9.853	-0.469	9.384	-0.126	0.152	0.278	33.755

Fig. 12: Oxide-reduction graph glycine vs. IVM.

IVM and Interaction with the neurotransmitter histamine

Histamine is an excitatory neurotransmitter produced by hypothalamic neurons, gastric mucosal cells, mast cells, and blood basophils. In the central nervous system, it is important for wakefulness, blood pressure, pain, and sexual behavior. In addition, it increases the acidity of the stomach.

It can be seen that both options for the HOMO-LUMO gap have similar values, around -9.1 eV. The electron transfer coefficient (ETC) is lower when IVM acts as an oxidant, which confirms that IVM is an excellent oxidant of HISTAMINE.

Table 9: IVM – histamine interaction. Oxide-Reduction Table.

Data	Name	Reducing agent	Oxidizing agen	Homo	Lumo	Bg	E-	E+	EP	ETC
436	IVM	IVM	IVM	-9.722	-0.469	9.253	-0.103	0.152	0.255	36.288
443	Histamine	HTM	HTM	-9.190	0.675	9.865	-0.134	0.163	0.297	33.218
Option 1	IVM vs. Histamine	IVM	HTM	-9.722	0.675	10.398	-0.103	0.163	0.266	39.088
Option 2	Histamine vs. IVM	HTM	IVM	-9.191	-0.469	8.722	-0.134	0.152	0.286	30.495

Fig. 13: Oxide-Reduction graph histamine vs. IVM.

IVM and Interaction with the neurotransmitter noradrenaline

Norepinephrine is a neurotransmitter related to motivation, alertness and wakefulness, level of consciousness, perception of sensory impulses, regulation of sleep, appetite and sexual behavior, and neuromodulation of reward, learning, and memory mechanisms.

These findings open up exciting possibilities for the future of pharmacology, suggesting that IVM could be a powerful tool for modulating neurotransmitter levels and potentially treating a wide range of neurological conditions, sparking curiosity and further exploration in the field.

Table 10: IVM – Noradrenaline interaction. Oxide-Reduction Table.

Data	Name	Reducing agent	Oxidizing agen	Homo	Lumo	Bg	E-	E+	EP	ETC
436	IVM	IVM	IVM	-9.722	-0.469	9.253	-0.103	0.152	0.255	36.288
444	Noradrenaline	NOR	NOR	-9.151	-0.004	9.147	-0.083	-0.222	0.139	65.809
Option 1	IVM vs. Noradrenaline	IVM	NOR	-9.722	-0.004	9.718	-0.103	-0.222	0.119	81.663
Option 2	Noradrenaline vs. IVM	NOR	IVM	-9.152	-0.469	8.683	-0.083	0.152	0.235	36.948

Fig. 14: Oxide-reduction graph noradrenaline vs. IVM.

IVM and Interaction with the neurotransmitter acetylcholine

Acetylcholine helps control memory and the action of specific muscles.

Both options for the HOMO-LUMO gap have similar values, around -9.2 eV. The ETC is lower when IVM acts as an oxidant, which confirms that IVM is an excellent oxidant of acetylcholine.

Table 11: IVM – Acetylcholine interaction. Oxide-Reduction Table.

Data	Name	Reducing agent	Oxidizing agent	Homo	Lumo	Bg	E-	E+	EP	ETC
436	IVM	IVM	IVM	-9.722	-0.469	9.253	-0.103	0.152	0.255	36.288

445	Acetylcholine	ACE	ACE	-9.241	1.034	10.276	-0.028	0.105	0.133	77.265
Option 1	IVM vs. Acetylcholine	IVM	ACE	-9.722	1.034	10.756	-0.103	0.105	0.208	51.714
Option 2	Acetylcholine vs. IVM	ACE	IVM	-9.242	-0.469	8.773	-0.028	0.152	0.180	48.739

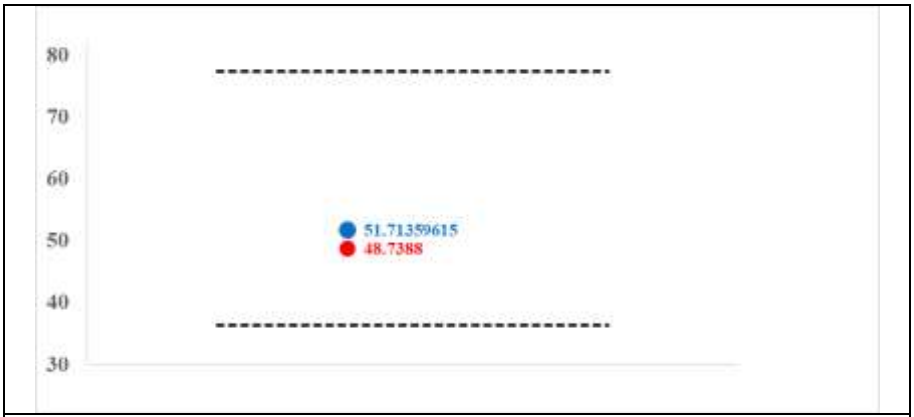


Fig. 15: Oxidation-reduction graph acetylcholine vs. IVM.

CONCLUSIONS

Aim

Analyze the relationship between IVM and neurotransmitters using quantum chemistry.

Thesis

Based on the results shown in the tables [3,4,5,6,7,8,9,10,11] and in the graphs [7,8,9,10,11,12,13,14,15] indicate that IVM is a better oxidant than antioxidant of neurotransmitters

Corollary

IVM has a promising inhibitory effect on the SARS-CoV-2 virus, which caused a global outbreak in 2020. IVM not only has strong effects on parasites but also has the potential to inhibit flavivirus replication, a finding that opens up new avenues for research. Targeting the NS3 helicase also blocks the nuclear transport of viral proteins by acting on α/β-mediated nuclear transport and exerts antiviral activity against HIV-1 and dengue viruses.

Thanks

I thank my mother for never stopping believing in me. Thank you for your love, support, effort, and dedication to me. I thank you because you formed me as a person and a functional human being for society. My words are scarce because I thank you very much. I can only say, thank you, mother.

I thank my father. You were my guide when I needed it most. Any mistake I made, you made me understand why it was wrong. You were also our example of knowing that people truly change with hard work, perseverance, and love. Thank you, father.

I thank my sister for being my faithful companion. This person never abandoned me, a clear example that if someone gives everything to her family, it is clearly you.

I thank my family—grandparents, uncles, cousins, etc. They were all vital parts of my life since, with their advice, love, and help, I could not have moved on; thank you very much.

I thank my girlfriend, Camila. You are a beacon of light in my life. I appreciate and am grateful for all the sacrifices you made and that you still make for me. Thank you for agreeing with me. I hope life fills us with moments and achievements together.

I thank my best friend, Yahir. He was an unconditional help during this stay. In fact, throughout your career, you have proven to be loyal and a good friend. Thank you for being a true friend.

I thank Dr. Manuel González for guiding me through this stay, for the knowledge I acquired, for his time, and for the opportunity to make this stay pleasant.

To the Autonomous University of Guerrero, the Faculty of Natural Sciences, and the Delfín program for giving me the opportunity to participate in this summer research stay. This summer will help train me as a professional or researcher and will have a big impact on my career.

To everyone, thank you for allowing me to achieve this goal.

Conflict of interests

There is no conflict of interest between our universities.

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