

IN SILICO ANALYSIS OF THE INTERACTIONS OF METFORMIN VS. AMINO ACIDS USING QUANTUM CHEMISTRY

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ABSTRACT

This paper examines the oxidative-reducing molecular characteristics at the amino acid level and metformin (MTF). This drug is top of the line and is used to treat diabetes. This disease is one of the most suffered and with the highest death rate in the country. In current statistics, scientists rank diabetes as the second leading cause of death. The Electron Transfer Coefficient (ETC) was used as the primary calculation tool. This concept is defined as the dimensionless parameter, describing an electrochemical interaction; they are interpreted as the number of times the potential energy is needed for the electron to jump from a prohibited band from one molecule to another. MTF is an antioxidant drug for both AA and nucleic acids.

None of the quantum interactions presented as an oxidizing agent that produces free radicals, being of vital importance for the stable replication of DNA and RNA and preventing the addition of inert elements that could structurally and functionally alter the cell.

KEYWORDS: Experimentation in silico; Metformin; amino acids; quantum chemistry; electron transfer coefficient.

INTRODUCTION

Mexico is on the list of the ten countries with the highest number of people living with diabetes and the second cause of death, affecting millions of people in the country. The increase in the prevalence of diabetes could be due to different factors such as increased life expectancy and prevalence of obesity-related to changes in lifestyles, which may be the

increase in the calories in the diet, reduction in physical activity, and changes in other diabetes-related factors.

The name diabetes mellitus (DM) comprises a group of metabolic diseases characterized by hyperglycemia is resulting from defects in insulin secretion, insulin action, or both. DM can be associated with acute complications that can lead to significant disturbances, such as precipitation of cardiovascular or neurological damage, coma, and life risk, in case of non-urgent treatment. Hyperglycemia in chronic diabetes is associated with long-term damage, which causes dysfunctions and multiple organic failures: especially eyes, kidneys, nerves, heart, and blood vessels.^[1,2]

In Mexico, DM type II is the most important cause of blindness, chronic kidney failure, and non-traumatic amputations and is one of the most common causes of hospitalization in adults. In addition, it increases the risk of myocardial or cerebral infarction and explains 30 % of overall mortality. Investigating risk factors, treatment, and complications is of paramount importance in reducing the burden of the disease and giving a higher quality of life to chronic degenerative patients. One of the goals to achieve in diabetic patients is glycemic control. However, studies have shown that in the development of diabetes complications, there are more factors involved than just hyperglycemia, ranging from diabetic foot, kidney damage or failure to nerve disturbances and blindness.

A prospective study of the United Kingdom Prospective Diabetes Study (UKPDS) showed that MTF treatment decreased mortality and cardiovascular events compared to insulin and sulfonylureas, even if they had the same effects and decreased glycemia in an overweight, diabetic population. The progress made in the treatment of the disease and the implementation of preventive measures is also discussed and the presence of diabetes complications in the population between 2012 and 2016.^[3,4]

Different medications and treatments in the pharmaceutical market have been implemented over the years. These drugs prevent and delay the onset of MD2. MTF has been the best treatment of all of these since 1957 in Europe and 1995 in Latin America. This drug is the first choice in the treatment of DM2 due to its therapeutic characteristics. MTF belongs to the biguanides family, which are molecules or groups of drugs that function as oral antidiabetic to treat DM.^[5-6]

The three leading causes of death for men and women in Mexico are heart disease, DM, and malignant tumors. Deaths from DM have escalated positions among leading causes of death; they occupy the second place between women and men from the reference period. In Mexico, DM II belongs to our second confirmed cause of death since during 2018 according to the press release PRESS COMMUNICATION NUM 538/19 from 31 October 2019 by INEGI, 88.4 % of the deaths were due to illnesses and health-related problems and 11.6 to external causes mainly accidents, homicides, and suicides. It is of utmost importance to optimize treatment to decrease the prevalence of DM in our country with MTF uses. Therefore, in this review, we analyzed the quantum, chemical, and biological activity of MTF in the bioactive sets of the AAs and dipeptides was carried out for the possible treatment of DM, as well as the observation of the first-line drug in DMII. It is molecular characteristics and its interaction at the systemic level with oxide-reduction by quantum physics.

MATERIALS AND METHODS

The ETC (electron transfer coefficient) is defined as a dimensionless parameter. This parameter describes a chemical-quantum interaction and is interpreted as the number of times the electron must jump into the Bang Gap (BG). The electrostatic Potential is the natural energy of the electron, which is used for the quantum leap. For example, if you have a BG of 40 and an ETC of 10, it means that the electron has a power of 4 times greater so that the electron jumps from the HOMO of one molecule to the LUMO of another.

This parameter describes a chemical-quantum interaction and is interpreted as the number of times the electron must jump into the Bang Gap (BG). The electrostatic Potential is the natural energy of the electron, which is used for the quantum leap. For example, If you have BG of 40 and an ETC of 10, it means that the electron has a power of 4 times more incredible so that the electron jumps from the HOMO of one molecule to the LUMO of another energy should jump to the Bang Gap (BG) and the electrostatic Potential if you have BG of 10, ETC of 40, it means you need 40 times the EP value in eV for what BG jump ten times the HOMO at LUMO.

In quantum theory, it is known as HOMO and LUMO, and in ancient theory are known as E- and E+ LUMO is defined as the range of electronic energy, which allows acceleration in electrons by the presence of electric currents and is also called the conduction band. HOMO is defined as the highest energy range occupied by electrons and is called the valence band. HOMO is the most-electron-filled orbital, while LUMO is the orbital that lacks electrons.

The HOMO equals zero (HOMO 0). It is the last layer full of orbitals which means it is in the last orbital valence. LUMO is equal to zero (LUMO 0) is the last layer that lacks electrons.^[13]

The BG is defined as the energy difference between the valence band and the driving band. There are no electronic states available in the BG; this means that electrons cannot increase their energy when an electric field is applied.

EP is defined as the total potential energy of the molecule. An electrostatic field vector is defined as the Potential that the electron needs to jump the Bohr radius (0.53 Armstrong) by its calculated natural electromotive force (EMC). The negative E-value (E-) is the electrostatic Potential with negative poles, while the positive E- value (E+) is the Potential of the proton-electron; The EP, in other words, means that having 1 EP has 1 volt for Armstrong. The EP is obtained by the absolute difference of E- and E+.

Tables 1 and 2 show the parameterization of the simulator.

Table 1: Parameters used for quantum calculations of molecular orbitals HUMO y 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 gradient of	0.1 Kcal/Mol
State Lowest Convergent Limit	0.01		1000 maximum cycles
Interaction Limit	50	Termination condition or	
Accelerate Convergence	Yes	Screen refresh period	

Table 2: Parameters used for the quantum calculations of the electrostatic potential of the molecules.

Parameter	Value	Parameter	Value
Molecular Property	Property Electrostatic	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	Default	Isosurface	0.015

Layout		Rendering: Total charge density contour value	
Contour Grid: Starting Value	Default	Rendering Wire Mesh	-

SE-PM3 is a molecular modeling program used by scientists to analyze the quantum composition of scientist to analyze the quantum composition of molecules for HUMO-LUMO, BG EP, and other properties.

(Hyperchem, hypercube, Multi in para Windows, serie 12-800-1501800080) (Multi in South 1236-301 Tlacoquemecatl Insurgentes Col. del Valle, Benito Juárez, DF, México C.P.03200). In figure 1, the individual quantum wells are schematized. The dotted lines indicate the bottom of each well of both pure substances. Green and purple wells are the results of cross banding. The probability zones for the interactions are also shown. The highest probability zone is below the blue line (bottom of the well). The average probability zone is located between the dotted lines. The most unlikely área is located above the red dotted line.

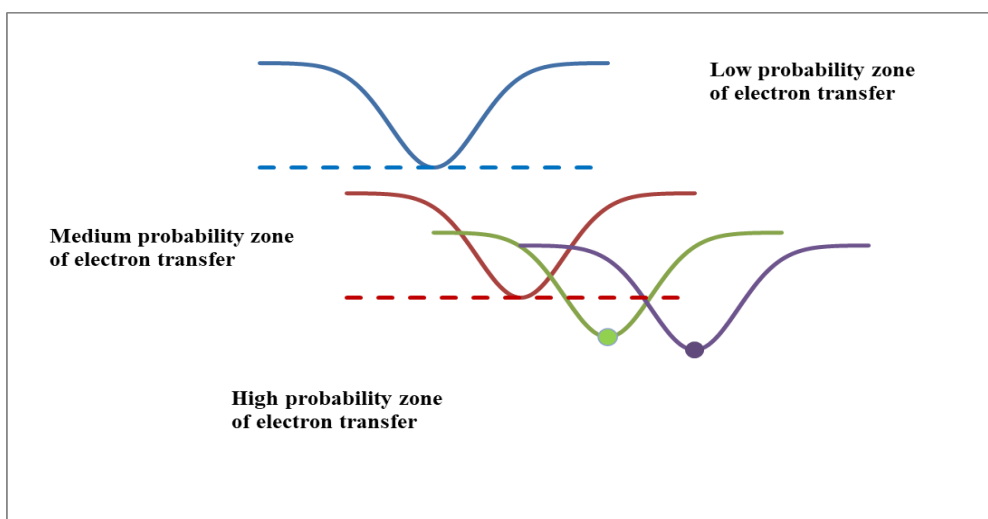


Figure 1: Quantum wells.

In figure 2, a general quantum well is shown; you can see the quantum soup when many substances interact. In this article, general quantum wells are presented in the form of tables. It is interpreted that the more profound the molecular interactions in the well, the more stable they are or, the more strongly they are attracted with greater force.

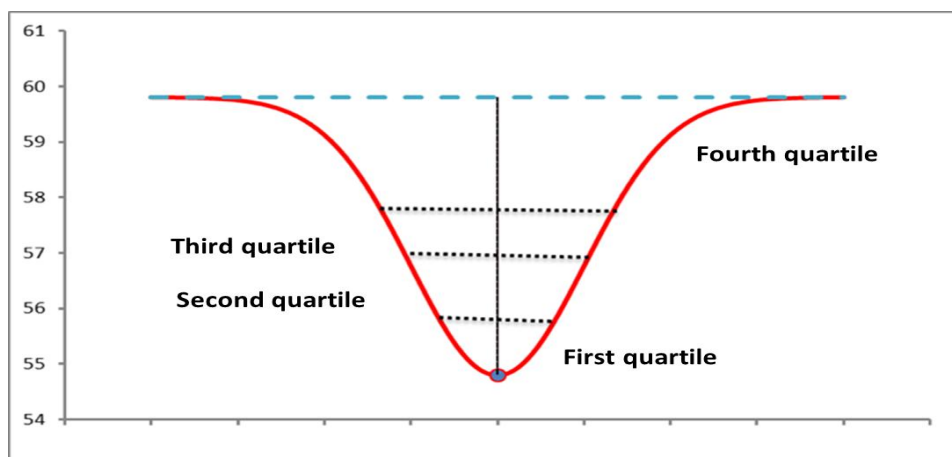


Figure 2: General quantum well.

RESULTS AND DISCUSSION

In Figure 3, four results of the molecular simulation of MTF are presented. In this figure, part B, we can see that the positive pole predominates. In sections C and D, we can see that both HOMO and LUMO occupy the same atoms; with this, it can be said that the molecule forms micelles.

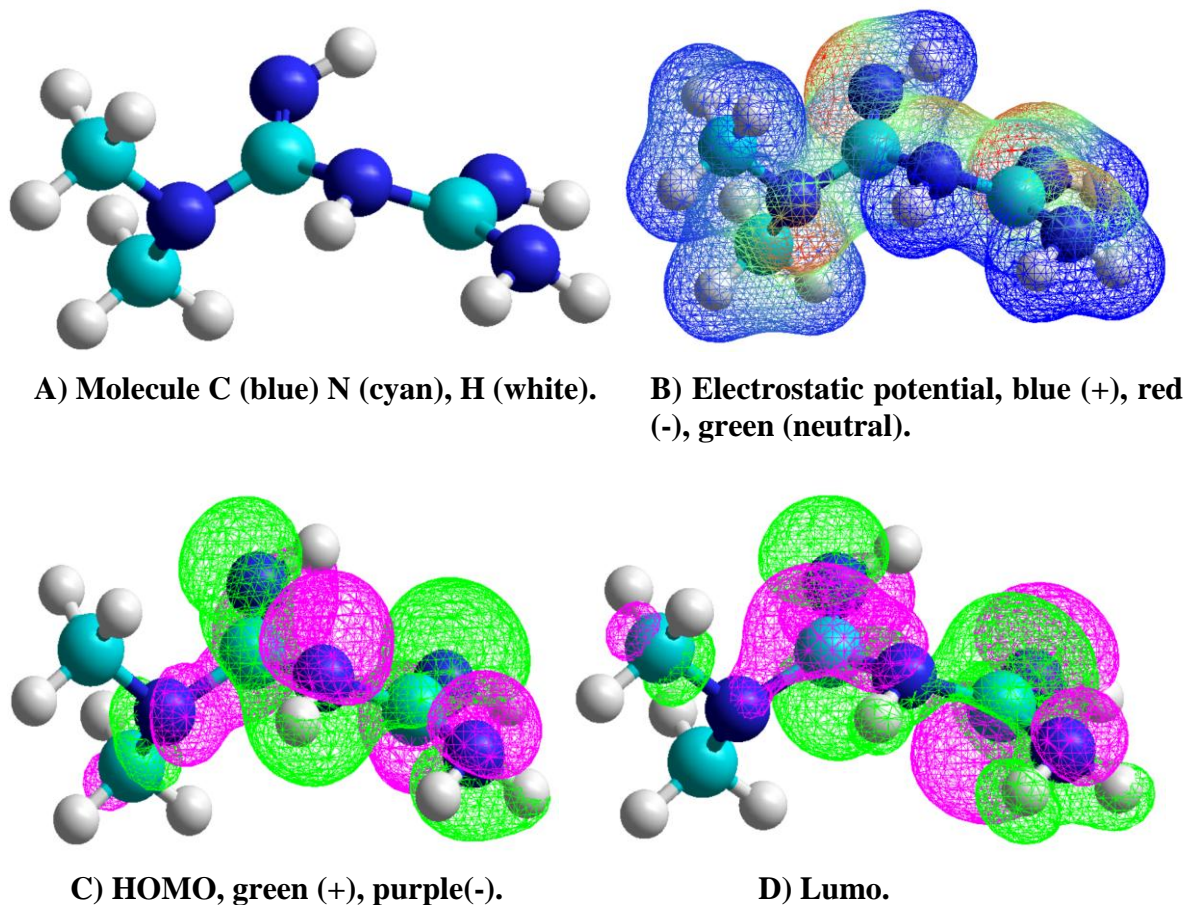


Figure 3: Four representations of the MTF molecule.

Table 3 shows the quantum well of pure substances, AAs, and MTF. As can be seen, the MTF is ranked 16th in the well. This means that MTF degrades relatively quickly. It does not stay in the body. In contrast, AA Arg (interaction 1 in the well) is very stable in biological tissues, and Val is the least stable AA of all.

Table 3: Quantum well of Aas and Substances ordered.

No.	Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
21	Val	Val	-9.914	0.931	10.845	-0.131	0.109	0.24	45.188
20	Ala	Ala	-9.879	0.749	10.628	-0.124	0.132	0.256	41.515
19	Leu	Leu	-9.645	0.922	10.567	-0.126	0.13	0.256	41.279
18	Phe	Phe	-9.553	0.283	9.836	-0.126	0.127	0.253	38.879
17	Gly	Gly	-9.902	0.902	10.804	-0.137	0.159	0.296	36.5
16	MTF	MTF	-9.374	0.64	10.014	-0.152	0.123	0.275	36.414
15	Ser	Ser	-10.156	0.565	10.721	-0.108	0.198	0.306	35.037
14	Cys	Cys	-9.639	-0.236	9.403	-0.129	0.14	0.269	34.956
13	Glu	Glu	-10.374	0.438	10.812	-0.111	0.201	0.312	34.655
12	Ile	Ile	-9.872	0.972	10.844	-0.128	0.188	0.316	34.316
11	Thr	Thr	-9.896	0.832	10.728	-0.123	0.191	0.314	34.167
10	Gln	Gln	-10.023	0.755	10.778	-0.124	0.192	0.316	34.108
9	Asp	Asp	-10.37	0.42	10.79	-0.118	0.204	0.322	33.509
8	Asn	Asn	-9.929	0.644	10.573	-0.125	0.193	0.318	33.249
7	Lys	Lys	-9.521	0.943	10.463	-0.127	0.195	0.322	32.495
6	Pro	Pro	-9.447	0.792	10.238	-0.128	0.191	0.319	32.095
5	Trp	Trp	-8.299	0.133	8.431	-0.112	0.155	0.267	31.577
4	Tyr	Tyr	-9.056	0.293	9.349	-0.123	0.193	0.316	29.584
3	His	His	-9.307	0.503	9.811	-0.169	0.171	0.34	28.855
2	Met	Met	-9.062	0.145	9.207	-0.134	0.192	0.326	28.243
1	Arg	Arg	-9.176	0.558	9.734	-0.165	0.199	0.364	26.742

The results are shown in the well of Table 4 MTF as a reducing agent (antioxidant) or as an oxidant agent compared to pure AA. In detail is an antioxidant agent of all AAs without exception mixed with some pure AA.

Table 4: Interactions of MTF with AA in their pure form.

No.	Reducing agent	Oxidizin agent	HOMO	LUMO	BG	E-	E+	EP	ETC
34	Ser	Ser	-10.156	0.565	10.721	-0.108	0.198	0.306	35.037
33	Cys	Cys	-9.639	-0.236	9.403	-0.129	0.14	0.269	34.956
32	Glu	Glu	-10.374	0.438	10.812	-0.111	0.201	0.312	34.655
31	MTF	Phe	-9.374	0.283	9.657	-0.152	0.127	0.279	34.614
30	Ile	Ile	-9.872	0.972	10.844	-0.128	0.188	0.316	34.316
29	Thr	Thr	-9.896	0.832	10.728	-0.123	0.191	0.314	34.167
28	Gln	Gln	-10.023	0.755	10.778	-0.124	0.192	0.316	34.108

27	Arg	MTF	-9.176	0.64	9.816	-0.165	0.123	0.288	34.084
26	His	MTF	-9.307	0.64	9.948	-0.169	0.123	0.292	34.067
25	Asp	Asp	-10.37	0.42	10.79	-0.118	0.204	0.322	33.509
24	Asn	Asn	-9.929	0.644	10.573	-0.125	0.193	0.318	33.249
23	MTF	Gly	-9.374	0.902	10.275	-0.152	0.159	0.311	33.04
22	Lys	Lys	-9.521	0.943	10.463	-0.127	0.195	0.322	32.495
21	Pro	Pro	-9.447	0.792	10.238	-0.128	0.191	0.319	32.095
20	Trp	Trp	-8.299	0.133	8.431	-0.112	0.155	0.267	31.577
19	MTF	Cys	-9.374	-0.236	9.138	-0.152	0.14	0.292	31.296
18	MTF	Trp	-9.374	0.133	9.506	-0.152	0.155	0.307	30.966
17	MTF	His	-9.374	0.503	9.877	-0.152	0.171	0.323	30.579
16	MTF	Ile	-9.374	0.972	10.346	-0.152	0.188	0.34	30.428
15*	MTF	Thr	-9.374	0.832	10.206	-0.152	0.191	0.343	29.755
14	MTF	Lys	-9.374	0.943	10.317	-0.152	0.195	0.347	29.731
13	MTF	Pro	-9.374	0.792	10.166	-0.152	0.191	0.343	29.638
12	Tyr	Tyr	-9.056	0.293	9.349	-0.123	0.193	0.316	29.584
11	MTF	Gln	-9.374	0.755	10.129	-0.152	0.192	0.344	29.444
10	MTF	Asn	-9.374	0.644	10.018	-0.152	0.193	0.345	29.038
9	His	His	-9.307	0.503	9.811	-0.169	0.171	0.34	28.855
8	MTF	Ser	-9.374	0.565	9.939	-0.152	0.198	0.35	28.396
7	MTF	Arg	-9.374	0.558	9.932	-0.152	0.199	0.351	28.296
6	Met	Met	-9.062	0.145	9.207	-0.134	0.192	0.326	28.243
5	MTF	Tyr	-9.374	0.293	9.666	-0.152	0.193	0.345	28.019
4	MTF	Glu	-9.374	0.438	9.812	-0.152	0.201	0.353	27.797
3	MTF	Met	-9.374	0.145	9.519	-0.152	0.192	0.344	27.671
2	MTF	Asp	-9.374	0.42	9.794	-0.152	0.204	0.356	27.511
*1	Arg	Arg	-9.176	0.558	9.734	-0.165	0.199	0.364	26.742

In table 5, the quantum soup of AA and MTF is shown, all against all: a) protein chains, b) di-peptides, c) tripeptides. Their first interaction is in position 16; this means that it does not intervene in the fundamental metabolic processes of proteins. MTF starts its antioxidation or reduction from interaction 16.

Table 5: Quantum soup. Interactions between AA and MTF in cross-bands. Only 25 calculations out of 461 are presented here.

No.	Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
25	MTF	Tyr	-9.374	0.293	9.666	-0.152	0.193	0.345	28.019
24	Arg	Pro	-9.176	0.792	9.968	-0.165	0.191	0.356	28.001
23	Trp	Glu	-8.299	0.438	8.737	-0.112	0.201	0.313	27.913
22	His	Gln	-9.307	0.755	10.062	-0.169	0.192	0.361	27.873
21	Arg	Gln	-9.176	0.755	9.931	-0.165	0.192	0.357	27.818
20	MTF	Glu	-9.374	0.438	9.812	-0.152	0.201	0.353	27.797
19	Trp	Met	-8.299	0.145	8.444	-0.112	0.192	0.304	27.775
18	MTF	Met	-9.374	0.145	9.519	-0.152	0.192	0.344	27.671
17	Trp	Asp	-8.299	0.420	8.719	-0.112	0.204	0.316	27.591

16	MTF	Asp	-9.374	0.420	9.794	-0.152	0.204	0.356	27.511
15	His	Asn	-9.307	0.644	9.952	-0.169	0.193	0.362	27.491
14	Arg	Asn	-9.176	0.644	9.820	-0.165	0.193	0.358	27.431
13	His	Ser	-9.307	0.565	9.872	-0.169	0.198	0.367	26.900
12	Arg	Ser	-9.176	0.565	9.741	-0.165	0.198	0.363	26.835
11	His	Arg	-9.307	0.558	9.865	-0.169	0.199	0.368	26.808
10	Arg	Arg	-9.176	0.558	9.734	-0.165	0.199	0.364	26.742
9	Arg	Arg	-9.176	0.558	9.734	-0.165	0.199	0.364	26.742
8	His	Tyr	-9.307	0.293	9.600	-0.169	0.193	0.362	26.519
7	Arg	Tyr	-9.176	0.293	9.469	-0.165	0.193	0.358	26.449
6	His	Glu	-9.307	0.438	9.746	-0.169	0.201	0.370	26.340
5	Arg	Glu	-9.176	0.438	9.615	-0.165	0.201	0.366	26.269
4	His	Met	-9.307	0.145	9.453	-0.169	0.192	0.361	26.184
3	Arg	Met	-9.176	0.145	9.321	-0.165	0.192	0.357	26.110
2	His	Asp	-9.307	0.420	9.728	-0.169	0.204	0.373	26.079
1	Arg	Asp	-9.176	0.420	9.596	-0.165	0.204	0.369	26.006

In Table 6, the quantum soup of the puric and pyrimidine bases of the nucleic acids RNA and DNA. The interaction of the first attack of MTF is towards the hydroxylated tautomer of uracil U2. In addition, this attack is an antioxidant. Then, it is seen that it does not bother any of the nucleic acids at all.

Table 6: Quantum soup of nitrogenous bases and MTF. The interactions of the components of DNA and RNA are shown here.

N	Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
31	MTF	C	-9.374	-0.344	9.030	-0.152	0.161	0.313	28.849
30	A	A	-8.654	-0.213	8.441	-0.140	0.156	0.296	28.518
29	A	A	-8.654	-0.213	8.441	-0.140	0.156	0.296	28.517
28	U1	U2	-9.710	-0.415	9.295	-0.126	0.202	0.328	28.340
27	G	MTF	-8.537	0.640	9.177	-0.152	0.172	0.324	28.324
26	MTF	G	-9.374	-0.206	9.168	-0.152	0.172	0.324	28.296
25	T	U2	-9.441	-0.415	9.026	-0.123	0.202	0.325	27.773
24	MTF	T	-9.374	-0.475	8.899	-0.152	0.169	0.321	27.722
23	A	C	-8.654	-0.344	8.310	-0.140	0.161	0.301	27.610
22	MTF	U1	-9.374	-0.511	8.863	-0.152	0.171	0.323	27.439
21	U2	U2	-9.910	-0.415	9.495	-0.147	0.202	0.349	27.208
20	U2	U2	-9.910	-0.415	9.495	-0.147	0.202	0.349	27.206
19	G	A	-8.537	-0.213	8.324	-0.150	0.156	0.306	27.202
18	A	G	-8.654	-0.206	8.448	-0.140	0.172	0.312	27.078
17	C	A	-9.142	-0.213	8.929	-0.174	0.156	0.330	27.058
16	A	T	-8.654	-0.475	8.179	-0.140	0.169	0.309	26.471
15	G	C	-8.537	-0.344	8.193	-0.150	0.161	0.311	26.345
14	C	C	-9.142	-0.344	8.798	-0.174	0.161	0.335	26.265
13	C	C	-9.142	-0.344	8.798	-0.174	0.161	0.335	26.263
12	A	U1	-8.654	-0.511	8.143	-0.140	0.171	0.311	26.185

11	G	G	-8.537	-0.206	8.331	-0.150	0.172	0.322	25.873
10	G	G	-8.537	-0.206	8.331	-0.150	0.172	0.322	25.872
9	C	G	-9.142	-0.206	8.936	-0.174	0.172	0.346	25.827
8	MTF	U2	-9.374	-0.415	8.959	-0.152	0.202	0.354	25.308
7	G	T	-8.537	-0.475	8.062	-0.150	0.169	0.319	25.273
6	C	T	-9.142	-0.475	8.667	-0.174	0.169	0.343	25.270
5	C	U1	-9.142	-0.511	8.631	-0.174	0.171	0.345	25.019
4	G	U1	-8.537	-0.511	8.026	-0.150	0.171	0.321	25.003
3	A	U2	-8.654	-0.415	8.239	-0.140	0.202	0.342	24.092
2	C	U2	-9.142	-0.415	8.727	-0.174	0.202	0.376	23.212
1	G	U2	-8.537	-0.415	8.122	-0.150	0.202	0.352	23.074

CONCLUSIONS

In all the cited literature, it was found that MTF is a drug used with great benefits for many years in patients with diabetes. However, it is crucial to consider that the interactions that this drug has with multiple AAs allow an extraordinary intervention in many metabolic processes, which undoubtedly can generate improvement in a host of conditions if studied further.

At present, the purpose of a large number of specialties in the chemical and medical areas have been given the task of seeking substances "antioxidants," which can improve the metabolic functions of our body without the production of free radicals, and the interactions we find between MTF and AAs, indicating that they participate and interact with many components, but without changing the nature of the substances.

By analyzing the tables of interaction with AAs, we can highlight that the AAs themselves, depending on their conformations, can interact with each other (Table 3). Later, when joining the MTF with the AAs, we can see that with the AAs from 1-15 it does not establish any interaction, but from 16 to 461, it joins stably, interacting, coupling, but without causing alterations in the products or the release of toxic residues (antioxidant function) (Table 4). By making all the AAs interact with each other and with the MTF (Table 5), the "Quantum Soup" is established, a relationship in which they interact directly but remain stable in their form and function, showing that the MTF does not cause alterations in the conformation or arrangement of the amine chains.

One of the most remarkable interactions of MTF is its role as an antioxidant. In table 6, it can be seen that MTF has no toxic relationship with bases C and G.

On the other hand, the U-MTF interaction does not allow the release of free radicals. This fact is vital for the stable replication of DNA and RNA (interaction U8 and 20, table 6). In

addition, these interactions prevent other free substances that can structurally and functionally alter the cell.

The performance of these "In Silico" studies allows us to observe, in a numerical way, the interactions of many components with substances to be investigated, making significant advances in developing new chemical components and giving way to laboratory experimentation.

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