



ANALYSIS OF THE EFFECT OF SILDENAFIL (VIAGRA) ON NITROGENOUS BASES OF RNA AND DNA USING QUANTUM METHOD

Juan Jesús García-Mar³, Oscar Sánchez-Parada¹, Manuel Aparicio-Razo^{2,3}, Emmanuel Vázquez³-López, Iliana Herrera-Cantú³, Karina García-Aguilar.^{3,5} Erick Pedraza-Gress³, Lillhian Arely Flores-González³ and Manuel González-Pérez^{3,4*}

¹Escuela de Medicina Universidad Popular Autónoma del Estado de Puebla.

²Benemérita Universidad Autónoma de Puebla, Facultad de Ciencias de la Electrónica

³Universidad Popular Autónoma del Estado de Puebla A.C. (UPAEP). Centro.

⁴Interdisciplinario De Posgrados (CIP). Posgrado en Ciencias de la Ingeniería Biomédica.

⁴Sistema Nacional De Investigadores. Nivel 1.

⁵Instituto Tecnológico Superior de Coahuila de Coahuila, Academia de ingeniería Bioquímica.

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ABSTRACT

Sildenafil is a medication used to treat male erectile dysfunction. It is an inhibitor of one of the phosphodiesterases, and during clinical studies, it was found to be more effective in the treatment of impotence. Sildenafil is active in 70% of the subjects with the impotence of diverse etiology. The objective of the study is to determine the interactions of the drug vs. nitrogenous bases (NBs). The Hyperchem Professional software was used the parametric semi-empirical parametric method 3 (SE-PM3). It was found that the interactions of the pure NBs and the drug have a very high probability that they occur. The interactions of the pairs of NBs and sildenafil also have a very high probability that they will occur. In both cases, it can be predicted that this drug brings many health problems including mutations.

KEYWORDS: Sildenafil, Nitrogen Bases, Quantum method, Hyperchem, SE-PM3.

*Corresponding Author

**Dr. Manuel González-
Pérez**

Universidad Popular
Autónoma del Estado de
Puebla A.C. (UPAEP).
Centro Interdisciplinario De
Posgrados (CIP). Posgrado
en Ciencias de la Ingeniería
Biomédica.

manuel.gonzalez@upaep.mx

INTRODUCTION

The discovery of the nitric oxide (NO) pathway, research that earned the Nobel Prize, facilitated the path to study and the subsequent development of an effective therapy to treat erectile dysfunction (ED). Sildenafil citrate (SC) was the first oral drug, with proven effectiveness, approved by the health authorities to treat erection problems of any etiology. This drug is a selective inhibitor of phosphodiesterase type 5.^[1] SC produces a significant increase in the concentrations of cyclic guanosine monophosphate (cGMP) in the penis (glans, corpora cavernosa, and corpus spongiosum). This increase in cGMP activity facilitates relaxation of the smooth muscle and favors the induction and maintenance of the physiological erectile response to adequate sexual stimulation. Subsequently, extensive clinical experience has corroborated it in more than 20 million patients treated worldwide.^[2]

The frequency of sildenafil adverse events is comparable with clinical practice. This effects are: headaches (16%, between 7 and 25%); facial flushing (10%, between 7 and 34%), dyspepsia (7 %, between 1 and 11%), nasal congestion (4%, between 4 and 19%), and transient mild visual disturbances (3%). %, between 1 and 6%).^[3-7] In these studies, there was no priapism, and the percentage of dropouts due to NB was similar to that of placebo (2.5% vs. 2.3%). Most are due to fear that the exertion of sexual activity will precipitate another myocardial infarction, but 10% to 15% is due to organic causes of impotence.^[4]

Morales *et al.*^[5] evaluated the tolerance of sildenafil in 18 double-blind studies in clinical phase II / III, and the results obtained showed that sildenafil was very well tolerated.

Padma-Nathan *et al.*^[6] review AAs in 13 published series and post-marketing, in 5,295 patients. Most of the problems were mild. Some case of priapism was described, but when it had been administered simultaneously with other drugs that cause it. The problems referred to are a headache (between 7 and 39%) and facial flushing (between 7 and 34%). Moreover, enhanced penile erection had been a significant advancement in the treatment of erectile dysfunction.^[7]

The vasodilating action of sildenafil affects both the arteries and the veins, so the most frequent side effects of sildenafil are a headache and facial flushing^[8]

The incidence of myocardial infarction was 1.7/100 patient-years (95% CI, 0.8 to 2.6) in the sildenafil group and 1.4/100 patient-years (95% CI, 0.2 to 2.6) in the placebo group.^[9]

A total of 69 deaths have been reported to the FDA as of August 26, 1998, in patients who have used Sildenafil. Twenty-one were due to unknown causes, two due to stroke, and 46 related to probable cardiac events. Twelve deaths involved a possible interaction between Sildenafil and nitrates.^[10-12]

The nitrogenous bases are the fundamental structural part of the DNA and RNA nucleic acids. In previous publications, we have studied the interactions of the nitrogenous bases and their possible mutations meticulously.^[13-15]

On the other hand, we have also worked using quantum simulation, especially the SE-PM3.^[16,17]

The objective of this work was to analyze the interactions of the nitrogenous bases vs. sildenafil.

MATERIALS AND METHODS

SE-PM3 is a molecular modeling program used by scientists to analyze the quantum composition of molecules and to obtain HOMO-LUMO, BG, EP, and other properties. These data are used to form the table where the ETCs of the interaction of Sildenafil and NB is.

Hyperchem Professional Software performed Molecular Modeling and Analysis of Sildenafil and NB (Hyperchem, Hypercube, Multi On for Windows, Series 12-800- 1501800080. Multi On, South 1236-301 Tlacoquemecatl Insurgentes Col. Del Valle, Benito Juarez, DF, Mexico C.P. 03200).

Table 1. Parameters used for quantum computing molecular orbitals-HUMO and LUMO^[14, 15]

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/Amol
State Lowest Convergent Limit	0.01	Termination condition or	195 maximum cycles
Interaction Limit	50	Termination condition or	In vacuo
Accelerate Convergence	Yes	Screen refresh period	1 cycle

Table 2. Parameters used to visualize the map of the electrostatic potential of the molecules^[14, 15]

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	

RESULTS AND DISCUSSION

Table 3 shows the ETCs of the pure substances in question. We can see in this table that Sildenafil is a more stable substance than BN because it has the smallest ETC of all.

Table 3. NB Pure and Sildenafil.

No.	Cede	Acepta	HOMO	LUMO	BG	E-	E+	EP	ETC
1	Uracil 1	Uracil 1	-9.710	-0.511	9.2	-0.126	0.171	0.297	30.975
2	Timine	Timine	-9.441	-0.475	8.966	-0.123	0.169	0.292	30.707
3	Adenine	Adenine	-8.654	-0.213	8.441	-0.14	0.156	0.296	28.518
4	Urecil 2	Urecil 2	-9.91	-0.415	9.495	-0.147	0.202	0.349	27.208
5	Cytosine	Cytosine	-9.142	-0.344	8.799	-0.174	0.161	0.335	26.265
6	Guanine	Guanine	-8.537	-0.206	8.331	-0.15	0.172	0.322	25.872
7	<i>Sildenafil</i>	<i>Sildenafil</i>	-8.788	-1.049	7.739	-0.144	0.178	0.322	24.034

Table 4. Cross-Band. NBs vs. Sildenafil.

No.	Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
1	Sildenafil	Adenine	-8.788	-0.213	8.575	-0.144	0.156	0.300	28.584
2	Uracil 1	Sildenafil	-9.71	-1.049	8.661	-0.126	0.178	0.304	28.489
3	Timine	Sildenafil	-9.441	-1.049	8.392	-0.123	0.178	0.301	27.879
4	Sildenafil	Cytosine	-8.788	-0.344	8.444	-0.144	0.161	0.305	27.686
5	Urecil 2	Sildenafil	-9.91	-1.049	8.861	-0.147	0.178	0.325	27.263
6	Sildenafil	Guanine	-8.788	-0.206	8.582	-0.144	0.172	0.316	27.159
7	Sildenafil	Timine	-8.788	-0.475	8.313	-0.144	0.169	0.313	26.560
8	Sildenafil	Uracil 1	-8.788	-0.511	8.277	-0.144	0.171	0.315	26.277
9	Sildenafil	Urecil 2	-8.788	-0.415	8.373	-0.144	0.202	0.346	24.200
10	Sildenafil	Sildenafil	-8.788	-1.049392	7.739	-0.144	0.178	0.322	24.034
11	Adenine	Sildenafil	-8.654	-1.049	7.605	-0.14	0.178	0.318	23.914
12	<i>Cytosine</i>	<i>Sildenafil</i>	-9.142	-1.049	8.093	-0.174	0.178	0.352	22.990
13	<i>Guanine</i>	<i>Sildenafil</i>	-8.537	-1.049	7.488	-0.15	0.178	0.328	22.828

Figure 1 and 2 shows the quantum well of the cross-band interaction between sildenafil and guanine and cytosine respectively. This well is the deepest of all the possible intractables of Sildenafil vs. the BNs. It is observed that the Guanine: Sildenafil interaction is in the most probable zone.^[18] This means that Sildenafil is a very oxidizing agent for guanine.

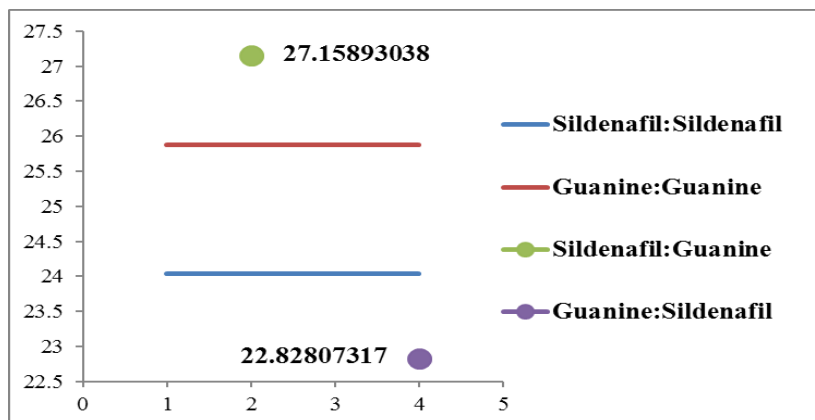


Figure 1. Quantum well. Guanine:Sildenafil (Interaction 13 table 4). It is observed that the Guanine:Sildenafil interaction is in the most probable zone. This means that Sildenafil is a very oxidizing agent for guanine.

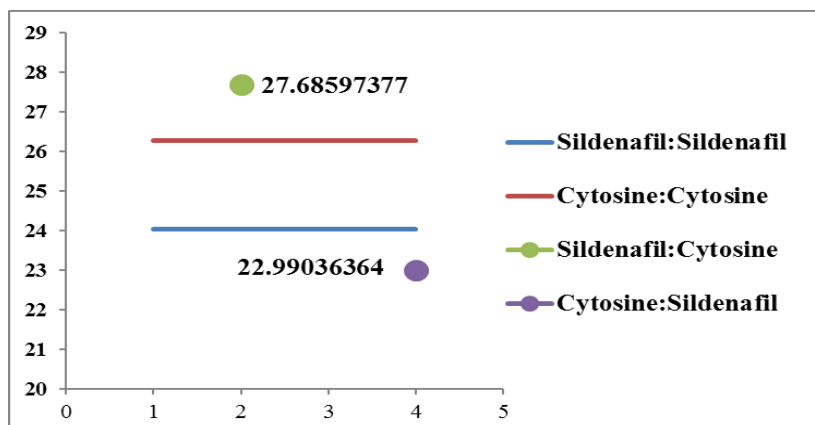


Figure 2. Syildenafil and Cytosine quantum well Sildenafil (Interaction 12 table 4). It is observed that the Cytosine:Sildenafil interaction is in the most probable zone. This means that Sildenafil is a very oxidizing agent for guanine.

We also calculate the interactions of all possible combinations of NBs pairs and sildenafil. We marked with asterisk the permitted base pairs as structure of both DNA and RNA.

The result are show in the table 5. It see that all pairs of NBs allowed have an ETC value below the ETC of sildenafil. Due to these low ETCs the nitrogenous bases have a very high probability of being oxidized by sildenafil. As a consequence of this, many dangerous side reactions are expected, including cancer mutations.

Table 5. Cross-Band between sildenafil vs. pairs of nitrogenous bases of DNA and RNA.

No.	Reducing Agent	Oxidizing Agent	HOMO	LUMO	BG	E-	E+	EP	ETC
1	Sildenafil	Uracil 1:Adenine*	-8.788222	-0.213	8.575222	-0.144	0.156	0.3	28.5840733
1	Sildenafil	Timine:Adenine*	-8.788222	-0.213	8.575222	-0.144	0.156	0.3	28.5840733
2	Sildenafil	Uracil 2:Adenine*	-8.788222	-0.213	8.575222	-0.144	0.156	0.3	28.5840733
3	Sildenafil	Adenine:Adenine	-8.788222	-0.213	8.575222	-0.144	0.156	0.3	28.5840733
4	Sildenafil	Guanine:Adenine	-8.788222	-0.213	8.575222	-0.144	0.156	0.3	28.5840733
5	Sildenafil	Cytosine:Adenine	-8.788222	-0.213	8.575222	-0.144	0.156	0.3	28.5840733
6	Uracil 1:Adenine*	Sildenafil	-9.71	-1.049392	8.660608	-0.126	0.178	0.304	28.4888421
7	Uracil 1:Cytosine	Sildenafil	-9.71	-1.049392	8.660608	-0.126	0.178	0.304	28.4888421
8	Uracil 1:Guanine	Sildenafil	-9.71	-1.049392	8.660608	-0.126	0.178	0.304	28.4888421
9	Uracil 1:Timine	Sildenafil	-9.71	-1.049392	8.660608	-0.126	0.178	0.304	28.4888421
10	Uracil 1:Uracil 1	Sildenafil	-9.71	-1.049392	8.660608	-0.126	0.178	0.304	28.4888421
11	Uracil 1:Uracil 2	Sildenafil	-9.71	-1.049392	8.660608	-0.126	0.178	0.304	28.4888421
12	Timine:Adenine*	Sildenafil	-9.441	-1.049392	8.391608	-0.123	0.178	0.301	27.8790963
13	Timine:Cytosine	Sildenafil	-9.441	-1.049392	8.391608	-0.123	0.178	0.301	27.8790963
14	Timine:Guanine	Sildenafil	-9.441	-1.049392	8.391608	-0.123	0.178	0.301	27.8790963
15	Timine:Timine	Sildenafil	-9.441	-1.049392	8.391608	-0.123	0.178	0.301	27.8790963
16	Timine:Uracil 1	Sildenafil	-9.441	-1.049392	8.391608	-0.123	0.178	0.301	27.8790963
17	Timine:Uracil 2	Sildenafil	-9.441	-1.049392	8.391608	-0.123	0.178	0.301	27.8790963
18	Sildenafil	Uracil 1:Cytosine	-8.788222	-0.344	8.444222	-0.144	0.161	0.305	27.6859738
19	Sildenafil	Timine:Cytosine	-8.788222	-0.344	8.444222	-0.144	0.161	0.305	27.6859738
20	Sildenafil	Uracil 2:Cytosine	-8.788222	-0.344	8.444222	-0.144	0.161	0.305	27.6859738
21	Sildenafil	Adenine:Cytosine	-8.788222	-0.344	8.444222	-0.144	0.161	0.305	27.6859738
22	Sildenafil	Guanine:Cytosine*	-8.788222	-0.344	8.444222	-0.144	0.161	0.305	27.6859738
23	Sildenafil	Cytosine:Cytosine	-8.788222	-0.344	8.444222	-0.144	0.161	0.305	27.6859738
24	Uracil 2:Adenine*	Sildenafil	-9.91	-1.049392	8.860608	-0.147	0.178	0.325	27.2634092
25	Uracil 2:Cytosine	Sildenafil	-9.91	-1.049392	8.860608	-0.147	0.178	0.325	27.2634092
26	Uracil 2:Guanine	Sildenafil	-9.91	-1.049392	8.860608	-0.147	0.178	0.325	27.2634092
27	Uracil 2:Timine	Sildenafil	-9.91	-1.049392	8.860608	-0.147	0.178	0.325	27.2634092
28	Uracil 2:Uracil 1	Sildenafil	-9.91	-1.049392	8.860608	-0.147	0.178	0.325	27.2634092
29	Uracil 2:Uracil 2	Sildenafil	-9.91	-1.049392	8.860608	-0.147	0.178	0.325	27.2634092

30	Sildenafil	Uracil 1:Guanine	-8.788222	-0.206	8.582222	-0.144	0.172	0.316	27.1589304
31	Sildenafil	Timine:Guanine	-8.788222	-0.206	8.582222	-0.144	0.172	0.316	27.1589304
32	Sildenafil	Uracil 2:Guanine	-8.788222	-0.206	8.582222	-0.144	0.172	0.316	27.1589304
33	Sildenafil	Adenine:Guanine	-8.788222	-0.206	8.582222	-0.144	0.172	0.316	27.1589304
34	Sildenafil	Guanine:Guanine	-8.788222	-0.206	8.582222	-0.144	0.172	0.316	27.1589304
35	Sildenafil	Cytosine:Guanine*	-8.788222	-0.206	8.582222	-0.144	0.172	0.316	27.1589304
36	Sildenafil	Uracil 1:Timine	-8.788222	-0.475	8.313222	-0.144	0.169	0.313	26.5598147
37	Sildenafil	Timine:Timine	-8.788222	-0.475	8.313222	-0.144	0.169	0.313	26.5598147
38	Sildenafil	Uracil 2:Timine	-8.788222	-0.475	8.313222	-0.144	0.169	0.313	26.5598147
39	Sildenafil	Adenine:Timine*	-8.788222	-0.475	8.313222	-0.144	0.169	0.313	26.5598147
40	Sildenafil	Guanine:Timine	-8.788222	-0.475	8.313222	-0.144	0.169	0.313	26.5598147
41	Sildenafil	Cytosine:Timine	-8.788222	-0.475	8.313222	-0.144	0.169	0.313	26.5598147
42	Sildenafil	Uracil 1:Uracil 1	-8.788222	-0.511	8.277222	-0.144	0.171	0.315	26.2768952
43	Sildenafil	Timine:Uracil 1	-8.788222	-0.511	8.277222	-0.144	0.171	0.315	26.2768952
44	Sildenafil	Uracil 2:Uracil 1	-8.788222	-0.511	8.277222	-0.144	0.171	0.315	26.2768952
45	Sildenafil	Adenine:Uracil 1*	-8.788222	-0.511	8.277222	-0.144	0.171	0.315	26.2768952
46	Sildenafil	Cytosine:Uracil 1	-8.788222	-0.511	8.277222	-0.144	0.171	0.315	26.2768952
47	Sildenafil	Guanine:Uracil 1	-8.788222	-0.511	8.277222	-0.144	0.171	0.315	26.2768952
48	Sildenafil	Uracil 1:Uracil 2	-8.788222	-0.415	8.373222	-0.144	0.202	0.346	24.2000636
49	Sildenafil	Timine:Uracil 2	-8.788222	-0.415	8.373222	-0.144	0.202	0.346	24.2000636
50	Sildenafil	Uracil 2:Uracil 2	-8.788222	-0.415	8.373222	-0.144	0.202	0.346	24.2000636
51	Sildenafil	Adenine:Uracil 2*	-8.788222	-0.415	8.373222	-0.144	0.202	0.346	24.2000636
52	Sildenafil	Cytosine:Uracil 2	-8.788222	-0.415	8.373222	-0.144	0.202	0.346	24.2000636
53	Sildenafil	Guanine:Uracil 2	-8.788222	-0.415	8.373222	-0.144	0.202	0.346	24.2000636
54	Sildenafil	Sildenafil	-8.788222	-1.049392	7.73883	-0.144	0.178	0.322	24.033634
55	Adenine:Adenine	Sildenafil	-8.654	-1.049392	7.604608	-0.14	0.178	0.318	23.9138616
56	Adenine:Cytosine	Sildenafil	-8.654	-1.049392	7.604608	-0.14	0.178	0.318	23.9138616
57	Adenine:Guanine	Sildenafil	-8.654	-1.049392	7.604608	-0.14	0.178	0.318	23.9138616
58	Adenine:Timine*	Sildenafil	-8.654	-1.049392	7.604608	-0.14	0.178	0.318	23.9138616
59	Adenine:Uracil 1*	Sildenafil	-8.654	-1.049392	7.604608	-0.14	0.178	0.318	23.9138616
60	Adenine:Uracil 2*	Sildenafil	-8.654	-1.049392	7.604608	-0.14	0.178	0.318	23.9138616
61	Cytosine:Adenine*	Sildenafil	-9.142	-1.049392	8.092608	-0.174	0.178	0.352	22.9903636

62	Cytosine:Cytosine	Sildenafil	-9.142	-1.049392	8.092608	-0.174	0.178	0.352	22.9903636
63	Cytosine:Guanine*	Sildenafil	-9.142	-1.049392	8.092608	-0.174	0.178	0.352	22.9903636
64	Cytosine:Timine	Sildenafil	-9.142	-1.049392	8.092608	-0.174	0.178	0.352	22.9903636
65	Cytosine:Uracil 1	Sildenafil	-9.142	-1.049392	8.092608	-0.174	0.178	0.352	22.9903636
66	Cytosine:Uracil 2	Sildenafil	-9.142	-1.049392	8.092608	-0.174	0.178	0.352	22.9903636
67	Guanine:Adenine	Sildenafil	-8.537	-1.049392	7.487608	-0.15	0.178	0.328	22.828073
68	Guanine:Cytosine*	Sildenafil	-8.537	-1.049392	7.487608	-0.15	0.178	0.328	22.828073
69	Guanine:Guanine	Sildenafil	-8.537	-1.049392	7.487608	-0.15	0.178	0.328	22.828073
70	Guanine:Timine	Sildenafil	-8.537	-1.049392	7.487608	-0.15	0.178	0.328	22.828073
71	Guanine:Uracil 1	Sildenafil	-8.537	-1.049392	7.487608	-0.15	0.178	0.328	22.828073
72	Guanine:Uracil 2	Sildenafil	-8.537	-1.049392	7.487608	-0.15	0.178	0.328	22.828073

* Pairs of NBs allowed as structures of DNA and RNA. The ETCs of the permitted NBs have values smaller than the ETC of the Sildenafil. The NBs are strongly oxidized by Sildenafil.

Figure 3 shows the interaction of (cytosine:guanine)-Sildenafil. The ETC of the cytosine: guanine-Sildenafil iteration has the smallest value of all possible interactions. For this reason, it is located in the deepest of the quantum well and is considered a zone of maximum probability of occurrence.

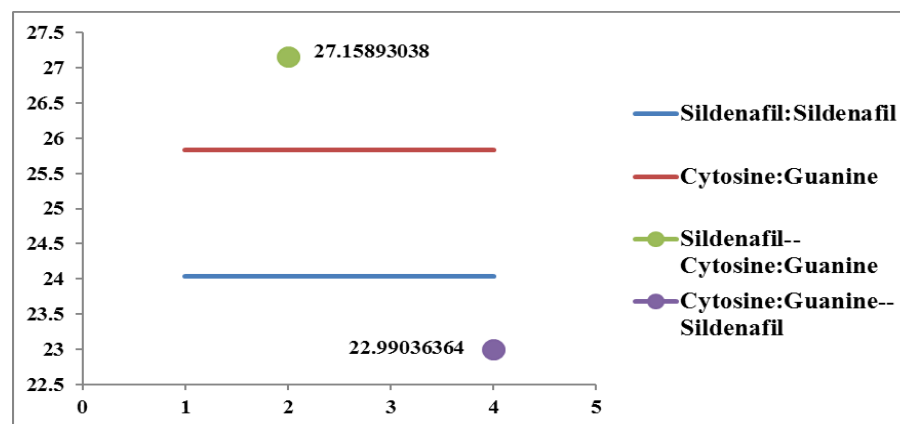


Figure 3. (Cytosine:Guanine)-Sildenafil quantum well.

Figure 4 shows the interaction of (adenine:timine)-Sildenafil. The ETC of the adenine:timine-Sildenafil iteration has the smallest value of all possible interactions. For this reason, it is located in the deepest of the quantum well and is considered a zone of maximum probability of occurrence.

On the other hand, it can be seen in this table 5 that structural RNA pairs are also affected; as the pairs adenine: uracils (the two tautomers of uracil).

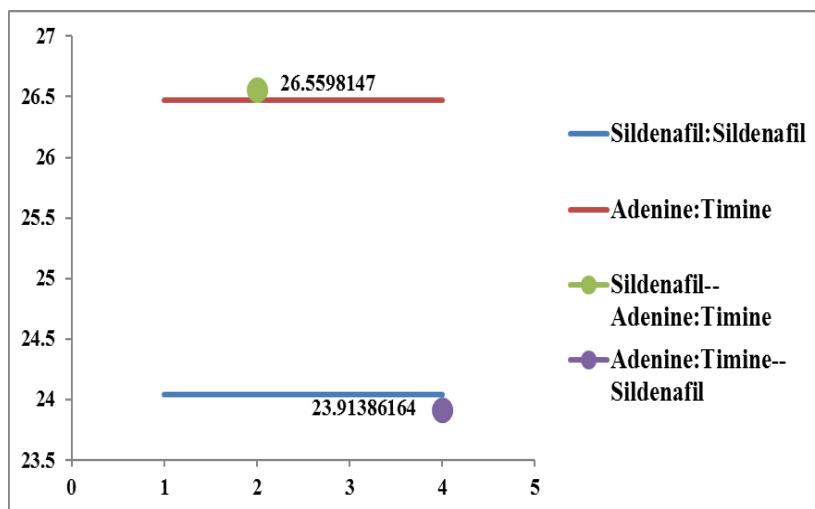


Figure 4 shows the interaction of Adenine:Timine with the Sildenafil in the area of the high probability.

CONCLUSIONS

There are investigations in which it is said that sildenafil (Figure 5) is not a drug with serious side effects. There are other investigations that affirm the opposite. Our research will help clarify these doubts.

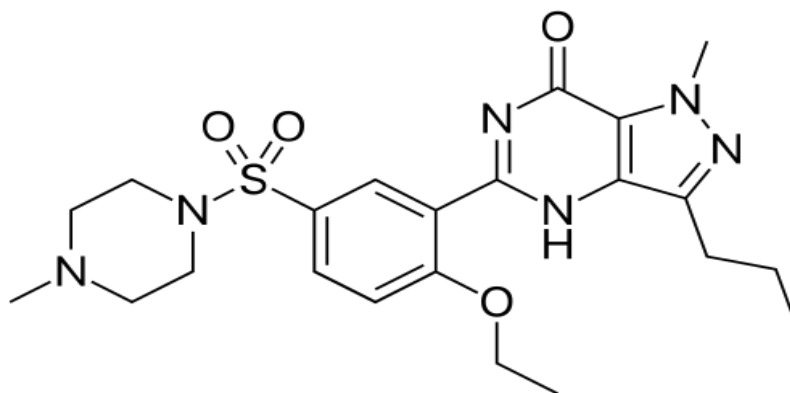


Figure 5. 1-((3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo(4,3-d)pyrimidin-5-yl)-4-ethoxyphenyl)sulfonyl)-4-methylpiperazine citrate. Sildenafil or Viagra.

We found that

1. The individual interactions of the pure BNs with sildenafil coincide with the findings reported in the scientific literature (table 1 and 2).
2. The interactions cytosine: sildenafil and guanine: sildenafil are the highest probability that occur; however, almost all BNs interact with sildenafil with high probabilities.
3. There is a very worrying conclusion. We found that the interactions between the permitted structural pair of NBs, of both DNA and RNA have a high probability of interaction with sildenafil (Table 5).
4. These interactions can cause many health problems, including mutations.

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