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SEMI-EMPIRICAL QUANTUM ANALYSIS OF METHOD 3 OF THE INTERACTION OF FENTANYL WITH OPIOID RECEPTORS μ, κ AND δ.

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ABSTRACT

Fentanyl (FE) is a potent opioid analgesic its main therapeutic effects are analgesia and sedation, as well as physiological functions such as breathing, gastrointestinal transit and stress response, as well as endocrine and immune functions. The main objective of this work is to determine the quantitative semi-empirical analysis of Method 3 (SE-PM3), the interaction between FE and the main human opioid receptors. Hyperchem is a molecular modeling program that allows researchers to do chemical simulations that facilitate the entry of multiple data and apply electron transfer coefficient (ETC) theory. We found that FE is more likely to interact with Aspartic Acid (Asp), Glutamine (Glu) and Methionine (Met) as a reducing agent than as an oxidant. These amino acids are found to be higher in the κ receptor compared to μ and δ. The team concluded that the receptor with the most interaction of FE is the receptor κ to act as a reducer agent of amino acids Asp, Glu and Met.

KEYWORDS: Fentanyl, Opioid Receptors, Quantum Chemistry, Hyperchem.

INTRODUCTION

FE is a potent opioid analgesic. Its main therapeutic effects are analgesia and sedation. This drug has favorable pharmacokinetics for having a faster analgesic response than morphine because it is very liposoluble because it facilitates its rapid passage of the blood-brain barrier.

The United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the transdermal needle-free fentanyl system for the patient. Transdermal fentanyl (FET) has several potential advantages compared to patient controlled analgesic devices (PCA). The FET does not require intravenous lines and eliminates the possibility of errors in drug administration, observed with manually programmed standard PCA devices.[1]

Patients with cancer require potent analgesia with opioids. A comparative study of FET and oral morphine was carried out in the Department of Anesthesiology, Tongde Hospital, Zhejiang Province, Hangzhou-310012.[2] The study showed no significant difference between FE and oral morphine regarding pain management in patients with cancer[2-4] FET was found to decrease the incidence of constipation, nausea, vomiting, drowsiness, urinary retention and a higher incidence of skin irritation. The FET for the treatment of moderate or severe cancer pain has more advantages compared to oral morphine.[2, 3]

The opioid system plays a central role in nociception and analgesia; it also regulates numerous physiological functions such as breathing, gastrointestinal transit and stress response, as well as endocrine and immune functions. The opioid receptor family consists of three members encoding μ, δ and κ.[5, 6]

Opioid receptors are the specific sites where the endogenous and exogenous opioid agonists interact to exhibit their actions. The researchers found that opioid receptors are composed of seven transmembrane segments coupled to the inhibitory G protein formed of 3α, β and γ subunits. Opiate binding stimulates the exchange of guanosine triphosphate (GTP) and guanosine diphosphate (GDP) in the G protein complex and decreases intracellular cyclic adenosine monophosphate (cAMP) through the inhibition of adenylate cyclase. It modulates the release of nociceptive neurotransmitters such as substance P, the amino butyric amino acid (GABA), dopamine, acetylcholine, and noradrenaline. The β and γ subunits interact with the channels causing cellular hyperpolarization and inhibit neuronal activity.[7]

Opioid receptors may function physiologically and functionally with beta-adrenergic receptors that may further emphasize the sympathy-opioid bond. Opioids affect immune function in different ways depending on the factors of the drugs, host and duration of exposure.[5] Data suggest that the immune modulatory effects of different opioids depend more on their molecular structure than their interaction with the μ receptor.[8]

Computational quantum chemistry is a valuable tool for the development of atomic and molecular structures also provide a more accurate description of electrical effects than empirical methods. The application of chemical quantum tools represents an important reality that has already reached an evident degree of maturity.[9-11]

MATERIAL AND METHODS

Software and Simulation

It used Hyperchem molecular simulator for Windows Serial # 12-800-1501800080 SE-PM3 to extracting the molecules.

Hyperchem is a molecular modeling program that allows researchers to perform chemical simulations that facilitate multiple data entry. Through the program, researchers analyze the quantum composition of molecules and other properties. These data are used to form Table 3 where ETC of the interaction of FE and the amino acids of the opioid receptors.

ETC Theory

Researcher Manuel González-Pérez has applied the theory of ETC since 2014. The theory is based on three fundamental aspects.

1. The calculation of bandgap electron band (BG) differentiates between HOMO and LUMO.
2. Calculation of the electrostatic potential of the molecule (EP).
3. The ETC as the band prohibited divided by the electrostatic potential difference.

The ETC is interpreted as the number of times it needs its electrostatic potential to skip the band prohibited. When comparing the interaction of two substances by this theory, there is a range between the ETC of a substance A and an ETC of substance B. Therefore; there are 3 zones in which the ETC value of its cross bands can fall.[9-11]

Table 1.[11] 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 (Conjugated 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.[11] Parameters used to visualize 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	

National Center for Biotechnology Information (NCBI) extracts the amino acid sequence of the opioid receptors.

• Receptor μ: UniProtKB / Swiss-Prot: P35372.2

• Receptor κ: PRF: 2111227A

• Receptor δ: GenBank: AAA18789.2

RESULTS AND DISCUSSION

Table: 3. Cross bands between FE-FE y amino acids- amino acids

Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
FE	FE	-8.751517	0.170052	8.921569	-0.089	0.126	0.215	41.4956698
Ala	Ala	-9.878766	0.749123	10.627889	-0.124	0.132	0.256	41.5151914
Arg	Arg	-9.176235	0.5579196	9.7341546	-0.165	0.199	0.364	26.742183
Asn	Asn	-9.929083	0.644205	10.573288	-0.125	0.193	0.318	33.2493333
Asp	**Asp**	**-10.36987**	**0.4201105**	**10.7899805**	**-0.118**	**0.204**	**0.322**	**33.5092562**
Cys	Cys	-9.638768	-0.2355544	9.4032136	-0.129	0.14	0.269	34.9561844
Gln	Gln	-10.0231	0.7548746	10.7779746	-0.124	0.192	0.316	34.1075146
Glu	**Glu**	**-10.37416**	**0.4382972**	**10.8124572**	**-0.111**	**0.201**	**0.312**	**34.6553115**
Gly	Gly	-9.902413	0.9015826	10.8039956	-0.137	0.159	0.296	36.4999851

His	His	-9.307456	0.5031155	9.8105715	-0.169	0.171	0.34	28.8546221
Ile	Ile	-9.872066	0.971656	10.843722	-0.128	0.188	0.316	34.3155759
Leu	Leu	-9.645295	0.9220657	10.5673607	-0.126	0.13	0.256	41.2787527
Lys	Lys	-9.520605	0.9427313	10.4633363	-0.127	0.195	0.322	32.4948332
Met	**Met**	**-9.061968**	**0.1451009**	**9.2070689**	**-0.134**	**0.192**	**0.326**	**28.2425426**
Phe	Phe	-9.553019	0.2833091	9.8363281	-0.126	0.127	0.253	38.8787672
Pro	Pro	-9.446512	0.7919495	10.2384615	-0.128	0.191	0.319	32.0954906
Ser	Ser	-10.15642	0.5648013	10.7212213	-0.108	0.198	0.306	35.0366709
Thr	Thr	-9.896441	0.8319785	10.7284195	-0.123	0.191	0.314	34.1669411
Trp	Trp	-8.29852	0.1325693	8.4310893	-0.112	0.155	0.267	31.5771135
Tyr	Tyr	-9.056	0.2925489	9.3485489	-0.123	0.193	0.316	29.5840155
Val	Val	-9.913814	0.9311865	10.8450005	-0.131	0.109	0.24	45.1875021

Table 3 shows the data extracted from the Hyperchem program of each of the amino acids and FE. In this table, we obtain the limits of each amino acid and FE. From Table 3 we obtain the cross bands of FE with each of the amino acids shown in Table 4 and 5. We highlight in bold the amino acids with which the FE interacts, comparing Tables 4 and 5.

In Table 4 are the crossed bands having the FE as reducer agent shows a greater affinity with Asp (31.302), Glu (31.689) and Met (31.660) due to its low ETC in the respective order (figure 1-3). The difference between the FE interaction with Asp, Glu, and Met is minimal. FE is unlikely to interact with Valine (Val) because of its high ETC (48,902).

Table: 4. Band crosses between FE as reducing agent with amino acids as the oxidant.

Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
FE	FE	-8.751517	0.170052	8.921569	-0.089	0.126	0.215	41.4956698
FE	Ala	-8.751517	0.749123	9.50064	-0.089	0.132	0.221	42.9893213
FE	Arg	-8.751517	0.5579196	9.3094366	-0.089	0.199	0.288	32.3244326
FE	Asn	-8.751517	0.644205	9.395722	-0.089	0.193	0.282	33.3181631
FE	Asp	-8.751517	0.4201105	9.1716275	-0.089	0.204	0.293	31.3024829
FE	Cys	-8.751517	-0.2355544	8.5159626	-0.089	0.14	0.229	37.1876096
FE	Gln	-8.751517	0.7548746	9.5063916	-0.089	0.192	0.281	33.8305751
FE	Glu	-8.751517	0.4382972	9.1898142	-0.089	0.201	0.29	31.6890145
FE	Gly	-8.751517	0.9015826	9.6530996	-0.089	0.159	0.248	38.9237887
FE	His	-8.751517	0.5031155	9.2546325	-0.089	0.171	0.26	35.5947404
FE	Ile	-8.751517	0.971656	9.723173	-0.089	0.188	0.277	35.1017076
FE	Leu	-8.751517	0.9220657	9.6735827	-0.089	0.13	0.219	44.1716105
FE	Lys	-8.751517	0.9427313	9.6942483	-0.089	0.195	0.284	34.1346771
FE	Met	-8.751517	0.1451009	8.8966179	-0.089	0.192	0.281	31.6605619
FE	Phe	-8.751517	0.2833091	9.0348261	-0.089	0.127	0.216	41.8278986
FE	Pro	-8.751517	0.7919495	9.5434665	-0.089	0.191	0.28	34.0838089
FE	Ser	-8.751517	0.5648013	9.3163183	-0.089	0.198	0.287	32.4610394
FE	Thr	-8.751517	0.8319785	9.5834955	-0.089	0.191	0.28	34.2267696
FE	Trp	-8.751517	0.1325693	8.8840863	-0.089	0.155	0.244	36.4101898
FE	Tyr	-8.751517	0.2925489	9.0440659	-0.089	0.193	0.282	32.0711557
FE	Val	-8.751517	0.9311865	9.6827035	-0.089	0.109	0.198	48.9025429

Table 5 we find that the FE as oxidant agent has more affinity with Arg (32,117) and His (32,127) but are within the average probability zone (figure 4 and 5). The difference in their interaction is minimal between the FE as an oxidizer with Arg and His. It hardly interacts FE as Oxidant agent with Glu and Ser by its high ETC.

Table 6 shows the composition of μ, κ, and δ opioid receptors. This table emphasizes that the κ receptor is the opioid receptor containing more amino acids with which the FE has more interaction (Asp 3.75%, Glu 2.25% and Met 3.50%). The μ receptor is the opioid receptor with the lowest content of these amino acids (Asp 5.43%, Glu 3.10% and Met 1.55%). The amino acids Asp, Glu, and Met, are not predominantly predominant in any of the receptors however because of their low ETC they interact with FE.

Table: 5. Bands cross between FE as oxidant agent and amino acids as reductant

Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
FE	FE	-8.751517	0.170052	8.921569	-0.089	0.126	0.215	41.4956698
Ala	FE	-9.878766	0.170052	10.048818	-0.124	0.126	0.25	40.195272
Arg	FE	-9.176235	0.170052	9.346287	-0.165	0.126	0.291	32.1178247
Asn	FE	-9.929083	0.170052	10.099135	-0.125	0.126	0.251	40.2355976
Asp	FE	-10.36987	0.170052	10.539922	-0.118	0.126	0.244	43.1964016
Cys	FE	-9.638768	0.170052	9.80882	-0.129	0.126	0.255	38.4659608
Gln	FE	-10.0231	0.170052	10.193152	-0.124	0.126	0.25	40.772608
Glu	FE	-10.37416	0.170052	10.544212	-0.111	0.126	0.237	44.490346
Gly	FE	-9.902413	0.170052	10.072465	-0.137	0.126	0.263	38.298346
His	FE	-9.307456	0.170052	9.477508	-0.169	0.126	0.295	32.1271458
Ile	FE	-9.872066	0.170052	10.042118	-0.128	0.126	0.254	39.5358976
Leu	FE	-9.645295	0.170052	9.815347	-0.126	0.126	0.252	38.9497897
Lys	FE	-9.520605	0.170052	9.690657	-0.127	0.126	0.253	38.3029921
Met	FE	-9.061968	0.170052	9.23202	-0.134	0.126	0.26	35.5077692
Phe	FE	-9.553019	0.170052	9.723071	-0.126	0.126	0.252	38.5836151
Pro	FE	-9.446512	0.170052	9.616564	-0.128	0.126	0.254	37.8604882
Ser	FE	-10.15642	0.170052	10.326472	-0.108	0.126	0.234	44.1302222
Thr	FE	-9.896441	0.170052	10.066493	-0.123	0.126	0.249	40.4276827
Trp	FE	-8.29852	0.170052	8.468572	-0.112	0.126	0.238	35.5822353
Tyr	FE	-9.056	0.170052	9.226052	-0.123	0.126	0.249	37.0524177
Val	FE	-9.913814	0.170052	10.083866	-0.131	0.126	0.257	39.2368327

Table: 6. Composition of opioid receptors

amino acids			Receptor μ		Receptor κ		Receptor δ	
a	A	Ala	6	4.65%	26	6.50%	47	12.63%
r	R	Arg	8	6.20%	19	4.75%	23	6.18%
n	N	Asn	3	2.33%	24	6.00%	10	2.69%
d	**D**	**Asp**	**7**	**5.43%**	**15**	**3.75%**	**14**	**3.76%**
c	C	Cys	5	3.88%	17	4.25%	14	3.76%
q	Q	Gln	1	0.78%	7	1.75%	4	1.08%
e	**E**	**Glu**	**4**	**3.10%**	**9**	**2.25%**	**8**	**2.15%**
g	G	Gly	3	2.33%	15	3.75%	20	5.38%
h	H	His	2	1.55%	7	1.75%	3	0.81%
i	I	Ile	14	10.85%	35	8.75%	22	5.91%
l	L	Leu	16	12.40%	37	9.25%	40	10.75%
k	K	Lys	4	3.10%	12	3.00%	12	3.23%
m	**M**	**Met**	**2**	**1.55%**	**14**	**3.50%**	**12**	**3.23%**
f	F	Phe	8	6.20%	20	5.00%	18	4.84%
p	P	Pro	4	3.10%	23	5.75%	25	6.72%
s	S	Ser	12	9.30%	32	8.00%	27	7.26%
t	T	Thr	6	4.65%	37	9.25%	20	5.38%
w	W	Trp	3	2.33%	7	1.75%	6	1.61%
y	Y	Tyr	5	3.88%	15	3.75%	12	3.23%
v	V	Val	16	12.40%	29	7.25%	35	9.41%
		Total	**129**	100.00%	**400**	100.00%	**372**	100.00%

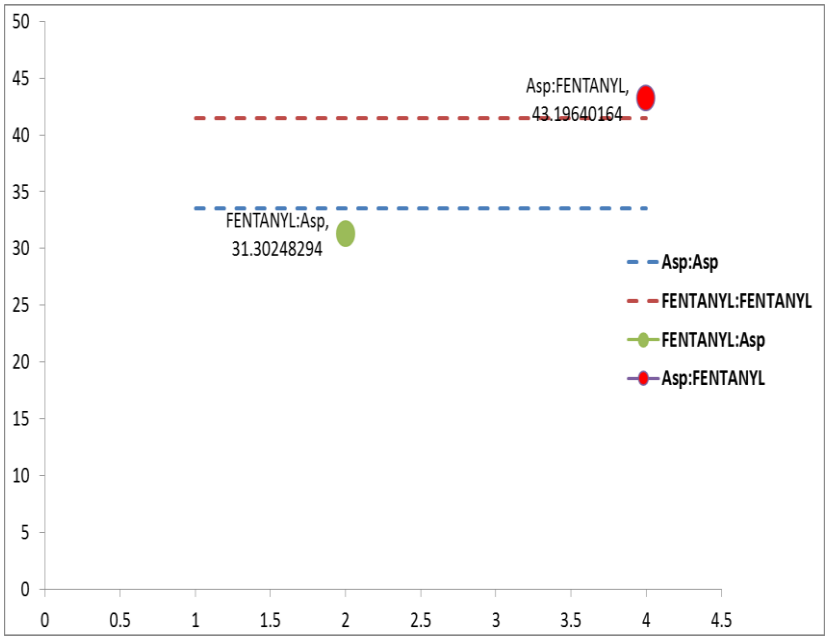

Figure: 1. The boundaries in the dotted lines of the FE (red) and Asp (blue) are observed. Points represent quantum wells. It is observed that the FE-Aps (green dot) is in a high probability and in a low probability the Asp-FE (red dot) acts as an oxidant.

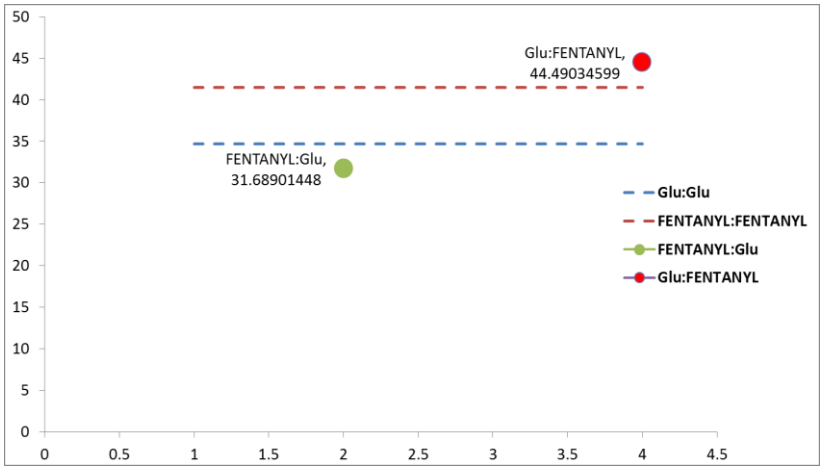

Figure 2. The boundaries are shown in dotted lines FE (red) and Glu (blue). The quantum wells between FE-Glu (green dot) are observed in a high probability whereas the Glu-FE (red dot) is in a low probability zone.

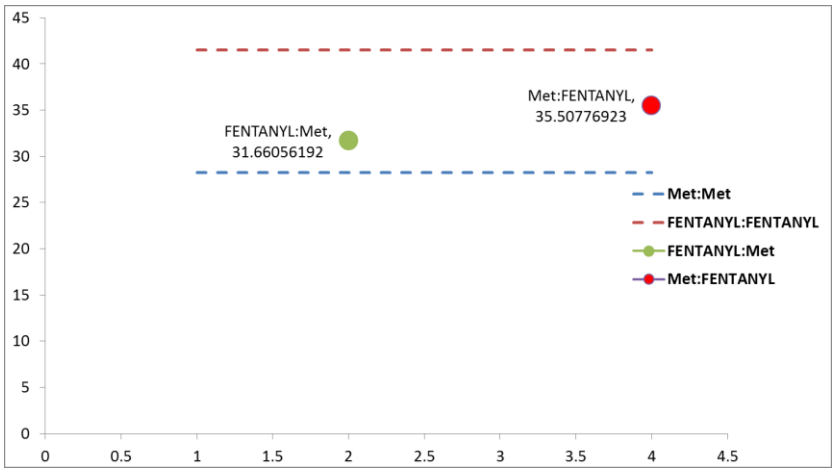

Figure: 3. The dotted-line boundaries of FE (red) and Met (blue) are observed. The FE-Met interaction (Green Point) is in a half-probability zone as is Met-FE (Red Point).

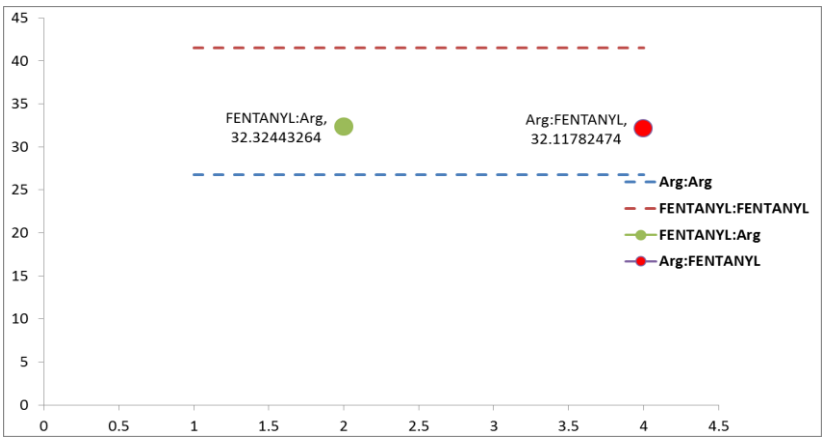

Figure: 4. The boundaries in dotted line FE (red) and Arg (blue). Both are in an average probability

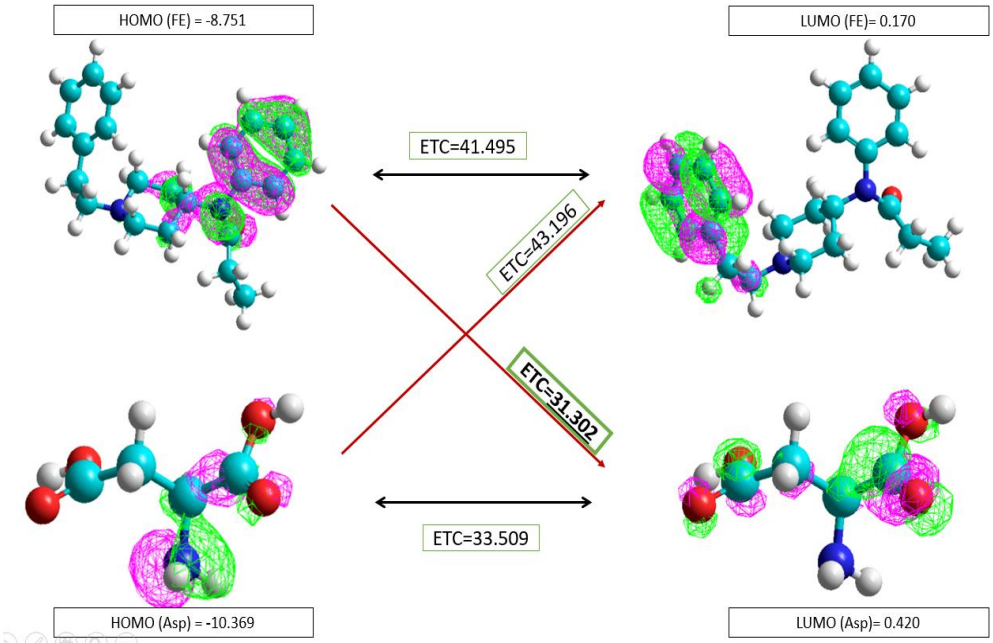

Figure: 6. Graphical representation of the cross bands FE-Asp.

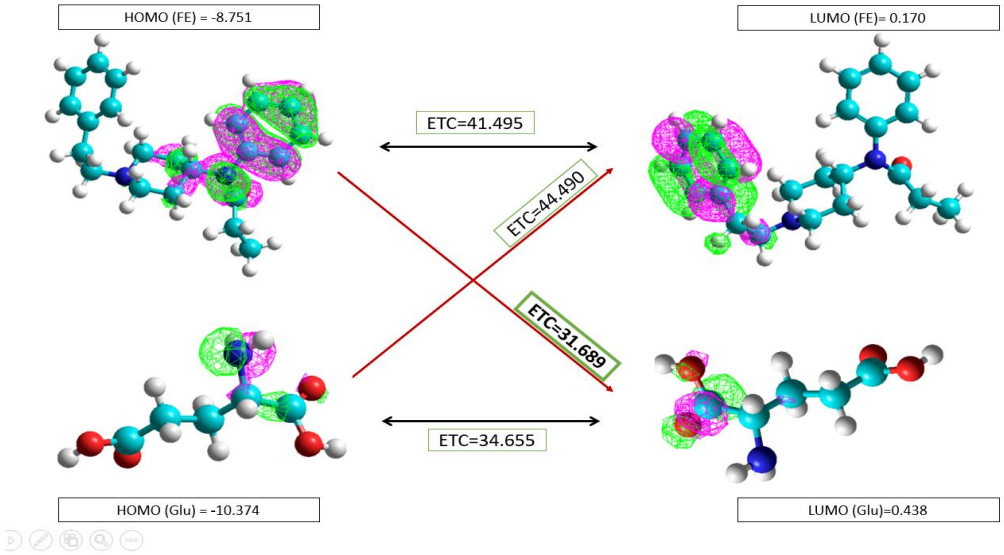

Figure: 7. Graphical representation of the cross bands FE-Glu

CONCLUSION

The FE as a reducer has a higher affinity with Asp, Glu, and Met than as an oxidant against His and Arg. The FE is located in a high probability zone with Asp and Glu as a redactor agent and a half with Met. The probability that FE acts as an oxidizer of His and Arg is in a medium probability zone. These amino acids are not found in a majority in the receptor structure however the κ receptor is the one containing Asp, Glu, and Met more than the other receptors μ and δ. The team concluded that the receptor with the most interaction with the FE is the receptor κ acting as a reducer of amino acids Asp, Glu, and Met.

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