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# QUANTUM ANALYSIS OF THE INTERACTION BETWEEN AMINO ACIDS OF THE M-OPIOID RECEPTOR AND THE MORPHINE

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## ABSTRACT

Morphine is a synthetic opiate isolated from the plant of Papaver somniferum.[1] This drug belongs to the family of Opioid Analgesics (OA) which are μ-opioid receptor (MOR) agonists.[2] MOR is a G protein-coupled receptor (GPCR), and it exists in the Central Nervous System (CNS) and gastrointestinal tract.[5] The aim of the study is to determine, using the Semi-empirical parametric method 3 (SE-PM3) quantum method, which amino acid of the μ receptor has higher affinity with morphine. Hyperchem Professional Software performed Molecular Modeling and Analysis of Morphine and Amino Acids (AA) (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). The Figure 1 shows in a circle the Morphine-Asp interaction which has a high probability as an antioxidant agent. On the other hand, the Asp-Morphine interaction (illustrated as a square) has a low probability. In the Figure 2 the circle represents the Morphine-Glu interaction, located in a high probability zone (antioxidant agent). On the other hand, the Glu-Morphine interaction (shown as a square) is in a low probability zone. We conclude that Glu (glutamic acid) is the amino acid in MOR that has

higher affinity with M, despite having an ETC lower than the other amino acids studied, its probability is much greater.

**KEYWORDS:** Morphine, Amino Acids, Quantum method, Hyperchem, SE-PM3.

## INTRODUCTION

The Morphine is a synthetic opiate isolated from the plant of Papaver somniferum.[1] This drug belongs to the family of OA which are MOR agonists.[2] The MOR is a GPCR, and it exists in the CNS and gastrointestinal tract.[5]

This opioid increase pain tolerance and decreases discomfort. MOR regulate pain modulation and analgesia.[3] The Morphine is an MOR agonist used to treat moderate to severe pain;[2] also, relieves pain in patients requiring OA for more than one day.[1]

When an orthosteric agonist like Morphine activates the receptor, it causes severe pain relief but also results in unwanted effects.[4] The effects of MOR agonists are well known.[2] In the CNS and the Gastrointestinal System (GS) Morphine has huge effects: analgesia, anxiolysis, euphoria, sedation, and respiratory depression and GS smooth muscle contraction.[1] Among these associated effects, the most serious is respiratory depression; also, it can alter the mood, present euphoria, dysphoria, and drowsiness.[1][5]

Hyperchem is a molecular modeling program. Hyperchem's graphical interface allows researchers to perform chemical simulations that facilitate multiple data entry. Through the program, researchers analyze the Electro Transfer Coefficient (ETC) of each interaction. The ETC is the parameter that identifies the probability of a union between several compounds.[6][7]

The aim of the study is to determine, using the SE-PM3 quantum method, which amino acid of the μ receptor has higher affinity with Morphine.

## 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 Morphine and AA are.

Hyperchem Professional Software performed Molecular Modeling and Analysis of Morphine and Amino Acids (AA) (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 - HOMO and LUMO[7][8]**

| 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.[7][8]**

| 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

In Table 3 the amino acids with which morphine has a high affinity as antioxidant were observed in bold and underlined. On the other hand, the amino acids with which Morphine has a high affinity as an oxidant is in contrast.

**Table: 3. Cross bands of Morphine-Morphine and amino acid-amino acid.**

| Reducer Agent | Oxidizer Agent | HOMO | LUMO | BG | E- | E+ | EP | ETC |
|---|---|---|---|---|---|---|---|---|
| MORPHINE | MORPHINE | -8.799184 | 0.19319795 | 8.99238195 | -0.0798 | 0.161 | 0.2408 | 37.34377886 |
| Ala | Ala | -9.878766 | 0.749123 | 10.627889 | -0.124 | 0.132 | 0.256 | 41.51519141 |
| Arg | Arg | -9.176235 | 0.5579196 | 9.7341546 | -0.165 | 0.199 | 0.364 | 26.74218297 |
| Asn | Asn | -9.929083 | 0.644205 | 10.573288 | -0.125 | 0.193 | 0.318 | 33.24933333 |
| **Asp** | **Asp** | **-10.36987** | **0.4201105** | **10.7899805** | **-0.118** | **0.204** | **0.322** | **33.50925621** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cys | Cys | -9.638768 | -0.2355544 | 9.4032136 | -0.129 | 0.14 | 0.269 | 34.95618439 |
| Gln | Gln | -10.0231 | 0.7548746 | 10.7779746 | -0.124 | 0.192 | 0.316 | 34.10751456 |
| **Glu** | **Glu** | **-10.37416** | **0.4382972** | **10.8124572** | **-0.111** | **0.201** | **0.312** | **34.65531154** |
| Gly | Gly | -9.902413 | 0.9015826 | 10.8039956 | -0.137 | 0.159 | 0.296 | 36.49998514 |
| His | His | -9.307456 | 0.5031155 | 9.8105715 | -0.169 | 0.171 | 0.34 | 28.85462206 |
| Ile | Ile | -9.872066 | 0.971656 | 10.843722 | -0.128 | 0.188 | 0.316 | 34.31557595 |
| Leu | Leu | -9.645295 | 0.9220657 | 10.5673607 | -0.126 | 0.13 | 0.256 | 41.27875273 |
| Lys | Lys | -9.520605 | 0.9427313 | 10.4633363 | -0.127 | 0.195 | 0.322 | 32.49483323 |
| **Met** | **Met** | **-9.061968** | **0.1451009** | **9.2070689** | **-0.134** | **0.192** | **0.326** | **28.24254264** |
| Phe | Phe | -9.553019 | 0.2833091 | 9.8363281 | -0.126 | 0.127 | 0.253 | 38.87876719 |
| 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 | 35.03667092 |
| Thr | Thr | -9.896441 | 0.8319785 | 10.7284195 | -0.123 | 0.191 | 0.314 | 34.16694108 |
| Trp | Trp | -8.29852 | 0.1325693 | 8.4310893 | -0.112 | 0.155 | 0.267 | 31.57711348 |
| Tyr | Tyr | -9.056 | 0.2925489 | 9.3485489 | -0.123 | 0.193 | 0.316 | 29.58401551 |
| Val | Val | -9.913814 | 0.9311865 | 10.8450005 | -0.131 | 0.109 | 0.24 | 45.18750208 |

In table 3 show the compared to the ETCs of the amino acids. Morphine is an excellent antioxidant in the Morphine-Asp interaction (Table 4). Morphine is also an excellent antioxidant in the Morphine-Glu interaction (Table 4).

**Table: 4. Morphine Cross Bands as Reducer with Amino Acids**

| Reducer Agent | Oxidizer Agent | HOMO | LUMO | BG | E- | E+ | EP | ETC |
|---|---|---|---|---|---|---|---|---|
| MORPHINE | MORPHINE | -8.799184 | 0.19319795 | 8.99238195 | -0.0798 | 0.161 | 0.2408 | 37.34377886 |
| MORPHINE | Ala | -8.799184 | 0.749123 | 9.548307 | -0.0798 | 0.132 | 0.2118 | 45.08171388 |
| MORPHINE | Arg | -8.799184 | 0.5579196 | 9.3571036 | -0.0798 | 0.199 | 0.2788 | 33.56206456 |
| MORPHINE | Asn | -8.799184 | 0.644205 | 9.443389 | -0.0798 | 0.193 | 0.2728 | 34.61652859 |
| **MORPHINE** | **Asp** | **-8.799184** | **0.4201105** | **9.2192945** | **-0.0798** | **0.204** | **0.2838** | **32.48518147** |
| MORPHINE | Cys | -8.799184 | -0.2355544 | 8.5636296 | -0.0798 | 0.14 | 0.2198 | 38.96100819 |
| MORPHINE | Gln | -8.799184 | 0.7548746 | 9.5540586 | -0.0798 | 0.192 | 0.2718 | 35.15106181 |
| **MORPHINE** | **Glu** | **-8.799184** | **0.4382972** | **9.2374812** | **-0.0798** | **0.201** | **0.2808** | **32.89701282** |
| MORPHINE | Gly | -8.799184 | 0.9015826 | 9.7007666 | -0.0798 | 0.159 | 0.2388 | 40.62297571 |
| MORPHINE | His | -8.799184 | 0.5031155 | 9.3022995 | -0.0798 | 0.171 | 0.2508 | 37.09050837 |
| MORPHINE | Ile | -8.799184 | 0.971656 | 9.77084 | -0.0798 | 0.188 | 0.2678 | 36.48558626 |
| MORPHINE | Leu | -8.799184 | 0.9220657 | 9.7212497 | -0.0798 | 0.13 | 0.2098 | 46.33579457 |
| MORPHINE | Lys | -8.799184 | 0.9427313 | 9.7419153 | -0.0798 | 0.195 | 0.2748 | 35.45092904 |
| **MORPHINE** | **Met** | **-8.799184** | **0.1451009** | **8.9442849** | **-0.0798** | **0.192** | **0.2718** | **32.90759713** |
| MORPHINE | Phe | -8.799184 | 0.2833091 | 9.0824931 | -0.0798 | 0.127 | 0.2068 | 43.91921228 |
| MORPHINE | Pro | -8.799184 | 0.7919495 | 9.5911335 | -0.0798 | 0.191 | 0.2708 | 35.41777511 |
| MORPHINE | Ser | -8.799184 | 0.5648013 | 9.3639853 | -0.0798 | 0.198 | 0.2778 | 33.70765047 |
| MORPHINE | Thr | -8.799184 | 0.8319785 | 9.6311625 | -0.0798 | 0.191 | 0.2708 | 35.56559269 |
| MORPHINE | Trp | -8.799184 | 0.1325693 | 8.9317533 | -0.0798 | 0.155 | 0.2348 | 38.03983518 |
| MORPHINE | Tyr | -8.799184 | 0.2925489 | 9.0917329 | -0.0798 | 0.193 | 0.2728 | 33.32746664 |
| MORPHINE | Val | -8.799184 | 0.9311865 | 9.7303705 | -0.0798 | 0.109 | 0.1888 | 51.53797934 |

Table 5 shows that the Arg-Morphine interaction has the highest affinity (ETC = 28.740), followed by His-Morphine interaction (ETC = 28.789).

**Table: 5. Morphine Cross bands as Oxidizer with Amino Acids**

| Reducer Agent | Oxidizer Agent | HOMO | LUMO | BG | E- | E+ | EP | ETC |
|---|---|---|---|---|---|---|---|---|
| MORPHINE | MORPHINE | -8.799184 | 0.19319795 | 8.99238195 | -0.0798 | 0.161 | 0.2408 | 37.34377886 |
| Ala | MORPHINE | -9.878766 | 0.19319795 | 10.07196395 | -0.124 | 0.161 | 0.285 | 35.34022439 |
| **Arg** | **MORPHINE** | **-9.176235** | **0.19319795** | **9.36943295** | **-0.165** | **0.161** | **0.326** | **28.74059187** |
| Asn | MORPHINE | -9.929083 | 0.19319795 | 10.12228095 | -0.125 | 0.161 | 0.286 | 35.39259073 |
| Asp | MORPHINE | -10.36987 | 0.19319795 | 10.56306795 | -0.118 | 0.161 | 0.279 | 37.8604586 |
| Cys | MORPHINE | -9.638768 | 0.19319795 | 9.83196595 | -0.129 | 0.161 | 0.29 | 33.90333086 |
| Gln | MORPHINE | -10.0231 | 0.19319795 | 10.21629795 | -0.124 | 0.161 | 0.285 | 35.84665947 |
| Glu | MORPHINE | -10.37416 | 0.19319795 | 10.56735795 | -0.111 | 0.161 | 0.272 | 38.8505807 |
| Gly | MORPHINE | -9.902413 | 0.19319795 | 10.09561095 | -0.137 | 0.161 | 0.298 | 33.87788909 |
| **His** | **MORPHINE** | **-9.307456** | **0.19319795** | **9.50065395** | **-0.169** | **0.161** | **0.33** | **28.78986045** |
| Ile | MORPHINE | -9.872066 | 0.19319795 | 10.06526395 | -0.128 | 0.161 | 0.289 | 34.82790294 |
| Leu | MORPHINE | -9.645295 | 0.19319795 | 9.83849295 | -0.126 | 0.161 | 0.287 | 34.28046324 |
| Lys | MORPHINE | -9.520605 | 0.19319795 | 9.71380295 | -0.127 | 0.161 | 0.288 | 33.72848247 |
| Met | MORPHINE | -9.061968 | 0.19319795 | 9.25516595 | -0.134 | 0.161 | 0.295 | 31.3734439 |
| Phe | MORPHINE | -9.553019 | 0.19319795 | 9.74621695 | -0.126 | 0.161 | 0.287 | 33.95894408 |
| Pro | MORPHINE | -9.446512 | 0.19319795 | 9.63970995 | -0.128 | 0.161 | 0.289 | 33.35539775 |
| Ser | MORPHINE | -10.15642 | 0.19319795 | 10.34961795 | -0.108 | 0.161 | 0.269 | 38.47441617 |
| Thr | MORPHINE | -9.896441 | 0.19319795 | 10.08963895 | -0.123 | 0.161 | 0.284 | 35.52689771 |
| Trp | MORPHINE | -8.29852 | 0.19319795 | 8.49171795 | -0.112 | 0.161 | 0.273 | 31.10519396 |
| Tyr | MORPHINE | -9.056 | 0.19319795 | 9.24919795 | -0.123 | 0.161 | 0.284 | 32.56759842 |
| Val | MORPHINE | -9.913814 | 0.19319795 | 10.10701195 | -0.131 | 0.161 | 0.292 | 34.61305462 |

The figure 1 shows in a circle the Morphine-Asp interaction which has a high probability as an antioxidant agent. On the other hand, the Asp-Morphine interaction (illustrated as a square) has a low probability.

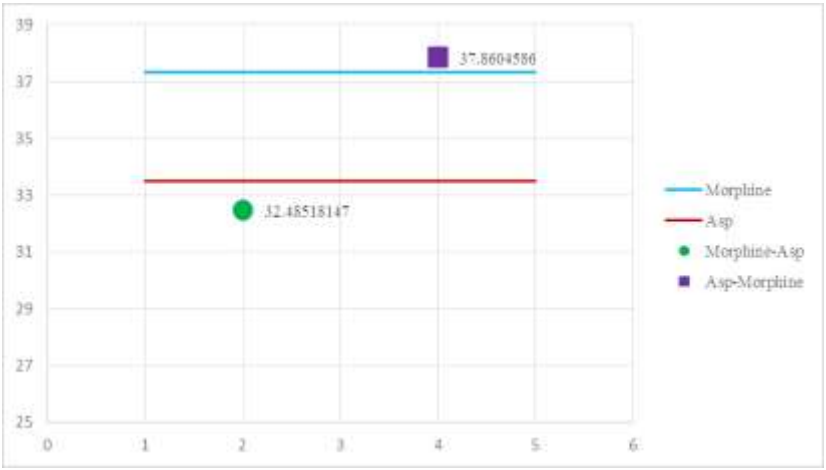


**Figure: 1. Morphine and Asp quantum well**

In the figure 2 the circle represents the Morphine-Glu interaction, located in a high probability zone (antioxidant agent). On the other hand, the Glu-Morphine interaction (shown as a square) is in an area of low probability.

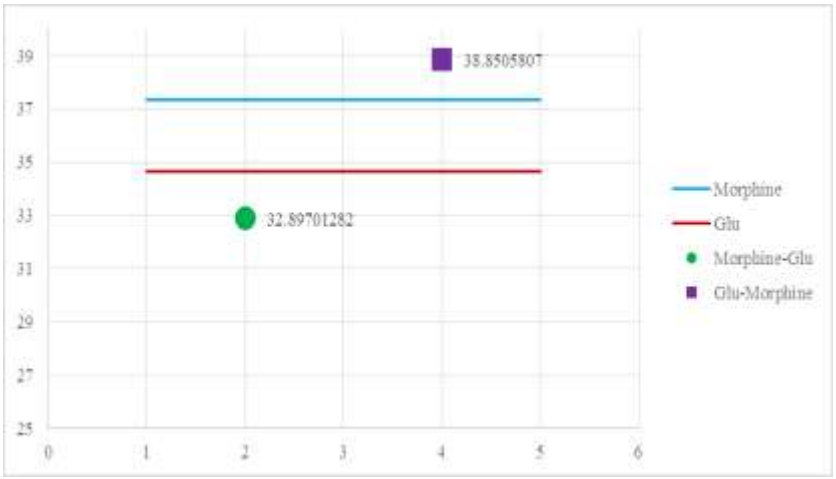


**Figure: 2. Morphine and Glu quantum well**

Figure 3 shows the Morphine-Met and Met-Morphine interactions in the half-probability zone.

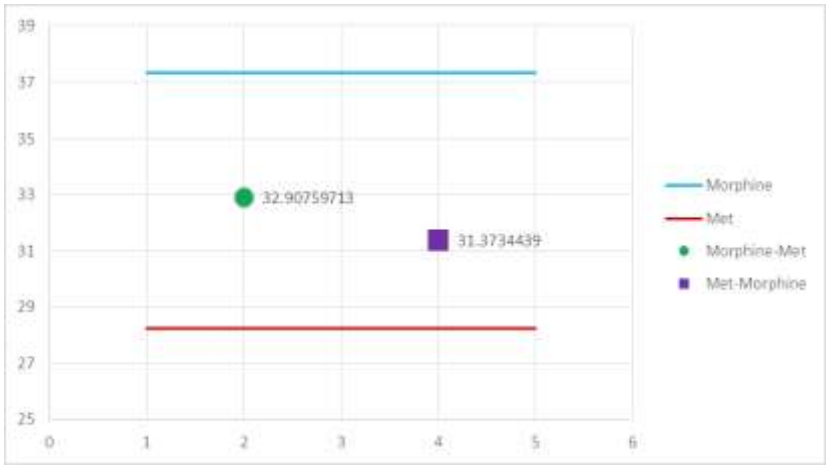


**Figure 3. Morphine and Met quantum well**

In Figure 4, the interactions between Morphine and Arg are in a medium probability zone.

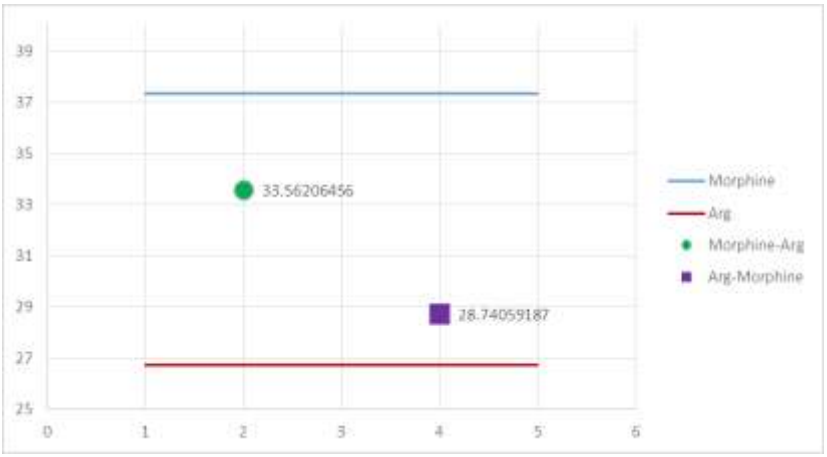


**Figure: 4. Morphine and Arg quantum well**

In Figure 5, the Morphine-His interaction is around average probability (circle). The His-Morphine interaction is in the high probability zone.


**Figure: 5. Morphine and His quantum well**

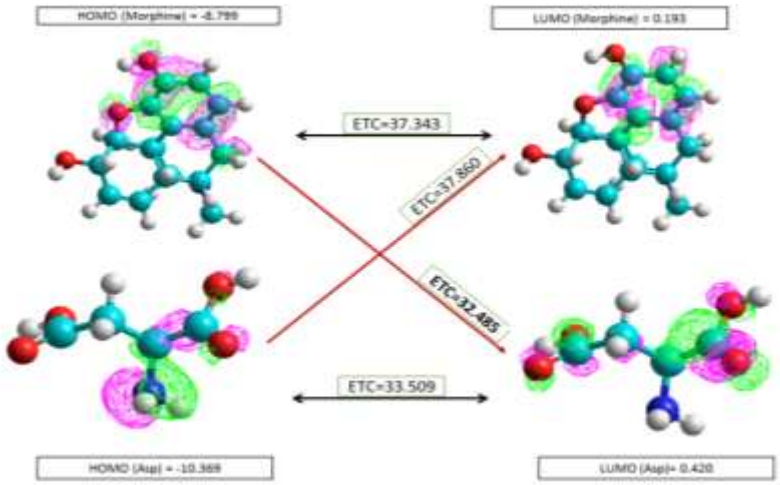


**Figure 6. Electron exchange between Morphine and Asp. The highest probability is in Morphine-Asp (ETC = 32.485).**

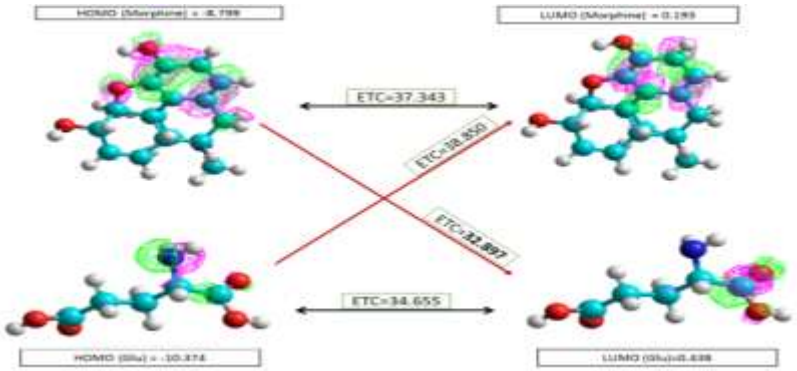


**Figure: 7 Electron exchange between Morphine and Glu. The highest probability is Morphine-Glu (ETC = 32.897).**

## CONCLUSIONS

1. Morphine has the highest ETCs with the amino acids His (Histidine), Arg (Arginine), Asp (aspartic acid), Glu (glutamic acid) and Met (Methionine).
2. The ETCs of the interaction of Morphine-Asp, Morphine-Glu, and Morphine-Met were 32.485, 32.897 and 32.907 respectively.
3. Amino acids that are highly likely to be antioxidants are Arg with Morphine with an ETC = 28.740 and His with Morphine with an ETC = 28.789.
4. Morphine-Asp is the second interaction that has the highest probability of electron exchange.
5. The location of Morphine-Asp (ETC = 32.485) has a difference of 1.024 against the lower limit (Asp ETC = 33.509).
6. Morphine is an excellent antioxidant against Asp.
7. Morphine-Glu is the interaction that has the highest probability of electron exchange.
8. The location of Morphine-Glu (ETC = 32.897) has a difference of 1,785 against the lower limit (Gluc ETC = 34.655).
9. Morphine is an excellent antioxidant against Glu.
10. The Morphine relationship with methionine, morphine with arginine and Morphine-His have an average probability of electron exchange, except His-Morphine.
11. The His-Morphine interaction has a high probability of electron exchange.
12. Morphine is an excellent antioxidant against His.

We conclude that Glu (glutamic acid) is the amino acid in MOR that has higher affinity with Morphine, despite having a lower ETC than the other amino acids studied, its probability is much higher.

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