



## Antidepressant Activity of Curcumin by Monoamine Oxidase–A Inhibition

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### ABSTRACT

Antidepressant activity of curcumin (Cur), as a very well-known herbal product, has been investigated within this work. Two tautomeric forms of Cur–a and Cur–b in addition to the reference structure of Moclobemide (Moc) have been optimized first to evaluate molecular descriptors for ligands. Subsequently, monoamine oxidase–A (MAO–A) has been prepared as receptor for molecular docking (MD) simulation. Interacting systems of ligand–receptor have been very well determined in both of quantitative and qualitative aspects. The results indicated that both of Cur–a and Cur–b are good ligands for interactions with MAO–A even better than Moc, in which Cur–a is more favorable, But based on the interaction of Moc with flavin group of MAO–A, Cur could be employed as a complementary compound for antidepressant activity. All the interacting mechanism of ligand–receptor are very well recognized with this work.

**Keywords:** Curcumin · Monoamine oxidase–A · Moclobemide · Antidepressant · *In silico*

### Introduction

Depression disorder has widely been spread all around the world regarding the World Health Organization (WHO) statistical reports [1]. Symptoms such as low-level mood, loss of interest, lack of motivation, eating and sleeping problems, and couples of cognitive variations are diagnosed for depression disorder [2]. Although the main genetic initiation of depression has not been recognized yet, but pathophysiological monoamine hypothesis claims that the neurotransmitters changes in brain may lead to

depression [3]. The monoamine oxidase (MAO) enzyme is available in two A and B forms, in which the MAO–A degenerates serotonin and norepinephrine leading to depression whereas MAO–B degenerates dopamine and betaphenylamine leading to Alzheimer [4, 5]. Hereby, MAO–A enzyme inhibition has been among the pioneering pharmacological treatments for depression, in which Moclobemide (Moc) (Fig. 1) is in this group [6, 7]. Moreover, many herbal remedies such as Hypericum and Saffron have shown potency for depression

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treatments [8]. Further herbs such as *Curcuma longa* are also supposed to have potency for depression treatments [9].

*Curcuma longa* or Turmeric has been used for thousands of years in nutritional and medical treatments, in which recent studies showed the characteristics and potential medicinal benefits of its main component; Curcumin (Cur) (Fig. 2) [10]. Enzymatic interactions of Cur have been recently investigated based on experimental and computational methods in many signaling pathways of disorders including depression [11]. Based on the *in vitro* and *in vivo* results, Cur has successfully inhibited MAO enzyme and it showed also positive effects on depression symptoms [12–14]. Cur has two keto–enol tautomeric forms (Fig. 2), in which they could be converted to each other during structural conformation changes. Within this work, the structural properties of Cur tautomers are studied and their corresponding activities on MAO–A inhibition are examined by *in silico* methodologies. Evaluating the molecular scale descriptors of Cur tautomers and clarifying the mechanism of their interactions with MAO–A enzyme are the main purposes of this work to show the antidepressant activity of Cur by MAO–A inhibition through ligand–receptor interactions. The obtained quantitative and qualitative achievements of this work are summarized in Tables 1 and 2 and Figs. 1–3. It is worth to note that the computational works could always reveal important information in addition to experiments for the investigated systems [15–20].

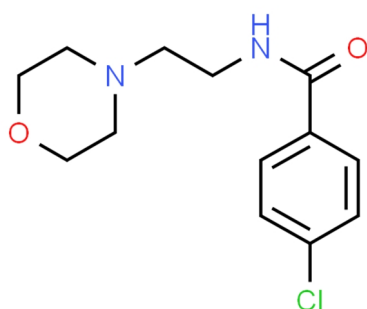


Fig. 1. 2D view of Moclobemide (Moc).

## Materials and Methods

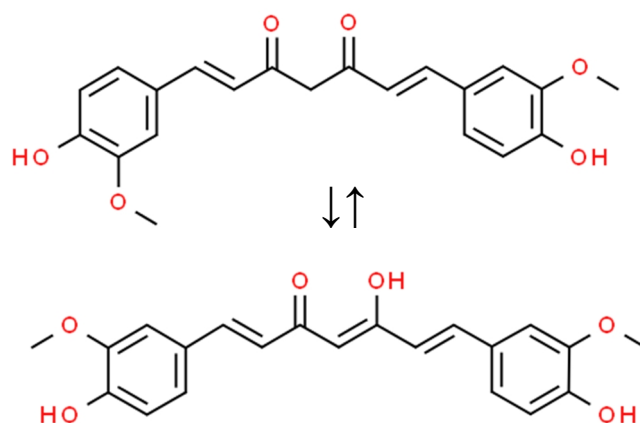
This work is performed by *in silico* approach on ligand–receptor interacting system, in which the details are described in the following three steps. First step; 3D molecular structures of the reference Moc (Moclobemide) (Fig. 1) and the investigated tautomers of Cur (Curcumin) (Fig. 2) have been obtained from the ChemSpider (CS) databank [21] and used as is to prepare the ligand counterparts. The CS ID, formula, molecular weight (MW) and oil/water partition coefficient (LogP) have been directly obtained from the CS databank and they have been included in Table 1. To ease, the keto–form of Cur is designated by Cur–a and the enol–form is designated by Cur–b. Single–point energy calculations have been performed for each of ligand molecules based on the B3LYP/3–21G\* density functional theory (DFT) methodology as implemented in the Gaussian 09 package [22]. By performing this step, molecular descriptors including total energy (ET), energies of the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO), energy gap (EG), ionization potential (IP), electron affinity (EA) and dipole moments (DM) have been evaluated for all three molecular ligands (Table 1 and Figs. 1 and 2). The values of ET, HOMO, LUMO and DM are directly obtained from the computed output files whereas the values of EG, IP and EA are obtained by equations 1 to 3, respectively.

$$EG = LUMO - HOMO \quad (1)$$

$$IP = -HOMO \quad (2)$$

$$EA = -LUMO \quad (3)$$

Second step; 3D structure of MAO–A (Monoamine Oxidase–A) enzyme has been obtained from the Protein Data Bank [23] (PDB ID: 2BXR) to prepare the receptor counterpart. To this aim, the chain–A of enzyme including flavin–adenine dinucleotide (FAD) coenzyme has been extracted from the original 2BXR PDB file by Discovery Studio package [24]. The prepared macromolecular system of MAO–A has been assigned as receptor here.



**Fig. 2.** 2D views of keto and enol forms of Curcumin; Cur-a (top) and Cur-b (bottom).

Third step; ligand and receptor structures have been prepared for Molecular Docking (MD) simulations using the AutoDockTools–1.5.6 [25]. The size of Grid Box has been assigned as 100×100×100 to involve the ligand–receptor interacting system. To perform MD simulations, 500 conformational changes of ligand have been run based on the Genetic Algorithm (GA) as implemented in the AutoDock–4.2.6 package [25].

The quantitative and qualitative results of ligand–receptor interactions are summarized in Table 2 and Fig. 3. The values of binding energy (EB) and inhibition constant (KI) could show the potency of ligand to inhibit the receptor activity. Moreover, qualitative description of interacting amino acids with ligands and the interactions types could reveal insightful information about the ligand–receptor interacting complex system [26].

**Table 1:** Molecular Descriptors\*

Ligand	Moc	Cur-a	Cur-b
CS ID	4087	839564	4445080
Formula	C <sub>13</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub>	C <sub>21</sub> H <sub>20</sub> O <sub>6</sub>	C <sub>21</sub> H <sub>20</sub> O <sub>6</sub>
MW	269	368	368
LogP	0.84	2.92	2.85
ET eV	–33184	–34194	–34195
HOMO eV	–5.59	–5.68	–5.45
LUMO eV	–1.26	–1.90	–2.08
EG eV	4.33	3.78	3.37
IP eV	5.59	5.68	5.45
EA eV	1.26	1.90	2.08
DM Debye	2.94	1.79	4.06

\*See Figs. 1 and 2 for graphical representations.

## Results and Discussion

First, the ligand structures including Moc (Fig. 1), Cur-a and Cur-b (Fig. 2) have been optimized based on DFT calculations to evaluate the molecular descriptors in addition the obtained descriptors from CS (Table 1). Based on the chemical formulas, it is noted that Cur-a and Cur-

b are only different in the keto and enol position in the middle part and their formulas and MW are the same. However, the values of LogP are different for two tautomeric forms. Comparing with reference structure, Moc is a lighter molecule and its lower value of LogP shows its higher hydrophilicity versus Cur structures. The values of

ET show that Cur-b is somehow more stable than Cur-a, in which the values of HOMO and LUMO also detect the effects of tautomerism. All other generated descriptors from the molecular orbital energies show significant differences among the investigated ligands. Cur-a and Cur-b are different only in a hydrogen atom position, but they show significant electronic properties with more than the total energy. Comparing with the reference structure, Moc also shows characteristic

properties versus Cur structures. Hereby, different interacting properties could be expected for the ligands versus the enzyme structure through formations of ligand-receptor complexes. Subsequently, the interacting systems of ligand-receptor have been investigated based on MD simulations to evaluate the values of EB and KI quantitative parameters in addition to the qualitative interacting representations (Table 2 and Fig. 3).

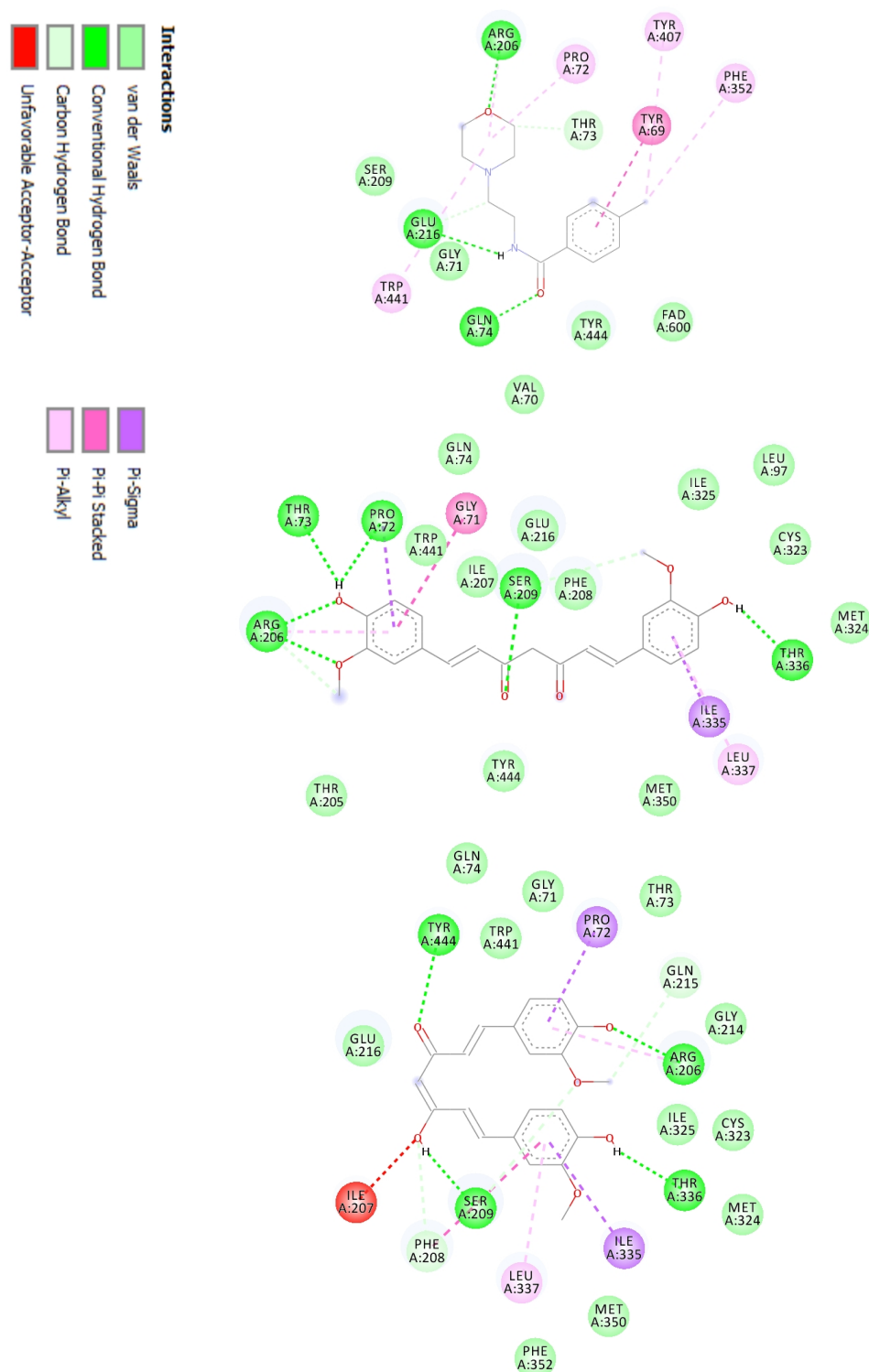
**Table 2:** Molecular Docking Results\*

Ligand	Moc	Cur-a	Cur-b
EB kcal/mol	-7.95	-9.78	-9.76
KI nM	1490	67.5	70.59
HB-Interactions	GLN <sub>74</sub> , ARG <sub>206</sub> , GLU <sub>216</sub>	PRO <sub>72</sub> , THR <sub>73</sub> , ARG <sub>206</sub> , SER <sub>209</sub> , THR <sub>336</sub>	ARG <sub>206</sub> , SER <sub>209</sub> , THR <sub>336</sub> , TYR <sub>444</sub>
Non-HB-Interactions	TYR <sub>69</sub> , VAL <sub>70</sub> , GLY <sub>71</sub> , PRO <sub>72</sub> , THR <sub>73</sub> , SER <sub>209</sub> , PHE <sub>352</sub> , TYR <sub>407</sub> , TRP <sub>441</sub> , TYR <sub>444</sub> , FAD <sub>600</sub>	GLY <sub>71</sub> , GLN <sub>74</sub> , LEU <sub>97</sub> , THR <sub>205</sub> , ILE <sub>207</sub> , PHE <sub>208</sub> , GLU <sub>216</sub> , CYS <sub>323</sub> , MET <sub>324</sub> , ILE <sub>325</sub> , ILE <sub>335</sub> , LEU <sub>337</sub> , MET <sub>350</sub> , TRP <sub>441</sub> , TYR <sub>444</sub>	GLY <sub>71</sub> , PRO <sub>72</sub> , THR <sub>73</sub> , GLN <sub>74</sub> , ILE <sub>207</sub> , PHE <sub>208</sub> , GLY <sub>214</sub> , GLN <sub>215</sub> , GLU <sub>216</sub> , CYS <sub>323</sub> , MET <sub>324</sub> , ILE <sub>325</sub> , ILE <sub>335</sub> , LEU <sub>337</sub> , MET <sub>350</sub> , TRP <sub>441</sub>

\*See Fig. 3 for graphical representations.

Examining the quantitative values indicates that the binding strength is different among the ligands. The efficacy of ligands could be ordered in Cur-a > Cur-b > Moc, which shows that Cur-a could better interact with MAO-A in comparison with Cur-b tautomer and Moc. Cur-b was slightly more stable than Cur-a regarding ET values, in which Cur-a is now more efficient for interaction than Cur-b. Values of LogP also proposed more hydrophobicity for Cur-a regarding other two ligands, in which the results of Table 2 and Fig. 3 show that non-hydrogen bonds play dominant roles of ligand-receptor interactions with better condition for Cur-a. Therefore, Cur-a could be proposed for stronger interactions with amino acids in non-hydrogen bond system. Comparing the results of KI also confirms the above achievements, in which the lowest KI belongs to Cur-a versus Cur-b and Moc. MD simulations are crucial for the mechanistic investigations of ligand-receptor complex systems, in which the

structural configurations of ligands and also the intermolecular localization of ligand and receptor could be very well recognized in both of quantitative and qualitative aspects of MD results [27, 28]. FAD is one of the important counterparts of MAO-A, in which initiates its oxidation function. Although both of Cur-a and Cur-b show good interacting properties with MAO-A, but none of them interact with FAD whereas the reference Moc shows such interaction. Since interaction of ligand with FAD is dominant for inhibiting MAO-A activity, Cur could not be supposed as inhibitor but its function could be as a complementary component for Moc pharmacotherapy. Moreover, structural modifications could be performed on Cur to evaluate the desired inhibitor. By the way, the antidepressant activity of Cur could be considered by its strong interactions with MAO-A enzyme, in which so many amino acids of receptor are trapped by the ligand.



**Fig. 3.** 2D views of ligand–receptor interacting complexes; Moc...MAO–A (top), Cur–a...MAO–A (middle), Cur–b...MAO–A (bottom).

Moc interacts with FAD of MAO–A not in proper mode of interactions regarding the values of EB and KI. Therefore, Cur–a could be supposed as a complementary material for the antidepressant activity in combination with the well-known Moc.

### Conclusion

Within this work, the antidepressant activity of Cur was investigated based on the *in silico* approaches. Two tautomers of Cur–a and Cur–b were investigated regarding the Moc reference

structure. Some trends could be summarized by the obtained results. First, the optimization processes indicated that Cur-b is stronger than Cur-a, in which the interacting systems showed that Cur-a is a better ligand. Second, most of amino acids of the receptor are in non-hydrogen bonds with the ligand, in which the higher value of LogP for Cur-a could be considered as good advantage of contributing to such interactions. Third, none of Cur-a and Cur-b interact with FAD of MAO-A, but both of them are in strong interactions with the enzyme to show a complementary of antidepressant activity in

combination with Moc. And finally, the interaction mechanism of Cur have very well been recognized based on the obtained quantitative and qualitative results by both of DFT calculations and MD simulations, in which the results indicated that the investigated Cur structures are supposed to be considered in further investigations for antidepressant activity evaluations.

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