In *silico* Analysis and Molecular Docking of Newly Synthesized Chlorinated Tetracyclic as Antidepressant Agents

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Abstract

*To clarify the molecular basis of the chlorinated tetracyclic as antidepressant agents, computational studies were carried out. Molecular docking was carried out using Molegro Virtual Docker program; the 3D crystal structure of the recruited models were downloaded from PDB database (PDB ID: 2A65; l 2QJU). The optimized compounds and protein models were loaded to Molegro Virtual Docker program and the binding affinity as MolDock score function was calculated. The MolDock scores are in consistency with the theoretically calculated lipophilicity Clog P, The docking results of the all compounds **1-10** and reference drug maprotiline **11** showed significant interactions with binding site of the recruited models. Lipophilicity appears to play crucial role in these interactions.*

Keywords: *Molecular docking, Binding affinity, Lipophilicity, Tetracyclic, Antidepressants.*

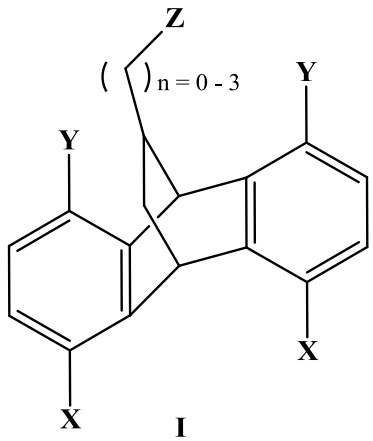
الملخص

لتوضيح الأساس الجزيئي لمركبات مكلورة رباعية الحلقات كمضادات الاكتئاب ، تم إجراء الدراسات الحاسوبية لها. حيث تم دراسة الإلتحام الجزيئي لها باستخدام برنامج Molegro Virtual Docker ؛ تم تنزيل البنية البلورية ثلاثية الأبعاد لنماذج البروتينات ذات العلاقة من قاعدة بيانات بنك البروتينات PDB (PDB ID: 2A65; l 2QJU) تم تحميل المركبات المراد دراستها ونماذج البروتين على برنامج Molegro Virtual Docker ليتم حساب قابلية الارتباط بين المركبات ونماذج البروتينات كدالة MolDock. أظهرت هذه الحسابات التوافق بين قابلية الارتباط كدالات MolDock و درجة الإستشحام المحسوبة نظريًا Clog P ، كما أظهرت نتائج الإلتحام لجميع المركبات تحت الدراسة 1−10 و كذا للمرجع الدوائي المابروتيلين 11 أن هناك تداخلات ذات أهمية مع مواقع الربط لنماذج البروتنات المستخدمة. ولذا فإن الإستشحام يبدو تلعب دورا حاسما في هذه التداخلات كما يبدو.

1. Introduction

The monoamine transporters that modulate the neurotransmitter concentrations are considered the targets for a wide range of drugs including selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressant (TCAs). As the eukaryotic monoamine transporters are unavailable for crystallographic studies, the mechanism of the antidepressants is not fully understood [1]. LeuT, a bacterial homologue of monoamine transporters extracted from the eubacterium *Aquifex aeolicus*, is amenable for structural analysis and has proven to be a valuable paradigm for understanding the structure function relationships[1-2] . Molecular docking is an energy-based scoring function method to determine the energetically most favorable mode of the ligand when bind to the particular target [3]. The general hypothesis of the molecular docking is that lower energy value represents better protein

ligand binding in comparison to higher energy score. Therefore, molecular docking can be formulated as an optimization strategy, where the goal is to identify the ligand binding conformation with the lowest energy [4]. The predicting of binding affinity of new compounds to the specific target is a key step to success in the drug design process. Zhou et al,2007, determined how antidepressants block neurotransmitter reuptake based on LeuT-Desipramine structure and reported that Desipramine binds at the inner end of the extracellular cavity of the transporter exhibiting its activity by restricts conformational changes and thus blocks substrate transport [5].



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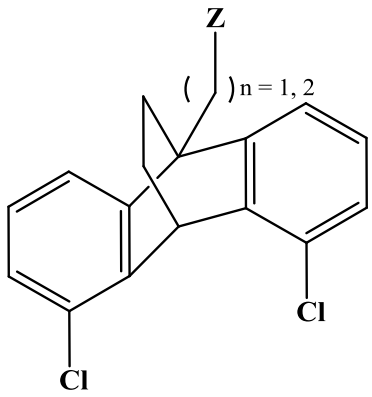

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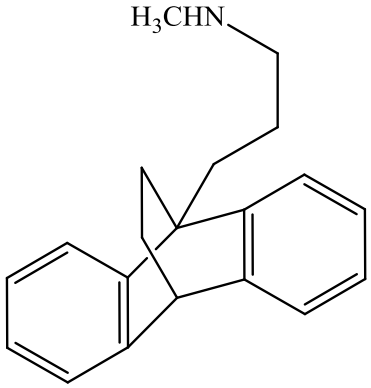


Maprotiline 11
Ludiomil

I	n	X	X	Y	Y	Z
1	**0**	H	H	Cl	Cl	CHO
2	**0**	Cl	Cl	H	H	CHO
3	**2**	Cl	Cl	H	H	CHO
4	**2**	Cl	Cl	H	H	$CO_2CH_2CH_3$
5	**2**	Cl	Cl	H	H	CH_2OH
6	**1**	H	H	Cl	Cl	$NHCH_3$
7	**1**	Cl	Cl	H	H	$NHCH_3$
8	**3**	Cl	Cl	H	H	$NHCH_3$

II	n	Z
9	**1**	CHO
10	**2**	$NHCH_3$

Scheme 1. The chlorinated tetracyclic compounds **1-10** and the reference drug, maprotiline **11**

The bacterial and tricyclic models were deposited in PDB under the access numbers 2A65 and 2QJU respectively. Recently, our group has successfully synthesized several novel chlorinated tetracyclic class of 9,10-dihydro-9,10-ethanoanthracene substituted in C-11 position by a straight chain alkyl of 1,3 carbon atoms of which are substituted by different functional groups (**I; 1-8**) and chlorinated class of 9,10-dihydro-9,10-ethanoanthracene substituted in C-9 position by a straight chain alkyl of two carbon atom of which are substituted by different functional groups (**II; 9, 10**). Both classes are related in structure to maprotiline **11** [6] as well as we tested their activates as antidepressants [6b] and as antiproliferative agents [6d]. In this study, the binding affinity as MolDock score function of these new compounds as well as the reference drug, maprotiline, to the bacterial 2A65 and Tricyclic 2QJU models have been investigated**.**

2. Experiment

2.1. Calculation of Log P Values

The log P values of the chlorinated tetracyclic compounds **1-10** and reference drug maprotiline **11** were estimated with a routine method called calculated log P (Clog P) using a familiar ChemDraw software; ChemDraw® Ultra, version 12, 1986-2009, Cambridge Soft Corp, USA. Results were given in **Table 1**.

2.2. PASS Prediction

Prediction of activity spectra (PASS) was carried out to predict antidepressant activity of the chlorinated tetracyclic compounds **1-10** and reference drug maprotiline **11** [7]. The structure of the compounds **1-10** and reference drug maprotiline **11** were drawn using a familiar ChemDraw software; ChemDraw® Ultra, version 12, 1986-2009, Cambridge Soft Corp, USA**.** The structures of these compounds were saved as MDL Mol files (*.mol) and directly uploaded in the PASS prediction website "http://195.178.207.233/PASS/index.html."

2.3. Molecular Docking

The docking studies of the chlorinated tetracyclic compounds **1-10** and reference drug maprotiline **11** were carried out and the binding affinities scores were calculated as follows. First, the 3D crystal structure of LeuT, a bacterial homologue of BATs, and homology model with access PDB codes 2A65 and 2QJU were downloaded from protein data bank (PDB; http://www.rcsb.org/pdb). ChemDraw Ultra/ Chem3D Pro 12 program was used to draw the 3D structures of the ligands and to pre-optimize the ligand with its function MM force field then saved as MOL File (.mol) format. The optimized ligands and protein models were loaded to Molegro Virtual Docker (MVD 2013.6.0.0 [win32]) program. The MolDock scores were calculated and presented in Table 3 and Table 4.

3. Results and discussion

3.1. Calculation of Log P Values

Lipophilicity is a physicochemical property that plays a crucial role in drug discovery and development [8]. In particular, for effective drugs acting on central nervous system (CNS), they have to cross blood brain barrier (BBB). Thus drugs efficiency has been correlated with optimum lipophilicity (Log P) [9]. Lipophilicity of maprotiline **11** as well the chlorinated tetracyclic compounds are expressed in term of Clog value and shown in **Table 1**.

Table 1. Calculated Log P values of the chlorinated tetracyclic compounds **1-10** and maprotiline **11**.

Compound #	Clog P
1	4.36
2	4.36
3	4.96
4	**5.83**
5	5.43
6	4.8
7	4.8
8	5.57
9	4.68
10	5.29
Maprotiline 11	4.59

It's clear there is a significant enhancement in lipophilicity of all maprotiline analogues **6**, **7**, **8** and **10** as well intermediates **4**, **5**, **9** and **3** compared to the reference drug, maprotiline **11**, this may refer to incorporated chlorine atoms. On the other hand, the intermediate aldehydes **1** and **2** displayed relatively lower Clog P value than the reference drug, maprotiline **11**, due to the presence of the polar carbonyl group.

3.2. Molecular Docking

Prediction of activity spectra (PASS) is an online tool which predicts different types of activities based on the structure of the compound [10]. PASS analysis of the tetracyclic compounds **1-10** and maprotiline **11** predicts amongst other activities, antidepressant activity with probability to be active (Pa) values presented in **Table 2**. Designing new antidepressant agents requires the identification of targets. The monoamine transporters are considered the targets for a wide range of antidepressant drugs. Molecular docking has recently been used to obtain insights into the molecular mechanism of protein–ligand interactions. Molecular docking studies were carried out to evaluate the binding affinity of the chlorinated tetracyclic compounds **1-10** and maprotiline **11** with the active site of the monoamine transporters; bacterial 2A65 and Tricyclic 2QJU models. Compounds have been ranked according to their binding affinity and presented in **Table 3.**

Table 2. Probability to be active (Pa) values of the tetracyclic compounds **1-10** and maprotiline **11**

Compound	Pa
1	0.162
2	0.162
3	0.171
4	0.278
5	0.297
6	0.619
7	0,619
8	0,659
9	0.265
10	0.728
Maprotiline 11	0.921

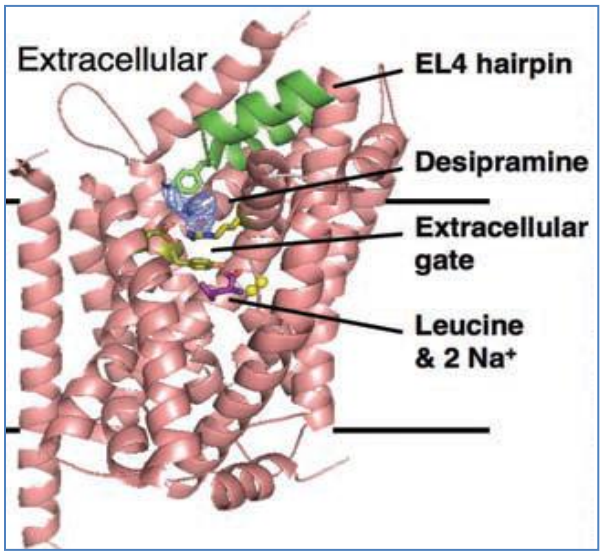
3.2.1. The Docking with 2A65, Bacterial Model

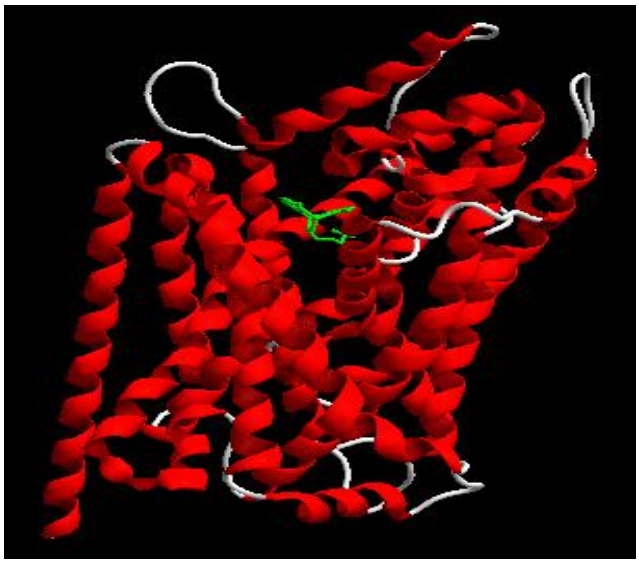
The binding affinity of the chlorinated tetracyclic compounds **1-10** and maprotiline **11** has been investigated through LeuT; docking studies and results have been described. **Table 3** shows the ranking of this study as binding affinity scores.

Table 3. The binding affinity scores of the docked compounds with 2A65, bacterial model.

Ligand	MolDock Score
1	-89.1706
2	-82.3257
3	-98.8884
4	-98.8806
5	-99.3451
6	-84.6831
7	-92.2505
8	-104.728
9	-85.0983
10	-88.7094
Maprotiline 11	-89.7575

The ligands docking with LeuT, 2A65 shows no significant hydrogen bond and these interactions may attribute to hydrophobic interactions. Compound **8**, the most similar chemical structure to maprotiline **11**, has highest MolDock score **-104.728**. The superimposition of Compound **8** on maprotiline **11** in the binding site shows an inversion of the whole molecule leading to a different binding mode (**Figure 1, c, d**). The MolDock scores of compounds **1**, **6** and **7** are closer to maprotiline **11**. The most biologically active compound **7**, as tested by FST [6b], has higher MolDock score **-92.2505** and the inactive compound **2** has the lowest MolDock score **-82.3257**, in comparison to the others tested [6b]. The MolDock scores of **1** and **2** are less than maprotiline **11** and are in consistency with the calculated lipophilicity Clog P, as depicted in **Table 3**.





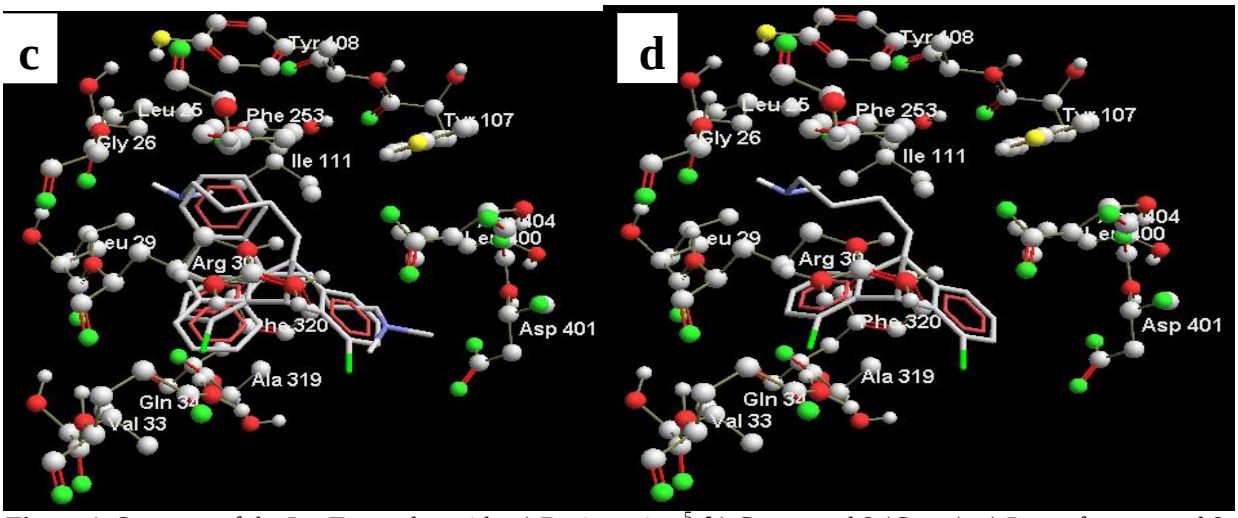


Figure 1. Structure of the LeuT complex with: **a**) Desipramine [5], **b**) Compound **8** (*Green*), **c**) Pose of compound **8**, **d**) Pose of compound **8** superimposed with reference drug maprotiline **11**.

3.2.2. The Docking with 2QJU, TCA Model

The binding affinity of the chlorinated tetracyclic compounds **1-10** and maprotiline **11** has been investigated through pdb id; 2QJU, TCA Model docking studies and results have been described. **Table 4** shows the ranking of this study as binding affinity scores.

Table 4. The binding affinity scores of the docked compounds with 2QJU, TCA model.

Ligand	MolDock Score
1	-77.2186
2	-95.8998
3	-98.1783
4	-105.428
5	-95.8982
6	-98
7	-105.662
8	-96.1411
9	-90.2699
10	-90.6495
Maprotiline 11	-87.6779

Compound **7** showed highest MolDock score -105.662 and formation of hydrogen bond between its amine group and oxygen of Ala 319 with the bond distance is 2.62 Å (**Figure 2, a**). MolDock score of **3** is -98.1783, whereas the creation of hydrogen bond between its carbonyl group of oxygen and the amine group of Ala 319 and bond distance is 3.09 Å. Compound **1** exhibited the lowest MolDock score -77.2186, however, a hydrogen bond formed between its oxygen of carbonyl group and amine group of Gln 34 with the bond distance is 3.17 Å. Compound **10** and maprotiline **11** are structurally similar and observed that docking results are almost comparable. Compound **10** and maprotiline **11** exhibited MolDock scores -90.6495 and -87.6779 respectively and formation of hydrogen bond between their amine group and the oxygen of Asp 404 and Asp 401 with the bond distances are 2.96 and 2.93 Å respectively. However, compounds **8** and **5**

showed no hydrogen bond and found that these compounds have good binding scores -96.1411 and -95.8982 which may refer to their internal energy and lipophilicity.

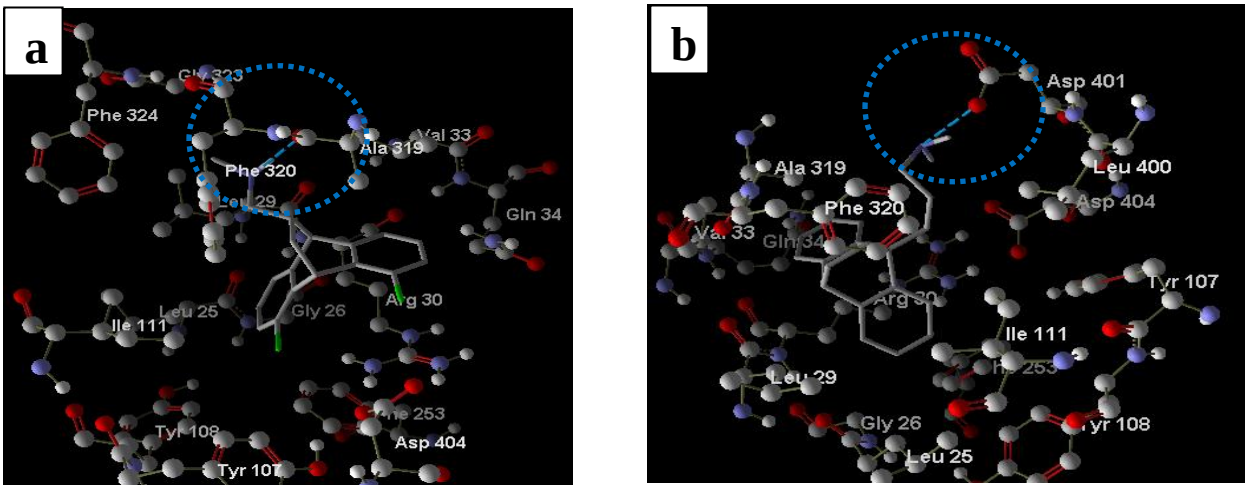


Figure 2. Binding sit of 2QJU with poses of: a) compound **7** and b) maprotiline **11**. H-bond (*Blue dashes*)

4. Conclusion

The docking results of these chlorinated tetracyclic showed significant interactions with binding site of the antidepressant models. Lipophilicity appears to play crucial role in these interactions. These results may aid toward the rational design and synthesis of the new antidepressant-like compounds and consequently will provide insight into the discovery of novel antidepressant agents.

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Competing interests

The author declare that they have no competing interests.

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