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Comparative Examination of Moclobemide, Tranylcypromine, Phenelzine and Isocarboxazid for Monoamine Oxidase–A Inhibition

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ABSTRACT

The ligand–receptor complex formations between the monoamine oxidase–A (MAO–A) enzyme and its known inhibitors have been examined based on the in silico approach. The conformational structure of each ligand including moclobemide, tranylcypromine, phenelzine and isocarboxazid, has been allowed to relax during Molecular Docking (MD) simulation process. The quantitative binding energy and inhibition constant in addition to the qualitative interacting amino acids and types of interactions indicated that moclobemide and isocarboxazid could be considered for better enzyme inhibition whereas phenelzine could not be proposed for this purpose. Moreover, types of interactions and also number of interacting amino acids showed the favorability of moclobemide and isocarboxazid in comparison with other investigated ligands structures for MAO–A inhibition.

Keywords: Moclobemide · Tranylcypromine · Phenelzine · Isocarboxazid · Monoamine oxidase · Inhibition

Introduction

Depression is one of the most important mood disorders, in which so many people all around the world are challenging with it [1]. The main initiation of this disorder has not been recognized yet; but monoamine oxidase–A (MAO–A) enzyme inhibition could be proposed for its pharmacotherapy treatment in addition to psychotherapies [2]. Unfortunately, a certain inhibitor of MAO–A has not been yet introduced either, in which so many works have been dedicated to evaluate new inhibitors for this dominant enzyme for mood balance [3]. Moclobemide, tranylcypromine, phenelzine and isocarboxazid (Fig. 1) are all possible inhibitors of MAO–A [4–8], in which they will be examined here by their enzyme inhibition activities. Although they are all known as MAO–A inhibitors, but their efficacy are different person to person [9]. Discovering a new drug for introducing to pharmacotherapists is sometimes based on the available drugs by knowing carefully about their mechanistic actions [10]. Computer–aided drug design (CADD) approaches could help very much

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to achieve detailed information about the complicated biological systems of ligand–receptor interactions [11–15]. Moreover, theses information could help to see the advantage/disadvantage of a ligand (drug) for interacting with receptor (enzyme) as an inhibitor. Based on these aspects, five of known MAO–A inhibitors will be examined here to compare their efficacy for enzyme inhibitions. Molecular scale examinations could be very well performed by the in silico approaches, in which the theory could provide insightful information for in vitro and in vivo analyses [16–25]. Herein, this in silico work will be performed at the molecular scale to examine MAO–A inhibition regarding five ligands including moclobemide, tranylcypromine, phenelzine and isocarboxazid.

Materials and Methods

This work has been performed at the molecular scale obtaining the 3D molecular structures of ligands (Fig. 1) including moclobemide (4087), tranylcypromine (18369), phenelzine (3547) and isocarboxazid (3628) from the ChemSpider structural bank [26] and that of MAO–A enzyme receptor (2BXR) form the Protein Data Bank [27]. The molecular files have been prepared for Molecular Docking (MD) simulations by the AutoDock–Tools program to be run by the AutoDock4 program [28]. The genetic algorithm for ligand conformational localization with 200 numbers of runs versus the receptor has been employed for the MD simulations in 70*70*70 dimensions of grid box. The quantitative results including the binding energies (BE) and inhibition constants (IK) have been evaluated to compare the efficacy of ligands versus the receptor (Table 1). Moreover, the interacting amino acids (AA) have been also evaluated for a qualitative examination of ligand–receptor interactions (Table 2). Moreover, the graphical representations of ligand–receptor complexes have been exhibited in Fig. 2 for visual analysis of the obtained results.

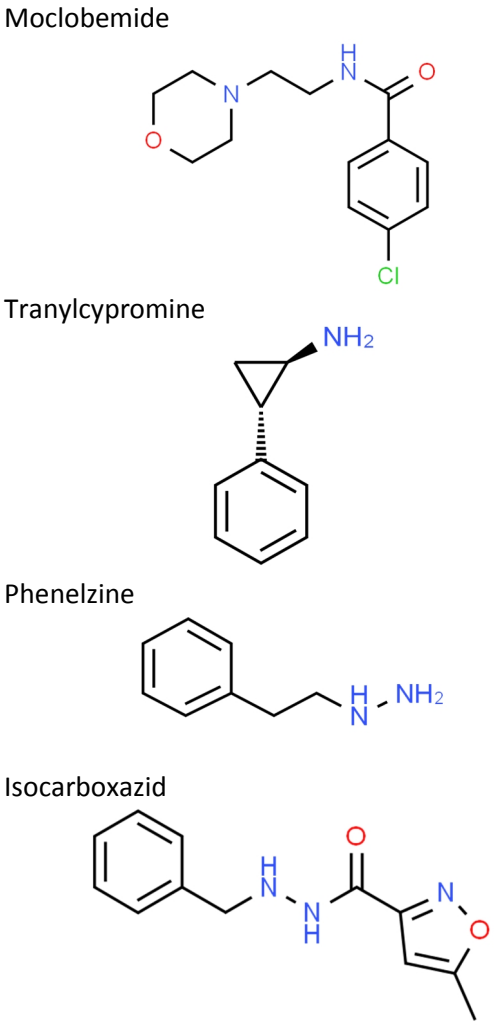

Fig. 1. 2D view of ligand molecular structures obtained from ChemSpider [26].

Table 1: Molecular Docking Quantitative Properties*

Property	BE kcal/mol	IK nM
Moclobemide	–7.95	1490
Tranylcypromine	–6.58	15050
Phenelzine	–5.63	74710
Isocarboxazid	–7.11	6140

*See Figs. 1 and 2 for graphical representations.

Results and Discussion

The results of this work, which have been obtained by the in silico MD simulations, are all summarized in Tables 1 and 2 and also in a graphical representation of ligand–receptor interacting complexes of Fig. 2. The obtained molecular structures of ligands including moclobemide, tranylcypromine, phenelzine and isocarboxazid are exhibited in Fig. 1. The MD simulations have

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been performed to locate the best ligand conformation versus the receptor based on the minimum values of BE and IK [24]. The results could indicate that moclobemide, as the selective inhibitor of MAO–A, is the best one among other investigated ligands by comparing the values of BE and IK. Isocarboxazid could be seen as a competitor for moclobemide, but with lower efficacy based on the quantitative values. Phenelzine is at the last position for inhibiting MAO–A regarding other ligands and the other two ones are almost in the middle positions.

Table 2: Molecular Docking Qualitative Properties*

Property	H–Bonds AA	Non–H–Bonds AA
Moclobemide	GLN74, ARG206, GLU216	TYR69, VAL70, GLY71, PRO72, THR73, SER209, PHE352, TYR407, TRP441, TYR444, FAD600
Tranylcypromine	GLU216	TYR69, VAL70, GLY71, PRO72, THR73, GLN74, ARG206, ILE207, SER209, ARG217, TRP441, TYR444
Phenelzine	TYR69, GLN74, GLU216	VAL70, GLY71, PRO72, THR73, ARG206, SER209, TRP441, TYR444, FAD600
Isocarboxazid	GLN74, TYR444, ILE207	TYR69, VAL70, GLY71, PHE208, SER209, GLU216, PHE352, TYR407, TRP441, FAD600

*See Figs. 1 and 2 for graphical representations.

Although the quantitative values could yield sensible information, but they are not still enough for making conclusion about the structural examinations and the qualitative results should be also examined carefully. To this aim, the qualitative results of Table 2 indicate important notes on interacting AA of enzyme with the ligand structure. For MAO–A inhibition, it is very much important that the flavin adenine dinucleotide (FAD) coenzyme should be interacted with the ligand to inhibit its catalytic activity [29]. Therefore, by the advantage of qualitative analysis of the MD simulation results, it could be found that four of ligands are in interaction with FAD but tranylcypromine does not interact with it. Moreover, the types of interactions and also the number of interacting AAs are very much important to be found for the interacting ligand–receptor complexes. Both of hydrogen bonds (H–Bonds) and non–hydrogen bonds (Non–H–Bonds) interactions are important for the ligand–receptor complex formations. The investigated ligands show contributions to both of H–Bonds and Non–H–Bonds interactions with AAs of enzyme. These information could be also compared with the quantitative BE and IK values, in which the number of interactions for moclobemide is larger than all of other ligands and its corresponding BE and IK values are more favorable. The qualitative analyses of interacting ligand–receptor complexes are very well exhibited in Fig. 2 based on their interacting AAs and types of interactions. The graphical representation shows that the conformational localization of a ligand is very much dominant for contributing to more favorable interactions with the receptor, in which the characteristic properties of ligands are also very much important to be considered. By the way, the interacting ligand–receptor complexes of this work reveal that moclobemide and isocarboxazid could be considered as better inhibitors of MAO–A in comparison with the other investigated inhibitors. The molecular scale studies always yield insightful information about the smallest size of compounds, in which the achievements could be very well used for further investigations.

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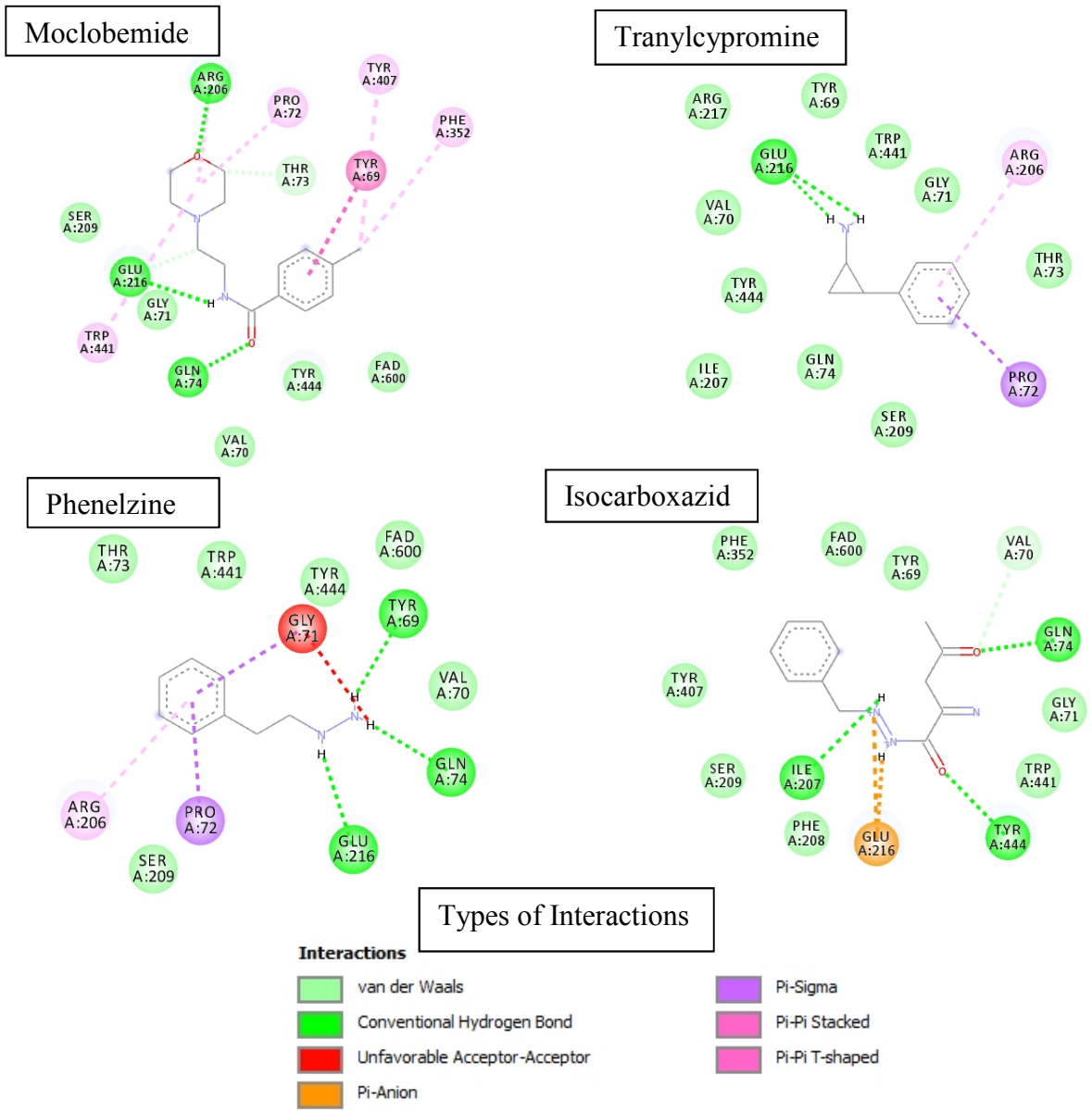

Fig. 2. 2D views of interacting ligand–receptor complexes.

Conclusion

The *in silico* based achievements of this work indicated that the quantitative and qualitative analyses of ligand–receptor interactions are very much important to examine the efficacy of ligand for enzyme inhibition. Moclobemide, as the well–known selective inhibitor of MAO–A, showed the best properties for enzyme inhibition while isocarboxazid showed also competitive properties for MAO–A inhibition. All ligands shoed interaction with FAD but tranylcypromine was an exception not to interact with FAD. Both of H–Bonds and Non–H–Bonds were presented in the ligand–receptor complexes. And finally, although the known inhibitors are doing reasonably, but the way of further investigations on MAO–A inhibition is still open for the researchers. Improving both of pharmacokinetic and pharmacodynamic properties are crucial to achieve better efficacy for novel MAO–A inhibitors.

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References

1. K.S. Grotmol, H.C. Lie, J.H. Loge, N. Aass, D.F. Haugen, P.C. Stone, S. Kaasa, M.J. Hjermstad; Patients with advanced cancer and depression report a significantly higher symptom burden than non–depressed patients. Palliat. Support. care 17 (2019) 143–149.
2. M.B. Youdim; Monoamine oxidase inhibitors, and iron chelators in depressive illness and neurodegenerative diseases. J. Neural Transmis. 125 (2018) 1719–1733.
3. Q. Lv, X. Yang, M. Wang, J. Yang, Z. Qin, Q. Kan, H. Zhang, Y. Wang, D. Wang, Z. He; Mitochondria–targeted prostate cancer therapy using a near–infrared fluorescence dye–monoamine oxidase A inhibitor conjugate. J. Control. Rel. 279 (2018) 234–422.
4. W.Y. Kim, M. Won, A. Salimi, A. Sharma, J.H. Lim, S.H. Kwon , J.Y. Jeon, J.Y. Lee, J.S. Kim; Monoamine oxidase–A targeting probe for prostate cancer imaging and inhibition of metastasis. Chem. Commun. 55 (2019) 13267–13270.
5. Z. Liu, K. Yang, X. Yan, T. Wang, T. Jiang, Q. Zhou, J. Qi, N. Qian, H. Zhou, B. Chen, P. Huang; The effects of tranylcypromine on osteoclastogenesis in vitro and in vivo. The FASEB J. 33 (2019) 9828–9841.
6. J.S. Fowler, N.D. Volkow ,G.J. Wang , N. Pappas, J. Logan, C. Shea, D. Alexoff, R.R. MacGregor, D.J. Schlyer, I. Zezulkova, A.P. Wolf; Brain monoamine oxidase A inhibition in cigarette smokers. Proc. Nat. Acad. Sci. 93 (1996) 14065–14069.
7. C. Noble, N.B. Holm, M. Mardal, K. Linnet; Bromo–dragonfly, a psychoactive benzodifuran, is resistant to hepatic metabolism and potently inhibits monoamine oxidase A. Toxicol. lett. 295 (2018) 397–407.
8. P. Baldinger–Melich, G. Gryglewski, C. Philippe, G.M. James, C. Vraka, L. Silberbauer,T. Balber, T. Vanicek, V. Pichler, J. Unterholzner,G.S. Kranz; The effect of electroconvulsive therapy on cerebral monoamine oxidase A expression in treatment–resistant depression investigated using positron emission tomography. Brain Stimul. 12 (2019) 714–723.
9. M. Naoi, W. Maruyama, M. Shamoto–Nagai; Type A monoamine oxidase and serotonin are coordinately involved in depressive disorders: from neurotransmitter imbalance to impaired neurogenesis. J. Neural Transmis. 125 (2018) 53–66.
10. H. Chen, O. Engkvist, Y. Wang, M. Olivecrona, T. Blaschke; The rise of deep learning in drug discovery. Drug Discover. Today 23 (2018) 1241–1250.
11. M. Soleimani, M. Mirzaei, M.R. Mofid, G. Khodarahmi, S.F. Rahimpour; Lactoperoxidase inhibition by tautomeric propylthiouracils. Asian J. Green Chem. 4 (2020) 1–10.
12. P.A. Ghamsari, M. Samadizadeh, M. Mirzaei; Cytidine derivatives as inhibitors of methyltransferase enzyme. Eurasian Chem. Commun. 1 (2019) 310–317.
13. H. Yousefvand, M. Mirzaei, M. Tabbakhian; Investigating chitosan–curcumin nanorings for containing fluorouracil. Turk. Comput. Theor. Chem. 1 (2017) 6–12.
14. E. Naderi, M. Mirzaei, L. Saghaie, G. Khodarahmi, O. Gulseren; Relaxations of methylpyridinone tautomers at the C60 surfaces: DFT studies. Int. J. Nano Dimen. 8 (2017) 124–131.
15. M. Mirzaei; Effects of carbon nanotubes on properties of the fluorouracil anticancer drug: DFT studies of a CNT–fluorouracil compound. Int. J. Nano Dimen. 3 (2013) 175–179.
16. M. Mirzaei; Uracil–functionalized ultra–small (n, 0) boron nitride nanotubes (n= 3–6):

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Computational studies. Superlat. Microstruct. 57 (2013) 44–50.

17. M. Mirzaei, N.L. Hadipour; Study of hydrogen bonds in crystalline 5–nitrouracil. Density functional theory calculations of the O–17, N–14, and H–2 nuclear quadrupole resonance parameters. J. Iran. Chem. Soc. 6 (2009) 195–199.
18. M. Mirzaei, M. Meskinfam, M. Yousefi; Covalent hybridizations of carbon nanotubes through peptide linkages: a density functional approach. Comput. Theor. Chem. 981 (2012) 47–51.
19. M. Mirzaei; Formation of a peptide assisted bi–graphene and its properties: DFT studies. Superlat. Microstruct. 54 (2013) 47–53.
20. A. Kouchaki, O. Gulseren, N. Hadipour, M. Mirzaei; Relaxations of fluorouracil tautomers by decorations of fullerene–like SiCs: DFT studies. Phys. Lett. A 380 (2016) 2160–2166.
21. A.G. Gilani, V. Taghvaei, E.M. Rufchahi, M. Mirzaei; Photo–physical and structural studies of some synthesized arylazoquinoline dyes. Spectrochim. Acta A 185 (2017) 111–124.
22. M. Aghazadeh, M. Mirzaei; Hydrogen bond interactions in sulfamerazine: DFT study of the O–17, N–14, and H–2 electric field gradient tensors. Chem. Phys. 351 (2008) 159–162.
23. O.M. Ozkendir, M. Mirzaei; Alkali metal chelation by 3–hydroxy–4–pyridinone. Adv. J. Chem. B 1 (2019) 10–16.
24. A.N. Esfahani, M. Mirzaei, Flavonoid derivatives for monoamine oxidase–A inhibition. Adv. J. Chem. B 1 (2019) 19–22.
25. R. Baniasadi, K. Harismah, M. Sadeghi, M. Mirzaei; Adsorption of vitamin C on a fullerene surface: DFT studies. J. Nanoanalys. 4 (2017) 1–7.
26. H.E. Pence, A. Williams; ChemSpider: an online chemical information resource. J. Chem. Educ. 87 (2010) 1123–1124
27. P.W. Rose, A. Prlić, A. Altunkaya, C. Bi, A.R. Bradley, C.H. Christie, et al.; The RCSB protein data bank: integrative view of protein, gene and 3D structural information. Nucleic Acids Res. 45 (2017) D271–D281.
28. G.M. Morris, R. Huey, W. Lindstrom, M.F. Sanner, R.K. Belew, D.S. Goodsell, A.J. Olson; Autodock4 and AutoDockTools4: automated docking with selective receptor flexiblity. J. Computat. Chem. 16 (2009) 2785–2791.
29. H. Nazemi, M. Mirzaei, E. Jafari; Antidepressant activity of curcumin by monoamine oxidase–A inhibition. J. Adv. Chem. B 1 (2019) 3–9.

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