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ISSN: 2278-1862

Journal of Applicable Chemistry

2019, 8 (3): 1155-1160

(International Peer Reviewed Journal)

Molecular Docking Study of an Isoxazole Derivative: 5-(3-Methylthiophen-2yl)- 3-(3,4,5-trimethoxyphenyl) Isoxazole

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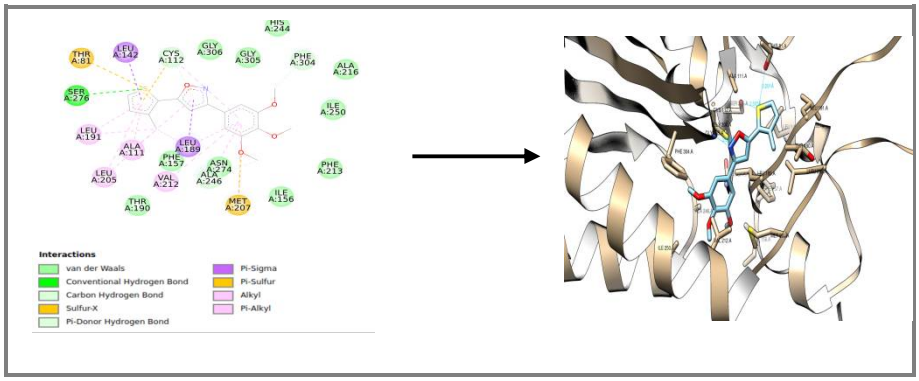
Accepted on 30th March, 2019

ABSTRACT

The 5-(3-Methylthiophen-2yl)- 3-(3,4,5-trimethoxyphenyl) Isoxazole compound comprises three distinct units, 3-methylthiophene ring, a five-membered isoxazole ring and a trimethoxyphenyl ring. The compounds bearing heterocyclic ring systems such as thiophene and an isoxazole moieties are reported to posses numerous useful biological activities. In the view of this authors are aimed to perform molecular docking for anti-bacterial, anticancer and antidepressant activities for the protein targets (1HNJ), (1JNX) and (1XRW) respectively to evaluate their binding energies to the above mentioned target proteins using a tool Auto Dock 4.2. The docking results showed that the compound displayed relatively better binding energy for anti-bacterial and anti-depressant activities than anti-cancer activity.

Graphical Abstract



Keywords: Molecular docking, Anti-cancer, Anti-depressant, Anti-bacterial, Binding affinities.

INTRODUCTION

The world health organization report shows that every day nearly fifty thousand people including men, women and children are dying due to various diseases, besides this the rate of suicidal deaths also increasing in men and women in the age group of (15-45) in olden days, but today's scenario is

changed, the suicidal death are most commonly observed in the age group of (12-25) and particularly this rate is more in WHO Europe region in Lithuania country shown in the figure 1. [1], further this number is raised up-to 60% during the span of last 45 years due to various mental health disorders.

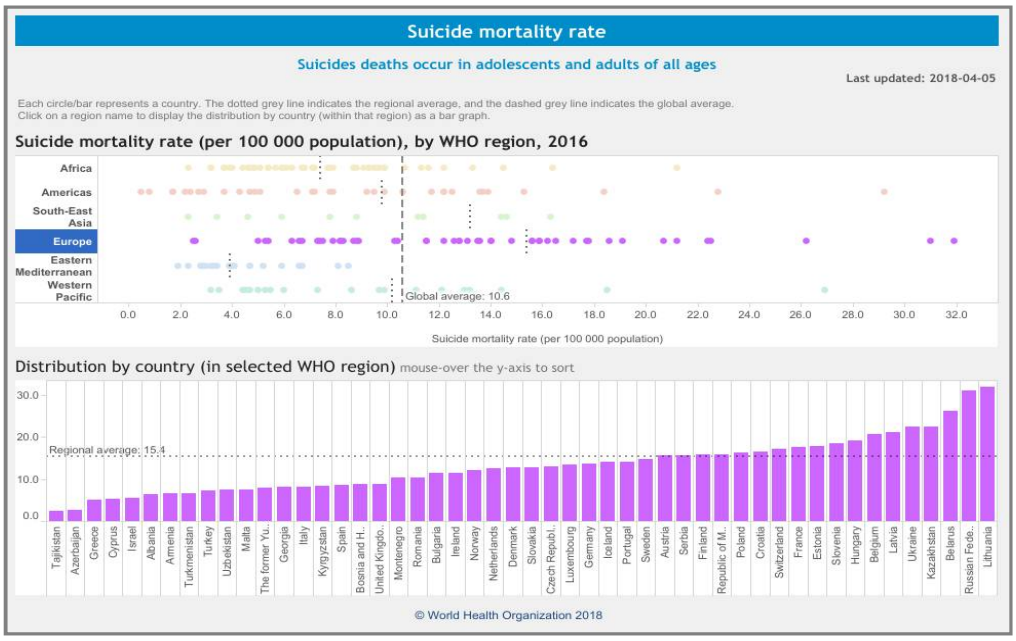


Figure 1. The suicidal mortality is nearly 31 deaths per every 1,00,000 population in Lithuania country it is the recorded higher rate.

In order to overcome these authors are made extensive literature survey on organic compounds bearing heterocyclic compounds such as isoxazoles [2-6], thiophenes [7-9], chalcones [10], benzophenones [11-13], piperazine [14] etc. these are accounted for most of the important biological activities such as anti-bacterial, anti-microbial, anti-fungal, anti-inflammatory, anti-oxidant, anti-cancer, anti-depressant etc, due to its proper binding with host molecules, owing to this significance the molecular docking was performed for the titled compound since it is bearing two heterocyclic ring systems such as isoxazole and thiophene moieties. The isoxazole is the five-membered heterocyclic nuclei containing oxygen atom at first position and nitrogen atom at second position whereas thiophene also a five-membered heterocyclic compound with sulfur as a heteroatom they are shown in figure 2.

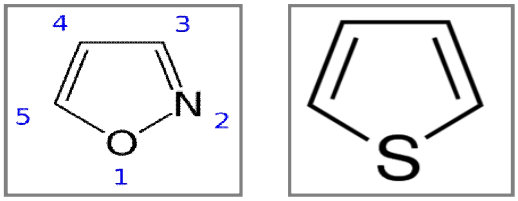


Figure 2. Five membered heterocyclic compounds
Isoxazole and Thiophene

The molecular docking was performed for titled compound for three important activities viz., anti-bacterial, anticancer and antidepressant. The antibacterial is meant for anything that destroys bacteria or suppresses their growth or their ability to reproduce. Heat, chemicals such as chlorine, and antibiotic drugs all have antibacterial properties. The cancer is a very unique disease causes abnormal cell growth and spreads to all other parts of the body. Possible symptoms are an abnormal bleeding, prolonged cough, weight loss etc., these may indicate cancer. The anti-cancer agents may prohibit

spreading cancerous cells to other parts of the body. Finally the antidepressants are a class of drugs that lowers depressive disorders by regulation of chemical imbalances of neurotransmitters in the brain.

MATERIALS AND METHODS

Crystal structure of anti-bacterial (PDB ID: 1HNJ), anticancer (PDB ID: 1JNX) and antidepressant (PDB ID: 1XRW) target protein were obtained from Protein Data Bank [**15**]. Three dimensional (3D) structures of the compounds were converted from CIF Format to Mol2 format by MarvinSketch [**16**]. AutoDock 4.2 [**17**] tools used to simulate the binding conformations between the compounds and protein. AutoDock with grid maps of (60×60×60) was applied to explore the binding sites of the target protein. The sites with lowest binding energies were further analyzed using AutoDock 4.2. The grid box size set to (60×60×60Å) and a grid spacing of 0.375 Angstrom. Center of the grid box set to the center of the protein. Number of GA Runs was 250. Population size was set to 150 with 2,500,000 energy evaluations (medium) and conformational searching was done using the Lamarckian genetic algorithm (LGA). The lowest energy conformation was used for further analysis. The reader may be referred for crystal and molecular structure data and to ORTEP of the titled compound [**18**].

RESULTS AND DISCUSSION

Molecular docking is an important tool in structural molecular biology and computer-assisted drug design. The main goal of molecule-protein docking is to predict the dominant binding mode(s) of a molecule with a protein of known three-dimensional structure [**19**]. According to the Auto-dock result (Table 1), it can be inferred that the compound 5-(3-methylthiophene-2-yl)-3-(3,4,5-trimethoxy phenyl) isoxazole is binding to antibacterial, anti-cancerous and anti-depressant target protein with binding energies of -8.04, -5.87, -9.47 kcal mol^{-1} respectively as shown in the figures 3, 4 and 5, high binding affinities may exhibits all of these activities. The binding energy of the compound with anti-depressant (-9.47 kcal mol^{-1}) is relatively larger than all other activities which shows a higher anti-depressant activity of the compound and also this value is in agreement with the binding affinities of some of the standard drugs such as duloxetine, maprotiline, mianserin, mirtazapine, nortriptyline used to treat anti-depressant activities [**20**].

Table 1. Binding energies of the titled compound

PDB ID	Target type	Binding Energy (kcal mol^{-1})
1HNJ	Anti-bacterial	-8.04
1JNX	Anti-cancer	-5.87
1XRW	Anti-depressant	-9.47

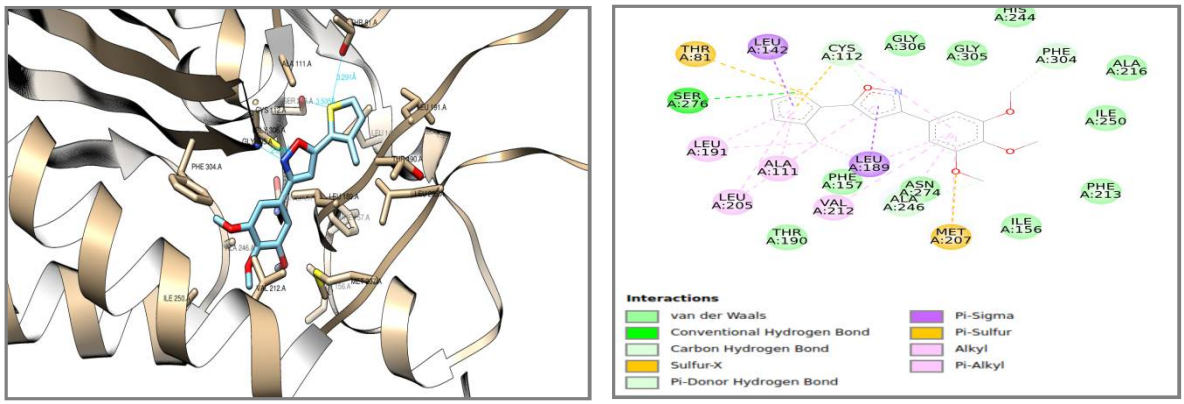


Figure 3. Molecular docking of the Compound 5-(3-Methylthiophene-2-yl)-3-(3,4,5-rimethoxyphenyl) isoxazole bound with Protein, (a) Anti-bacterial target

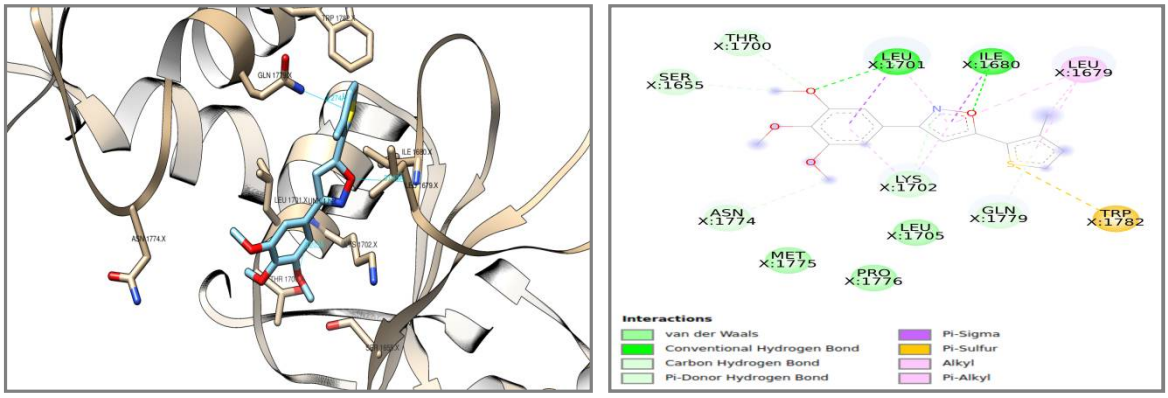


Figure 4. Molecular docking of the Compound 5-(3-Methylthiophene-2-yl)-3-(3,4,5-rimethoxyphenyl) isoxazole bound with Protein, (b) Anti-cancer target.

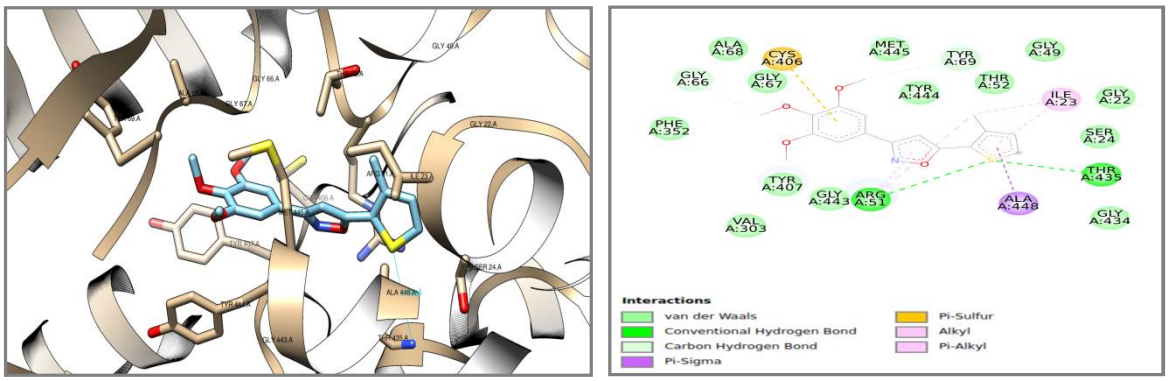


Figure 5. Molecular docking of the Compound 5-(3-Methylthiophene-2-yl)-3-(3,4,5-rimethoxyphenyl) isoxazole bound with Protein, (c) Anti-depressant target.

APPLICATION

This compound may be used to treat the biological activities such as anti-bacterial, anticancer and antidepressant activities.

CONCLUSION

The results of molecular docking showed that the titled compound exhibited relatively better binding affinity for anti-depressant activity than other two activities which was performed. Further the reports of World Health Organization (WHO) shows besides natural, accidental or other diseases, the suicidal becoming as a more common one due to various mental disorders in-order to overcome this, the compound may be used to treat them.

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