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Review Article

In –Silico Approach for Assessment of Antimicrobial Potential of some Pyrazolidine-3, 5-Dione Derivatives

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Abstract: ***Background:*** Resistance to antibacterial drugs is a trouble in the worldwide public health that must be conquered immediately by finding new antibacterial drugs.Pyrazolidine-3, 5-dione derivatives of heterocyclic compounds were used as active agents against pathogenic microorganisms. This study has been carried out to rationally design three synthesized derivatives was assayed for antimicrobial potential by using *in-silico* molecular docking approach. ***Methods:*** Molecular docking of Isoleucyl-transfer RNA (tRNA) synthetase (IleRS) with three Pyrazolidine-3, 5-dione synthesized derivatives was carried out by AutoDock. ***Result:*** The molecular docking result revealed that synthesized compound 5(a-c) showed encouraging docking score as compared to standard ligand Gentamicin. The docking score found to be - 8.23, - 8.63, -6.89 &-8.30 kcal mol^{-1} respectively.

Keywords: Heterocyclic compounds, Pyrazolidine-3, 5-dione, molecular docking & Isoleucyl-transfer RNA (tRNA) synthetase (IleRS).

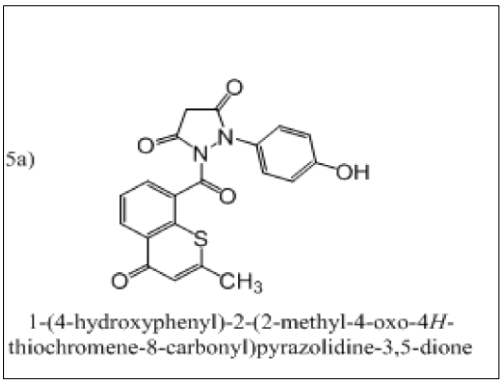
INTRODUCTION

Globally, infectious diseases are a major cause of death and a challenge for public health. Human health is seriously threatened by infections brought on by harmful germs [1, 2]. The need for innovative, safe, and efficient antimicrobial medicines has been driven by rising drug resistance cases, unfavourable antibiotic side effects, and the reemergence of previously identified illnesses. Virtual screening techniques used in drug development, such as drug-likeness, ADMET, and DFT analysis, use computation to quickly and cheaply identify compounds that are likely to demonstrate physiological activity [3]. Due to the robust and wide-ranging action of the pyrazole scaffold, also known as 1, 2-diazole, which is a member of one of the most significant classes of heterocycles, pyrazole has been considered to be a very important nucleus in terms of pharmacology. Its broad spectrum of activities, including anti-inflammatory, antipyretic, analgesic, antitubercular, antiviral, antihypertensive, antiglaucoma, antioxidant, antidepressant, anxiolytic, neuroprotective, antimicrobial, cytotoxic, antiproliferative, antidiabetic, anticancer, and anti-alzheimer, have drawn the attention of thousands of researchers around the world [4].

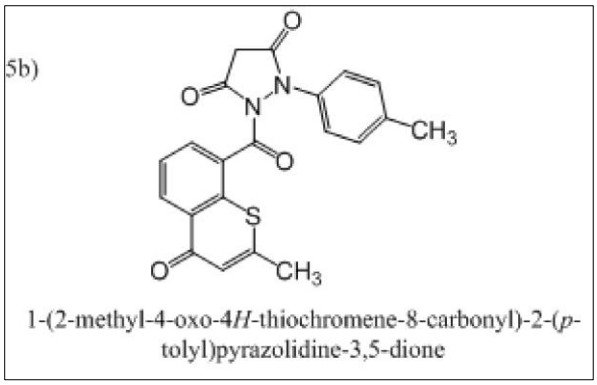
EXPERIMENTAL WORKS

Ligand Preparation

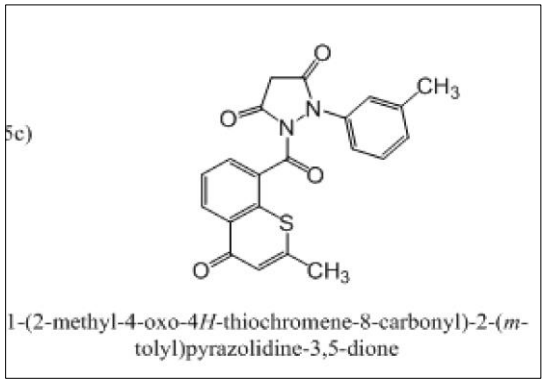
2D Structure of ligands 1a, 1b, and 1c was drawn using ChemDraw [K.R. Cousins *et al*]. The two-dimensional structures of ligand were converted into 3-D structures with optimized 3D geometry by using Chem3D software. The optimized structure was saved in PDB format for AutoDock compatibility [5].



1-(4-hydroxyphenyl)-2-(2-methyl-4-oxo-4*H*-thiochromene-8-carbonyl)pyrazolidine-3,5-dione



1-(2-methyl-4-oxo-4*H*-thiochromene-8-carbonyl)-2-(*p*-tolyl)pyrazolidine-3,5-dione



1-(2-methyl-4-oxo-4*H*-thiochromene-8-carbonyl)-2-(*m*-tolyl)pyrazolidine-3,5-dione

Preparation of the Grid File

The regions of interest used by Auto dock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing between grid points can be adjusted with another thumbwheel, the value in the study taken is 0.392 Å and No. of points considered are 40, 40 and 40 points in the x, y, and z dimensions are67.561, 31.934 and 19.359 as x, y, z centers [6].

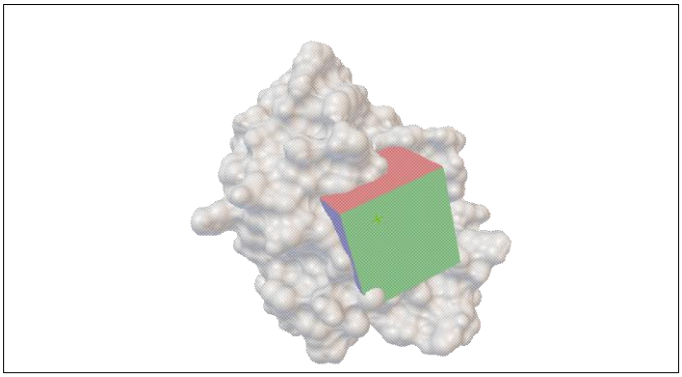


Figure 1: Grid Box Covering All Active Sites in Receptor

Preparation of the Docking File

All the calculations were carried out by using Autodock4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [7].

Docking of Isoleucyl-Transfer RNA (Trna) Synthetase (Ilers)

Crystal Structure

The crystal structure of the protein consisting of receptor associated with bound ligand is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (1WNZ.pdb) registered in the Protein data bank was used. The bound ligand 2'-(L-valyl) amino-2'-deoxyadenosine (2VA) was found within the receptor [8]

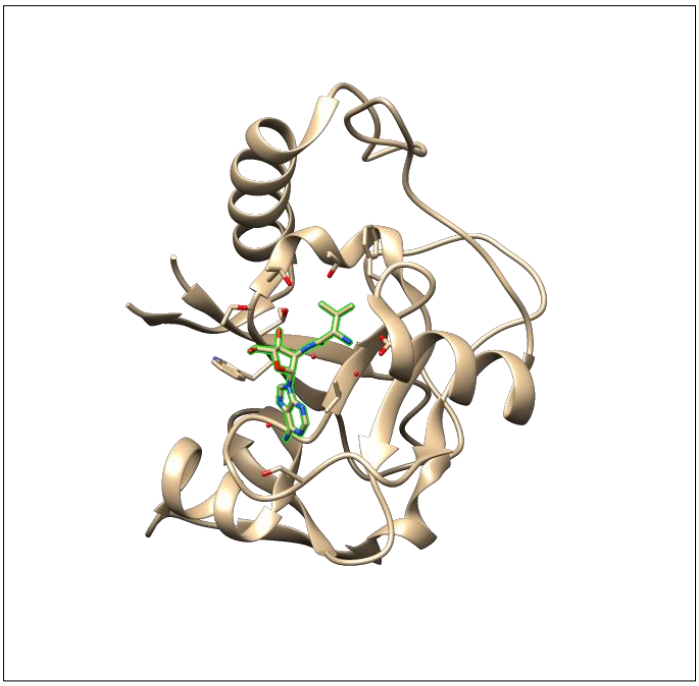


Figure 2: Crystal Structure of Ilers Enzyme with Bound Ligand 2VA (PDB ID-1WNZ)

Processing of Protein

The downloaded receptor protein is having a single chain A, which has been selected for the experimental purpose. The bound ligand 2VA was separated from the macromolecular complex by using software Chimera [9].

Molecular Docking Simulation Studies

Docking of ligands 5a, 5b and 5c against IleRS enzyme was performed by Autodock. All the bonds of ligand were kept flexible, while no residues in receptor were made flexible [10].

Toxicity & ADME-T Studies

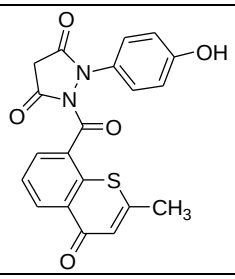
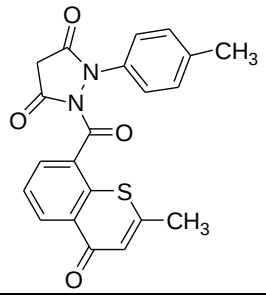
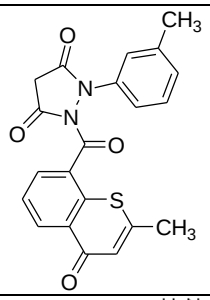
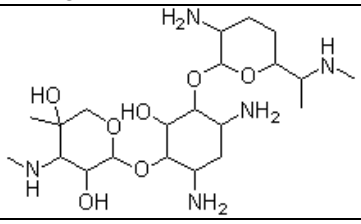
The ligand molecules 5a, 5b and 5c are studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME- T properties [11, 12].

RESULT AND DISCUSSION

Antibiotic resistance among bacteria is currently on a phenomenal rise, and this poses a real threat to global health. Particularly concerning are contaminations caused by methicillin-safe Penicillin-safe Staphylococcus aureus (MRSA) Vancomycin-safe strain of Streptococcus pneumoniae Since many of these organisms are resistant to a few kinds of established anti-microbials, Enterococcus and Mycobacterium tuberculosis are the two most common ones. The search for novel antibacterial drugs that inhibit essential bacterial targets and are unaffected by mechanisms of current chemotherapeutic agent resistance is being driven by this circumstance. The aminoacyl-tRNA synthetase (AaRS) enzymes have been the focus of recent study for the development of antibacterial drugs in this area. By catalysing the creation of aminoacyl-tRNAs, these enzymes serve crucial roles in protein biosynthesis [13]. With this endeavor, synthesized compound 5(a-c) has been identified as ligand and their aminoacyl-tRNA synthetase (AaRS) enzymes inhibitory activity has been checked *in-silico* with the help of docking approach.

The molecular docking result revealed that synthesized compound 5(a-c) showed encouraging docking score as compared to standard ligand Gentamicin. The docking score found to be - 8.23, -8.63, -6.89 &-8.30 kcal mol^{-1} respectively (Table 1) .The interaction of ligand hits to targeted site was tabulated in Table 1. Hence from above finding it can be predicted synthesized compound 5(a-c) exhibited good inhibitor of IleRS enzyme in increasing order 5c>5b>5a. The pharmacokinetic profiling of the ligand has revealed that compound 5(a-c) are having good pharmacokinetic profile without presence of any major toxic effects The pharmacokinetic and toxicity profiling results were shown in (Figure 7-9) were observed in docking studies of IleRS enzyme with ligands 5a, 5b and 5c.

Table 1: Result of Docking of Against Ilers Enzyme

S. No	Compound Name	Structure	B.E.	H-Bond	Residual Interaction	
					Pi-Interaction	van der Waals
1	5a		-8.23	Thr230, Asp328, Ser310	Trp227, Val318	Asp313, Val309, His319, Thr228, Tyr308, Thr233
2	5b		-8.63	Ser310	Phe324, Val318, Ala321, His319, Trp227	Gly314, Val309, Thr230, Thr228, Ala321
3	5c		-8.30	Ser310	Val318, Trp227	Gly316, Gly314, Thr233, Asp313, Thr228, Tyr308, Thr229
4	Gentamicin		-7.30	Thr230, Asp328	Val318, Trp227	Gly316, Gly314, Thr233, Asp313, Thr228, Tyr308, Thr229

INTERACTIONS

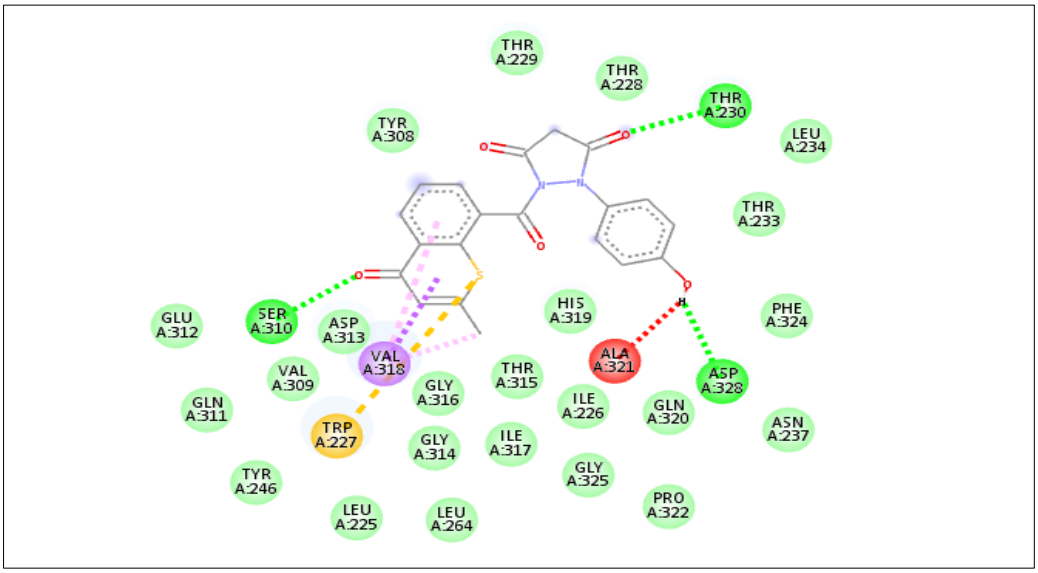


Figure 3: Two Dimensional Binding Interaction of Ligand 1a with Ilers

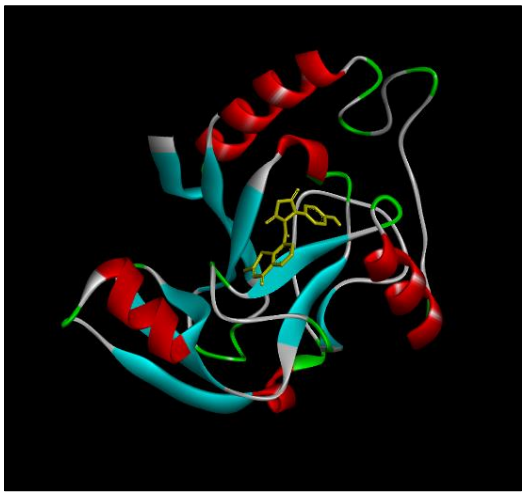


Figure 4: Three Dimensional Binding Interaction of Ligand 1a with Ilers

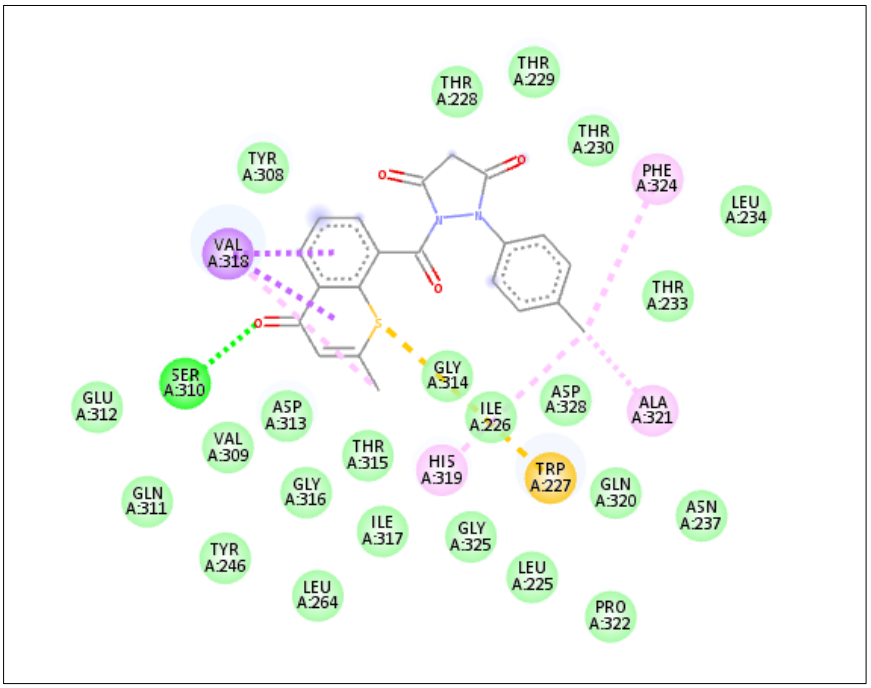


Figure 5: Two Dimensional Binding Interaction of Ligand 1b with Ilers

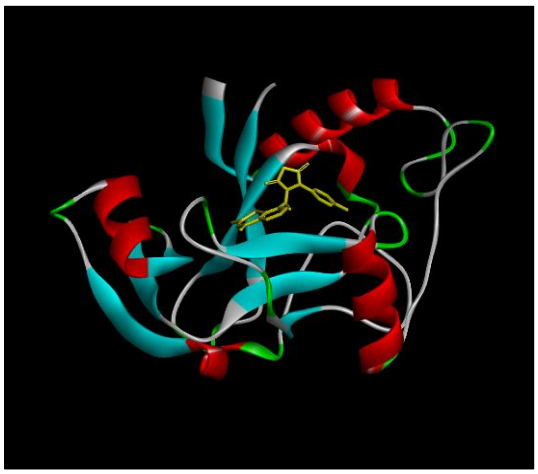


Figure 6: Three Dimensional Binding Interaction of Ligand 1b with Ilers

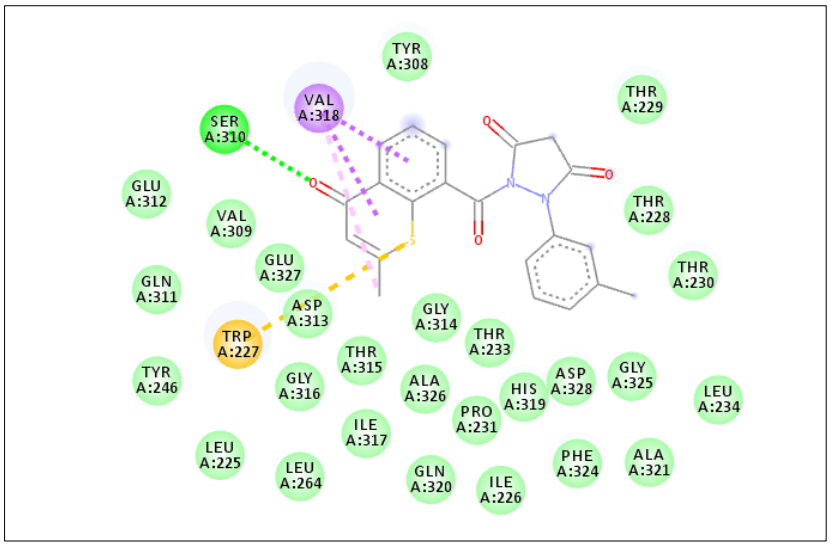


Figure 7: Two Dimensional Binding Interaction of Ligand 1c with Ilers

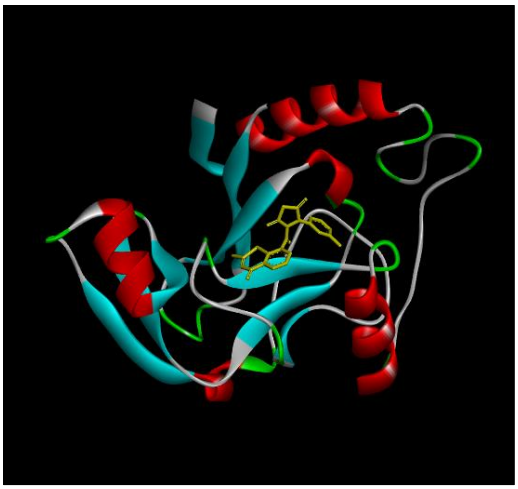


Figure 8: Three Dimensional Binding Interaction of Ligand 1c with Ilers

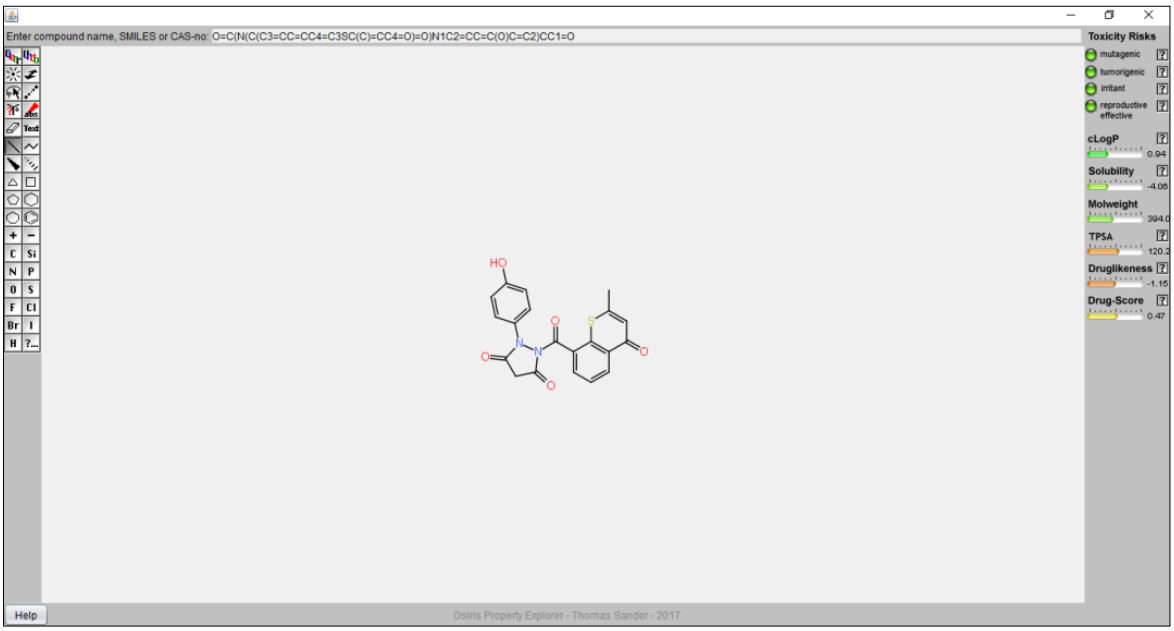


Figure 9: Pharmacokinetic and Toxicity Profiling of Ligand 5a

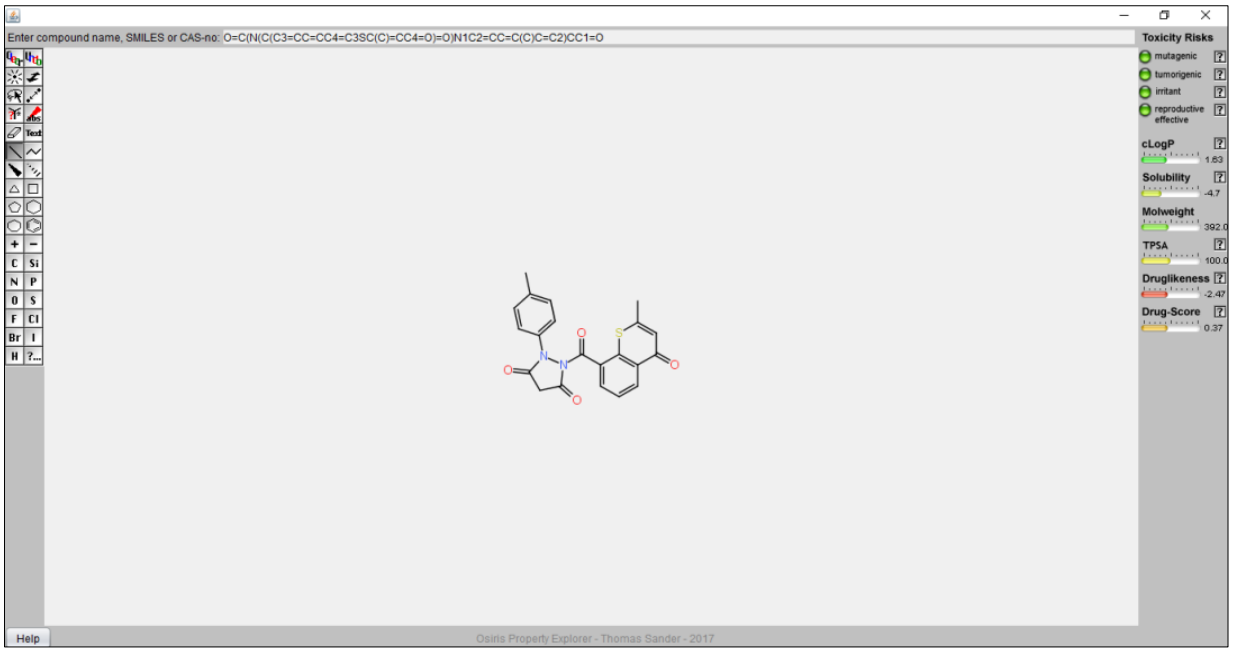


Figure 10: Pharmacokinetic and Toxicity Profiling of 5b

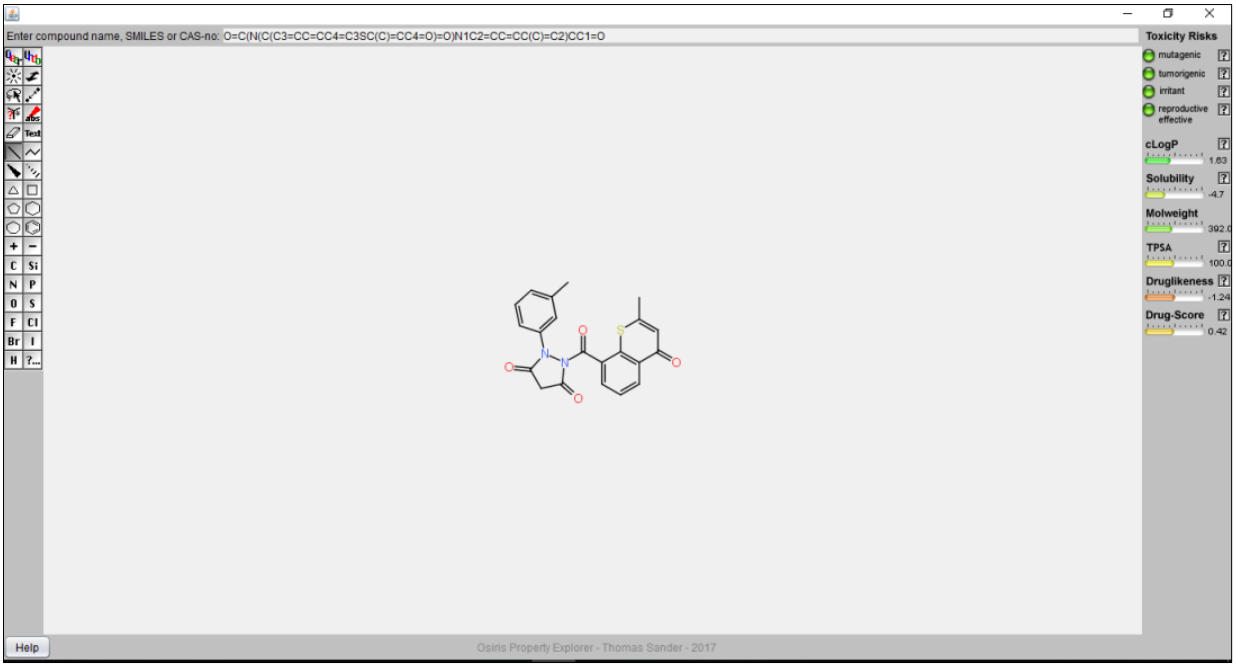


Figure 11: Pharmacokinetic and Toxicity Profiling of Ligand 5c

CONCLUSIONS

The molecular docking approach executed by Auto dock is very advantageous to predict and confirm the compound of a drug candidate as an anti-microbial agent. The selected compounds have been docked to the IleRS enzyme receptor. Therefore, further research is desirable using more ligand from derivatives to generate the best conformation of the ligand-receptor complex.

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