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AN APPROACH OF COMPUTER AIDED DRUG DESIGN TOOLS FOR *IN SILICO* STUDIES ON THIAZOLE DERIVATIVES AS CYP450 INHIBITOR AND ITS LEAD OPTIMIZATION

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ABSTRACT

This paper reports on the designing of the new thiazole derivatives that could useful in development of drug candidate for various medicinal activities. Based on the computer aided drug design the drug likeness predicted through Lipinski rule of five. The cytochrome P450 is an enzyme involved in various metabolic biotransformation's of endogenous and exogenous substances. The use of computational methods used to develop the CYP450 inhibitors in order to find agent with desired properties. Moreover, the current status of knowledge about the use of the computational approach in studies of ligand-enzyme interactions for CYP450. Research on the inhibitors of CYP450 are designed and calculated its properties like atom properties, bond properties, Torsion properties, angle properties and spectral analysis was also reported.

KEYWORDS

Thiazole derivative, CPY450 inhibitors and Computer aided drug design.

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INTRODUCTION

Thiazoles are the important heterocyclic compounds belong to the family of azoles[1]. It contains one sulfur and one nitrogen as heterocyclic atoms in five membered ring system[2]. Thiazole as pharmacophore involved in various remarkable biological activities like antiprotozoal, antifungal, antibacterial, antitubercular, anthelmintic, antidiabetic, anti-inflammatory, antihypertensive, anticancer and others also and the isomers of thiazole has been used in pharmaceuticals, agrochemicals and

photosensitizer[3,4]. The moiety of thiazole ring is also found in natural compounds like alkaloids, flavonoids, steroids as well as some of the vitamins[5,6]. The design and derivative of organic compounds containing more than one thiazole ring enhanced the therapeutic area of lead compounds. Through the literature survey the thiazole scaffolds se as parent moiety and derivatization is done by using various computational application in Computer aided drug design[7-9].

The interest in the derivatization of compounds containing the thiazole moiety just because of higher number of utilities in the fields of pigments, sensitizer, sunscreens, crystal growth, chromophores and dyes. Furthermore, thiazole moiety and its derivatives have attracted a great deal of interest due to their wide range of pharmaceutical applications[10,6]. Recent research indicates that some of thiazole derivatives are inhibitors of enzyme such as CYP450 enzymes. In this synthesis, structure, physical, chemical properties and spectral characterization like UV, IR, 1H NMR, 13C NMR, Mass spectra and biological activities has been investigated. Computer aided drug design is an computational tool to develop new drug candidate by creation, modification, analysis, optimization using various software's[11,12].

MATERIAL AND METHODS

Software used for lead optimization

Chem Draw Ultra8.0, Avogadro, OCHEM database

Although computational methods

Have been significantly developed, a further improvement of virtual procedures could have an impact on their use-fulness in the design of drugs targeting CYP enzymes by predicting the site of metabolism and drug-drug interactions and determining the potential toxicity of substrates and their metabolites.

RESULTS AND DISCUSSION

In this study the computational tools like CHEM DRAW ULTRA, AVAGARDO and OCHEM database are used to develop various hypothetical Thiazole derivatives. By the help of chemical reaction of thiazole, we prepared 10 derivatives. After that investigation of its potential derivative which having significant properties was done. Comprehensive studies of the Quantum Approaches on the Thiazole derivatives like derivative-9 and derivative-10 were found to be CYP450 enzymes inhibitors interactions. The design and development of potent and selective inhibitors for individual CYP enzymes seems to be an achievable target.

Chemical Reaction[13]

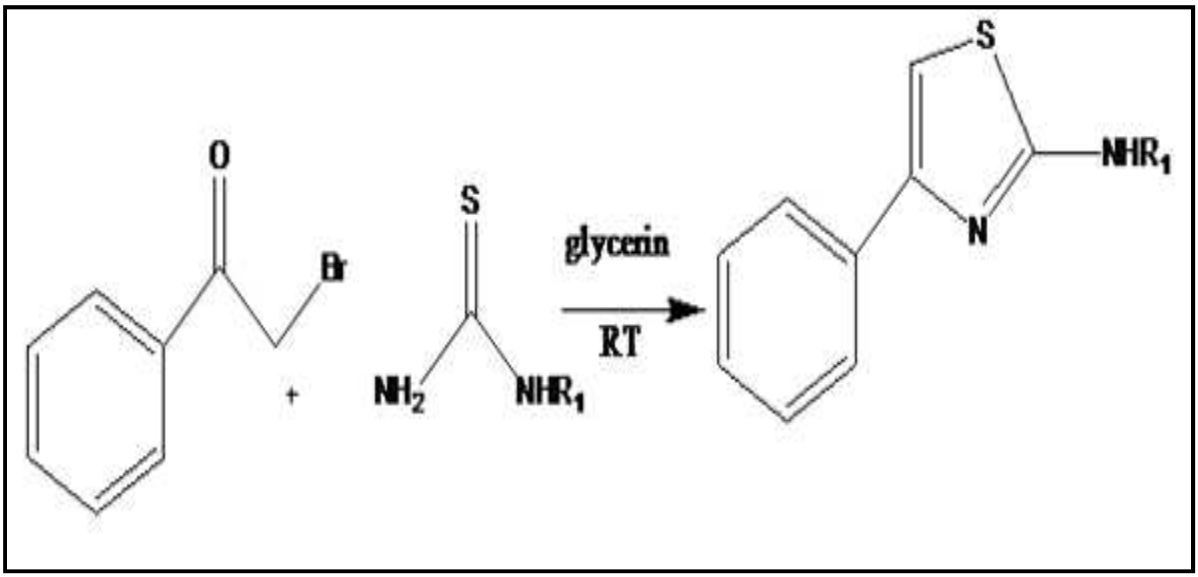


Figure No.1: Novel Thiazole derivatives with elemental analysis

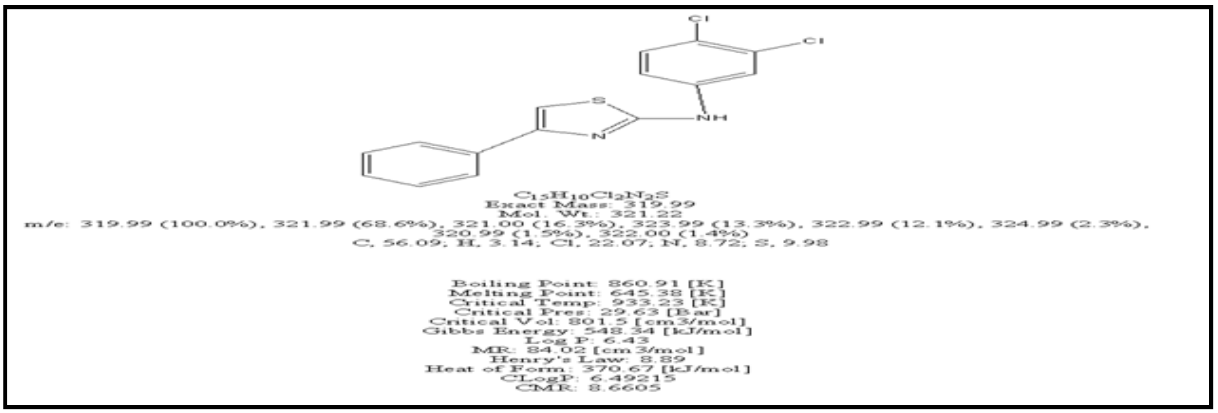


Figure No.2: TD-1

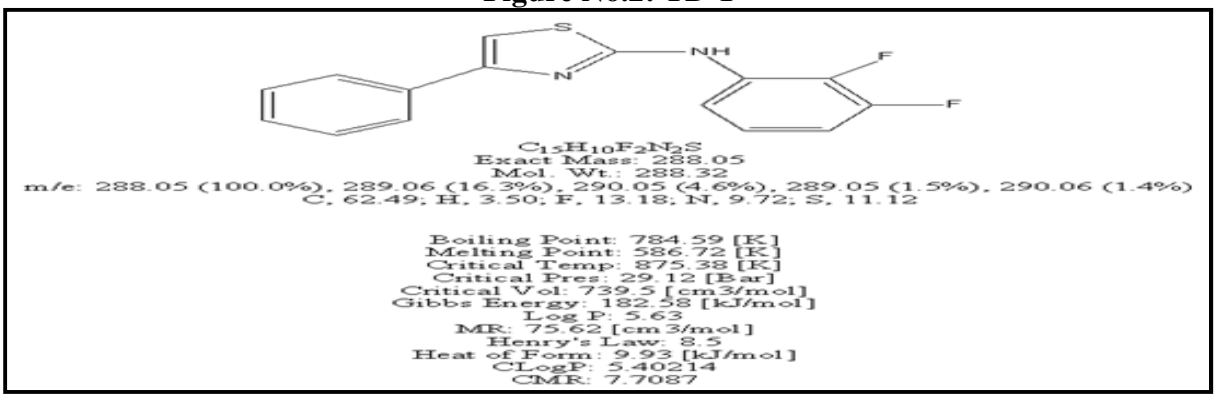


Figure No.3: TD-2

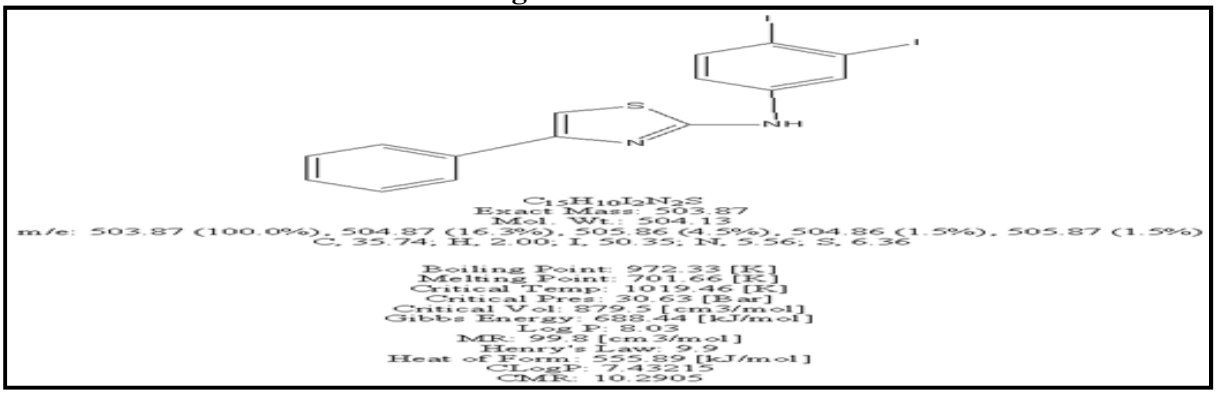


Figure No.4: TD-3

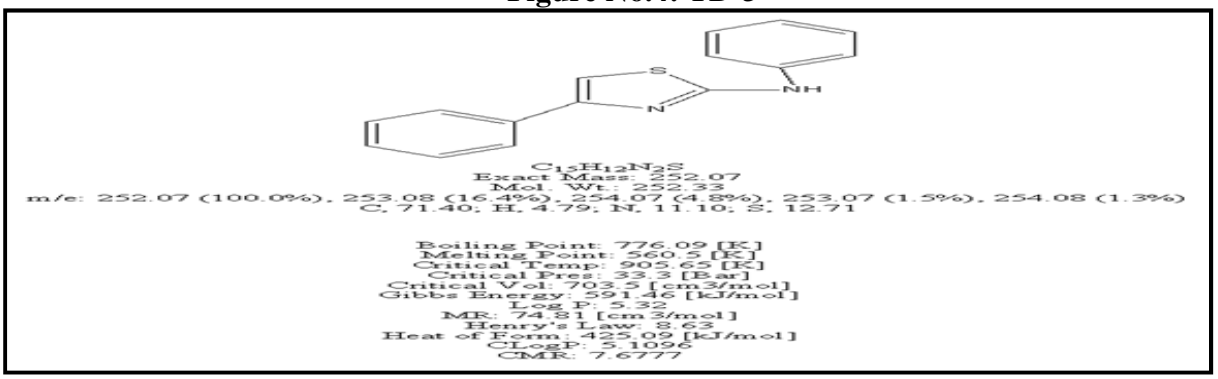


Figure No.5: TD-4

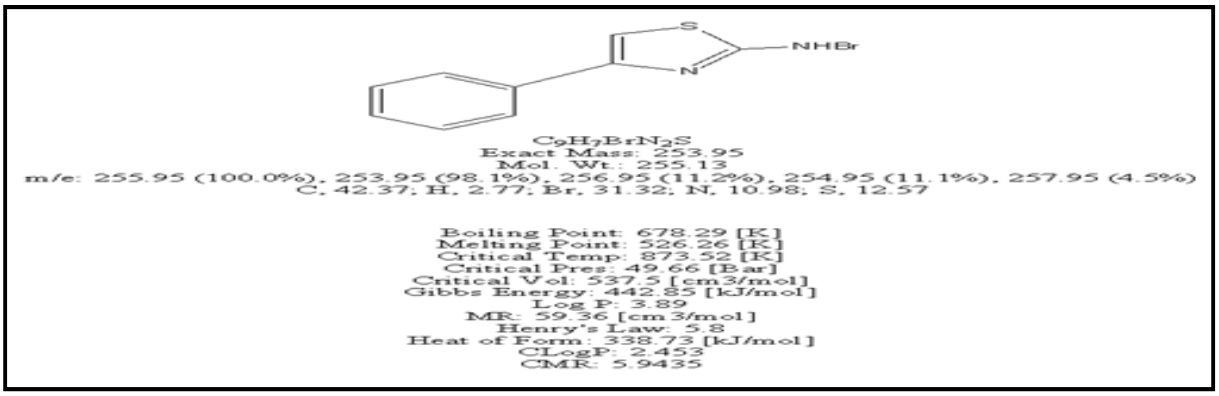


Figure No.6: TD-5

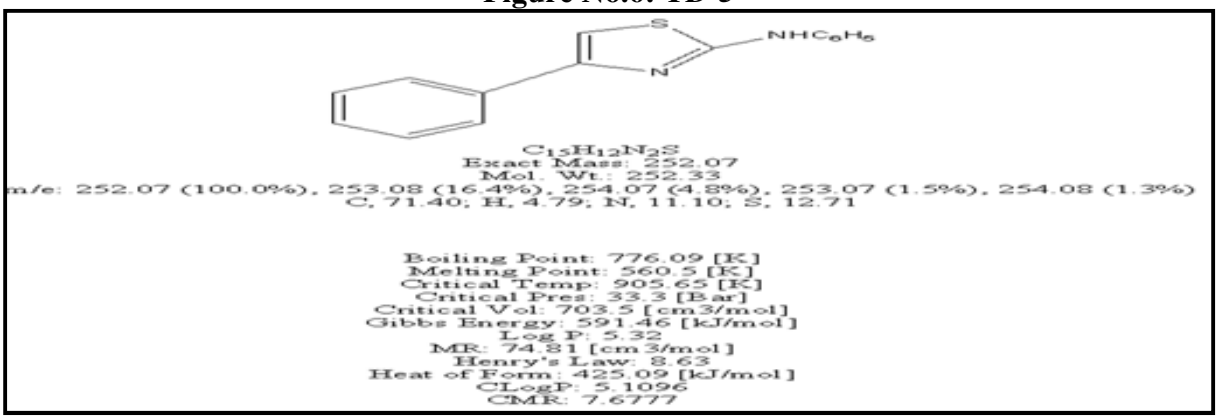
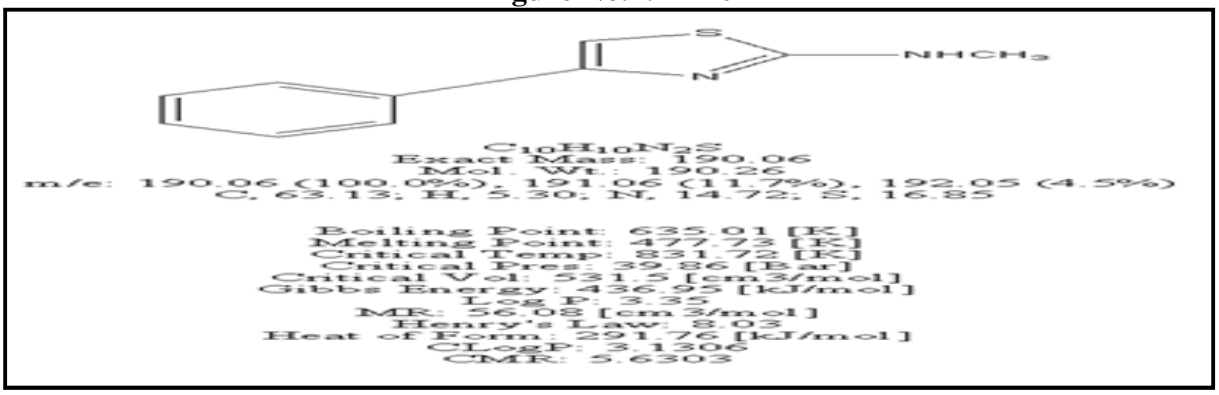


Figure No.7: TD-6



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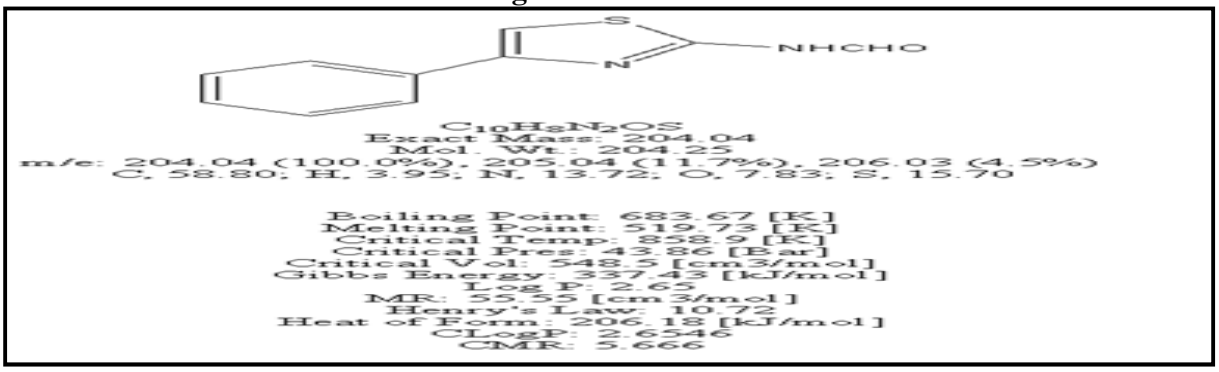

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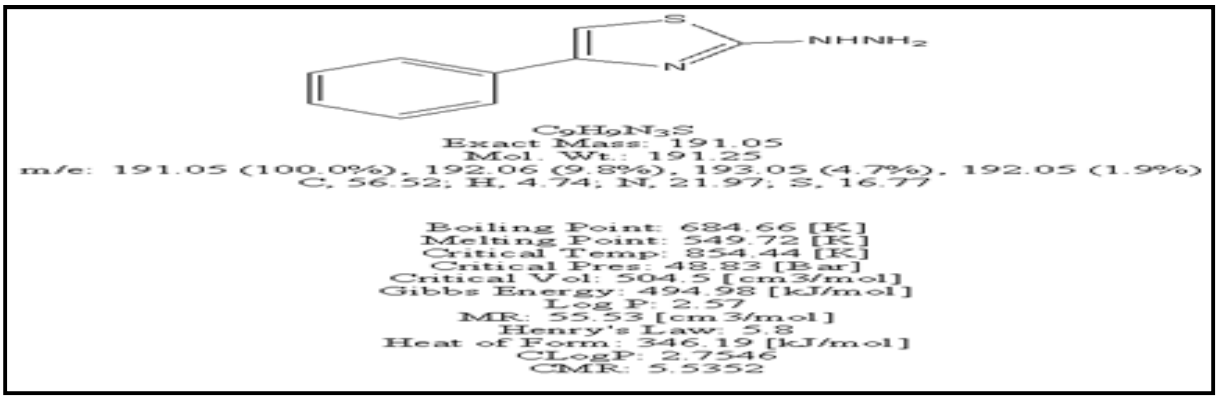

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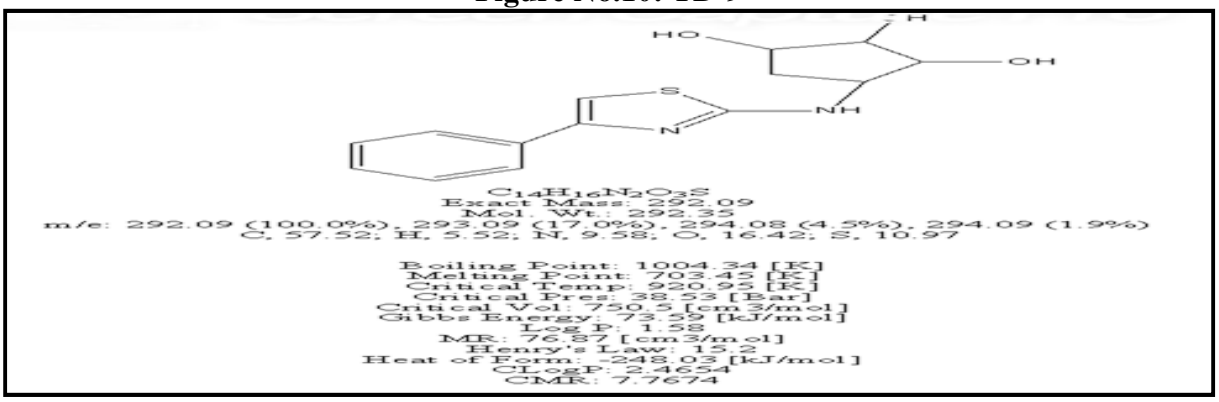

Figure No.11: TD-10

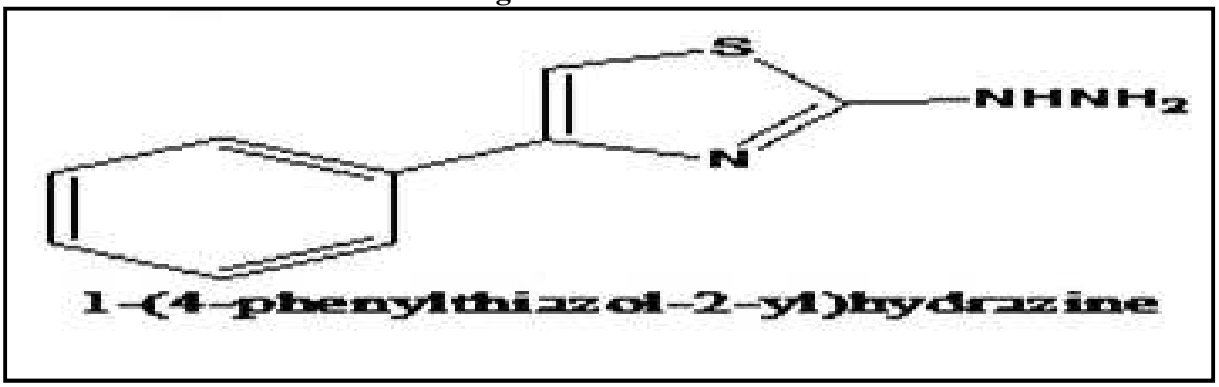

Figure No.12: TD-9

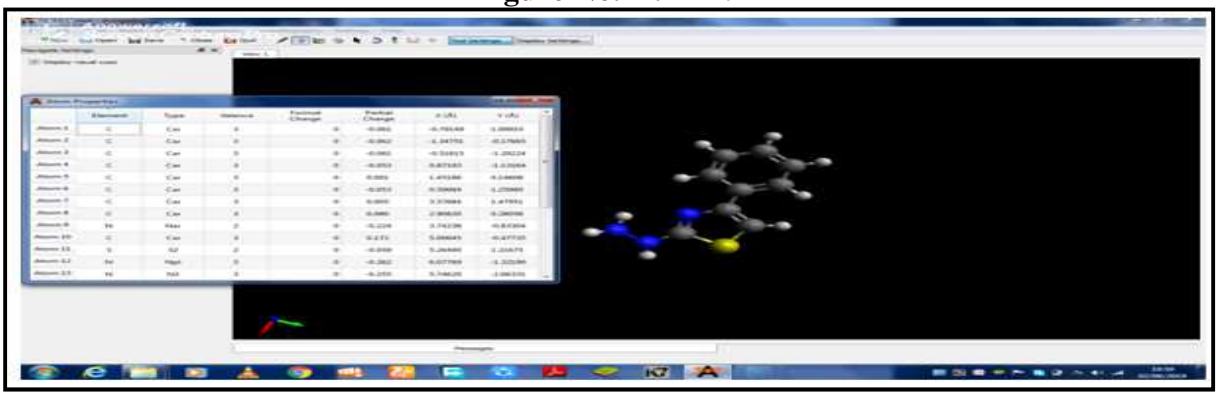

Figure No.13: Atom Properties with 3D View

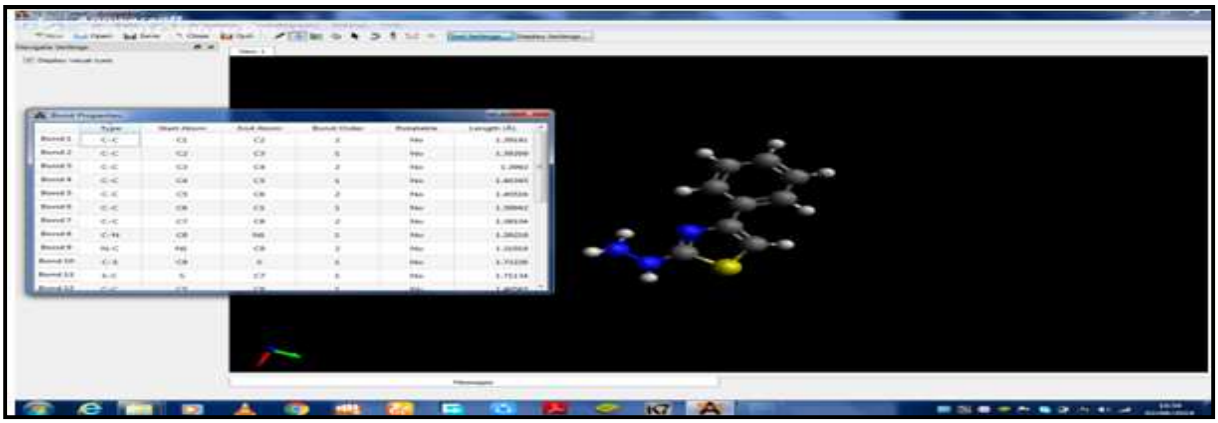

Figure No.14: Bond Properties with 3D View

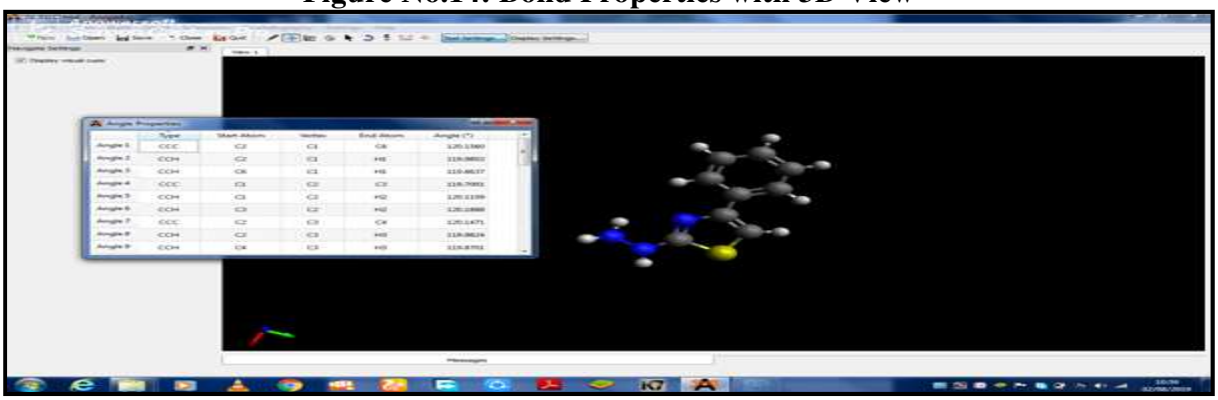

Figure No.15: Angle Properties with 3D View

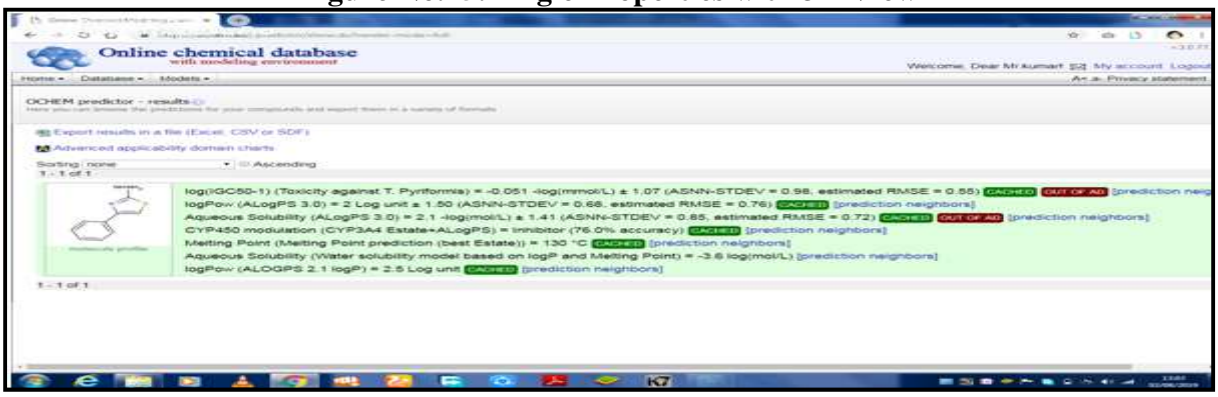

Figure No.16: Ochem database prediction results as CYP450 inhibitor

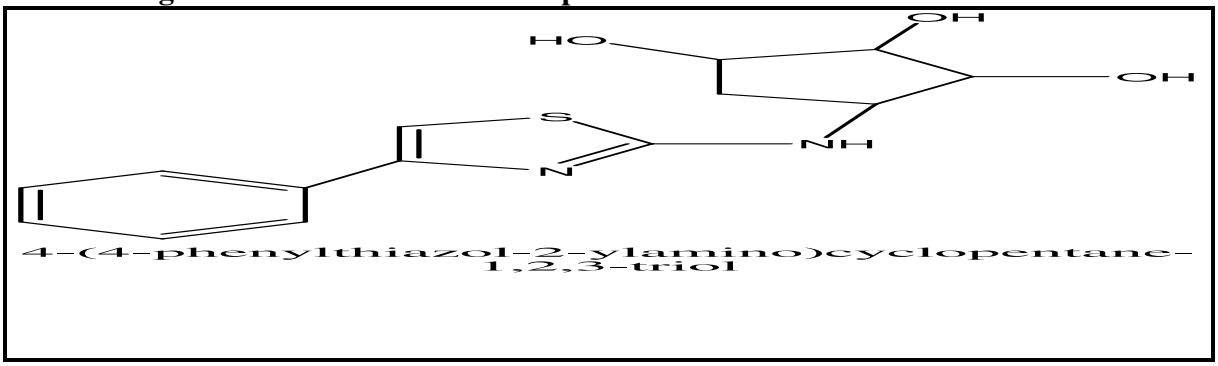

Figure No.17: TD-10

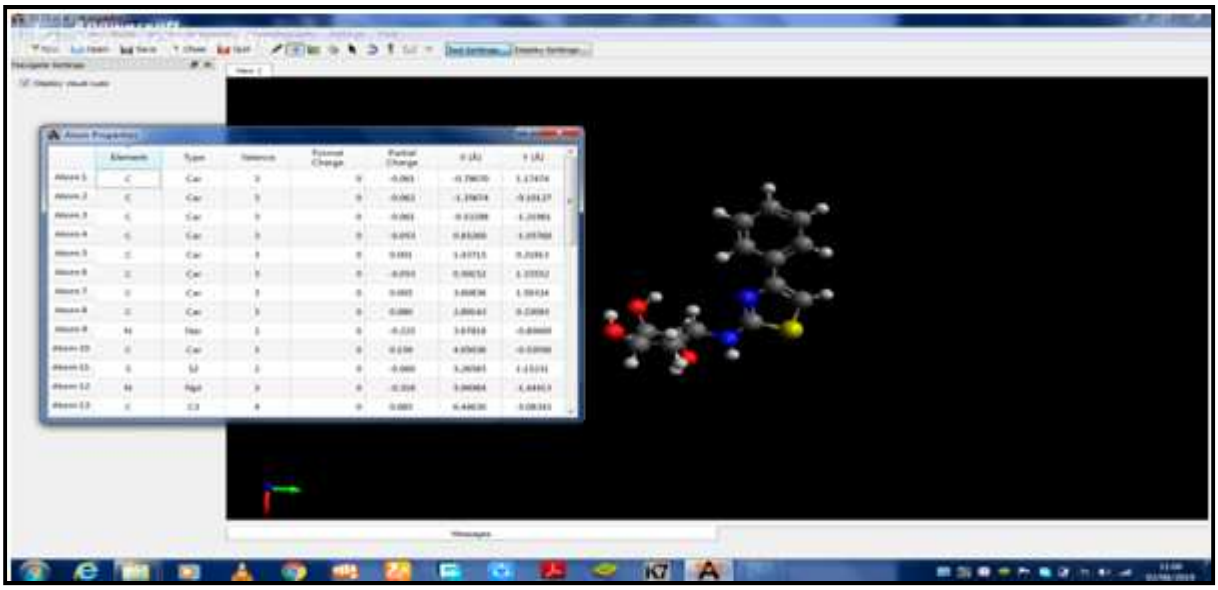

Figure No.18: Atom Properties with 3D View

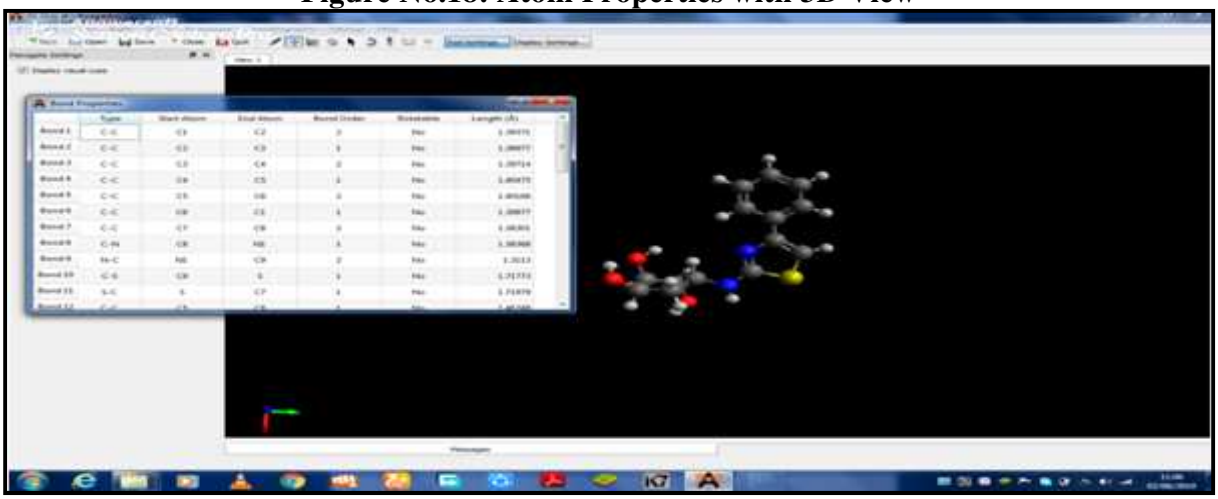

Figure No.19: Bond Properties with 3D View

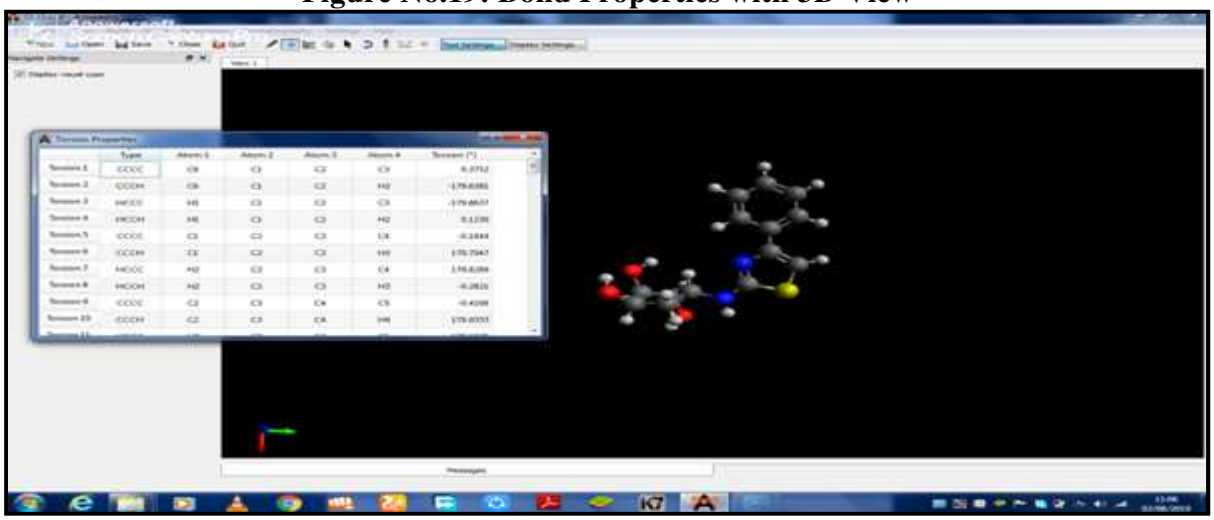

Figure No.20: Torsion properties with 3D View

Figure No.21: Ochem database prediction results as CYP450 inhibitor

CONCLUSION

Computational studies contribute to a batter understanding of ligand-enzyme interaction and other chemical properties. Studies with the use of computational tools provides a rationalization of selectivity of ligands towards the CPY450 enzyme. Derivative compounds were ascertained on the basis of their spectral data (IR and 1H NMR). Furthermore, Computational methods have been significantly developed, for improvement of the design of drugs targeting enzyme CYP450 predicting the properties of derivatives and determining the hypothetical reactions. Computational structure-based ligand design is a promising technique to develop new drug candidate. The results indicated some of the derivatized compounds exhibited good CYP450 inhibitor activity. The proposed models could predict the activity with reasonable accuracy and will be useful in the near future for finding potent CYP450 inhibitor molecules in our group.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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