Research Article

Synthesis, PASS Prediction and Docking Studies of Anti-inflammatory Activity of Novel Series of 2, 6-Bis (P-Chlorobenzoyl) *3, 6-Diphenyl-4-Methylthiamorpholine 1, 1-Dioxide*

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ABSTRACT

2, 6-Bis (P-Chlorobenzoyl) 3, 6-Diphenyl-4-Methylthiamorpholine 1, 1-Dioxide(**D1**) had been synthesized by condensing 4, 4'-dichlorodiphenacyl sulphonewith Benzaldehyde and methyl amine. The structure of the compound was confirmed by ^{1}HNMR, ^{13}CNMR. The synthesized compound was analysed for anti-inflammatory activity through *in silico* methods. PASS prediction tool was used to screen the biological activities of **D1** and further docking studies were performed to validate the activity predicted. The probable activity (Pa) of **D1** using PASS was found to be 0.572. Four poses of the compound were docked with anti-inflammatory protein (PDB ID: 2OFU) using Discovery studio V4.0 The result indicates- the synthetic compound **D1** is considered as the lead compound due to its desirable interaction with the target inflammatory protein, the hydrogen bond interactions, LibDock Score (65.444) and minimum binding energy (-96.0845) respectively. Hydrophobic interactions are high, good interaction possess were seen with (66.578) LibDockScore and least binding energy (-97.4584). Hence, this compound may be explored as a potential lead molecule for further development.

Keywords: 2, 6-Bis (P-Chlorobenzoyl) *3, 6-Diphenyl-4-Methylthiamorpholine 1, 1-Dioxide,* spectral studies, Anti-inflammatory, PASS, Docking, Discovery Studio.

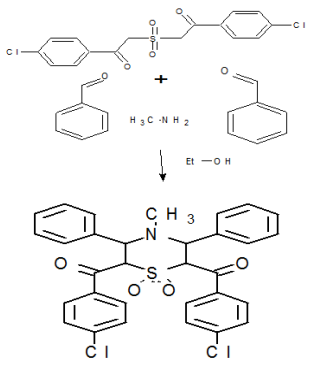
INTRODUCTION

A survey of synthesis of Substituted Thiamorpholine1, l-Dioxides revealed the moiety have attracted a great deal of interest of medicinal chemists, biochemist, pharmacologist and rendered as a lead molecule for designing potential bioactive agents. Show potent pharmacological activities of antimicrobial activity[1-3], antibacterial, antiviral[4], antimalarial, antidiabetic, antidepressant, sedative[5], tranquilizers, hypoglycaemic, antipileptics, antitubercular, antitumor, bactericidal and parasitical agent[6]. The large numbers of Biologically active molecules that contain heterocyclic rings has played important roles in the drug discovery process and exhibit various biological activities[7]. The compound **D1** was synthesized by the reaction of 4, 4'-dichlorodiphenacyl sulphone,with Benzaldehyde and Methyl amine shown in Scheme 1.

The commonly used drugs for inflammatory conditions are non-steroidal anti-inflammatory drugs, which have natural product or synthetic organic compound significantly towards the development of modern medicine. The synthetic novel derivatives have become a source of newer compounds with significant anti-inflammatory activities[8].

Several experimental protocols of inflammation are used for evaluating the potency of drugs.[9,10]. The increase in prevalence of multiple drug resistance is a serious concern in the medicinal field, the development of new synthetic alternative anti-inflammatory drugs has become an indispensable need[11,12]. PASS Online prediction therefore plays an essential role in screening of synthesized or available drug providing relevant information about the drugs' potential[13]. As part of the investigation on the mechanism of the anti-inflammatory activity protein to ability involve the lymphocyte-specific kinase. A small molecule inhibitor of Lck is expected to be useful in the treatment of T cell-mediated autoimmune and inflammatory disorders and/or organ transplant rejection[14].

Molecular Docking is an important methodology that can be used in the study of protein Ligand interaction properties such as binding energy, hydrogen bond donor/acceptor, hydrophobicity and polarizability. In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Molecular docking studies indicate how two or more molecular structures interact with each other for example, drug and enzyme or receptor of protein, fit together. Molecular docking softwares are mainly used in drug research[15-20].



Scheme 1: Synthetic scheme for2, 6-bis (p-chlorobenzoyl) *3, 6-diphenyl-4-methylthiamorpholine 1, 1-dioxide***.** (D1)

MATREIALS AND METHODS

Preparation of 2, 6-bis (p-chlorobenzoyl) *3, 6-diphenyl-4-methylthiamorpholine 1, 1-dioxide*.(D1)

A mixture 4, 4'-Dichloro diphenyl sulphone (0.01mole), Benzaldehyde (0.02mole) and 25% aqueous solution ofmethylamine (0.01mole) were condensed in the presence of ethanol (10ml) for half an hour. The precipitate was filtered, washed with ethanol and recrystallized from ethanol.

In silico Prediction of Biological Activity

The Internet version of the program, PASS server, contains about 31 000 biologically active substances in the training set and predicts biological activity spectra for 319 types of pharmacological effects, action mechanisms and specific toxicities. From the 'Prediction Results' window, the user obtains the total number of chemical descriptors of the substance. Also reported are the number of descriptors which are completely new compared with the descriptors of sub-stances from the PASS training set and comments on the interpretation of prediction results'. If Pa>0.7, the substance is very likely to exhibit the activity in experiment, but the chance of the substance being the analogue of a known pharmaceutical agent is also high. If 0.5<Pa<0.7, the substance is likely to exhibit the activity in experiment, but the probability is less, and the substance is unlike to bepharmaceutical agents. If Pa<0.5, the substance is unlikely to exhibit the activity in experiment. However, if the presence of this activity is confirmed in the experiment the substance might be a new chemical entity. Figure one shows the predicted biological activity spectrum for 2, 6-bis (p-chlorobenzoyl) *3, 6-diphenyl-4-methylthiamorpholine 1, 1-dioxide* as an example of PASS online server.

Pa	Pi	Activity
0,610	0,005	5 Hydroxytryptamine uptake stimulant
0,649	0,051	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
0,619	0,059	Glycosylphosphatidylinositol phospholipase D inhibitor
0,563	0,004	CYP2C10 substrate
0,654	0,097	Phobic disorders treatment
0,601	0,047	5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor
0,572	0,038	Antiinflammatory
0,557	0,026	Analgesic
0,516	0,066	CYP3A2 substrate
0,509	0,073	Nicotinic alpha2beta2 receptor antagonist
0,467	0,034	Cytochrome P450 stimulant

Figure 1: Example output page of the PASS online, showing the predicted biological activity spectrum for 2, 6-bis (p-chlorobenzoyl) 3, 6-diphenyl-4-methylthiamorpholine 1, 1-dioxide

Docking Studies

Molecular Docking using Discovery Studio 4.0

Computational studies of the newer derivatives were performed using Discovery studio V4.0 software. The target site for the study of anti-inflammatory activity of the 2, 6-bis (p-chlorobenzoyl) 3, 6-diphenyl-4-methylthiamorpholine 1, 1-dioxidederivatives was selected from the PDB. The PDB Id is 2OFU, which is a lymphocyte-specific kinase protein containing chain analong with interactive water molecules. The protein was downloaded from the PDB into the work space. The preparation for the Ligand and the protein were done using 'Ligand Preparation' and 'Protein Preparation Wizard' respectively shown in Figure 2. The different conformations of the Ligand were designed and the best pose of the molecules were selected, then the Define editing binding site was generated using the option 'Define and Editing site from current selection'. The job was monitored periodically and the results were obtained after the 'Analyze Ligand Poses Step'.

RESULTS AND DISCUSSION

2, 6-bis (p-chlorobenzoyl) *3, 6-diphenyl-4-methylthiamorpholine 1, 1-dioxide*, Yield 97%. ^{1}H MP 188-190°C. ^{1}H NMR: δ6.544-6.566 (d, 2H) (C2,C6); δ4.437-4.459 (d,2H)(C3,C5); δ7.146-7.926(m,18H) (aromatic) ; δ1.696(s,1CH_3). ^{13}CNMR 68.34(C3,C5), 69.38(C2,C6), 39.02-40.02(N-CH_3),130.43-139.63(Aromatic), 187.71(CO) represented in Figures 3 and 4.

Molecular Docking Studies

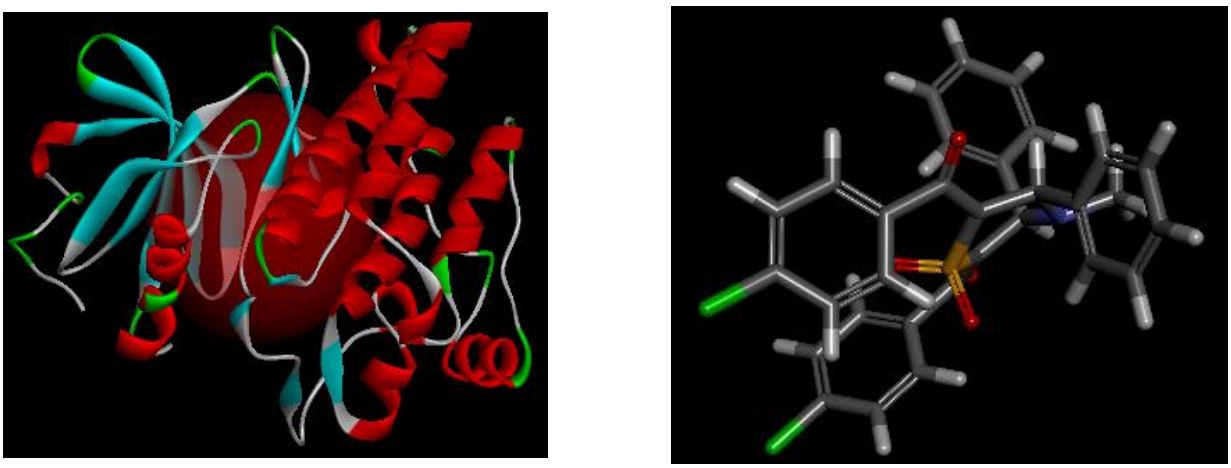
Molecular Docking using Discovery Studio 4.0

Molecular docking experimental evidence shows that there are variations in protein structure observed when **D1**is bound to it. The molecular docking approach can be used for the study of interactions such as hydrogen bond interaction and hydrophobic interaction between a protein and a small molecule at the atomic level.

The docking study was carried out with **D1** which was docked with inflammatory target protein. The compound showed best interaction with the active site receptors. Docked poses of the compound and protein (anti-inflammation) with interaction is presented in Figures 5 and 6.

The histograms showing residues of **D1,** Hydrogen, Hydrophobic and Favorable are represented in Figure 7. The dock score values include CDOCKER energy, Libdock score, Binding energy, Hydrogen bond interaction and distance are shown in Table 1.

The dock score values include CDOCKER energy, Libdock score, Binding energy, hydrophobic interaction and distance are shown in Table 2. Thus, molecular docking studies showed that the compound- 2, 6-bis (p-chlorobenzoyl) *3, 6-diphenyl-4-methylthiamorpholine 1, 1-dioxide*can be considered to be a better inhibitor with stronger affinity with inflammatory protein 2OFU.



A B

Figure 2: (A) Protein Preparation of 2OFU (B) Ligand Preparation of 2, 6-bis (p-chlorobenzoyl) 3, 6-diphenyl-4-methylthiamorpholine 1, 1-dioxide**.**

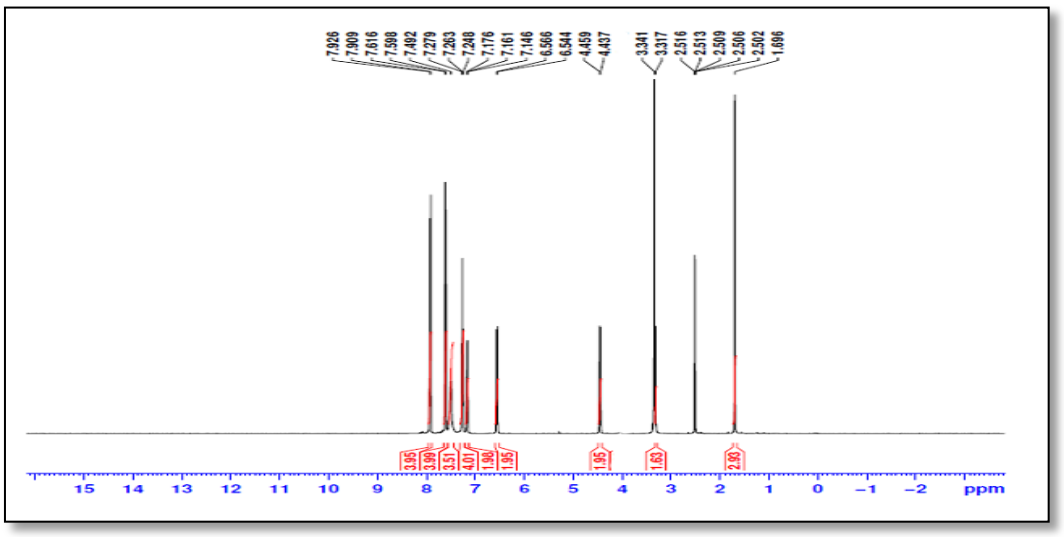


Figure 3: [1]H NMR spectrum of the compound2, 6-bis (p-chlorobenzoyl) *3, 6- diphenyl-4-methylthiamorpholine 1, 1-dioxide* (D1)

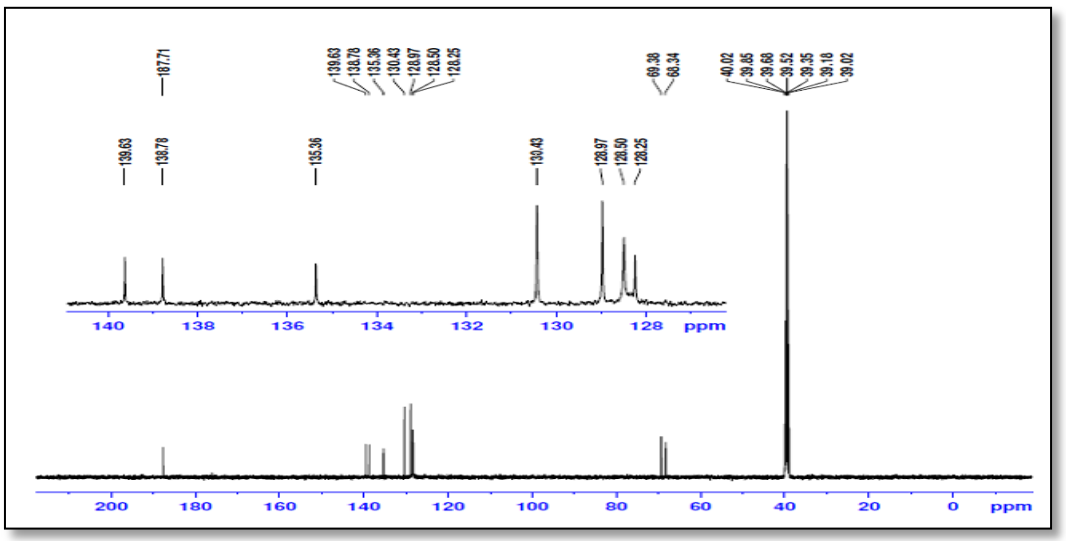


Figure 4: [13]C NMR Spectrum of the compound 2, 6-bis (p-chlorobenzoyl) *3, 6-diphenyl-4-methylthiamorpholine 1, 1-dioxide* (D1)

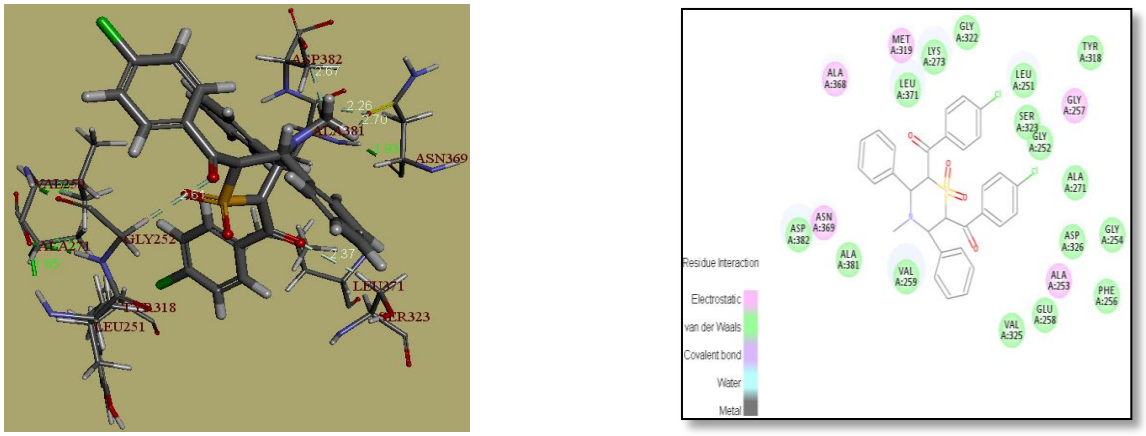


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Figure 5: Summary of docked pose of compound(**D1**)(A) Hydrogen bond interaction (B) 2D Diagram

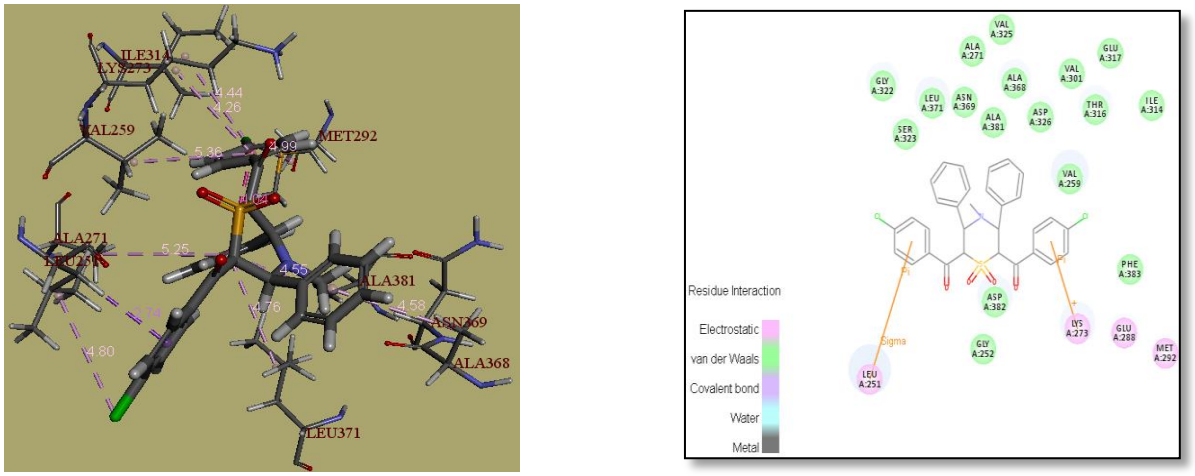
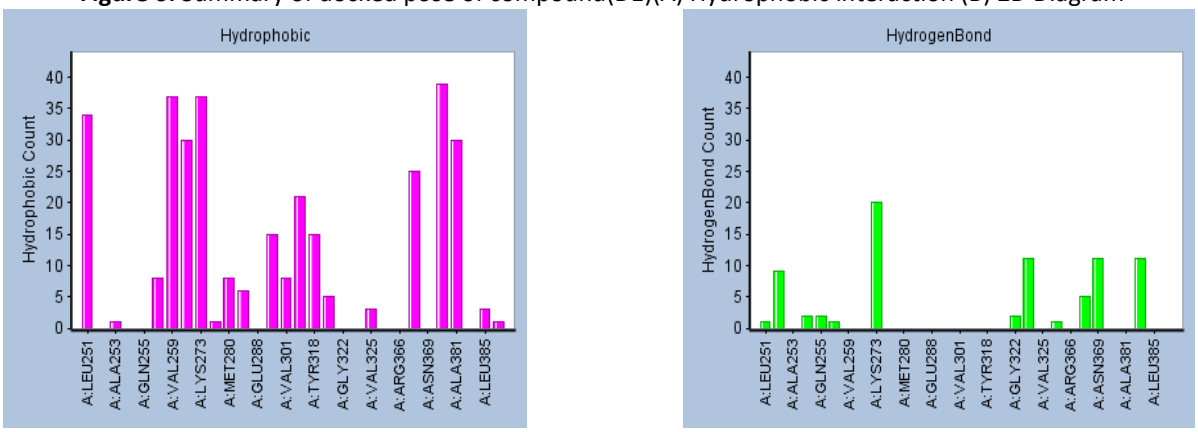


Figure 6: Summary of docked pose of compound(D1)(A) Hydrophobic interaction (B) 2D Diagram



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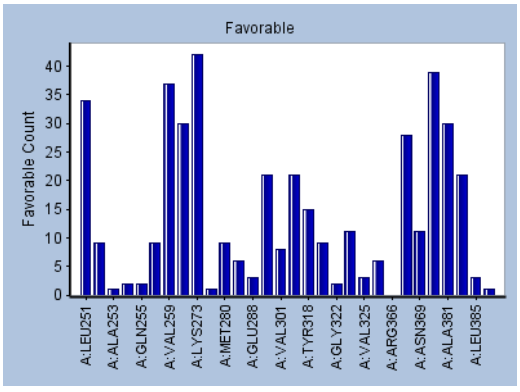

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Figure 7: Docked Residue Interaction Histograms (A) Hydrophobic (B) Hydrogen bond (C) Favorable Residues

Table 1: Results of Protein Ligand Complex with Hydrogen Bond Interaction

S. No.	Name	CDOCKER Energy	LibDock Score	Binding Energy	Hydrogen Bond Interaction	Distance (Å)
1	D1	23.375	65.444	-96.0845	C-H…O ASN 369 SER 323 C-H…O GLY 252 C-H…O C-H…O ASP 382 C-H…O ASN 369	2.26 2.37 2.61 2.67 2.70

Table2: Results of Protein Ligand Complex with Hydrophobic Interaction

S. No	Name	CDOCKER Energy	LibDock Score	Binding Energy	Hydrophobic Interaction	Distance(Å)
1	**D1**	23.779	66.578	-97.4584	LEU 251 C-H…N C-H…O LYS 273 C-H…O ILE 314 C-H…O ALA 381 C-H…O ALA 368 C-H…O LEU 371 C-H…O LEU 251 C-H…O MET 392 C-H…O ALA 271 C-H…O VAL 259	2.74 4.26 4.44 4.55 4.58 4.76 4.80 4.99 5.25 5.36

CONCLUSION

The present method is very simple, mild and efficient for the synthesis of 2, 6-bis (p-chlorobenzoyl) 3, 6-diphenyl-4-methylthiamorpholine 1, 1-dioxide.

In addition, this protocol has advantages in terms of short reaction time, solvent-free reaction, high yield, easy work-up and eco-friendly. We believe that this method is a useful addition to that of Substituted Thiamorpholine1,l-Dioxides compound which shows excellent biological activities. Docking studies were performed with inflammatory protein receptor using discovery studio 4.0.

From the discovery studio studies the best pose was obtained with least binding energy value calculated.

The interaction with active site residues indicate that **D1** can be considered as effective suppresser of inflammatory protein LCK. Synthesis of **D1** derivatives with more active constituents possessing anti-inflammatory can be performed.

Further *in vitro* and *in vivo* studies have to be performed to confirm the study.

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