Leishmaniasis is one of the most dreadful diseases as a leading cause of death in most of the developed countries. In the given study molecular docking study was performed on the library of coumarin analogues as anti-leishmaniasis agents. Total 300 coumarins analogues were taken from Pubmed and were studied using a molecular docking study on trypanothione reductase from Leishmania infantum (PDB code: 2JK6 and 2P18) and Leishmania mexicana (PDB code: 3PP7).

Molecular docking result revealed that most active compound COU-130 and COU-220 bind to the active site of the protein with amino acids present in the various proteins. In PDB 2JK6 the active compound binds to the amino acid thr-51 and ser-14 were binding to the active site, and in PDB 3PP7 the active compound binds amino acid thr-26 and in PDB 2P18 the active compound binds to the amino acid phe-219 and try-212. Further in vitro and in vivo study of selected coumarin analogues can be studied for their therapeutic potential in treating leishmaniasis.

Keywords: Coumarins, leishmaniasis, molecular docking.

INTRODUCTION
Objective of the current work was to identify more potent and highly effective novel compound for the treatment of leishmaniasis, which could be further used as a therapeutic agent in treating leishmaniasis.

Leishmaniasis is one of the most dreadful diseases and is a leading cause of deaths in developing countries. Leishmaniasis is a complex disease mostly found in the Indian sub-Continent caused by Leishmania spp. and carried by sand fly. Clinical classification of the disease comprises visceral and cutaneous Leishmaniasis, but the infection remains asymptomatic in many cases. Compared to chemical synthesis, plant derived natural products represents an attractive source of biologically active agents since they are natural and are economic to afford.

Leishmania has an intricate life cycle and one of the most developed forms, the amastigote which is present in the immunological cell of the host organism, which makes the targeting of the drug more challenging. Compared to chemical synthesis, plant derived natural products represents an attractive source of biologically active agents since they are natural and are economic to afford.

OBJECTIVE

Objective of the given work is to identify more potent and highly effective novel compound for the treatment of leishmaniasis, which could be further used as a therapeutic agent in treating leishmaniasis.

Excessive use of Antimonal as a primary drugs in treatment of the disease, their therapeutic window is short and they posses heavy metal toxicity as well. However they are being regularly used as a major drug in the third world countries.

MATERIALS AND METHODS

Molecular Docking: Molecular docking is an important tool in drug discovery and CADD; the importance of ligand-protein docking is that it predicts a predominant binding mode between the three dimensional protein structures and the ligand. Use of docking in virtual-screening has become very important because, it helps in the screening of large libraries. Using different scoring functions helps in understanding the binding affinity of the compound and proposing structural hypothesis. Molecular docking was performed by
Molecular docking was employed to identify the best geometry of ligand-receptor complex. In the present study 300 coumarin analogues were docked on the active site of three different [PDB code 2JK6; 3PP7; 2P18] retrieved from protein data bank. The coumarins are of great interest due to their pharmacological properties. In particular, their physiological, bacteriostatic and anti-tumor activity makes these compounds attractive backbone derivatisation and screening as novel therapeutic agents. Coumarins are naturally occurring benzopyrones. It consists of benzene ring with a pyrone ring. The coumarins consist of umbelliferone, esculetin and scopoletin. The coumarins are of great interest due to their pharmacological properties. In particular, their physiological, bacteriostatic and anti-tumor activity makes these compounds attractive backbone derivatisation and screening as novel therapeutic agents.

SAR prediction
On the basis of energy map generated from the following PDB, structures were selected on the basis of molecular weight. The energy map predicts the presence of different energies in the protein, which helps in the prediction of structures. On the basis of energy map it was determined that presence of an electron donating and withdrawing group will give a more efficient binding. The SAR prediction was done on Molegro Virtual Docker 6.0.

Docking Protocol

1. Protein preparation
Various proteins were downloaded from the Protein data bank PDB for standard bioinformatics (RSCB) that contains various X-ray crystal structures for proteins and other macromolecules. Then it was corrected by addition of missing hydrogen, atoms and incorrect bonding types and the charges were balanced.

2. Ligand preparation
Ligands were downloaded from the small molecules site ‘PubChem’, in SDF format.

3. Docking
Molecular docking was performed on the respective proteins retrieved from the protein data bank in Molegro Virtual Docker ver. 6.0.

4. Validation
Each and every docking run needs to be validated before the run. It’s carried out by re-docking the co-crystallized ligand that is present in the protein, with the same protein. The re-docked ligand is then compared with the original one by superimposition.

RESULTS AND DISCUSSION
Molecular docking results revealed that most active compound COU-130 and COU-220 binds to the active site of the protein [PDB code: 2JK6, 2P18 and 3PP7]. In PDB 2JK6 the active compound binds to the amino acid thr-51 and ser-14 were binding to the active site Figure 2a, and in PDB 3PP7 the active compound binds amino acid thr-26 Figure 2b and in PDB 2P18 the active compound binds to the amino acid phe-219 and try-212 Figure 2c.

Molecular docking helps in understanding the binding of the compound on the active site of the protein, this study helps in determining the binding of coumarin analogues which can be used in designing in effective and less toxic compounds against the treatment of Leishmaniasis. The crystal structure superposition of the structure and the final conformations suggests that the ligands were docked into the same site of binding and have a close resemblance to the pose of the ligand which was present in the crystal structure.

CONCLUSION
Molecular docking helped in understanding the efficacy of binding of the particular group of coumarins. The coumarins selected on the basis of the lowest binding energy. The molecules were selected on the basis of a lower molecular weight; so that it will have an efficient binding on the selected proteins. The given study is valuable, inexpensive and important for further in vitro and in vivo studies. Selected coumarins analogues can be studied for their therapeutic potential in treating Leishmaniasis.

ACKNOWLEDGMENT
I would like to thank Prof. Rajesh Sharma Head, School of Pharmacy, DAVV, Indore for providing the facility for the work. I would also like to thank Dr. E. Manivannan for guidance on this topic.

CONFLICT OF INTEREST
"No conflict of interest associated with this work”.

REFERENCES


Figure 1: Structure of (a). coumarin, (b). COU-130(7-(4-methyl-5-phenyl-2H-1,2,3-triazol-2-yl)-3-phenyl-2H-chromen-2-ol) (c). COU-220 (4-methoxy-2H-chromen-2-ol)

Table 1: Coumarin Analogues used in the study

<table>
<thead>
<tr>
<th>Coumarin Analogue</th>
<th>Structure</th>
</tr>
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<tbody>
<tr>
<td>1H-2-Benzopyran-1-one</td>
<td>5-formyl-6-hydroxy coumarin</td>
</tr>
<tr>
<td>2H-Chromen-2-one</td>
<td>2-oxo-2h-1-benzopyran-7-carboxylic acid</td>
</tr>
<tr>
<td>8-aza-coumarin</td>
<td>7,8-Methylenedioxy coumarin</td>
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<tr>
<td>3,4-dihydrocoumarin</td>
<td>2-Ox-2H-chromene-6-carboxylic acid</td>
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<td>5,6,7,8-tetradeuteriochromen-2-one</td>
<td>[1,3]Dioxolo[4,5-g]chromen-6-one</td>
</tr>
<tr>
<td>3,4,5,6,7,8-hexadeuteriochromen-2-one</td>
<td>2-Ox-2H-chromene-4-carboxylic acid</td>
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<tr>
<td>2H-1-Benzopyran-2-one</td>
<td>Coumarin-3-carboxylic acid</td>
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<td>Octahydrocoumarin</td>
<td>4-Hydroxy-5,7-dimethyl-2H-1-benzopyran-2-one</td>
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<tr>
<td>Octahydro-2H-chromen-2-one</td>
<td>4-Methoxy-3-methyl-2H-chromen-2-one</td>
</tr>
<tr>
<td>epoxy coumarin</td>
<td>7-(N,N-dimethylamino)-4-hydroxy coumarin</td>
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<tr>
<td>5-Methylcoumarin</td>
<td>2H-1-Benzopyran-2-one</td>
</tr>
<tr>
<td>7-Methylcoumarin</td>
<td>7-methoxy-8-methyl-chromen-2-one</td>
</tr>
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<td>3-Methylcoumarin</td>
<td>6-amino-7-methoxy-4-methylchromen-2-one</td>
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<td>8-Methylcoumarin</td>
<td>6-Hydroxy-2-oxo-2H-chromene-3-carboxylic</td>
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<td>4-Methylcoumarin</td>
<td>7-Hydroxy-3,4,8-trimethylcoumarin</td>
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<td>coumarin hydrazone</td>
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<td>2H-1-Benzopyran-3-carboxamide</td>
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<tr>
<td>coumarin-6-one</td>
<td>Coumarin-6-one</td>
</tr>
<tr>
<td>coumarin-6-one</td>
<td>Coumarin-6-one</td>
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<td>Coumarin-6-one</td>
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<td>coumarin-6-one</td>
<td>Coumarin-6-one</td>
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<tr>
<td>Name</td>
<td>Structure</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
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<tr>
<td>Coumarin 3,4-epoxide</td>
<td>5-amino-6-hydroxy-4-methylcoumarin</td>
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<td>8-Hydroxycoumarin</td>
<td>8-amino-7-hydroxy-4-methyl-2H-chromen-2-one</td>
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<td>6-Hydroxycoumarin</td>
<td>7-dihydroxy-4-methyl coumarin</td>
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<td>2-Thiocoumarin</td>
<td>methoxy-8-hydroxy coumarin</td>
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<td>8-amino-3,4-dihydro-coumarin</td>
<td>4-Hydroxy-7-methoxy coumarin</td>
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<td>coumarin water</td>
<td>4-Methylphapthetin</td>
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<td>4-Methyl(5,6,7,8-2H4)coumarin</td>
<td>5,7-dihydroxy-4-methylcoumarin</td>
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<tr>
<td>7-HydroxyCoumarin-13C3</td>
<td>6-Methylcesuletin</td>
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<td>7-hydroxycoumarin</td>
<td>6-Methylcesuletin</td>
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<td>7-Hydroxy Coumarin-13C6</td>
<td>coumarin ethanol</td>
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<td>6-Methyloctahydrocoumarin</td>
<td>6-hydroxy-4,4-dimethyl-3,4-dihydro-2H-1-benzopyran-2-one</td>
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<td>7-Ethynylcoumarin</td>
<td>7-Mercapto-4-methyl-2H-chromen-2-one</td>
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<td>ethynyl coumarin</td>
<td>4-hydroxy-3-(hydroxyl amino)coumarin</td>
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<td>3-Cyanocoumarin</td>
<td>3-Amino-4,7-dihydroxy coumarin</td>
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<td>8-formyl coumarin</td>
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<td>4,6,7-trihydroxy coumarin</td>
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<tr>
<td>2-oxo-2H-chromene-4-carbaldehyde</td>
<td>4,5,7-Trihydroxy coumarin</td>
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<td>Coumarin-6-carboxaldehyde</td>
<td>2H-1-Benzopyran-2-one</td>
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<td>3,6-Dimethyl-2H-1-benzopyran-2-one</td>
<td>3-Methyl-6-chlorocoumar</td>
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<td>4,7-dimethylchromen-2-one</td>
<td>6-chloro-7-hydroxy-2H-chromen-2-one</td>
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<td>3-Ethyl-2H-1-benzopyran-2-one</td>
<td>methyl coumarin hydrochloride</td>
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<td>6-aminomethylcumarin</td>
<td>6-Aminocoumarin hydrochloride</td>
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<td>4-Methylumbelliferson sodium</td>
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<td>5-methoxy-2H-chromen-2-one</td>
<td>7-(Propargyloxy) coumarin</td>
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<td>7-hydroxy-8-methylcumarin</td>
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<td>Monosodium esculetin</td>
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<td>4-Methoxy coumarin</td>
<td>6-cyano-7-methoxy coumarin</td>
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<td>8-methoxycoumarin</td>
<td>3-azidomethyl coumarin</td>
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<tr>
<td>6-Hydroxy-4-methylcumarin</td>
<td>4-(allylarnino) coumarin</td>
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</tbody>
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7-Methoxycoumarin
coumarin-6,8-dicarbaldehyde
6-(isoxazol-5-yl)coumarin
coumarin-6,7-dicarbaldehyde
6-(2-butyloxy)coumarin
3,4-Diaminocoumarin
dihydrofuro-[3,2-g]coumarin-6-one
3-(1,3,4-triazol-2-yl)coumarin
2H-1-Benzopyran-2-one
3-Glyoxylycoumarin
7-Dimethylamino-4-ethynyl-coumarin
3-methyl-thia-coumarin
3-allyl-4-hydroxycoumarin
3-cyano-4-n-propyl coumarin
hydroxyaminocoumarin
7-glycidycoumarin
4-(trifluoromethyl)coumarin
aminohydroxy coumarin
3-acetyl-5-methyl-coumarin
3-(trifluoromethyl)chromen-2-one
4,7-Dihydroxycoumarin
4-allyl-3-hydroxy-coumarin
4-oxadiazolyl coumarin
5,7-dihydroxy-2H-chromen-2-one
6-methyl-3-acetyl coumarin
3-(1,3,4-oxadiazol-2-yl)coumarin
6,7-Dihydroxycoumarin
6-(Allyloxy)coumarin
6-(2-butyloxy)coumarin
7,8-Dihydroxycoumarin
4-allyloxy coumarin
4-Methyl-7-(3-hydroxy-1-propynyl)coumarin
fluoromethyl coumarin
7- Allyloxy coumarin
7-(2-Butyloxy)coumarin
8-fluoro-4-hydroxy-2H-chromen-2-one
3-acetyl-7-methyl-2H-chromen-2-one
3-(2,5-Dihydrofuran-2-yl)coumarin
3-Chlorocoumarin
coumarin KOH
7-(1-Methylpropargyloxy)coumarin
4-chloro-2H-chromen-2-one
3-Butylcoumarin
4-(4-Hydroxy-1-butylnyl)coumarin
6-Chlorocoumarin
3-azido-7-hydroxycoumarin
Giparmene
coumarin hydrochloride
3-Acetamidocoumarin
6-prenyl-coumarin
2H-1-Benzopyran-2-one
6-Acetamidocoumarin
dimethyl-allyl coumarin
6-Methyl-2-oxo-2H-chromene-3-carbonitride
coumarin isothiocyanate
isopentenyl coumarin
3-Cyano-4-methylcoumarin
dimethylaminomethyl coumarin
3-(4-Pentenyl)coumarin
4-Coumarin
dimethylaminomethyl coumarin
3-(1’,1’-dimethylallyl) coumarin
7H-Furo[3,2-g]chromen-7-one
7-(Ethylamino)-4-methylcoumarin
4,4-dichloro-2H-chromen-2-one
7H-Furo[3,2-g]chromen-7-one
cyclopropyl coumarin
4,6-Dimethyl-7-methylaminocoumarin
N-(Coumarin-3-yl)acrylamide
isopropenyl coumarin
7-Dimethylamino-4-methylcoumarin
4-azido-3-ethyl-coumarin
coumarin isocyanate
5-Fluoroangelicin
5- Allyl-6-(methyl amino)coumarin
7-(2-oxoethyl)coumarin
acetylated coumarin
4-Methyl-6,7,8,9-tetrahydro-2H-pyran-[3,2-g]quinolin-2-one;
3-Acetylcoumarin
7-carbonyl-methoxy coumarin
7-(Acryloyloxy)coumarin
4-isopropyl coumarin
carbonyl methoxy coumarin
4-Methoxypsoralen
4,5,7-Trimethyl-2H-chromene-2-one
7-hydroxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde
8-Methoxypsoralen
5,7,8-trimethyl-coumarin
Acetaldehyde
6-(but-3-enyloxy)-coumarin
3-Propylcoumarin
4-Formyl-7-methoxy coumarin
6-crotyloxy-coumarin
4-hydroxy-3-iminomethyl-coumarin
7-acetoxycoumarin
(e)-6-(2-butenyloxy)coumarin
2-oxo-2H-chromene-3-carboxamide
2H-1-Benzopyran-4-carboxylic acid
7-crotyloxy-coumarin
4-(2-aminoethyl)-coumarin
(2-Oxo-2H-chromen-3-yl)acetic acid
(E)-7-(2-butenyloxy)coumarin
7-Dimethylaminocoumarin
coumarin-4-acetic acid
2H-1-Benzopyran-2-one
4-(ethylamino)chromen-2-one
Methyl coumarin-3-carboxylate
7-(but-3-enyloxy)-coumarin
7-(Ethylamino)coumarin
coumarin-4-carboxamidoxime
4-(but-3-enyloxy)-coumarin
coumarin boronic acid
7-amino-4-carbamoyl coumarin
2-Propenoic acid
(2-oxochromen-7-yl)boronic acid
6-hydroxy-5,7,8-trimethyl coumarin
4-azido-3-ethyl-chromen-2-one

Table 2: Code with resolution

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<thead>
<tr>
<th>Code</th>
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<th>Resolution</th>
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<tr>
<td>2JK6</td>
<td>Structure of Trypanothione Reductase from Leishmania infantum</td>
<td>2.95 Å</td>
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<tr>
<td>3PP7</td>
<td>Crystal structure of Leishmania mexicana pyruvate kinase in complex with the drug suramin, an inhibitor of glycolysis.</td>
<td>2.35 Å</td>
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<tr>
<td>2P18</td>
<td>Crystal structure of the Leishmania infantum glyoxalase II</td>
<td>1.8 Å</td>
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Figure 2: Binding to the active site

Figure 3: Energy Maps

Table 3: The Molecular docking score

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<tr>
<th>Compound Name</th>
<th>PDB code</th>
<th>Moldock score</th>
<th>Rerank score</th>
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<tr>
<td>COU-130</td>
<td>2JK6</td>
<td>-172.948</td>
<td>-122.454</td>
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<tr>
<td>COU-130</td>
<td>3PP7</td>
<td>-127.413</td>
<td>-100.061</td>
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<td>COU-220</td>
<td>2P18</td>
<td>-116.818</td>
<td>84.5171</td>
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