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RESEARCH ARTICLE

COUMARIN ANALOGUES AS A POTENTIAL INHIBITOR OF LEISHMANIASIS: A MULTI-TARGETING PROTEIN INHIBITION APPROACH BY MOLECULAR DOCKING

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ABSTRACT
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.

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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. Leishmaniase 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[1]. 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[2]. 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 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 Antimonals 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[3,4].

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 Molegro Virtual Docker 6.0, molecular docking was employed to identify the best geometry of ligand-

receptor complex. In the present study 300 coumarin analogue were docked on the active site of three different [PDB code 2JK6[5]; 3PP7[6]; 2P18[7] retrieved from protein data bank.

The coumarins are of great interest due to their pharmacological properties[8]. In particular, their physiological, bacteriostatic and anti-tumor activity makes these compounds attractive backbone derivatisation and screening as novel therapeutic agents[9].

Coumarins are naturally occurring benzopyrones. It consists of benzene ring with a pyrone ring. The coumarins consist of umbelliferone, esculetin and scopoletin[10]. 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[11].

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 a electron donating and with drawing group will give a efficient binding. The SAR prediction was done on Molegro Virtual Docker 6.0.

Docking Protocol

1. Protein prepration

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 prepration

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[12].

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 Leishmanisis.

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.

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CONFLICT OF INTEREST

"No conflict of interest associated with this work".

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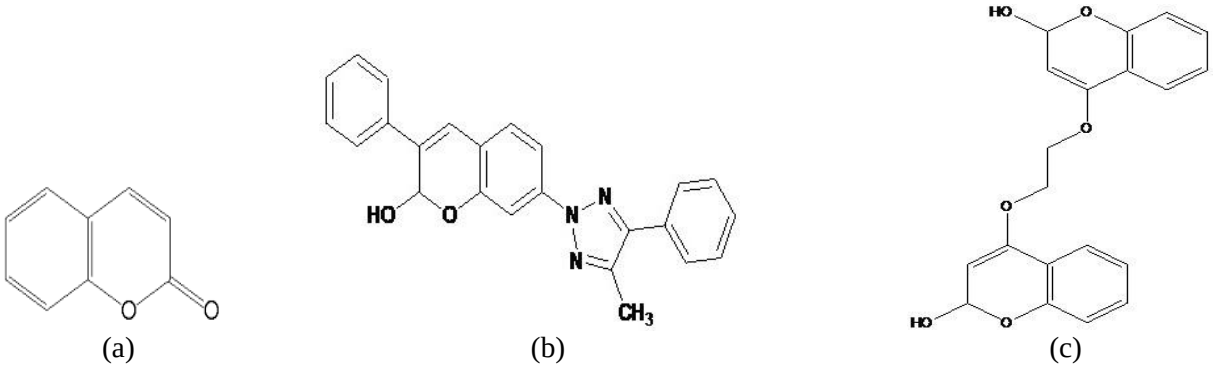


(a) (b) (c)

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

1H-2-Benzopyran-1-one	5-formyl-6-hydroxy coumarin	6-methoxy-3,4-dimethyl-coumarin
2H-Chromen-2-one	2-oxo-2h-1-benzopyran-7-carboxylic acid	2h-1-benzopyran-2-one
8-aza-coumarin	7,8-Methylenedioxycoumarin	7-Hydroxy-3,4,8-trimethylcoumarin
3,4-dihydrocoumarin	2-Oxo-2H-chromene-6-carboxylic acid	7-hydroxy-4-propyl-2H-chromen-2-one
5,6,7,8-tetradeuteriochromen-2-one	[1,3]Dioxolo[4,5-g]chromen-6-one	4-Ethyl-5-hydroxy-7-methyl-2H-chromen-2-one
3,4,5,6,7,8-hexadeuteriochromen-2-one	2-Oxo-2H-chromene-4-carboxylic acid	7-methoxy-3,4-dimethyl-2H-chromen-2-one
2H-1-Benzopyran-2-one	Coumarin-3-carboxylic acid	7-Ethoxy-4-methylcoumarin
Octahydrocoumarin	2H-1-Benzopyran-2-one	4,4,6,8-Tetramethyl-2-chromanone
Octahydro-2H-chromen-2-one	4-Hydroxy-5,7-dimethyl-2H-1-benzopyran-2-one	2H-1-Benzopyran-3-carboxamide
epoxy coumarin	4-Methoxy-3-methyl-2H-chromen-2-one	7-(N,N-dimethylamino)-4-hydroxycoumarin
5-Methylcoumarin	2H-1-Benzopyran-2-one	2H-1-Benzopyran-2-one
7-Methylcoumarin	7-methoxy-8-methyl-chromen-2-one	7-Amino-4-(methoxymethyl)-2H-chromen-2-one
3-Methylcoumarin	5-hydroxy-4,7-dimethyl-2H-chromen-2-one	6-amino-7-methoxy-4-methylchromen-2-one
8-Methylcoumarin	7-Methoxy-4-methylcoumarin	2-oxo-2H-chromene-3-carbothioamide
4-Methylcoumarin	7-Ethoxycoumarin	Artemicapin C
6-Methylcoumarin	7-hydrazinyl-4-methyl-2h-chromen-2-one	6-Hydroxy-2-oxo-2H-chromene-3-carboxylic acid
coumarin hydrazone	4-Methylamino-3-aminocoumarin	8-hydroxy-2-oxo-2H-chromene-3-carboxylic acid
4-Amino-chromen-2-one	3,4-dihydro-4,5,7-trimethyl	7-Hydroxycoumarin-3-carboxylic acid
3-Aminocoumarin	2H-1-Benzopyran-2-one	4-amino-3-nitro-2H-chromen-2-one
6-Aminocoumarin	7-Nitrocoumarin	5-Methoxy-7-(hydroxymethyl)coumarin
coumarin-6-one	7-amino-3-hydroxy-4-methyl-coumarin	Hydroxymethylmethoxycumarin
4-Hydroxycoumarin	Amino methoxy coumarin	2H-1-Benzopyran-2-one
Chroman-2,3-dione	4-methyl-1-aminoxy-coumarin	5,6-dihydroxy-4,7-dimethyl-coumarin
5-Hydroxycoumarin	7-amino-4-methoxy-coumarin	7-(2-hydroxyethyloxy)coumarin
7-hydroxycoumarin	7-hydroxy-4-(amino methyl)coumarin	coumarin acetic acid

Cont.....

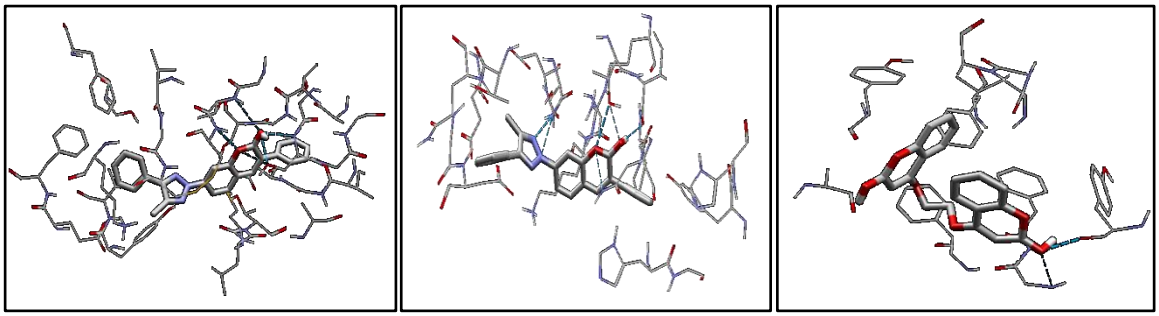
Coumarin 3,4-epoxide	5-amino-6-hydroxy-4-methyl-coumarin	3,4-Dimethoxy-2H-chromen-2-one
8-Hydroxycoumarin	8-amino-7-hydroxy-4-methyl-2H-chromen-2-one	2h-1-benzopyran-2-one
6-Hydroxycoumarin	7-dihydroxy-4-methyl coumarin	4,5-Dimethoxy-2H-1-benzopyran-2-one
3-Hydroxycoumarin	4-methyl-7 -hydroxy-coumarin alcohol	2H-1-Benzopyran-2-one
2-Thiocoumarin	methoxy-8-hydroxy coumarin	4-ethyl-5,7-dihydroxychromen-2-one
8-amino-3,4-dihydro-coumarin	4-Hydroxy-7-methoxycoumarin	7-Hydroxy-4-methoxymethylcoumarin
coumarin water	4-Methyldaphnetin	7-Hydroxy-6-methoxy-4-methyl-2H-chromen-2-one
4-Methyl(5,6,7,8-2H4)coumarin	5,7-dihydroxy-4-methylcoumarin	4,7-Dimethoxycoumarin
7-Hydroxy Coumarin-13C3	4-Methylesculetin	3,7-Dimethoxycoumarin
7-hydroxycoumarin	6-Methylesculetin	8-Hydroxy-7-methoxy-4-methyl-2H-chromen-2-one
7-Hydroxy Coumarin-13C6	coumarin ethanol	4-Methyl-7-methoxy-6-hydroxycoumarin
6-Methyloctahydrocoumarin	6-hydroxy-4,4-dimethyl-3,4-dihydro-2H-1-benzopyran-2-one	7,8-Dimethoxycoumarin
7-Ethynylcoumarin	7-Mercapto-4-methyl-2H-chromen-2-one	6,7-dimethoxycoumarin
ethynyl coumarin	4-hydroxy-3-(hydroxyl amino)coumarin	5,7-Dimethoxycoumarin
3-Cyanocoumarin	3-Amino-4,7-dihydroxycoumarin	6-hydroxy-4,4,7-trimethyl-3,4-dihydrocoumarin
8-formyl coumarin	7-amino-4-fluoromethyl coumarin	6-Methoxy-4,4-dimethyl-2-chromanone
2-Oxo-2H-chromene-7-carbaldehyde	4,6,7-trihydroxycoumarin	6-hydroxy-5,7,8-trimethyl-chroman-2-one;
2-oxo-2H-chromene-4-carbaldehyde	4,5,7-Trihydroxycoumarin	5-Methyl-4-(methylthio)coumarin
Coumarin-6-carboxaldehyde	2H-1-Benzopyran-2-one	4-Hydroxy-3-nitrocoumarin
3,6-Dimethyl-2H-1-benzopyran-2-one	3-Methyl-6-chlorocoumarin	7-Hydroxy-8-(hydroxyaminomethyl)coumarin
4,7-dimethylchromen-2-one	6-chloro-7-hydroxy-2H-chromen-2-one	7-Hydroxy-8-(aminooxy methyl)coumarin
3-Ethyl-2H-1-benzopyran-2-one	methyl coumarin hydrochloride	3-Amino-4,7-dihydroxy-8-methylcoumarin
6-aminomethylcoumarin	6-Aminocoumarinhydrochloride	8-fluoro-3-carboxy-coumarin
6-Amino-4-methyl-2H-chromen-2-one	4-Methylumbelliferone sodium	4,7,8-trihydroxy-3-methyl
3-(Aminomethyl)-2H-chromen-2-one	6,7-Dihydroxycoumarin sodium salt	7,8-Dihydroxy-6-methoxycoumarin
7-Amino-4-methylcoumarin	propynyloxy coumarin	7-ethoxy-4-fluoro-coumarin
4-Hydroxy-3-methyl-2H-chromen-2-one	4-hydroxy-3-(prop-2-ynyl)-2H-coumarin	7-(2-fluoroethyloxy)-coumarin
4-Hydroxy-6-methylcoumarin	6-(2-propynyl-oxy)coumarin	Coumarin-3-carboxylic acid chloride
Hydroxymethyl coumarin	2H-1-Benzopyran-2-one	chloromethyl amino coumarin
6-(hydroxymethyl)-2H-chromen-2-one	2H-1-Benzopyran-2-one	3-Chloro-7-hydroxy-4-methyl-2H-chromen-2-one
5-methoxy-2H-chromen-2-one	7-(Propargyloxy) coumarin	4-(chloromethyl)-6-hydroxy-2H-chromen-2-one
7-hydroxy-8-methylcoumarin	4-propargylthio-coumarin	hydroxybenzo coumarin
5-methylumbelliferone	Monosodium esculetin	3-furyl coumarin
4-methylumbelliferone	cyanomethoxy coumarin	3-furanyl coumarin
4-Methoxycoumarin	6-cyano-7-methoxy-coumarin	6-(3-pyrazolyl)coumarin
8-methoxycoumarin	3-azidomethyl coumarin	pyrazolyl coumarin
6-Hydroxy-4-methylcoumarin	4-(allylamino)coumarin	Benzo[d,E]-3-H-coumarin

Cont.....

7-Methoxycoumarin	coumarin-6,8-dicarbaldehyde	6-(isoxazol-5-yl)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-Glyoxyloylcoumarin	7-Dimethylamino-4-ethynyl-coumarin
3-methyl-thia-coumarin	3-allyl-4-hydroxycoumarin	3-cyano-4-n-propyl coumarin
hydroxyamino-coumarin	7-glycidylcoumarin	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-butynyloxy)coumarin
7,8-Dihydroxycoumarin	4-allyloxycoumarin	4-Methyl-7-(3-hydroxy-1-propynyl)coumarin
fluoromethyl coumarin	7-Allyloxycoumarin	7-(2-Butynyloxy)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-butynyl)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-carbonitrile	coumarin isothiocyanate	isopentenyl coumarin
3-Cyano-4-methylcoumarin	dimethylaminomethyl coumarin	3-(4-Pentenyl)coumarin
Angelicin	4-(propylamino)chromen-2-one	3-(1',1'-dimethylallyl)-coumarin
7H-Furo[3,2-g]chromen-7-one	7-(Ethylamino)-4-methylcoumarin	,4-dichloro-2h-chromen-2-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	acetylhydroxy-coumarin	4-Methyl-6,7,8,9-tetrahydro-2H-pyrano[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-chromen-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-methoxycoumarin	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

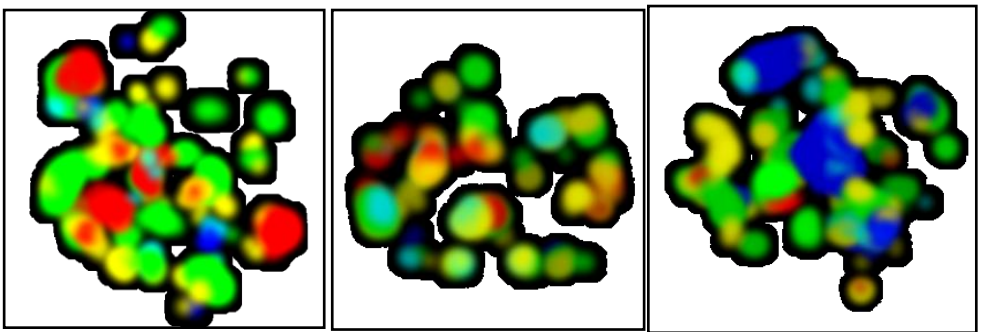
Table 2: Code with resolution

Code	Name	Resolution
2JK6	Structure of Trypanothione Reductase from Leishmania infantum	2.95 Å
3PP7	Crystal structure of Leishmania mexicana pyruvate kinase in complex with the drug suramin, an inhibitor of glycolysis.	2.35 Å
2P18	Crystal structure of the Leishmania infantum glyoxalase II	1.8 Å



a **b** **c**

Figure 2: Binding to the active site



2JK6 **2P18** **3PP7**

Figure 3: Energy Maps

Green: Steric Favourable, Blue: H-acceptor, Yellow: H-donor, Red: Electostatic

Table 3: The Molecular docking score

Compound Name	PDB code	Moldock score	Rerank score
COU-130	2JK6	-172.948	-122.454
COU-130	3PP7	-127.413	-100.061
COU-220	2P18	-116.818	84.5171