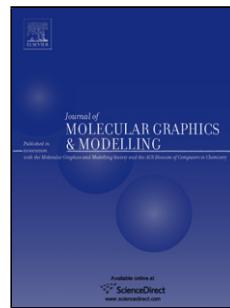


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Author: Ghalia Sabbagh Noura Berakdar



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Docking Studies of Flavonoid Compounds as Inhibitors of β -ketoacyl acyl carrier protein synthase I (Kas I) of *Escherichia Coli*

Ghalia Sabbagh* and Noura Berakdar**

Department of Pharmaceutical Chemistry, Faculty Of Pharmacy, University of Aleppo

Aleppo University Street, Aleppo, Syria

*professor at the department of Pharmaceutical Chemistry and Quality Control

**MSC Department of Pharmaceutical Chemistry, Of Pharmacy, University of Aleppo Syria

Graphical abstract

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Highlights.

- β -ketoacyl-acyl carrier protein synthase I (FabB) may be one of the most attractive biochemical pathways to be used as the target for new antibacterial agents.
- Flavonoids are naturally occurring polyphenolic compounds that they have been reported to possess many useful properties, including anti-inflammatory activity, oestrogenic activity, enzyme inhibition, antimicrobial activity.
- We suggest two flavonoid compounds ,Genistein and Isorhamnetin, can be used as a hit molecule against the fatty acid synthase in bacteria.
- Genistein and Isorhamnetin, have similar binding poses and interactions with β -ketoacyl acyl carrier protein synthase I compared to the standard (Thiolactomycin).
- This *in silico* study is actually an added advantage to screen the β -ketoacyl acyl carrier protein synthase I inhibition.

ABSTRACT

Escherichia coli is one of the most frequent causes of many common bacterial infections, including cholecystitis, bacteremia, cholangitis, urinary tract infection (UTI), traveler's diarrhea and other clinical infections such as neonatal meningitis and pneumonia. The fatty acid biosynthesis is essential for the bacterial viability and growth. There are three types of β -ketoacyl acyl carrier protein synthase (KAS) which are important for overcoming the bacterial resistance problem. β -ketoacyl acyl carrier protein synthase I (KAS I) is member of the condensing enzyme family, which is a

key catalyst in bacterial fatty acid biosynthesis, and thus an attractive target for novel antibiotics related to the elongation of unsaturated fatty acids in bacterial fatty acid synthesis and can be a good therapeutic target of designing novel antibiotics. In this report, we performed docking study of *Escherichia coli* (KAS I) and 50 flavonoids. Out of these 50 flavonoids, there are two compounds, genistein and isorhamnetin, that showed the superior binding energy while fully satisfying the conditions of drug likeliness. The predicted binding energy of Genistein and Isorhamnetin toward KAS I are -135.76 kcal/mol and -132.42 kcal/mol, respectively. These energies favorably compare to the biding energy of known drugs Thiolactomycin and Cerulenin that are -90.26 kcal/mol and -99.64 kcal/mol, respectively. The method used was docking with the selected *Escherichia coli* (KAS I-PDB ID -1FJ4) using iGemdock. This was also found to obey the Lipinski's guidelines of five and to show the drug likeliness and bioavailability.

Key Words: *E. coli*, FAS, KAS I, Flavonoid, Docking, iGemdock.

Abbreviations

ACP: Acyl Carrier Protein.

ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity.

E. coli: *Escherichia coli*.

FAS: Fatty Acid Synthases.

FabB: β -ketoacyl -ACP synthase I

FabF: β -ketoacyl -ACP synthase II

FabH: β -ketoacyl -ACP-synthase III

iGemdock: iGeneric Evolutionary Method Docking

KAS: β - ketoacyl acyl carrier protein synthase.

PDB: Protein Data Bank.

QSAR: Quantitative structure–activity relationship.

TLM: Thiolactomycin.

INTRODUCTION

Escherichia coli (*E. coli*) is a gram-negative, facultative anaerobe, rod-shaped bacterium of the genus Escherichia that is commonly found in the lower intestine of warm-blooded organisms (endotherms)^[1]. Most (*E. coli*) strains are harmless but some serotypes can cause serious food poisoning in their hosts and are, occasionally, responsible for product recalls due to food contamination^[2,3].

The harmless strains are part of the normal flora of the gut, and can benefit their hosts by producing vitamin K₂^[4] and preventing colonization of the intestine with pathogenic bacteria^[5, 6]. (*E. coli*) and other facultative anaerobes constitute about 0.1% of gut flora^[7] and fecal oral transmission is the major route through which pathogenic strains of the bacterium cause disease. Cells are able to survive outside the body for a limited amount of time which makes them ideal indicator organisms to test environmental samples for fecal contamination^[8,9]. There is, however, a growing body of research that has examined environmentally persistent (*E. coli*) which can survive for extended periods outside of the host^[10].

Drug resistance in infectious organisms has become a serious medical problem and the inhibition of the fatty acid synthesis has emerged as a promising target for the development of novel therapeutic agents. Lipid synthesis is not only essential to cell viability but also to specificity for bacteria^[11]. There are two major types of the fatty acid synthesis. Type I is a system exists in higher organisms such as mammals^[12]. Type II is fatty-acid synthases exist in bacteria and plants. The type II system has been most extensively studied in *Escherichia coli*. It is well known that three types of β -ketoacyl acyl carrier protein synthase (KAS) enzymes, KAS I (FabB), KAS II (FabF) and KAS III (FabH) have emerged as important regulators of the initiation and elongation steps in the pathway. These enzymes catalyze the Claisen condensation reaction, transferring an acyl primer to malonyl-ACP and thereby creating a β -ketoacyl -ACP that has been lengthened by two carbon units^[13].

(KAS I) is related to the elongation of an intermediate in unsaturated fatty acid synthesis, whereas (KAS II) controls the thermal regulation of fatty acid composition. (KAS III) catalyzes the first condensation step in the pathway and is thus ideally situated to govern the rate of fatty acid synthesis. (Kas I) is composed of two identical 42.6-kDa subunits homodimer and has both malonyl-ACP and fatty acyl-ACP binding sites^[12]. The active site of (KAS I) forms a catalytic triad hole which consists of His-His-Cys^[14, 15]. This illustrates that the two histidine active sites architecture are critical to enzyme-antibiotic interaction. These data provide a structural framework for understanding antibiotic sensitivity within this group of enzymes^[16].

Flavonoids are becoming the subject of medical research and they have been reported to possess many useful properties, including anti-inflammatory, oestrogenic, enzyme inhibition, antimicrobial^[17, 18], antiallergic, antioxidant^[19], vascular and cytotoxic antitumour activities. The basic structural feature of flavonoid compounds is the 2-phenyl-benzo pyrane or flavane nucleus which consists of two benzene rings (A and B) linked through a heterocyclic pyrane ring (C)^[20], (Figure 1). They can be further classified by their chemical structures, that is flavones, flavonols, flavanols, flavanones, isoflavones, and anthocyanins . The *in silico* method is used to analyze a set of drug candidates toward the known binding site, to generate candidate

molecules, to check for their drug likeness, to dock them with the target, to rank them according to their binding energies, and further to optimize the molecules.

In this work, we computationally predict that two flavonoids genistein and isorhamnetin can be used as potential drug candidates against Gram-negative *Escherichia coli* (*E. coli*) based on their good binding energy toward KAS I active site.

MATERIALS AND METHODS

Receptors selected for this study

The protein -required for the docking studies- has been retrieved from the Protein Data Bank (PDB) [21]. The protein has (1FJ4) a resolution factor of 2.35 Å.

We defined the active site of (KAS I) based on the x-ray complex structure of KAS I protein and Thiolactomycin. TLM is a unique thiolactone molecule containing natural product that inhibits bacterial and plant type II fatty acid synthases (FASII) (Figure 2), but not type I, which provide essential building blocks for bacterial cell walls [23,24]. Thiolactomycin inhibits bacterial cell growth through inhibition of the β -ketoacyl -ACP synthase activity of type II fatty acid synthases. TLM has only modest antibacterial activity due to drug resistance *E. coli* exhibits to this drug [22, 24,25].

Preparation of Ligand Library

Chemical structures were retrieved from ZINC database [26]. The mol2 structural formats of all the 50 components were generated from the ZINC database. The set of ligand molecules selected for this study were 50 flavonoids compounds from different plant sources and which have been selected after an extensive literature survey that was performed to hunt for flavonoids that have antimicrobial activities via pubmed site [27-34]. The literature on flavonoids and antimicrobial activities have been collected from this database. The flavonoids have aroused considerable interest recently because of their potential beneficial effects on human health. They also have been reported to have anti-microbial, anti-inflammatory, anti-tumor and anti-oxidant activities [35- 67] and many flavonoids display low toxicity [68] in mammals. In fact we have selected 50 flavonoid without sugars (only the aglycones) as the anti-bacteria effectiveness increased when the sugar is separated [68]. They were also selected in accordance with the Lipinski's guidelines of five. Table I is shown the chemical structure of 50 flavonoids wtih the two reference.

These phytochemicals were screened *in silico* for their inhibitory activity against the selected enzyme molecules; in comparison with Thiolactomycin (TLM), Cerulenin (CER) which are known as inhibitors of (KAS I) [69,70]. Therefore, we found a natural compounds that have the inhibitory properties of the enzyme (Kas I), and with properties better than TLM and CER. Cerulenin is an irreversible inhibitor of β - ketoacyl-ACP synthases I and II but differs in the fact that Cerulenin is not a selective antibacterial because it is also a potent inhibitor of the condensation reaction catalyzed by the mammalian multifunctional (type I) fatty-acid synthase [71]. In fact

this study shows that the most of flavonoids were better than 3,6-Dihydroxyflavone which was reported [72].

Docking and Screening

In this research, we use iGemdock program, which was used in various previous researchs^[73, 74, 75] and it is available for free^[76,77].

iGemdock v2.1

Docking software iGemdock was used to dock the protein of the enzyme (Kas I) with 50 flavonoids. IGemdock is an integrated virtual screening (VS) environment from preparations through post-screening analysis with pharmacological interactions iGemdock provides interactive interfaces to prepare both the binding site of the target enzyme and the screening compound library. Each compound in the library is then docked into the binding site by using the in-house docking tool iGemdock.

Subsequently, iGemdock generates protein-compound interaction profiles of electrostatic (E), hydrogen-bonding (H) and Van der Waal's (V) interactions. Based on these profiles and compound structures. IGemdock infers the pharmacological interactions and clusters the screening compounds for the post-screening analysis. Finally, iGemdock ranks and visualizes the screening compounds by combining the pharmacological interactions and energy-based scoring function of iGemdock.

Rapid virtual screenings of the 50 ligand compounds were performed in the docking tool iGemdock. The docking used the "accurate" protocol by setting a population size of 300, with 80 generations and 10 solutions. After the completion of the docking, the post docking analysis was performed to find the docking pose and its energy values. The empirical scoring function of iGemdock was estimated using:

$$\text{Energy} = \text{vdW} + \text{Hbond} + \text{Elec}$$

Table II illustrates the result of the ten compounds based on the most favorable binding energy of flavonoids.

RESULTS AND DISCUSSION

In silico, docking studies were carried out using iGemdock v2.1. The results showed that all the selected flavonoids presented more favorable binding energy ranging from -135.76 kcal/mol to -103.82 kcal/mol when compared to that of the reference (-90.26 kcal/mol). Therefore, these molecular docking analyses could lead to further development of potent (Kas I) inhibitors for the prevention and treatment for diseases caused by (*E. coli*). Table II summarizes results of the docking study based on binding energies. The energy, representing the best binding energy of inhibitors of this enzyme, was identified by the molecular docking procedure. In addition, Figure 3 shows the TLM mimics malonyl-ACP in the (Kas I) active site and binds on the malonyl-ACP side of the active site. It forms two strong hydrogen bonds with both active site histidines His333 and His298 contribute to the stabilization of the protein-inhibitor complex. Also, figure 4 illustrates the interactions of genistein and isorhamnetin with protein pocket which have the most favourable binding energy and clarifies the hydrogen bonding and Van der Waal's interactions with the amino acids.

Table III shows pharmacological interactions and residues involved in the binding site for genistein and isorhamnetin. The pharmacological interactions are useful for understanding ligand binding mechanisms of a therapeutic target. These interactions are often inferred from a set of active compounds that were acquired by experiments.

Post Screening Analysis

The performed docking study against the KAS I receptor revealed that all flavonoid compounds identified in this study have a superior binding energy in comparison to the reference compound TLM. The analysis identified genistein (Zinc-18825330) and isorhamnetin (Zinc-517261) as having the most favorable binding energy of -135.76 kcal/mol and -132.42 kcal/mol, respectively. Genistein is a phytoestrogen that belongs to the category of isoflavones aglycones. Isorhamnetin is a flavonoid, which occurs naturally in plants, but is also a metabolite of quercetin (isorhamnetin is methylated quercetin). Both compounds are known for their antimicrobial activity^[20, 36]. The drug-receptor interactions and the fitness score of the compounds suggest that these leads can be developed into potential antimicrobial drugs against gram-negative *Escherichia coli*.

Lipinski's guidelines

The ability to predict the pharmaceutical properties of compounds based on their structure is important. There are specific rules that apply to predict activity. Lipinski's guidelines of five is a refinement of drug-likeness and is used to predict whether a chemical compound will have pharmacological or biological activity as an orally active drug in humans. This rule was formulated by Christopher A. Lipinski in 1997, based on the observation that most medication drugs are relatively small, lipophilic molecules. The Lipinski "guidelines of Five" states that compounds are likely to have good absorption and permeation in biological systems and are more likely to be successful drug candidates if they meet the following criteria:

1. The molecular weight of less than 500 mg/mol
2. Has a high lipophilicity ($\log P$ less than 5)
3. Hydrogen bond donors less than 5
4. Hydrogen bond acceptor is less than 10

The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their Absorption, Distribution, Metabolism and Excretion ("ADME"). The rule is important for drug development where a pharmacologically active lead structure is optimized step-wise for increased activity and selectivity, as well as drug-like properties as described by Lipinski's guidelines^[78,79,80].

Veber rule and Molar Refractivity

1-Veber Rule: In particular, compounds which meet only the two criteria of:

- a) 1-rotatable bond count ≥ 10 .
- b) 2-polar surface area (PSA) equal to or less than 140 \AA^2

are predicted to have good oral bioavailability.

2-Molar Refractivity: between (40-130) is used as measurement of the real volume of the molecule and it is also related to the forces which govern the ligand-receptor interactions^[80].

The 10 high ranked lead molecules were prioritized to follow Lipinski's guidelines of five, veber rule and molar refractivity^[81] based on the drug likeliness properties are listed in Table IV.

CONCLUSION

The results of the present study clearly demonstrated that the *in silico* molecular docking studies of selected flavonoids with (Kas I) enzyme exhibited binding interactions and warranted further studies needed for the development of potent (Kas I) inhibitors for the treatment of *Escherichia coli*. These results clearly indicated that genistein and isorhamnetin have similar binding sites and interactions with (Kas I) compared to the standard.

This *in silico* studies are actually an added advantage to screen the (Kas I) inhibition. Flavonoids may serve as useful leads in the development of clinically useful (Kas I) inhibitors. Further, investigations on the above compounds need *in vitro* and *in vivo* studies to develop potential chemical entities for the prevention and treatment of *Escherichia coli* infections.

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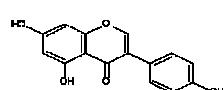
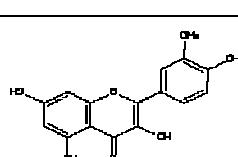
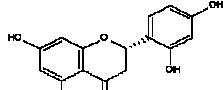
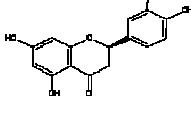
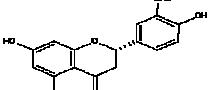
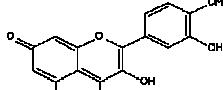
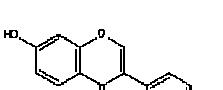
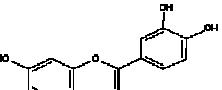
Figure 1.. The skeleton structure of the flavones (a class of flavonoids), with rings named and positions numbered

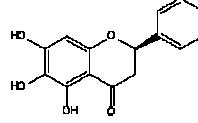
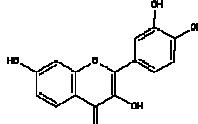
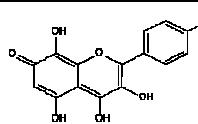
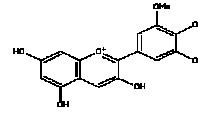
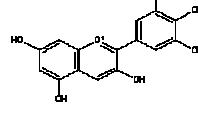
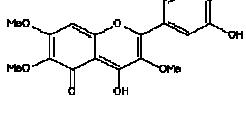
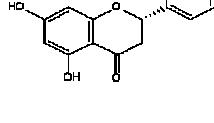
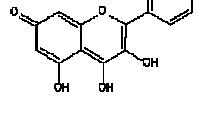
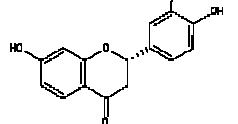
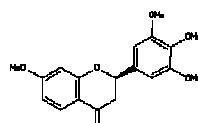
Figure 2: the structure of TLM.

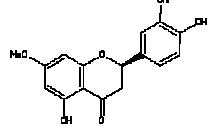
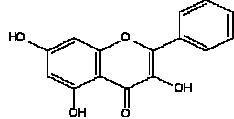
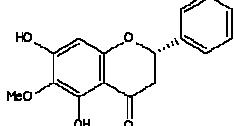
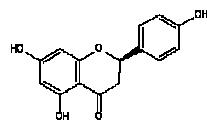
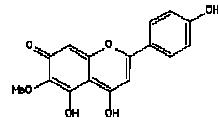
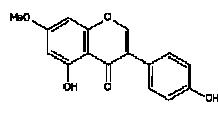
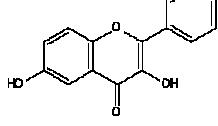
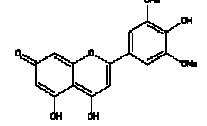
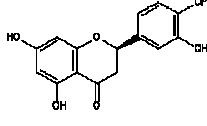
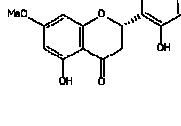
Figure 3: Detail of TLM-FabB cocrystal highlighting placement of isoprene side chain. TLM binds on the malonyl-ACP side of the active site and forms two strong hydrogen bonds with both active site histidines.

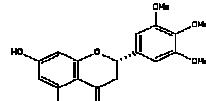
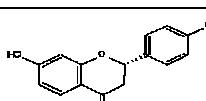
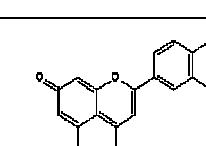
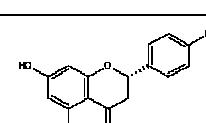
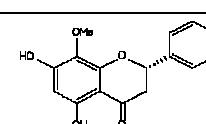
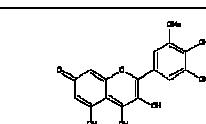
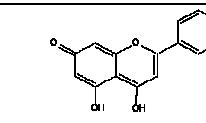
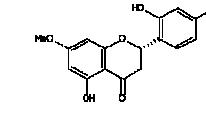
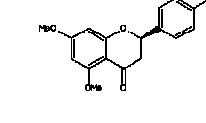
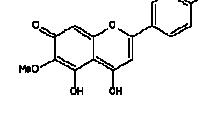
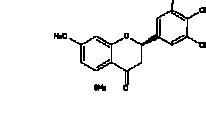
Figure 4: Predicted docking pose of (A) Genistein (B) Isorhamnetin lie within the active site of the target protein (PDB ID- 1FJ4). Pink color represents the corresponding ligand molecule, green and grey color represents the amino acids involved in hydrogen bonding and van der Waals interactions respectively.

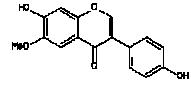
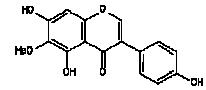
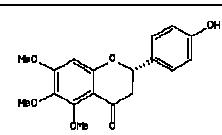
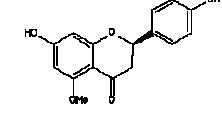
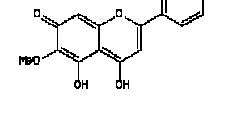
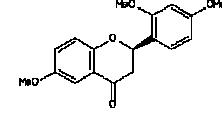
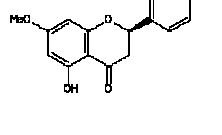
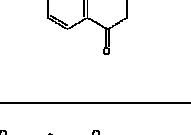
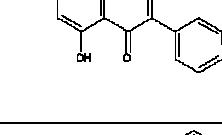
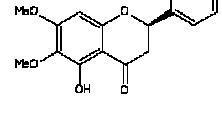
Table I: The structure of 50 screened flavonoid compounds used in this study

S.No.	Compound ID	Chemical Name	IUPAC Name	Compound Structure	References
1	Zinc-18825330	Genistein	5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one		20,36
2	Zinc-517261	Isorhamnetin	3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl)chromen-4-one		20,36
3	Zinc-14728050	Steppogenin	2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-2,3-dihydrochromen-4-one		39
4	Zinc-58116	Eriodictyol	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-2,3-dihydrochromen-4-one		35
5	Zinc-4098322	Homoeriodictyol	5,7-dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-2,3-dihydrochromen-4-one		40
6	Zinc-6484604	Tamarixetin	3,5,7-Trihydroxy-2-(3-hydroxy-4-methoxyphenyl)-4-benzopyrone		41
7	Zinc_18847034	Daidzein	7-hydroxy-3-(4-hydroxyphenyl)chromen-4-one		36
8	Zinc-18185774	Luteolin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4-one		34,36

9	Zinc-14806959	Baicalein	5,6,7-trihydroxy-2-phenylchromen-4-one		37
10	Zinc-39111	Fisetin	2-(3,4-dihydroxyphenyl)-3,7-dihydroxychromen-4-one		35,36
11	Zinc-6536276	Herbacetin	3,5,7,8-tetrahydroxy-2-(4-hydroxyphenyl)chromen-4-one		42
12	Zinc-3954302	Petunidin	2-(3,4-dihydroxy-5-methoxyphenyl)-3,5,7-trihydroxychromenium		36
13	Zinc-897714	Malvidin	3,5,7-trihydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl)chromenium		36
14	Zinc-6018556	Casticin	5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-3,6,7-trimethoxy-4H-chromen-4-one		43
15	Zinc-73693	Pinocembrin	5,7-dihydroxy-2-phenyl-2,3-dihydro-4H-chromen-4-one		36
16	Zinc-3869768	Kaempferol	3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one		20,35,36
17	Zinc-4098238	butin	2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydro-4H-chromen-4-one		33
18	Zinc-4349009	7,3',4',5'-Tetramethoxyflavone	7-methoxy-2-(3,4,5-trimethoxyphenyl)-2,3-dihydrochromen-4-one		38

19	Zinc-1081534	Sternbin	2-(3,4-dihydroxyphenyl)-5-hydroxy-7-methoxy-2,3-dihydrochromen-4-one		44
20	Zinc-120273	Galangin	3,5,7-trihydroxy-2-phenylchromen-4-one		35,36
21	Zinc-5998641	dihydrooroxylin A	5,7-dihydroxy-6-methoxy-2-phenyl-2,3-dihydrochromen-4-one		46
22	Zinc-1785	Naringenin	5,7-dihydroxy-2-(4hydroxyphenyl)-2,3dihydrochromen-4-one		36,18
23	Zinc-5732241	Hispidulin	5,7-dihydroxy-2-(4-hydroxyphenyl)-6-methoxychromen-4-one		45
24	Zinc-18847044	Prunetin	5-hydroxy-3-(4-hydroxyphenyl)-7-methoxychromen-4-one		46
25	Zinc-57648	3,6-Dihydroxyflavone	3,6-dihydroxy-2-phenylchromen-4-one		39
26	Zinc-5998961	tricin	5,7-dihydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl)chromen-4-one		47
27	Zinc-39091	Hesperetin	5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydrochromen-4-one		36
28	Zinc-14806240	Dihydroechioidinin	hydroxy-2-(2-hydroxyphenyl)-7-methoxy-2,3-dihydrochromen-4-one		48

29	Zinc-4348805	5,7-Dihydroxy-3',4',5'-trimethoxyflavone	5,7-dihydroxy-2-(3,4,5-trimethoxyphenyl)-2,3-dihydrochromen-4-one		49
30	Zinc-985403	Liquiritigenin	7-hydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one		33
31	Zinc-5733652	Diosmetin	5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)chromen-4-one		50
32	Zinc-2146973	Isosakuranetin	5,7-dihydroxy-2-(4-methoxyphenyl)-2,3-dihydrochromen-4-one		51
33	Zinc-14807112	Dihydrowogonin	5,7-dihydroxy-8-methoxy-2-phenyl-2,3-dihydrochromen-4-one		52
34	Zinc-6483609	Syringetin	3,5,7-trihydroxy-2-(4-hydroxy-3,5-dimethoxy-phenyl)-chromen-4-one		53
35	Zinc-3872070	Chrysin	5,7-dihydroxy-2-phenylchromen-4-one		36,53
36	Zinc-14728065	Cajanin	3-(2,4-dihydroxyphenyl)-5-hydroxy-7-methoxychromen-4-one		54
37	Zinc-161951	Naringenin trimethyl ether	5,7-dimethoxy-2-(4-methoxyphenyl)-2,3-dihydrochromen-4-one		55
38	Zinc-5733553	Pectolinarigenin	5,7-dihydroxy-6-methoxy-2-(4-methoxyphenyl)chromen-4-one		56
39	Zinc-2576433	3',4',5',5,7-Pentamethoxyflavone	5,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)-2,3-dihydrochromen-4-one		57

40	Zinc-5999205	Glycitein	7-hydroxy-3-(4-hydroxyphenyl)-6-methoxychromen-4-one		36,57
41	Zinc-899915	tectorigenin	5,7-dihydroxy-3-(4hydroxyphenyl)-6-methoxychromen-4-one		58
42	Zinc-1685698	4'-Hydroxy-5,6,7-trimethoxyflavanone	2,3-Dihydro-2-(4-hydroxyphenyl)-5,6,7-trimethoxy-4H-1-benzopyran-4-one		60
43	Zinc-5999024	Naringenin 5-methyl ether	7-hydroxy-2-(4-hydroxyphenyl)-5-methoxy-2,3-dihydro-4H-chromen-4-one		59
44	Zinc-899093	Pectolinarigenin	5,7-dihydroxy-6-methoxy-2-(4-methoxyphenyl)chromen-4-one		61
45	Zinc-57857	6,2',4'-Trimethoxyflavanone	2-(2,4-dimethoxyphenyl)-6-methoxy-2,3-dihydro-4H-chromen-4-one		62
46	Zinc-1561069	Naringenin 7,4'-dimethyl ether	5-hydroxy-7-methoxy-2-(4-methoxyphenyl)-2,3-dihydrochromen-4-one		65
47	Zinc-57919	7-Hydroxyflavanone	7-hydroxy-2-phenyl-2,3-dihydrochromen-4-one		61
48	Zinc-2149675	5,7-Dihydroxyisoflavanone	5,7-dihydroxy-3-phenylchromen-4-one		63
49	Zinc-14807049	Onysilin	5-hydroxy-6,7-dimethoxy-2-phenyl-2,3-dihydrochromen-4-one		66

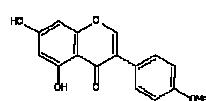
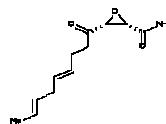
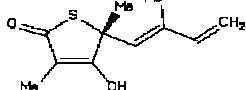
50	Zinc-18847037	Biochanin A	5,7-dihydroxy-3-(4-methoxyphenyl)chromen-4-one		64
51	ZINC-1532443	Cerulenin	3-[<i>(4E,7E)</i> -nona-4,7-dienoyl]oxirane-2-carboxamide		16
52	Zinc-4099011	Thiolactomycin	5-hydroxy-2,4-dimethyl-2-[<i>(1E)-2-methylbuta-1,3-dienyl</i>]thiophen-3-one		16

Table II: The docking binding energy values results using iGEMDOCK

S.No.	Chemical Name	Vanderwaals force (kcal/mol)	H Bond (kcal/mol)	Total binding Energy (kcal/mol)
1	Genistein	-111.61	-24.15	-135.76
2	Isorhamnetin	-107.62	-24.79	-132.42
3	Steppogenin	-102.84	-27.92	-130.76
4	Eriodictyol	-94.06	-35.29	-129.35
5	Homoeriodictyol	-100.80	-27.85	-128.65
6	Tamarixetin	-102.75	-25.86	-128.60
7	Daidzein	-105.14	-23.45	-128.58
8	Luteolin	-91.39	-34.09	-125.48
9	Baicalein	-93.62	-31.48	-125.10
10	Fisetin	-94.89	-29.43	-124.31
11	3,6Dihydroxy flavone	-106.86	-12.57	-119.42
12	Cerulenin	-74.81	-24.83	-99.64
13	Thiolactomycin	-80	-10.26	-90.26

Table III : Pharmacological interactions and Residues involved in the binding site.

PDB ID	Predicted Pharmacologica Interactions	Genistein	Isorhamnetin
1FJ4	H-S ASP- 265	-2.5	-2.2
	ASP-268 H-M	-2.5	-0.6
	GLY-299-H-M	-3.5	-0.6
	VAL-270-H-M	-2.9	-2.7
	THR-302-H-S	0	-3
	ASP-306-H-M	0	-2.9
	ASP-306-H-S	0	-2.5
	GLY-393-H-M	-3.5	-3.5
	GLY-394-H-M	-3.5	-4.6
	VAL-270-V-M	-5.7	-5.3
	ALA-271-V-M	-8	-8.5
	PRO-272-V-M	-6.8	-5.9
	PRO-272-V-S	-11	-10.7
	HIS-298-V-S	-8	-3.4
	GLY-299-V-M	-2.5	-4.1
	GLY-305-V-M	-5.9	-8.2
	VAL-270-V-M	0	0
	PHE-390-V-M	0	0

	GLU-309-V-S	-4.7	-1.3
	PHE-390-V-M	-4.3	-3.1
	PHE-390-V-S	-4.7	-6.4
	GLY-391-V-M	-9	-7.7
	PHE-392-V-M	-5.3	-4.7
	PHE-392-V-S	-5.6	-5.2
<p>The green and grey color represents the amino acids involved in(H) hydrogen bonding and(V) van der Waals are interaction types</p> <p>M and S are Main chain and Side chain.</p>			

Table IV: The Lipinski's and Veber properties of the selected 10 ligands

Chemical name	Molecular Formula ¹	[*] M W ² g/mol	logP ^{1#}	[*] X logP ²	[*] HD ²	[*] HA ²	[*] RB ²	[*] (PSA) ² A°	[*] MR ³
	Value to be	500<	5<		5<	10<	=10<	140<=	40-130
Genistein	C ₁₅ H ₁₀ O ₅	270.24	2.37	2.27	3	5	1	91	69.85
Isorhamnetin	C ₁₆ H ₁₂ O ₇	316.26	1.70	1.99	4	7	2	120	78.11
Steppogenin	C ₁₅ H ₁₂ O ₆	288.25	1.84	2.03	4	6	1	107	72.13
Eriodictyol	C ₁₅ H ₁₂ O ₆	288.25	1.45	1.63	4	6	1	107	72.13
Homoeriodictyol	C ₁₆ H ₁₄ O ₆	302.28	1.93	1.94	3	6	2	96	76.93
Tamarixetin	C ₁₆ H ₁₂ O ₇	316.26	1.67	1.99	4	7	2	120	78.11
Daidzein	C ₂₁ H ₂₂ O ₉	254.24	2.49	2.56	2	4	1	71	67.97
Luteolin	C ₂₁ H ₂₀ O ₁₁	286.23	1.82	1.97	4	6	1	111	71.73
Baicalein	C ₁₅ H ₁₀ O ₅	272.25	2.24	2.13	3	5	1	87	70.25
Fisetin	C ₁₅ H ₁₀ O ₆	286.24	1.87	1.97	4	6	1	111	71.43
3,6Dihydroxy flavone	C ₁₅ H ₁₀ O ₄	254.24	2.72	2.94	2	4	1	70	67.67
Cerulenin	C ₁₂ H ₁₇ NO ₃	223.27	0.87	0.50	2	4	7	73	60.68
Thiolactomycin	C ₁₁ H ₁₄ O ₂ S	209.29	2.52	2.16	0	8	2	40	61.82

1-calculated by ALOGPS 2.1 program <http://www.vcclab.org/lab/alogs/start.html.2>

2- Calculated by [www.zinc.docking.o](https://pubchem.ncbi.nlm.nih.gov/search/search.cgi)

<https://pubchem.ncbi.nlm.nih.gov/search/search.cgi>

3- Calculated by ACD (Available Chemical Directory)

*PSA: Polar Surface Area,*MW: Molecular weight, *HD: H bond donor, *HA : H bond acceptor.

*RB : rotatable bonds. *MR: Molar refractivity

#Octanol/Water partition coefficient