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IN-SILICO SEARCH OF SOME CHEAP ANTIBIOTICS FOR TUBERCULOSIS PART-II

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ABSTRACT

In an attempt to search a new class of antibacterial drugs, for treatment of tuberculosis molecular docking studies with proteins 1EYN was carried out using some chromene derivatives. Some of the chromene derivatives were found to have binding energy and docking pattern very close to the originally docked molecule in 1EYN while some other show higher docking scores compared to the originally docked ligand in 1EYN protein. The quick prop results reveal that these molecules are non-toxic. The results reveal that chromenes may exhibit significant antibiotic activities against tuberculosis and indicate that this class of natural product should be considered further in the development of new and more potent antibiotics of Tuberculosis.

KEYWORD: docking, in-silico, 1EYN, chromene derivatives antibiotic, quick prop, druggability.

1. INTRODUCTION

Tuberculosis is a major cause of illness and death worldwide, each year 8 million new cases appear and 2 million people die of TB.[1] Mycobacterium tuberculosis (MTB) is the causative agent of TB. The existing drugs, although of immense value in controlling the disease to the extent that is being done today, have limitations in treating drug-resistant TB. Besides high level of adverse effect of the existing drugs (eg. Rifampicin) their inability to act upon latent form of bacillus limits their use. This limitation has led the chemists to search new drugs.

Computer aided drug discovery has simplified and accelerated the research; computer aided analysis of metabolic network has provided insight into an organism's ability to grow under

specific conditions. The metabolic network analyses can be used to identify organism specific essential genes by predicting the attentions of microbial growth of specific deletion mutants.[2-4]

Antibacterials are inhibitors of certain bacterial enzymes, all enzymes specific to bacteria can be considered as drug targets.[5] Metabolic genes that are essential for pathogen growth but are not present in humans constitute actual and potential drug targets. Amir et al[6] have identified five unique metabolic pathways in M tuberculosis C-5 branched dibasic acid metabolism, carbon fixation pathway in prokaryotes, methane metabolism, lipopolysaccharide bio synthesis and peptidoglycan biosynthesis; 55 enzymes out of 60 (except sl. nos. 21,22,49, 52, & 60) mentioned in Table-1were found essential for M. Tuberculosis life cycle.

Table 1

S. no.	Entry no.	Protein name	Essential enzyme
1	Rv1820	Acetolactate synthase	Yes
2	Rv0951	Succinyl-CoA synthetase subunit beta	Yes
3	Rv2987c	Isopropylmalate isomerase small subunit	Yes
4	Rv1475c	Aconitate hydratase (EC: 4.2.1.3)	Yes
5	Rv0066c	Isocitrate dehydrogenase (EC: 1.1.1.42)	Yes
6	Rv2454c	2-Oxoglutarate ferredoxin oxidoreductase subunit beta (EC: 1.2.7.3)	Yes
7	Rv1240	Malate dehydrogenase (EC: 1.1.1.37)	Yes
8	Rv1098c	Fumarate hydratase (EC: 4.2.1.2)	Yes
	Rv0247c	Fumarate reductase iron-sulfur subunit (EC: 1.3.99.1)	Yes
10	Rv3356c	Bifunctional 5,10-methylene-tetrahydrofolate dehydrogenase/5,10-methylene-tetrahydrofolate Cyclohydrolase (EC: 1.5.1.5 3.5.4.9)	Yes
11	Rv0951	Succinyl-CoA synthetase subunit beta (EC: 6.2.1.5)	Yes
12	Rv0904c	Putative acetyl-coenzyme A carboxylase carboxyl transferase subunit beta (EC: 6.4.1.2)	Yes
13	Rv0973c	Acetyl-/propionyl-coenzyme A carboxylase subunit alpha (EC: 6.3.4.14)	Yes
14	Rv1492	Methylmalonyl-CoA mutase small subunit (EC: 5.4.99.2)	Yes
15	Rv3667	Acetyl-CoA synthetase (EC: 6.2.1.1)	Yes
16	Rv0409	Acetate kinase (EC: 2.7.2.1)	Yes
17	Rv0408	Phosphate acetyltransferase (EC: 2.3.1.8)	Yes
18	Rv0243	Acetyl-CoA acetyltransferase (EC: 2.3.1.9)	Yes
19	Rv0860	Fatty oxidation protein FadB	Yes
20	Rv3667	Acetyl-CoA synthetase (EC: 6.2.1.1)	Yes
21	Rv0373c	Carbon monoxyde dehydrogenase large subunit (EC: 1.2.99.2)	No
22	Rv2900c	Formate dehydrogenase H (EC: 1.2.1.2)	No

23	Rv1023	Phosphopyruvate hydratase (EC: 4.2.1.11)	Yes
24	Rv1240	Malate dehydrogenase (EC: 1.1.1.37)	Yes
25	Rv0070c	Serine hydroxymethyltransferase (EC: 2.1.2.1)	Yes
26	Rv2205c	Hypothetical protein	Yes
27	Rv0761c	Zinc-containing alcohol dehydrogenase NAD dependent AdhB (EC: 1.1.1.1)	Yes
28	Rv0489	Phosphoglyceromutase (EC: 5.4.2.1)	Yes
29	Rv0363c	Fructose-bisphosphate aldolase (EC: 4.1.2.13)	Yes
30	Rv2029c	Phosphofructokinase PfkB (phosphohexokinase) (EC: 2.7.1.—)	Yes
31	Rv1908c	Catalase-peroxidase-peroxynitritase T KatG (EC: 1.11.1.6)	Yes
32	Rv0070c	Serine hydroxymethyltransferase (EC: 2.1.2.1)	Yes
33	Rv0728c	D-3-phosphoglycerate dehydrogenase (EC: 1.1.1.95)	Yes
34	Rv0505c	Phosphoserine phosphatase (EC: 3.1.3.3)	Yes
35	Rv0884c	Phosphoserine aminotransferase (EC: 2.6.1.52)	Yes
36	Rv0409	Acetate kinase (EC: 2.7.2.1)	Yes
37	Rv0408	Phosphate acetyltransferase (EC: 2.3.1.8)	Yes
38	Rv3667	Acetyl-CoA synthetase (EC: 6.2.1.1)	Yes
39	Rv2611c	Lipid A biosynthesis lauroyl acyltransferase (EC: 2.3.1. —)	Yes
40	Rv0114	D-alpha,beta-D-heptose-1,7-biphosphate phosphatase (EC: 2. —.—.—)	Yes
41	Rv0113	Phosphoheptose isomerase (EC: 5.—.—.—)	Yes
42	Rv1315	UDP-N-acetylglucosamine 1-carboxyvinyltransferase (EC: 2.5.1.7)	Yes
43	Rv0482	UDP-N-acetylenolpyruvoylglucosamine reductase (EC: 1.1.1.158)	Yes
44	Rv2152c	UDP-N-acetylmuramate-L-alanine ligase (EC: 6.3.2.8)	Yes
45	Rv2155c	UDP-N-acetylmuramoyl-L-alanyl-D-glutamate synthetase (EC: 6.3.2.9)	Yes
46	Rv2157c	UDP-N-acetylmuramoylalanyl-D-glutamyl-2,6-diaminopimelate-D-alanyl-D-alanyl ligase MurF	
47	Rv2156c	Phospho-N-acetylmuramoyl-pentapeptide-transferase (EC: 2.7.8.13)	Yes
48	Rv2153c	Undecaprenyldiphospho-muramoylpentapeptide beta-N-acetylglucosaminyltransferase (EC: 2.4.1.227)	Yes
49	Rv2911	D-alanyl-D-alanine carboxypeptidase (EC: 3.4.16.4)	No
50	Rv2981c	D-alanyl-alanine synthetase A (EC: 6.3.2.4)	Yes
51	Rv2136c	Undecaprenyl pyrophosphate phosphatase (EC: 3.6.1.27)	Yes
52	Rv2911	D-alanyl-D-alanine carboxypeptidase (EC: 3.4.16.4)	No
53	Rv2158c	UDP-N-acetylmuramoylalanyl-D-glutamate-2,6-diaminopimelate ligase (EC: 6.3.2.13)	Yes
54	Rv2157c	UDP-N-acetylmuramoylalanyl-D-glutamyl-2,6-diaminopimelate-D-alanyl-D-alanyl ligase MurF	Yes
55	Rv2156c	Phospho-N-acetylmuramoyl-pentapeptide-transferase (EC: 2.7.8.13)	Yes
56	Rv2153c	Undecaprenyldiphospho-muramoylpentapeptide	
		beta-N-acetylglucosaminyltransferase (EC: 2.4.1.227)	Yes
57	Rv3910	Transmembrane protein	Yes

58	Rv0016c	Penicillin-binding protein PbpA	Yes
59	Rv2163c	Penicillin-binding membrane protein PbpB	Yes
60	Rv2911	D-alanyl-D-alanine carboxypeptidase (EC: 3.4.16.4)	No

These targets are potential targets for rational drug design. In this work we have chosen the enzyme n-acetyl glucosamine-1-carboxy transferase, alias murA as the target. This enzyme transfers carboxyvinyl group and catalyzes the first committed step in the biosynthesis of bacterial cell wall peptidoglycan. Its other biological functions include cell shape, etc.

The crystal structure of udp-n- n-acetyl glucosamine-1-carboxy transferase murA chain (syn: enoylpyruvate transferase,) obtained from the organism taxid:550 expressed in Escherichia coli (expression system taxid :562) was established in the year 2000 by Schonbrumm et al.[7] The resolution was 1.70A R factor 0.180 and R free 0.210. The PDB Id is 1EYN.The structure is co-crystallized with -8-anilino-1-naphthalene sulfonate (ANS).

In continuation of our work[8-11] pertaining to our molecular docking studies for identification of potentially effective cheap antibiotics[8] and anti HIV drugs,[9-11] in this paper we report the results of molecular docking studies of some natural occurring chromene derivatives on target proteins designated by PDB 1EYN.

Chromene (Benzopyran) is one of the privileged medicinal pharmacophore which appears as an important structural component in natural compounds and generated great attention because of their interesting biological activity. It is a heterocyclic ring system consisting of a benzene ring fused to a pyran ring. Chromene constitute the basic backbone of various types of polyphenols and widely found in natural alkaloids, tocopherols, flavonoids, and anthocyanins.[12] It is known that certain natural and synthetic chromene derivatives possess important biological activities such as antitumor, antivascular,[13] antimicrobial,[14] antioxidant,[15] TNF-α inhibitor,[16] antifungal,[17] anticoagulant, antispasmolytic, estrogenic,[18] antiviral,[19] anti-helminthic, anticancer,[20] anti-HIV,[17] antitubercular,[21] anti-inflammatory,[22] herbicidal, analgesic and anticonvulsant[23] activity. A key feature is that the lipophilic nature of the benzopyran derivatives helps to cross the cell membrane easily.[24] Among the all heterocyclic compounds, oxygen heterocycles are special because of their wide occurrence and broad pharmaceutical significance. The druggability of these compounds having good docking scores is also being reported.

2. MATERIAL AND METHODS

The molecular docking studies were carried out on glide 5.0 platform of Schrodinger 2012 software. The druggability was also studied with the help of quick prop program of the same software.LD50, LC50 and EC50 and ADMET plot have been computed from Accelrys Discovery Studio Client 2.5. The target protein 1EYN was downloaded from the site RCSB.org. The general description of target proteins have been described below:- **1EYN**: This target protein was isolated from Enterobacter cloacae micro-organism. The crystal structure of 1EYN having structure weight 45313.33 was determined by Schonbrunn E, Eschenburg S, Luger K, Kabsch W, Amrhein N using X-ray diffraction at a resolution of 1.7 Å.The molecule is monomeric.

Computational studies

The molecular docking studies were done on the protein 1EYN by downloading it on the glide software of Schrodinger 2012. The validation of the docking protocol was carried out by removing the co-crystallized originally docked molecule from the binding site and re-docking it to the 1EYN. We found very good agreement between the localization of the inhibitor 1EYN upon docking and from crystal structure.

Protein preparation: The downloaded protein had some problems, so preparation of protein was needed before docking. This was done in the protein preparation wizard from the workflow menu following the method prescribed by Schrodinger 2012 user manual.

Ligand Preparation: The initial structures of all the ligands were drawn with Chem-Draw ultra 8.0 and the structures were optimized on Chem3D ultra 8.0. The saved mol files of these structures were imported and prepared by the method prescribed in the manual of the Maestro 9.3 of Schrodinger 2012 version software and these prepared molecules were finally docked with the two desired target proteins.

Receptor Grid Generation

Receptor grid of the prepared 1EYN protein were generated before docking following the prescribed method.

The docking of the ligands to the generated receptor grid was carried out without imposing any constraint. The docking pose, binding energy and details of other interactions including the ligand interaction diagram, were visualized on the monitor.

The drug properties were determined on the quick prop protocol of the same software.

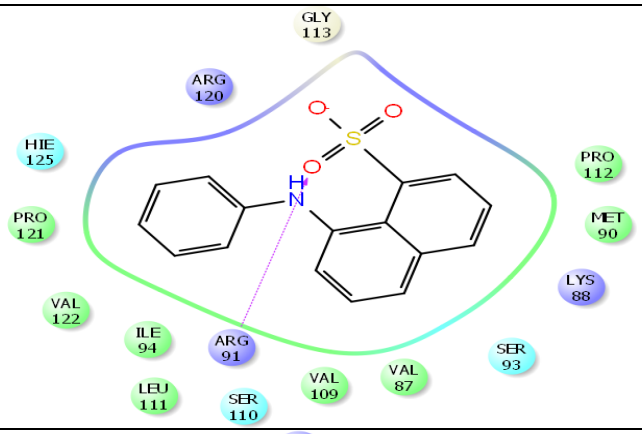
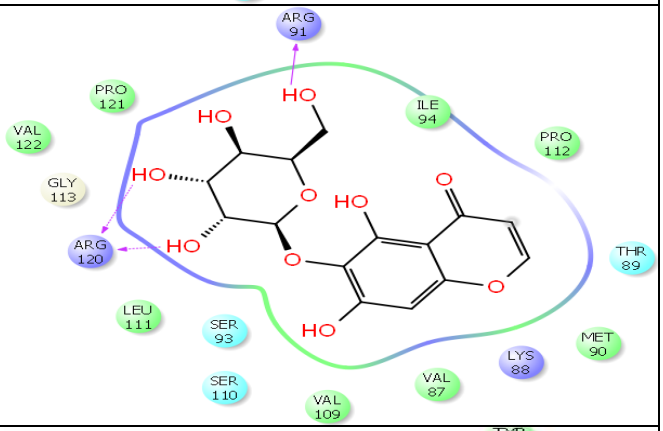
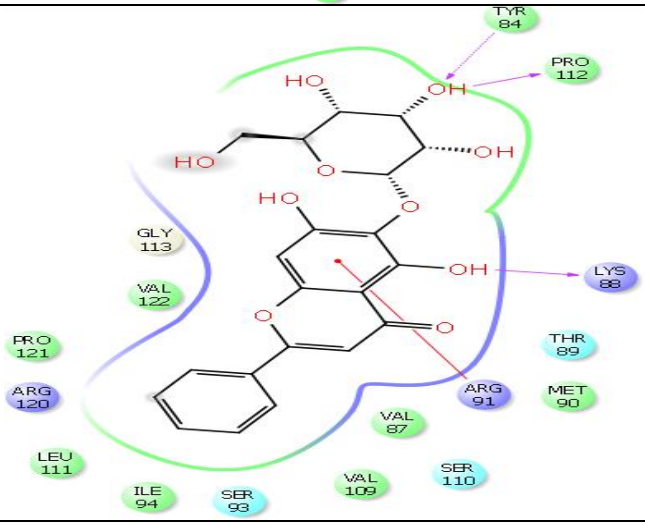
3. RESULTS AND DISCUSSION

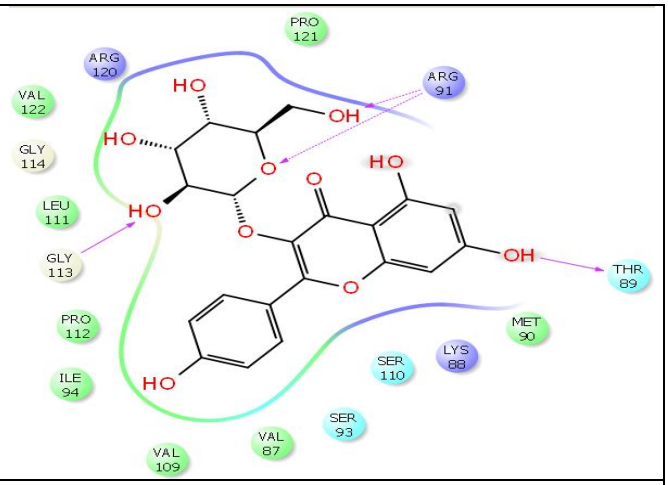
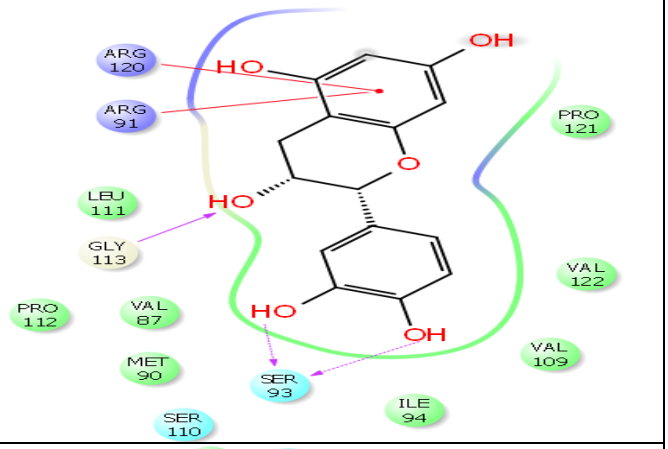
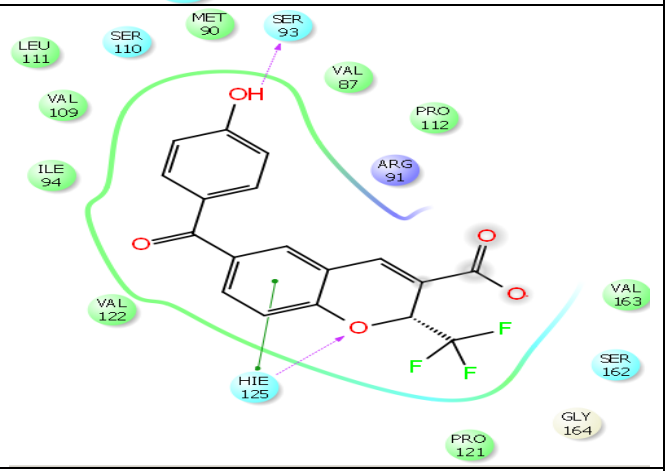
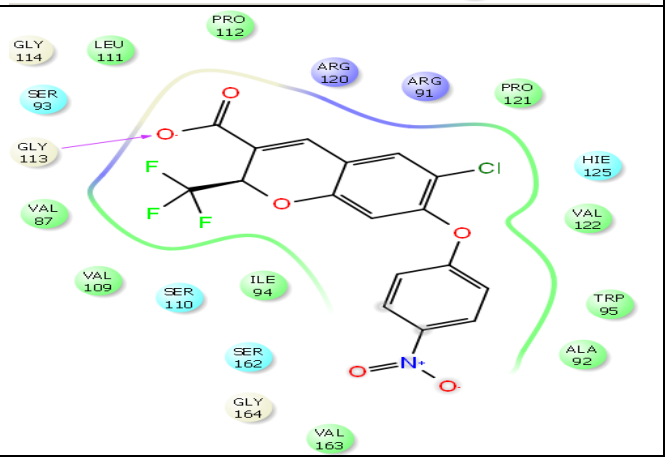
The results of molecular docking, LD50,LC50 and EC50 of originally co-crystallized ligand 8-(phenylamino)naphthalene-1-sulfonate (I), and some chromenes derivatives 5,7-dihydroxy-6-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (II), 5,7-dihydroxy-2-phenyl-6-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (III), 5,7-dihydroxy-2-(4-hydroxyphenyl)-3-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one(Kaempferol-3-O-glucoside),(IV), (2R,3R)-2-(3,4-dihydroxy phenyl)chromane-3,5,7-triol (V), 6-(4-hydroxybenzoyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid,(VI), 6-chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (VII), 5,6,7-trihydroxy-4H-chromen-4-one,(VIII), and 2-(3,4-dihydroxyphenyl)-4H-benzo[g]chromene-3,4,8,9-tetraol,(IX)with the target proteins IEYN appear in Table2 and 3 respectively. The drug candidate (III) has exhibited docking score (7.10) than originally docked ligand (I). From the Table2 it is clear that drug candidate ((II) is the best with docking score of -8.12 with the target proteins. 8-(phenylamino) naphthalene-1-sulfonate (originally docked ligand)(I) held through hydrogen bonding with ARG 91 amino acids of the protein. The virtual drug candidate (II) having highest docking score is also held through hydrogen bonding with amino acid ARG91 and showing similar docking parameters. The other drug candidates also show similarities in the interactions with the amino acids are remarkable. The conformational pose of the highest docking scorer (II) appears in the fig1.

The results of toxicity study namely LC50, LD50 and EC50 appear in Table-3. It is apparent that all the drug candidates have virtually lower toxicity.

The druggability of (I), (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX), have been computed by quick prop program and the reports appear in the Table4. From the perusal of Table-4 it is clear that all these compounds are good drug candidates. There similarities with other drugs have been tabulated in Table5. The interaction diagram of all the investigated chromenes derivatives along with the re-docked co-crystallized ligand with the proteins 1EYN have been shown in Table 2. Drugs most similar to highest docking score of originally docked ligand and chromene derivatives have been summarized in Table 4.

Table 2. Docking score and interaction diagram of originally re-docked ligand and chromene derivative

Ligands	Docking Score	Interaction diagram
8-(phenylamino)naphthalene-1-sulfonate (originally docked ligand) (I)	-6.1	
5,7-dihydroxy-6-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (II)	-8.12	
5,7-dihydroxy-2-phenyl-6-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (III)	-7.10	

5,7-dihydroxy-2-(4-hydroxyphenyl)-3-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one(Kaempferol-3-O-glucoside), (IV)	-6.85	
(2R,3R)-2-(3,4-dihydroxyphenyl)chromane-3,5,7-triol (V)	-6.13	
6-(4-hydroxybenzoyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid,(VI)	-5.97	
6-chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (VII)	-5.80	

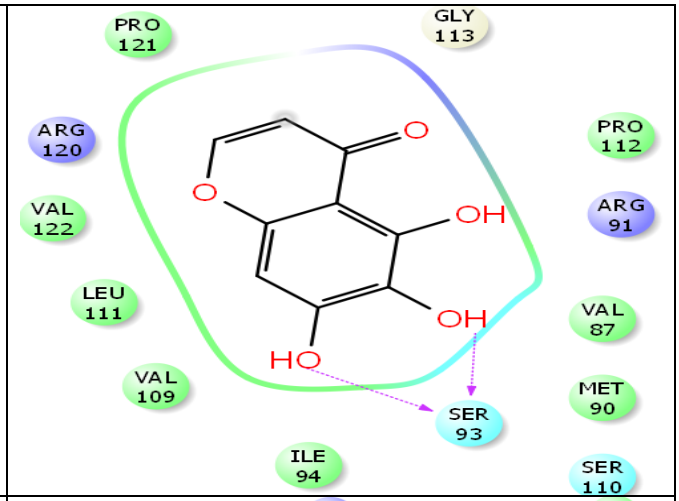
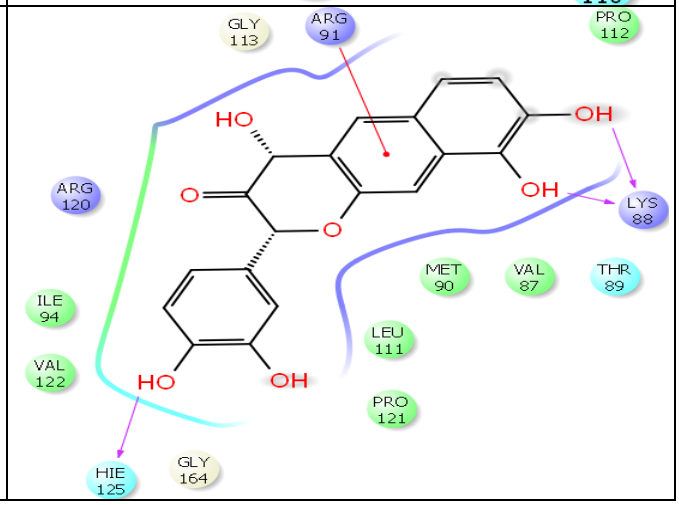
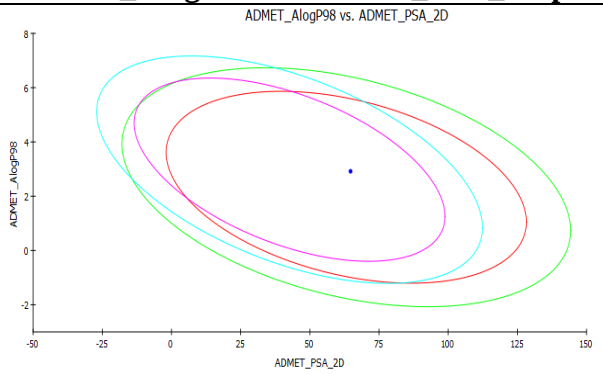
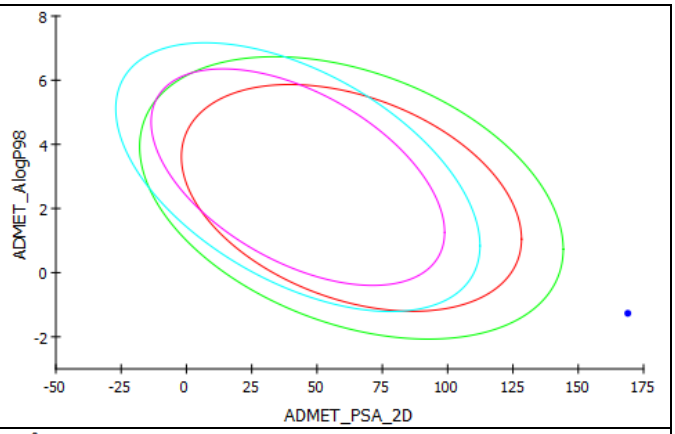
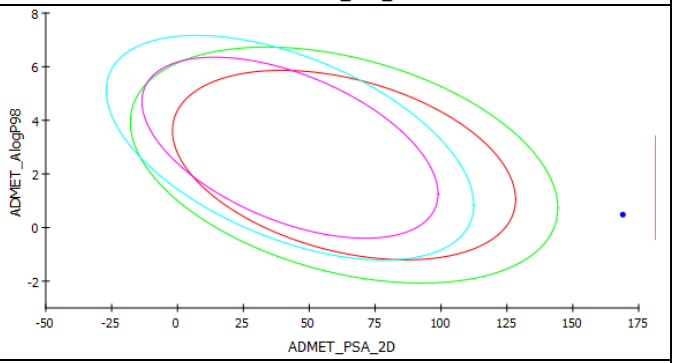
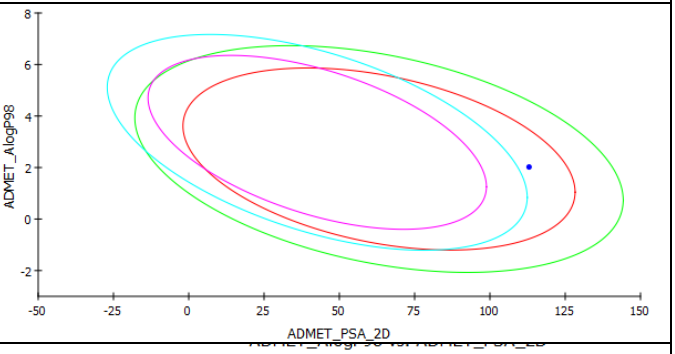
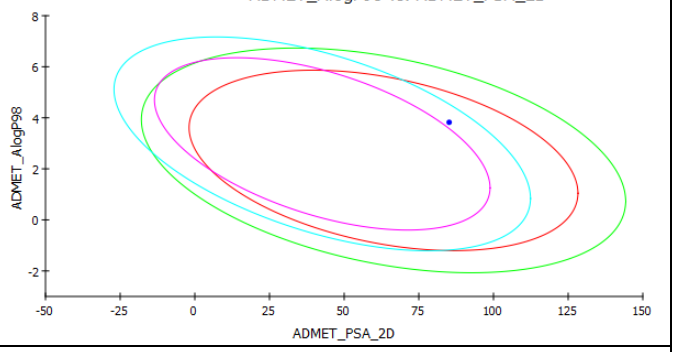
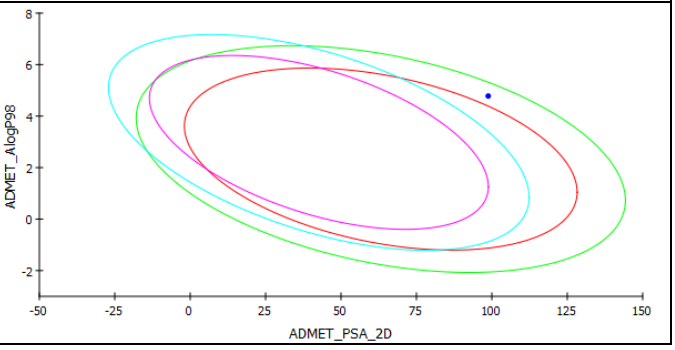
5,6,7-trihydroxy-4H-chromen-4-one,(VIII)	-5.78	
2-(3,4-dihydroxyphenyl)-4H-benzo[g]chromene-3,4,8,9-tetraol, (IX)	-5.73	

Table 3 Results of LD50, LC50, EC50 and ADMET plots of originally co-crystallized ligand and chromene derivative.

Ligands	computed rat oral LD50	Rat Inhalation LC50	DaphniaEC50	ADMET_Alog998 vs ADMET_PSA_2D plots
(I)	0.7008	0.3178	0.29043	

(II)	1.3470	0.3432	18.7216	
(III)	0.5046	0.32135	5.580	
(IV)	-	-	-	-
(V)	0.8078	2.1547	20.555	
(VI)	0.2482	3.529	0.5616	
(VII)	0.0461	1.852	0.0840	

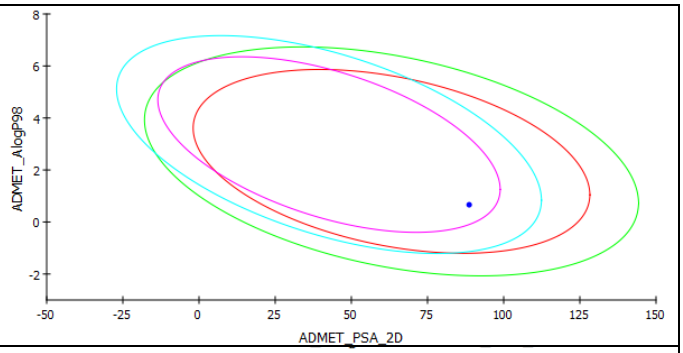
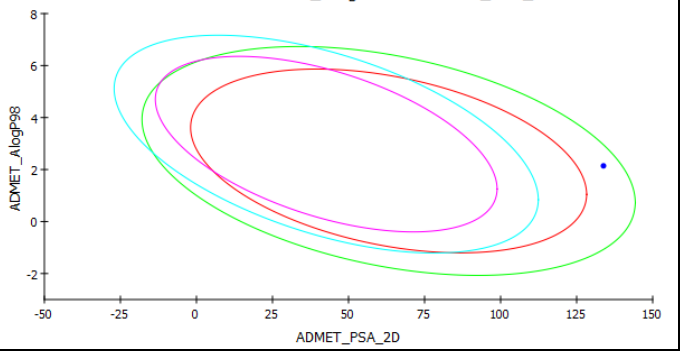
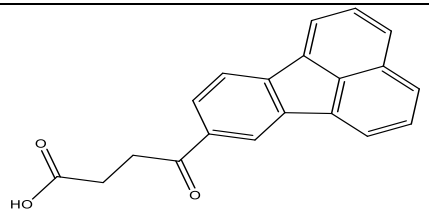
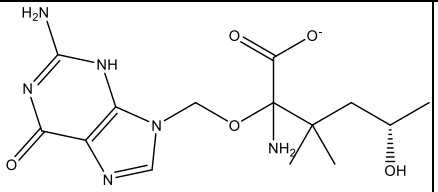
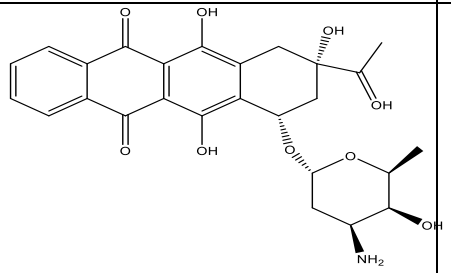
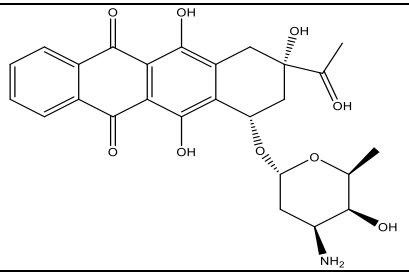
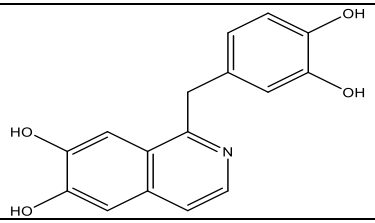
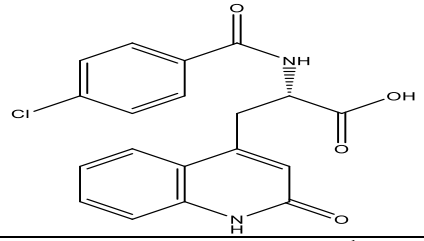
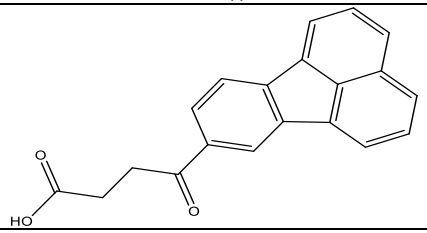
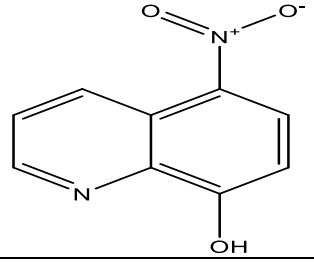
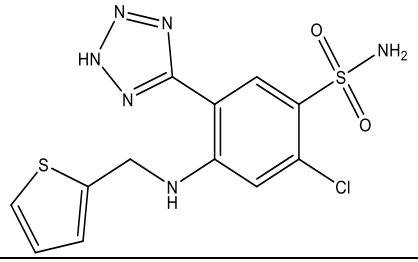
(VIII)	0.6715	3.628	14.055	
(IX)	0.9644	0.876	1.726	

Table 4. Drugs most similar to highest docking score of originally docked ligand and chromene derivatives

Drug candidates	Most Similar drug	Structure	% similarity	Used as
8-(phenylamino)naphthalene-1-sulfonate (originally docked ligand) (I)	Florantyrone		92.88	treatment of biliary dyskinesia
5,7-dihydroxy-6-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one (II)	Valganciclovir		74.42	treatment of cytomegalovirus infecti ons.
5,7-dihydroxy-2-phenyl-6-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one, (III)	Idarubicin		75.17	anthracycline antileuke mic drug.
5,7-dihydroxy-2-(4-hydroxyphenyl)-3-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-4H-chromen-4-one(Kaempferol-3-O-glucoside), (IV)	Idarubicin		71.31	anthracycline antileuke mic drug.

(2R,3R)-2-(3,4-dihydroxyphenyl)chromane-3,5,7-triol (V)	Papaveroline		85.23	treatment of mental disorders
6-(4-hydroxybenzoyl)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid,- (VI)	Rebamipide		94.63	mucosal protection, healing of gastroduodenal ulcers, and treatment of gastritis.
6-chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (VII)	Florantyrone		88.33	in the treatment of biliary dyskinesia.
5,6,7-trihydroxy-4H-chromen-4-one, (VIII)	Nitroxoline		91.03	combatingbiofilm infections.
2-(3,4-dihydroxyphenyl)-4H-benzo[g]chromene-3,4,8,9-tetraol, (IX)	Azosemide		78.31	high-ceiling diuretic agent

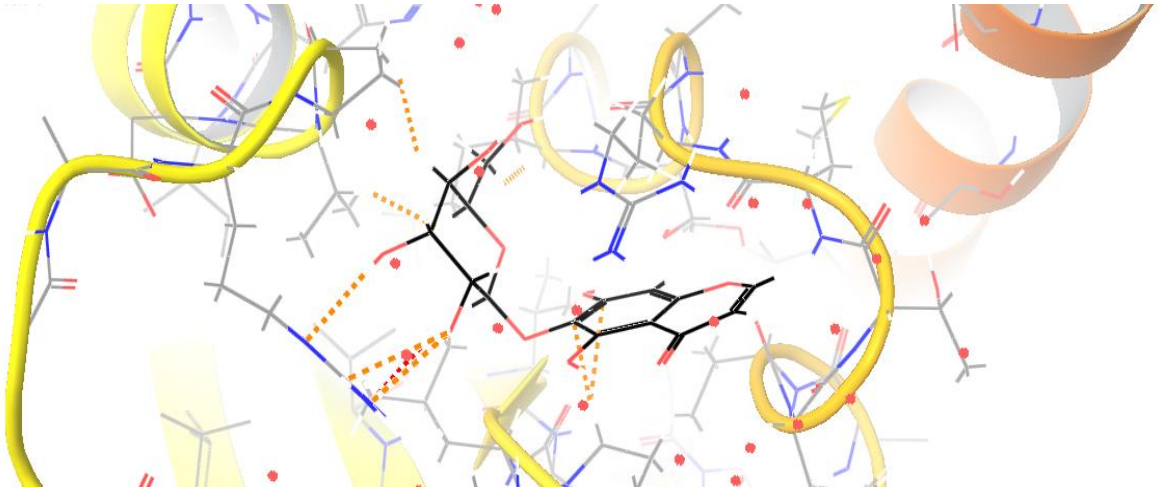


Figure 1. Orientation of selected highest docking scorer chromene derivative (black color)

Table 5 QikProp properties of originally docked ligand and chromene derivative.

		I	II	III	IV	V	VI	VII	VIII	IX	
Solute Weight	Molecular	299.344	356.285	432.383	448.382	290.272	364.277	415.709	194.143	354.315	(130.0 / 725.0)
Solute SASA	Total	498.27	520.205	653.684	640.567	510.995	571.845	589.01	357.063	584.89	(300.0 /1000.0)
Solute SASA	Hydrophobic	0	118.982	90.295	95.855	65.09	17.08	12.526	0	36.293	(0.0 / 750.0)
Solute SASA	Hydrophilic	110.298	247.282	274.152	319.162	238.488	190.594	194.555	186.628	273.244	(7.0 / 330.0)
Solute SASA	Carbon Pi	386.591	153.941	289.237	225.551	207.417	267.393	237.676	170.435	275.354	(0.0 / 450.0)
Solute SASA	Weakly Polar	1.382	0	0	0	0	96.779	144.253	0	0	(0.0 / 175.0)
Solute	Molecular	875.152	935.86	1180.616	1187.228	867.034	995.686	1036.557	569.876	1013.047	(500.0 /2000.0)

Volume (A^3)										
Solute vdW Polar SA (PSA)	61.72	165.453	171.099	185.801	114.873	103.898	109.976	98.888	140.627	(7.0 / 200.0)
Solute No. of Rotatable Bonds	4	9	9	10	5	4	4	3	5	(0.0 / 15.0)
Solute as Donor - Hydrogen Bonds	2	5	5	6	5	2	1	2	5	(0.0 / 6.0)
Solute as Acceptor - Hydrogen Bonds	4.5	12.25	12.25	13	5.45	5.75	4.5	3.75	7.45	(2.0 / 20.0)
Solute Globularity (Sphere = 1)	0.888	0.889	0.826	0.846	0.861	0.843	0.841	0.931	0.834	(0.75 / 0.95)
Predictions for Properties:										
QP Polarizability (Angstroms^3)	29.993M	26.990M	38.078M	37.092M	27.315M	33.679M	35.030M	16.354	33.807M	(13.0 / 70.0)
QP log P for hexadecane/gas	10.439M	11.023M	14.291M	14.456M	10.523M	10.498M	10.765M	6.719	12.592M	(4.0 / 18.0)
QP log P for octanol/gas	15.670M	23.369M	27.603M	29.595M	19.669M	18.884M	17.931M	11.461	23.876M	(8.0 / 35.0)
QP log P for water/gas	10.778M	21.104M	22.528M	24.352M	15.570M	11.955M	9.142M	8.968	18.417M	(4.0 / 45.0)
QP log P for octanol/water	2.99	-1.26	-0.168	-0.829	0.448	2.901	3.903	0.154	0.471	(-2.0 / 6.5)
QP log S for aqueous solubility	-3.132	-1.451	-2.906	-2.481	-2.609	-4.432	-5.362	-1.213	-3.425	(-6.5 / 0.5)
QP log S - conformation independent	-4.411	-2.449	-4.092	-4.066	-3.474	-5.172	-6.768	-2.314	-4.334	(-6.5 / 0.5)
QP log K hsa Serum Protein Binding	-0.192	-0.964	-0.72	-0.79	-0.425	-0.113	0.239	-0.584	-0.335	(-1.5 / 1.5)
QP log BB for brain/blood	-0.607	-2.063	-2.655	-3.009	-1.885	-1.227	-1.158	-1.053	-2.357	(-3.0 / 1.2)
No. of Primary Metabolites	2	6	6	7	7	2	2	3	6	(1.0 / 8.0)
Predicted CNS Activity (-- to ++)	-	--	--	--	--	--	--	--	--	

HERG K+ Channel Blockage: log IC50	-3.38	-4.055	-5.72	-5.092	-4.778	-3.536	-3.432	-3.462	-5.531	(concern below -
Apparent Caco-2 Permeability (nm/sec)	225	44	24	9	54	39	35	168	25	(<25 poor, >500
Apparent MDCK Permeability (nm/sec)	128	17	9M	3M	21	64	106	72	9	(<25 poor, >500
QP log Kp for skin permeability	-1.806	-4.671	-4.689	-5.647	-4.704	-3.706	-3.884	-4.071	-5.105	(Kp in cm/hr)
Jm, max transdermal transport rate	3.453	0.269	0.011	0.003	0.014	0.003	0	1.01	0.001	(micrograms/cm^2
Lipinski Rule of 5 Violations	0	1	1	2	0	0	0	0	0	(maximum is 4)
Jorgensen Rule of 3 Violations	0	0	0	2	1	0	0	0	0	(maximum is 3)
% Human Oral Absorption in GI (+-20%)	87	36	38	14	61	72	78	68	55	(<25% is poor)
Qual. Model for Human Oral Absorption	HIGH	Medium	Medium	Medium	Medium	HIGH	HIGH	Medium	Medium	(>80% is high)

CONCLUSIONS

The main purpose of this study was to search (In-Silico) some potentially cheap and naturally occurring effective antibiotics for tuberculosis. Some readily accessible chromenes derivatives have been found in this study to be virtually more active and less toxic when the molecular docking studies were carried out against proteins with PDB ID IEYN. In-silico-study have shown that it has good resemblance with originally co-crystallized ligand 8-(phenylamino) naphthalene-1-sulfonate in binding energy and the interaction pattern with amino acids in the cavity of the protein IEYN. Some of the chromenes derivatives show higher docking value comparable to originally docked ligand. The quick prop program predicts that it can be used as a drug candidate. Further work pertaining to experimental verification of these predictions may be carried out in the laboratories which have the adequate facilities.

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REFERENCES

1. S. H. E. Kaufmann, "Envisioning future strategies for vaccination against tuberculosis," *Nature Reviews Immunology*, 2006; 6(9): 699–704.
2. A. M. Feist, C. S. Henry, J. L. Reed et al., "A genome-scale metabolic reconstruction for *Escherichia coli* K-12MG1655 that accounts for 1260 ORFs and thermodynamic information," *Molecular Systems Biology*, 2007; 3: 121.
3. N. C. Duarte, M. J. Herrg˚ard, and B. Ø. Palsson, "Reconstruction and validation of *Saccharomyces cerevisiae* iND750, a fully compartmentalized genome-scale metabolic model," *Genome Research*, 2004; 7: 1298–1309.
4. A. K. Chavali, J.D.Whittemore, J. A. Eddy, K. T.Williams, and J. A. Papin, "Systems analysis of metabolism in the pathogenic trypanosomatid *Leishmania major*," *Molecular Systems Biology*, 2008; 4: 177.
5. M. Y. Galperin and E. V. Koonin, "Searching for drug targets in microbial genomes," *Current Opinion in Biotechnology*, 1999; 10(6): 571–578.
6. *Mycobacterium tuberculosis* H37Rv: *In Silico* Drug Targets Identification by Metabolic Pathways Analysis, Asad Amir et.al *International Journal of Evolutionary Biology, 2014, 1-8.*

7. Schonbrunn Journal: *Proc.Natl.Acad.Sci.USA*, 2000; 97: 6345-6349.
8. K.K.Srivastava1, Shubha Srivastava , Md. Tanweer Alam, Rituraj, In silico search of some cheap antibiotics Part-1,*World Journal of Pharmacy and pharmaceutical sciences*, 2014; 3(5): 1314-1333.
9. K.K.Srivastava1, Shubha Srivastava, Md. Tanweer Alam, Rituraj, Molecular docking studies and theoretical investigation of anti-hiv activity of some succinic acid *World Journal of Pharmacy and pharmaceutical sciences*, 2014; 3(2): 1912-1923.
10. K.K.Srivastava1, Shubha Srivastava , Md. Tanweer Alam, Rituraj, In silico identification of Novel HIVProtease inhibitors (PIs) using ZINC drug Database, *International Journal of Pharma Sciences and Research*, 2014; (5): 947-952.
11. Qiao Ren, Woon-Yew Siau, Zhiyun Du, Kun Zhang, Jian Wang. Expeditious assembly of a 2-Amino-4H-chromene skeleton by using an enantioselective mannich intramolecular ring cyclization–tautomerization cascade sequence. *Chem Eur J* 2011; 17:7781–7785.
12. Henriette G, Lorraine L, Bettina H, Clemence D, Kelly Dong, Irenej K, et al. Antivascular and antitumor evaluation of 2-amino-4-(3- bromo-4,5-dimethoxy-phenyl)-3-cyano-4*H*-chromenes, a novel series of anticancer agents. *Mol Cancer Ther*, 2004; 3(11): 1375- 84.
13. Chetan BS, Nimesh MS, Manish PP, Ranjan GP. Microwave assisted synthesis of novel 4*H*-chromene derivatives bearing phenoxypyrazole and their antimicrobial activity assess. *J Serb Chem Soc*, 2012; *77*: 1–17.
14. Milan M, Mirjana M, Desanka B, Sanja M, Neda N, Vladimir M, et al. In vitro antioxidant of selected 4-Hydroxy-chromene-2-one derivatives-SAR, QSAR and DFT studies. *Int J Mol Sci*, 2011; 12(5): 2822-41.
15. Jie-Fei Cheng, Akira Ishikawa, Yoshinori Ono, Thomas Arrhenius, Alex Nadzan. Novel Chromene Derivatives as TNF-α Inhibitors. *Bioorg Med Chem Lett* 2003; 13: 3647–3650.
16. Suresh T, Arunima V, Atin K, Sandeep G, Prarthana VR, Ganesh RK. Novel chromeneimidazole derivatives as antifungal compounds: synthesis and in vitro evaluation. *Acta Pol. Pharm*, 2010; 67: 423-427.
17. Nareshkumar Jain, Jiayi Xu , Ramesh MK ,Fuyong Du , Guo Jian- Zhong , Emmanuel Pacia, et al. Identification and Structure−Activity Relationships of Chromene-Derived Selective Estrogen Receptor Modulators for Treatment of Postmenopausal Symptoms. *J Med Chem*, 2009; *52*(23):7544–7569.
18. Mori J, Iwashima M, Takeuchi M, Saito H. A synthetic study on antiviral and antioxidative chromene derivative. *Chem Pharm Bull*, 2006; 54(3): 391-6.

19. Aliaa MK, Manal MK, Eman k Abd El-all and Heba AH Elshemy. Design and synthesis of substituted chromenes as potential anticancer agents. *IJPRD*, 2012; 4(3): 310-322.
20. Denish CK, Hetal KP, Nilesh KG. Synthesis, characterization & anti-HIV activity of 4-Hydroxy-3-(5-methylisoxazol-3- yl)pyrano(3,2-C)chromene-2,5-dione. *AJBPR* 2012; 2(2):126- 130.
21. Nimesh RK, Dhaval DH, Prashant TM, Saurabh KP. Synthesis and evaluation of in vitro antitubercular activity and antimicrobial activity of some novel 4*H*-chromeno[2,3-*d*]pyrimidine via 2- amino-4-phenyl-4*H*-chromene-3-carbonitriles. *Med Chem Res*, 2011; 20(7): 854-864.
22. Nitin K, Sushil K, Himanshu G, Sharma PK. 3-Hydroxy-2- (substituted phenyl) -4*H*-chromen-4-one derivatives- synthesis, spectral characterization and pharmacological screening. *WRJB*, 2012; 1(1): 1-5.
23. Bhat MA, Siddiqui N, Khan SA. Synthesis of novel 3-(4-acetyl- 5H/methyl-5-substituted phenyl-4,5-dihydro-1,3,4-oxadiazol-2- yl)-2H-chromen-2-ones as potential anticonvulsant agents. *Acta Pol Pharm*, 2008; 65(2): 235-39.
24. Nicolaou KC, Pfefferkorn JA, Roecker AJ, Cao GQ, Barluenga S, Mitchell HJ. Natural Product-like Combinatorial Libraries Based on Privileged Structures. 1. General Principles and Solid-Phase Synthesis of Benzopyrans. *J Am Chem Soc* 2000; 122: 9939-9953.