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Insilico Evaluation and Antioxidant Activity of [(2E)-7 Hydroxy-4-Methyl-2H-Chromen-2-Ylidene] Amino Derivatives

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ABSTRACT

Coumarin Schiff bases (1-14) synthesized by microwave irradiation method, were evaluated by insilico techniques and for their antioxidant activity by ferric reducing antioxidant power (FRAP) assay. The results from insilico techniques showed that all the compounds exhibit drug likeness satisfying Lipinski rule of five having the ability to behave as drugs. These findings revealed that they are active nuclear receptor, GPCR ligand and enzyme inhibitors. Insilico OSIRIS predictions indicate that all the compounds suffer from teratogenic effect, compounds **9, 14** possesses mutagenic toxicity. OCHEM results clearly indicate that they are inhibitors of CYP1A2 a subtype of cytochrome P450. Compound 8 gave FRAP value nearer to the standard. The study provides a good scope for further development of novel targeted molecules.

Keywords: Microwave irradiation, insilico, FRAP, OCHEM, OSIRIS.

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INTRODUCTION

Coumarin derivatives have been of great interest because of their role in natural and synthetic organic chemistry. Many products which contain a coumarin subunit exhibit biological activity such as molluscicides, [15] anthelmintic, hypnotic, insecticidal[16] activity and some are serving as anticoagulant agents[17]and fluorescent brighteners. So coumarin containing a Schiff base are expected to have enhanced antitumor and other biological activities. Schiff bases form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications that include antibacterial[1-7], antifungal[4-7]and antitumor activity[8-9].They have been studied extensively as a class of ligands[10-12]and are known to coordinate with metal ions through the azomethine nitrogen atom. A Schiff base named after Hugo, Schiff is a compound a functional group that contains a carbon-nitrogen double bond with the N-atom connected to an aryl (or) alkyl group not hydrogen. Schiff base is a broad sense have the general formula R1 R2 C=NR3, were 'R' is an organic side chain in this definition. Azomethine group (–C=N–) containing compounds typically known as Schiff bases have been synthesized by the condensation of primary amines with active carbonyls. Schiff base complexes play a vital role in designing metal complexes related to synthetic and natural oxygen carriers[13]. Metal complexes make these compounds effective as stereospecific catalysts towards oxidation, reduction, hydrolysis, biological activity and other transformations of organic and inorganic chemistry[14]. In organic compounds the presence of –C=N– along with other functional groups form more stable complexes compared to compounds with only –C=N– coordinating moiety.

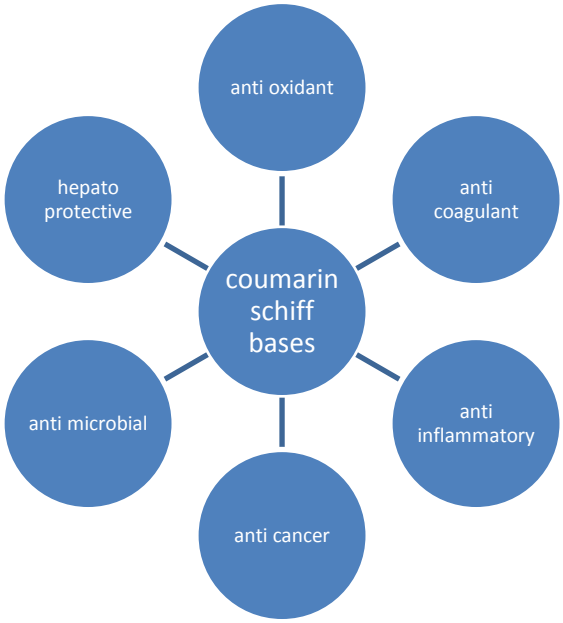


Figure 1: Applications of coumarin Schiff bases

Microwave irradiation of organic reactions has rapidly gained popularity as it accelerates the reaction towards a variety of synthetic transformations, Solventless procedures without the use of supporting reagents and hence eco-friendly. Chemical transformations that took hours or even days to complete can now be accomplished in minutes. Microwave energy offers numerous benefits for performing synthesis such as increased reaction rates, enhanced yields and cleaner chemistries.

MATERIAL AND METHOD

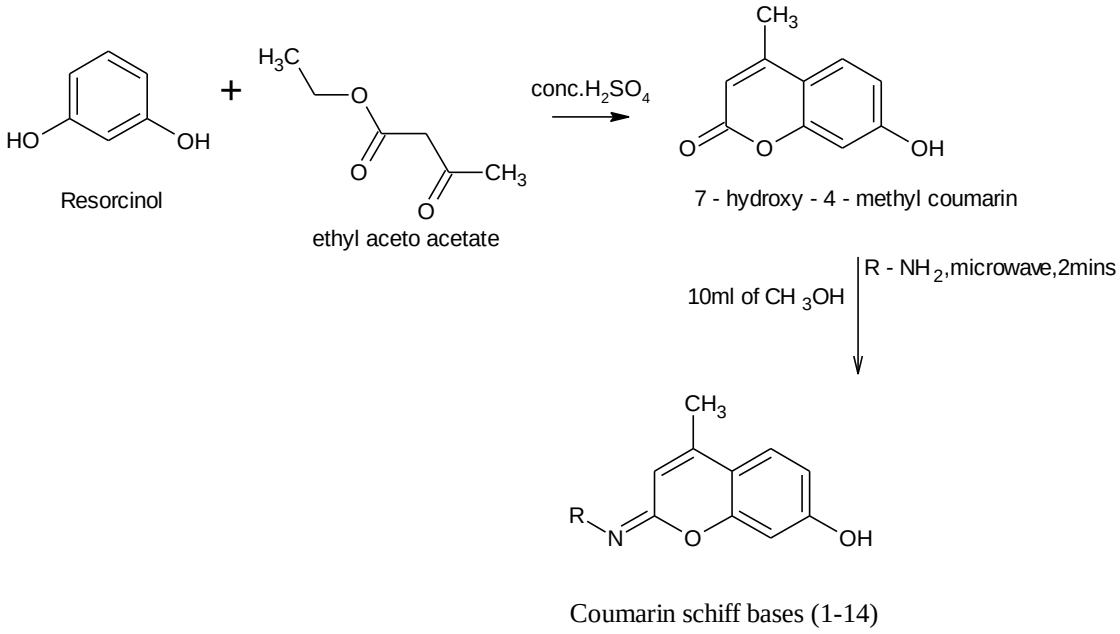
SYNTHETIC PROCEDURE:

Synthesis of STEP1: Synthesis of 7- hydroxyl-4-methyl coumarin

The synthesis of 7 hydroxy 4 methylcoumarin was performed by the Pechmen condensation of resorcinol and ethyl acetoacetate under microwave irradiation. The optimum reaction conditions are 5.5 g of resorcinol, 6.8 ml ethyl acetoacetate, 1.5 ml concentrated sulfuric acid, 240 W microwave power and 6 min microwave irradiation. The yield reaches 84.1%. The melting point of 7 hydroxy 4 methylcoumarin is 189℃ to 192℃. The product was recrystallized from aqueous ethanol and confirmed by thin layer chromatography and melting point.

STEP-2: Synthesis of coumarin Schiff bases[18-21]

Coumarin Schiff bases were preceded by dissolving 0.002moles of step 1 product and 0.04 moles of different aromatic amines in alcohol. The reaction mixture was kept in microwave for 2minutes, then the reaction mixture was added to crushed ice with continuous stirring and then filtered, dried and product recrystallized from alcohol. The purity of the product was confirmed by thin layer chromatography and melting point. The procedure was illustrated under the scheme.



Coumarin schiff bases (1-14)

R-C5H5N, -C4H3N2, -COC6H4, -C6H5, -C6H4SO2NH2, -C6H4OH, -C6H4OCH3, -C6H4COCH3, -C6H4N(OH)2, -C6H4Cl, -C6H5NH2, -C6H4COOH, -C4H3N2O2, -C12H12N

INSILICO AND TOXICITY PREDICTIONS:

The *Insilico*[22-23] and toxicity predictions for the synthesized compounds were carried out by using three online software's.

Molinspiration cheminformatics[24] used for calculation of important molecular properties like logP, Polar surface area, Number of hydrogen bond donors, Number of hydrogen bond acceptors, Number of rotatable bonds, Volume, Number of violations from rule of five. It is used to predict bioactive scores for the most important drug targets like GPCR ligand, Kinase inhibitors, Ion channel modulators, nuclear receptors, Protease inhibitors, Enzyme inhibitors. The results were tabulated in Table 1 & 2.

OSIRIS[25] used to estimate the risks of side effects, such as mutagenic, tumorigenic, irritant and reproductive effects, as well as drug-relevant properties including cLogP, LogS (solubility), MW and drug-likeness. The observations were given in Table 3.

OCHEM (Online Chemical Modeling Environment)[26] is a unique and a web-based platform that aims to automate and simplify the typical steps required for QSAR modeling. The predictions were given in Table 4.

Table 1: Mollinspiration drug likeness properties

Compound Code	Compound IUPAC Names	Log P	Polar Surface Area	H- Bond Acceptors	H- Bond Donors	Volume
1	(2E)-4-methyl-2-[(pyridine-4-yl)imino]-2h chromen-7-ol amine	2.72	54.71	3	1	224.695
2	(2E)-4-methyl-2-[(pyrimidin-2-yl)imino]-2H-chromen-7-ol amine	3.51	47.37	3	0	220.538
3	N-(2E)-7-hydroxy-4-methyl-2H-chromen-2-ylidene] benzamide	3.18	58.89	3	1	256.582
4	2E)-4-methyl-2-(phenyl imino)-2H-chromen-7-ol	3.94	41.82	2	1	228.851
5	4-{[(2E)-7 hydroxy-4-methyl-2H-chromen-2-ylidene]amino}benzene-1-sulfanamide	2.55	101.98	4	2	271.571
6	(2E)-2-[(4-hydroxy phenyl)imino]-4-methyl-2H-chromen-7-ol	3.61	62.05	3	2	236.869
7	-(2E)-2[(4-methoxy phenyl)imino]-4-methyl-2H-chromen-7-ol	3.78	51.05	3	1	254.397
8	N-[7-hydroxy-4-methyl-2H-chromen-2-yl]-N-phenyl acetamide	3.40	49.77	3	1	287.548
9	-(2E)-2-{[4-(dihydroxyamino)phenyl]imino}-4-methyl-2H-chromen-7-ol	3.20	65.29	4	2	252.185
10	(2E)-2[(4-chloro phenyl)imino]-4-methyl-2H-chromen-7-ol	5.36	21.59	1	0	242.387
11	(2E)-4-methyl-2-[2-phenyl hydrazine-1-ylidene]-2H-chromen-7-ol	3.89	53.85	3	2	241.253
12	4-{[(2E)-7hydroxy-4-methyl-2H-chromen-2-ylidene]amino}benzoic acid	4.42	58.89	3	1	255.852
13	6-{[(2E)-7hydroxy-4-methyl-2H-chromen-2-ylidene]amino}-1,3-diazinane-2,4-dione	0.61	100.02	4	3	236.789
14	-(2E)-2{[2-amino-1-(naphthalene-1-yl)ethyl]imino}-4-methyl-2H-chromen-7-ol	3.99	67.84	3	2	317.761

Table 2: Bioactive Scores

Compound	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	-0.61	-0.79	-0.43	-0.56	-0.95	-0.07
2	-0.55	-0.81	-0.37	-0.51	-0.96	-0.12
3	-0.55	-0.80	-0.60	-0.35	-0.85	-0.20
4	-0.72	-1.07	-0.77	-0.68	-1.16	-0.20
5	-0.60	-1.00	-0.56	-0.69	-0.63	-0.02

6	-0.65	-1.02	-0.69	-0.59	-1.05	-0.18
7	-0.63	-1.04	-0.66	-0.56	-1.02	-0.21
8	0.12	-0.14	-0.16	0.31	0.02	0.10
9	-0.70	-0.98	-0.75	-0.58	-1.04	-0.28
10	-0.65	-1.02	-0.72	-0.62	-1.11	-0.22
11	-0.70	-0.88	-0.43	-0.83	-0.92	-0.20
12	-0.53	-0.96	-0.64	-0.34	-0.87	-0.12
13	-0.70	-1.26	-0.60	-0.46	-1.12	-0.02
14	-0.25	-0.45	-0.26	-0.26	-0.31	-0.06

Table 3: OSIRIS Calculations

Compound	Toxicity Risks				Molecular Properties Calculation				
	MUT	TUMO	IRRI	REP	M.W	CLP	logS	DL	DS
1					252	1.67	-2.23	-2.26	0.31
2					253	1.48	-2.29	-1.83	0.32
3					279	2.86	-3.31	-1.41	0.3
4					251	2.67	-3.02	-2.65	0.28
5					332	-0.21	-3.56	-3.94	0.26
6					267	2.32	-2.72	-4.14	0.27
7					281	2.6	-3.04	-5.18	0.21
8					285	2.86	-5.37	-2.86	0.25
9					298	2.07	-3.66	-6.73	0.09
10					286	3.28	-3.76	-3.32	0.25
11					266	4.48	-3.01	-2.46	0.14
12					295	2.16	-3.03	-4.66	0.27
13					278	2.86	-2.37	-0.6	0.25
14					261	3.17	-3.08	0.14	0.19
Tetracycline					444.4	-1.33	-1.83	5.43	0.81
Fluconazole					323	-0.11	-2.17	1.99	0.87

MUT: Mutagenic; **TUMO:** Tumorogenic; **IRRI:** Irritant; **REP:** Reproductive Effective; **CLP:** ClogP; **Log s:** Solubility mol/lit; **DL:** Drug-Likeness; **DS:** Drug-Score. **MW:** Molecular weight

Table 4: Online Chemical Modelling

Compound	Aq. Solubility	LOG IGC50	AMES	CYP3A4	CYP2D6	CYP2C19	CYP2C9	CYP1A2
1	3.63	1.39	Inactive	+	+	+	+	+
2	2.83	0.89	inactive	-	+	-	-	+
3	4.86	1.61	Inactive	+	+	+	+	+
4	4.49	1.8	Inactive	+	+	+	+	+
5	3.52	2.25	Inactive	+	-	+	+	+

6	4.28	1.54	Inactive	+	+	+	+	+
7	4.79	2.01	Inactive	+	+	+	+	+
8	4.16	0.39	inactive	-	+	+	+	-
9	4.83	2.53	Active	+	-	+	+	+
10	5.33	2.16	Inactive	+	+	+	+	+
11	4.99	1.79	Active	+	+	+	+	+
12	3.89	1.46	Inactive	-	-	-	+	-
13	2.36	0.33	Inactive	-	-	-	-	+
14	3.66	1.75	Active	-	+	+	+	+
Flucanozole	1.8	-0.15	inactive	-	-	-	-	-

+ Inhibitor, - Non inhibitor, AQ-aqueous, IGC 50-Environmental toxicity

Table 5: IC_{50} Values

Compound	IC_{50} µg/ml
1	13.9
2	15
3	13.2
4	11
5	18.5
6	14.7
7	14.9
8	8.3
9	11
10	13.7
11	15.2
12	13
13	10.5
14	12
Ascorbic acid	7

ANTI OXIDANT ACTIVITY:

Ferric reducing assay:

1ml of test sample of DMF (N,N-Dimethyl formamide) extract in different concentrations were mixed with 1ml of 0.2M sodium phosphate buffer (p^H-6.6) and 1ml of 1% potassium ferricyanide in separate test tubes. The reaction mixtures were incubated in a temperature-controlled water bath at 50^0C for 20 min followed by addition of 1ml of 10% trichloroacetic acid. The mixtures were then centrifuged for 10 min at room temperature. The supernant obtained (1ml) was added with 1ml of deionised water 200µl of 0.1%$FeCl_3$. The blank was prepared in the same manner as the samples except that 1% potassium ferricyanide was replaced by distilled water. The absorbance of the reaction mixture was measured at 700 nm. The IC 50 values were shown in Table 5.

RESULTS AND DISCUSSION

By this study it was predicted that compounds obey Lipinski rule of five and found to be the

compound 8 is active inhibitor of GPCR, Nuclear receptor, Protease and Enzyme targets.Insilico OSIRIS predictions indicate that all the compounds suffer from teratogenic toxicity. The compounds 9, 14 possesses mutagenic and 9, 11 exhibits tumorogenic toxicities.

OCHEM results clearly indicate that they act as inhibitors of CYP1A2 a subtype of cytochrome P450. The compound 8 has shown antioxidant activity nearer to the standard Ascorbic acid, it has high reducing potential due to presence of carbonyl group.

CONCLUSION:

In silico evaluation was carried out by Molinspiration, OCHEM, and OSIRIS softwares. All the compounds exhibited drug likeness and obeys Lipinski rule of five. This software predicted bioactive scores for which the compounds exhibited nuclear receptor, GPCR ligand and enzyme inhibitors. The values ranged from -0.5 to 0.5 showing that the molecules are moderately active to active against the targets.

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