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DIVALENT METAL COMPLEX OF COUMARIN: SYNTHESIS & CYTOTOXIC EVALUATION

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Keywords:

Coumarins, Schiff Base, Pechmann reaction, Anticancer activity

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ABSTRACT: Introduction: Coumarins are secondary metabolites widely spread in nature. Due to their broad pharmacological activities, many natural and synthetic coumarins and more complex related derivatives are of interest. The coumarin is extremely variable in structure due to the various types of substitutions in their basic structure, influencing their biological activity. Metal complexes of coumarins obtained revealed higher biological activity than their ligand. Metal complexes play a vital role as chemotherapeutic agents. **Methods:** 7-amino-4-methylcoumarin refluxed with substituted aromatic aldehydes in absolute alcohol in presence of acetic anhydride and was washed with cold water to give Schiff bases of 7-amino-4-methylcoumarin (4a-4j). Further, the metal complexes of coumarin Schiff base (5a-5j) were synthesized by dissolving both Schiff base of 7-amino-4-methylcoumarin and metal sulphates in methanol and are stirred at 250C with dropwise addition of a dil. ammonia. **Result and Conclusion:** Screening the copper metal complexes against breast cancer cell line (MDA MB 231) with standard Paclitaxel using MTT assay method. The synthesized metal complexes show anticancer activity in a concentration-dependent manner. The IC_{50} values of metal complexes were found as 258.3, 256.2, 241.3, 262.1, 178.10, 257.8, 175.2, 272.1, 178.3 and 280.6 µg/ml respectively, when compared to standard Paclitaxel IC_{50} 257 µg/ml under experimental conditions. The primary *in-vitro* anticancer activity results revealed that 5a, 5b, 5c and 5d showed good anticancer activity.

INTRODUCTION: Cancers or tumors are groups of cells that have undergone unregulated growth and will often form a mass or lump that may distribute diffusely [1]. Tobacco use is the cause of about 22% of cancer deaths. Another 10% are due to obesity, poor diet, lack of physical activity, and excessive drinking of alcohol. Other factors include certain infections, exposure to ionizing radiation and environmental pollutants.

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In the developing world, 15% of cancers are due to Helicobacter pylori, hepatitis B, hepatitis C, human papillomavirus infection, Epstein-Barr virus, and human immunodeficiency virus. Approximately 5-10% of cancers are due to inherited genetic defects from a person's parents [2].

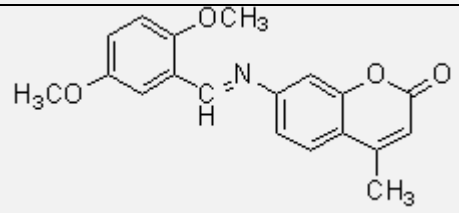
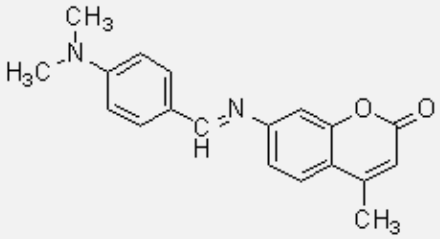
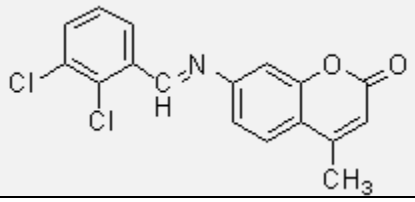
Coumarins are secondary metabolites widely spread in nature and found in green plants, fungi, bacteria, in some animal species. Many natural and synthetic coumarins and more complex related derivatives are of interest due to its broad pharmacological activities, including anti-bacterial 3, 4, anti microbial 5, anti-thrombotic, vasodilator scavenging of reactive oxygen species and anti-tumorigenic, appears to be based on coumarin

nucleus. The coumarin is extremely variable in structure, due to the various types of substitutions in their basic structure, influencing their biological activity [6, 7]. Coumarin (2-H-1-benzopyran-2-one) originates from a wide variety of plants, animals, bacteria, and fungi and contains a class of the phenolic group composed of fused benzene and α-pyrone ring. As we know, coumarin's pharmacological action depends on the nature of the group present and its substitution pattern on the basic nucleus. Some reports have shown that substitution at the C-4 position of coumarin exhibits tremendous cytotoxic activity [8-11] in various cancer cell lines. Coumarins have been investigated for the complexing ability with metals.

Metal complexes of coumarins obtained revealed higher biological activity than their ligand [12]. Metal complexes of O, S, and N containing Schiff bases have been the subject of current growing interest because it has a wide range of pharmacological activities1 [13-15]. Metal complexes play a vital role as chemotherapeutic agents1 [16-29]. Earlier platinum complex cisplatin was most commonly used as an effective drug. Because of its limited use and resistance, research is been diverted to other metals which show better activity; they started using physiological metals. One of them is copper [30-33], which plays a major role in the human system. Another most important reason to use copper metal is the perspective of adopting cytotoxic mechanism and has a great variety of complexing abilities [34].

MATERIALS AND METHODS: The title compounds were synthesized as per scheme I. m-aminophenol condensed with ethyl acetate in the presence of ethyl chloroformate to give 3-hydroxyphenylurethane (1). This condensation with the ethyl acetoacetate in 75% sulphuric acid gives rise to 7-carbethoxyamino-4-methylcoumarin (2). This on refluxing with the mixture of sulphuric acid and glacial acetic acid followed by diluting with water and next made alkaline with the mixture of sodium hydroxide and sodium carbonate to form 7-amino-4-methylcoumarin (3). This product was further refluxed with substituted aromatic aldehydes in absolute alcohol in the presence of acetic anhydride and was washed with cold water to give Schiff bases of 7-amino-4-methyl coumarin (4_a-4_j). Further, the metal complexes of coumarin Schiff base (5_a-5_j) were synthesized by dissolving both Schiff base of 7-amino-4-methyl coumarin and metal sulphates in methanol and are added dropwise and stirred at 25°C with the dropwise addition of a dilute solution of ammonia [35].

TABLE 1: STRUCTURE AND CHEMICAL NAME OF SCHIFF BASES OF 7-AMINO-4-METHYL COUMARIN

Compound	Structure	Chemical name
4a		7-[2,5-dimethoxybenzylideneamino]-4-methyl-2H-chromen-2-one
4b		7-[4-dimethylaminobenzylideneamino]-4-methyl-2H-chromen-2-one
4c		7-[2,3-dichlorobenzylideneamino]-4-methyl-2H-chromen-2-one

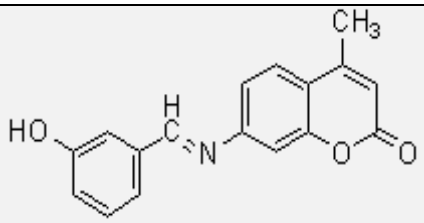
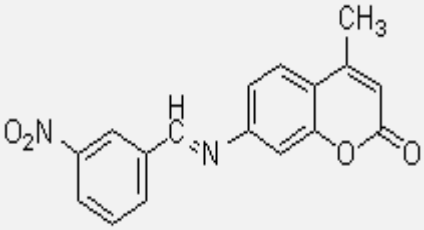
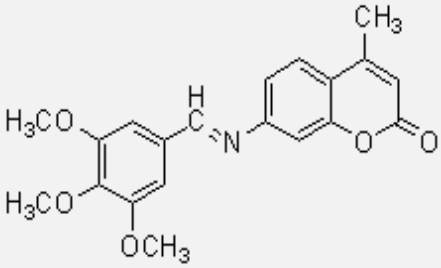
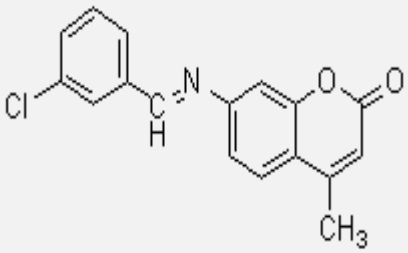
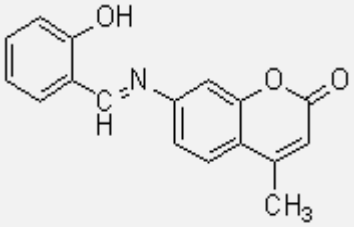
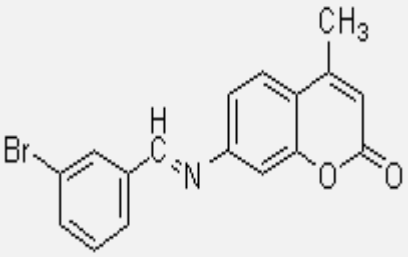
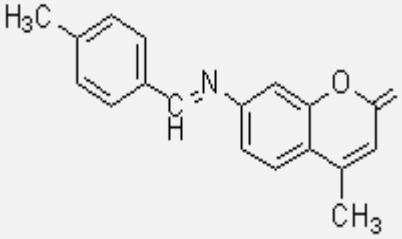
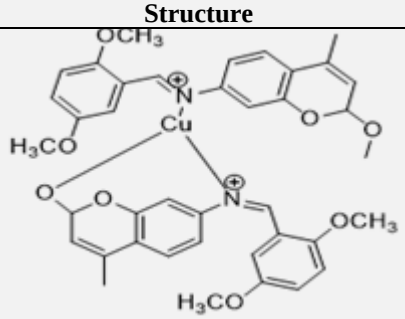
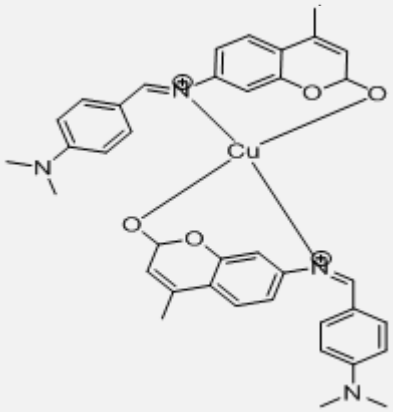
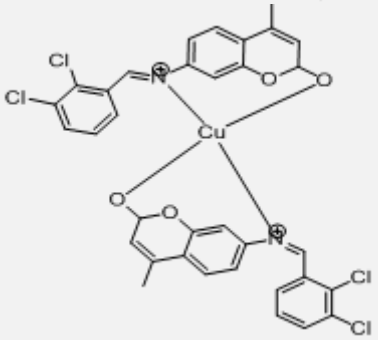
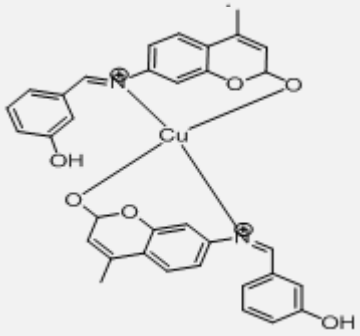
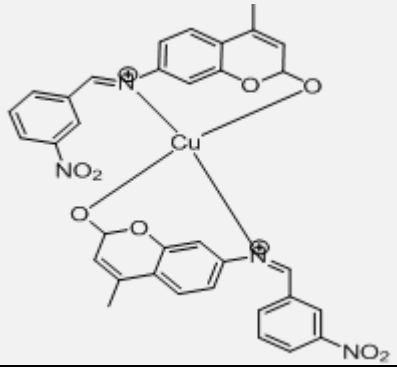
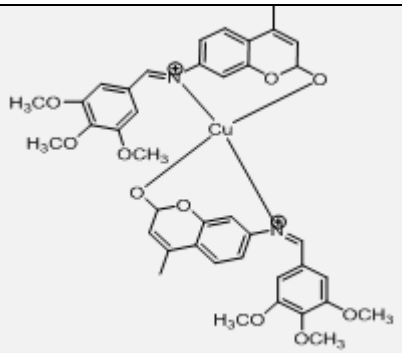
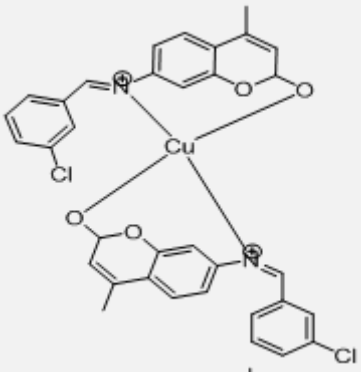
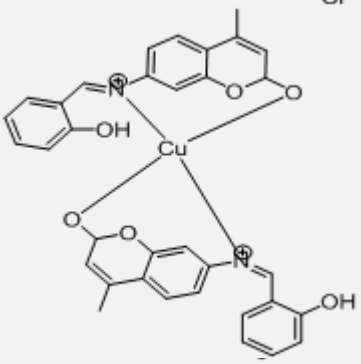
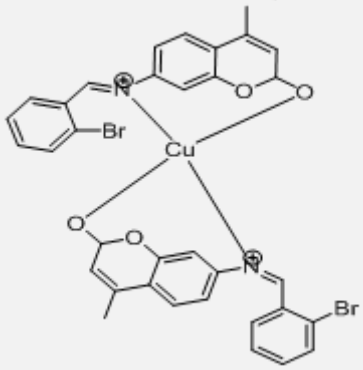
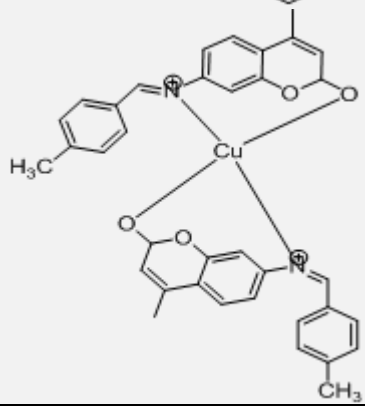
4d		7-[3-hydroxybenzylideneamino]-4-methyl-2H-chromen-2-one
4e		7-[3-nitrobenzylideneamino]-4-methyl-2H-chromen-2-one
4f		7-[3,4,5-trimethoxybenzylideneamino]-4-methyl-2H-chromen-2-one
4g		7-[3-chlorobenzylideneamino]-4-methyl-2H-chromen-2-one
4h		7-[2-hydroxybenzylideneamino]-4-methyl-2H-chromen-2-one
4i		7-[3-bromobenzylideneamino]-4-methyl-2H-chromen-2-one
4j		7-[4-methylbenzylideneamino]-4-methyl-2H-chromen-2-one

TABLE 2: STRUCTURE AND CHEMICAL NAME OF A COPPER COMPLEX OF SCHIFF BASES OF 7-AMINO-4-METHYL COUMARIN

Compound	Structure	Chemical name
5a		Copper complex of Schiff base of 2,5-dimethoxybenzaldehyde
5b		Copper complex of Schiff base of 4-dimethylaminobenzaldehyde
5c		Copper complex of Schiff base of 2,3-dichlorobenzaldehyde
5d		Copper complex of the Schiff base of 3-hydroxybenzaldehyde
5e		Copper complex of the Schiff base of 3-nitrobenzaldehyde

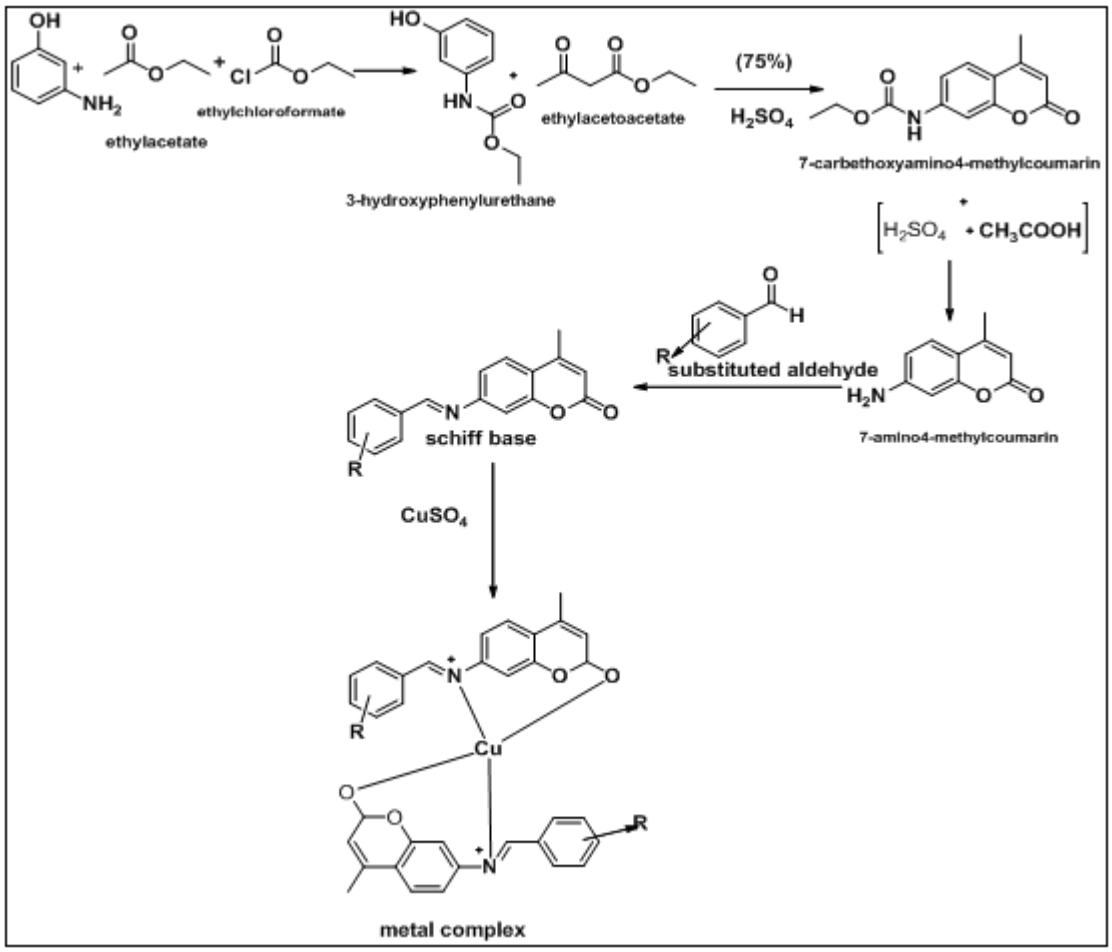
5f		Copper complex of Schiff base of 3,4,5-trimethoxybenzaldehyde
5g		Copper complex of Schiff base of 3-chlorobenzaldehyde
5h		Copper complex of Schiff base of 2-hydroxybenzaldehyde
5i		Copper complex of Schiff base of 3-bromobenzaldehyde
5j		Copper complex of Schiff base of 4-methylbenzaldehyde

***In-vitro* Anticancer Activity [36, 37, 38]:**

Cytotoxicity by MTT Assay: The human carcinoma cell lines were purchased from the national center for cell sciences (NCCS) in Pune. The cell line was cultured in DMEM with low glucose medium (Cat No-11965-092), which was supplemented with 10% heat-inactivated fetal calf serum (FBS) and 1% antibiotic-antimycotic 100X solution and incubated in a CO_2 incubator [Eppendorf, New Brunswick, Galaxy 170 R, Germany] maintained at 310K in 5% CO_2 and 95% humidity until the completion of the experiment. The cells were seeded at a density of approximately 5×10^3 cells [well in a 96-well flat-bottomed microplate and maintained at 310K in 95% humidity and 5% CO_2 overnight. Then different concentrations [i.e., 31.25, 62.5, 125, 250, and 500 µg/ml] of the complex were added to the wells, which were incubated for another 48 hours. The cells were washed twice with phosphate buffer solution and 20µl of 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) staining solution (5mg/ml in phosphate buffer solution) was added to each well, which was then incubated at 310K. After 4 hours, the formazan formed was dissolved in the 100µl of dimethylsulfoxide (DMSO), and the absorbance was recorded at 570 nm using the microplate reader.

The principle of MTT Assay: This is a colorimetric assay that measures the reduction of yellow 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The MTT enters the cells and passes into the mitochondria, where it is reduced to an insoluble, colored (dark purple) formazan product. The cells are then solubilized with an organic solvent (*e.g.*, DMSO, isopropanol), and the released; solubilized formazan reagent is measured spectrophotometrically. Since, the reduction of MTT can only occur in metabolically active cells, the level of activity is a measure of the viability of the cells.

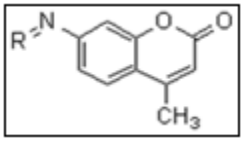
Synthetic Studies [35]:



RESULTS AND DISCUSSION:

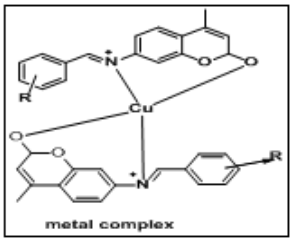
Synthesis: Title compounds were synthesized as shown in Scheme I. The physical data of the synthesized. Schiff bases of 7-amino-4-methylcoumarins are given in **Table 3,** and the Copper metal complexes of those are given in **Table 4.**

TABLE 3: PHYSICAL DATA OF N-SUBSTITUTED SCHIFF BASES OF 7-AMINO-4-METHYL COUMARIN



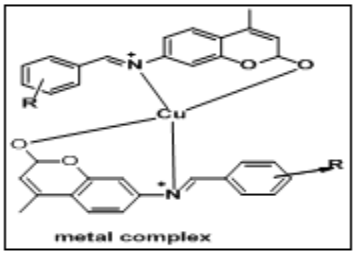
Compound*	R	Colour	% yield	Melting Point (°C)	Rf value#	Molecular Formula
4a	o,m-$C_2H_6O_2$-C_7H_4	Yellow	87.3%	178-179	0.62	$C_{19}H_{17}O_4N$
4b	p-$N(CH_3)_2C_7H_5$	Yellow	71.69%	>300	0..78	$C_{19}H_{18}O_2N_2$
4c	o,m-Cl_2-C_7H_4	Light brown	63.98%	150-152	0.51	$C_{17}H_{11}O_2NCl_2$
4d	m-OH-C_7H_5	Light brown	82%	184-186	0.74	$C_{17}H_{13}O_3N$
4e	m-NO_2-C_7H_5	Yellow	73.4%	192-194	0.43	$C_{17}H_{12}O_4N_2$
4f	o,m,p-$C_3H_9O_3$-C_7H_3	Pale red	71.35%	>300	0.69	$C_{20}H_{19}O_5N$
4g	m-Cl-C_7H_5	Pale brown	78%	217-218	0.75	$C_{17}H_{12}O_2NCl$
4h	o-OH-C_7H_5	Pale brown	74.18%	162-164	0.81	$C_{17}H_{13}O_3N$
4i	m-Br-C_7H_5	Yellow	70%	154-156	0.6	$C_{17}H_{12}O_2NBr$
4j	p-CH_3-C_7H_5	Yellow	80%	>300	0.72	$C_{18}H_{15}O_2N$

TABLE 4: PHYSICAL DATA OF COPPER METAL COMPLEXES OF N-SUBSTITUTED SCHIFF BASES OF 7-AMINO-4-METHYL COUMARIN



Compound*	R	Colour	% yield	Melting Point (°C)	Molecular Formula
5a	o,m-$C_2H_6O_2$-C_7H_4	Mint Green	82.3%	265-268	$C_{38}H_{34}O_8N_2Cu$
5b	p-$N(CH_3)_2C_7H_5$	Blue	75.19%	250-252	$C_{38}H_{36}O_4N_4Cu$
5c	o,m-Cl_2-C_7H_4	Violet	60.55%	281-282	$C_{34}H_{22}O_4N_2Cl_4Cu$
5d	m-OH-C_7H_5	Blue	60.9%	234-236	$C_{34}H_{26}O_6N_2Cu$
5e	m-NO_2-C_7H_5	Mint Green	65%	244-246	$C_{34}H_{24}O_8N_4Cu$
5f	o,m,p-$C_3H_9O_3$-C_7H_3	Blue	68.35%	280-285	$C_{40}H_{38}O_{10}N_2Cu$
5g	m-Cl-C_7H_5	Purple	68.18%	257-258	$C_{34}H_{24}O_4N_2Cl_2Cu$
5h	o-OH-C_7H_5	Blue	66.50%	283-285	$C_{34}H_{26}O_6N_2Cu$
5i	m-Br-C_7H_5	Blue	70.20%	276-278	$C_{34}H_{24}O_4N_2Br_2Cu$
5j	p-CH_3-C_7H_5	Blue	80%	280-282	$C_{36}H_{30}O_4N_2Cu$

TABLE 5: CELL VIABILITY (MDA MB 231) OF COPPER METAL COMPLEXES OF N-SUBSTITUTED SCHIFF BASES OF 7-AMINO-4-METHYL COUMARIN BY MTT ASSAY



Compound*	R	Concentration (µg/ml)					
		0	**31.25**	**62.5**	**125**	**250**	**500**
5a	o,m-$C_2H_6O_2$-C_7H_4	-	95.12	81.20	72.25	60.78	55.00
5b	p-$N(CH_3)_2C_7H_5$	-	95.03	72.01	70.19	72.80	48.44
5c	o,m-Cl_2-C_7H_4	-	92.20	75.60	72.25	60.12	48.00
5d	m-OH-C_7H_5	-	82.32	80.29	75.32	69.91	54.55
5e	m-NO_2-C_7H_5	-	94.24	77.44	68.41	60.14	90.12
5f	o,m,p-$C_3H_9O_3$-C_7H_3	-	95.52	82.25	76.83	65.15	57.98
5g	m-Cl-C_7H_5	-	83.48	70.31	73.25	63.12	60.03
5h	o-OH-C_7H_5	-	95.13	82.23	78.56	72.88	51.53
5i	m-Br-C_7H_5	-	97.50	76.88	72.02	80.83	54.38
5j	p-CH_3-C_7H_5	-	96.50	86.59	80.22	75.17	76.25
Standard drug (Paclitaxel)		-	98.56	81.94	65.73	56.17	49.23
Control		100	-	-	-	-	-

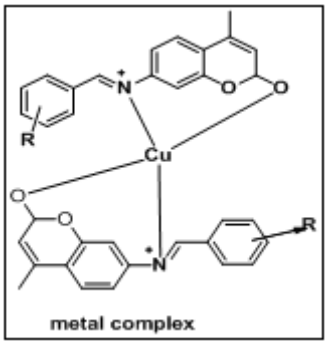
Standard drug - Paclitaxel - 0.3µM or 257µg/ml

Surviving cells (%) = Mean OD of test compound / Mean OD of Nagative control × 100

Inhibiting cells (%) = 100-surviving cells DMSO concentration is less than 1.5% in Experiments

Table 5 discloses the cell viability % of a copper metal complex of N substituted Schiff base 7-amino-4-methylcoumarin with the standard paclitaxel against MDA-MB231.

TABLE 6: IC_{50} VALUES (MDA MB 231) OF COPPER METAL COMPLEXES OF N-SUBSTITUTED SCHIFF BASES OF 7-AMINO-4-METHYL COUMARIN



Compound*	R	IC_{50} value in µg/ml
5a	o,m-$C_2H_6O_2$-C_7H_4	258.3
5b	p-$N(CH_3)_2C_7H_5$	256.2
5c	o,m-Cl_2-C_7H_4	241.3
5d	m-OH-C_7H_5	262.1
5e	m-NO_2-C_7H_5	178.10
5f	o,m,p-$C_3H_9O_3$-C_7H_3	257.8
5g	m-Cl-C_7H_5	175.2
5h	o-OH-C_7H_5	272.1
5i	m-Br-C_7H_5	178.3
5j	p-CH_3-C_7H_5	280.6

Table 6 discloses the IC_{50} value of copper metal complex of N substituted Schiff base 7-amino-4-methylcoumarin with the standard paclitaxel against MDA-MB231. The anticancer activity screening of the copper metal complexes against breast cancer cell line (MDA MB 231) with standard Paclitaxel by using MTT assay method. The higher toxicity of the synthesized compounds than standard Paclitaxel induces death.

The synthesized metal complexes show anticancer activity in a concentration-dependent manner. The IC_{50} values o metal complexes, which are screened against MDA MB 231 breast cancer cell line, were found as 258.3, 256.2, 241.3, 262.1, 178.10, 257.8, 175.2, 272.1, 178.3 and 280.6, respectively, when compared to standard Paclitaxel IC_{50} 257 µg/ml under experimental conditions.

Among the synthesized compounds, 5a shows %cell viability of 95.12, 81.20, 72.25, 60.78 and 55 at concentration 31.5, 62.5, 125, 250 and 500 µg/ml respectively. Compound 5b shows 95.03, 72.01, 70.19, 72.80 and 48.44 at concentration 31.5, 62.5, 125 and 500 respectively.

Compond 5c 92.20, 75.60, 72.25, 60.12 and 48 at concentrations 31.5, 62.5, 125, 250 and 500 µg/ml respectively. Compound 5d shows 82.32, 80.29, 75.32, 69.91 and 54.5 at com-centrations 31.5, 62.5, 125, 250 and 500 µg/ml respectively. Standard Paclitaxel showed 98.56, 81.94 and 65.73, 56.17 and 49.23 at concentrations 31.5, 62.5, 125, , 250 and 500 µg/ml respectively. All the above compounds showed good anticancer activity.

CONCLUSION: The primary *in-vitro* anticancer activity results revealed that compouds of copper complex of 7-(2,5-dimethoxybenazylideneamino)-4-methyl-2H-chromen-2-one(5a), copper complex of 7 - (4 - dimethylaminobenazylideneamino) - 4-methyl - 2H – chromen – 2 - one(5b), 7-(2,3-dichlorobenazylideneamino)-4-methyl-2H-chromen -2-one(5c) and 7-(3-hydroxybenazylideneamino)-4-methyl-2H-chromen-2-one(5d) showed good anticancer activity.

The main objective of our synthesized compounds is to have better anticancer activity with lesser side effects, but we partially succeeded, as all the synthesized compounds other than 5a, 5b, 5c and 5d did not show a good anticancer activity. The compounds 5a, 5b, 5c and 5d showed good activity compared to standard. The possible improvements in the anticancer activity can be achieved by slight modifications in the ring substituents and /or extensive additional fractionation warrants further investigation. Further investigation is necessary for this field in search of potent anticancer activity.

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