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Synthesis, Molecular Modeling and Cytotoxicity Study of New 3-Phenyl Coumarin Derivatives against *in vitro* Cell Lines

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In pursuit of more effective cancer treatments, researchers embarked on a study to enhance the coumarin derivative's therapeutic potential. These compounds, known for their anticancer properties, have faced challenges such as increased toxicity and drug resistance. The research aimed to design, synthesize and assess new 3-phenyl coumarin derivatives specifically for breast and lung cancer treatment. Utilizing 3-oxoacyl-reductase (1T8I), a series of compounds were synthesized from aromatic aldehydes and phenylacetic acid. Among the synthesized 11 compounds that were examined, compounds **C01**, **C04**, **C05** and **C08** had significant cytotoxic effects on both MCF-7 and MRC-5 cell lines. Particularly, compound **C08**, featuring ethoxy and nitrate substitution, exhibited remarkable potential against both cancer cell lines, emphasizing its promise for further exploration in cancer therapy.

Keywords: Cancer, Cytotoxicity, Coumarin, MRC-5 cell lines, MCF-7 cell lines.

INTRODUCTION

Cancer will eventually surpass cardiovascular diseases as the leading cause of death in future [1]. Recent reports from the World Health Organization (WHO) indicate that cancer has been ranked as the second leading cause of death across the globe. GLOBOCAN estimates that 18 million new cancer cases and 9.6 million cancer deaths occurred in middle and low-income nations, with over 70% of these deaths occurring in developed and developing countries [2,3]. Men are more likely to get lung, prostate and stomach cancers *versus* women, who are more likely to develop breast, cervical, thyroid and colorectal cancers. The global death rate for lung and breast cancer is especially concerning because of insufficient efforts in cancer prevention, diagnosis and treatment. As a result, developing innovative anticancer drugs stands out as a difficult issue for medicinal chemists to combat the global spread of cancer [4]. Anticancer drugs work in several methods to prevent cancer cell division, including cytoskeleton disrupting agents, DNA crosslinking agents and antimetabolites [5]. The majority of anticancer medicines destroy cancer cells by inducing apoptosis in them [6]. Apoptosis promotes homeostasis and eliminates damaged cells. It is the outcome of a complicated interaction between pro and anti-apoptotic molecules [7].

Of their diverse pharmacological and biological properties, natural and synthesized coumarin based molecules have caught the curiosity of medicinal chemists and drug design specialists. The encouraging indication for the future of this field is the increasing number of publications focusing on coumarin-based molecules. Coumarin derivatives found to exert different therapeutic activities like anti-depressant [8], antiviral [9], anticancer [10], antileishmanial, antitubercular [11], antimalarial, antibacterial [12], analgesic [13], anti-inflammatory [14], anticonvulsant [15], antioxidant [16], antimicrobial, antifungal [17], *etc*. Designing molecules using molecular modelling studies accelerates the finding of new active compounds. Molecular modelling studies of 3-phenyl coumarin derivatives with targeted proteins like 3-oxoacyl-reductase (DNA topoisomerase I PDB: 1T8I) will help find compounds with potential cytotoxicity and anticancer activity. In present study, 11 derivatives of coumarin were synthesized, characterized and evaluated for their cytotoxicity under *in vitro* studies against lung and breast cancer using the cell lines MRC-5 and MCF-7.

EXPERIMENTAL

Chemicals and solvents were procured from Sigma-Aldrich and Merck. On the Veego melting point apparatus (VMP PM, 32/1105), the melting point of 3-phenyl coumarin derivatives was measured and are uncorrected. Thin layer chromatography (TLC) was done by using (G-60 mesh) silica gel. Reactions monitored by precoated TLC and visualized either by iodine vapours or under UV cabinet. The R_f values of the synthesized compounds were calculated using *n*-hexane:ethyl acetate (8:2) and then the absorbance was noted using UV spectroscopy. Using KBr as reference, the IR spectra of intermediate and final derivatives were obtained using a Fourier transform infrared spectrophotometer (Jasco FTIR). ^{1}H NMR spectra were acquired using a BRUKER spectrometer using $CDCl_3$ as solvent.

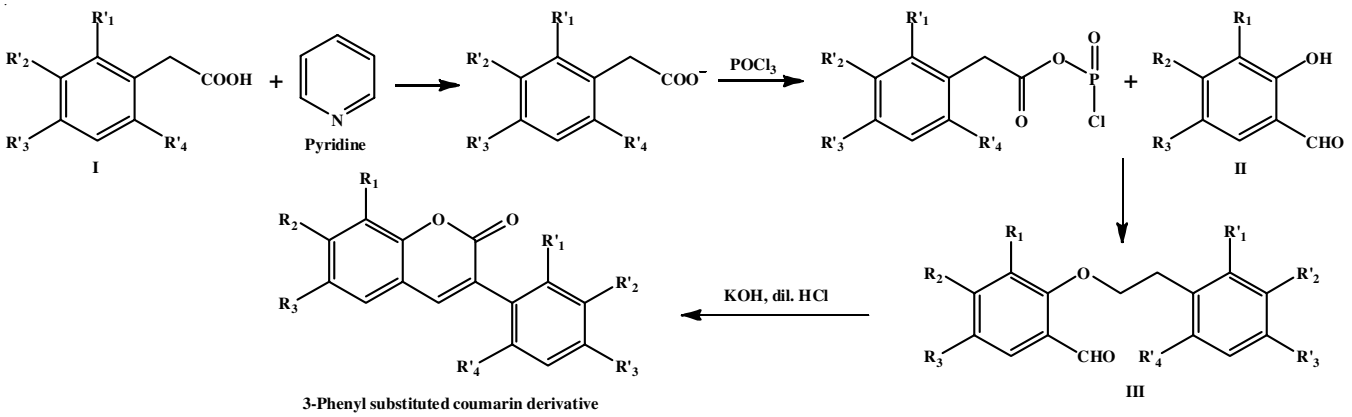
Synthesis of 3-phenyl coumarin derivatives: The coumarin derivatives was synthesized by following the reported procedure [18]. Breifly, phenylacetic acid (**1**) (1.5 mmol) dissloved in pyridine mixed with aromatic aldehyde (**2**) (1 mmol) followed by the addition of $POCl_3$ (1.5 mmol) and then ester (**3**) reacts with potassium hydroxide (4 mmol) to obtain substituted coumarin by Knoevenagel condensation reaction. Then the reactions were worked up with ice-cold water and dil. HCl. The white solid product was obtained and the recrystallization was done using ethanol (**Scheme-I**).

6-Bromo-3-(4-methoxyphenyl)-2*H*-chromen-2-one (C01): Yield: 86.9%, R_f: 0.51, m.p.: 331-332 ºC; IR (KBr, ν_{max}, cm^{-1}): 2877 (C-H), 1673 (C=O), 1276 (C-O-C), 1469, 1427, 1565, 1612 (C=C), 1071, 1210 (O-CH_3), 539 (C-Br). ^{1}H NMR (400 MHz $CDCl_3$) δ ppm: 6.97 (1H, d), 7.63 (1H, d), 7.67 (1H, s), 7.70 (1H, s), 7.00 (2H, d), 6.53 (2H, d), 3.72 (3H, s), UV spectra: Absorbance maxima were obtained at 221.65, 251.10 and 335.64 nm. Elemental analysis: calcd. (found) % for $C_{16}H_{11}O_3Br$: C 58.03 (58.035); H, 3.35 (3.34); Br, 24.13 (24.30); O. 14.49 (14.48).

8-Methoxy-3-*p*-tolyl-2*H*-chromen-2-one (C02): Yield: 70.1%, R_f: 0.63, m.p.: 266-267 °C, IR (KBr, ν_{max}, cm^{-1}): 2900 (C-H), 1718 (C=O), 1517, 1420 (C=C), 1286 (C-O-C), 1210 (O-CH_3), 714, 769 (CH_3 mono substituted benzene); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.25 (3H, s), 3.73 (3H, s), 6.63 (1H, d), 7.07 (1H, d), 7.10 (1H, t), 7.11 (2H, d), 7.14 (2H, d), 7.61 (1H, s). UV spectra: Absorbance maxima were obtained at 217.88, 264.24 and 273.04 nm. Elemental analysis: calcd. (found) % for $C_{17}H_{14}O_3$: C, 76.68 (76.70); H, 5.30 (5.29); O, 18.05 (18.02).

3-(3,4-Dimethoxyphenyl)-6-nitro-2*H*-chromen-2-one (C03): Yield: 79.4%, R_f: 0.79, m.p.: 327-328 ºC, IR (KBr, ν_{max}, cm^{-1}): 2883 (C-H), 1705 (C=O), 1579 (NO_2), 1458, 1480, 1500, 1663 (C=C), 1333 (C-O-C), 1014, 1200 (O-CH_3). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.71 (6H, s), 6.60 (1H, d), 7.14 (1H, d), 7.30 (1H, d), 7.50 (1H, s), 8.25 (1H, d), 8.32 (1H, s). UV spectra: Absorbance maxima were obtained at 206.67, 232.42 and 312.21 nm. Elemental analysis: calcd. (found) % for $C_{17}H_{13}NO_6$: C, 62.39 (62.36); H, 4.00 (4.08); N, 4.28 (4.35); O, 29.33 (29.32).

6-Bromo-3-(4-hydroxyphenyl)-8-methoxy-2*H*-chromen-2-one (C04): Yield: 75.2%, R_f :0.84, m.p.: 347-348 ºC, IR (KBr, ν_{max}, cm^{-1}): 2980 (C-H), 1654 (C=O), 1579, 1475, 1448



Compound	R_1	R_2	R_3	R'_1	R'_2	R'_3	R'_4
C01	H	H	Br	H	H	OCH_3	H
C02	OCH_3	H	H	H	H	CH_3	H
C03	H	H	NO_2	H	OCH_3	OCH_3	H
C04	OCH_3	H	Br	H	H	OH	H
C05	OC_2H_5	H	H	H	H	F	H
C06	OCH_3	H	H	H	H	NO_2	H
C07	OH	H	H	H	H	H	OCH_3
C08	OC_2H_5	H	H	H	H	NO_2	H
C09	H	H	Br	H	H	OH	H
C10	H	H	Br	H	H	Br	H
C11	OC_2H_5	H	H	H	H	H	OH

Scheme-I: Synthesis of 3-phenyl coumarin derivatives

(C=C), 1275 (C-O-C), 1079, 1203 (O-CH_3), 574 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.87 (3H, s), 4.52 (1H, s), 6.67 (1H, s), 6.80 (2H, d), 7.31 (1H, s), 7.36 (2H, d), 8.00 (1H, s). UV spectra: Absorbance maxima were obtained at 226.10, 265.15, 345.76 nm, Elemental analysis: calcd. (found) % for $C_{16}H_{11}O_4Br$: C, 55.36 (55.31); H, 3.19 (3.20); Br, 23.02 (23.01); O, 18.43 (18.42).

8-Ethoxy-3-(4-fluorophenyl)-2*H*-chromen-2-one (C05): Yield: 83.2%, R_f: 0.24, m.p.: 284 ºC, IR (KBr, ν_{max}, cm^{-1}): 2980 (C-H), 1715 (C=O), 1448, 1475, 1579, 1654 (C=C), 1168 (C-O-C), 1002 (C-F), 1079, 1072, 1219 (O-C_2H_5). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.33 (3H, d), 3.98 (2H, s), 6.96 (1H, d), 6.97 (2H, d), 7.11 (1H, d), 7.19 (1H, s), 7.40 (1H, s), 8.16 (1H, d) UV spectra: Absorbance maxima were obtained at 220.00, 263.94 and 341.52 nm. Elemental analysis: calcd. (found) % for $C_{17}H_{13}O_3F$: C, 71.82 (71.83); H, 4.61 (4.60); F, 6.68 (6.69); O, 16.88 (16.84).

8-Methoxy-3-(4-nitrophenyl)-2*H*-chromen-2-one (C06): Yield: 84.7%, R_f : 0.59, m.p.: 297 ºC, IR (KBr, ν_{max}, cm^{-1}): 2926 (C-H), 1715 (C=O), 1431, 1524, 1597, 1560 (C=C), 1348, 1597 (NO_2), 1184 (C-O-C), 1014, 1255 (O-CH_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.87 (3H, s), 4.50 (1H, s), 6.67 (1H, s), 6.80 (2H, d), 7.31 (1H, s), 7.36 (2H, d), 8.00 (1H, s). UV spectra: Absorbance maxima were obtained at 207.27, 266.67 and 341.50 nm. Elemental analysis: calcd. (found) % for $C_{16}H_{11}NO_5$: C, 55.36 (55.35); H, 3.19 (3.18); Br, 23.02 (23.01); O, 18.43 (18.42).

8-Hydroxy-3-(2-methoxyphenyl)-2*H*-chromen-2-one (C07): Yield: 87.3%, R_f: 0.68, m.p.: 268 °C, IR (KBr, ν_{max}, cm^{-1}): 2960 (C-H), 1712 (C=O), 1240 (OH), 1145 (C-O-C), 1028, 1392 (O-CH_3), 1436, 1469, 1496, 1500, 1601 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 4.98 (1H, s), 6.50 (1H, d), 6.88 (1H, d), 6.91 (1H, t), 7.16 (1H, d), 7.51 (1H, d), 7.26 (1H, d), 9.94 (1H, t). UV spectra: Absorbance maxima were obtained at 204.55, 273.33 and 340.50 nm. Elemental analysis: calcd. (found) % for $C_{16}H_{12}O_4$: C, 71.64 (71.65); H, 4.51 (4.50); O, 23.86 (23.84).

8-Ethoxy-3-(4-nitrophenyl)-2*H*-chromen-2-one (C08): Yield: 82.5%, R_f: 0.67, m.p.: 311 ºC, IR (KBr, ν_{max}, cm^{-1}): 2960 (C-H), 1712 (C=O), 1427, 1524, 1604 (C=C), 1348, 1524 (NO_2), 1111 (C-O-C), 1014, 1248 (O-C_2H_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.35 (3H, t), 3.97 (2H, q), 6.63 (1H, s), 6.94 (1H, d), 7.21 (1H, t), 7.70 (2H, d), 8.03 (1H, s), 8.23 (2H, t). UV spectra: Absorbance maxima were obtained at 219.70, 267.88 and 345.50 nm. Elemental analysis: calcd. (found) % for $C_{17}H_{13}NO_5$: C, 65.59 (65.60); H, 4.21 (4.21); N, 4.50 (4.49); O, 25.70 (25.68).

6-Bromo-3-(4-hydroxyphenyl)-2*H*-chromen-2-one (C09): Yield: 83.5%, R_f : 0.71, m.p.: 317 ºC, IR (KBr, ν_{max}, cm^{-1}): 3649, 3018, 2877 (C-H), 1673 (C=O), 1428, 1465, 1560, 1609 (C=C), 1264 (C-O-C), 1326, 1212 (OH), 537 (C-Br). ^{1}H NMR (400 MHz $CDCl_3$) δ ppm: 6.73 (1H, s), 7.09 (1H, s), 7.25 (1H, s), 7.25 (1H, s), 7.62 (1H, s), 8.16 (1H, s), 7.80 (1H, d), 6.73 (1H, d), 5.1 (1H, s). UV spectra: Absorbance maxima were obtained at 22.42, 251.52 and 337.27 nm. Elemental analysis: calcd. (found) % for $C_{15}H_9BrO_3$: C, 56.81 (56.82); H, 2.86 (2.86); Br, 25.20 (25.19); O, 15.13 (15.12).

6-Bromo-3-(4-bromophenyl)-2*H*-chromen-2-one (C10): Yield: 83.5%, R_f : 0.53, m.p.: 380 ºC, IR (KBr, ν_{max}, cm^{-1}): 3020, 2875 (C-H), 1718 (C=O), 1600, 1580, 1500, 1450 (C=C), 1278 (C-O-C), 627, 538 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.43 (1H, s), 7.31 (1H, s), 7.28 (1H, s), 7.09 (1H, s), 7.62 (1H, s), 7.80 (1H, s), 8.16 (1H, d). UV spectra: Absorbance maxima were obtained at 226.67, 250.61 and 335.45 nm. Elemental analysis: calcd. (found) % for $C_{15}H_8O_2Br_2$: C, 56.45 (56.46), H, 2.53 (2.57); Br, 25.04 (25.03); F, 5.95 (5.94); O, 10.03 (10.02).

8-Ethoxy-3-(2-hydroxyphenyl)-2*H*-chromen-2-one (C011): Yield: 78.8%, R_f: 0.84, m.p.: 282 ºC, IR (KBr, ν_{max}, cm^{-1}): 2892 (C-H), 1696 (C=O), 1458, 1506, 1585, (C=C), 1111 (C-O-C), 1264, 1069 (OC_2H_5), 1218, 1403 (OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.35 (3H, t), 4.08 (2H, q), 6.68 (1H, t), 6.78 (1H, d), 6.81 (1H, d), 6.89 (1H, t), 6.94 (1H, d), 7.06 (1H, t), 7.20 (1H, d), 7.80 (1H, s). UV spectra: Absorbance maxima were obtained at 221.04, 262.53 and 337.92 nm, Elemental analysis: calcd. (found) % for $C_{17}H_{14}O_4$: C, 72.33 (72.34); H, 5.00 (4.99); O, 22.67 (22.66).

MTT based cytotoxicity studies: Cell cytotoxicity assays were conducted using MCF-7 human breast cancer cells and normal human lung fibroblast MRC-5 cells. At 37 ºC and 5% CO_2, both cell lines were cultured in full DMEM media. In 96-well tissue culture plates with a flat bottom, 20,000 cells of each of MRC-5 and MCF-7 cell types were planted. Serial dilutions of compounds, procainamide (Sigma) and 5-azacytidine (Sigma) ranging from 16-1000 µM were prepared. In triplicate, cells were treated with each drug plus a control. Compounds were gently mixed with a multi-channel pipette on the lowest suck setting and plates were incubated at 37 ºC with 5% CO_2 for 24 h. After 24 h plates were observed for cell death and 20 µL of MTT was added in each well and incubated for 4 h at 37 ºC. The medium was then removed from the plate and 100 µL of DMSO (Sigma, USA) was added to each well. To dissolve the blue-coloured formazan crystals, plates were incubated at 37 ºC with 5% CO_2 for 30 min. In an ELISA plate reader, the absorbance was recorded at 560 nm with a reference wavelength of 650 nm and the percentage of cell viability and cell toxicity was computed.

RESULTS AND DISCUSSION

Molecular docking studies: A molecular docking study was done by using 3-oxoacyl-reductase (human DNA topoisomerase I PDB code: 1T8I). The energy of optimization ($\Delta G_{protein}$) was found to be -13386.73 Kcal. The synthesized coumarin derivatives that exhibited considerable interaction were chosen for synthesis based on the docking scores (Table-1). Hydrophobic interactions were observed in compounds **C01**, **C02**, **C04**, **C05**, **C06**, **C07** and **C09**, while van der Waal interactions were observed in compounds **C01**, **C02**, **C05** and **C07** with their respective target molecules (Table-2).

Initially according to PASS prediction results, eleven coumarin derivatives were designed for docking studies. The preliminary docking studies of procaine hydrochloride and coumarin analogues on (4-ethyl-4-hydroxy-1,12-dihydro-4*H*-2-oxa-6,12a-diaza-dibenzo[*b*,*h*]fluorene-3,13-dione) reductase of anticancer human DNA topoisomerase I (PBD code: 1T8I) were carried out using VLife Sciences docking software. Among

TABLE-1
BINDING ENERGY OF SYNTHESIZED 3-PHENYL COUMARIN DERIVATIVES

Compound	PLP score	Energy of ligand after optimization (ΔG_{ligand}) (Kcal)	Energy of complex after optimization ($\Delta G_{complex}$) (Kcal)	$\Delta G_{binding} = G_{complex} - (\Delta G_{ligand} + \Delta G_{protein})$ (Kcal)
C01	-99.7546	86.2384	-15037.4909	-1736.9990
C02	-90.6569	80.7773	-15087.5048	-1781.5518
C04	-99.1826	125.5328	-16137.1023	-2875.9040
C05	-94.8982	76.4900	-16459.8299	-3239.5896
C06	-93.8986	88.7657	-15435.4243	-2137.4597
C07	-98.4428	48.1423	-1508.2412	-1689.6533
C08	-98.9683	109.6901	-16861.3399	-3583.6997
C09	-98.4203	64.5905	-15673.2542	-2351.1144
Procaine	-72.1600	121.1759	-19851.6157	-6586.0616

TABLE-2
DOCKING INTERACTIONS OF SYNTHESIZED 3-PHENYL COUMARIN DERIVATIVES WITH 3-OXOACYL-REDUCTASE (DNA TOPOISO-MERASE I PDB: 1T8I)

Compound	Type of interaction			
	Hydrogen		Hydrophobic	
EHD	DA113D		DA 113D	
	ARG64A		DC 112D	
C01	DA113D 1296H	2.398	DT10B 358C	4.473
			DT10B 359C	3.881
C02	–		1 DT10B 358C	4.878
			TGP11C 399C	4.677
C04	NTGP11C 408H	2.523	TGP11C 385C	4.604
	DC112D 1261H	2.366	DC112D 1241C	2.786
	PTR723A 10340H	1.656	DA113D 1285C	3.884
C05	DA113D 1299H	2.406	DT10B 368C	4.032
	ARG364A	2.157	TGP11C 392C	3.427
	PTR723A 10340H	2.265	DA113D 1280C	4.472
C06	TGP11C 408H	1.415	TGP11C387C	4.743
	ARG364A4410H	1.873	DC112D1241C	4.653
	PTR723A10340H	1.601	DA113D 1285C	2.982
C09	TGP11C408H	1.976	TGP11C 385C	4.127
	DC112D 1259H	2.154	DA113D 1275C	3.948
	van der Waal			
C01	DT10B 361N, DT10B 362C, TGP11C 418H, DC112D 1243N, TGP11C 418H, DC112D 1241C, TGP11C 399C			
C02	DT10B 359C, TGP11C 384N, DT10B 362C, TGP11C 384N, DT10B 363O, TGP11C 385C, DT10B 364N, TGP11C 384N			
C05	DT10B 365C, TGP11C 388N, DT10B 378H, TGP11C 389N, DT10B 378H, TGP11C 389N, TGP11C 389N			
C07	DT10B 359C, TGP11C 385C, DT10B 361N, DT10B 365C, TGP11C 386N, DT10B 375H, TGP11C 384N			

the synthesized coumarin derivatives, only six compounds had shown significant interactions (Table-1).

The Gibb's energy and the PLP score were determined, both of which indicate that the ligand has a favourable binding affinity for 3-oxoacyl-reductase enzymes present. Compound **C04** (Figs. 1 and 2) showed hydrogen bond interactions and hydrophobic bond interactions, respectively. The active site of the human DND topoisomerase I consist of the amino acid residues: (DA 113D, ARG 364D, DA 112D) were found to be involved in the interactions with ligands. The docking studies indicate that substitutions like $-OC_2H_5$, -OH, $-NO_3^-$ and -F on the coumarin ring at R_3 and R_1' and similar substitutions on the phenyl ring represent the significant binding interactions.

Cytotoxicity studies

Cytotoxicity study on MRC-5 cell lines: When cells in culture are exposed to anticancer inhibitors, they exhibit potent cell death. The MRC-5 cell lines viability was determined using the MTT test. All the compounds were tested from 16-1000 µM concentrations, with procaine hydrochloride and 5-azacy-

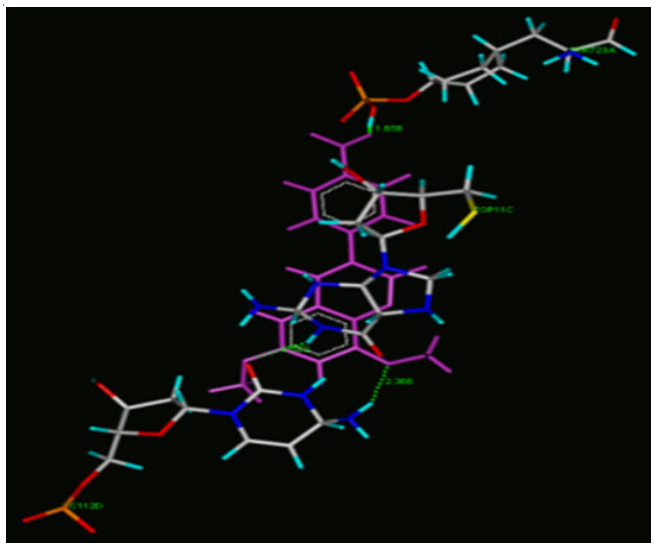


Fig. 1. Hydrogen bond interaction of compound **04** with charge residue (NTGP11C 408H, DC112D 1261H, PTR723A 10340H) of protein 1T8

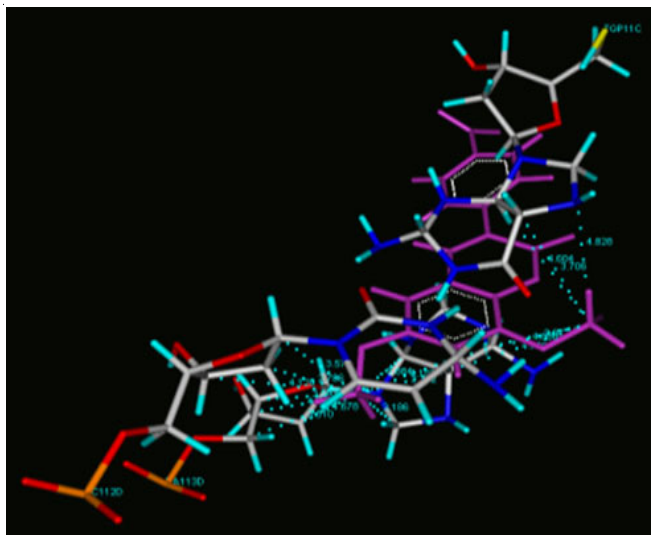


Fig. 2. Hydrophobic bond interaction of compound **04** with charge residue (TGP11C 385C, DA113D 1272C, DA113D 1285C) of protein 1T8I

tidine (5-AZA) as positive controls. Out of all the compounds **C01**, **C04**, **C05** and **C08** showed between 9-27% cell viability at 1000 µM concentration. Procaine hydrochloride exhibited only to 2% cell viability at 1000 µM. When the synthesized compounds were compared to positive control compounds with compound **C05** and **C08** showed the promising results. While other compounds also had a higher affinity (Table-3).

MTT assay on MCF-7 cell lines: Compounds **C01**, **C04**, **C05** and **C08** will be analyzed using the MTT assay on MCF-7 cell lines (Table-4) due to their harmful effects shown in MRC-5 cell lines. Compounds **C05** and **C08** shows high cytotoxic activity as compared to other compounds as well as the positive controls. The control, 5-azacytidine was found to be most potent followed by procaine, while 5-azacytidine was observed to be equally toxic to both MRC-5 and MCF-7 cell lines, procaine displays selective toxicity to MCF-7 cell lines.

Conclusion

Coumarin derivatives were designed in such a way that they can exhibit better binding interactions with 3-oxoacyl-reductase. Out of 11 compounds, synthesized five compounds have shown the potential cytotoxicity activities for *in vitro* cell lines studies of breast and lung cancer. This can be attributed to the substitution pattern. Substitution of groups like –OH, -OC_2H_5, -NO_3, -F on the 3-phenyl coumarin moiety was found to be potent and essential for exerting significant cytotoxicity against the studied MRC-5 and MCF-7 cell lines. Compounds **C05** [8-ethoxy-3-(4-fluorophenyl)-2*H*-chromen-2-one] and **C08** [8-ethoxy-3-(4-nitrophenyl)-2*H*-chromen-2-one] have been found to show significant cytotoxic activity. Based on the cytotoxicity studies and MTT assay on the cell lines both compounds with compound **C05** and **C08** have promising futures as a potent drug in the treatment of breast and lung cancer.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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TABLE-3
CYTOTOXICITY ASSAY DATA OF MRC-5 CELL LINES

Compound	Cell viability (%)							
	1000 µM	500 µM	250 µM	125 µM	62.5 µM	31.25 µM	16 µM	CC µM
C01	26.0396	86.6602	93.0262	86.1804	91.2667	89.0275	94.3698	100.00
C04	29.7007	92.7595	100.701	100.839	100.868	89.0275	100.506	100.00
C05	19.2598	93.9116	97.5053	99.5554	99.3461	100.092	100.401	99.999
C08	9.9391	86.4343	88.5254	93.0831	88.2037	94.2895	91.9035	100.00
5AZA	4.1514	4.0976	4.0058	5.6297	32.6712	36.4669	65.4555	100.00
PROCAIN	2.0969	2.7699	16.7923	31.5591	59.5867	66.9966	87.8913	100.00

TABLE-4
CYTOTOXICITY ASSAY DATA OF MCF-7 CELL LINES

Compound	Cell viability (%)							
	1000 µM	500 µM	250 µM	125 µM	62.5 µM	31.25 µM	16 µM	CC µM
C01	26.0396	86.6602	93.0262	86.1804	91.2667	89.0275	94.3698	100.00
C04	29.7007	92.7595	100.701	100.839	100.868	100.092	100.506	100.00
C05	19.2598	93.9116	97.5053	99.5554	99.3461	100.470	100.401	99.999
C08	9.8391	86.4343	88.5254	93.0831	88.2037	94.2895	91.9035	100.00
5AZA	4.1514	4.0976	4.0058	5.6297	32.6712	36.4669	65.4555	100.00
PROCAIN	2.0969	2.7699	16.7923	31.5591	59.5867	66.9966	87.8913	100.00

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