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SYNTHESIS AND ANTICANCER EVALUATION OF SOME CHROMENONE DERIVED CHALCONES

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ABSTRACT

A new series of 6/7-substituted-chromenone chalcone derivatives (**15a-d**) was designed and synthesized utilizing acid catalyzed condensation methodology. The synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, UV, ATR and mass spectroscopy, and evaluated for their cytotoxic activity against colon (HCT-116 and COLO-205), leukemia (HTP-1) and lung (NCIH-322) cancer cell lines. Compound **15d** (7-Chloro-3-(3-oxo-3-(4-phenoxy-phenyl)prop-1-enyl)-4H-chromen-4-one) emerged as the most promising cytotoxic agent among all the synthesized derivatives (**15a-d**) by exhibiting significant IC_{50} against colon cancer cell line (HCT-116), can be subjected to advanced investigations.

KEYWORDS: Chromenone, Chalcone, Anticancer, Colon Cancer.

1. INTRODUCTION

Cancer is a major human health problem throughout the world. It is expected that by 2030, the global burden of new cancer cases will rise to 21.4 million.[1,2] Regardless of all the advancements made in cancer chemotherapy, complete control on malignancies is still a distinct dream. Therefore, design and development of novel anticancer agents continue to be a key area of activity for medicinal chemists.[3-7] Moreover, major efforts are being directed toward the synthesis of new cost effective molecules with improved anticancer activity and minimal toxicity.[8-11]

Heterocyclic chalcone exhibited enhancement of their anti-proliferation activity, against both sensitive as well as resistant cancerous cells in this regard.[12] Substituted pyridine-2-yl chalcone (**1,** Fig. 1) has proven real potent against human mammary adenocarcinoma cells (MCF-7, IC_{50} = 6.7 µM).[13] Thiol ester substituted furanyl chalcone (**2**) has also been found to exhibit significant anticancer activity against TK-10 (human kidney carcinoma).[14] Besides this, substituted oxathiolone fused chalcone (**3**) has demonstrated enhanced activity in comparison to its aurone analogous.[15]

Next, a major breakthrough in the discovery of hybrid chalcones has come from indolyl chalcones, wherein, compound (**4**) has been identified as the most effective and selective anticancer agent with IC_{50} values 0.03 µM against PaCa-2 cell lines.[16] In imidazo[2,1-b]pyridine/pyrimidine chalcone derivatives, compound (**5**) has revealed promising anticancer activity with enhancement in the expression of p27 and TNFR1 proteins.[17] Subsequently, thiazolyl–chalcone (**6**) has been evaluated to be effective against human gastric cancer BGC-823.[18] Correspondingly, 6-quinolinyl and quinolinyl N-oxide chalcones[19], chromene-based chalcones[20], thiophene and furan substituted chalcone derivatives[21] also have presented appreciable cytotoxic activities. Lately, some novel quinoline-2-one based chalcones have been synthesized, where, compound (**7**) has unveiled remarkable activity against 50 human tumor cell lines, including, HCT-116 (Colon) and LOX IMVI (human melanoma) cells.[22]

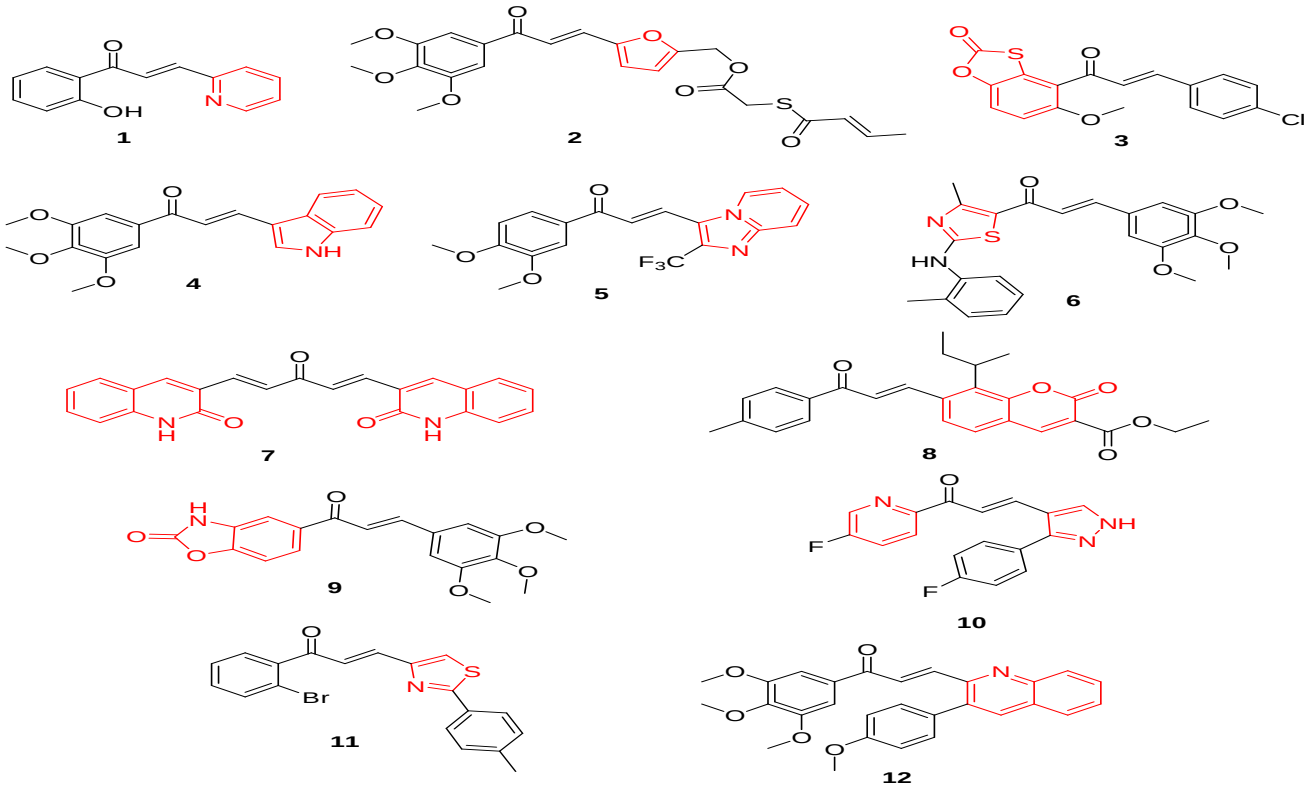


Figure. 1: Heterocyclic Chalcones with Anticaner Potential.

Additionally, a coumarin–chalcone hybrid compound S009-131 (**8**) having an ester chain substitution at 3-position of coumarin ring has displayed 30-folds more selectivity towards cervical carcinoma (C33A) cells over normal fibroblasts NIH3T3 while exhibiting an IC_{50} of 3.59 µM.[23,24] Further, extension of research on hybrid chalcones has led to discovery of some more compounds such as benzoxazolone derivative (**9**)[25] and imidazo[2,1-b][1,3,4]thiadiazole-chalcones (Kamal *et al.*, 2014), which display high cytotoxic efficacy. Also, some newly developed pyrazole chalcones (**10**)[26], thiazolic chalcones (**11**)[27] and chalcone-triazole derivatives[28] have evidenced moderate to good anticancer activity against different tested cancer cell lines. Despite of the earlier reports, 3-phenylquinolinyl chalcone derivatives (**12**) have also proven active against different breast cancer cell lines *viz*. MCF-7, MDA-MB-231 and SKBR-3 with IC_{50} values of 1.05, 0.75 and 0.78 µM respectively without any significant cytotoxicity to the normal H184B5F5/M10 cell lines.[29]

Likewise, growing interest in the biological activities of natural/synthetic heterocycles, has also led to the discovery of several chromen-4-one based molecules with better anticancer efficacy.[30-35] Hence, our research article explores the synthesis, characterization and anticancer studies of chromenone chalcone derivatives (**15a-d**).

2. MATERIALS AND METHODS

2.1. General Information: Starting materials, reagents and solvents were purchased from commercial suppliers Aldrich Chemical Company (U.S.A) and were purified/distilled/crystallized before use.

A Bruker AVANCEII 400 NMR spectrometer was used to record ^{1}H-NMR and ^{13}C-NMR. Chemical shifts (δ) have been reported as downfield displacements from TMS used as internal standard and coupling constants (*J*) are reported in Hz. ATR spectra were recorded with a Bruker ALPHA ATR-8400S spectrophotometer on Zinc Selenium optics. Mass spectra (ESI-MS) were recorded on a Bruker Daltonics Esquire 300 mass spectrometer. Ion trap (Agilent) AP 2000 (SCIEX) spectrometer was also used to record the mass spectra. All melting points are uncorrected and measured in open glass-capillaries on a Veego (make) MP-D digital melting point apparatus. A SHIMADZU UV/VIS 1800 spectrophotometer was used for UV analysis. Weighing balance, (CY220) of Denver Instruments was used for weighing of compounds. TLC was performed on pre-coated silica gel G TLC plates.

2.2. Synthesis of 6/7-Substituted 3-(3-oxo-3-(4-bromophenyl)prop-1-enyl)-4H-chromen-4-one derivatives (15a-d): A mixture of 6/7-substituted-3-formyl-4H-chromen-4-one (**13a-d,** 1.414 moles) and 4-Bromoacetophenone (**14,** 0.9433 moles) along with glacial acetic acid (10 ml, 0.175 moles) and perchloric acid (0.05 ml, 0.831 mmoles) was warmed in a round bottom flask till the reactants were completely consumed (Scheme 1, monitored by TLC, EtOAc/$CHCl_3$:C_6H_{14}, variable ratio).After completion of the reaction, mixture was cooled to 0^{o}C resulting in precipitation of the crude products (**15a-d**) as solid powders. Further, the obtained

crude products were filtered, washed with distilled water, and dried. Thereafter, some of the obtained products were purified through re-crystallisation using EtOAc as solvent and rest were subjected to column chromatography (silica gel 60-120 mesh, eluent Hexane::EtOAc) to yield the purified chromeno-chalcones **(15a-d)** that were further characterized spectroscopically (^{1}H-NMR, ^{13}C-NMR, UV, IR and Mass Spectroscopy).

2.3. Characterization of compounds

2.3.1. 3-(3-Oxo-3-(4-bromo-phenyl)prop-1-enyl)-4H-chromen-4-one 3a: Compound **3a** is yellow solid; Yield: 70%; mp: 178-180^{o}C; UV (MeOH) λ_{max}: 244 nm; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.66 (d, 1H, *J* = 15.2 Hz, –CH=C-), δ 8.31 (dd, 1H, *J* = 8.0 Hz and 1.6 Hz, C_5-H), 8.22 (s, 1H, C_2-H), 7.99-7.96 (m, 2H, Ar-H), 7.75-7.71 (m, 1H, C_7-H), 7.66-7.63 (m, 2H, Ar-H), 7.53-7.48 (m, 3H, –C=CH-C=O, C_6-H and C_8-H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm)**:** 187.48, 175.30, 160.62, 155.09, 136.92, 136.32, 134.98, 131.85, 130.76, 129.43, 125.87, 125.52, 124.58, 123.29, 118.69, 117.31; ATR (ZeSe optics)/cm^{-1}: 3136.77, 2944.52, 2835.35, 1707.56, 1516.22, 1413.13, 1292.69, 687.72; ESI-MS: m/z 355.91 $[M + 1]^+$ (52.5%), 357.93 $[M + 1 + 2]^+$ (54.4%).

2.3.2. 6-Methyl-3-(3-oxo-3-(4-bromo-phenyl)prop-1-enyl)-4H-chromen-4-one 3b: Compound **3b** is red solid; Yield: 73%; mp: 134-136^{o}C; UV (MeOH) λ_{max}: 222 nm; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.65 (d, 1H, *J* = 15.2 Hz, –CH=C-), 8.20 (s, 1H, C_2-H), 8.08 (d, 1H, *J* = 1.2 Hz, C_5-H), 7.99-7.96 (m, 2H, Ar-H), 7.66-7.62 (m, 2H, Ar-H), 7.54 (dd, 1H, *J* = 8.2 Hz and 2.0 Hz, C_7-H), 7.49 (d, 1H, *J* = 15.2 Hz, –C=CH-C=O), 7.41 (d, 1H, *J* = 8.4 Hz, C_8-H), 2.50 (s, 3H, CH_3-Hs); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm)**:** 187.74, 175.25, 160.35, 153.36, 137.02, 136.55, 135.35, 132.52, 131.82, 130.65, 130.10, 129.56, 128.89, 123.20, 118.13, 117.32, 20.15; ATR (ZeSe optics)/cm^{-1}: 3100.01, 2988.66, 1753.30, 1652.50, 1488.04, 1272.73, 761; ESI-MS: m/z 370.01 $[M + 1]^+$ (62.5%), 372.02 $[M + 1 + 2]^+$ (62.0%).

2.3.3. 7-Chloro-6-fluoro-3-(3-oxo-3-(4-bromo-phenyl)prop-1-enyl)-4H-chromen-4-one 3c: Compound **3c** is yellow solid; Yield: 65%; mp: 229-231^{o}C; UV (MeOH) λ_{max}: 288 nm; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ8.60 (d, 1H, J=15.6 Hz, –CH=C-), 8.19 (s, 1H, C_2-H), 8.02 (d, 1H, J=8.4 Hz, C5-H), δ 7.96 (d, 2H, *J*=8.4 Hz , Ar-H), 7.68 (d, 2H, *J*=8.8 Hz, Ar-H), 7.55 (d, 1H, J=5.6 Hz, C8-H),7.40 (d, 1H, J=15.2 Hz, –C=CH-C=O); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm)**:** 187.63, 174.66, 160.57, 158.99, 150.22, 136.38, 135.94, 132.14, 130.68, 130.44, 128.68, 127.35, 125.06, 124.69, 123.73, 121.65, 118.37; ATR (ZeSe optics)/cm^{-1}: 3153.40, 2975.00, 1712.92, 1666.70, 1593.50, 1442.71, 1324.98, 764.54, 730.37; ESI-MS: m/z 406.90 $[M - 1]^+$ (20.5%), 408.92 $[M - 1 + 2]^+$ (27.0%), 410.93 $[M - 1 + 4]^+$ (6.3%).

2.3.4. 7-Chloro-3-(3-oxo-3-(4-bromo-phenyl)prop-1-enyl)-4H-chromen-4-one 3d: Compound **3d** is yellow solid; Yield: 73%; mp: 208-210^{o}C; UV (MeOH) λ_{max}: 285 nm; ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 8.62 (s, 1H, C_2-H), 8.50 (d, 1H, *J* = 15.6 Hz, –CH=C-), 8.21 (d, 1H, *J* = 8.4 Hz, C_5-H), 7.95 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.68 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.63 (d, 1H, *J* = 1.6Hz, C_8-H), 7.57 (d, 1H, *J* = 15.6 Hz, –C=CH-C=O), 7.48 (dd 1H, *J* = 8.4 Hz and 1.6 Hz, C_6-H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ (ppm): 187.51, 174.71, 160.74, 155.42, 138.85, 136.77, 135.92, 135.09, 131.23, 129.43, 127.41, 126.75, 123.56, 122.66, 120.01, 118.23; ATR (ZeSe optics)/cm^{-1}: 3160.00, 2980.04, 1700.00, 1654.12, 1584.53, 1285.98, 767.50, 700.54; ESI-MS: m/z 390.75 $[M + 1]^+$ (7.0%), 392.75 $[M + 1 + 2]^+$ (9.9%), 394.77 $[M + 1 + 4]^+$ (2.5%).

2.4. Pharmacology

2.4.1. Cell lines: Colon (HCT-116 and COLO-205), leukemia (HTP-1) and lung (NCIH-322) cancer cell lines were sub-cultured every two to three days. All cells were maintained in RPMI-1640 medium and supplemented with fetal bovine serum (10%), 100 units/ml penicillin and 100 µg/ml streptomycin (complete medium), respectively.

2.4.2. Preparation of test and standard solutions

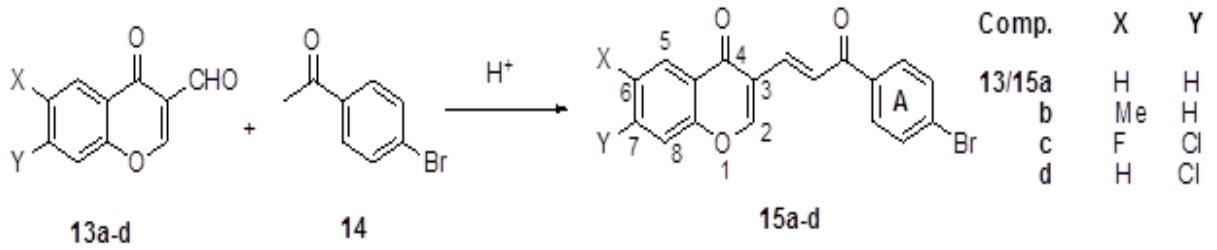
All compounds (**15a–d**) were dissolved separately in DMSO to prepare the stock solution of 2×10^{-4} µM concentration. Stock solutions were further diluted with complete growth medium supplemented with 50 µg/ml gentamycin to obtain test concentration of 100 µM. Paclitaxel was dissolved in DMSO and stock solution of 2×10^{-3} µM concentration was prepared.5-Flurouracil was dissolved in double distilled water and stock solution of 2×10^{-3} µM concentration was prepared. Stock solutions were further diluted with complete growth medium supplemented with 50 µg/ml gentamycin to obtain the desired concentration.

2.4.2. Cytotoxic analysis: The exponentially growing cells were seeded in 96 wells cell culture plates (1×10^4 cells/well) and incubated in a CO_2 incubator (100 µL/well of DMEM medium, 37^{o}C, 5% CO_2, 95% relative humidity) for 24 h. After 24 h, compounds (**15a–d)** and positive controls (100 µL/well) were added in quadruplets and the plates were further incubated in the CO_2 incubator for 48 h. Suitable controls were also included in each experiment. After 48 h chilled trichloroacetic acid (50% w/v, 50 µL) was laid gently on top of the medium in all wells. The plates were incubated at 4^{o}C for one hour to fix the cells. All the contents of the wells were gently pipetted out and discarded. The plates were washed five times with distilled water to remove trichloroacetic acid, the growth medium, low molecular weight metabolites and serum proteins etc. After this treatment, sulphorhodamine-B (0.4% SRB in 1% acetic acid, 100 µL/well) was added to each well of the 96 well plates for 30 min. Excess of the dye was washed off using 1% acetic acid and plates were air-dried. Tris buffer (10 mM, pH 10.5, 100 ml/well) was added to each well and plates were shaken on a mechanical stirrer for 10 min and the absorbance was recorded on an ELISA plate reader at 540 nm. The viability of cells was

evaluated by the trypan blue exclusion method immediately before setting up the experiment for cytotoxicity determination. Cells with >98% viability were used in the assay.

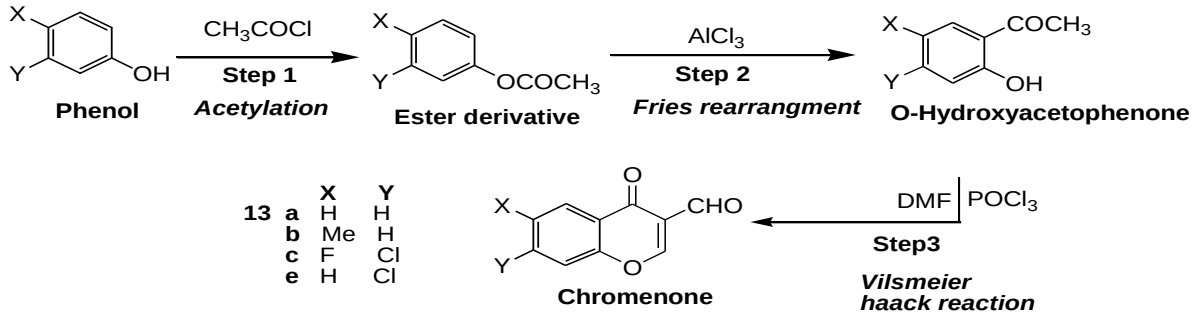
3. RESULTS AND DISCUSSION

3.1. Chemistry: The proposed compounds (15a-d, Scheme 1) were synthesized by reacting 6/7-substituted-3-formyl-4H-chromen-4-one derivatives (13a-d) with various *p*-Bromoacetophenone (14) in acidic medium.[36]



Scheme. 1: Synthesis of 6/7-substituted-3-(3-oxo-3-(4-Bromo-phenyl)prop-1-enyl)-4H-chromen-4-one derivatives (15a-d).

All 6/7-substituted-3-formyl-4H-chromen-4-one derivatives (**13a-d**) were synthesised by reported methods (Scheme 2).[37-40] The obtained crude chromeno-chalcone derivatives (**15a-d**) were purified by crystallization/column chromatography and characterized spectroscopically (^{1}H-NMR, ^{13}C-NMR, Mass, UV and ATR).



Scheme. 2: Synthesis of 6/7-Substituted-3-formylchromen-4-one (13a-d).

^{1}H-NMR spectra of all the synthesized compounds (**15a-d**) in common displayed, besides resonances in the aromatic region, a downfield 1H doublet (assigned to –CH=C- proton of propenone moiety) at ~ δ8.6 ppm. Corresponding –C=CH-C=O proton appeared as a multiplet at ~δ7.3-7.6 ppm in most of the compounds. However, it also appeared as a ^{1}H doublet at ~δ7.4-7.6 ppm in some cases; *J* values calculated for the doublets given by –CH=C- and –C=CH-C=O protons in various compounds, came out to be ~ 15.2-15.4 Hz; a characteristic of the protons having *trans* configuration.C_2-H proton of chromen-4-one nucleus appeared as ^{1}H singlet at ~ δ8.2 ppm in $CDCl_3$ soluble compounds, whereas in DMSO-d_6 soluble sample, a more downfield shift for this proton was observed (1H singlet at ~ δ8.62 ppm). In ^{13}C-NMR spectra, characteristic downfield shifts, for the carbonyl carbon of propenone fragment and C_4 carbon of chromen-4-one nucleus, were observed at ~ δ187 ppm and ~ δ175 ppm respectively. ATR spectra revealed a band in the characteristic absorption range of 1750–1700 cm^{-1} assigned to the stretching vibrations of carbonyl group of propenone fragment. The position of this band depends on the nature of attached groups.Stretching vibrations of carbonyl group present in the chromen-4-one nucleus manifested at around 1660–1620 cm^{-1}. Mass spectra of halogenated derivatives clearly revealed the isotopic clusters predicted for chlorinated (3:1 relative isotopic abundance), brominated (1:1 relative isotopic abundance) and chloro-brominated (3:4:1 relative isotopic abundance) molecules.

3.2. Pharmacological evaluation

All the synthesized compounds (**15a–d**) were evaluated for their *in-vitro* cytotoxicity against colon (HCT-116 and COLO-205), leukemia (HTP-1) and lung (NCIH-322) cancer cell lines.[41-44] Their cytotoxicity potential has been expressed in terms of percentage (%) growth inhibition of cancer cell proliferation, at a concentration of 100 µM for each compound (Table 1).

Table. 1: *In-vitro* cytotoxicity of 6/7-substituted-3-(3-oxo-3-(4-bromo-phenyl)prop-1-enyl)-4H-chromen-4-one derivatives (15a-d) against different human cancer cell lines.

S. No.	Compound	X	Y	Z	R	Colon		Leukemia	Lung
						HCT-116	COLO-205	THP-1	NCIH322
						% Growth inhibition at 100 micromolar			
1	**15a**	H	H	H	Br	12	0	41	0
2	**15b**	Me	H	H	Br	1	0	20	0
3	**15c**	F	Cl	H	Br	14	11	21	0
4	**15d**	H	Cl	H	Br	**87**	32	**82**	53
*	**5-Fu**					67	70	72	-
**	**Paclitaxel**					-	-	-	65

* 5-FU was used at the concentration of 20µM.** Paclitaxel was used at the concentration of 1.0µ

Further, IC_{50} value (*i.e.* concentration required to inhibit cancer cell proliferation by 50% after exposure of cells to the test compound) was also determined for the significantly active derivative **15d** (Table 2).

Table. 2: IC_{50} (µM) values[a] of most active compound (15d) against different human cancer cell line.

Compound	Colon		Leukemia	Lung
	HCT-116	Colo-205	THP-1	NCIH322
15d	78.9	>100	80.4	>100

[a]*IC_{50}, 50% inhibitory concentration represents the mean from dose response curves of number of experiments.*

Among the tested compounds (**15a-d,** Table 2), compound **15d** demonstrated maximum inhibition of 87% against colon cancer cell line (HCT-116) with an IC_{50} value of 78.9 µM.

5. CONCLUSIONS

Acid catalyzed condensation reactions of differently substituted 3-formyl-4H-chromen-4-one derivatives (**13a-d**) with *p*-Bromoacetophenone (**14**) is utilized as a facile route to proposed chromen-4-one-3-yl chalcone derivatives (**15a-d**). In pharmacological evaluation results Compound **15d** has emerged as most promising candidate due to its significant activity against colon cancer cell line (HCT-116). It can be used as lead for further modifications.

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