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Synthesis And Biological Evaluation of Novel Benzopyran-2-One And 1, 2, 4-Triazole Hybrid Derivatives as Cytotoxic Agents

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ABSTRACT

Triazole's anti-inflammatory properties in cellular assays and benzopyran-2-one's cytotoxic effects against multi-drug resistant cancer cell lines led us to design and synthesize their hybrid compounds and investigate their antiproliferative activity against a panel of five cancer cell lines. Compounds FE-e, FE-f, FE-o and FE-q displayed significant antiproliferative activities against all the cancer cell lines tested, and IC_{50} values were in the range of 162-164µM/mL against MDA-MB-231, MCF-7, CaCO2, HUT102 and HUT78 cancer cells, while they were minimally cytotoxic to the HEK-293 and LLC-PK1 normal cell lines. All the compounds were screened for cytotoxicity using MTT assay. Overall, these findings suggest that new benzopyran-2-one-triazole hybrid compounds, particularly FE-e, FE-f, FE-o and FE-q, exhibited promising cytotoxic activity mediated via inhibition of cancer cell proliferation and induction of apoptosis across these cancer cell lines. Additionally, these are selective anticancer agents, potentially safe for human cells, and could be synthesized at low cost.

Keyword: *antiproliferative; apoptosis; benzopyran-2-one; coumarin; drug discovery; triazole; protein tyrosine kinase*

1. INTRODUCTION

The patient's cancer stage and type are the main determinants of cancer therapy. Targeted therapy, immunotherapy, hormone therapy, radiation, chemotherapy, and surgery are some of the available treatment options [1, 2]. The objectives of treatment are to eradicate cancer cells, restrict their proliferation and dissemination, and eventually cure the disease or prolong the patient's life [3]. Chemotherapy, which has several inherent disadvantages, is still the most common treatment option for cancer despite tremendous advancements in cancer therapy. New compounds are still required to improve personalization, safety, and efficacy while remaining reasonably priced in order to address the drawbacks of chemotherapy, like medication cost, poor personalized service, limited effectiveness, side effects and drug resistance [4–6]. Targeted therapeutic "small molecule" medications are now often used to treat cancer because they are more effective and safe than conventional chemotherapy medications [4].

A number of studies in recent years reviewed benzopyran-2-ones, sometimes called coumarins, and classified them as secondary metabolites [7–11]. With a wide range of pharmacological characteristics, including anti-HIV, antihypertensive, antimicrobial, anti-diabetic, anti-inflammatory, anti-tubercular, anti-allergic, and anti-cancer, the benzopyran-2-one skeleton has consistently been utilized as a model for the creation of new compounds with a variety of medicinal properties [7–11]. Based on tests performed on different tumor cell lines, 3-substituted benzopyran-2-one derivatives have been shown to be

promising antibiotics. Furthermore, it was observed that several cell lines (HUT78, HUT102, MCF7, and MDA-MB) were cytotoxically affected by 7-methoxy benzopyran-2-one derivatives [17].

Triazole is another significant heterocyclic skeleton of contemporary interest, and it exhibits intriguing biological activity together with a few naturally occurring triazole derivatives [19–22].

The fusion of triazole and 3-substituted benzopyran-2-one scaffolds into a single framework, resulting in a hybrid molecule (Figure 1), is of particular interest to initiate a chemical entity that exhibits enhanced pharmaceutical activity compared to the individual components, given the fascinating biological properties of these scaffolds in drug discovery and medicinal chemistry. Triazoles and benzopyran-2-ones, the two ingredients, have each been well explored separately; however, their combination to create novel hybrid compounds has not yet been investigated. Their fusion was expected to provide molecules with enhanced biological activity, making it a focal point of our research.

To potentially exhibit pharmacological action, we hypothesized that a novel series of compounds may be synthesized by conjugating triazoles to benzopyran-2-one at position 3 using different aromatic halides (Figure 1). Benzopyran-2-one nucleus is conjugated to the triazole scaffold in an initial investigation. A library of compounds was then synthesized by adding various aromatic halides to the triazole ring at position 5, and their antiproliferative activity against a panel of distinct cancer cell lines was assessed. In order to show their potential as antiproliferative drugs, they were further tested for kinase inhibitory action, proteolytic human serum stability, and apoptotic activity.

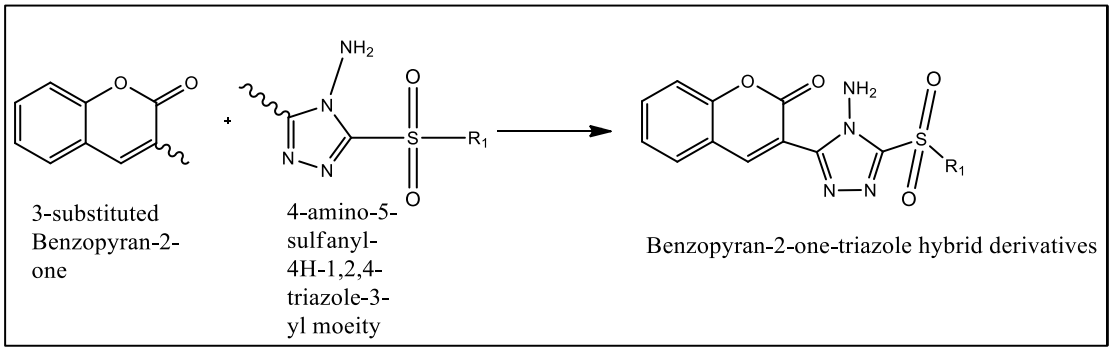


Fig.1: Design of benzopyran-2-one-triazole hybrid derivatives

2. MATERIAL AND METHODS

2.1 Instrumentation

Infrared spectroscopy: Using a Bruker Alpha FT-IR spectrophotometer (Billerica, MA, USA), infrared spectra were captured. Frequencies were recorded on a cm^{-1}. UV-Vis Spectroscopy: Using a Shimadzu UV-2600/2700 UV-VIS recording spectrophotometer (Shimadzu Corporation, MD, USA), UV data was captured in methanol. Mass spectroscopy: Using a Bruker Q-TOF LC/MS mass spectrophotometer (Billerica, MA, USA), the mass spectra were captured. The results were presented as m/z (percentage of relative intensity of the most significant fragments).

Nuclear magnetic resonance spectroscopy: The Bruker Acend 400 spectrometer (Billerica, MA, USA) that operated at 100.62 MHz for ^{13}C and 400.15 MHz for ^{1}H was used to record the ^{13}C and ^{1}H NMR spectra. The solvent peaks were used to calibrate the spectra, and the coupling constant values (J) were supplied in Hz. The chemical shift values were expressed in δ (ppm) scale with respect to tetramethylsilane (TMS) as an internal reference. DEPT (distortionless enhancement by polarization transfer) was also used to assign values (underlined values).

2.2. Materials

2-hydroxybenzaldehyde and diethylpropanedioate was procured from Sigma-Aldrich. Using precoated Merck silica gel 60 F254 (Merck) plates with a layer thickness of 0.2 mm, analytical TLCs were carried out. The petroleum ether/ethyl acetate system was used as an analytical control. Iodine vapor, UV detection (254 nm and 366 nm), and potassium permanganate stain (made by dissolving 1.5 g of $KMNO_4$, 10 g K_2CO_3, and 1.25 mL 10% NaOH in 200 mL water) were used to observe the spots. All solvents and chemicals used for the conjugate synthesis were of analytical quality and procured from Sigma-Aldrich, Merck & Co., and CDH test reagent suppliers.

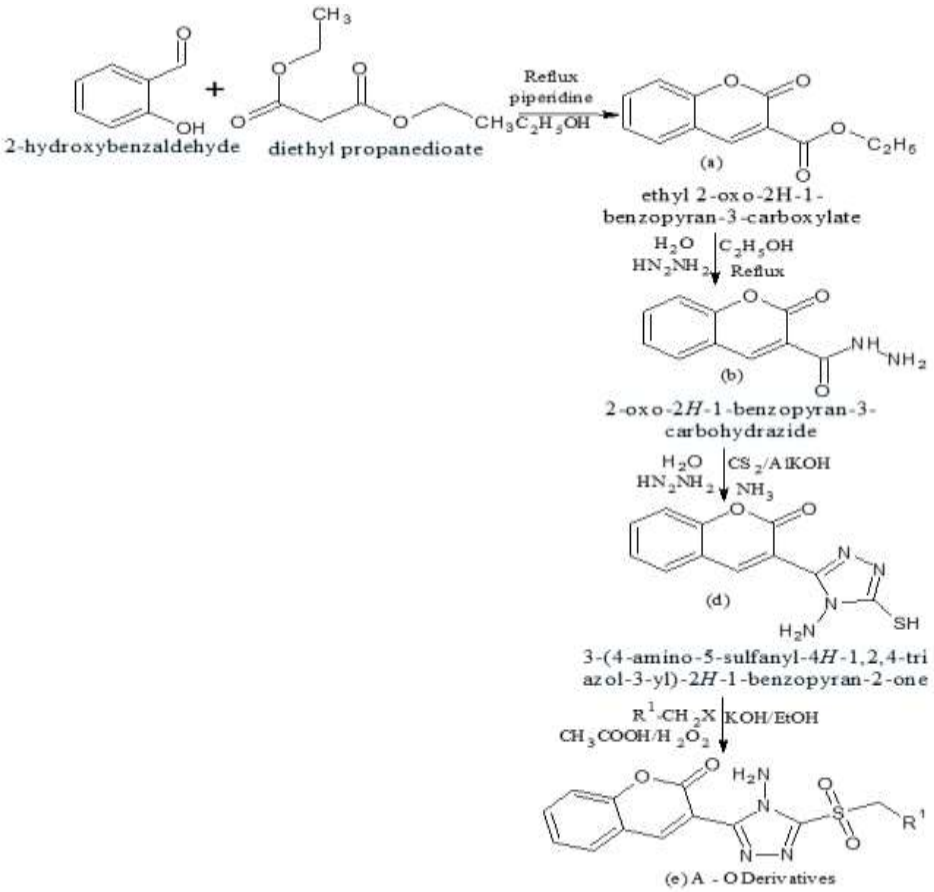


Fig. 2: Scheme 1: Synthetic scheme for the synthesis of benzopyran-2-one-triazole derivatives.

2.3. Synthesis

2.3.1. Step-I: General Procedure for the Synthesis of ethyl-2-oxo-2H-1-benzopyran-3-carboxylate (a)

The Knoevenagel synthesis of 2-hydroxybenzaldehyde (1.5 mol) with diethyl malonate (2.25 mol) was carried out using catalyst, alcoholic piperidine solution (20 ml). This reaction leads to the formation of Ethyl ester a form of 2-oxo-2H-1-benzopyran-3-carboxylate (a). At 60°C, the reaction mixture was then agitated for 4 hrs. TLC [petroleum ether-ethyl acetate 50:50] was used to monitor the reaction until it was finished, and once the reaction is completed 500 mL of cold water was added to the reaction mixture. In order to improve purity, the resultant residue was subsequently recrystallized in ethanol.

Step-II: Preparation of 2-oxo-2*H*-1-benzopyran-3-carbohydrazide (b)

2-Oxo-2H-1-benzopyran-3-carboxylic acid ethyl ester (a) (0.0562 mol) was liquefied in 100 ml of ethanol and mixed with hydrazine hydrate (0.1686 mol) at room temperature. The reaction was stirred for 2 hrs. The completeness of the reaction was assessed by TLC using a solvent system of petroleum ether and ethyl acetate in a 50:50 ratio. A silvery product was then obtained and the solution was filtered and quenched with water followed by rinsing with water (3 x 50 mL). After that the product was air-dried and recrystallized using ethanol.

Step-III: Preparation of 3-(4-amino-5-mercapto-4*H*-1,2,4-triazole-3-yl)-2*H*-1-benzopyran-2-one (d)

2-Oxo-2H-1-benzopyran-3-carbohydrazide (b) (0.0562 mol) was liquefied in 100 ml of methyl alcohol and mixed with hydrazine hydrate (0.1686 mol) and the reaction was allowed stir for 2 h. A silver product was obtained, which was then poured in ice water, filtered, and splashed with ethanol. The resultant product was treated with 1.5 ml of carbon disulfide in 6 g of alcoholic KOH and the reaction combination was refluxed for 4 h. 3 ml of ammonia added dropwise. The final step involved recrystallization of the product from ethanol and drying under vacuum to give 3-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)-1-benzopyran-2-one (d). The presence of a single spot on the TLC plate confirms the purity of the product.

Step-IV: Preparation of Derivatives of 3-(4-amino-5-sulfanyl-4*H*-1,2,4-triazole-3-yl)-2*H*-1-benzopyran-2-one [(e)-A-O)]

3-(4-Amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)-2H-1-benzopyran-2-one (d) (6 g, 1 mol) and acetic acid (3 ml), was mixed with 6 g of KOH in 25 ml of alcohol and various aromatic halides (RCH2X) (3.3 ml, 0.5 mol). The reaction mixture was treated with hydrogen peroxide (1 mol) and allowed to stir for 4 h. the reaction progress was monitored by TLC and the combination was filtered to give a precipitate. Excess chloride was removed using low-pressure distillation and the product was recrystallized from the alcohol.

2.4 PHARMACOLOGICAL ACTIVITY

2.4.1 invitro Anticancer Activity

Advanced malignancies that do not respond well to CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) include lung and liver cancers. Based on evidence supporting the efficacy of etoposide (E) in CHOP administration, we administered CHOEP chemotherapy to patients with advanced lung cancer.

Materials and Methods

The following human and animal The National Centre for Cellular Sciences (NCCS), located in the Indian city of Pune, provided the following tumor cell lines: human T lymphocytes (HUT102 and HUT78), breast cancer (MCF-7 and MDA the MB-231), and humanoid node rectal adenocarcinoma cell line (Caco-2). These compartment outlines were cultured in DMEM to evaluate the antibody response to twenty substances. Sigma-A Chemical Inc. (St. Louis, USA) provides tissue culture medium, supplements, dyes, metabolic drugs, dimethyl sulfoxide, phosphate-buffered saline (PBS), and other necessary drugs. Cells were cultured in 25 cm^2 culture dishes in DMEM supplemented 10% FBS, glutamine, bicarbonate of soda, and antibiotics including 100 U/ml penicillin and 100 milligrams per milliliter of doxycycline. The cells in culture were maintained in a chamber containing 5% CO_2 and moisture at 37 °C (VWR, USA).

The dose of a drug that causes 50% cell inhibition is called IC_{50} value and is expressed in µM. Table 1 lists the IC_{50} values of the studies. Out of 22 compounds tested on various cancer cell lines, 6 compounds (FE-e, FE-f, FE-o, and FE-q) showed good toxicity in different cells. The components used to make CHOP include prednisone (1 µM, P), vincristine sulfate (260 nM, O), doxorubicin hydrochloride (1.5 µM, H), and cyclophosphamide monohydrate (5.84 µM, C). Other drugs like ruxolitinib, sorafenib, and dasatinib are from Lucknow-based MRD Bio-Tech. We obtained CHOEP-resistant cells with five times the IC_{50} of each cell line. The dose was increased after three cycles. To increase sensitivity to CHOEP, parental cell lines were cultured without further treatment. Cells used in this study were able to tolerate a dose twice the IC_{50}.

Microculture tetrazolium (MTT) assay

In sterilized 96-effectively flat-bottom plates, cytotoxic experiments were conducted with a seed concentration of one hundred 10µ cells/mL in full growth media. Each well contained 100 µl of suspensions of cells from the HUT102, HUT78, MDA-MB-231, MCF-7, and CaCO2 cell lines. After that, the plates were kept in 5% CO_2 for an entire overnight at 37°C to promote cell attachment. To the proper wells, add the usual solution, 500 µg/mL CHOEP, and 500 µg/mL of novel benzopyran analogs. As an oversight, untreated cells (0 µg/mL) were used. On a single plate, three concentrations of treated, unattended, and empty cells were tested. For dependability, the complete procedure has been carried out on three separate occasions.

The 72-hour treatment period was chosen based on previous studies showing that treatment effects are time-dependent. In every well, add 20 µl of MTT solution and continue to culture for an extra 4 hours after the initial 37 degrees Celsius and five percent carbon dioxide immersion. Careful consideration was given to the culture medium to remove MTT crystals without disturbing them. Add 100 µl of DMSO solution to respectively glowing to liquefy the blue formazan tint. The optical thickness (OD) of formazan remained measured at 430 nm using a spectrophotometer (Infinite M200 PRO), indicating the number of living cells with metabolism. The experiment was conducted three times.

After 4 h of incubation to produce formazan, linear interpolation is used to generate a dose-response curve (showing the percentage of survival versus concentration), and the OD value is used to determine the IC_{50}, which is the lower allowed higher concentration of the newly synthesized benzopyran derivative. For survival of 50% of the cells (HUT102, HUT78, MDA-MB-231, MCF-7, and CaCO2), Cell survival histograms were generated using GraphPad Prism Software 5.0.

3. RESULTS AND DISCUSSION

3.1 Chemistry

The synthesis methods for benzopyran-2-one-triazole conjugates are shown in Scheme 1. The synthesis occurred in four to five steps, i.e., first, the ethyl-2-oxo-2H-1-benzopyran-3-carboxylate was synthesized from 2-hydroxybenzaldehyde, diethylpropanedioate, piperidine and ethanol via knoevengel condensation reaction [34]. 2-oxo-2H-1-benzopyran-2-one-3-carbohydrazide was synthesized readily and in good yields using hydrazine and ethanol. 3-(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)-2h-1-benzopyran-2-one was synthesized using hydrazine, carbon disulfide and alcoholic KOH. 3-(4-amino-5-sulfonyl-4H-1,2,4-triazol-3-yl)-2h-1-benzopyran-2-one was synthesized using acetic acid, aromatic halide and alcoholic KOH.

3.2 Biological Evaluation

3.2.1. *In Vitro* Cytotoxicity against Cancer Cells-MTT Assay

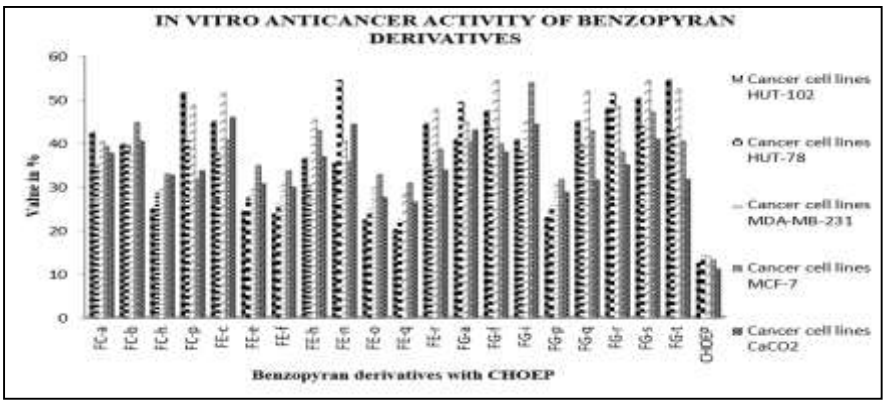
Cytotoxic effects on cancer cells were evaluated as IC_{50} values (Table 1) and compared with untreated cells. To calculate the IC_{50} of each derivative, the proportion of lockup survival was plotted against the attentiveness of each compound. Use a linear regression model to determine the IC_{50} value.

Yy= mx + c.

Here, y=50, the parameters, m and c, came from the feasibility graphs. The experiment was run in duplicated.

Table 1: IC_{50} of synthesized compounds against human T lymphocytes (HUT102 and HUT78), breast cancer (MCF-7 and MDA-MB231), and humanoid node rectal adenocarcinoma cell line (CaCO2)

Derivatives of Benzopyran	% Cell viability Values of Various Cancer cell lines					IC50 in µm/ml
	HUT-102	HUT-78	MDA-MB-231	MCF-7	CaCO2	
FC-a	42.35	34.66	40.26	39.12	37.52	221
FC-b	39.66	39.27	37.61	44.61	40.28	208
FC-h	24.85	28.66	29.47	32.81	32.49	164
FC-p	51.42	40.46	48.55	31.55	33.56	190
FE-c	44.85	37.58	51.34	40.56	45.74	194
FE-e	24.22	27.36	29.45	34.72	30.56	165
FE-f	23.70	26.10	30.44	33.55	29.78	162
FE-h	36.43	30.12	45.25	42.73	36.78	188
FE-n	35.42	54.29	40.31	35.66	44.21	197
FE-o	22.35	24.55	29.74	32.66	27.45	163
FE-q	20.16	22.45	28.41	30.75	26.41	164
FE-r	44.35	34.85	47.62	38.46	33.70	200
FG-a	4083	49.27	44.70	40.15	42.85	210
FG-f	47.29	43.16	54.28	39.75	37.82	207
FG-i	40.67	38.10	44.85	53.73	44.20	196
FG-p	22.90	25.60	30.42	31.55	28.64	164
FG-q	44.88	39.42	51.76	42.67	31.42	194
FG-r	47.96	51.26	48.28	37.85	34.85	189
FG-s	50.25	43.75	54.26	46.95	40.75	201
FG-t	54.37	42.74	52.18	40.29	31.60	180
CHOEP	12.46	14.10	13.95	13.10	11.08	12



Fig, 3: % values of various cell lines

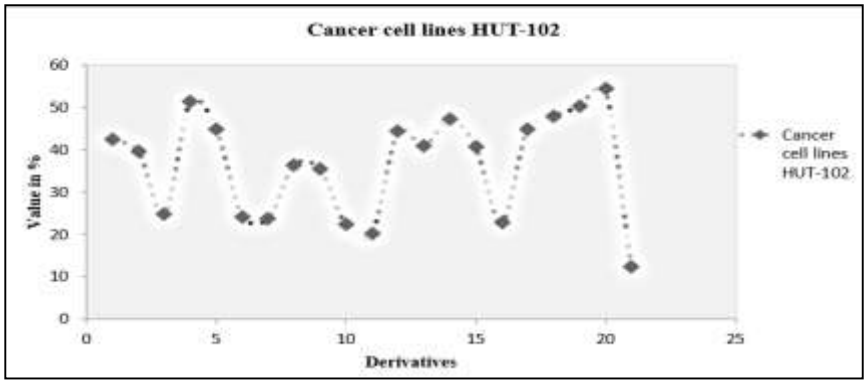


Fig. 4: % values of various cell lines HUT-102

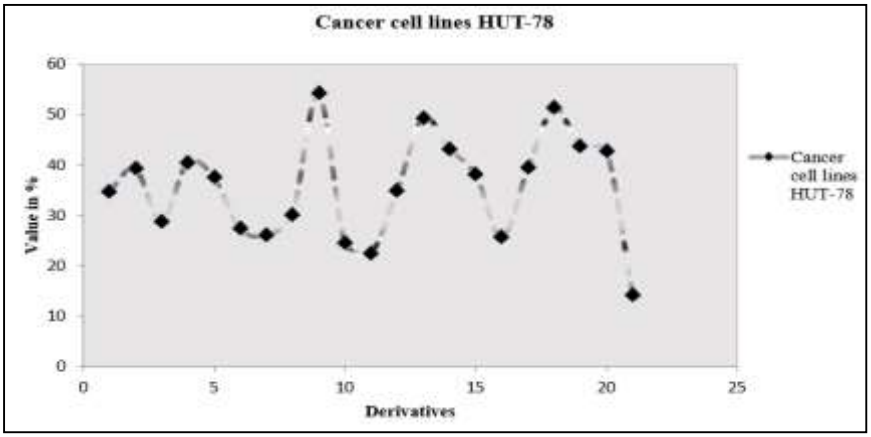


Fig. 5: % values of various cell lines HUT-78

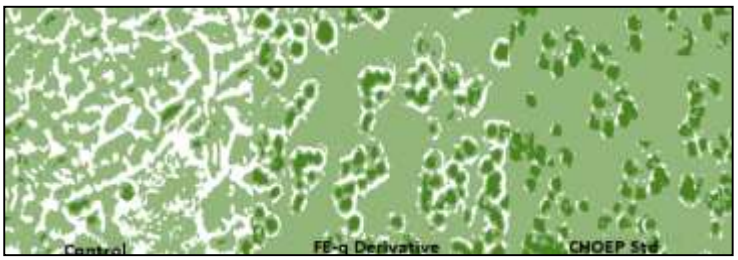


Fig. 6: MCF-7 cell line at 500µg/ml

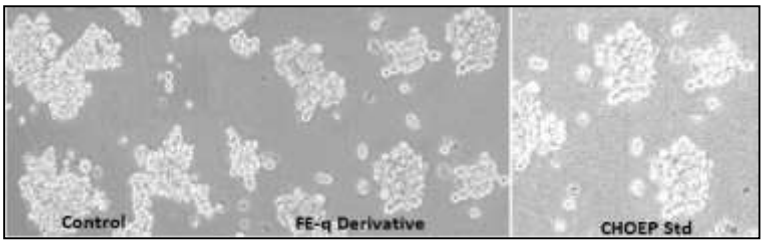


Fig.7: HUT-102 cell line at 500µg/ml

Fig. 8: CaCO2 cell line at 500µg/ml

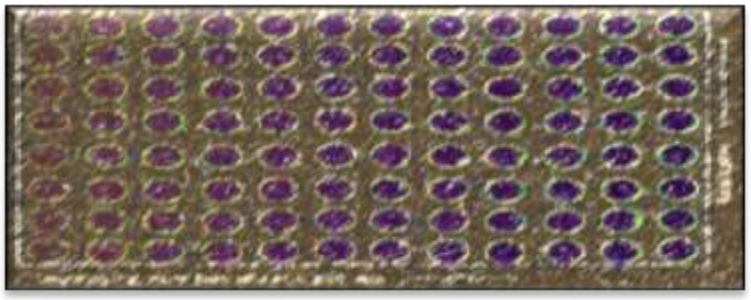


Fig. 9: 96 well microtiter plates

Statical investigation

The *in vitro* anticancer activity of the combined drug was evaluated by measuring cell growth in 96-well microtiter plates using a method based on cell-mediated reduction of tetrazolium salts to water-insoluble formazan crystals. Strains used for testing included HUT-102, HUT-78, MDA-MB-231, MCF-7, and CaCO2. Benzopyran derivatives showed anti-inflammatory activity against HUT-102 and CaCO2 cell lines. More importantly, compounds FE-q and FE-o exhibited potent anti-inflammatory activity in all tested cell lines including HUT-102, HUT-78, MDA-MB-231, MCF-7, and CaCO2. Furthermore, these compounds showed high safety and exhibited very low cytotoxicity against the cell lines. Molecular docking studies supported the results of antiviral activity and pointed out the potential of these derivatives for further modification in the development of new antiviral drugs.

4. DISCUSSION

This study provides evidence that synthetic flavonoid products have cytotoxic potential against various cancer cells, including HUT102, HUT78, MDA-MB-231, MCF-7, and CaCO2. The significant activity of compounds FE-e, FE-f, FE-o, and FE-q suggests their promise as candidates for further development of cancer therapy. Given their unique pharmacological properties, these derivatives may contribute to the continued development of cancer treatment strategies. These findings not only demonstrate the therapeutic potential of these compounds but also indicate that their mechanisms of action need to be further investigated. Future studies should focus on elucidating the molecular pathways involved in their anti-inflammatory activity, which may inform the design of better treatments and plans. As our understanding of these flavonoid derivatives improves, we may be able to uncover new therapeutic avenues that could be effective in the ongoing fight against cancer and improve patient outcomes. The insights from this study cover the way for the growth of new-fangled treatments that could have a major impact on cancer care worldwide

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