ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal
www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2025, Vol. 41, No.(2):
Pg. 584-608

A Comprehensive Review on Chromene Derivatives: Potent Anti-Cancer Drug Development and Therapeutic Potential

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http://dx.doi.org/10.13005/ojc/410229

(Received: February 07, 2024; Accepted: March 11, 2025)

ABSTRACT

Chromene derivatives are a notable category of naturally occurring chemicals recognized for their varied pharmacological attributes. These heterocyclic structures demonstrate the capacity to engage with diverse cellular targets, enhancing their wide range of biological activities. Compounds derived from chromene exhibit antitumor, antioxidant, anti-inflammatory, anticoagulant, anticonvulsant, diuretic, hepatoprotective, antispasmodic, antifungal, antimicrobial, estrogenic, antiviral, anthelmintic, anti-HIV, antitubercular, hypothermic, herbicidal, vasodilatory, and analgesic properties. Their promise in cancer therapy has spurred the creation of new derivatives with improved therapeutic effectiveness. Structure-activity relationship (SAR) studies indicate that alterations to the chromene core, by targeted functionalization, can markedly improve their bioactivity. The review presents an overview of the anticancer effects of chromene derivatives, emphasizing recent developments in their structural alterations and modes of action.

Keywords: 2*H*-chromene, 4*H*-chromene, One-pot three-component synthesis, Anti-cancer activity.

INTRODUCTION

Worldwide, cancer is a significant public health issue. According to incidence and death statistics, it is rising in developing and developed nations. Considering advances in diagnosis and treatment, cancer remains to be the 2nd foremost reason of death internationally, after cardiovascular disease. Lung cancer exhibits the greatest fatality rates across all cancer forms in both genders. Conversely, breast cancer ranks as the second foremost reason for mortality associated with cancer in women. Despite numerous cancer treatment methods, research into new chemotherapeutic drugs continues. Because cancer is complicated and malignant cells are drug-resistant[1], breast cancer kills many women worldwide. Elevated 17β-estradiol, a female sex hormone, causes breast cancer[2]. Multidrug resistance (MDR) is a key cause for therapeutic failure in the studies of cancer. Resistance to a medicine can be inherited or acquired; combination medications have been tried to address these hurdles. New medication design materials are still needed to overcome this issue[3].

Chemotherapeutic drugs generally target

rapidly reproducing cells; nevertheless, usually lack selectivity, impacting both malignant and healthy tissues. Although significant advances in cancer prevention and treatment, traditional chemotherapeutic agents including 5-fluorouracil, paclitaxel, cisplatin, and docetaxel are still extensively utilized, while cancer persists as a severe health concern[4]. The continuous pursuit of new anticancer medicines and innovative treatment methodologies constitutes a dynamic research domain, motivated by the necessity to discover novel biological targets and create therapies that exhibit superior efficacy, enhanced selectivity, diminished toxicity, and minimal adverse effects[5].

Heterocyclic compounds are of significant importance in the field of drug development, as evidenced by the fact that over 70% of therapeutic drug compounds currently documented in the previous studies belong to this category. The oxygen-containing heterocycles stand out among these abundant heterocyclic compounds due to their significant prevalence in nature and their wide-ranging biological and pharmacological significance. The "chromene" heterocyclic scaffolds found in these *O*-heterocycles are notable for their biological activity[6,7].

The chromene unit is found in many different kinds of organic compounds. 4*H*-chromenes have a potent cytotoxic impact against a variety of human cancer cell lines through a variety of different mechanisms. These pathways contains depolarization of microtubules and disturbance of the tumor vasculature. CrolibulinTM (EPC2407), a chromene analog, is now participating in clinical trials to treat advanced solid malignancies. These trials are in Phase I/II[8]. Many scientists are looking for novel chromenes because of the promising anti-cancer effects of a number of chromenes found in medicinal plants. Various biological activity evaluations are attributed to chromenes, including anti-cancer, antibacterial, antiviral, anti-inflammatory, antipyretic, and ulcerogenic[9-12].

The benzene ring of chromenes is fused to a pyran nucleus, making them a heterocyclic chemical. In 2*H*-chromenes I, C-2 forms a double bond with oxygen (2-oxo-2*H*-chromene, also known as coumarin), (2-imino-2*H*-chromene), inside the 2*H*-chromene-2-thione structure may establish a single bond with two different substituents (X, Y) or engage in alternative bonding arrangements. In 4*H*-chromene derivatives (III and IV), the carbon at the 4-position can either exhibit sp^3 hybridization or form a double bond with a heteroatom, hence affecting the compound's structural and electrical characteristics. The 4*H*-chromones are particularly important, especially if the 2-position contains an aromatic ring. These later chemicals, usually referred to as flavones, are frequently found in normal goods, and the existence of this structure in dietary products has been linked to a number of health benefits, thus elevating the significance of this nucleus[13].

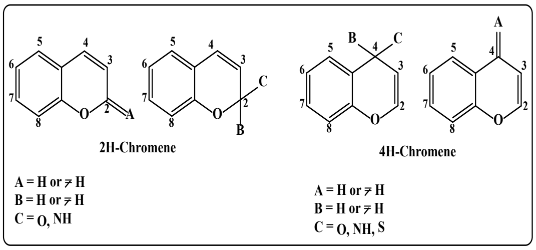


Fig. 1. 2H-Chromene & 4H-Chromene

This review offers a comprehensive and current overview of synthetic methodologies, reaction systems, biological activities, and structure-activity relationships (SAR) concerning the nucleus of 2*H*/4*H*-chromene and its implication in the progress of bioactive compounds, by addressing the absence of recent consolidated updates. This review seeks to aid medicinal chemists and researchers in the creation and optimization of innovative 2*H*/4*H*-chromene-based compounds for the treatment of serios medical condition and possible industrial applications.

Nature-based anti-cancerous chromene derivatives

Mallotus apelta (Lour.) Müll.Arg has been utilized for the handling of chronic hepatitis in traditional Chinese medicine for centuries. Seven compounds (including six novel chromene based derivatives called malloapeltas C-H and one previ125 kit-8 (CCK-8) experiment to assess the cytotoxicity of each medication. Six medicines exhibited notable their inhibitory impact on expansion and persistence on the TOV-21G ovarian cancer cell line, with GI$_{50}$ rates extending between 0.06-10.39 µM and the value of IC$_{50}$ between 1.62-10.42 µM. The mechanism of apoptosis was investigated using three of the most cytotoxic compounds. The stimulation of caspase 8, 9, and PARP, along with the overexpression of Bax and Bak and a reduction of Bcl-xL and enduring, served as indicators that compounds **1a** & **1b, 2,** and **3** (Fig. 2) triggered apoptosis. Additional research revealed that compounds **2, 3** effectively suppressed the NF-κB signaling pathway[12].

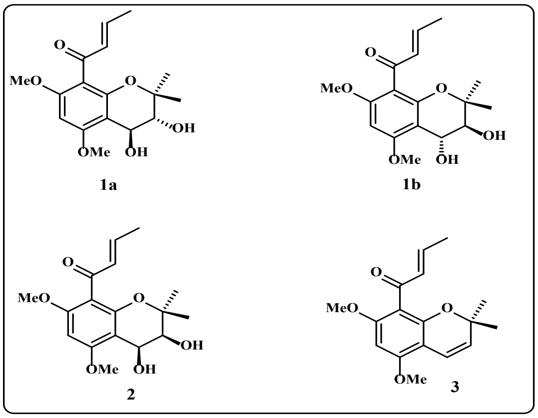


Fig. 2. Chemical structures of compounds 1-3

Figure 3 shows the chromene compound psoralidin 4, which occurs naturally in *Psoralea corylifolia*. This compound's potent cytotoxic effects against numerous cancerous lines of cell, containing those of the gastric, colon, and breast, led to its identification as a promising anticancer agent[14,15]. As a small component like of Neo-tanshinlactone **5** (Fig. 3) was separated from the ethanolic root extract of *Salvia miltiorrhiza*. The anticancer properties of this chromene were evaluated against several therapeutically relevant patient breast cancer cell types. The findings indicated low ED50 ranges 0.20 to 0.60 μg/mL for both estrogen receptor-positive (ER+) lines of cell, like MCF-7 receptor and ZR-75-1 receptor, as well as for one ER-/HER-2 carrying cell line, SK-BR-3[16,17]. Additionally, the marine organism *Aplidium conicum* was obtained off the coast of Sardinia, Italy, to yield the thiaplidiaquinones **A 6** and **B 7** Fig. 3. Using a human leukemia T line cell, researchers examined the impact of these complex compounds on the survival of cell. Additionally, the technique of flow cytometry and propidium iodide (PI) stains allowed the observation of a dramatic decrease in nuclear DNA in the treated cells. Reactive oxygen species (ROS) were also produced in high quantities by the cells in response to both compounds. Therefore, induction of cell death via the apoptotic pathway was inferred for Thiaplidiaquinones **6** and **7**[18].

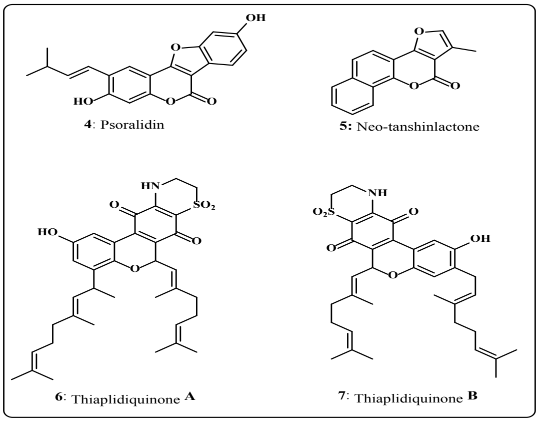


Fig. 3. Chemical structures of compounds 4-7

The Coumarins **8** (Fig. 4), derived from the *Mammea americana* plant found in tropical and subtropical regions, was discovered to hinder the induction of hypoxia-inducible factor-1 (HIF-1) in the prostate and the breast cancerous lines of cell. These specific dihydroxy-coumarins, possessing isoprenyl groups, exhibited notable potency with EC50 values mostly below 10 μM for the breast cancer cells like T47D as well as for the prostate cancer cell line like PC-3. Coumarins featuring a 6-prenyl-8-(3-methyloxobutyl) components explained the heightened effectiveness in inhibiting HIF-1[19]. Two different compounds, **9** and **10** (Fig. 4), were extracted from the fruit as well as from the bark of stem of the Calophyllum plant, found primarily in tropical rain forests. They were checked for their cytotoxicity employing the line cell KB, and the results showed that at concentrations ranging from 4-8 μg/mL, they inhibited the growth of the KB cells by up to 50%[20].

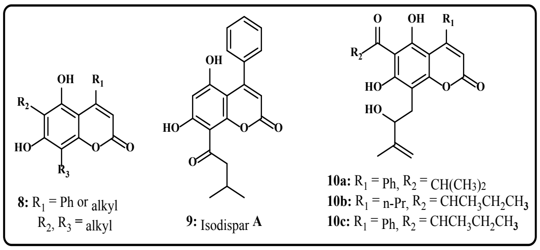
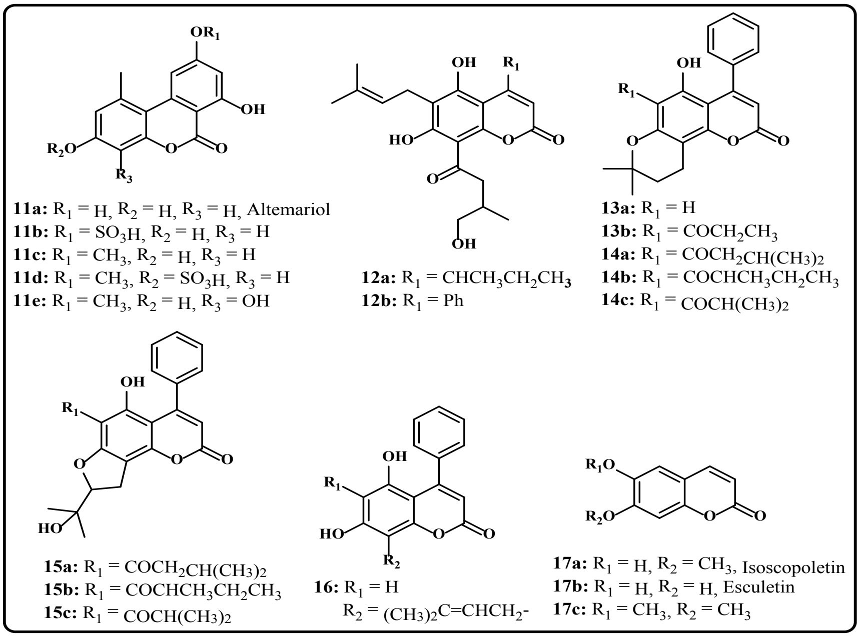


Fig. 4. Chemical structures of compounds 8-10

In the Egyptian plant *Polygonum senegalense*, the fungus Alternaria species produced several natural compounds known as chromenes **11a-e**, as seen in Fig. 5. The cytotoxic efficacy of these agents versus L5178Y murine lymphoma cells was evaluated. In particular, compounds **11a-c** showed significant efficacy, with

EC50 ranging from 1.7-7.8 µg/mL. Additionally, 24 distinct protein kinases were tested to determine these isolated chromenes' *in vitro* inhibitory capability. These substances successfully inhibited several enzymes, according to the study's findings, and they showed promising IC_{50} values of less than 10 µg/mL[21,22]. The *Kielmeyera albopunctata* plant is native to the Brazilian plateau and can grow freely. Two compounds, **12a** and **12b** (Fig. 5), were separated from the dichloromethane stem bark that is the extract of the plant and tested for their cytotoxicity. These drugs shown anticancer efficacy against multiple human cancer cell lines, including KB is the verbal epidermoid carcinoma, prostate cancer from LNCaP, and lung cancer from Lu1 and colon cancer from Col2, with an ED50 ranging from 11.1–19.8 µg/mL[23]. Compounds based on chromene have been seperated from the fresh leaves of the *Marila pluricostata* tree, endemic to Panama, Colombia, and Costa Rica. Compounds **13a, 13b,** and **16** were found to be novel compounds, and chromenes **14a-c** and **15a-c** were known derivatives. Anticancer activity was shown by this group of chemicals in the cancer lines cell GI50, MCF-7, SF-268, and with H-480 values are very low like of 0.1 µg/mL[24]. The effectiveness of the naturally occuring coumarins **17a–c** (Fig. 5) was obtained regarding their capacity to cleave DNA. This judgment was made in light of the fact that substances that can damage DNA strands have shown potential as anti-tumor therapies. The roots of *Mallotus resinosus* were used to produce these particular compounds. Although they were not particularly successful in causing DNA cleavage, the researchers noted that these substances showed potential as building blocks for synthetic derivatives[25].



11a: $R_1 = H, R_2 = H, R_3 = H$, Altemariol
11b: $R_1 = SO_3H, R_2 = H, R_3 = H$
11c: $R_1 = CH_3, R_2 = H, R_3 = H$
11d: $R_1 = CH_3, R_2 = SO_3H, R_3 = H$
11e: $R_1 = CH_3, R_2 = H, R_3 = OH$

12a: $R_1 = CHCH_3CH_2CH_3$
12b: $R_1 = Ph$

13a: $R_1 = H$
13b: $R_1 = COCH_2CH_3$
14a: $R_1 = COCH_2CH(CH_3)_2$
14b: $R_1 = COCHCH_3CH_2CH_3$
14c: $R_1 = COCH(CH_3)_2$

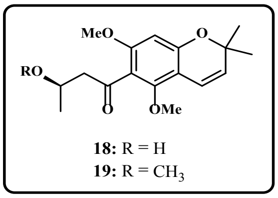
15a: $R_1 = COCH_2CH(CH_3)_2$
15b: $R_1 = COCHCH_3CH_2CH_3$
15c: $R_1 = COCH(CH_3)_2$

16: $R_1 = H$
$R_2 = (CH_3)_2C{=}CHCH_2$-

17a: $R_1 = H, R_2 = CH_3$, Isoscopoletin
17b: $R_1 = H, R_2 = H$, Esculetin
17c: $R_1 = CH_3, R_2 = CH_3$

Fig. 5. Chemical structures of compounds from11-17

The leaves of the *Euphorbiaceae* plant Mallotus apelta Muell.-Arg. yielded two novel benzopyrans Fig. 6, designated **18** and **19**. Detailed spectroscopic analyses were used to infer their molecular structures, emphasizing one and two dimentional techniques like mass spectrometry (MS) as well as nuclear magnetic resonance (NMR) data. In conjunction with an IC_{50} of 0.49 µg/mL versus human hepatocellular carcinoma represented by Hep-2 and 0.540 µg per mL against rhabdomyosarcoma (RD), Compound **18** displayed potent cytotoxic effects in the realm of biological activity. Additionally, compound **19** demonstrated an average activity level toward the Hep-2 cell line, having an alternative value of IC_{50} is of 4.22 µg/mL, as determined through *in vitro* assays[26].



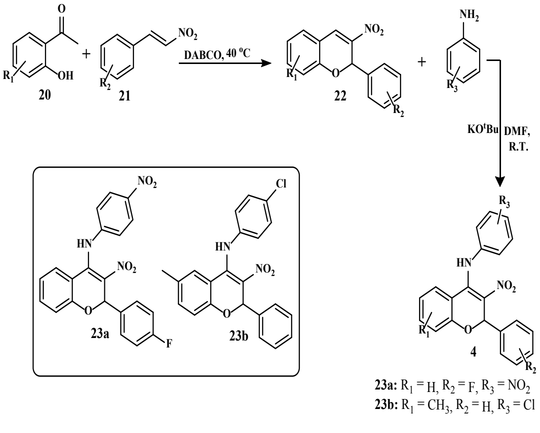
18: R = H
19: $R = CH_3$

Fig. 6. Chromene 18 & 19

Synthetic anti-cancerous chromene derivatives

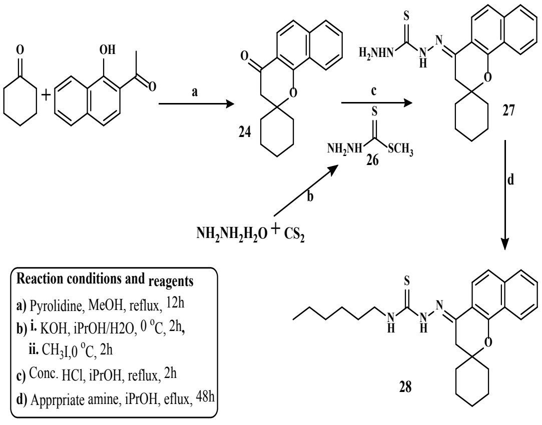
Synthetic routes for anti-cancerous chromene derivatives

Numerous chromene derivatives with promising anticancer activity have been synthesized, with some exhibiting cytotoxic impacts on cancerous cell lines at different concentrations. The aminated nitrochromenes **23a-23b** have been synthesized by using salicylic acid **20** and nitrostyrene **21** to get an intermediate nitrochromene **22** in the existance of DABCO which is 1,4-Diazabicyclo[2.2.2]octane at 40°C temperature. The final product was obtained by oxidative Michael addition reaction of conjugate aniline with intermediate **22** in the existance of DMF (dimethyl formamide) and basic condition at room temperature Scheme 1. MTT assay assessed the cell growth inhibitory/cytotoxicity of **23a** and **23b** compounds on HepG2 (Human heptoma cells) and HEK293 (Human embryonic kidney cells). Compounds **23a** and **23b** were tested in HEK293 cells at 0-200 µM concentrations for **24** and **48** hours. In HepG2 cells, compounds D19 and D22 were tested at 0–100 µM concentrations during 48 hours. Cytotoxicity studies on HEK293 cells indicate that compounds **23a** and **23b** do not inhibit cell growth in the examined concentration range, instead for a small inhibition at 100 µM. Concentration-dependent cell growth inhibition by **23a** and **23b** compounds showed IC_{50} average values of 18.33 µM and 26.22 µM. These findings concluded that the compounds present **23a** and **23b** inhibit cancer cell multiplication without damaging normal cells[27].

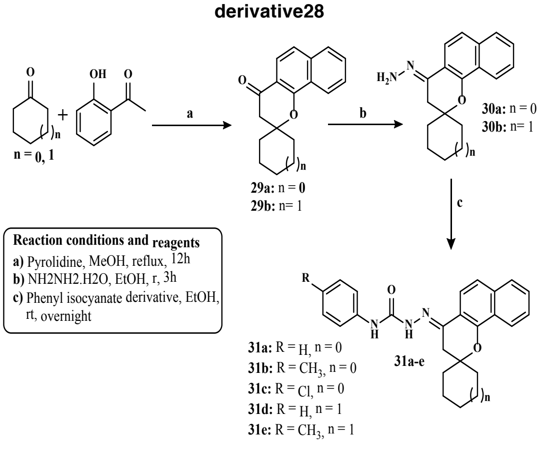


Scheme 1. Synthetic route for compounds 23a and 23b

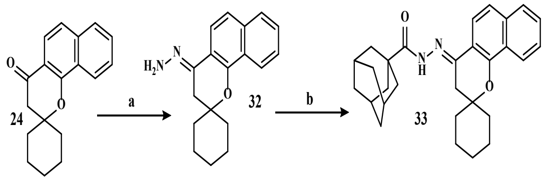
Kabbe's multi-component reaction was used to thermally condense cyclohexanone, pyrrolidine, and 1'-hydroxy-2'-acetonaphthone in methanol to yield compound **24**. The methyl hydrazine-carbodithioate **26** joined with spirobenzo[h]chromenone compound **24** to yield intermediate **27**. The S-methyl functional group was displaced during the condensation process of the middle products 26 with corresponding reflux of amines in isopropanol for 48 hours until methyl mercaptan changing stopped, yielding the final targeted thiosemicarbazide compound **28** Scheme 2. The precursors materials **29a** and **29b** were synthesized utilizing Kabbe's multicomponent process. The compounds **29a**, and **b** react with hydrated hydrazine to form hydrazone derivatives **30a,b**. Hydrazone derivatives coupled directly with various phenyl isocyanates to provide the definitive tailored semi carbazide molecules **31a-e** Scheme 3. Similar to the preceding reaction, compound **24** reacts with hydrated hydrazine to produce the intermediate hydrazone chromene **32**. In the existance of triethylamine, the middle products **32** was refluxed directly with adamantyl carbonyl chloride to produce the intended outcome **33** in high yield Scheme 4[28].



Scheme 2. Route for the formation of chromene-based derivative28



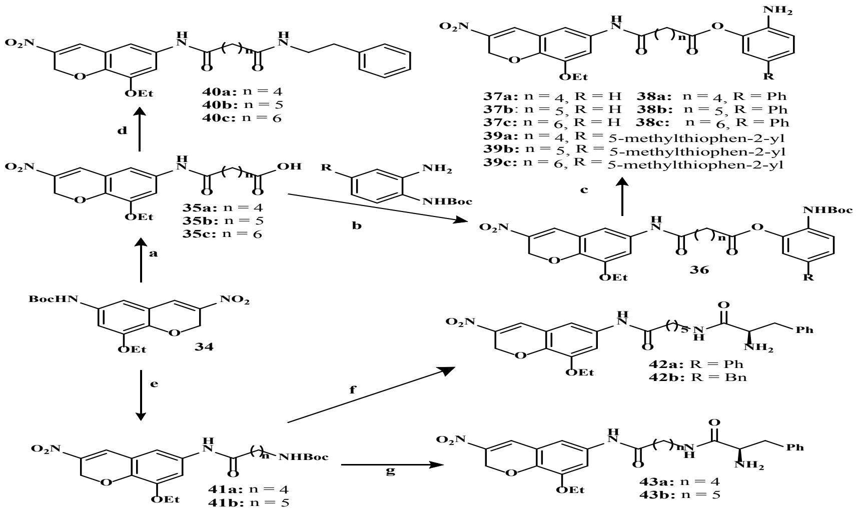
Scheme 3. Route for the formation of chromene-based derivative 31a-e



Reaction conditions and reagents
a) NH2NH2.H2O, EtOH, r, 3h; **b)** Adamantyl carbonyl chloride, TEA, THF, reflucx, 2 h

Scheme 4. Route for the formation of chromene-based derivative 33

Eight compounds (**27, 28, 31a–e**, and **33**) exhibited significant anticancer action, with value of IC_{50} between 1.78 and 5.47 μM, surpassing those of sorafenib (between 3.6 and 6.2 μM) and erlotinib (IC_{50} more than 20 μM). A mechanistic investigation was conducted on selected compounds **28, 31c**, and **33** against key anticancer targets, including B-RAF, EGFR, and tubulin. These compounds demonstrated stronger EGFR binding affinity than B-RAF kinase. Compounds **28, 31c**, and **33** have comparable IC_{50} values to erlotinib for EGFR (1.4, 1.9, and 1.2 μM) and B-RAF kinase (2.7, 2.9, and 2.6 μM). Among them, compound **33**, a hydrazine derivative of spiro-benzo-chromene, exhibited the highest potency against EGFR (IC_{50} = 1.2 μM), indicating an optimal steric and electronic configuration for kinase inhibition. Additionally, compounds **28, 31c**, and **33** moderately inhibited tubulin polymerization. Docking simulations and *in vitro* assays support the potential of this spiro compound family as dual EGFR and B-RAF inhibitors, offering promising candidates for further anticancer drug development[28]. In the compound 6-, 7-, and 8-Carbon linear dicarboxylic acids was used to study the effects on the length of joiner on HDAC (histone deacetylases) inhibitory action. The amide **(40)** and ortho-aminoanilide **(37–39)** were employed as zinc-binding groups (ZBGs) in this series generated from dicarboxylic acids. The ortho-aminoanilide series' interior cavity motifs, phenyl **(38a-c)** and 5-methylthiophen-2-yl **(39a-c)**, are thought to enhanced the efficacy of inhibitory HDAC and selectivity of isoform. The 6-aminohexanoic acid as well as 5-amino pentanoic acid were utilized as linker motifs in addition to linear dicarboxylic acid, and the resulting ω-amides **(42)** and α-amino amides **(43a, 43b)** acted as ZBGs. Scheme 5 depicts the production of HDACi based on 8-ethoxy-3-nitro-2*H*-chromene[29].

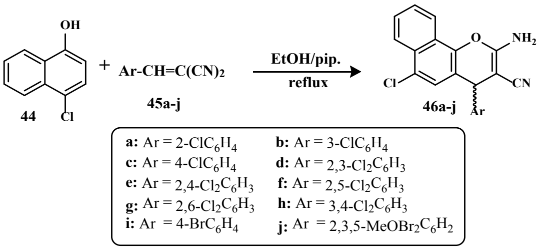


Reacion reagents and conditions
(a) i) TFA, CH_2Cl_2, 2 h; ii) $(CH_2)_n(COOH)_2$, HATU, Et_3N, DMF, 12 h:
(b) HATU, Et_3N, DMF, 4 h: **(c)** TFA, CH_2Cl_2, 2 h:
(d) $PhCH_2CH_2NH_2$, HATU, Et_3N, DMF, 4.5 h:
(e) i) TFA, CH_2Cl_2, 2 h; ii) $BocNH(CH_2)_nCOOH$, HATU, Et_3N, DMF, 12 h:
(f) i) TFA, CH_2Cl_2, 2 h; ii) RCH_2COOH, HATU, Et_3N, DMF, 8 h
(g) i) TFA, CH_2Cl_2, 2 h; ii) Boc-DPhe, HATU, Et_3N, DMF, 8 h

Scheme 5. Route for the formation of chromene-based derivatives

The inhibitory activity of a variety of HDACIs based on 8-ethoxy-3-nitro-2H-chromene against HDAC1, 2, and HDAC6 in MCF-7, A549, PC3, HeLa, and K562 cell lines was investigated. Compared to the basic drugs MS-275 and SAHA most coumarin derivatives exhibited stronger antiproliferative action teasted against the various five tumor lines cell. Strong HADC1 antagonists with IC_{50} amount in the nanomolar (nM) included compounds **37b, 37c, 38c, 39b, 43a** and **43b**. ZBG analogues **(40a, 40b, 42)** based on amides were high selective for HDAC2 and HDAC1. The phenyl internal cavity motif compounds **38b** and **38c** were more effective HADC1 inhibitors and selective over HADC2 than MS-275. D-Phe-derived compounds of ZBG were more effective HDAC inhibitors than their amide counterparts[29].

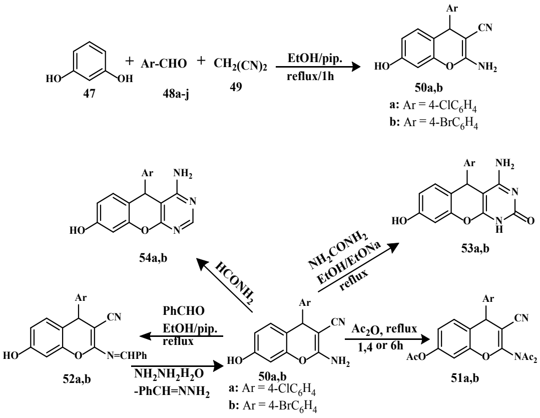
Scheme 6 depicts the synthetic approaches taken to produce the desired molecules. Desired products **46a-j** were obtained by reacting 4-chloro-1-naphthol **44** using α-cyano mono/di/tri substituted cinnamonitriles **45a-j** in ethanolic piperidine, which during reflux for one hour. Among recently synthesized compounds, analogs **46b, e, c, i, h** and **46d, j, f,** a exhibited strong inhibition towards MCF-7. Notably, analogs **46b, 46a–j,** especially **46e** and **46h**, showed high inhibition for HCT-116. In HepG-2, analogs **46e, h, b**, **46c, d, j** displayed significant inhibitory effects surpassing vinblastine and colchicine. Compound **46e** outperformed doxorubicin against HepG-2, while others showed varying activity levels across cell lines. Structure-activity relationship suggests mono/dichloro-substituents at the position of para in the ring of phenyl in 4H-benzo[h]chromene enhances anticancer activity[30,31]



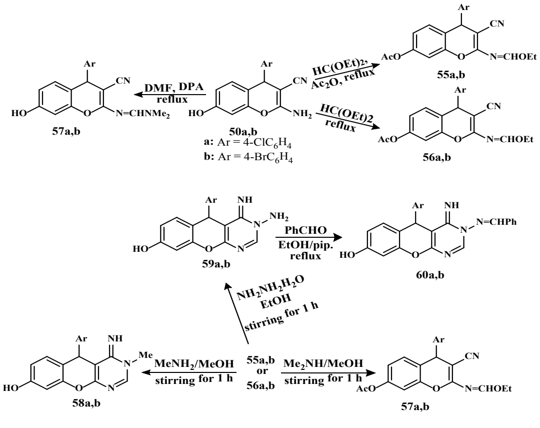
Scheme 6. Route for the formation of chromene-based derivatives 46a-j

Synthesized 4H-chromenes **(51, 52, 55–57)** and 5H-chromene 2,3-d-pyrimidines **(53, 54, 58–60)** Scheme 7 & 8 were examine versus HCT-116, A549, MCF-7, HepG-2 cancerous lines of cells. Some compounds **60a, 58a, 52b, 56a, 60b, 59b, 50b,** and **58b** inhibited MCF-7 cells strongly. **60b** outperformed vinblastine and colchicine in HCT-116 anti-tumor effects. Vinblastine and colchicine were less effective than compounds **59b, 52b, 58a, 60a, b, 56a, 58b, 59a, 50b, 52a, 56b, 55a,** and **57b** against HepG-2. Compared to conventional medications, compounds **59b, 50a, 58a, 59a, 58b, 60b, a, 55a, 50b, 56a,** and **57b** showed promising anticancer activity against A549.

SAR studies represented that pyrimidine nuclei at the position of 2 and 3 with specific hydrophilic groups or hydrophobic groups and chromene nuclei at the 2-position or 7-position increased activity compared to other hydrophobic groups. Additionally, choosing 4-bromophenyl over 4-chlorophenyl at the position of 5- or 4- decreased the logarithm of the partitioning factor, Log P. In vitro, anticancer activity was higher in compounds with pyrimidine moieties and 4*H*-chromenes than in independent derivatives[32].



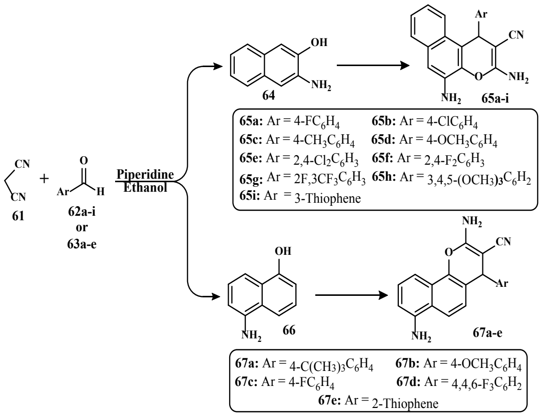
Scheme 7. Route for the formation of chromene-based derivatives



Scheme 8. Route for the formation of chromene-based derivatives

A new class of compounds was synthesized using Knoevenagel condensation and Michael addition adducts[33]. Two distinct chromene chemical families were generated using multi-component reactions (MCRs) to investigate their biological structure-activity relationship. The initial family resulted from the reaction between malononitrile **61**, aromatic aldehyde **62a-i** substituents, and 3-amino-

2-naphthol **64** in the presence of piperidine. Refluxing the solutions for 2 h led to compounds **65a-i** with yields ranging from 60% to 77% (Scheme 9). The same synthetic approach was applied to produce the second set of chromene derivatives. By reacting malononitrile 1 with various aldehydes **63a-e** and 5-amino-1-naphthol **66**, compounds **67a-e** were obtained. Three cell lines showed strong antiproliferative activity with IC_{50s} of 0.3 to 2 µg/mL for compounds **65a, 65b, 65c,** and **67c**. For the most significant compounds, the enzyme activity assays were used for apoptotic study to determine their antiproliferative effects[34].

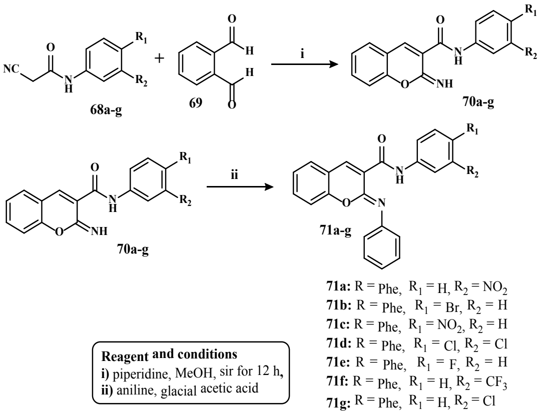


65a: Ar = $4\text{-}FC_6H_4$ **65b:** Ar = $4\text{-}ClC_6H_4$
65c: Ar = $4\text{-}CH_3C_6H_4$ **65d:** Ar = $4\text{-}OCH_3C_6H_4$
65e: Ar = $2,4\text{-}Cl_2C_6H_3$ **65f:** Ar = $2,4\text{-}F_2C_6H_3$
65g: Ar = $2F,3CF_3C_6H_3$ **65h:** Ar = $3,4,5\text{-}(OCH_3)_3C_6H_2$
65i: Ar = 3-Thiophene

67a: Ar = $4\text{-}C(CH_3)_3C_6H_4$ **67b:** Ar = $4\text{-}OCH_3C_6H_4$
67c: Ar = $4\text{-}FC_6H_4$ **67d:** Ar = $4,4,6\text{-}F_3C_6H_2$
67e: Ar = 2-Thiophene

Scheme 9. Synthesis of chromene derivatives 65a-i & 65a-e

The preparation of conjugated imino chromenes **70a-g** and derivatives of phenyl-imino chromene **71a-g** is illustrated in Scheme 10. Various conjugated 2-imino chromenes **70a-g** were produced using the Knoevenagel synthesis of 2-cyano acetamide **68a-g** and 2-hydroxy benzaldehyde. Subsequently, subjecting these 2-imino chromenes to a elementary reaction involving aniline in reacted acetic acid led to the conversion into their corresponding phenyl-iminochromenes with good yields ranging from 70% to 85%. Phenyl-iminochromene derivatives **71a-g** with percentage I of 31 to 50.7 exhibited greater cytotoxic efficacy compared to their imino chromene equivalents at a concentration of 10 µM that is quivalent to %I of range of 25.1 to 36.3 versus the MOLT-4 lines of cells. Notably, compound 8g displayed remarkable inhibitory capacity of 51.7% against the MOLT-4 cell line at a dose of 10 µM[35].

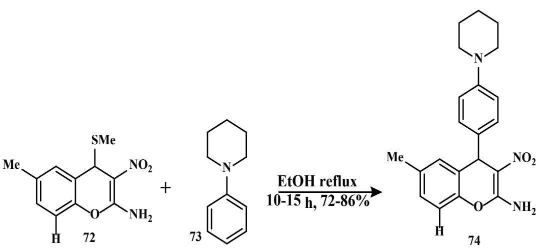


71a: R = Phe, R_1 = H, R_2 = NO_2
71b: R = Phe, R_1 = Br, R_2 = H
71c: R = Phe, R_1 = NO_2, R_2 = H
71d: R = Phe, R_1 = Cl, R_2 = Cl
71e: R = Phe, R_1 = F, R_2 = H
71f: R = Phe, R_1 = H, R_2 = CF_3
71g: R = Phe, R_1 = H, R_2 = Cl

Reagent and conditions
i) piperidine, MeOH, sir for 12 h,
ii) aniline, glacial acetic acid

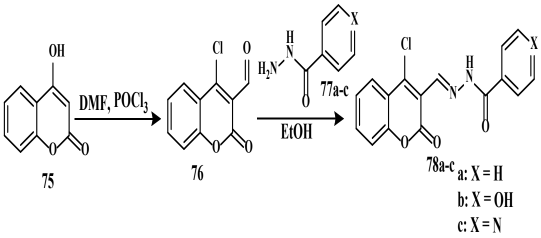
Scheme 10. Synthesis of chromene derivatives 71a-g

Compound **74** was prepared by reacting compound **72** with 1-phenylpiperidine **73** in the existance of solvent ethanol, and the mixture of reaction was refluxed for 1-15 h Scheme 11. Their effectiveness toward cancerous lines of cells HeLa, – A549, – Hep2 and was assessed. Compound **74**, identified as 6-methyl-3-nitro-4*H*-chromene-2-amine derivative substituted with a 4-(piperidin-1-yl)phenyl group at position 4, demonstrated the significant pronounced cytotoxic potential across each of the three cancerous lines cell (Hep2, A549, and HeLa), replacing IC_{50} amount from 0.75 ± 0.06, 4 ± 0.35, and 9 ± 0.73, respectively. Toxicity studies indicated the selective targeting of cancer cell lines by the 4-aryl-4*H*-chromenes[36].



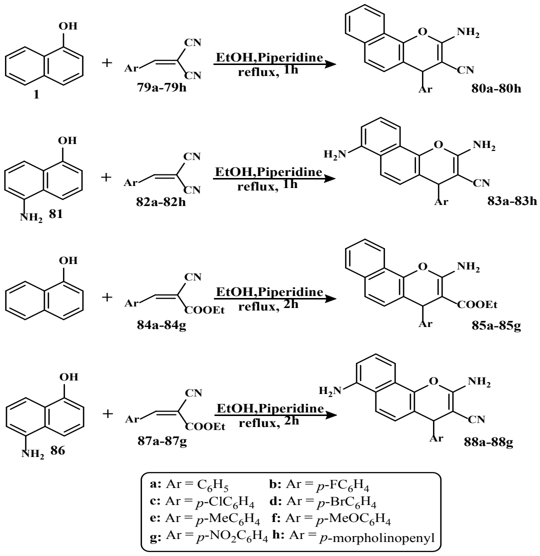
Scheme 11. Scheme for the preparation of chromene derivatives 74

Vilsmeier-Haack formylation of coumarin **75** yielded compound **76** Scheme 12. Compound **78a's** production is an example of the general process for synthesizing compounds **78a–c**. The MTT tetrazolgtium reduction assay shown influenced by concentration cytotoxic impacts on tumor-derived human lines of cells within the micromolar level. The series' strongest antiproliferative was Hydrazone **78a**. In the leukemia HL-60 cell line, compound **78a** has the most antiproliferative efficiency (IC_{50} 2.9 µM), Subsequently, compounds **78c** and **78b** were examined. Antiproliferative efficacy in leukemia HL-60 cell lineage (IC_{50} 2.9 ± 0.4 μM), followed by compounds **78c** and **78b**[37].



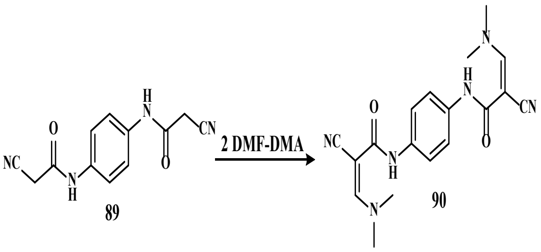
Scheme 12. Synthesis of chromene derivatives 78a-c

Treatment of a solution of 1-naphthol naphthol **81** in EtOH and piperidine with compounds **79a–79h** or **84a–84g** obtained in the formation of a new compound series Scheme 13. The mixture resulting from the reaction was heated while refluxing. After filtration, the solid products that were produced in this way were collected, washed with MeOH, and re-crystallized from ethyle alcohol or with thw benzene, respectively[38].



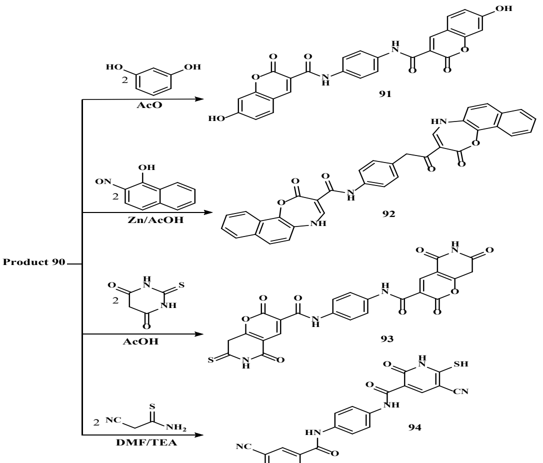
Scheme 13. Synthesis of chromene derivatives

The MTT colorimetric assay compared the synthesized compounds' in-vitro cytotoxic efficacy toward HepG-2, MCF-7, and HCT-116, lines of cells to vin-blastine and colchicine. Anti-tumor assessment showed chemicals **88c, 85d, 85b, 85e, 88g** (IC_{50} = 3.1 to 5.3 μg/mL) and **88c, 85d, 85b, 85e, 88g, 85c, 88e, 83f, 80a** (IC_{50} = 3.1-17.5 μg/mL) reduced MCF-7 growth contras to vinblastine and colchicine. Compared to colchicine, **85b, 85d, 85e, 80a, 88b, 88a, 88c, 80d, 80g, 80f, 80b, 80h, 88b, 88a, 88e, 80c, 83g, 80e, 88g, 83f, 80f** (IC_{50} = 2.9-32.2 μg/mL) decreased HCT-116 growth. Additionally, chemicals **85e, 80g, 80a, 85c** (IC_{50} = 2.5-4.1 μg/mL) and **85e, 80g, 80a, 85c, 85b, 85a, 88f, 88e** (IC_{50} = 2.5-10.4 μg/mL) decreased HepG-2 growth contras to vin-blastine and colchicine[38]. Compound **89** is the precursor for the production of novel heterocyclic substances. Consequently, the procedure of 1,4-Phenylenebis(2-cyanoacetamide), a dual-functional derivative of cyano-acetamide featuring a para-phenylene structure **89** with dimethylformamide-dimethylacetal (DMF and DMA) in mixing di-methylformamide, synthesizes enaminonitrile 90 Scheme 14.



Scheme 14. Synthesis of chromene derivative 90

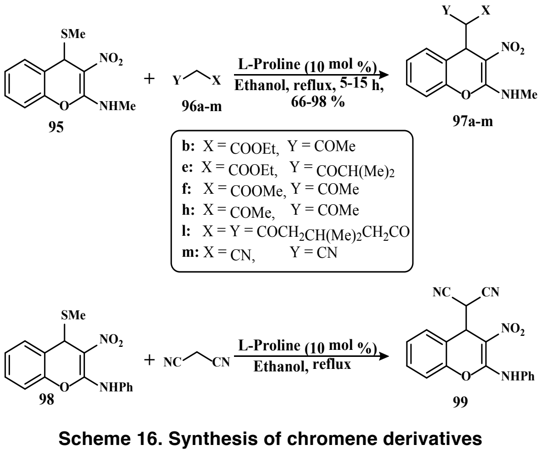
The chemical reactivity of enaminonitrile **90** has been examined with other phenolic and analogous chemicals, as depicted in Scheme 15. Upon refluxing chemical **90** with resorcinol in glacial acetic acid, a singular product, **91**, was obtained. Similarly, its interaction with 2-nitroso-1-naphthol in the presence of zinc metal and glacial CH_3COOH obtained in the synthesis of compound **92**. Furthermore, the reaction of **90** with acid of thiobarbituric under reflux in the acid of glacial acetic yielded the pyrano-[2,3-d]-pyrimidine compound **93**. Additionally, the reaction of **90** with thio-cyano-acetamide in N,N-dimethylformamide, catalyzed by triethylamine, yielded compound **94**[39].



Scheme 15. Synthesis of chromene derivatives 91-94

The newly substances produced were assessed for their anticancer efficiency *in vitro* utilizing the standard MTT assay. The evaluation was performed using a set of four human cancerous lines cell: HepG-2 (hepatocellular carcinoma in the liver), HCT-116 (colorectal carcinoma in the colon), MCF-7 (mammary gland carcinoma in the breast), and Hep-2 (epidermoid carcinoma in the larynx). The anticancer screening showed that compounds had the highest in vitro cytotoxic activity relative to 5-fluorouracil. additionally, the IC_{50} amount range of the substances are as follows: HepG-2 **(91, 92,** and **93**, IC_{50} = 2.41, 2.59 and 2.53 µg/mL), HCT-116 **(91, 92, 93,** and **94**: IC_{50} = 4.98, 5.44, 5.32, and 5.20 µg/mL), MCF-7 **(91, 92, 93,** and **94**: IC_{50} = 6.72, 6.99, 6.84, and 6.52 µg/mL). Further, the percentage of inhibition ranged from 3.47 to 4.06 g/mL for compounds **91, 92, 93,** and **94** when tested versus the lines of cells in breast cancer MCF-7. Some substance like 91 was the prominent active material in this study, especially versus human Hep-2., HepG-2, and HCT-116 Compound **94** also was a prominent active material in this study, especially against MCF-7[39].

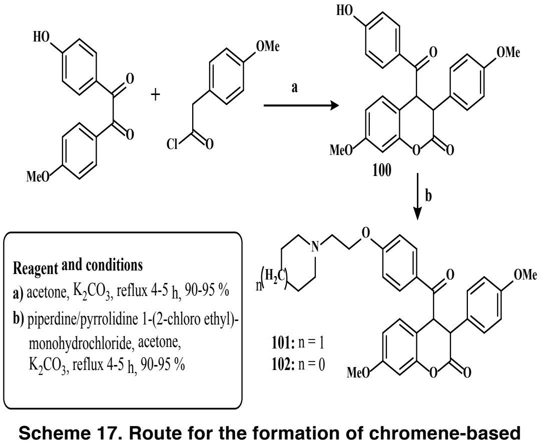
The active methine substituted 4*H*-chromene **97a-m** was prepared by reacting active methylene **96a-m** with C4-methanesulfanyl 4*H*-chromenes **95** (Schemes 16). Compared to the other solvents and bases that are currently using, it has been noted that in EtOH, the secondary amine L-proline refluxed is proved to be the most effective method for producing **97a-m** as a pale yellow solid with quantitative yield. In the same manner, compound **99** was prepared using compound **98** and active methylene[40].



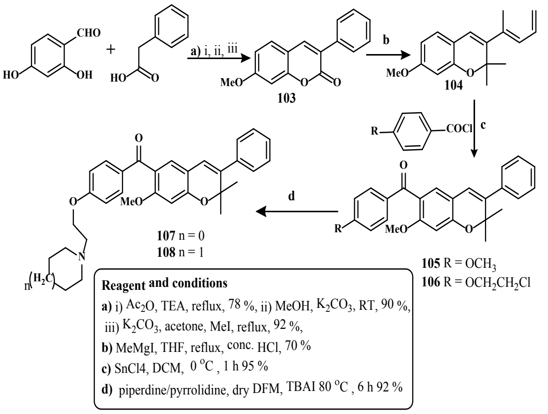
Scheme 16. Synthesis of chromene derivatives

The 4*H*-chromenes is a newly produced that were tested for their anti-cancerous characteristics by employing four different lines of cells. The results depicted that the 4*H*-chromenes with the C4-malononitrile conjugated were the highest effective at inducing programmed cell division. The results of the in silico investigations evaluated the combined relationship with the protein Bcl-2 matched the results of the *in vitro* studies. When taken together, the *in vitro* as well as in silico data proposed that the 4*H*-chromene **99** displayed IC_{50} values of HepG-2 (0.72 to 0.06 µM), A549 (1 to 0.08 µM), HeLa (0.7 to 0.05 µM), and HT-29 (0.85 to 0.07 µM), that this value is lead for the subsequent progress of more effective anti-cancerous compounds[40].

In the presence of reflux with acetone and dehydrated K_2CO_3, benzils, and phenyl or 4-methoxyphenyl acetyl chlorides produced coumarins 100 in its unadulterated state through straightforward crystallization in high yields (90–95%). The target compounds were produced in high yields via base-catalyzed O-alkylation of the hydroxy group in compounds 100 using piperidine/pyrrolidine 1-(2-chloroethyl) monohydrochlorides 101 & 102 Scheme 17. Pure 6-aroylated chromenes 105 and 106 were crystallized in good yield. The chemical reaction of component 106 with piperidine or with pyrrolidine in dry DMF at 80°C with TBAI produced alkylaminoalkoxy derivatives 107 and 108 Scheme 18[41].



Scheme 17. Route for the formation of chromene-based derivatives 101 & 102



Reagent and conditions

a) i) Ac_2O, TEA, reflux, 78 %, ii) MeOH, K_2CO_3, RT, 90 %, iii) K_2CO_3, acetone, MeI, reflux, 92 %,

b) MeMgI, THF, reflux, conc. HCl, 70 %

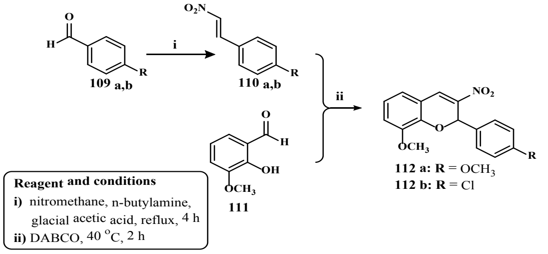
c) SnCl4, DCM, 0 °C , 1 h 95 %

d) piperdine/pyrrolidine, dry DFM, TBAI 80 °C , 6 h 92 %

Scheme 18. Route for the formation of chromene-based derivatives 107-108

In the breast cancer cells, the compounds **101** and **102** had IC_{50} amount of 5.7 and 12.8 µM in MCF-7 and 18.4 and 12.7 µM in MDA-MB 231, comparable to raloxifene as well as tamoxifen standards. Compounds **107** and **108** inhibited MCF-7 cells at 6.8 µM to 8.1 µM efficacy[41].

Scheme 19 depicts the synthetic route to produce the chromene derivatives **112a, b**. By Henry-Knoevenagel condensation of various benzaldehydes **109 h, l,** β-nitrostyrene's **110a, b** were created. High yields of the required **110a & b** were produced with little to no by-product. In the presence of a base called (DABCO), **110a, b** reacts with the suitable salicylaldehyde **111** to produce **112a, b,** the corresponding final products. Compounds **112a** and **b** were evaluated for cytotoxicity versus MDA-MB-231, T-47D, and MCF-7 lines cell of breast cancer. The compounds were more powerful than etoposide at cytotoxic activities versus chosen cell lines. The compound **112b** illustrated considerable activity against MCF-7 cells, with an IC_{50} of 0.2 µM, rendering it 36 times more potent than etoposide. The capacity of compounds **112a** and **112b** to trigger apoptosis was definitively established via acridine orange/ethidium bromide double labeling, TUNEL evaluation, and caspase-3 activation assays[42].



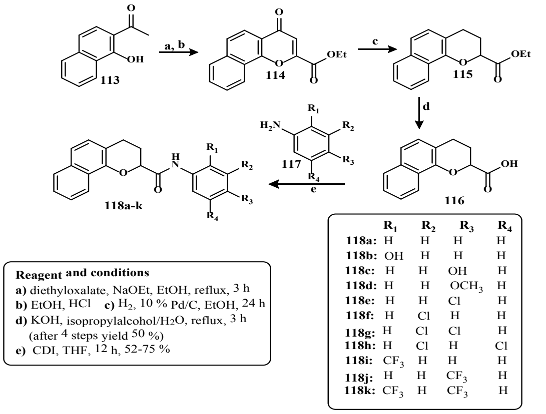
Reagent and conditions

i) nitromethane, n-butylamine, glacial acetic acid, reflux, 4 h

ii) DABCO, 40 °C, 2 h

Scheme 19. Route for the formation of chromene-based derivatives 112a-b

Synthesis of product **114** involved tandem cyclization with diethyl oxalate from commercial compound **113**. The Pd/C reduces compound **114** and yielded **115**. Ester 7 was hydrolyzed with KOH in aqueous solution of isopropyl alcohol, producing acid **116** with a 50% yield. Subsequent to the synthesis of acid 8, amidation was conducted utilizing various substituted anilines **(117)** alongside coupling agents, especially 1,1'-carbonyldiimidazole (CDI) in tetrahydrofuran (THF), resulting in the production of eleven derivatives **(118a-k)** as depicted in Scheme 20. The recently acquired N-aryl-3,4-dihydro-2*H*-benzo[h]chromene-2-carboxamide derivatives **(118a-k)** has enhanced regulatory and anti-proliferative characteristics relative to KL-1156. Compound **118i** demonstrated significant inhibition of LPS-induced NF-κB transcriptional efficiency and strong anti-proliferative effects on NCI-H23 lung cancer cells of lines[43].



Reagent and conditions

a) diethyloxalate, NaOEt, EtOH, reflux, 3 h

b) EtOH, HCl **c)** H_2, 10 % Pd/C, EtOH, 24 h

d) KOH, isopropylalcohol/H_2O, reflux, 3 h (after 4 steps yield 50 %)

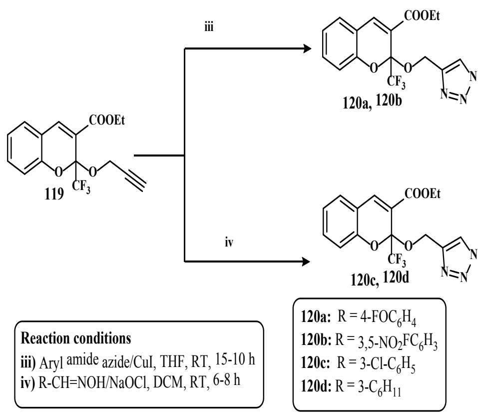
e) CDI, THF, 12 h, 52-75 %

	R_1	R_2	R_3	R_4
118a:	H	H	H	H
118b:	OH	H	H	H
118c:	H	H	OH	H
118d:	H	H	OCH_3	H
118e:	H	H	Cl	H
118f:	H	Cl	H	H
118g:	H	Cl	Cl	H
118h:	H	Cl	H	Cl
118i:	CF_3	H	H	H
118j:	H	H	CF_3	H
118k:	CF_3	H	CF_3	H

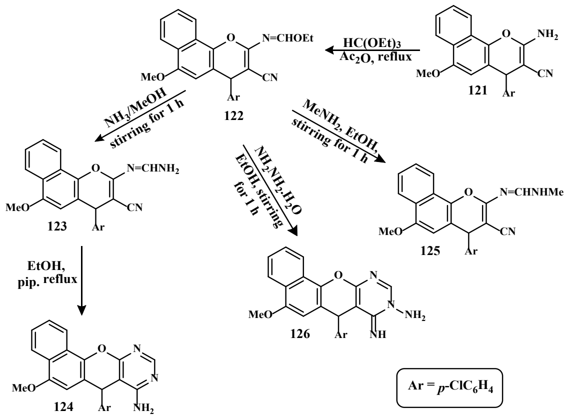
Scheme 20. Synthesis of chromene derivatives 118a-k

Under Sharpless conditions, the derivatives of chromene like O-propargylated **119** was interact with various azides conjugated, such as azides of alkyl or aryle, in THF to produce **120a, b, c, d,** respectively, in high yield Scheme 21. All products were tested for cytotoxicity versus four lines in cancerous cells. It has been observed that in A549 lung cancerous cells, DU145 prostate cancerereous cells, HeLa cervical cancerous cells, and MCF7 breast cancerereous cells, compounds like of **120a, c, d, b** exhibited potential activity at <20 IM concentration[44].

Product **122** was produced by refluxing compound **121** with triethyl orthoformate in acetic anhydride and benzene for 2 hours. The subsequent reactions of **122** resulted in the synthesis of fused heterotetracyclic complexes with a pyrimidine nucleus at the positions -2, -3 and a 4H-chromene group. Exposure of **122** to NH_3 gas in methanol at room temperature for one hour and obtained the formation of the open-chain product **123** (Scheme 22). The subsequent cyclization of **123** in ethanolic piperidine in the reflux yielded compound **124**. Furthermore, the reaction of imidate **122** with methylamine in ethanol at ambient temperature for one hour yielded the open-chain product **125**. The cycloaddition yield **126** was produced by reacting **122** with hydrazine hydrate. Compounds **126, 123, 124,** and **125** exhibited better anticancer activity towards the MCF-7, HCT, and HepG-2(IC_{50} = 3.0-9.4 µM, 1.7-7.4 µM, and 3.0-6.2 µM, respectively) compared to Vinblastine and Colchicine, while compound **126** (IC_{50} = 1.7 µM) performed better than Doxorubicin[45].

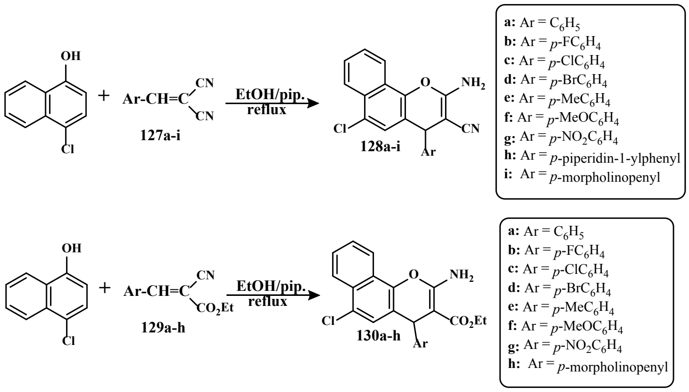


Scheme 21. Synthesis of chromene derivatives 120a-d



Scheme 22. Synthesis of chromene derivatives 121-126

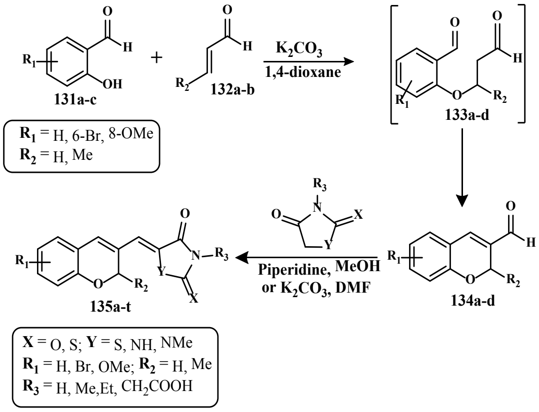
Treatment of 4-chloro-1-naphthol with **127a-i** formed the series of products **128a–i**. Similarly, the chmical reaction of 4-chloro-1-naphthol with **129a-h** yields **130a–h**, as shown in Scheme 23. Compounds **130e**, **128c**, **130f, b, d, 128d**, **130c,** a were the prominent active compound towards the MCF-7 with IC_{50} amount of 2.4-6.0 µg/mL, **130a** towards the HCT-116 with the IC_{50} amount of 2.7 µg/mL and **130a, 128e,** a against HepG-2 (IC_{50} = 3.5-5.0 µg/mL) as compared to standard drug[47,48].



Scheme 23. Synthesis of chromene derivatives 128a-i & 130a-h

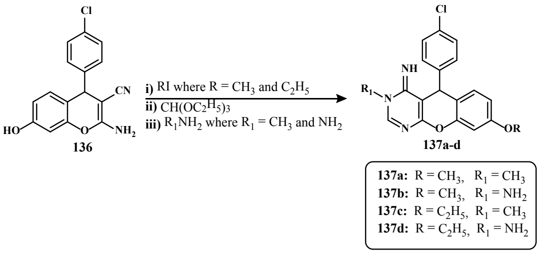
Scheme 24 outlines the series of preparation of a unique derivatives of chromene **(135a-t)** via the reaction of 2-hydroxy-benzaldehyde **131a-c** with either acrolein **132a** or 3-methylacrolein **133b** in the presence of K_2CO_3 to produce chromene-3-carbaldehyde **134a-d**. The chemical reaction, conducted under reflux in 1,4-dioxane, progressed via intermediates **133a-d**. The resultant compounds

135a-t were assessed for anticancer efficacy towards several cancerous lines cell. The hydantoin derivative **135o,** including a 6-bromo-2-methyl-2*H*-chromene core, had the most significant anticancer action, with efficacy comparable to that of cisplatin. The IC_{50} values of **135o** were established as 17.5 μM for A549 (epithelial adenocarcinoma), 10.6 μM for K562 (leukemia), 15.3 μM for MCF-7 (breast adenocarcinoma), 24.8 μM for MOLT-4 (acute lymphoblastic leukemia), and 25.2 μM for NIH/3T3 (mouse embryo fibroblasts, non-cancerous cells4).



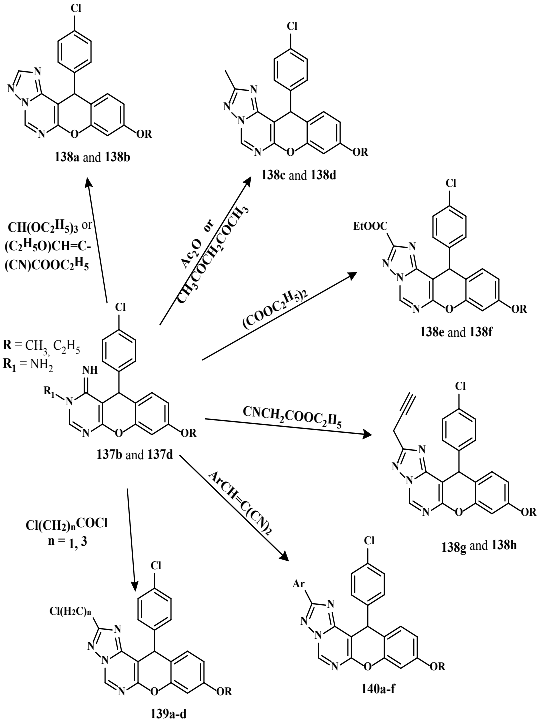
Scheme 24. Synthesis of chromene derivatives 135a-t

Compound **136** was synthesized according to the reported method; then, by a sequence of three-step synthesis, key intermediate **133a-d** were prepared in Scheme 25. Then, **137b** and **137d** were used to synthesize the series of chromene derivatives that can be seen in Scheme 26. In vitro, cytotoxicity was assessed on MCF-7 human breast carcinoma cells. Compounds **137a, 137b, 138f, 140c,** and **140f** showed potential for breast tumor cell pharmacological inhibitors. The most effective compounds were **137a** and **138f** with an IC_{50} amount of 0.007 μM, which had nearly twise the efficiency of colchicine with an IC_{50} amount of 0.013 μM. There are mainly three compounds **(137b, 140c, 140f)** with an IC_{50} amount of 0.008 μM (Fig. 7) demonstrated approximately one half of the efficiency of the colchicine. Two compounds, like **138a** and **138h** with an IC_{50} amount of 0.011 μM, inhibited breast cancerous cells almost as well as the +favourable control of results with an IC_{50} amount of 0.013 μM. Most of the compound like **139d** with IC_{50} vaules of 0.029 μM showed roughly one half of the action of the original which confirms the favourable control. Lastly, the compounds like of **138c** and **138g** with an IC_{50} amount of 0.033 μM, and 0.039 μM respectively are the lowest reactive[48].

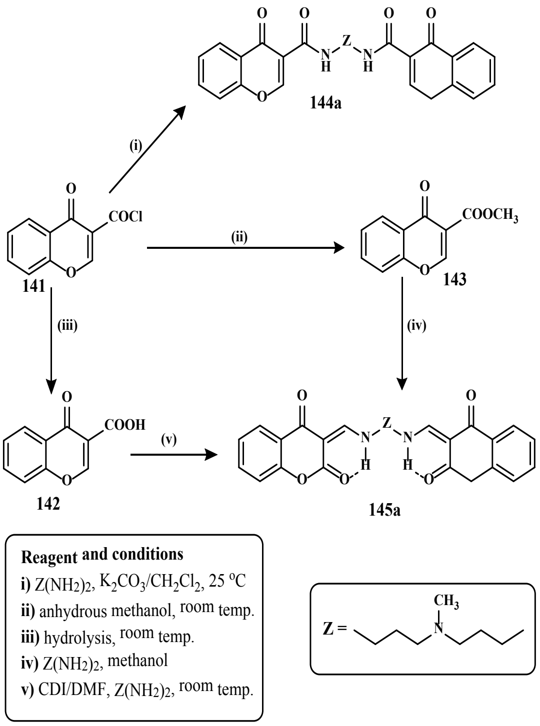


Scheme 25. Synthesis of chromene derivatives 137a-d

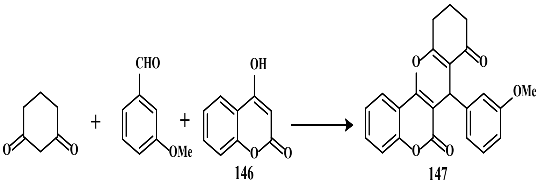
The initial compound, chromene derive compound like of 4-oxo-4H-chromene-3-carbonyl based chloride **141**, was hydrolyzed to generate 4-Oxo-4*H*-1-benzopyran-3-carboxylic acid **142**, and condensation with methyle alchol at ambient temperature yielded methyl 4-oxo-4*H*-1-benzopyran-3-carboxylate. Due to the varied reaaction ability of chromene derive compound like 4-oxo-4*H*-chromene-3-carbonyl based chloride 1 and its methyl ester **143** with elementry polyamines (a), two branches of materials were produced, only **144a** and **145a** showed in Scheme 27. The extremely violent melanoma lines cell A375 was used to test compounds **144a** and **145a** at both 50 and 75 μM concentrations *in vitro*. Compound **145a** outperformed compound **144a** in inducing apoptosis and cell cycle arrest[49].



Scheme 26. Route for the formation of chromene-based derivatives

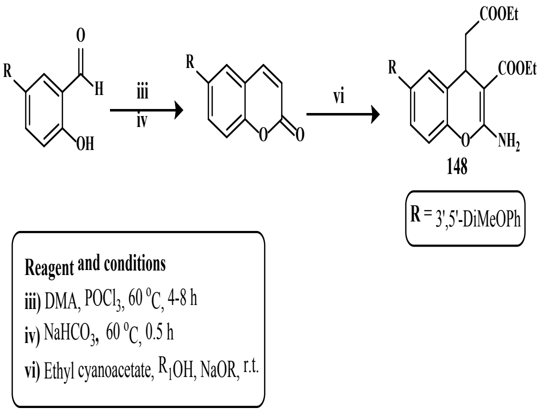


Scheme 27. Route for the formation of chromene-based derivatives



Scheme 28. Route for the formation of chromene-based derivatives 147

147 was obtained by synthesizing coumarin **146**, cyclohexadione, and arylaldehydes in various solvents (ethanol, acetic acid, acetonitrile, and benzene) (Scheme 28). Boiling acetic acid produced the maximum product (66-78 %). Four cancerous cell lines were employed to check these compounds' cytotoxic effects. The compound **147** demonstrated the highest activity on HeLa, LS180, MCF-7, and Raji (IC_{50} = 89.9, 99.7, 58.6, and 49.2 µM (Shafiee *et al.,* 2011). Synthesis for compound **148** has been shown in Scheme 29. Excitingly, research on drug-resistant cancerous cells such as mitoxantrone-(HL-60/MX2) and camptothecin-(CCRF-CEM/C2) has shown that **148** can selectively kill these cells while leaving parental cancer cells alone. The mechanism of **148** selectivities toward drug-resistant cancer cells is being studied in depth because of its ability to limit tumor cell development by inducing apoptosis. These findings point to **148** as a potentially effective therapeutic target for multidrug-resistant malignancies[50].

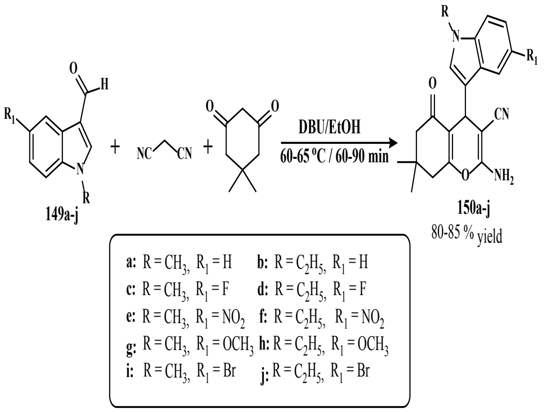


Scheme 29. Synthesis of chromene derivatives 148

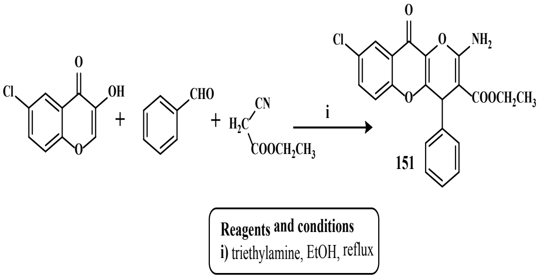
One pot synthesis

The standard reaction condition was then applied to a wider range of substrates, including malononitrile, 5,5-dimethylcyclohexane-1,3-dione, and N-substituted indole-3-carbaldehydes **149a-j** were synthesized, featuring electron-donating (OMe) and electron-loving (F, Br, and NO_2) groups at the 5th position of the ring, as depicted in Scheme 30. The derivatives **150a-j** were synthesized with satisfactory yields, varying from 80% to 85%, from obtained using the newly established one-pot, 3-component chemical reaction with various conjugate indole-3-carbaldehydes. The new chromene based derivatives like indole-tethered **150a–j** were tested for anticarcinoma activity towards lung carcinoma A549, the breast carcinoma MCF-7, and prostate carcinoma PC-3. As a conventional main drug, doxorubicin proved that most derivatives are cytotoxic. The compounds **150c** and **150d**, with a fluorine conjugate at the position of 5th place in the ring of indole, were the prominent effective versus all tested lines of cell, with IC_{50} values with range of 7.9 to 9.1 µM. Furthermore, materials **150g** and **150h** exhibited moderate inhibitory effects toward three cell lines, showing IC_{50} amount from 10.5 to 12.6 µM. Compounds **150e** and **150f** have lower potency in MCF-7 (IC_{50} values: 58.9-62.8 µM) and did not inhibit A549 or PC-3 cells[51].

Compound **151** was produced by one-pot, 3-component reactions of 6-chloro-3-hydroxychromone, aromatic aldehydes and ethyl cyanoacetate in ethanol with triethylamine as solvent and reflux Scheme 31[1]. The compounds **151** were tested against the SW480 line cell and human umbilical vein endothelial cells (HUVEC), and it appears to be a potential candidate for a cytotoxic agent. 10.8 ± 1.5 and 57.2 ± 3.2 μM, respectively, were the IC_{50} values[1].

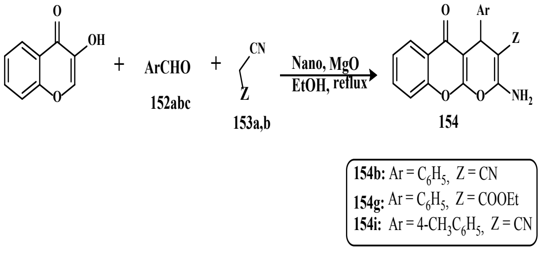


Scheme 30. Synthesis of chromene derivatives 150 a-j



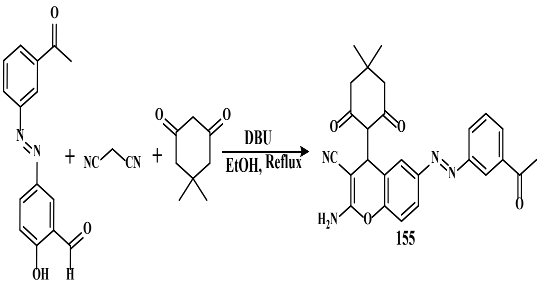
Scheme 31. Synthesis of chromene derivatives 151

A chemical reaction that involves three different reactants involving chromen based derivatives like of 3-hydroxy-4*H*-chromen-4-one, various carbon ring based aldehydes **152a,b,c,** (Scheme 32) and either malononitrile **153a** or ethyl cyanoacetate **153b** is carried out in ethyle alcohol at reflux with the existance of catalytic quantities of nano particles MgO. Most of the obtained compounds demonstrated inhibitory properties towards the formation of a colorectal cancerous line cell (Caco-2). The compound with the lowest IC_{50} value was 37 mg/mL, identified as compound **154i,** followed by compounds **154g** and **154b**. A significant portion of the synthesized compounds generally exhibited IC_{50} values below 100 mg/mL when tested on this specific cell line[52].



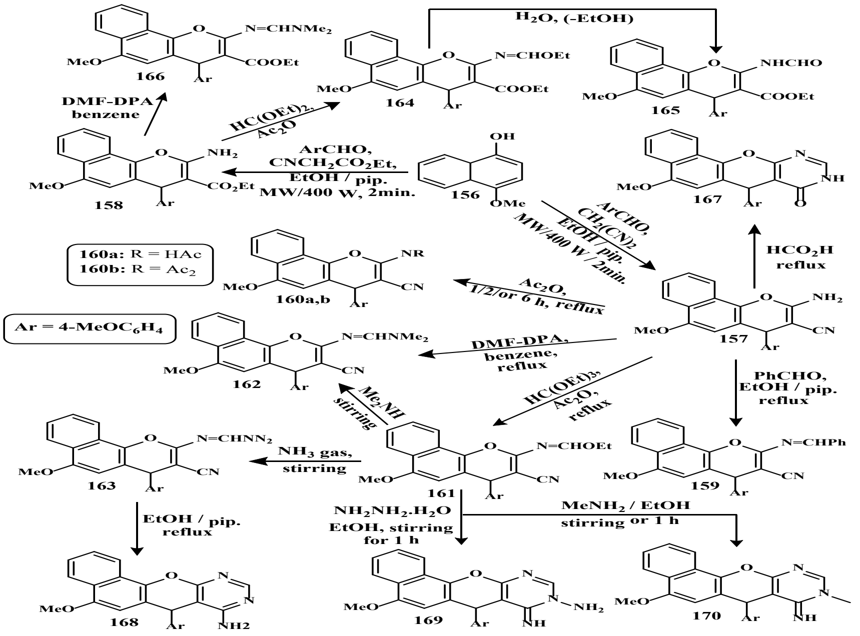
Scheme 32. Synthesis of chromene derivatives 154b, g & i

One-pot multicomponent reactions of malononitrile and dimedone with various azo aldehydes, involving Knoevenagel condensation and Michael addition, were conducted in ethanol employing DBU as a catalyst. The respective azo-chromene analogues were synthesized with satisfactory yields, as illustrated in Scheme 33. In MCF-7 cells, cytotoxicity was dose-dependent for compound **155**, celecoxib, and anastrozole with IC_{50} values of 19.8, 26.2, 24.7 μg/mL, respectively. Comparing the IC_{50} of material **155** to those of anastrozole and celecoxib demonstrates that it possesses more cytotoxic behaviour[2].



Scheme 33. Synthesis of chromene derivatives 155

The desired 4*H*-benzo[*h*]chromene derivatives, **157** and **158,** were synthesized through a one-pot, 3-component condensation of 4-methoxy-1-naphthol, 4-methoxybenzaldehyde, and malononitrile in an ethanolic solution with piperidine, conducted for two minutes at a temperature of **140**. After that, compounds **157** and **158** were utilized to synthesize several different chromene derivatives, and the chemical steps involved in their synthesis are outlined in Scheme 34 below. Compounds **161**, **163, 160a, 169,** and **170 (170, 169, 160a, 163** and **161)** were the prominent derivatives versus MCF-7 cancerous cells, being 1.3, 1.5, 5.1, 5.6, 6.8, and 3.6, 4.3, 14.8, 1, 16, 19.7 time effective than colchicine and vinblastine, accordingly. Additionally, some compounds **159, 160b, 167, 166** and **168** were also active. Compounds **160a, 170,** and **169** were also 2.2, 2.9, and 3.3 time effective than colchicine and vinblastine towards HCT-116 cancer cells. Meanwhile, compounds **159, 161, 167, 166, 160b, 163, 162, 165, 157, 168,** and **158** showed good active towards HCT-116 cancerous lines cells. However, compounds **160a, b, 170, 169,** and **159** were the most active in HepG-2 cytotoxicity (5.1, 1.2, 5.1, 5.8, 6.6 and 11.8, 2.7, 11.8, 13.3, 15.1, time effective than colchicine and vinblastine). Compounds **157, 162, 163,** and **167** were 1.1, 1.3, 1.5, and 2.0 times high effective than colchicine against HepG-2 cancer cells[5].

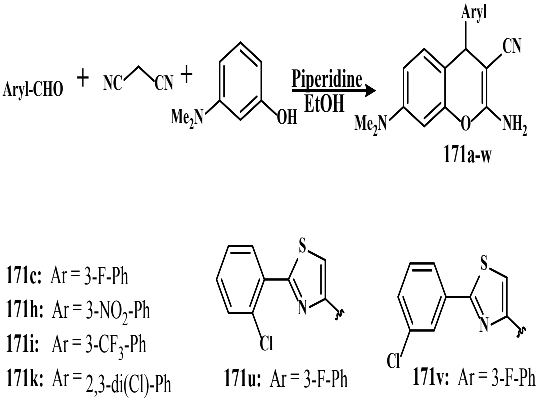


Scheme 34. Synthesis of chromene derivatives 157-170

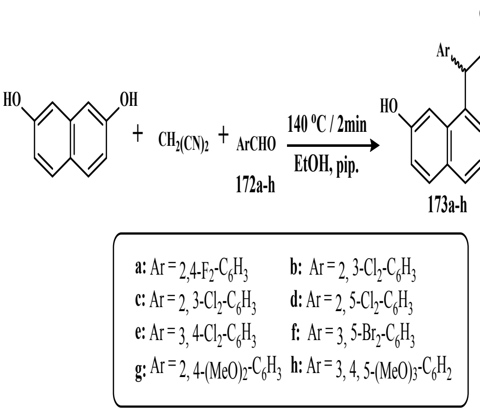
Overall, piperidine has been incorporated into the resulting mixture of 3-dimethylaminophenol, substituted aryl-benzaldehyde, and malonitrilein in the form of an ethanol-based solvent (Scheme 35). The resulting solution was agitated for a 12-h period at 35°C. Upon cooling, the accumulated material was filtered, cleaned with cold ethyle alcohol, and condensed from the solvent. All drugs were tested for Src kinase inhibition and cell growth in leukemia CCRF-CEM and HT-29 line cells. The **171c, 171h, 171i,** and **171k** conjugated chromenes with IC_{50} amount of 11.1 to 18.3 µM in Src kinase. Compound **171c** selectively inhibits Src values of IC_{50} is of 11.1 µM, compared to other kinases, including EGFR (IC_{50}>300 µM), Csk (101.7 µM), and Lck (46.8 µM). At 50 µM concentration, 3-chlorophenyl conjugated thiazole **171v** and 2-chlorophenyl substituted **171u** derivatives of chromene that reduced CCRF-CEM and HT-29 cell lines proliferation by 50% and 80%, respectively[53].

Microwave-assisted synthesis

Ethanolic solutions of **173a-h** were produced by exposing naphthalene-2,7-diol, malononitrile, aromatic aldehydes **172a-h,** and piperidine to microwave irradiation at 140°C for two minutes (Scheme 36). The highest yield of compound **173a-h** was achieved at 400 W and 2 minute. Compounds **173a-h** showed the strongest efffective versus SKOV-3, PC-3, and HeLa, that exihibits the IC_{50} values of 0.9-3.1, 0.8-3.7, and 1.7-5.7 µM. Some compounds **173f, 173h, 173c, 173a, 173e,** and **173b** showed strong efficiency towards the MCF-7/ADR cells (8.6-11.5 µM IC_{50}) and mild efficiency against HFL-1 and WI-38 cells (19.1-30.1 µM IC_{50}). The compounds like of **173a, 173b, 173c, 173d, 173e,** and **173f** exihibits P-gp progression and good function in the MCF-7/ADR lines, with IC_{50} amount of 18.7-34.6 µM, outperforming than the Doxorubicin with IC_{50} values of 50.9 µM. Additionally, Rho123 aggregation experiments demonstrated that chemicals **173a, 173b** and **173d** suppressed *P*-glycoprotein accumulation and efflux activity, whereas compounds **173c** and **173d** promoted apoptosis and triggered G1 phase cell cycle stop, **173a** and **173b** at S phase, and **173e** at G1/S phases[54].

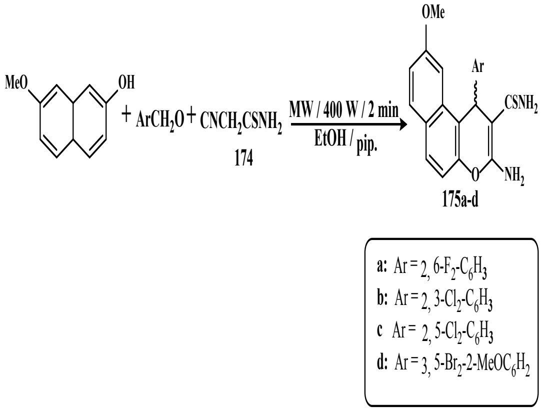


Scheme 35. Synthesis of chromene derivatives 170a-w



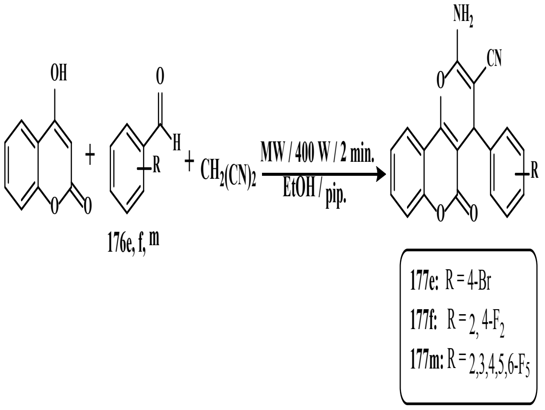
Scheme 36. Synthesis of chromene derivatives 173 a-h

Scheme **37** delineates the preparation of the required molecules **175a-d**. The procedure entailed the reaction of 7-methoxy-2-naphthol with various aromatic aldehydes in microwave irradiation at 140°C for two minutes, resulting in compounds **175a-d**. These products possess diverse conjugated (2,6-F_2; 2,3-Cl_2; 2,5-Cl_2; and 3,5-Br_2-2-OMe) affixed to the phenyl group of the 1*H*-benzo[f]chromene structure. Among the 1*H*-benzo[f]chromene-2-carbothioamide derivatives, the difluoro-substituted molecule had the greatest cytotoxic efficacy with IC_{50} amount of 5.4, 4.5 µM for MCF-7 and HepG-2, compared to the other halogenated derivatives tested versus PC-3, HepG-2, and MCF-7. The halogenated derivatives showed superior activity towards the PC-3 line cell with an IC_{50} amount of 1.1-2.7 µM) contras to the MCF-7 and HepG-2 cell lines[55].



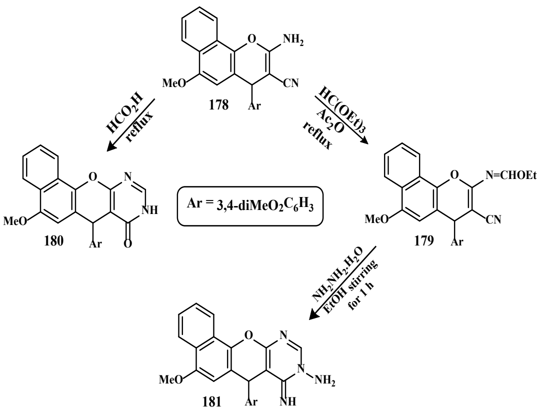
Scheme 37. Synthesis of chromene derivatives 175 a-d

The compounds **(177e, f, m)** illustrated in Scheme 38 were obtained by the chemical reaction of chromen-2-one with a variety of aryl aldehydes **176e, f, m,** piperidine 4 and malononitrile 3 in ethanol in microwave irradiation for 2 minutes. All synthesized compounds were tested through antitumor agent testing using MCF-7, HepG-2, and HCT-116, human cancerous lines cell. Compared to doxorubicin, the standard cytotoxic drugs, compounds **177e, 177f,** and **177m,** were the very effective versus all tested cancerous lines cell. The IC_{50} values were found to be 2.7, 0.6, and 0.32 M for MCF-7, 3.1, 0.2, and 1.7 M for HCT-116, and 2.2, 0.5, and 0.4 M for HepG-2, respectively[6].



Scheme 38. Synthesis of chromene derivatives 177e, f, & m

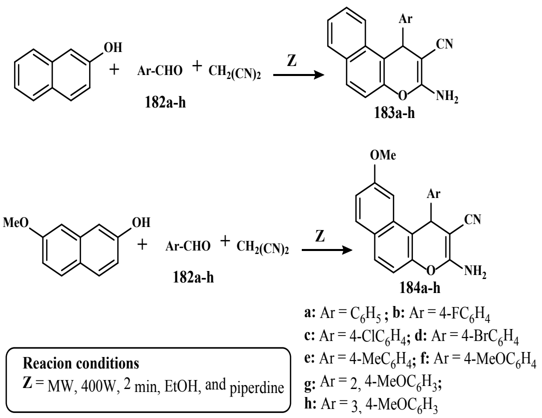
Scheme 39 illustrates the chemical reaction of β-enaminonitrile **178** with nucleophilic agent such as acetic anhydride and triethyl orthoformate, leading to the formation of the 4*H*-benzo[*h*]chromene derivative **179**. The main compounds in step 4 are useful starting materials for making a wide variety of new heterocyclic derivatives from 4*H*-benzo[*h*] chromene. Therefore, pyrimidine derivative **180** was produced when molecule **178** was condensed with formic acid. The cycloaddition product of aminoiminopyrimidine derivatives **181,** respectively, was obtained after treating the imidate **179** with the hydrazine hydrate in a methanolic solution at room temperature for 1 hour. The aminoimino derivative **181** showed strong anticancer effective versus MCF-7, HCT-116, and HepG-2 cancerous cell lines, with IC_{50} amount of 0.45, 1.7, and 0.7 µg/mL. Compounds **179, 180,** and **181** were chosen for cell cycle studies, apoptosis assays, caspase 3/7 activity assessment, and DNA fragmentation investigations. These 3-compounds of cytotoxic cause apoptosis by arresting the S and G2/M cell cycle. These chemicals also greatly reduce cancer cell invasion and migration[56].



Scheme 39. Preparation of chromene derivatives 178-181

Scheme 40 depicts the production of 3-amino-1-aryl-1*H*-benzo[*f*]chromene-2-carbonitriles **183a–h**. The chemicalreaction commenced by amalgamating 2-naphthol with aromatic aldehydes **182a–h** and malononitrile in the solution of ethanolic piperidine, thereafter subjected to microwave irradiation at 140°C for two minutes. In a similar manner, as illustrated in Scheme 40, the reaction of 7-methoxy-2-naphthol compound with the identical array of aromatic aldehydes **182a–h** and malononitrile yielded 3-amino-1-aryl-9-methoxy-1*H*-benzo[*f*]chromene-2-carbonitriles **184a–h**[57].

The synthesized compounds demonstrated strong and selective cytotoxic impact towards the three cancerous lines cell: MCF-7, HCT-116, and HepG-2. Compounds **183b-g,** and **184b-e,** and h exhibited the greatest activity against MCF-7 cells, with IC_{50} values between 0.18 and 5.7 µg/mL. Compounds **183b-d,** and g and **184b-e,** and h exhibited increased efficacy against HCT-116 cells, with IC_{50} amount of 0.6 to 2.5 µg/mL. Moreover, compounds **183b-d, f** and **g** and **184b-e** shown enhanced cytotoxicity (IC_{50} = 0.6–3.9 µg/mL) relative to Vinblastine and Colchicine (IC_{50} = 4.6 and 10.6 µg/mL, respectively). SAR research explained that the incorporation of halogen substituents (electron-loving groups) at the 4-position of the phenyl ring on the 1-position of the 1*H*-benzo[*f*] chromene core markedly improved antitumor activity. Conversely, electron-donating groups like of methyl or methoxy exhibited diminished efficacy. Moreover, the existance of a hydrogen atom at the 9-position was more advantageous for cytotoxic activity than a methoxy group[57].



Scheme 40. Synthesis of chromene derivatives 183a-h & 184a-h

Other synthesized anti-cancerous chromene derivatives

There have been many additional chromene compounds created several of which have potent anticancer properties. At doses in the low range like of µM and nM, they have repeatedly been shown to have cytotoxic impact on cancerous-based cell lines.

Coumarin derivatives **185** Fig. 7, with the 4,5-dihydropyrazole moiety, may suppress telomerase. Compound **185** (R_1 = H, R_2 = COMe, R_3 = Ph) shown notable efficacy against the human gastric cancerous cell line SGC-7901, with an IC_{50} amount of 2.69 µg/µL. Additionally, both this drug and its derivative **81** (R_1 = Br, R_2 = COMe, R_3 = Ph) demonstrated significant telomerase inhibition, with IC_{50} amount of 2 µM and 1.8 µM, respectively[58]. Additionally, compound **185** (R_1 = H, $R_2 = C_2OH_2N(nPr)_2$, $R_3 = 4\text{-}CF_3C_6H_4$) exhibited strong action with an IC_{50} amount of 0.98 µM. The in vivo study showed that this drug might suppress S180 and HepG2 tumor development and dramatically boost EAC tumor survival[59]. Compound **185**, with R_1 = H, $R_2 = C_2OH_2S(CH_2)_4CH_3$, $R_3 = 4\text{-}CF_3C_6H_4$, inhibited the telomerase with an IC_{50} of 0.92 µM[60].

Chromene derivatives labelled as **186** Fig. 7, featuring an amine group at the 4 positions, were subjected to tests to assess their capacity for hindering impeding cell growth in HeLa cells and DNA preparation in Ehrlich cells[61]. This investigation revealed that prominent of the compounds has an activity solely in the one of such evaluations, and there was no discernible correlation between the outcomes of the two tests. Generally, many compounds were recognized as agents with antiproliferative and cytotoxic properties, displaying notably low amount of IC_{50} with ranging from 1.74-12.9 µM. The efficacy of these compounds was influenced through amine group and the conjugated located on the organic ring of the derivatives of chromene structure. Notably, the cyclo alkylamino groups and the phenylamino groups emerged as the very potent amino substitutions. Furthermore, the existance of an extra aromatic ring within the chromene structure, resulting in a tricyclic core, improved the biological efficacy.

Xing *et al.,* studied 4H-chromene **187** Fig. 7 and chromene based derivatives' cytotoxicity for cancerous cell lines in recent years. They have concentrated on identifying compounds that specifically attack drug-resistant cancerous cells to address this issue. A compound **187**, with all groups are same ($R_1 = R_2$ = Et and R_3 = H), was checked on cancerous cells with increased Bcl-2 group protein expression. It overcomes medication resistance by acting as an antagonist and is selectively cytotoxic to malignant cells[62,63]. This compound elicited cell death via the endoplasmic reticulum (ER) pathway by enhancing ER stress and initiating the emission of ER-associated factors Ca^{2+}. This substance also inhibited the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase. Compound **187**, with $R_1 = R_2$ = Et and R_3 = 3,5-OMe, demonstrated µM cytotoxicity against over 11 cancerous cell lines, encompassing both hematologic and solid tumors cells[50,64]. This chromene was assessed in camptothecin- and mitoxantrone-resistant cancerous line cell (CCRF-CEM/C2 and HL-60/MX2). Remarkably, it normally eliminated drug-resistant cells over non-resistant ones. Analogues of compound **187** were generated by analyzing its structure and activity. According to Mooring *et al.,* study, these analogues have the same conjugated ways are present in R_3, though with $R_1 = R_2 = CH_2C\equiv CH$[65]. One compound showed increased effectivity in the multi-resistant drug HL60/MX2 line cells, with an average values IC_{50} of 640 nM.

Nonsteroidal derivatives of the chromene **188a** and **188b** Fig. 7 identified particular inhibiting agents of endothelial cells proliferation through an assessment of primary human vein endothelial cells[66]. These compounds share structural similarities with Alternariol natural derivatives, which also display anti-cancer effects.

Compound **189** Fig. 7 blocks heat shock protein 90 and suppresses HIF-α client protein, making them antiproliferative agents. These chromenes showed nM activity in H1299 large cancerous lung cells. The dose-dependent antiangiogenic actions were tested in zebrafish embryos[67].

Derivatives of neo-tanshinlactone **190,** Fig. 7 were synthesized and evaluated for their anticancer efficacy across many different cell lines, which includes breast cancer (HS 587-T, MCF-7, SK-BR-3, MDA-MB-231, ZR-75-1), non-small cell cancers like of the prostate (LN-CaP, PC-3), lungs (A549), colon (SW620), nasopharyngeal (KB), skin (A431), and a vincristine-resistant KB subline (KB-VIN)[68]. Of these, chromene 190, which possesses a methyl group at R_1 and either a methyl or ethyl group at R_3, had the highest potency in cell growth inhibition and selectivity. The results indicate that the furan moiety and the configuration of aromatic ring substitution are essential in influencing anticancer activity. These compound displayed an ED50 values of 0.18 µg/mL for ZR-75-1 and 0.45 µg/mL for MCF-7. In another study, the same group examined **190** analogues by various ring position substitutions[69]. Once again, chromenes were found to be effective anti-cancer drugs with values of ED50 below the 1 µg/mL. Additionally, the highest outcomes again came from the groups of methyl and alkyl in R_1 and R_3 respectively.

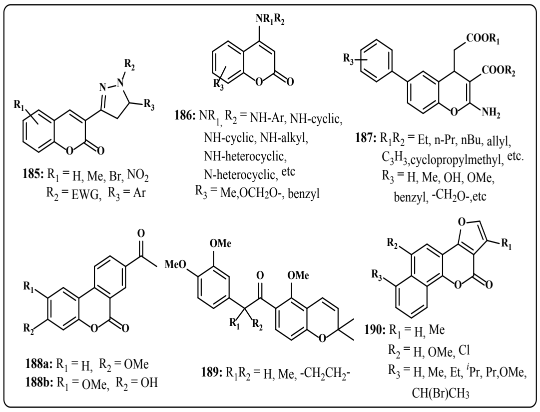


Fig. 7. Synthetic Chromene derivatives (185-190)

The anticancer efficacy of 2*H*-chromene **191** (Fig. 8) was assessed in various human cancer cell lines, including A549, K562, MCF-7, and MOLT-4[4]. Chromene **191**, characterized by a bromine atom at 6-position of the aromatic ring and a hydantoin moiety (X = O, Y = NH, and R_2 =

H) at the 3-position, shown considerable cytotoxic action, with IC_{50} values akin to those of cisplatin. Furthermore, compounds featuring a 6-membered ring and a 4-methoxyphenyl group in the amine moiety (R_3 = H or Me) exhibited significant anticancer activity towards many cancerous lines of cell, with ED50 values between 0.32 and 0.008 μM. Chandra *et al.,* examined the impact of compound **192** (Fig. 8) on estradiol-induced uterine hyperplasia in rate[70]. It is widely familiar with the name as estrogen that induced uterine tissue alternation can cause atypical hyperplasia and endometrial cancer. Compound **192** was delivered at dosages of 100 and 200 μg/kg, indicating its potential function in this investigation. These chromene chemical compounds triggered intrinsic apoptosis promotion of apoptosis by the inhibition of Akt function and the reduction of referred to as inhibitor of apoptosis protein levels. In addition, it prevented estradiol-induced uterine hyperplasia in rats.

Griffin and colleagues designed a set of inhibitors targeting protein kinase that are based on DNA (DNA-PK) to amplify the effectiveness for the faulty of DNA treatments for cancer therapy71. Chromenes labelled as **193** Fig. 8, featuring heterocyclic amines (piperidine) at the position-4, were investigated. Levels of inhibiting, quantified by IC_{50} values, ranged from 1.75 to 11.31 μM. The most potent result of IC_{50} was calculated of 1.75 μM that exihibits a morpholine group at 4-position in the chromene and additionally a group of methoxyl present at C6 of the ring. Compounds that impede endothelium cell growth are crucial for addressing conditions linked to angiogenesis, including solid tumors. The hypoxia-inducible factor (HIF) route is essential for cancerous cells' adjustment to hypoxic environments, facilitating therapeutic resistance and establishing it as a significant target for cancer therapy. In this context, 2*H*-chromenes 194 Fig. 8 exhibited the capacity to suppress HIF-1 in the hypoxia-treated people glioma cell line LN229-HRE-Lux[65,72].

Blagg *et al.,* Bras and colleagues investigated novobiocin analogues **195** and **196** Fig. 8, for their potential as antiproliferative agents and Hsp90 inhibitors, an attractive target in anticancer drug development[73-76]. Blagg and colleagues showed that the derivative of chromene **195,** with methyl groups at R_2 and R_1 at the aromatic ring's 8 position, inhibited Hsp90 protein-folding. Chromenes **195,** including conjugate of 2-indolyl moieties, was tested with antiproliferative properties in multiple cancerous lines cell, including colon (HCT116), breast (SkBr3, MCF-7), and pancreatic (PL45) cancer. This exploration yielded numerous intriguing compounds with low IC_{50} values. Bras and colleagues examined derivatives 196 without the noviose moiety. Positions 4 and 7 needed tosyl moiety substitutes for optimal results. These compounds killed MCF-7 cells and degraded Hsp90 client proteins[75]. Coumermycin A1 derivatives **197** Fig. 8 inhibited Hsp90 protein folding[77].

Synthesis and in vitro testing of coumarins **198** Fig. 9, with the hydrazide-hydrazone constituent was evaluated for its antiproliferative efficacy towards the human drug-resistant pancreatic cancer (Panc-1) and drug-sensitive cell lines (Hep-G2 and CCRF). Compound **198** that containing R_1 = 6-Br and R_2 = 2-thiophene cytotoxically active towards all examined cells (IC_{50}: 3.60-6.50 mM) and caused apoptotic and G2/M gene expression in resistant Panc-1 cells[78]. Synthetic 4-Arylcoumarin numbered **199** Fig. 9, evaluated for their ability to combat cancer. Compound displayed the most promising outcomes by effectively restraining the progress of the cell lines of CEM leukemia even at very low concentrations like of 0.083 and 0.52 μM. This particular compound hindered tubulin assembly to induce apoptosis and prompted cell death through an alternative pathway that doesn't involve apoptosis[79].

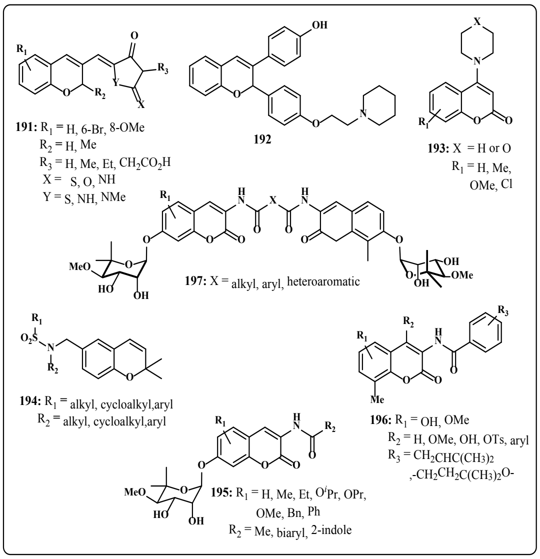


Fig. 8. Synthetic Chromene derivatives (191-196)

Analogous chromenes **200** Fig. 9, with an amine component in the 4 positions rather than of group of furan ring, inhibited tumor cell development[80]. The evaluation encompassed breast cancerous lines cell (SK-BR-3, MDA-MB-231, ZR-75-1), large cancerous cell of lungs (A549), prostate (DU145), along with cell lines of KB and KB-VIN. The amine component included conjugate group of aromatic, aliphatic, and heterocyclic, with the aromatic conjugate arrangement exhibiting the most potency, producing ED50 amount from 0.01 to 5.8 µM across the evaluated cell lines, making it the most convenient. Additionally, the 3-methylphenyl and 4-methoxy moieties with R_1 = H showed the highest ED50 values ranging from 0.01-0.76 µM), indicating cell growth inhibition. The same authors generated similar chromenes **201** Fig.9[81]. Certain compounds had a 5- or 6-membered ring linked to the aromatic chromene moiety rather than an additional chromene structure of **200** and also explored for the amine substituent.

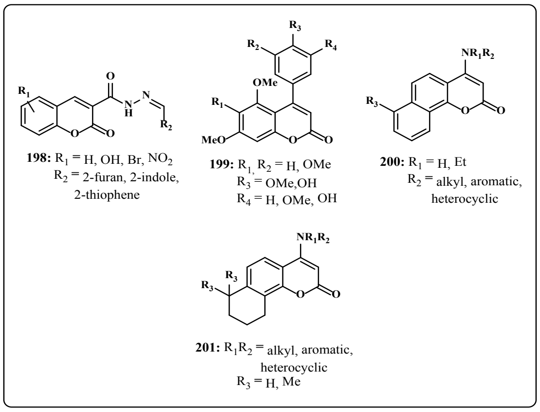


Fig. 9. Synthetic Chromene derivatives (198-201)

CONCLUSION

This review gives a current perspective that highlights the significance of the chromene structure in bioactive compounds. The structure of chromene is present in numerous natural compounds and has demonstrated interactions with diverse biological objectives, frequently providing a significant therapeutic advantage. The ring structure of 2H/4H-chromene has been utilized as the basis for creating new frameworks that show promise for identifying anticancer drugs and other biological uses. Microwave irradiation technique, one-pot preparation, and metal-catalyzed procedures, and other ecologically friendly methods are all available for creating the 2H/4H-chromene ring and derivatives of chromene. Among these, condensation and addition reactions like Michael addition and aldol condensation preparation methods are normally used to produce 4H-chromene analogues due to the ease with which starting materials can be obtained and the ability to yield a larger quantity of the final product via one-pot multicomponent preparation. The insertion of a wide range of C3-ester substitutions and C4-benzopyran alterations, particularly those involving changed aryl functionalities on chromene, is more beneficial for boosting anticancer activity. This current review describes various design approaches for 2H/4H-chromene compounds. These results highlight structural qualities that medicinal chemists can use as a reference when developing powerful chromene compounds.

Future outcomes

The domain of chromene chemistry provides motivation for medicinal chemists and biopharmaceutical organizations. The existing body of knowledge represents just a fraction of the significant possibilities within this particular chemical group. In their quest to find novel chemicals with increased biological efficiency, committed researchers still have many unexplored areas to discover.

ACKNOWLEDGEMENT

The authors would like to thank Jazan University for the valuable support.

Funding

This article received no external funding.

Conflict of Interest

The authors declare that there are no conflict of interest regarding the publication of this paper.

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