SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 6.
Issue: 4.
Page N. 73-85
Year: 2022

Review Article www.wjahr.com

OXYGEN CONTAINING HETEROCYCLIC SCAFFOLDS AS ANTICANCER AGENT- A REVIEW

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Received date: 04 February 2022 **Revised date:** 25 February 2022 **Accepted date:** 17 February 2022

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ABSTRACT

A cancer is a devastating problem which is depicted by the uncontrolled development and spread of abnormal cells by invasion and metastasis. According to world health organization (WHO), more than 80% of world's population relies on traditional medicines for their essential health care needs. Numerous naturally occurring compounds containing oxygen heterocycles, shows fascinating therapeutic activities. Oxygen containing heterocyclic compounds, present in most pharmaceuticals is currently marketed. A variety of Oxygen containing heterocyclic compounds showed anti-inflammatory, analgesic, neuroprotective, anti-hypertensive, anti-anxiolytic, anti-arrythmic, and prominent anti-tumour activities. Mostly drugs having oxygen heterocycles, found in the most abundant class of these anti-cancerous drugs. The oxygen containing heterocyclic compounds like benzopyran, coumarins, flavonoids, furans, pyrans, showed cytotoxic effects against various cancer cell lines viz; MCF-7, HeLa, MDA-MB-231, MCF-10A, OVCAR-3, PC-3, A-549. The studies also suggested that a non-aromatic ring can greatly affect the anti-tumour activity and cancer cell line selectivity.

KEYWORDS: Heterocyclic compounds, Scaffolds, Metastasis and Anti-tumor activity.

INTRODUCTION

Natural oxygen containing heterocycles has been one of the most significant sources for drugs and drug leads.[1] Tumours generally follows unusual metabolic pathways to obtain the energy and inabilities required for their persistant growth. oxygen- containing heterocyclic moiety, which exhibit an array of pharmacological properties (anticancer activities) against different human cancer cell lines. They are known to possess anti-tumour properties by inducing mitotic arrest and apoptosis.[2] Moreover, patients often develop resistance to chemotherapy thought to be due to the presence of residual cancer stem cells in tumour niches, hence the urgent need to identify novel therapeutics that target these slow-growing, highly drug resistant stem-like cancer cells.[3] Cancer is the second leading cause of mortality in the United States, after heart disease, and is responsible for about one out of every four deaths (American Cancer Society 2013). According to the most recent United States mortality data, 567,628 people died of cancer in 2009, with this being the main cause of death for persons between the ages of 40–79 years. It is estimated that in the year 2013, 1,660,290 new cancer cases will be diagnosed and about 580,350 Americans will die of cancer, accounting for approximately 1,600 deaths per day Cancer of the lung and bronchus is responsible for the greatest number of deaths, followed by prostate cancer for men or breast cancer for women, and colorectal cancer. However, cancer death rates have decreased slightly each year by about 1.8% for men and by 1.5% for women, according to the most recent statistics (2005–2009) from the Surveillance, Epidemiology, and End Results (SEER**)** Program of the U. S. National Cancer Institute. The decrease in number of deaths due to cancer has been a result of adopting healthier lifestyles, and from the earlier detection of certain cancers by routine prevention screening, as well as improvements in treatment.[4-8] Increasing evidence from both epidemiological and laboratory studies suggests that the dietary intake of flavonoids reduces the risk of developing certain types of cancers. Several types of flavonoids have been identified as having antiproliferative efficacy in various cancers, including silymarin, genistein, quercetin, daidzein, luteolin, kaempferol, apigenin, and epigallocatechin 3-gallate.[9] These afore mentioned compounds have been reported to

have anticancer and preventive effects against prostate, colorectal, breast, thyroid, lung, and ovarian cancers, among others.[10] Their chemopreventive efficacy is mediated by (1) inhibiting the development of new cancer cells;[11] (2) preventing carcinogens from reaching their activation sites; and [12](3) decreasing the toxicity of certain compounds by inhibiting their metabolism. The molecular mechanisms by which flavonoids produce their anticancer and preventive effects include (1) induction of apoptosis; (2) cell cycle arrest at G1 or G2/ M phase by inhibiting key cell cycle regulators such as cyclin-dependent kinases (CDKs).[13] (3) inhibition of metabolizing enzymes (notably cytochromes P450 [CYPs]), which inhibits the activation of numerous carcinogenic compounds.[14] (4) inhibition of reactive oxygen species formation primarily by activation of phase II metabolizing enzymes and (5) inhibition of vascular endothelial growth factor (VEGF)- and basic fibroblast growth factor (bFGF) mediated angiogenesis.[15]

REVIEW OF LITERATURE

BENZOPYRAN BASED ANTICANCER AGENTS

Gonzalez et al., were investigated and examined the pharmacological activities of benzopyran derivatives. They investigated the anti-proliferative and cytotoxic effects of compound (1) and (2) using a variety of in vitro cell-based assays. They showed that compound (1)and (2) induced mitochondrial mediated apoptosis in human breast cancer cell lines. The cytotoxic effects of (1) and (2) on human breast cancer cell-lines (MCF-7and MDA-MB231) and a human normal breast epithelial cell-line (MCF-10A) were evaluated using MTT assays. Results showed that relatively high cell viability inhibitory effect was observed in both breast cancer cell lines compared to normal breast cell-line after 48h of treatment. They were observed that compound (1) or (2) caused a significant decreased in cell growth as reflected in the reduction of cell confluency after 24h treatment.[16]

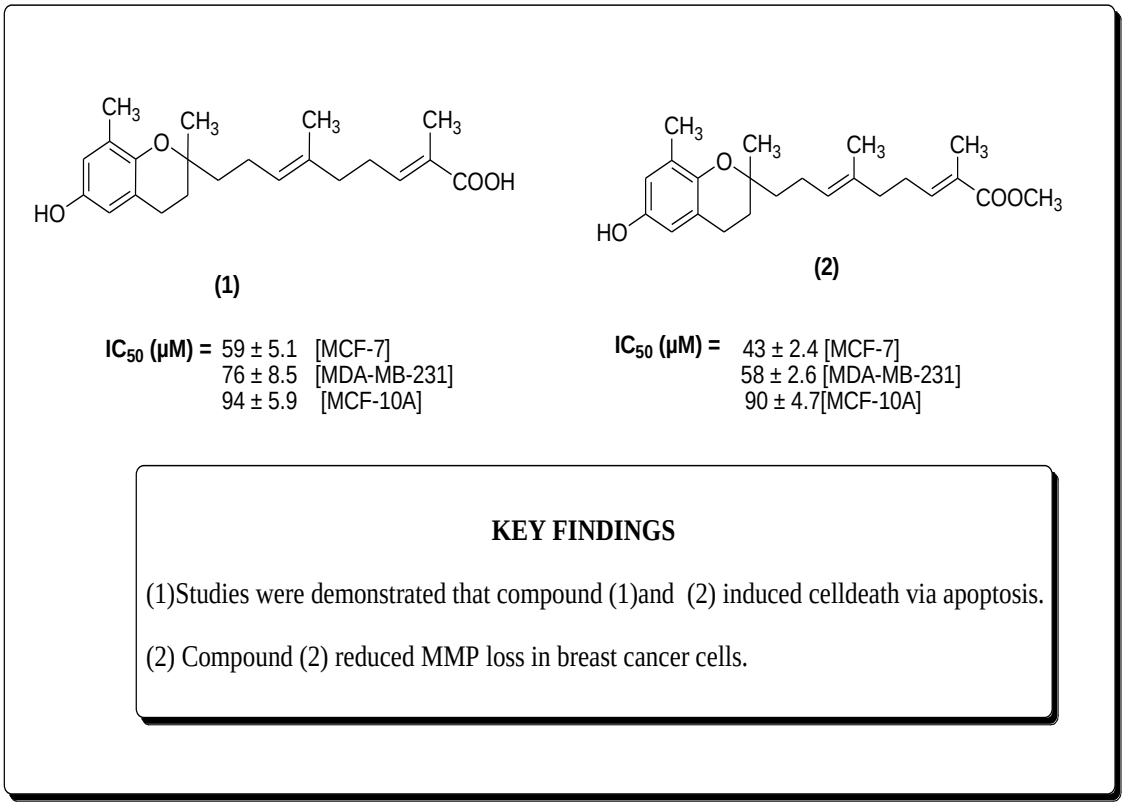
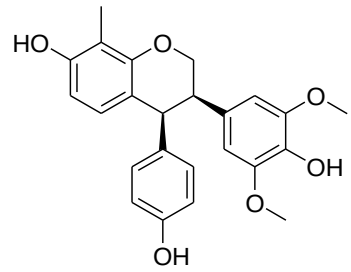


Figure: 1.1

Alvero et al., were investigated and synthesized the compound (3) Cantrixil against various cancer cell lines (Ovarian OVCAR-3[0.023±0.006], Prostate PC3[0.096±0.077], Lung Pancreatic Panc-1[0.467± 0.378], Colorectal HT-29[1.765 ± 1.385], Glioblastoma A172[0.051 ± 0.002]. TRX-E-002-1 showed broad cytotoxic activity against ovarian, prostate and lung cancer cells, with IC50 values ≤0.1 µM. Activity in pancreatic and colorectal cancer cells and glioblastoma cells was more variable. TRX-E002-1 was assessed against ovarian cancer stem cell line OCSC2, characterised by their expression of stem cell markers including CD44 and MyoD. TRX-E-002-1 is able to induce cell death in chemo-resistant CD44 +/ My D88+ OCSC clones.[17]



(**3**)

IC_{50} (μM) = 0.023 ± 0.006 [OVCAR-3]
0.096 ± 0.077 [PC3]
0.051 ± 0.002 [A172]

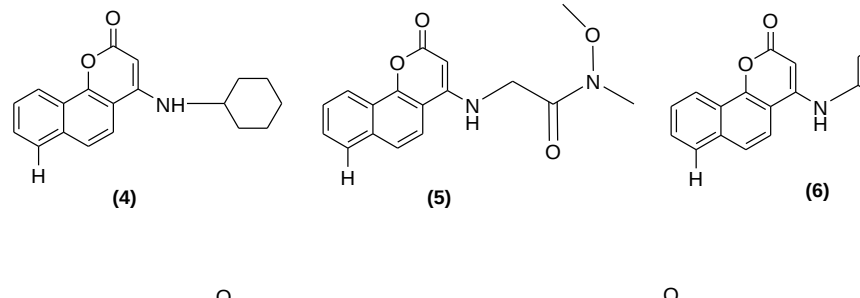
KEY FINDINGS

(1) Studies were demonstrated that compound (3) induced cell death via apoptosis.

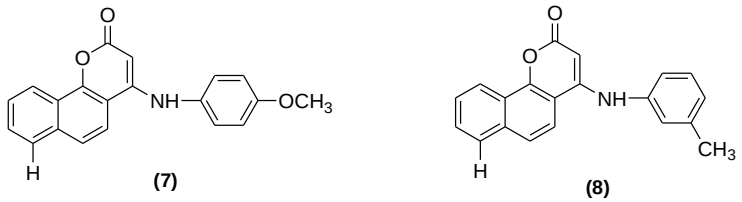
(2) The compound (3) anti-tumour activity was confirmed in vivo in a highly resistant ovarian cancer.

Figure: 1.2

Dong et al., were designed, synthesized, and evaluated 4-Amino-2H-benzo[h]chromen-2-one ABO analogs for cytotoxic activity. The compounds cyclohexyl (4), N-methoxy-N-methy lacetamide (5), and various aromatic derivatives (6), exhibited promising cell growth inhibitory activity with ED50 values of 0.01-2.1 μM against all tested tumor cell lines among all 4-substituted ABO analogs. The compound (7), (4′-methoxyphenyl derivative) and 8 (3′-methylphenyl derivative) showed the more potent antitumour activity against various cancer cell lines (A549, MDA-MB-231, ZR-75-1).[18]



(4) **(5)** **(6)**



(7) **(8)**

ED_{50}(μM)= 0.01-2.1[A549, MDA-MB-231, ZR-75-1]

KEY FINDINGS

(1) The substitutions on nitrogen of substituent hydrogen or ethyl are critical to the antitumor potency.

Figure: 1.3

COUMARIN BAESD ANTICANCER AGENTS

Alam et al., were isolated and evaluated two new sesquiterpene coumarins (compounds 9 and 10) have been carried out from Ferula narthex collected from Chitral, locally known as "Raw." They evaluvated for Anticancer activity of crude and all fractions have been carried out to prevent carcinogenesis by using MTT assay. The n-hexane fraction showed good activity with an IC50 value of 5.434 ± 0.249 µg/mL, followed by crude MeFn extract 7.317 ± 0.535 µg/mL, and CHCl3 fraction 9.613 ± 0.548 µg/mL. Compounds (9 and 10) were isolated from chloroform fraction. Among tested pure compounds, compound (9) showed good anticancer activity with IC50 value of 14.074 ± 0.414 µg/mL.[19]

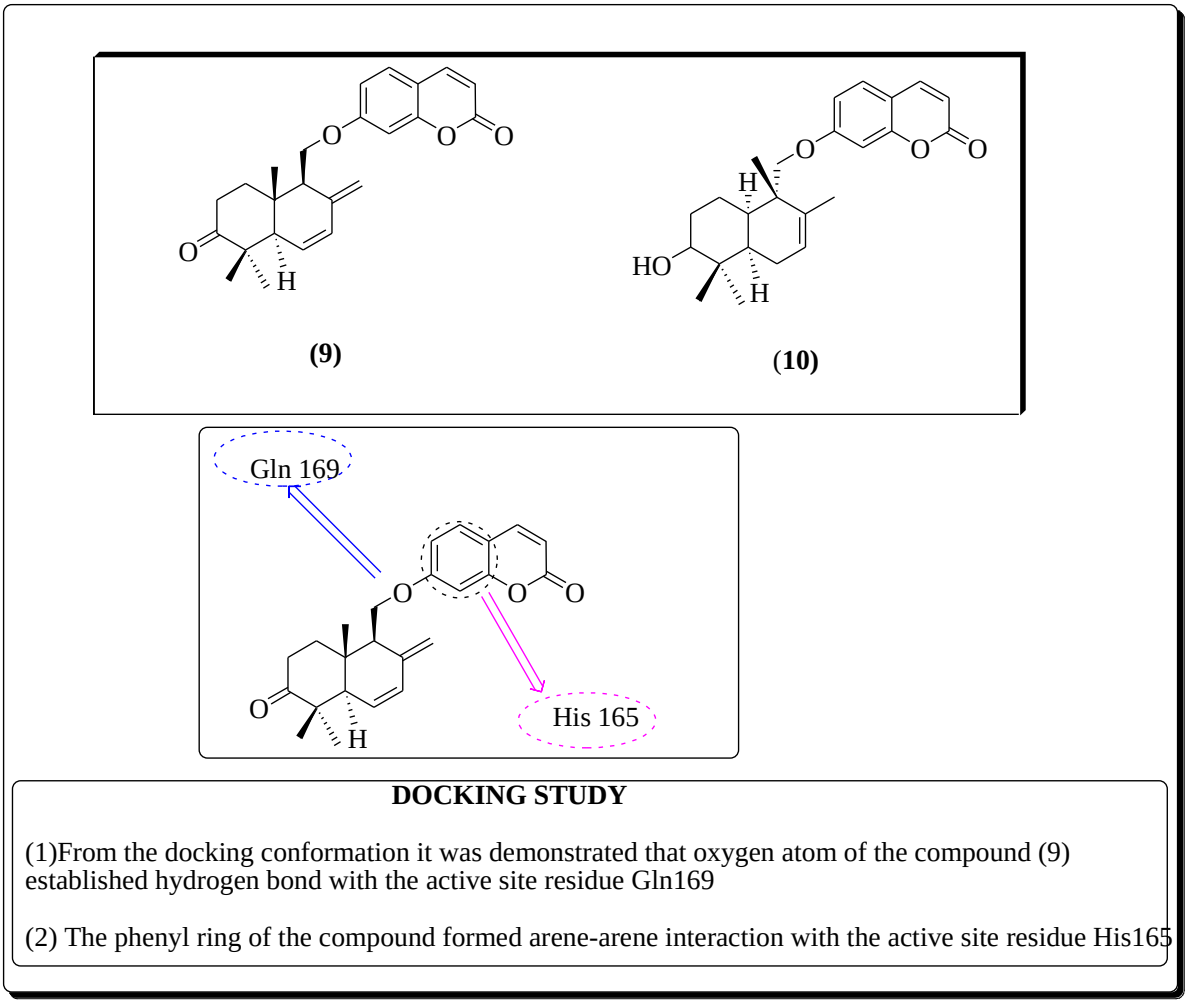


Figure: 2.1

Zhou et al., were investigated and observed that Among 36 analogues of coumarin, 6-chloro-4-(methoxyphenyl) coumarin showed the best anticancer activity (IC50 value about 200 nmol/L) in HCT-116 cells. The compound (11) showed broad spectrum of anticancer activity against 9 cancer cell lines derived from colon cancer, breast cancer, liver cancer, cervical cancer, leukemia, epidermoid cancer with IC50 value of 75 nmol/L–1.57 µmol/L but with low cytotocitity against WI-38 human lung fibroblasts (IC50 value of 12.128 µmol/L). The compound (11) (0.04–10 µmol/L) induced G2-M phase arrest in HeLa cells in a dose-dependent manner, which was reversible after the compound was removed. The compounds 11, 12, 13 and 14 are more potent against HeLa cancer cell lines.[20]

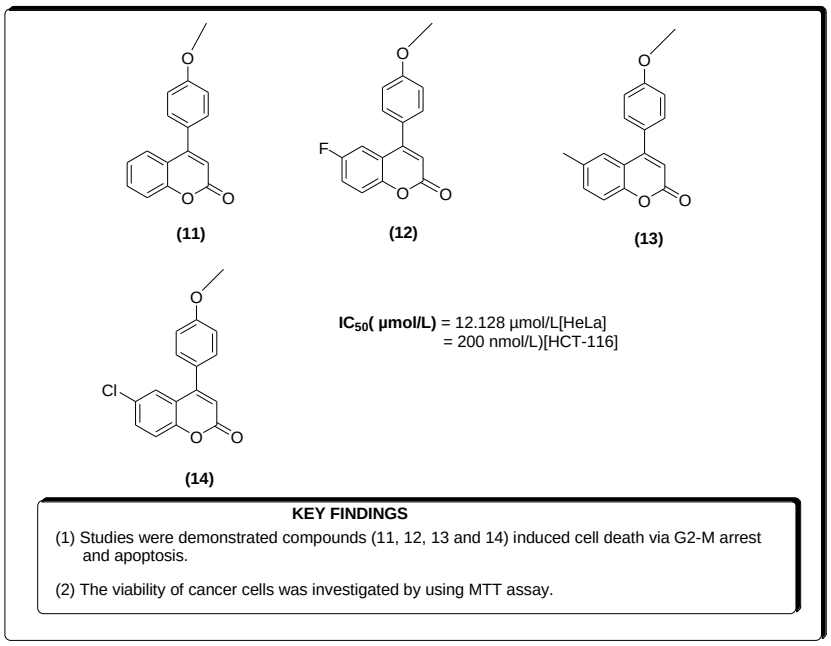


Figure: 2.2

Benna et al., were studied the Molecular docking and observed that MBDC binds well in the active site of tankyrase and interact with the amino acid residues. These results were compared with the anti cancer drug molecule warfarin derivative. The results showed that antiproliferative activity of MBDC and Warfarin derivative against MCF-7 breast cancer and HT-29 colon cancer cell lines at different concentrations exhibited significant cytotoxicity. The estimated half maximal inhibitory concentration (IC 50) value for MBDC and Warfarin derivative was 15.6 and 31.2 µg/ml, respectively. This enhanced cytotoxicity of MBDC in MCF-7 breast cancer and HT-29 colon cancer cell lines may be due to their efficient targeted binding and eventual uptake by the cells. Hence the compound (15) MBDC may be considered as a drug molecule for cancer.[21]

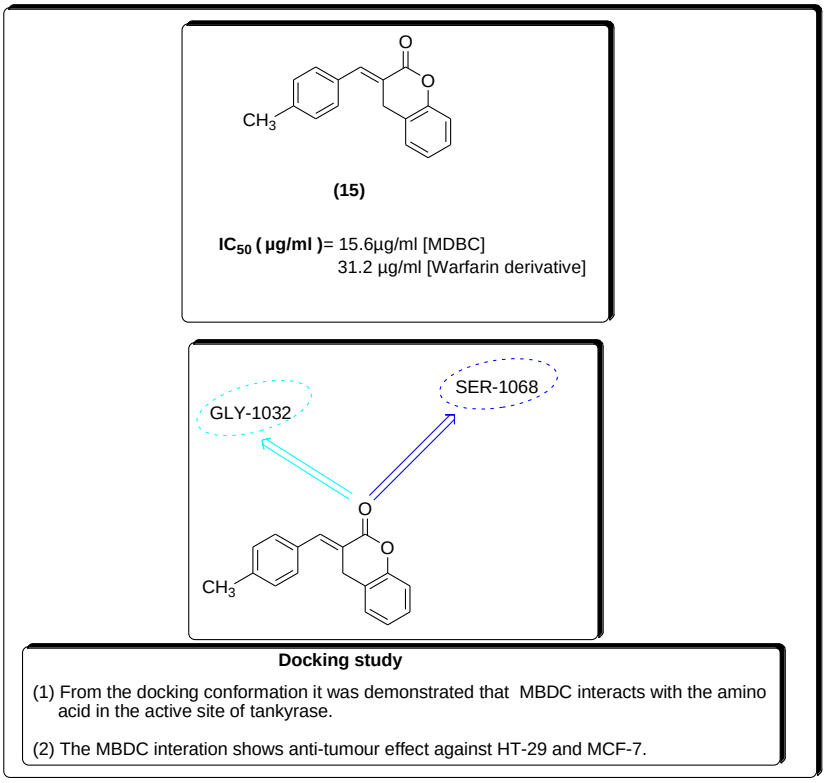


Figure: 2.3

Amin et al., were studied and observed that cancer is a fatal disease. They investigated, Coumarin derivative RKS262 as an analogue of Nifurtimox [compound (16)], a drug that induces the cytotoxic and antitumor effects in neuroblastoma in vivo and in vitro, showed very potent activity in ovarian cancer (OVCAR-3 cells, human ovarian epithelial adenocarcinoma cell line) chemoresistant to platinum-based drugs. Osthole (7-methoxy-8-(3- methyl-2-butenyl)coumarin) [compound (17)] which was extracted from many therapeutic plants such as Cnidium monnieri and Prangos ferulacea (L.) inhibited the growth of human lung cancer (A- 549 cancer cells) by inducing G2/M arrest and apoptosis. Cytotoxic activity on bladder cancer cells were investigated by on 7-isopentenyloxycoumarin (7-IP) [compound (18)] that can be synthesized both naturally and chemically and it exhibited selective cytotoxic effect on 5637 cells (bladder cancer) in comparison to normal HDF-1 cells (human dermal fibroblast).[22]

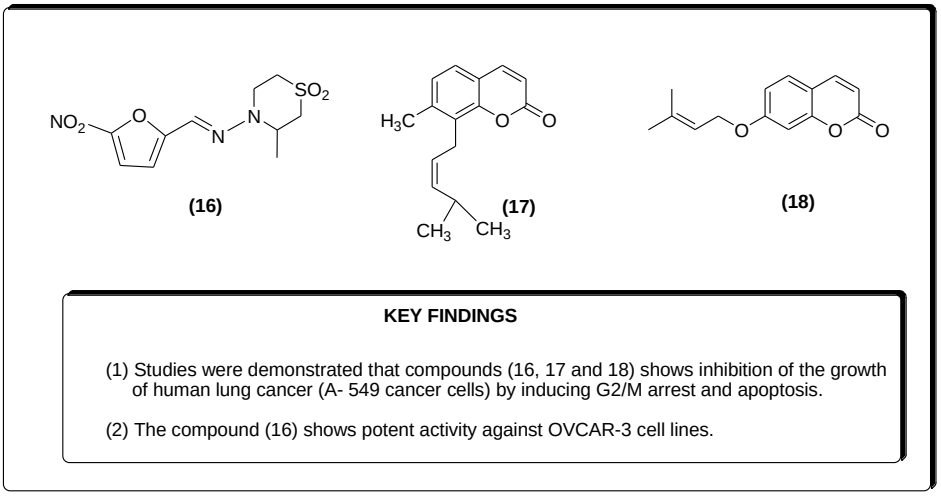


Figure: 2.4

FLAVONOID BASED ANTICANCER AGENT

Ghasemzadeh et al., were studied and evaluated the compounds (19, 20 and 21) as anticancer activity (against breast cancer cell lines MCF-7 and MDA-MB-231) in two varieties of Malaysian ginger, namely Halia Bentong and Halia Bara. The results of high performance liquid chromatography (HPLC) analysis showed that application of SA induced the synthesis of anthocyanin and fisetin in both varieties. The lowest value was recorded in the untreated control plants (42.5%–46.7%). These results indicate that SA can act not only as an inducer but also as an inhibitor of secondary metabolites. Meanwhile, the highest anticancer activity against MCF-7 and MDA-MB-231 cell lines were observed for H. Bara extracts treated with 10−5 M SA with values of 61.53 and 59.88%, respectively.[23]

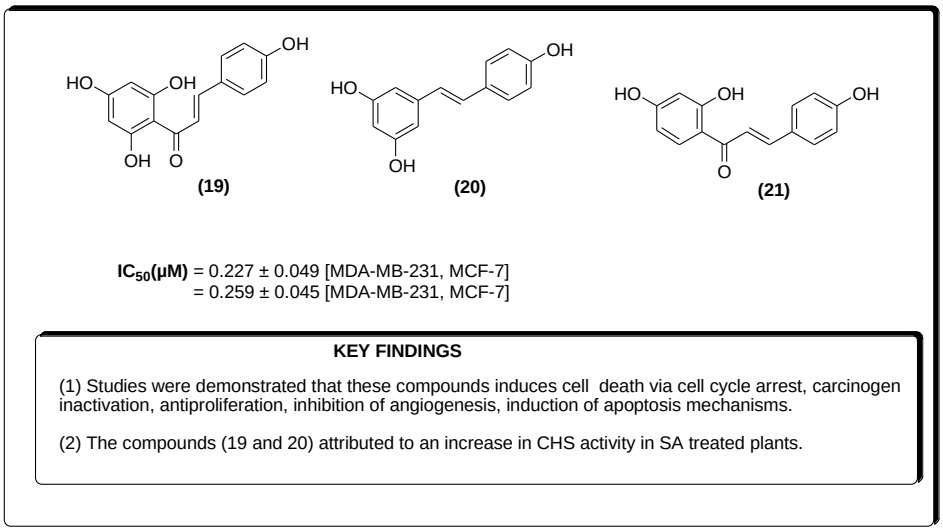


Figure: 3.1

Mohamed et al., were evaluated the Bioactivity-guided screening of C. angustifolia extracts, led to the isolation and identification of three flavonoids quercimeritrin (22), scutellarein (23) and rutin (24) reported for the first time from this plant, showed significant anticancer activity against MCF-7 (IC50, 4.0 μg/μL), HeLa (IC50, 5.45

µg/µL), Hep2 (IC50, 7.28 µg/µL) and low cytotoxicity against HCEC (IC50, 21.09 µg/µL). According to many research reports, the consumption of medicinal plants either in the form of raw extracts or chemical constituents is largely associated with lower risk of degenerative diseases caused by oxidative stress because they contain antioxidants such as phenolics, flavonoids, vitamins and carotenoids. Phenolic compounds such as phenolic acids and flavonoids are reported to be involved in various biochemical activities like antioxidant, antimicrobial, antithrombotic, antiartherogenic, antiinflammatory, anticarcinogenic and antimutagenic. They were also evaluvated and reported that synthetic antioxidants were the cause of carcinogenesis and liver damage in laboratory animals. Thus there is a need to explore and develop antioxidants of natural origin with greater efficacy and fewer side effects.[24]

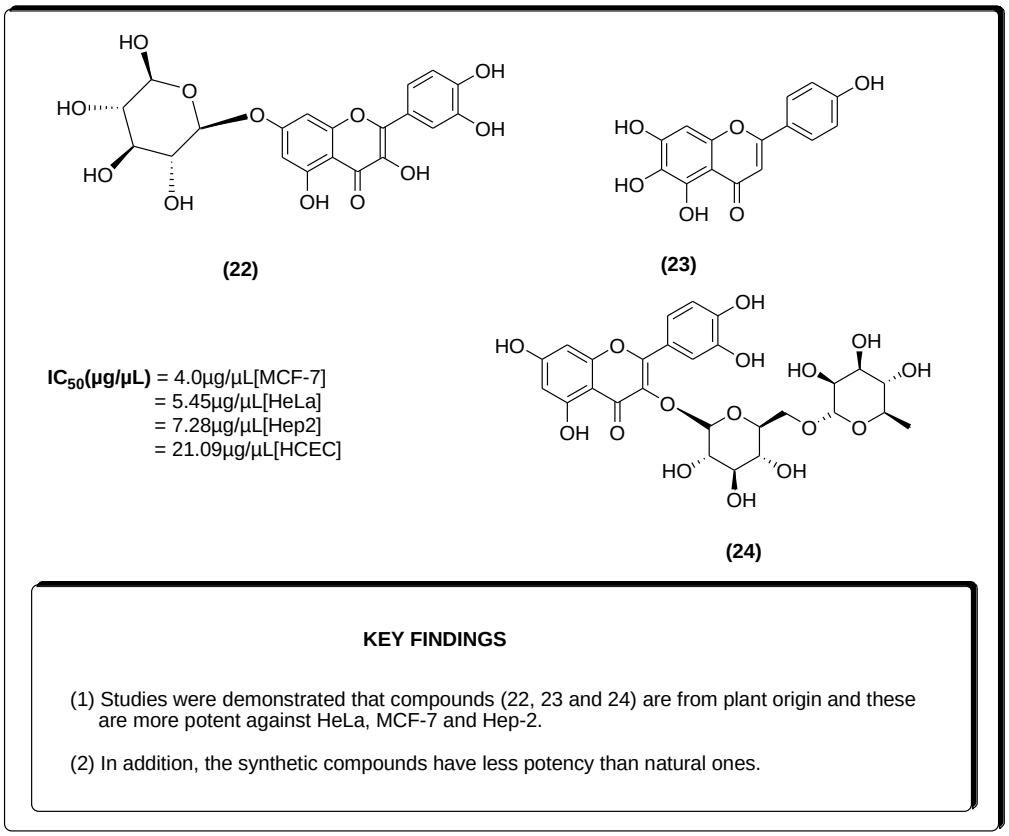


Figure: 3.2

Charles et al., were evaluated and found that flavonoids are polyphenols that are found in numerous edible plant species. Data obtained from preclinical and clinical studies suggest that specific flavonoids are chemo-preventive and cytotoxic against various cancers via a multitude of mechanisms. Flavonoids have been reported to have an excellent safety profile (no toxicity at up to 140 g/ day), with no known significant adverse effects. The pharmacological effects of flavonoids include antioxidant, anti-inflammatory, cardioprotect ive, hepatoprotective, antimicrobial, and anticancer. Increasing evidence from both epidemiological and laboratory studies suggests that the dietary intake of flavonoids reduces the risk of developing certain types of cancers Several types of flavonoids compounds (25, 26, 27, 28 and 29) have been identified as having antiproliferative efficacy in various cancers, including silymarin, genistein, quercetin, daidzein, luteolin, kaempferol, apigenin, and epigallocatechin 3-gallate. These mentioned compounds have been reported to have anticancer and preventive effects against prostate, colorectal, breast, thyroid, lung, and ovarian cancers, among others.[25]

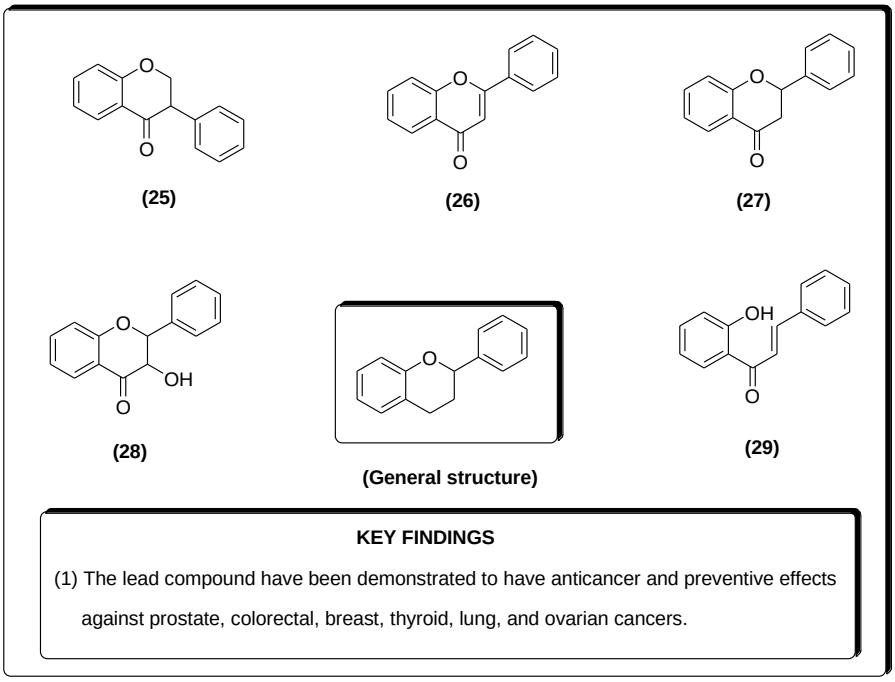


Figure: 3.3

Martinez et al., were observed that Proliferation assays showed that Oncamex treatment for 8h reduced cell viability and induced cytotoxicity and apoptosis, concomitant with increased caspase activation. Microarray analysis showed that Oncamex was associated with changes in the expression of genes controlling cell cycle and apoptosis. Fluorescence microscopy showed the compound's mitochondrial targeting and reactive oxygen species-modulating properties, inducing superoxide production at concentrations associated with antiproliferative effects. A preliminary in vivo study in mice implanted with the MDA-MB-231 breast cancer xenograft showed that Oncamex inhibited tumour growth, reducing tissue viability and Ki-67 proliferation, with no signs of untoward effects on the animals. Beyond their numerous roles in plant biology, flavonoid compounds (30 and 31) have long been identified as possessing a wide range of bioactivities, including protective and therapeutic effects against cancer, cardiovascular and neurodegenerative diseases, and thus have great potential for clinical application. Breast cancer cell lines MCF-7, MDA-MB-231, BT-549 and HBL-100 (all obtained from ATCC) were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% heat-inactivated foetal calf serum (FCS) and 100IUml1 penicillin/streptomycin. The LCC1, LCC2 and LCC9 (hormone-independent cells established by derivation of selected subpopulations of MCF-7 cells.[26]

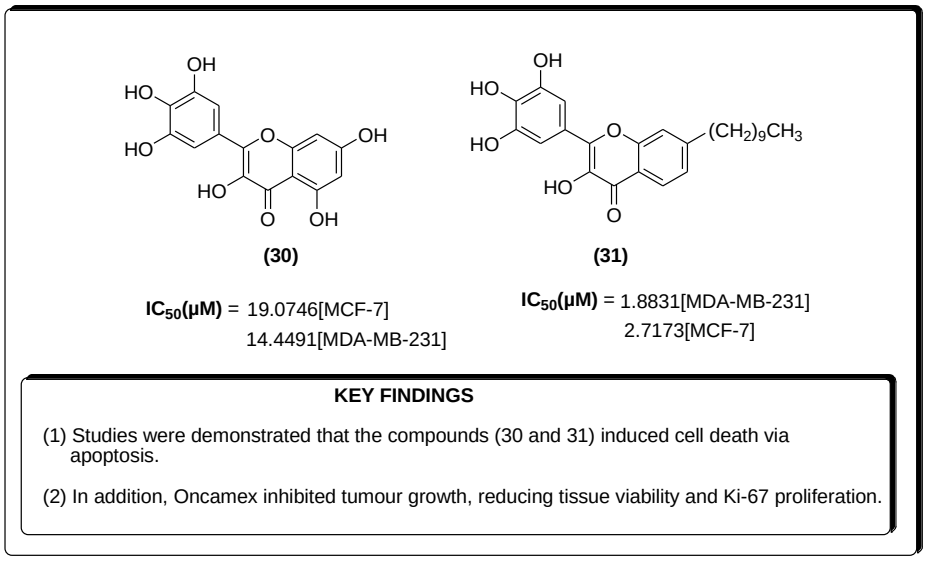


Figure: 3.4

FURAN BASED ANTICANCER AGENTS

Flynn et al., were designed and synthesized novel tubulin polymerization inhibitors from a series of benzo[b]furans with exceptional potency toward cancer cells, different cancer cell lines (against tubulin and MCF – 7 cell lines) and activated endothelial cells. They were also observed that Compounds (32 and 33) have potent anticancer activity against tubulin and MCF-7 cell lines.[27]

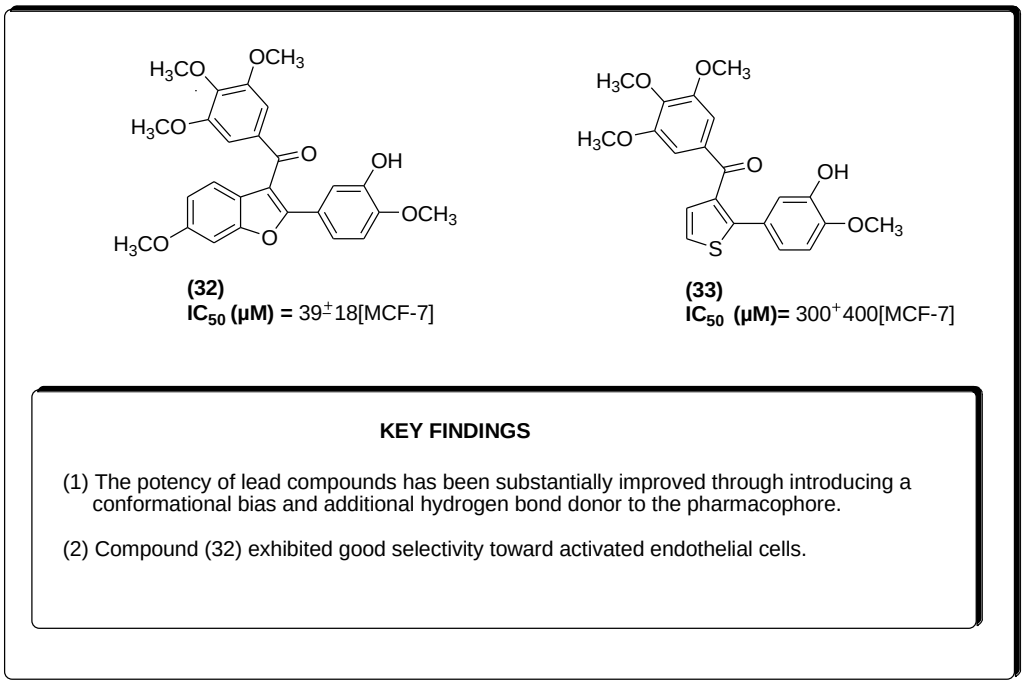


Figure: 4.1

Romagnoli et al., were synthesized and evaluated three different series of compounds in which different substituents were linked to the 3-amino position of the 2-(3′,4′,5′-tri methoxy benzoyl) benzo[b]furan or benzo[b] thiophene ring system. These substituents, corresponding to acetyl/ haloacetyl, α-bromoacryloyl and nitrooxyacetyl moieties had different electrophilic properties. The benzo heterocycle parent structures were selected because of their potent anticancer activity. They also evaluated that compounds (34 and 35) bearing a methoxy group at the 6-position of the benzo[b]furan skeleton, were have potent antiproliferative agents against the human chronic myelogenous K562 and murine L1210 leukemia cell lines.[28]

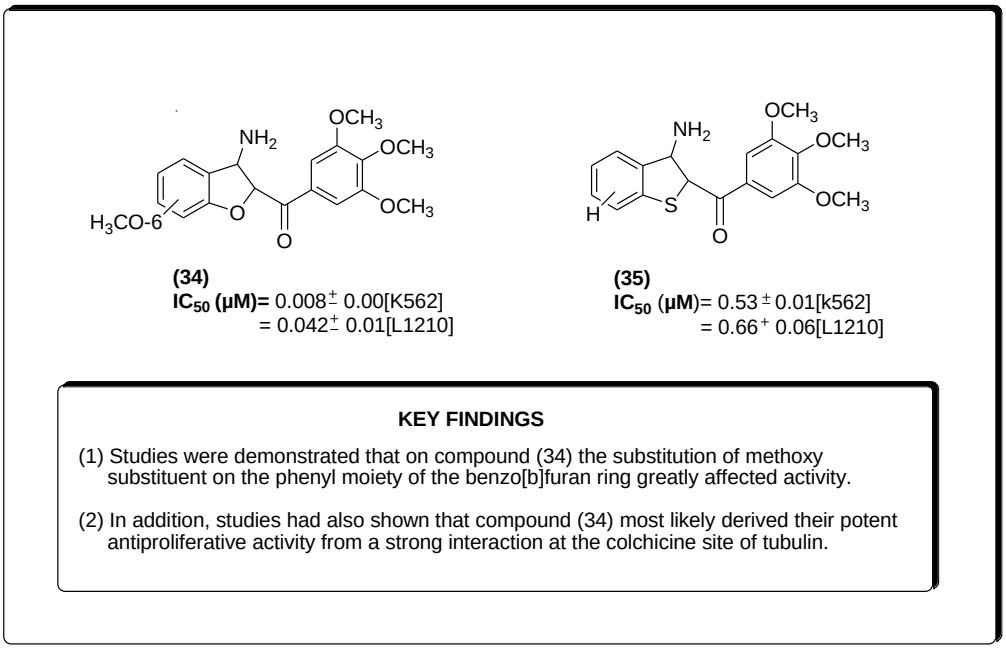
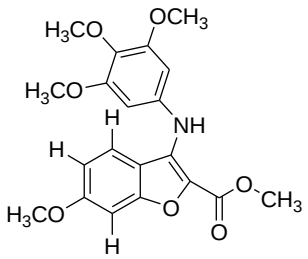


Figure: 4.2

Romagnoli et al., were studied and evaluated that compound (36) have potent anti-tumour activities against various cell lines (HeLa, A549, HT-29, Jurkat, RS 4;11, MCF-7, HL-60). The 2-methoxycarbonyl-3-(3′,4′,5′-trimethoxyanilino)-6-methoxybenzo[b]furan derivative had the greatest antiproliferative IC50 values, ranging from 0.3 to 27 nM against the seven cancer cell lines were also examined.[29]



(36)

IC_{50}(µM) = $2^{\pm}$ 0.1[HeLa]
= $0.3^{\pm}$0.1[RS4;11]
= 5^{+} 1[HL-60]

KEY FINDINGS

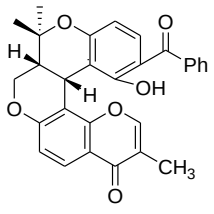
(1) Compound (36), in vitro was able to induce cell death via mitotic arrest followed by apoptosis.

(2) In addition, the compound (36) is a promising new tubulin binding agent with potential as an antitumor that could improve common anticancer therapies.

Figure: 4.3.

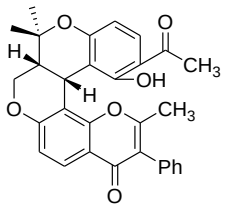
PYRAN BASED ANTICANCER AGENTS

Madda et al., were designed and synthesized an oxygen-containing heterocyclic moiety, which exhibit an array of pharmacological properties (anticancer activities) against different human cancer cell lines. They were showed that compounds (37 and 38) had exceptionally high cytotoxicity towards human cervical malingnant cells(HeLa). Compound (37) exhibited pronounced inhibitory action against both breast cancer cell lines (MDA-MB-231 and MCF-7). Furthermore compound (39) displayed high cytotoxicity against only (MDA-MB-231), while compound (38) demonstrated promising effects against human lung cancer cell line, A549 with an IC50 value of 2.53 µM.[30]



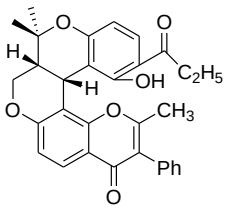
(37)

IC50(µM) =$1.5^{\pm}$ 0.08[HeLa]
=$5.68^{\pm}$0.13[MDA-MB-231]
=$6.24^{\pm}$0.19[MCF-7]



(38)

IC50(µM) =$6.15^{\pm}$ 0.09[MDA-MB-231]



(39)

IC50(µM) =$4.81^{\pm}$ 0.13[HeLa]
=2.53^{+}0.07[A-549]

KEY FINDINGS

(1) The lead compound (37) showed broad cytotoxicity against HeLa, MDA-MB-23 and MCF-7 cell lines.

(2) It suggested that the presence of pheny substitution on the carbonyl group and also the presence of mono methyl group on the chromenone moiety.

(3) In case of compounds (38) and (39) the cytotoxicity against Hela, MDA-MB-23 and MCF-7 cell lines due to presence of ethyl and methyl substituents on the carbonyl group.

Figure: 5.1

Dong Y et. al., were designed, synthesized compounds (40 and 41) and evaluated 4-Amino 2H-benzo[h] chromen -2-one for anticancer activity. Among all aromatic derivatives, 4'-Meo analog and 3'-Me analog were the most potent against all tested tumour cell lines (MDA-MB- 231, A549, SKBR-3, ZR-75-1)(ED50 values of 0.01-0.17µM). The results were indicated that an aromatic group is suitable to fit into the binding pocket of the target protein, resulting in potent activity.[31]

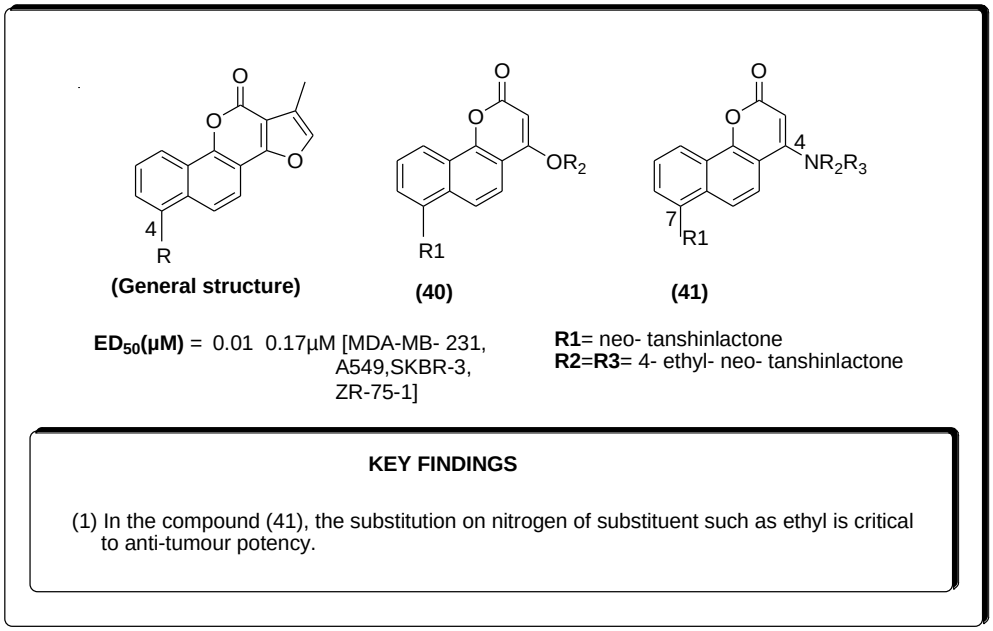


Figure: 5.2

Di Bussolo et. al., were designed and synthesized non-glucose glycoconjugated N- hydroxyindole inhibitors of human lactate dehydrogenase A(LDH-A) are promising therapeutic agents against cancer. They synthesized NHI-glucoconjugates (42) (β-DGlc(1), (43) α-D-Man(2), (44) β-D-Gul(3) and (45) NHIs) against cervical tumor and NSCLC.[32]

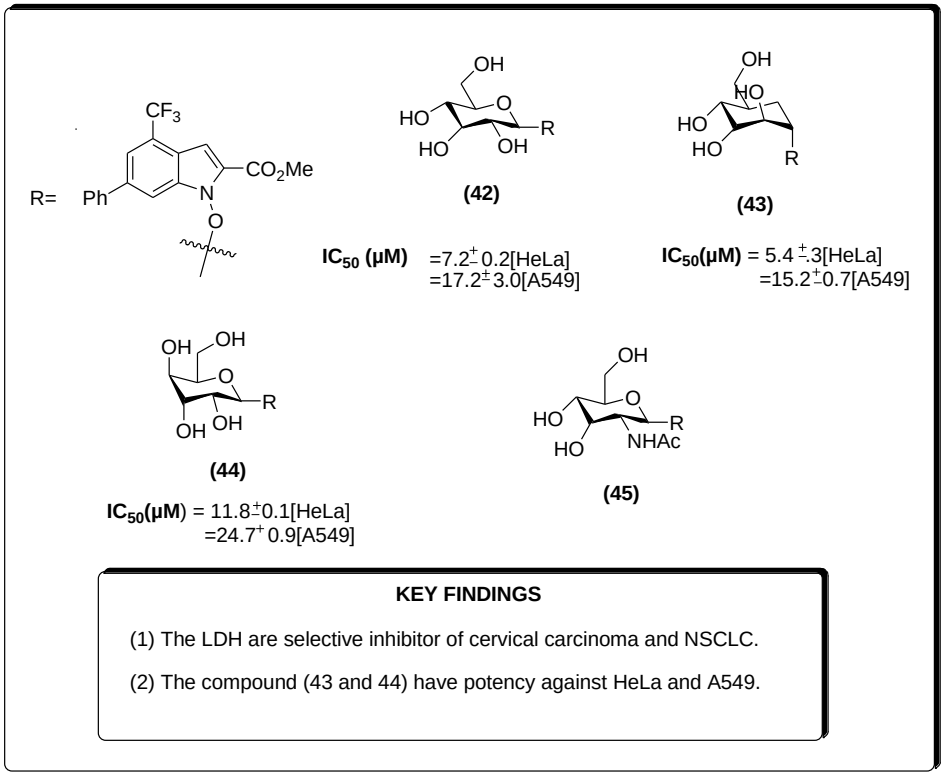


Figure: 5.3

CONCLUSION

This infinite review of literature brings to light on oxygen containing scaffolds. Oxygen heterocycles containing vast number of biological activities. Therefore, oxygen containing scaffolds continue to be blossoming field, it would also be interesting to see development of oxygen containing scaffolds as potentially active chemotherapeutic agent. This paper is an attempt to review the anticancer activity reported for oxygen heterocycles.

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