Review

Emerging Oxygen Based Heterocyclic Scaffolds as Potential Anticancer Candidates

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Emerging Oxygen Based Heterocyclic Scaffolds as Potential Anticancer Candidates

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Abstract: Oxygen based heterocyclic moieties hold an ample range of therapeutic activities. Heterocyclic molecules are nominated as vital components of an extensive array of structural motifs with both biological and pharmaceutical significance. The oxygen-based scaffolds act as anticancer candidates and are also present in numerous phytomolecules viz; irinotecan, camptothecin, topotecan, taxol, taxotere, podophylotoxin, etoposide, daunorubicin and teniposide. The architectural design of numerous structural motifs for amelioration of cancer has become progressively amplified in recent past years. Until now presently there is no strategic treatment which is so capable that can cure cancer from its roots. Henceforth, it is very indispensible to design novel anticancer structural motifs with least side effects. The oxygen containing heterocyclic scaffolds includes flavonoids, pyrans, xanthones and coumarins are of utmost importance in medical chemistry for the mitigation of cancer. This assemblage offers several recent developments as anticancer oxygen containing heterocyclic molecules all-round the globe and attracted the structural motifs of auspicious molecules, along with their mechanistic insights, IC_{50} values, structure–activity relationships, and molecular docking studies. The encouraging properties discovered by these oxygen-based scaffolds unconditionally engaging them at frontline in invention of potential drug candidates. Consequently, these probably will be of amazing attention to scientists working on the design and synthesis of antitumor candidates.

Keywords: cancer; phytomolecules; fused oxygen-based heterocycles; anticancer; flavonoids; coumarins

1. Introduction

Natural Products are the gold standard excellent prosperity of nature. Natural phytomolecules play a chief role in the alleviation of ample range of ailments and diseases viz; cancer [1,2] antioxidant, wound healing [3–5], microbial infections, antiviral, HIV [6,7], inflammation, liver, and respiratory disorders [8,9]. The therapeutic use of herbal remedies is owing to the presence of phytomolecules such as flavonoids, alkaloids, tannins, glycosides, triterpenoids, and phenolic molecules [10,11].

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Various tribal societies have been consuming herbal products since ancient times for the mitigation of cancer. To authenticate the traditional use of natural plants and their products, researchers from the globe were working diligently to establish the role of plants and their phytomolecules in the management of cancer because of their fewer side effects, economical, ease of accessibility are the topmost benefits of the natural products [12,13]. The hunt for phytomolecules in medicine, especially in the field of anticancer agents from the prehistoric periods. But the meticulous era for such type of research is momentously recent. Traditionally, plants-based products and plant extracts were the roots of numerous medicinal agents from which the budding lead molecules were designed to offer birth of potential therapeutic candidates. Several numbers of natural plants have been employed for the amelioration of cancer, few are in clinical use and certain in clinical development.

Cancer is an assemblage of diseases concerning abnormal cell growth with the uninterrupted spread to the other parts of the body. This illness is triggered by speckled agents such as, chemical compound and radiant energy [14–17]. There are numerous drugs which are used for management of this disease either by killing cancer cells or modify their progression. Oxygen containing heterocyclic scaffolds are regularly being used for the architecting of new chemical entities. Many of them are clinically approved drugs contain the oxygen based heterocyclic ring and acting as anti-cancer agents such as daunorubicin, irinotecan, camptothecin, topotecan, taxol, taxotere, podophylotoxin, etoposide and teniposide etc [18,19]. Introduction of oxygen heteroatoms enhances polarity, solubility, and hydrogen bonding capabilities leading to ADMET optimization for drug-gable physiognomies [20]. Heterocyclic molecules are nominated as vital components on an extensive array of structural motifs with both biological and therapeutic significance. The oxygen-based heterocycles are of utmost importance as these found as a great cohort of structures thru gigantic reputation in medicinal chemistry.

This assemblage offers several recent developments as anticancer oxygen containing heterocyclic molecules all-round the globe and attracted the structural motifs of auspicious molecules, along with their mechanistic insights, IC_{50} values, structure–activity relationships, molecular docking studies and interesting key findings of biological activities in the mitigation of several human cancer cell lines. The encouraging properties discovered by these oxygen-based scaffolds unconditionally engaging them at frontline for the invention of potential drug candidates. Consequently, these possibly will be of amazing attention to scientists facilitating them to embrace a most demanding and speedy target focused on drug discovery process as antitumor candidates.

In this era most commonly used antitumor drugs are analogs of phytomolecules which contains oxygen-based heterocycles such as oxitane, oxirane, furan, pyran, chromone and xanthone. Several booming phytomolecules includes camptothecin, irinotecan, topotecan, taxol, taxotere, podophylotoxin, teniposide and etoposide (Figure 1) have been emerged as drugs candidates after structural modification on the leads of natural origin [21–28].

Camptothecin (CPT) is an alkaloid isolated [29] from the stem wood of *Camptotheca acuminata* also documented as the ‘tree of love’ or ‘tree of joy’. It has also been obtained from *Mapia foetida* and *Ophiorrhiza pumila*. The anticancer potential of plants has been discovered using in vitro studies and in mouse leukemia cells. The results revealed in creation as a prospective antitumor agent. Currently, the foremost discovery leads to CPT scaffolds, such as irinotecan and topotecan are used in treatment of colon cancers and ovarian cancers [30,31].

Taxol (paclitaxel) and Taxotere (docetaxel) shown in (Figure 1) binds at taxane binding site. Paclitaxel was initially obtained from the bark of *Taxus brevifolia* which is famously known as the pacific yew tree. Docetaxel, isolated from *Taxus baccata* recognized as a European yew tree, is a semi-synthetic analog of Taxol and is clinically employed in the treatment of prostate, breast, non small cell lung and ovarian cancer. At low doses taxanes cause mitotic arrest and at high doses they act as microtubule stabilizing agents [32,33]. Several researchers have tried to synthesize its analogs and only a few of them were found to be active as compared to taxol. Georg *et al.* synthesized novel taxol analogs and demonstrated cytotoxicity towards B16 melanoma cells like taxol [34,35].

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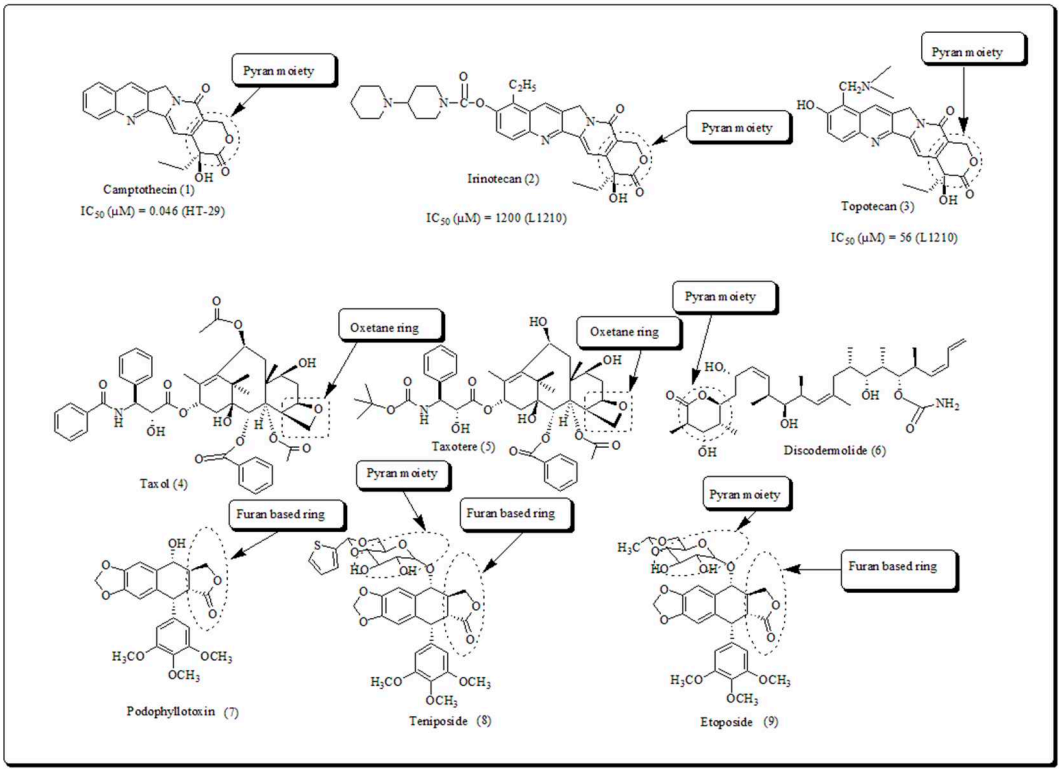

Figure 1. Oxygen-based heterocyclic phytomolecules with anticancer potential.

Discodermolide is isolated from the marine Caribbean deep sea sponge Discodermia dissolute [36]. It was primarily exhibited antifungal and immunosuppressive properties, but later on found to be a microtubule stabilizing candidate [37,38]. Discodermolide exhibiting anticancer potential against a diverse cell lines and found to be more potent than taxol (EC_{50} value of 2 μM [39]). Discodermolide is active against taxol resistant cell lines [39]. It can inhibit cell mitosis thru stimulating tubulin polymerization and thus persuade microtubule bundles in cells using in vitro studies [40,41].

Podophyllotoxin (PDT), a bioactive lignin, documented as May apple or American mandrake, obtained from *Podophyllotoxin peltatum* [25]. Podophyllotoxin has also been isolated from other species *P. emodi* and *P. pleianthum*. The semis synthetic derivatives of Podophyllotoxin, Teniposide and Etoposide are now widely recommended in the mitigation of numerous cancers [26]. Over the years, several derivatives of podophyllotoxin, have been synthesized and evaluated for cytotoxicity against A-549 and P-388 human cancer cell lines [27]. Zhang *et al* synthesized a new series of podophyllotoxin analogs and screened against human malignant cell lines such as RPMI-8226, HL-60 and A-549 [28].

This article also presents some recent advancement in the field of anticancer agents around the globe. The focus is on the structure-activity relationship in addition to the structure of the most promising molecules along with IC_{50} values against diverse human tumor cell lines and some interesting key findings. For presenting the different types of heterocycles and fused heterocycles, we have basically categorized these based on one of the hub functionalities of their chemical architecture. It also attempts to provide a comprehensive summary on the chemistry and structure of the most promising agent as anticancer agent along with their IC_{50} values and structure activity relationship. To the paramount of our understanding, this is the first comprehensive review of recent advancements in the domain of anticancer heterocycles which includes literature published during the previous years. We believe that the present review will provide medicinal and bioorganic chemists collective insights into the biological profiles of heterocycles having anti-proliferative activity, thus helping them adopt a more focused and speedier target-oriented drug discovery process. An in-depth summary of the structure-activity relationships and mechanistic insights exposed throughout the pharmacological screening of the potential oxygen containing heterocyclic

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compounds. The structures of the synthesized compounds discussed in this assemblage clearly highlight the promising and interesting antitumor profiles, structure of potent molecules, therapeutic actions, important key finding of molecular docking and mechanistic studies. For representing the antitumor potential of the oxygen-based heterocycles, we have categorized the significance of oxygen based heterocyclic structural moiety of other significant heterocycles such as pyran, furan, oxirane, oxitane and fused oxygen-based heterocycles. This organization is established on one of the central functionalities of their chemical structural architecture.

2. Pyran based oxygen containing heterocyclic scaffolds

The oxygen heteroatom is the building component of pyran, chromone, benzopyran, flavanoids, xanthones, coumarin, naphthoquinones, furan, benzofuran, oxirane and oxitane which display assorted therapeutic potential. Several natural compounds comprise pyrans and benzopyrans, exhibiting interesting therapeutic activities, have encouraged the researchers to design and synthesize novel scaffolds. Numerous pyran based heterocycles have been presented in (Figure 2) [42].

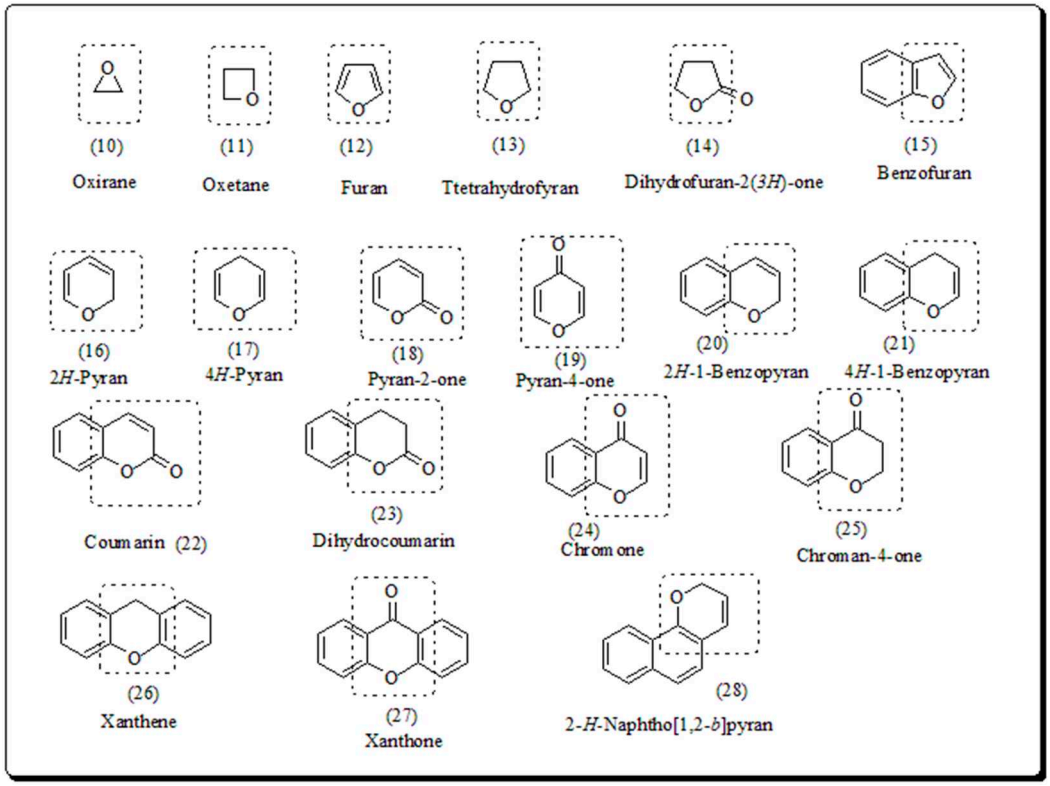

Figure 2. Structures of oxygen-based heterocycles.

It is well established that oxygen based heterocyclic compounds are chief building blocks of biologically active phytomolecules [43–45]. Oxygen based heterocyclic skeletons are vital structural components found extensively in natural compounds like sugars, flavonoids [46], anthraquinones [47] and coumarins [48]. Oxygen containing flavonoid-based pyran scaffolds (Figure 3), including calyxin F, calyxin G, calyxin I, calyxin L, epicalyxin G and epicalyxin F, obtained from seeds of *Alpinia blepharocalyx*. Epicalyxin F is a significant compound of this series, as an antitumor agent towards murine 26-L5 carcinoma and HT-1080 fibrosarcoma [49].

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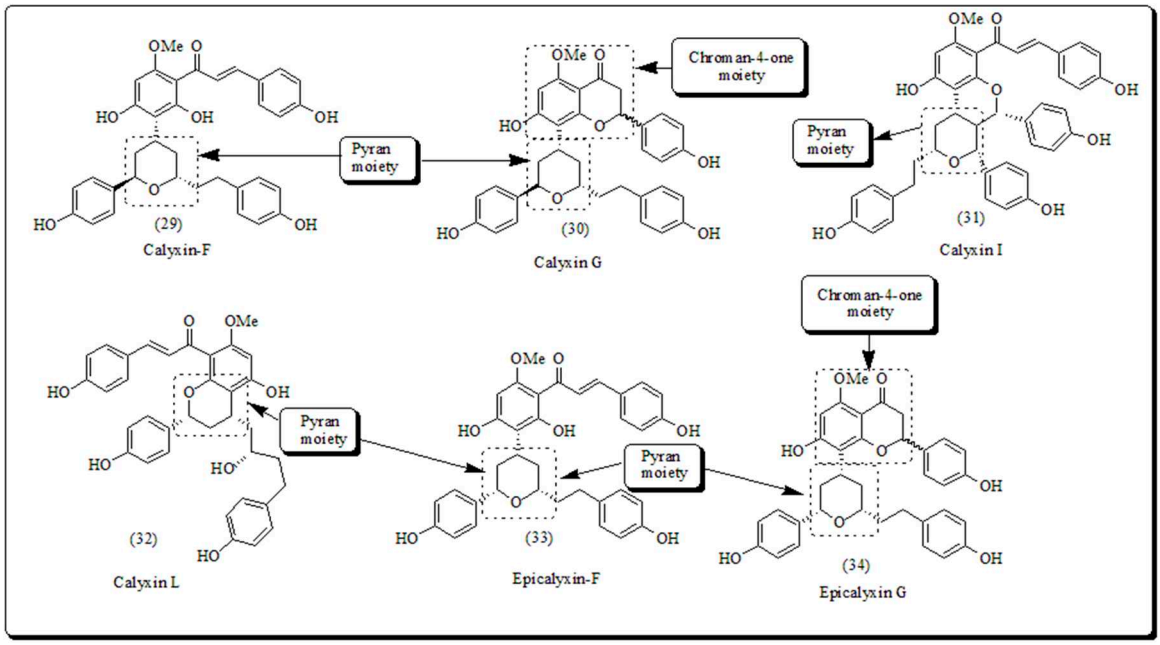

Figure 3. Pyran-based compounds isolated from plant species with cell killing potential.

The β-lapachone depicted in (Figure 4), is a pyran derivative, which displayed the ample range of therapeutic potential (including anti-inflammatory, anticancer and antibacterial) and thus having a significant role in drug development. Laninamivir presented in (Figure 4), administered by oral route and is structurally similar to Zanamivir which is prodrug of Laninamivir octanoate screened for its antiviral and anticancer potential. Zanamivir (Figure 4), was permitted for cure of influenza A and B virus. The drug is marketed by GlaxoSmithKline with the trade name of "Relenza" [50,51].

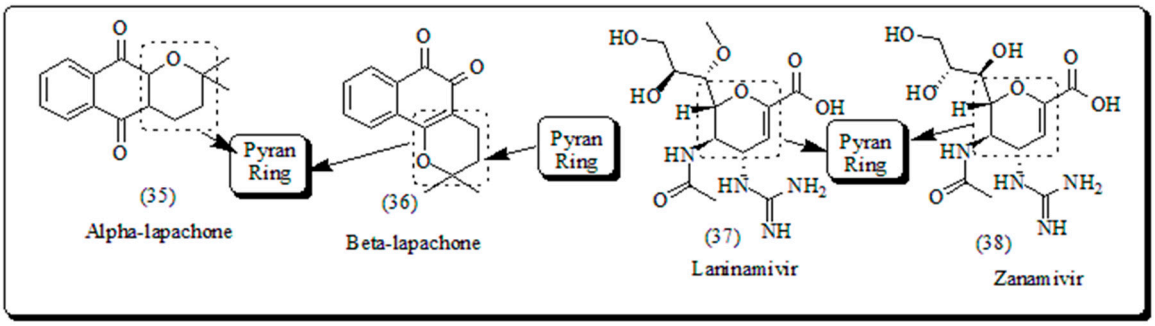

Figure 4. Pyran-based marketed drugs in preclinical/clinical phase.

Literature reports have revealed the richness of commercially existing therapeutic candidates containing pyran heterocycle. Oxygen based heterocyclic compounds (Figure 5) which having a chief part of structural motif in numerous synthetic natural and compounds, owning potential therapeutic profiles, due to their extensive range of pharmacological activities such as antituberculosis [52], anticancer [53,54], anti- human immunodeficiency virus (HIV) [55], antifungal [56], antimicrobial [57], calcium channel antagonist activity [58], antidiabetic, [59] and antiviral activities [60].

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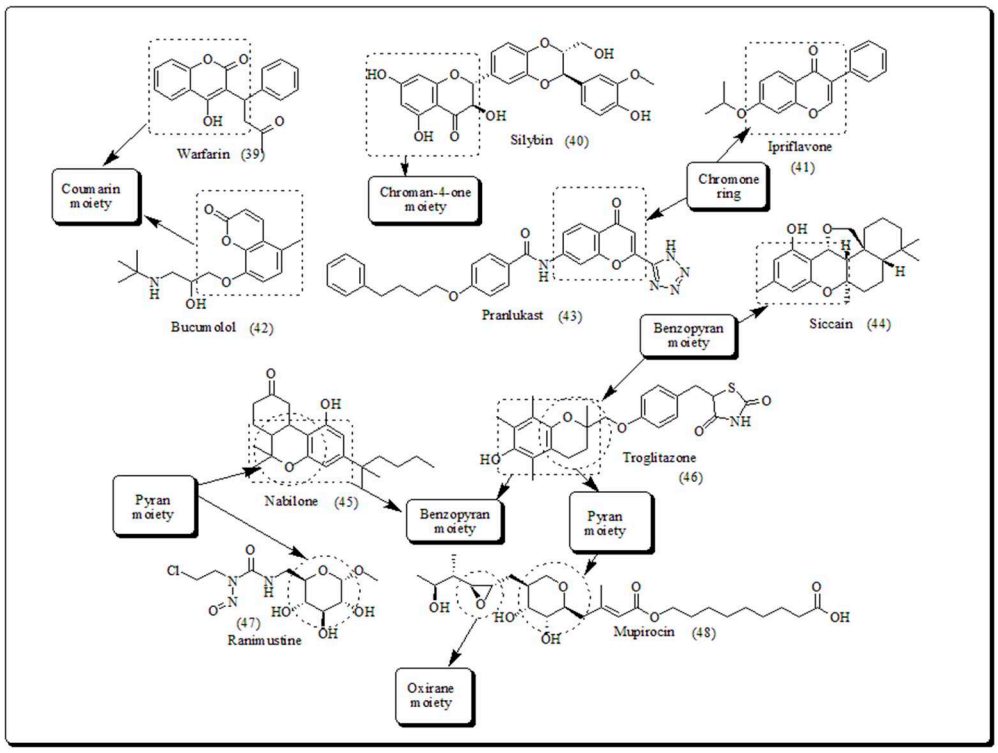

Figure 5. Structure of compounds entrenched with oxygen-based heterocycles.

Madda *et al.* established a new class of oxygen-based pyran analogs, and screened using *in vitro* assays towards diverse human malignant cells. The outcomes revealed that compounds displayed significant cytotoxicity against HeLa cells, human cervical malignant cells (Figure 6) [61].

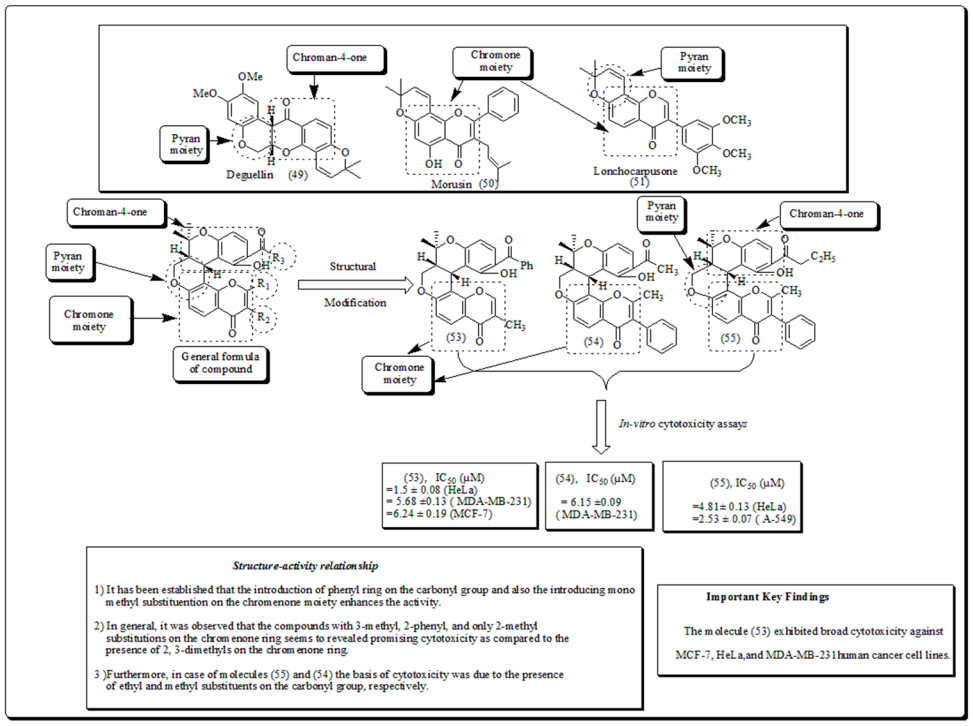

Figure 6. Structures of compounds along with their SAR reported by Madda *et al* [61].

Compound (53) demonstrated marked inhibitory action in both breast cancer cell lines, MCF-7 and MDA-MB-231. Moreover, compound (54) presented cytotoxicity only against MDA-MB-231,

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whereas compound (55) confirmed encouraging effects against A549, human lung cancer cell line, with IC_{50} of 2.53 μM [61]. In another study, Morales *et al*. synthesized and screened morpholine based pyran motiffs as potential PI3K inhibitors. Compounds presented in (Figure 7) which showed a remarked mTOR and PI3K enzymatic inhibition properties. The compound also exhibited aqueous solubility, and better activity when screened against PC-3 cells, while down-regulating the PI3K pathway as displayed through restraining pAKT-S473 expressions [62].

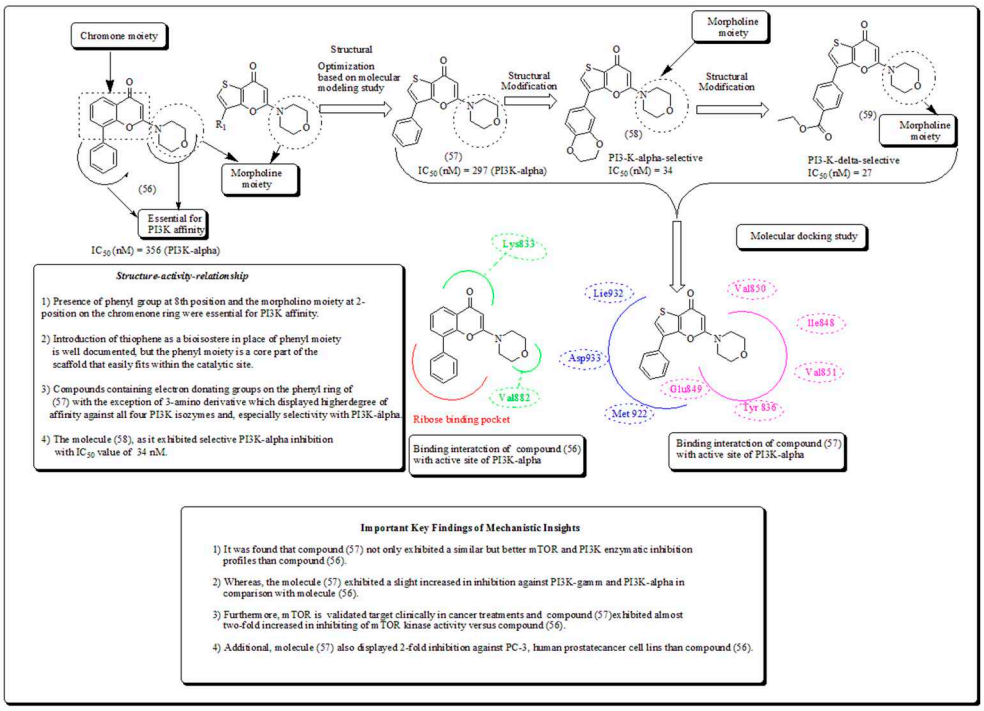

Figure 7. Structure of compound along with mechanistic insights and docking studies established by Morales *et al*. [62].

Naturally occuring pyranonaphthoquinones and their derived analogs, with capable antitumor potentials. Rhinacanthin O (Figure 8) isolated from *Rhinocanthus nasutus*, an Asian medicinal plant and its structure is naphthoquinone based compound consisting of oxirane and pyran heterocyclic compound, pyranokunthone B presented in (Figure 8) obtained from marine actinomycetes [63]. The compounds depicted in (Figure 8) have been examined for the mitigation of tumors connected with heaved NADH quinone oxidoreductase expressions.

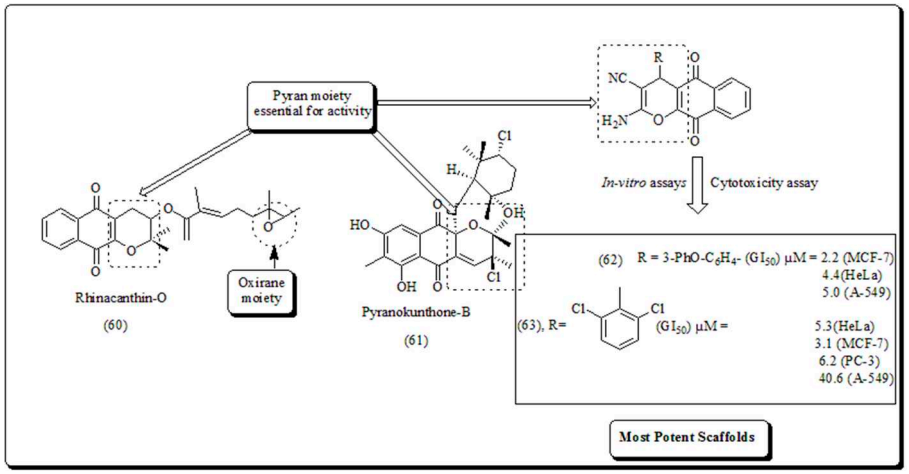

Figure 8. Structure of oxirane containing compound with anticancer capability.

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Frolova *et al.* synthesized and screened a series of compounds, exhibiting anti-proliferative activity and apoptotic potential against a panel of malignant cells [64]. Selected analogues displayed promising results against human cancer. The compound (62) and (63), exhibited anti-proliferative effects superior than α-lapachone [64].

Natural dihydropyranonaphthoquinones can be obtained from fungi, bacteria, and higher plants. Numerous scaffolds have certainly been found to hold diverse and noticeable biological actions, including antiparasitic, antimicrobial, anticancer and antiviral properties [65]. Eleutherin (64) pentalongin (66) and psychorubrin (65) are of compounds, which exhibited an interesting antimicrobial, phytotoxic antiparasitic, and antineoplastic properties. A new class of compounds (67-70) and their analogs have been screened towards human cancer cell lines by Thi *et al.* The results revealed that compound (67) exhibited IC_{50} value of 3.6 μM and 1.5 μM against Hep-G2 and KB malignant cells (Figure 9) [65].

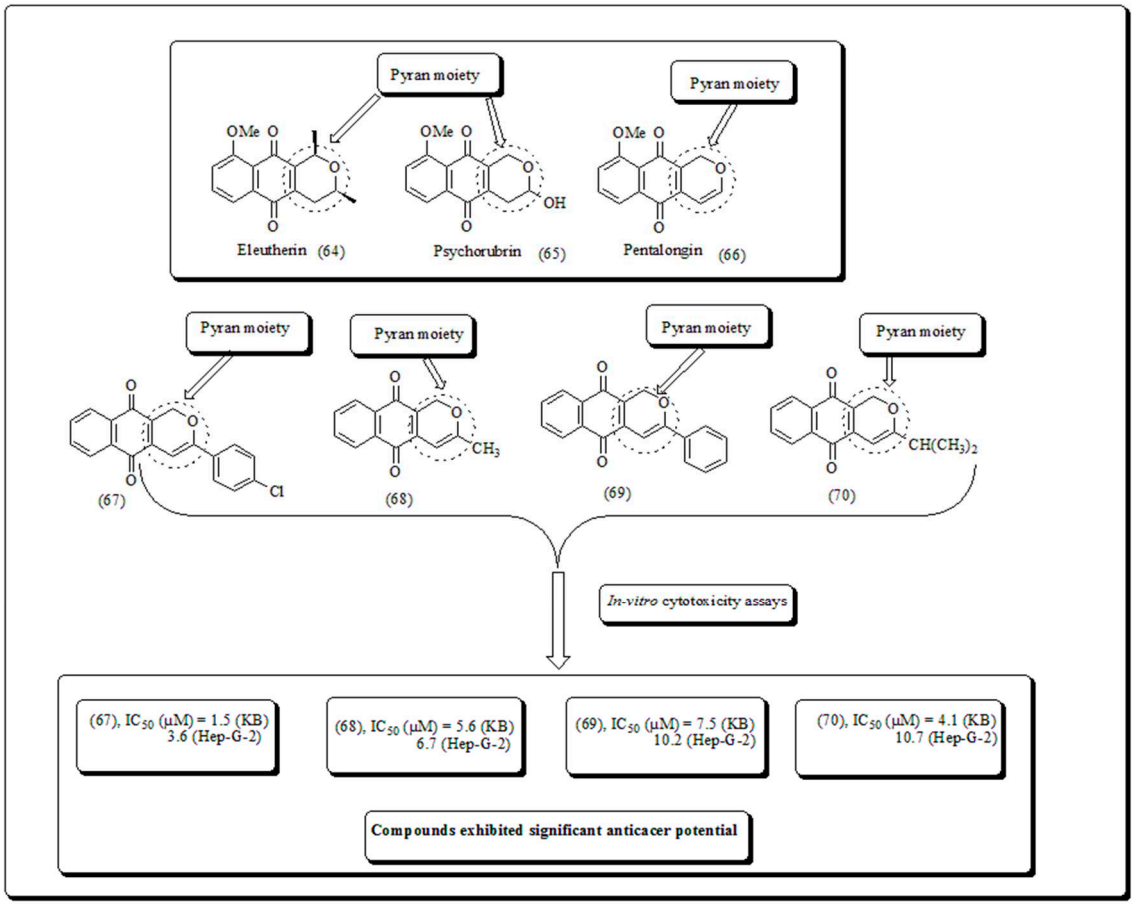

Figure 9. Bioactive natural and synthetic molecules with cell killing potential.

1. Flavone-based oxygen containing heterocyclic scaffolds

Flavonoids are plant-based poly phenolic compounds and are termed as secondary metabolites. Flavonoids are precursors of chalcones and present in numerous foods [66]. These are often described as their structures having (C_6–C_3–C_6) phenylbenzopyrone linkage. Flavonoids are categorized into such as flavones, flavanones, isoflavones, flavanols and flavanonols (Figure 10) [67]. Flavonoids exhibit an extensive range of pharmacological actions [68–70] including anti-mutagenic, antioxidant, and anti-proliferative activities. The antioxidants flavonoids are generally involved in angiogenesis, cell signaling and cell cycle regulation [71–74].

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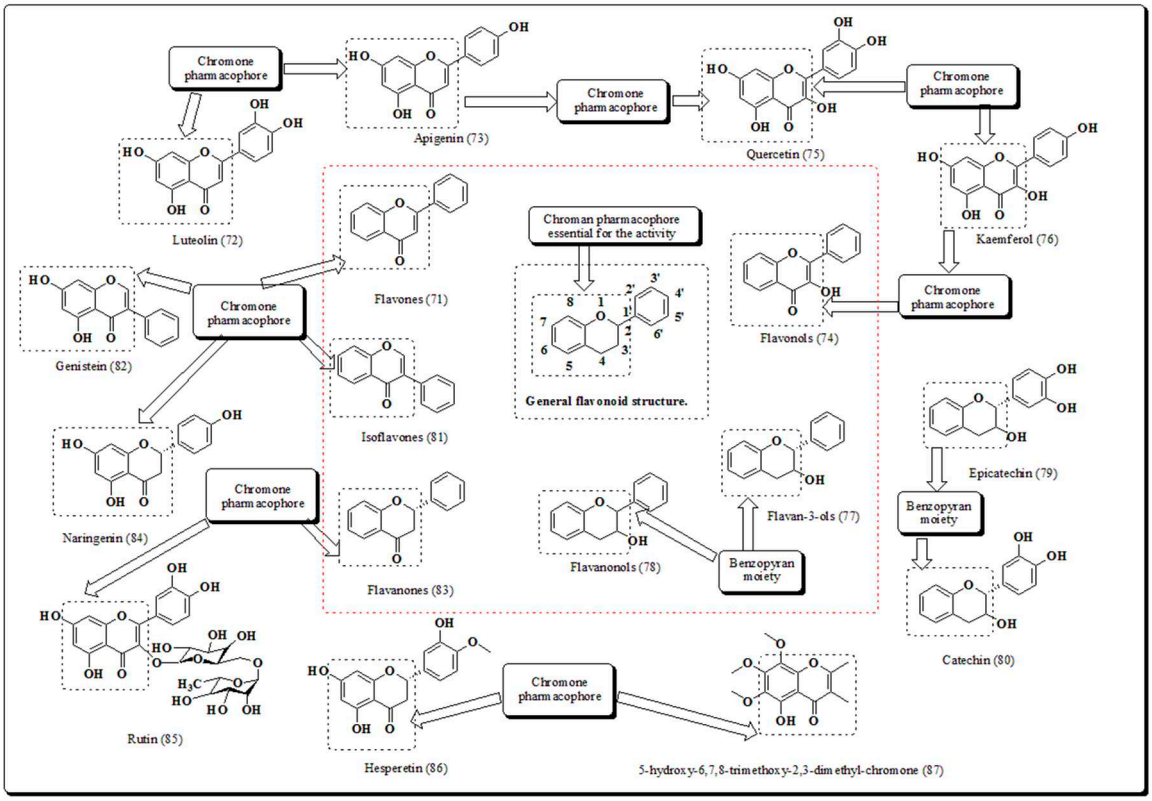

Figure 10. Structures of oxygen-based promising flavonoids.

Hesperitin and Naringenin belongs to flavanones, quercetin and kaempherol are flavonol derivative, luteolin and apigenin belongs to flavone, whereas, genistein sub classified into isoflavone and thought to be talented in the discovery of new lead chemotherapeutic agent for mitigation of cancer. Few years ago, Hsiao *et al.* recognized that flavanone and 2′-hydroxyflavanone decreased cell growth of A549, HA22T, and SK-Hepl cancer cells, whereas other flavanones (4′-hydroxy flavanone and 6-hydroxy flavanone) displayed little or almost no inhibition [75]. Furthermore, Choi *et al.* reported that 4′,7-dimethoxyflavanone, exhibited convincing anti-proliferative actions apoptosis and cell cycle in MCF-7 human breast cancer cell lines [76]. The outcomes of another research evaluated the anticancer actions of flavanone derivatives on human breast malignant cells and exhibited actions through p53-mediated cell and induce apoptosis in G1 phase of cycle arrest [77]. In another approach, Usman *et al.* presented the cytotoxic potential of flavanones obtained from bark of plant *Cryptocarya costata* [78]. Similarly, in another study, flavanones exhibited significant cytotoxic action on colorectal cancer cells via formation of apoptotic bodies and DNA fragmentation [79]. Flavonoids (Figure 11) exhibiting cell killing potential [77,80–83].

Kumar *et al.* reported the synthesis and evaluation of naphthoflavones (92-95) as anti-proliferative agents against a panel of human cancer cell lines. Compound (92) displayed noteworthy cytotoxicity towards MiaPaCa-2 cell lines, with IC_{50} values of 1.93 μM and 5.63 μM against MCF-7 cell lines. The molecule (92) was found to induce apoptosis which was established by DAPI staining, MMP loss, phase contrast microscopy and cell cycle arrest of 55.19 % at 20 μM in MiaPaCa-2 pancreatic cancer cells (Figure 12) [84].

Myricetin is one of the flavonoid-based phytomolecule and found in numerous natural sources. Outstandingly, those myricetin based subordinates are thought to exhibit anticancer potential, which have diminished pancreatic cancer via apoptosis [85,86]. In another finding, Xue *et al.* established a series of novel myricetin analogues [87]. It was established that analog (98) displayed significant action in MDA-MB-23, 1human breast cancer cells. The outcomes from the telomerase inhibition experiment also confirmed that compound (98) exhibited extraordinary action towards human MDA-MB-231 cells, with IC_{50} value in 0.91 μM. The molecular docking of scaffold 98, towards target site,

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revealed that the heterocyclic nucleus was intensely embedded into dynamic site, establishing hydrophobic associations with build-ups of Phe568, Pro627, with four methoxy groups having hydrophobic interactions with amino acid residues Phe568, Lys902, Pro627, Pro929 and Val904 presented in (Figure 13) [87].

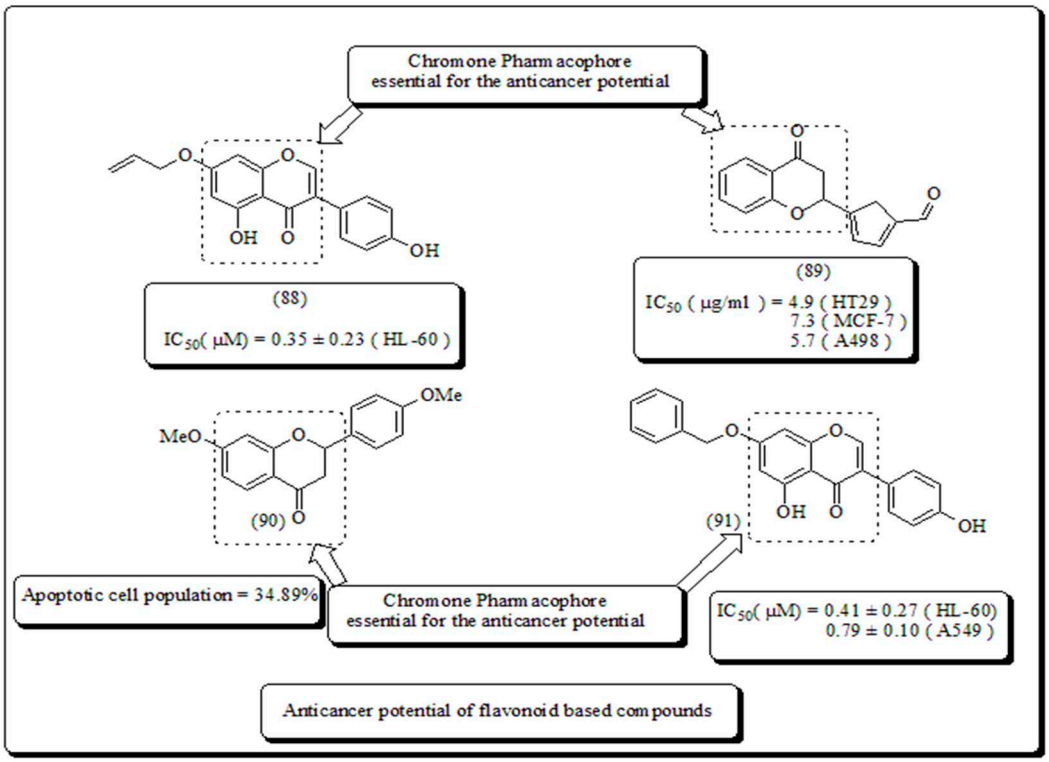

Figure 11. Anticancer potential of some flavonoid-based compounds [88–91].

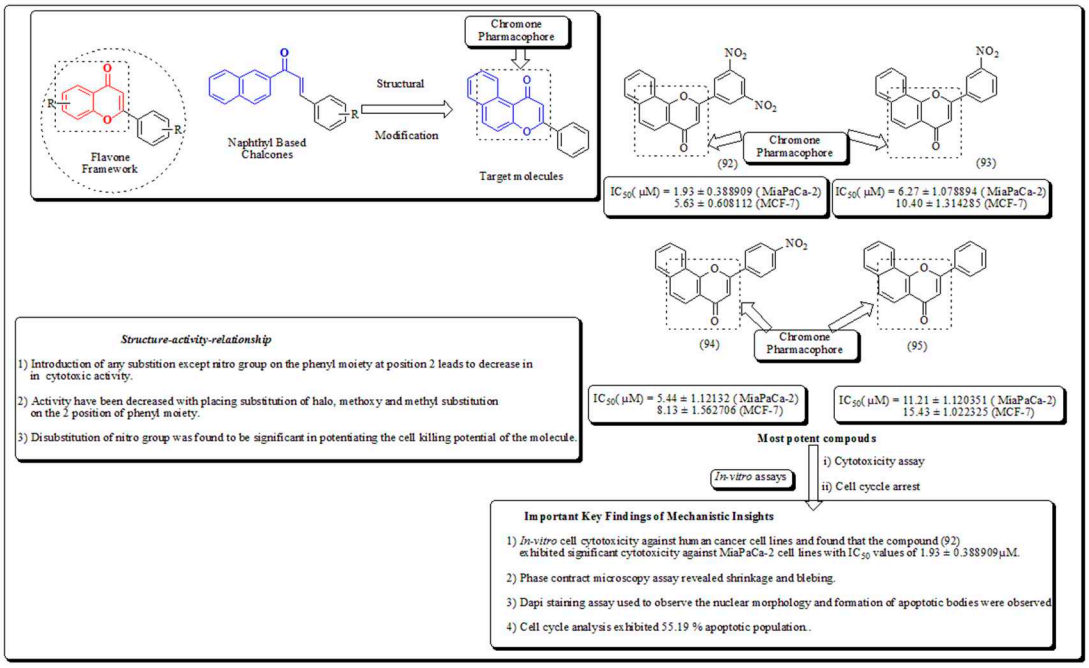

Figure 12. Structure of compounds **92**-**95**, along with mechanistic insights as anticancer agents.

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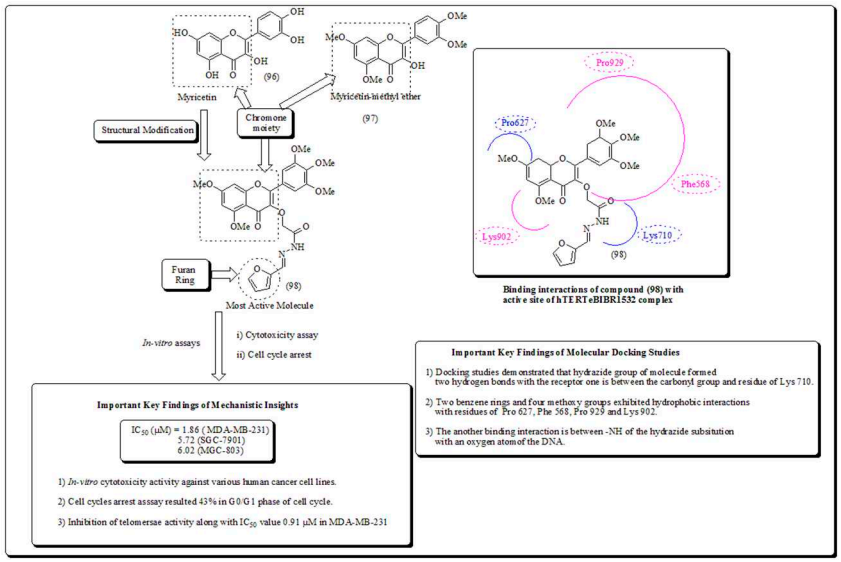

Figure 13. Structure of myricetin anticancer scaffold along with docking studies.

Safavi *et al.* conceded the synthesis and evaluated halogenated flavanones towards human cancer cells [88]. From all the synthesized analogs, 3′,7- dichloroflavanone (**99**) displayed potential activity in MCF-7, PC-3, LNCaP, Hep-G2, SK-NMC, and KB cells. However, compound (**102**) presented in (Figure 14) exhibited IC50 of 2.9 μM and was the most significant analog against MDA-MB-231 breast cells, and approximately 12 times more powerful, than etoposide. Thus, introduction of chloro group on chromanone moiety and on C-2 attached phenyl nucleus was used as structural modification to form a lead pharmacophore of flavanones. The analog (**102**) induces apoptosis from 21.37% and 66.19% in MDA-MB-231 and PC-3 cells, respectively.

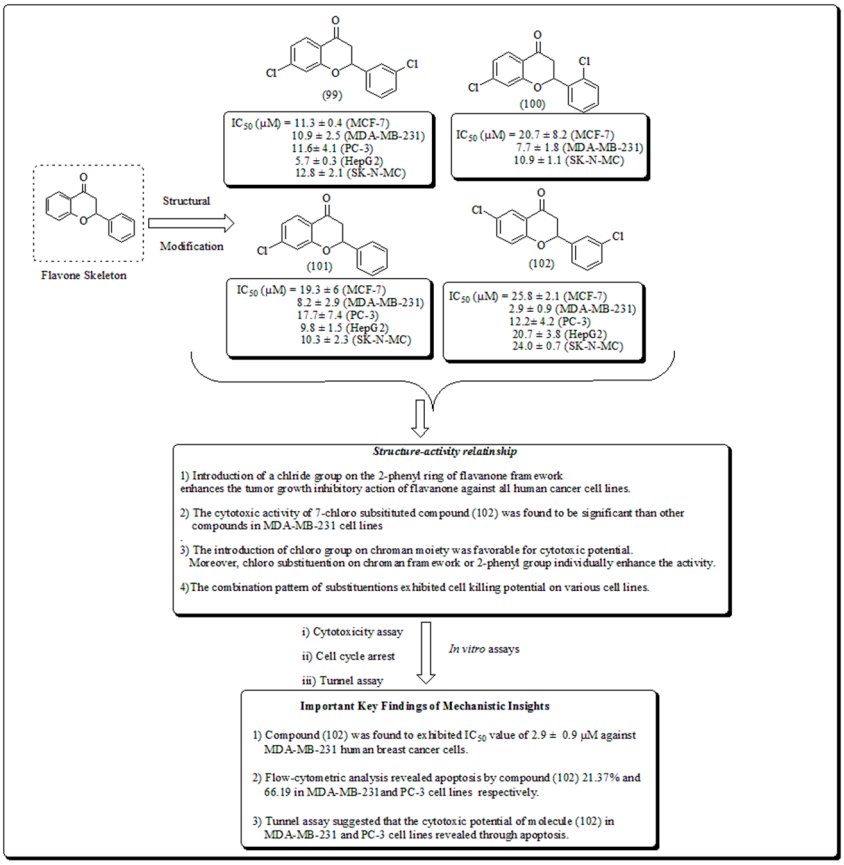

Figure 14. Structure flavanones as apoptosis-inducing compounds along with their important key findings.

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The results of TUNEL assays recommended that the cytotoxic potential of this analog in MDA-MB-231 and PC-3 cell lines exerted through apoptosis [88].

2. Coumarin-based oxygen containing heterocyclic scaffolds

Oxygen plays a chief role in the architecting of coumarins moiety which is an exceptional class of oxygen based heterocyclic scaffold, presenting a significant role in medicinal chemistry, owing to their ample range of pharmacological activities and structural diversity [89]. Coumarins perform a distinctive role in nature [90,91]. The incidence of coumarin heterocycle in phytomolecules exhibiting extensive activities such as anticancer [92,93] antitubercular [94], anti-HIV, [95] anti-influenza [96], antiviral [97], anti-Alzheimer [98,99], antimicrobial [100] and anti-inflammatory [101] actions makes it a fortunate structural motif [102]. Coumarin scaffolds explored through established biological actions of coumarin based hybrids as promising molecules (Figure 15) [103–107].

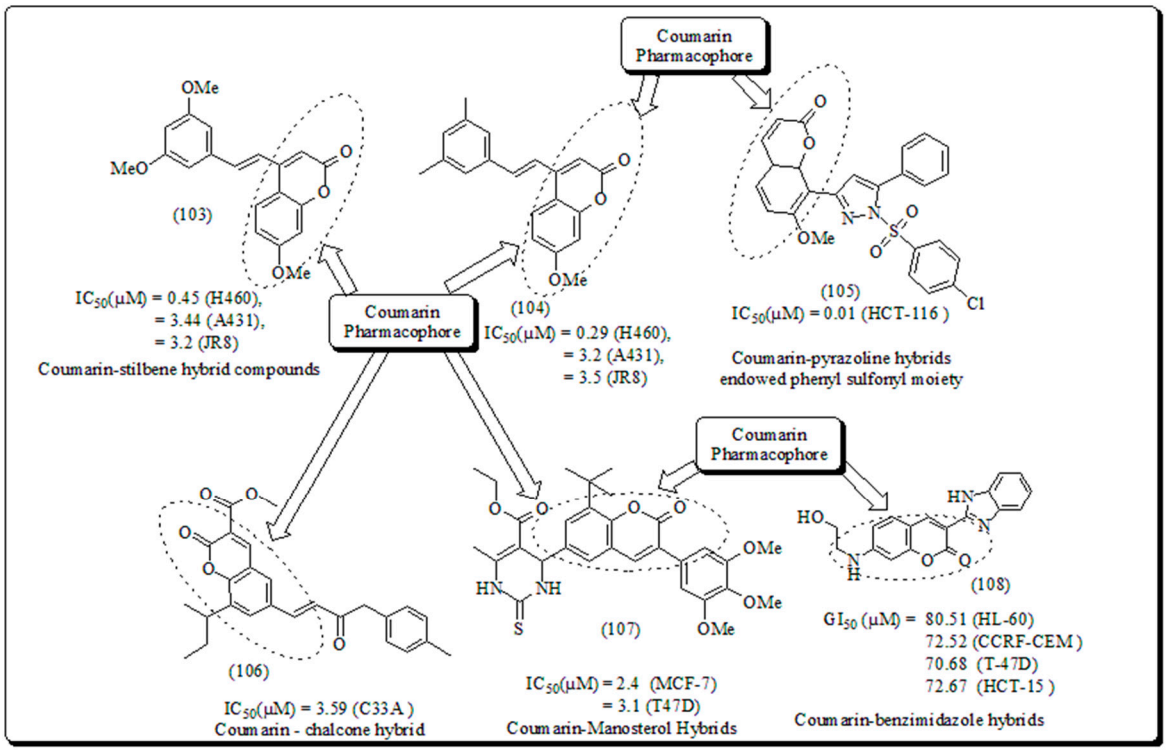

Figure 15. Structure of coumarin hybrids (**103**-**108**).

Coumarin hybrids are pyranocoumarin derivatives, having several structural arrangements between pyran and coumarin rings. The few important pyranocoumarins such as khellactone (109) obtained from *Ligusticum elatum* and xanthyletin (110) predominantly extracted from *Zanthoxylum americanum*, along with pyripyropenes (111) and arisugacins (112) presented in (Figure 16) [108].

A few years ago, Kumar and co-workers synthesized and evaluated coumarin hybrids [109]. The design strategy involved the merging of chalcone and coumarin hiring a pyran as a connector. All the analogs were evaluated against a panel of cancer cell lines. Compound 113 (Figure 17) exhibited probable effects in MiaPaCa-2 and HCT 116 cells with IC_{50} values of 4.3 and 1.4 μM, respectively. Compound **113** initiated apoptosis which was confirmed by MMP loss, Hoechst 33258 staining and cell cycle arrest with apoptotic population of 57.19% in a dose of 20 μM [109].

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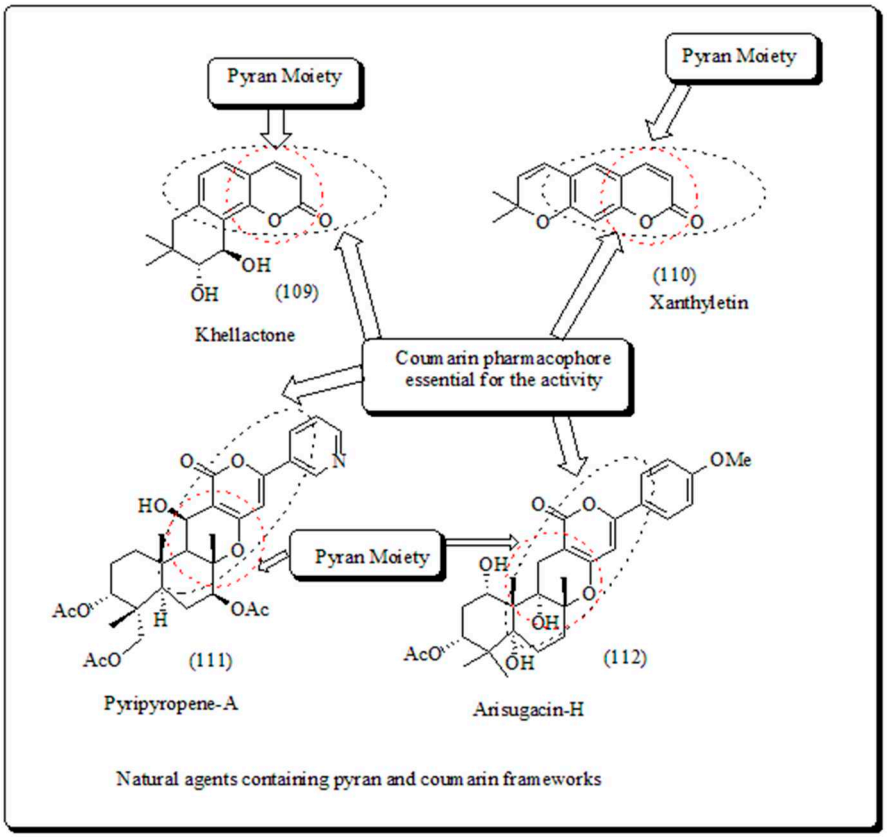

Figure 16. Naturally-occurring compounds (**109**-**112**) consisting pyran and coumarin scaffolds.

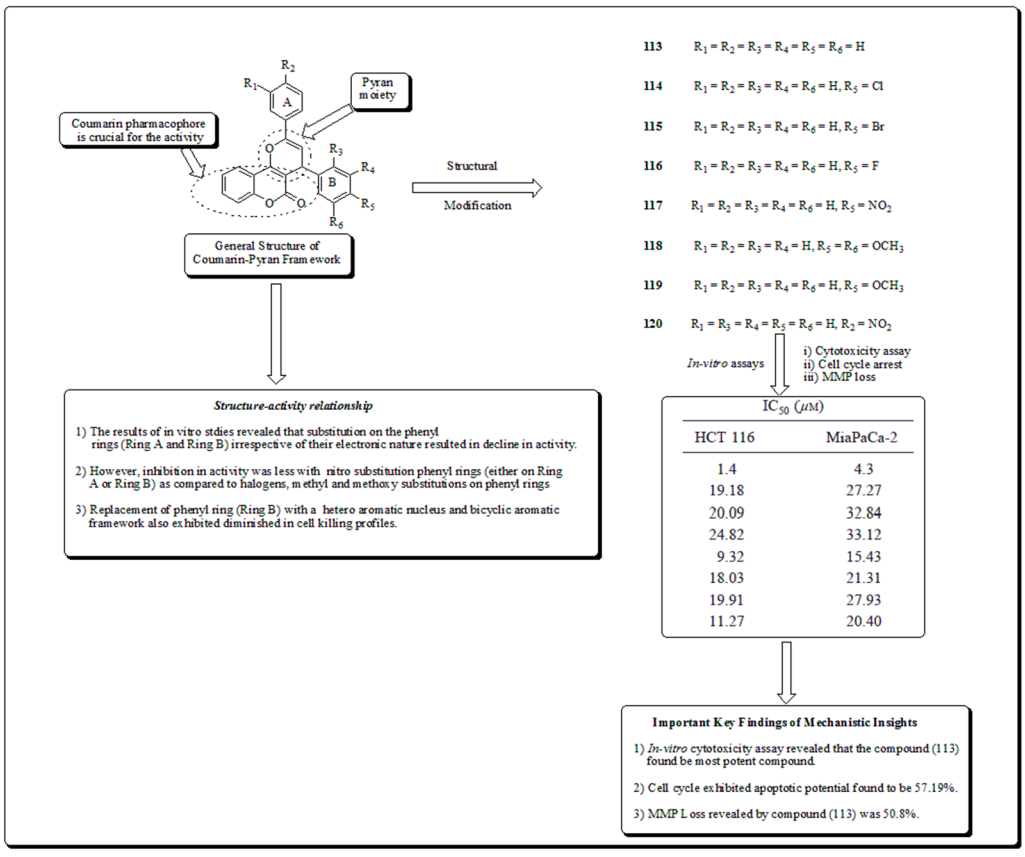

Figure 17. Most significant coumarins scaffolds reported by Kumar et al. [109].

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A decade ago, Hussain *et al.* further carried out a synthesis of coumarin molecules as potent anticancer agents towards breast cancer [110]. Compound (121) was established as ER-α selective and most potential from all synthesized analogs. The docking study displayed that analog (121) satisfactorily fits well into the receptor pocket of ER- α. The coumarin moiety and the p-methoxyphenyl substitution on the third position formed a hydrophobic binding interaction with amino acids such as Glu353, Phe404, Leu349 and Arg394, the introduction of amino alkoxy substitution, fixed the piperidine nucleus by forming hydrophobic interaction with residue like Trp383, Thr347, Asp351, Leu536 and Leu354. The introduction of methoxy on coumarin at the 7th position interacted with Arg394 and Glu353 presented in (Figure 18).

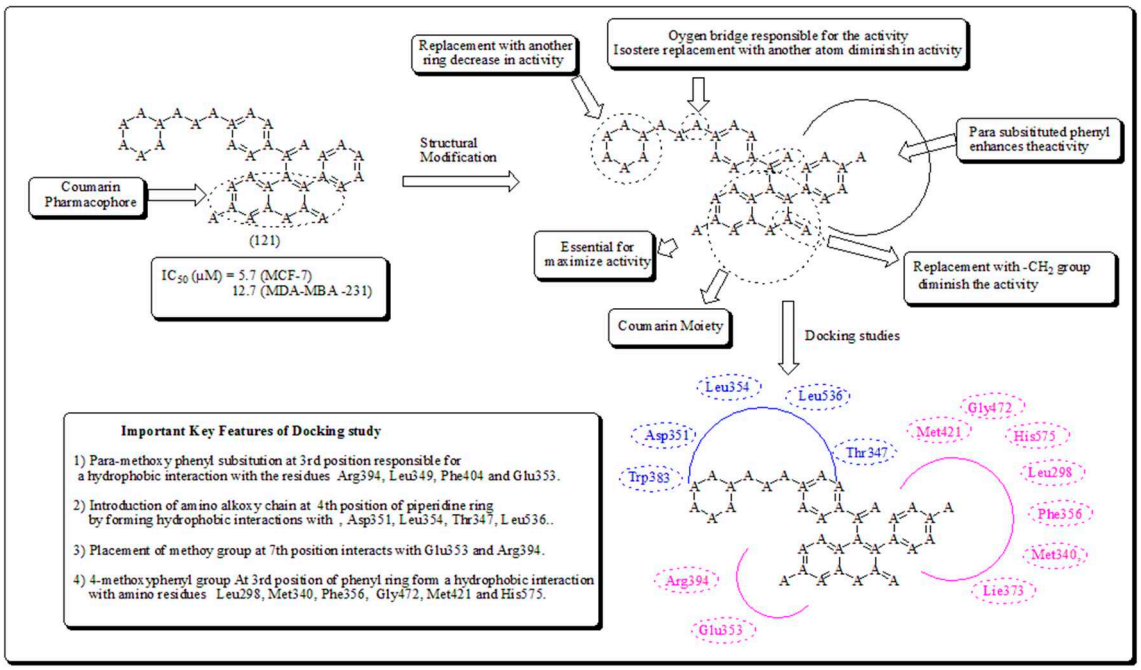

Figure 18. Structure of selective coumarin analog along with molecular modeling study.

The analog (121) had a comparable binding pattern for ER-β site, coumarin pharmacophore developing hydrophobic binding interactions with residues Glu305, Leu343, Arg346, Leu339 and Leu301. The 4-methoxyphenyl group formed a hydrophobic interaction with Met421, Met340, Gly472, Phe356, His575 and Leu298, which are indispensable for ER-β binding [110].

Coumarin is an amendment of benzopyran-2-one through introducing a direct heterocyclic substituent. For instance, a heteroaryl substitution is introduced at 3 or 4 position of coumarin moiety. Consequently, 3 and 4-heteroarylcoumarins are described to display significant therapeutic activities including anticancer [111], antibacterial, antimicrobial [112], DNA cleavage [113], antioxidant, anticholinesterase [114] and monoamine oxidase inhibitory action [115]. Encouraged from this, Yana and coworkers presented the synthesis and anti-proliferative screening against a panel of human cancer cell lines. The results of the study revealed that compound (123) exhibited significant anti-mitotic actions presented in (Figure 19) [116].

Another study showed the synthesis of coumarin derivatives with enhanced anticancer properties [117,118]. The resultant dimeric product was revealed to have more effective than of monomeric compound (with IC_{50} ~ 70 μmol/L) [119,120]. Prompted from this, the conception of molecular oligomerization lead to invention of two novel classes of dimeric analogs of triphenylethylene-coumarin hybrids [121,122]. The dimeric analogs displayed antitumor activities [123,124]. Similarly, Zhang and his coworkers further exposed new trimers of triphenylethylene–coumarin hybrids. The trimeric analog (124) revealed significant anti-proliferative activity with IC_{50} value of 7-9 μM range presented in (Figure 19) [125].

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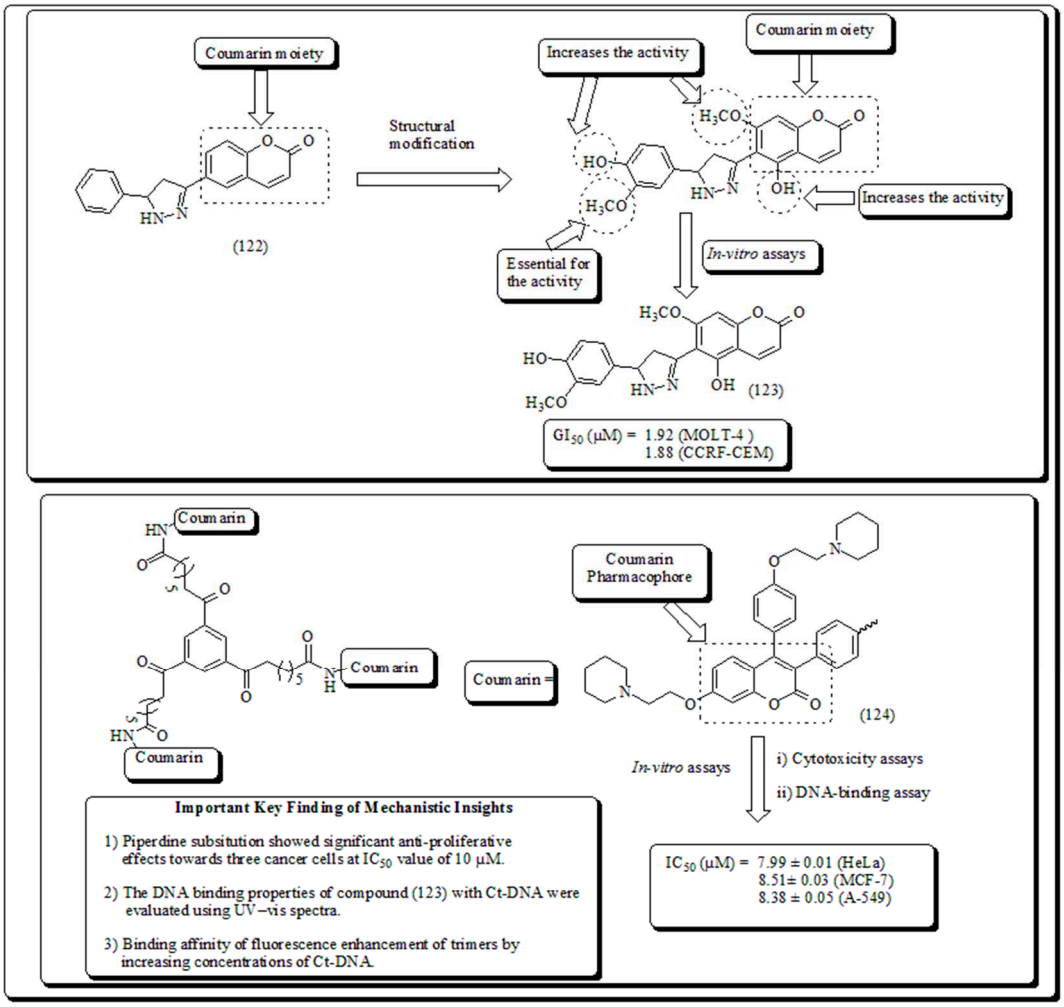

Figure 19. Structure of coumarin analogs and triphenylethylene–coumarin hybrids with cell killing potential reported by Garazd *et al.* [116] and Zhang *et al*. [125].

3. Xanthone-based oxygen-containing heterocyclic scaffolds

Xanthones and xanthenes are an exceptional class of oxygen containing tricyclic compounds in which pyran ring is fused with two benzene rings on both the sides and exhibited diverse attractive pharmacological effects, depending on nature and types of substituents [126–128]. Recently, xanthones and xanthenes have been appreciated as effective pharmacophore in the arena of medicinal world [129] Earlier, xanthones were publicized as larvicides, bug sprays, and ovicides [130]. Presently, several studies recognized that xanthone scaffolds are proficient to halt the progression of tumor cells and also holding anti-inflammatory and antioxidant actions [131]. Xanthones are primarily available in plants belong to Clusiaceae, Bonnetiaceae, Gentianaceae and Podostemaceae families [132]. Structures of natural xanthones presented in marketed formulations and potent cytotoxic compounds as reported by Lee *et al.* [133] and Laphookhieo *et al.* [134] were depicted in (Figure 20).

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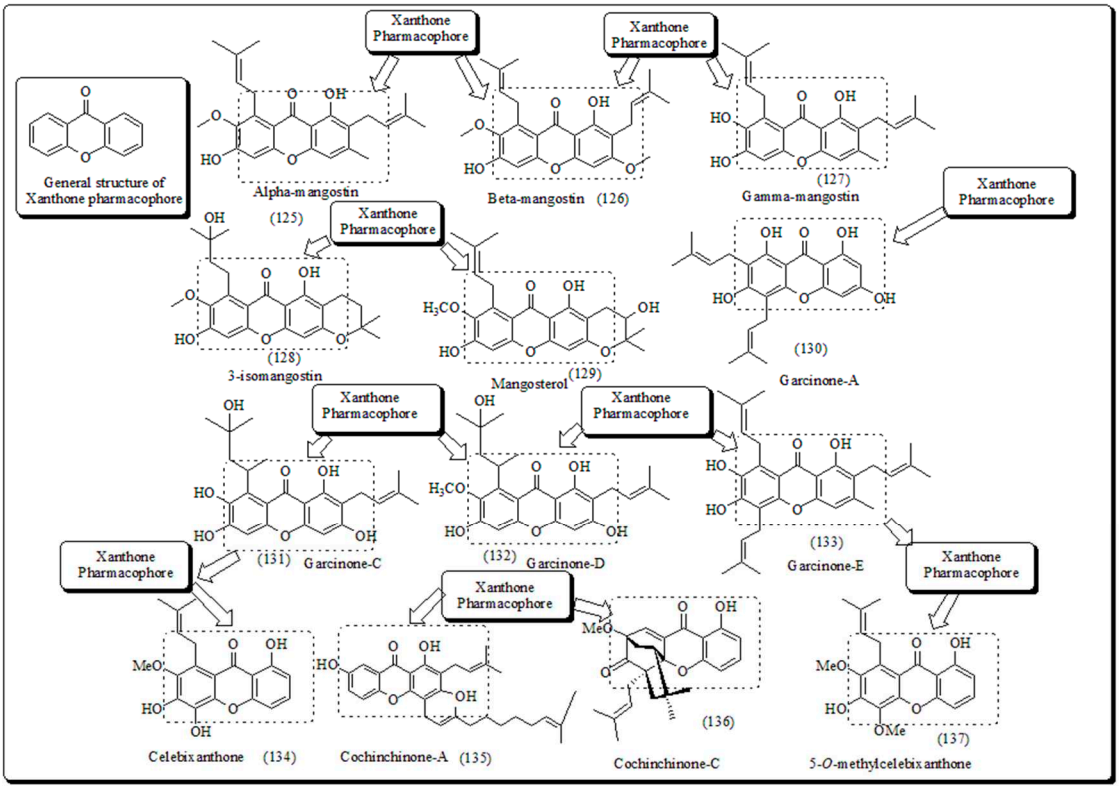

Figure 20. Structures of xanthones based compounds in marketed formulations.

Numerous man-made and naturally occurring xanthene scaffolds have been described to reveal anti-malarial [135], antitumor [136], anti-trypanosomal [137], and antileishmanial properties. In recent past years, the synthesis and evaluation of this class of molecules have been increased, both in the arena of material science and medicinal world. Predominantly, xanthones are well explored heterocyclic scaffolds with dibenzo-γ-pyrone structural motif [138–141]. Several xanthones isolated containing plant-based extracts are widely used in folklore medicines [142–146]. Furthermore, some marketed preparations containing xanthone as their structural unit presented in (Figure 20).

Inspired from previous findings Laphookhieo and his co-workers extracted α-mangostin, 5-*O*-methylcelebixanthone, β-mangostin, celebixanthone, cochinchinone A and cochinchinone C from roots of plant *Cratoxylum cochinchinense* [134]. These molecules were evaluated cytotoxic effects against human lung cancer, NCI-H187 cell line. Amongst these, α-mangostin, celebixanthone, cochinchinone A displayed cytotoxicity along with IC_{50} in a range of 0.65 to 5.2 μg/mL. Similarly, Chantarasriwong *et al.* recognized the set of Garcinia xanthones and tested for their anti-proliferative actions and inducing apoptosis towards human leukemic and colon HL-60 and HCT-116 cells respectively. Molecule (138) demonstrated to have maximum action against human colon cancer along with IC_{50} value 0.2 μM towards HCT-116, while another molecule (139) was the most effective Leukemia, HL-60 cells with IC_{50} value of 0.4 μM (Figure 21) [147].

In a parallel study, Matsumoto along with his coworkers established the xanthones isolated from *Garcinia mangostana* revealed a remarkable anticancer activity [148]. Nevertheless, α, β and γ-mangostins (126-127) were found to be active in a dose of 10 μM. The most potent molecule at such concentration was α-mangostin. The α-mangostin exhibited anti-proliferative actions leukemia cells like K562, U937 and NB4. Chiang *et al.* stated that concentrate of mangostin-organic pericarp displayed an intense anti-leukemic action, with IC_{50} of 159 and 61 μg/mL towards Raji and K562 cells respectively [149]. Prompted from these results, Balunas *et al.* have also evaluated all the three mangostins using a non-cell, chemical based microsomal aromatase hindrance experiment assay in IC_{50} value 4.97 μM against breast cancer, SK-BR-3 cells [150]. Recently, Jung *et al.* presented antitumor effect of these molecules in pre-neoplastic injuries persuaded using 7,12-dimethylbenz[a]anthracene

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(DMBA) in mouse mammary organ enlargement [151]. In another approach, Suksamrarn *et al.* extracted distinctive xanthones from mangosteen pericarp of fruit and screened it for antineoplastic activity against human cancer cells, including breast, small cell lung and mouth carcinoma; BC-1, NCI-H187 and KB cells with IC_{50} values of 3.53, 3.72 and 2.8 μg/mL respectively. However, α-mangostin (125) displayed the most noticeable result on BC-1 cell line, with IC_{50} value 0.92 μg/mL [152].

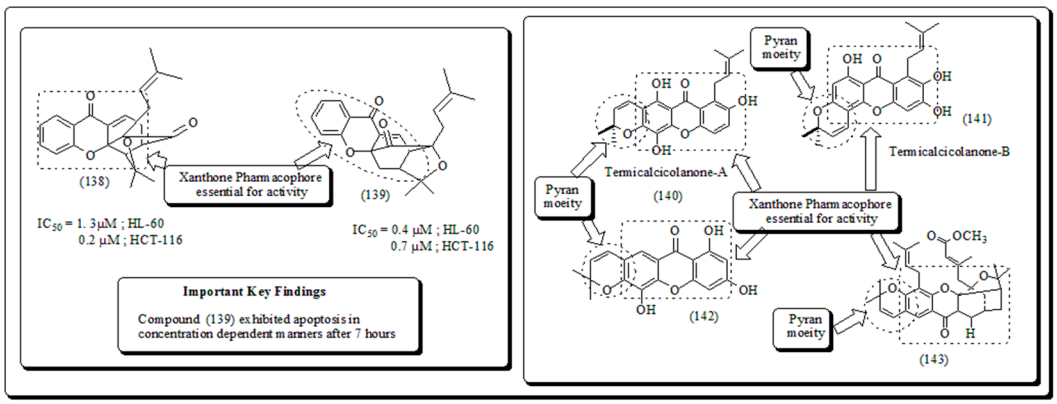

Figure 21. Structure of compounds, along with anti-proliferative potential.

Chen *et al.* proved that γ and α-mangostins produced noticeably cytotoxic effects towards RAW 264 cells and IC_{50} values of γ and α-mangostins were found to be 10.1 and 12.4 μM respectively [153]. Similarly, Watanapokasin *et al.* studied the anticancer action of mangostin xanthones, on colon malignant cells [154]. In addition, minor doses of the extract of mangostin were diminished the tumor volume in xenograft model. The mangosteen pericarp concentrate comprises of 25% α-mangostin reducing 50%–70% of tumor size in balb/c mice bearing colon tumor NL-17 xenografts model [154–157].

Cao *et al.* extracted two novel cytotoxic xanthones named termicalcicolanone B (141) and termicalcicolanone from the ethanolic extract of the plant *Terminalia calcicola* presented in (Figure 21) [158] These analogs were screened for their cytotoxic activity in ovarian cancer, A2780 cells having IC_{50} values of 8.1 and 40.6 μM respectively [158]. In another discovery, Han *et al.* isolated new prenylated xanthones, in addition to a few compounds from bark of *Garcinia lancilimba* [159]. These analogs were established their apoptotic potential through caspase-3 activation in HeLa-C3 cells. Similarly, Tao *et al.* extracted new xanthones, a pair of novel natural compounds from resin of *Garcinia hanburyi* [160]. These compounds were assessed for their cytotoxic effect against HeLa cervical carcinoma, along with adriamycin as reference standard and compound (143) exhibited cytotoxicity with IC_{50} value of 111 μM (Figure 21) [160].

Garcinia hanburyi, is a resin initially employed as folk medicine and pigment. In modern era, a group of xanthones (called *Garcinia* xanthones) were recognized as bioactive phytomolecules with potent therapeutic properties such as anti-HIV-1, antitumor, anti-inflammatory, antibacterial activities. The compounds were available in fruit, resin, and in other parts of the plant. Additionally, manifold mechanisms of cytotoxic activity were documented including apoptosis induction, cell cycle arrest, anti-angiogenesis and telomerase inhibition [161]. Caged xanthones obtained from *G. hanburyi* were examined for cytotoxic activities towards HCT-116, A 549, K 562/R, SMMC-7221, HepG2, Huh7 and SH-SY5Y cells of colon, lungs, doxorubicin-resistant K 562, hepatoma, hepatocellular, liver and neuroblastoma human cell carcinoma respectively The modified xanthones were induced apoptosis in HepG2 cells in a concentration dependent pattern [162,163]. Jang *et al.* described modified xanthones presented in (Figure 22) were selective against TrkA receptor, displaying a strong neurotrophic activity by selective binding to TrkA, through its provoking Akt/PI3-kinase/ and MAPK activation, tyrosine phosphorylation and thus inhibiting neuronal cell death [164].

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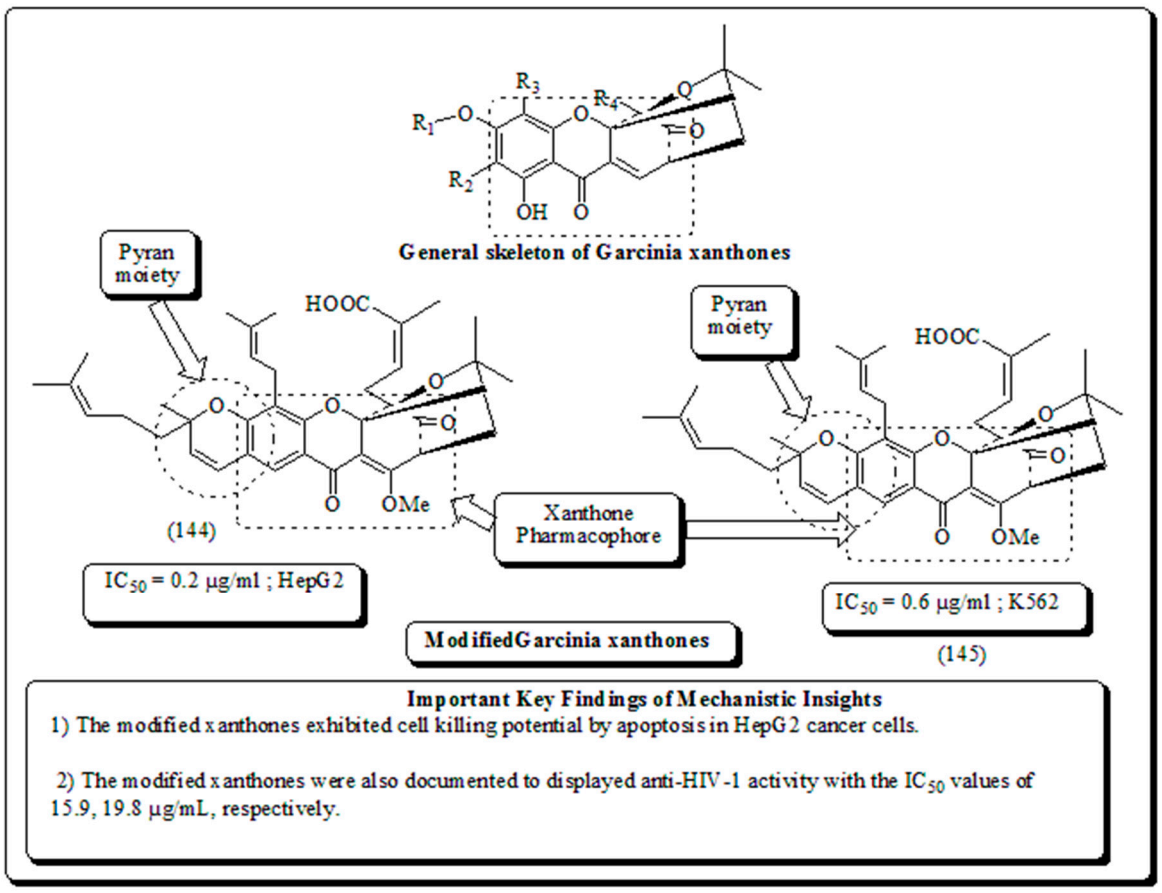

Figure 22. Structure of compounds as screened by Jang *et al.* [164].

Inspired by previous findings Zelefack *et al.* found butyraxanthones A-D, four known xanthones (**146**-**149**) from the bark of *Pentadesma butyracea* [165]. These compounds were assessed for in vitro anti-plasmodial actions against Plasmodium falciparum chloroquine-resistant strain along with cytotoxic effect in MCF-7 human breast tumor cell lines. It was found that among all screened analogs, only butyraxanthone D (149) was inactive with IC_{50} > 10 µg/mL, while compound **147** displayed significant cytotoxic effectiveness (Figure 23) [165,166].

Bhattacharya and his coworkers synthesized xanthenes from aryl aldehydes and β-naphthol catalyzed by $TaCl_5$ in solvent-free one-pot condensation conventional heating method [167]. All these xanthenes (Figure 23) were screened towards group human tumor cells including SW-620, Colo-205 (Colon), 502713, SKNSH (CNS), PC-3 (Prostate) and A-549 (Lung) sulforhodamine B assay. The compound 150 displayed IC_{50} values from 41.3 and 37.9 µM against 502713 and Colo-205 respectively, however compound (151) presented IC_{50} of 41.9 µM towards Colo-205 cells.165 Niu *et al.* isolated bracteaxanthenes and 1,4,5,6-tetrahydroxanthenes together along with 26 known molecules from ethanolic extract of stem bark of plant *Garcinia bracteata*. All compounds were assessed cell killing potential against HL-60 human leukaemic cells. The prenylated xanthones depicted in (Figure 23) displayed potent effects. Compounds **152**-**154** were found to be the most effective with GI_{50} values of 2.8, 3.4 and 3.1 µM respectively against HL-60 malignant cells [168].

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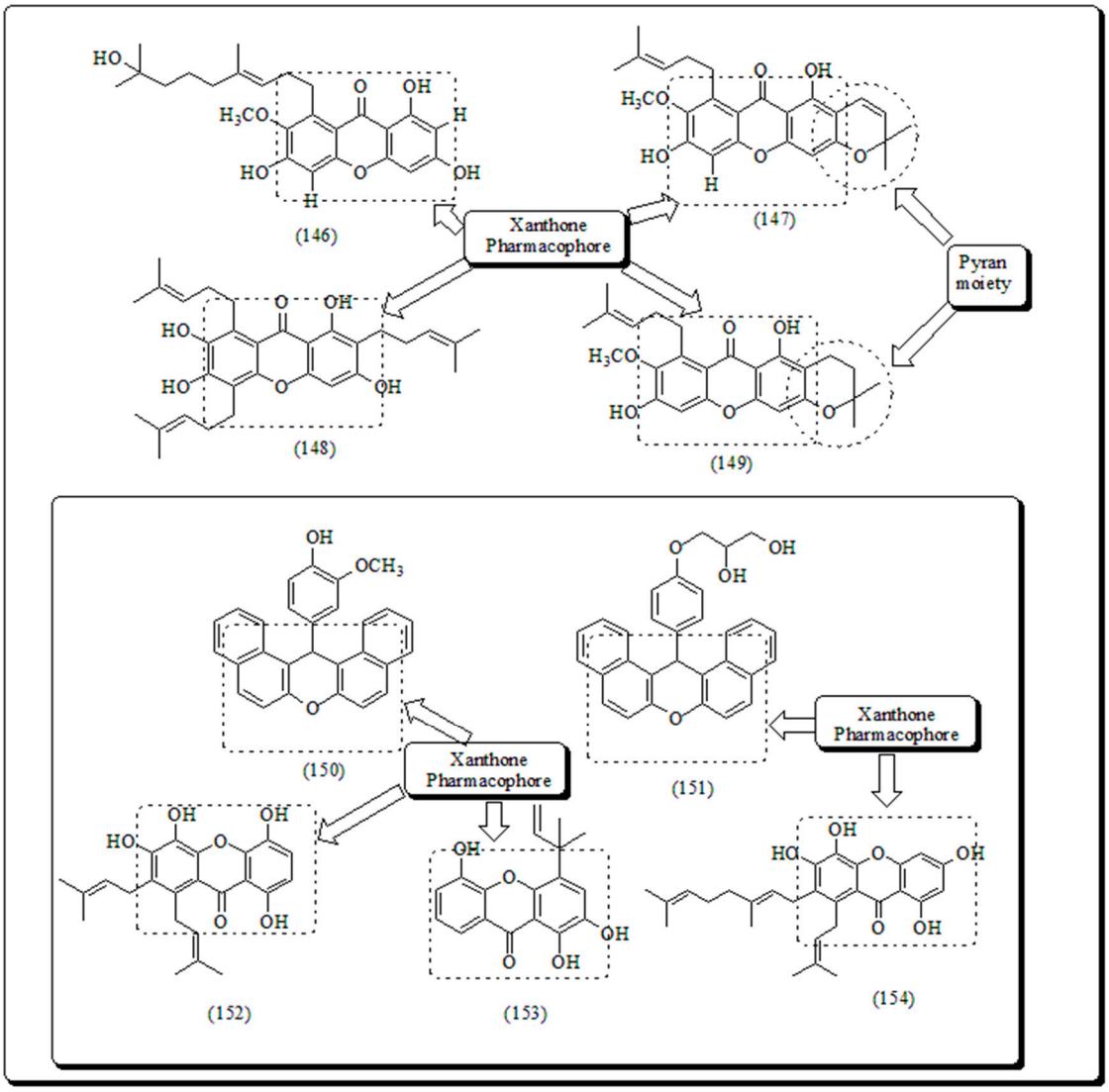

Figure 23. Most effective cytotoxic analogs (146-154) documented by Zelefack *et al.* [165] Mosoophon *et al.* [166] Bhattacharya *et al.* [167] and Niu *et al.* [168].

4. Miscellaneous oxygen-containing heterocyclic scaffolds

Numerous researchers around the globe were involved in the hunting of novel entities for the mitigation of diverse types of cancers. Several phytomolecules and their derivatives were clinically used against various cancers. Rhinacanthin O is pyran and oxirane based compound which (Figures 8 and 24) is isolated from *Rhinocanthus nasutus* and is therapeutically active towards breast cancer [63]. Similarly, taxols and phodophyllotoxins its derivatives consist ofoxitane and furan rings, respectively were also used clinically nowadays against the treatment of various cancers. Structure of compounds containing oxirane, oxitane and furan moieties presented in (Figure 24). Additionally, oxygen and nitrogen containing rings such as oxazole and iso-oxzole along with their anticancer potential were also discussed as follows.

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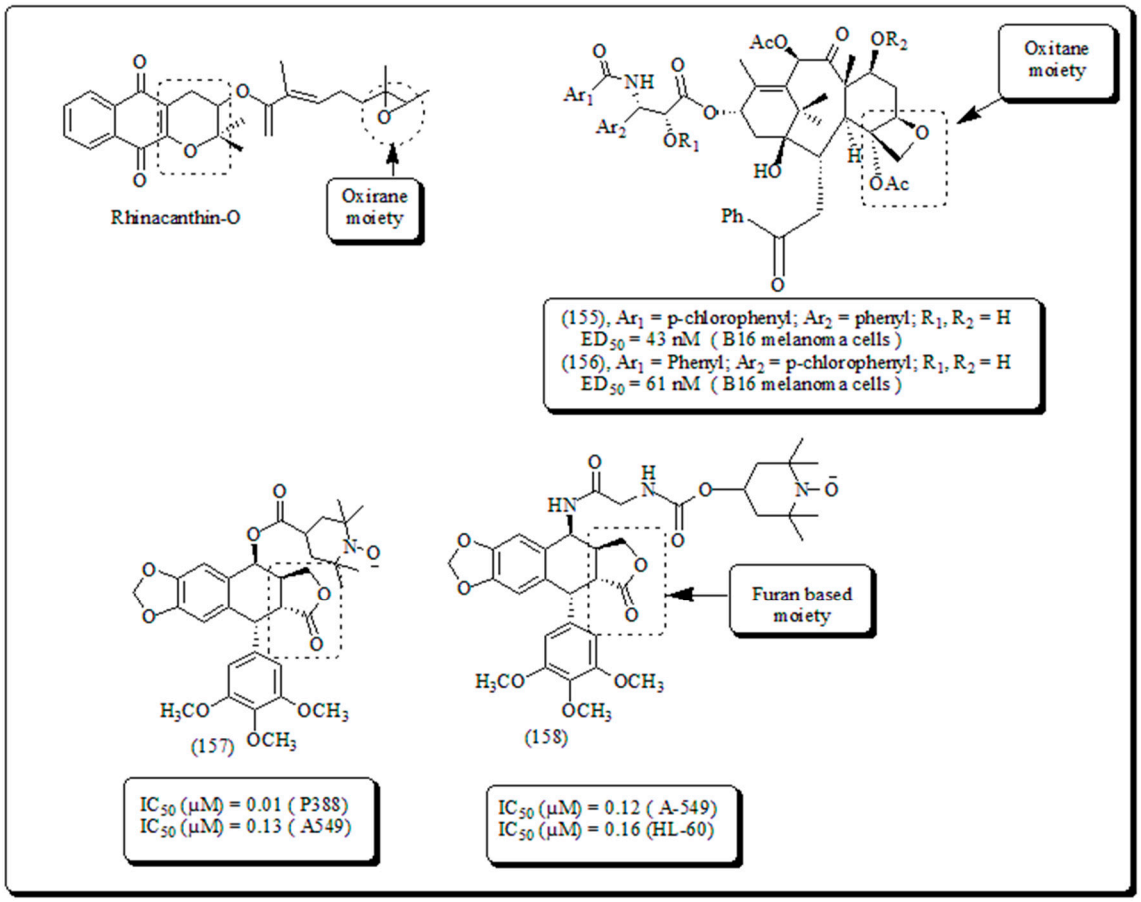

Figure 24. Structure of compounds containing oxirane, oxitane and furan moieties.

1,3,4-Oxadiazoles are noteworthy class of heterocyclic molecules with an extensive array of therapeutic activities including anticancer [169–172], antineoplastic [173], inhibition of tyrosinase [174] antiviral [175], fungicidal [176]. These play an important intermediate role in various organic synthesis reactions [177] and are usually used engaged as hole-blocking and electron transporting agents [178]. These structural motifs are extensively employed in medicinal chemistry and documented as privileged groups of structures. Furthermore, 1,3,4-oxadiazole, substituted 1,3,4-oxadiazoles and 1,2,4-oxadiazoles have been attracted because of their uses in photoluminescence, organic light-emitting diodes, material science and polymers. Moreover, 1,3,4-oxadiazole are exceptional bio-isosteres of esters and amides, which can impact noticeably in intensifying biological activities by involving in hydrogen bonding interactions with amino acid residue receptors [179].

Sankhe *et al.* recognized a series of substituted-1,3,4-oxadiazole analogs and evaluated for their antineoplastic action towards numerous human cancer cell lines using *in vitro* assays. Structure of several oxygen based heterocyclic compounds along with their mechanistic insights IC_{50} value and structural-activity relationship have been presented in Figures 25–29 [180].

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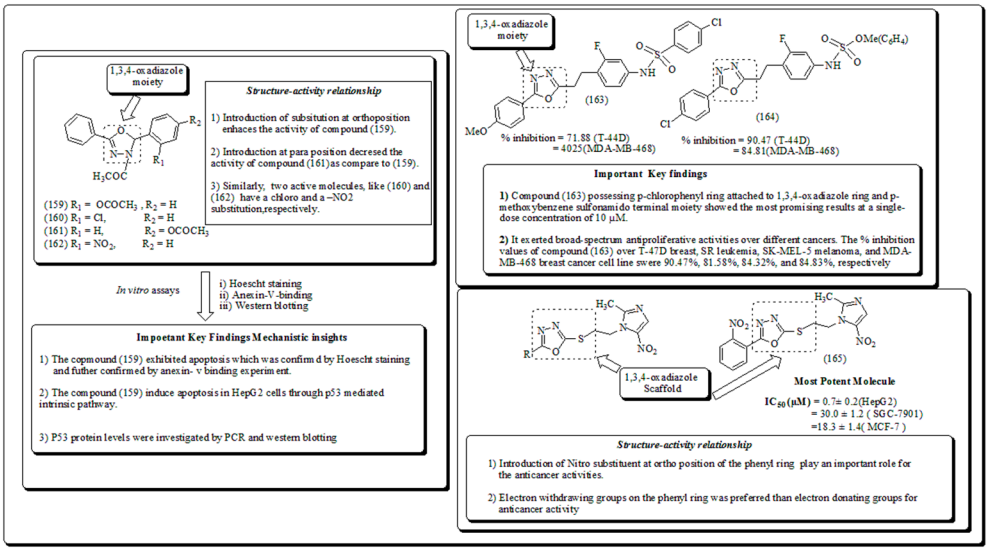

Figure 25. Structures of miscellaneous oxygen containing heterocyclic compounds along with mechanistic insights.

Mahmoud *et al.* designed a class of 1,3,4-oxadiazole analogs possessing sulfonamide moiety and screened against a panel of NCI-58 human cancer cell lines [181]. A library of new 1,3,4-oxadiazole thioether analogs based on 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole scaffold have been synthesized and evaluated for anticancer activity against three human cancer cell lines by Qian and coworkers. [182]. Naturally occurring oxazoles are recognized to exhibit diverse pharmacological activities. Labradorin 1(166) and Labradorin 2 (**167**), shown in Figure 26, were established to be cytotoxic against lung-NSC, malignant cells. Dalip *et al.* have presented compounds (**168-170**) as cytotoxic agents [183].

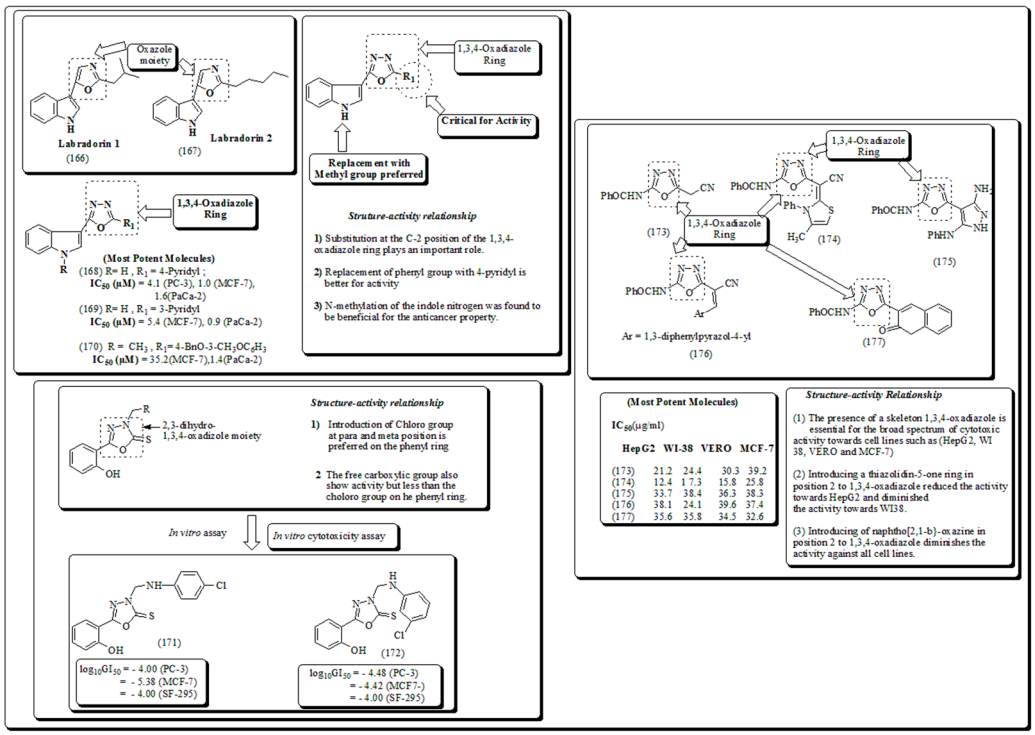

Figure 26. Structures of compounds (166-177) with anticancer potential and structure-activity relationships.

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Inspired from previous studies Ahmed *et al.* have described a class of substituted-1,3,4-oxadiazole analogs having anticancer activity. [184]. Samir and coworkers [185]. Presented 1,3,4-oxadiazole-based Heterocyclic analogs along with their mechanistic insights, IC_{50}, SAR and docking studies exhibited binding interactions with amino acid residues. 1,2,4-Oxadiazoles are formerly designated for selective inhibition of receptors including and benzodiazepines [186,187], 5-hydroxytry-ptamine (5-HT1B/D) [188,189] histamine-H3 [190], 5-HT4 [191] and muscarinic [192]. These also revealed anticancer [193,194] anti-inflammatory and anticancer properties [195,196]. Kumar *et al.* have established a set of substituted-1,2,4-oxadiazoles, 1,3,4- thiadiazole and their bioisosters and evaluated for their cytotoxic potential using *in vitro* studies and presented in Figure 27 [197,198].

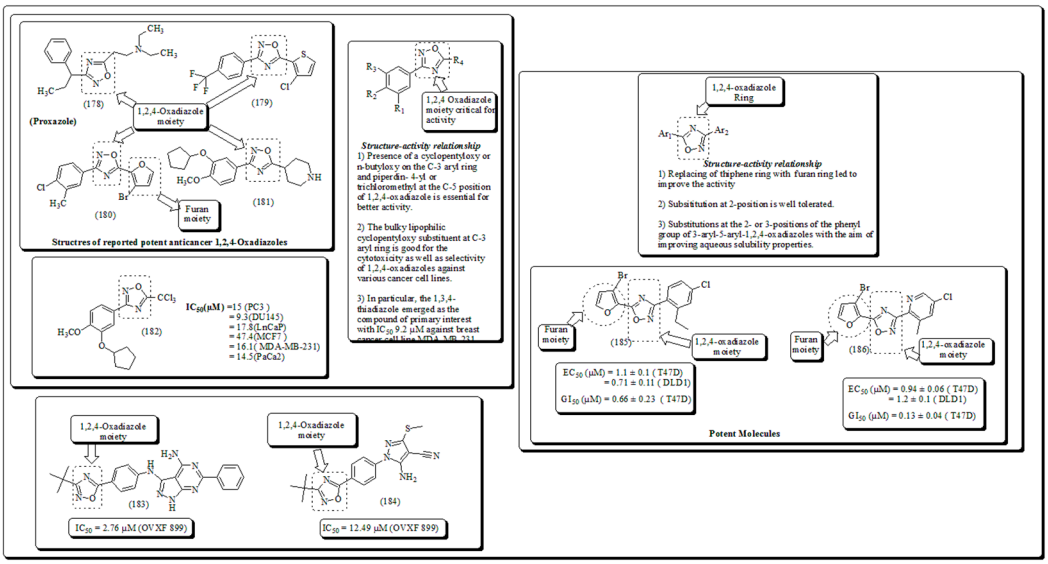

Figure 27. Structure of 1,2,4-oxadiazoles analogs and SAR studies.

Kemnitzer and coworkers [199] reported the synthesis and evaluation of substituted 1,2,4-oxadiazoles with the intention to enhance the water solubility Moreover, the structural activity relationship revealed that introduction of furan ring accelerating the anticancer activity and presented in Figure 28 [200,201].

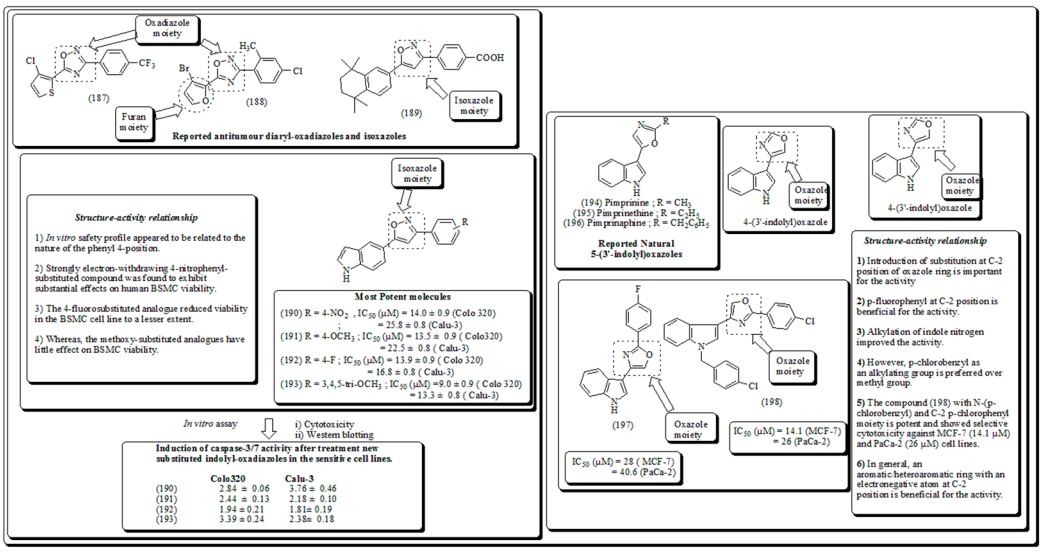

Figure 28. Structures of apoptotic antitumor agents.

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Puthiyapurayil, *et al.* have architectured and synthesized a novel combinatorial class of S-substituted-1,3,4-oxadiazole bearing N-methyl-4-(trifluoromethyl) phenyl pyrazole moiety and screened for in-vitro cytotoxic effects by MTT assay [202]. Recently, a series of quinoline derivatives have been screened as potential telomerase inhibitors by Juan *et al.* presented in Figure 29 [203,204]

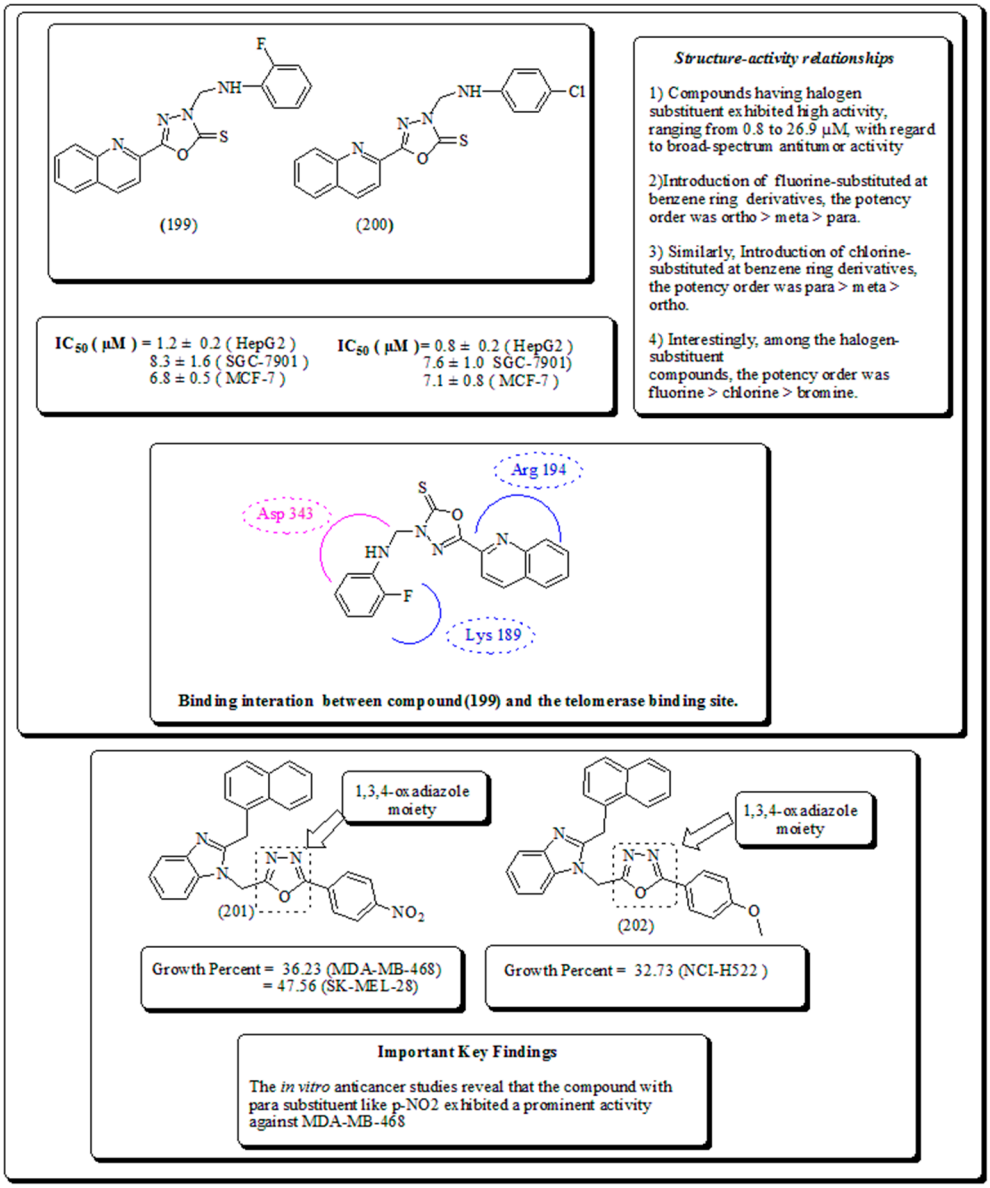

Figure 29. Structures of analogs reported by Jauan *et al.* [203] and Mohammad *et al.* [204].

5. Conclusions

The abovementioned report endeavored to ascertain that the oxygen containing heterocyclic scaffolds were considered as privileged structures and has accredited considerable attention in last decade from pharmaceutical, industrial and academic scientists. As revealed from several cited reports, the oxygen-based scaffold is essential in architecting of innumerable flavonoids, phenolic compounds, coumarins and xanthones present in numerous phytomolecules. Numerous oxygen based structural motifs exhibited astounding inhibitory actions along with their IC50 values in nano and micromolar range. The universal assumption is that oxygen-based compounds are the privileged heterocycles recognized to have comprehensive potential therapeutic activities, predominantly against diverse human cancers. There are ample evidence that, the deployment of oxygen based substituted scaffolds including furan, pyran, chromone, coumarin and xanthone analogs have offered the platform for innovative chemical entities which might be act as potential therapeutic candidates

with diverse array of pharmacological properties. Several i*n vitro*, *in silico* and *in vivo* studies have publicized that the oxygen based heterocyclic scaffolds with hypothetically useable structural motifs for development of anticancer and cytotoxic properties. Additionally, the structures of designed and synthesized compounds discussed in this assemblage noticeably highlighted the remarkable and promising cytotoxic profiles along with IC50 values, mechanistic insights, and their structure-activity relationships studies. The article also presented binding interactions with key amino acid residues in designated binding pockets of receptors, as validated by docking studies. In nutshell, the recorded activities, and recognized mechanisms of action, and can utilize hodgepodge of these oxygen based heterocyclics in the design of numerous novel structural frameworks.

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