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Review Article

Recent Advances in Oxygen-Containing Heterocycles as Anticancer Agents

Vinod Kumar Gurjar [a]*

[a*] *School of Pharmacy, Faculty of Pharmacy, Parul University, Vadodara, Gujarat-390760 India*

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Corresponding Author details:
Email: gurjarvinod79@gmail.com (V.K. Gurjar)

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ABSTRACT

Cancer is the second leading cause of mortality worldwide. Numerous deaths have been reported daily through cancer. To date, there are a number of approaches and therapeutics available on the market for cancer treatment. These therapeutics are either natural compounds or synthetic agents based on either a heterocyclic nucleus or someone else. Recently, a number of heterocycles have been utilized for cancer treatment. Oxygen containing heterocyclic compounds are also prevalent in cancer therapy. These oxygen-containing heterocycles are either three-, four-, or five-membered rigs, naturally occurring or synthetic agents. These oxygen-containing heterocycles are obtained from microorganisms or plant sources, and they have also been prepared in laboratories by numerous researchers. The present writeup reports various oxygen-containing heterocycles for their anticancer activities.

INTRODUCTION

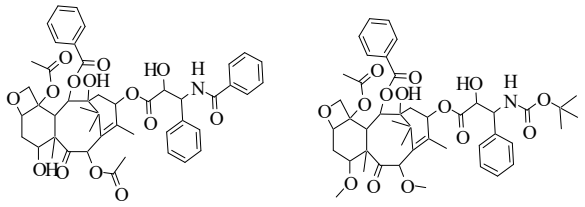
After ischemic heart disease, cancer is the second-leading cause of mortality worldwide. The number of cancer cases and deaths via cancer increases gradually, and around ten million deaths from cancer have been reported globally in 2020. Cancer is caused by uncontrolled cell proliferation or mutations that disrupt gene and protein regulation. Nonspecific chemotherapeutic medicines and multiple drug resistance are two major drawbacks of contemporary antitumor chemotherapy, and thus the invention of novel derivatives is critical to overcome the adverse effects and resistant relative problems of chemotherapeutic medications. Cancer has three features that distinguish it from benign tumours: self-limiting, non-metastasizing, non-invading, uncontrolled growth, invasion, and metastasizing [1-3].

Chemotherapy is the use of chemical compounds to treat malignant or infectious tumours, generally chemicals with pathogen-specific toxicity [4]. The major issue in medicinal chemistry research is to characterize novel structures that may be used as power selective and less toxic anticancer medicines [5].The history of heterocyclic chemistry began around 1800, along with the advancement of organic chemistry [6].

Heterocyclic compounds are a basic category of organic chemistry. Pharmacologically active heterocyclics have a notably active role as anticancer, analgesics, hypnotics, and antidepressant medicines, among the numerous therapeutic

uses [7]. Many heterocyclic compounds are also used as pesticides, weed killers, rodenticides, and insecticides. Heterocyclic compounds, such as thiamin, riboflavin, pyridoxol, nicotinamide, and ascorbic acid, are also important dietary components (vitamin C). To put it another way, heterocycle chemistry is at the core of medication development [8].

Oxygen-based heterocycles account for around 15% of all FDA-approved medicines. There are many FDA-approved oxygen-based anti-angiogenic cancer medicines now on the market. Some of these medicines (Figure 1) target microtubules and are based on the oxetane ring, for example, paclitaxel and cabazitaxel.



Paclitaxel (Taxol) Cabazitaxel (Jevtana)

Fig. 1. Oxygen-based anti-angiogenic agents.

The present write-up summarizes knowledge on numerous oxygen containing heterocyclic compounds with respect to their anticancer activities. The present review focuses on three-membered, four membered and five membered heterocyclic compounds that possess oxygen atoms for the treatment of cancer therapy.

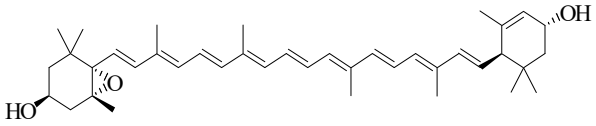
OXYGEN CONTAINING ANTICANCER HETROCYCLIES

Several oxygen containing heterocyclic compounds isolated from natural sources possess numerous biological activities. The naturally occurring oxygen containing heterocyclic compounds gain interest in the field of anticancer drug development. Many research programs are directed toward developing novel slants to an assortment of heterocyclic compounds for anticancer activity, particularly oxygen containing three membered heterocyclic compounds.

THREE-MEMBERED RINGS WITH OXYGEN-HETEROATOM

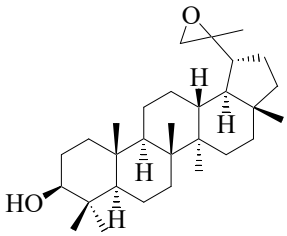
The three-membered ring heterocycles containing oxygen atoms termed oxirane (or ethylene oxide), prepared by nucleophilic reactions. Commercially, oxirane is an important bulk industrial chemical prepared by the direct reaction of oxygen with ethylene. Compounds with one or more oxirane rings occur naturally in abundance. These compounds are frequently physiologically active and show promise for therapeutic use. The fungal product (−)-ovalicin, containing two oxirane rings, can impede the formation of solid tumors by cutting off their blood supply. Fosfomycin, an oxirane containing drug, is used as an antibiotic, particularly in treating urinary tract infections [9].

Behbahani isolated and reported three naturally occurring plant compounds, i.e., eugenol, lupeol, and lutein, in *O. basilicum*, *A. maurorum*, and *C. officinalis*, respectively [10]. The epoxide forms of these compounds were also found in *C. officinalis*, which showed more cytotoxicity as compared to lutein, lupeol and eugenol. The authors reported cytotoxicity studies, expression levels of apoptosis-regulatory genes, and real-time polymerase chain reaction assay for p53, bcl-2, bax and caspase-3 for all lupeol, lutein and eugenol and their epoxides. Results showed augmented expression level of all p53, bax and caspase-3 (except bcl-2 level) by epoxide forms of lupeol, lutein and eugenol in both breast cancer cell lines (MDA-MB-231 and MCF-7) and normal breast cell line (MCF 10A). These results suggested that epoxidation of naturally occurring compounds may be a potential drug candidate for cancer therapy (Figures 2-4).



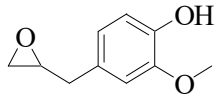
Lutein epoxide

Fig. 2. Structure of lutein epoxide ((1R,3S,6S)-6-((1E,3E,5E,7E,9E,11E,13E,15E,17E)-18-((1R,4R)-4-hydroxy-2,6,6-trimethylcyclohex-2-en-1-yl)-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaen-1-yl)-1,5,5-trimethyl-7-oxabicyclo[4.1.0]heptan-3-ol).



Lupeol epoxide

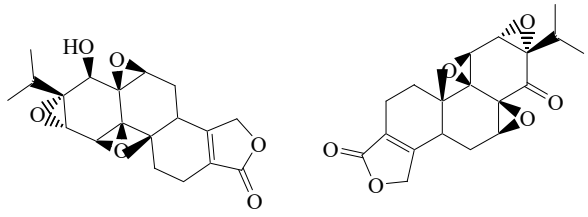
Fig. 3. Structure of lupeol epoxide ((1R,3aR,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bS)-3a,5a,5b,8,8,11a-hexamethyl-1-(2-methyloxiran-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol).



Eugenol epoxide

Fig. 4. Structure of eugenol epoxide (2-methoxy-4-(oxiran-2-ylmethyl)phenol)

Triptolide (1) and triptonide (2) are two commercially available diterpenoid epoxide isolated from *Tripterygium wilfordii's*, possess numbers of biological activities (Figure 5).



Triptolide (1) **Triptonide (2)**

Fig. 5. Structure of triptolide (**1**) and triptonide (**2**) obtained from *Tripterygium wilfordii* Hook.

Zhou et al., synthesized three types of new triptolide analogues: 3,11-olefin (3–5), five-membered unsaturated lactam ring (6–7), and A/B cis ring junction (8–14) [11]. The findings showed that the planar structure of a five-membered unsaturated D-ring, the C-ring three-dimensional structure, and the trans A/B-ring junction may have an influence on the cytotoxic activity. Compound (**4a**) was considerably more active than the parent natural triptolide, with an IC_{50} value of 0.05 nM for SKOV-3 cells, indicating that the 9,11-b-epoxide group of triptolide is essential and not unchangeable even when generating powerful anticancer analogues (Figure 6).

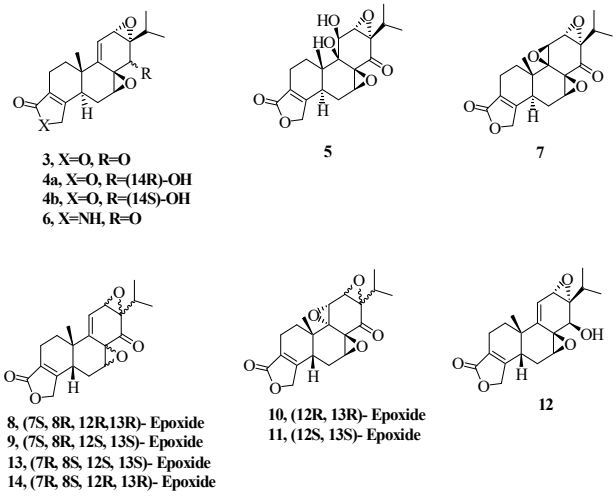


Fig. 6. Triptolide analogues (**3**–**14**).

Psorospermin, derived from *Psorospermum febrifugum*, is made up of a xanthone scaffold and has been shown to have strong anticancer action against human and murine cancer cell lines (Figure 7). Acronycine, derived from *Acronychia baueri* Schott, has a broad spectrum of action against a number of solid cancers. Due to acronycine's low clinical efficacy, medicinal chemists developed a number of acronycine derivatives with better anticancer activity and less cytotoxicity to normal cells than acronycine. S23905-1 had greater anticancer activity than acronycine against *in vivo* colon 38 adenocarcinoma and murine P388 leukemia, as well as *in vitro* L1210 cell lines. The finding of acronycine epoxide (Figure 7), which was isolated from multiple *Sarcomelicope* species, has confirmed the theory that acronycine's anticancer effects *in vivo* are mediated by biotransformation to the equivalent epoxide, acronycine epoxide. Psorospermin is an oxirane ring containing DNA alkylating agent, reacts with the N-7 of the guanine base, and S23906-1 is an alkylating agent that reacts with the N-2 of the guanine base of DNA. The researchers developed dihydrobenzofuro[4,5-b][1,8]naphthyridin6-one and their derivatives with an oxiranyl functional group that can serve as an electrophile. rac-2 with (2R*,20'S) stereochemistry had doxorubicin comparable anticancer activity in all cancer cell lines examined, while rac-1 with (2R*,20'R)-stereochemistry

had greater anticancer activity compared to doxorubicin and rac-2 against all cancer cell lines examined, although doxorubicin had equal anticancer activity [12].

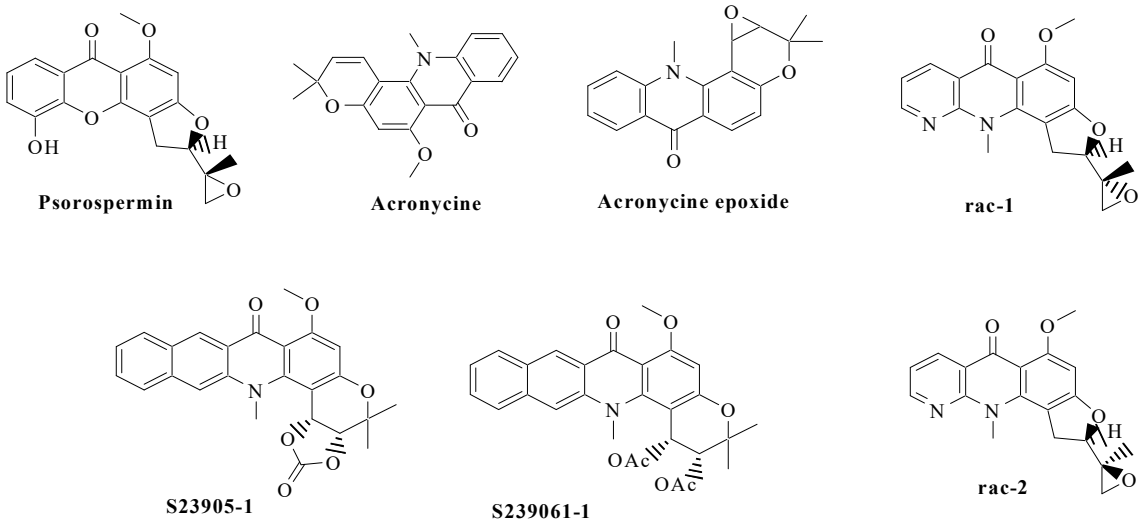
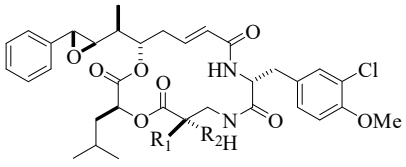


Fig. 7. Structures of acronycine derivatives.

Cancer chemotherapeutics that target the tubulin protein have proven effective in human cancer therapy. Cryptophycins (Cr) have similar clinical potential. Cryptophycins are 16-membered macrolide antimitotic agents identified in *Nostoc* sp. cyanobacteria. Tubulin protein is their molecular target, and they are the most effective known stabilizers of microtubule dynamics, depolymerizing microtubules at greater doses. They also deactivate the Bcl2 protein and induce an apoptotic response more quickly and at far lower doses than currently used drugs. Lilly is testing Cr-52, a synthetic counterpart, as a therapy for solid tumours in clinical trials. P-glycoprotein and multidrug resistance protein (MRP)-mediated efflux, which impair the natural product anticancer drugs paclitaxel and vinblastine, are bypassed by Cryptophycin-52, allowing it to start apoptosis considerably more quickly (Figure 8) [13].



Cryptophycin- R1= Me, R2=H
Cryptophycin 52- R1=R2= Me

Fig. 8. Structure of cryptophycins.

Ouédraogo et al., using the 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) test on B16 melanoma and P388 leukemia cell lines, investigated the cytotoxicity of oxaziridines photogenerated following irradiation of chlordiazepoxide (CDZ) and its metabolites *in vitro* and compared it to that of the anticancer medication melphalan [14]. They reported that oxaziridines exhibited the same cytotoxicity as melphalan in the extended time-exposure experiment, with the toxicity being greater when oxaziridines were photogenerated in the presence of cells. On the B16 melanoma cell line, oxyaziridines had a greater effect than on the P388 leukemia cell line. The benzodiazepine receptors on the melanoma B16 cell line might explain this. Fluorescence microscopy observations of cellular lysis lead to the idea that oxaziridines have an action mechanism on the cellular membrane (Figure 9).

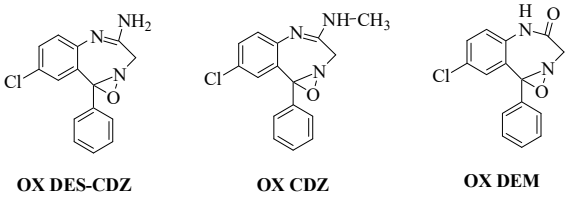
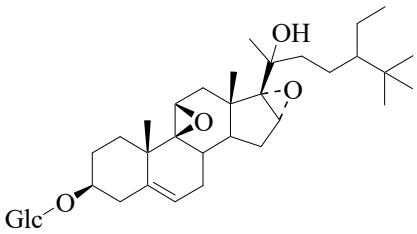


Fig. 9. Structures of OXDES-CDZ-photoproduct of the metabolites (desmethylchlordiazepoxide) of CDZ; OX CDZ-photoproduct of CDZ; OX DEM- photoproduct of metabolites (demoxepam) of desmethylchlordiazepoxide.

Zubair et al., investigated the ethyl acetate extract of the aerial portions of *Begonia* sp. and yielded a novel steroid glycoside, 9(11),16(17)-dioxirane-20,25-dihydroxy—sitosterol-3-O-glucopyranoside (Figure 10) [15]. The compound was shown to be more powerful and selective against the T47D than any other cell lines (T47D, HeLa, WiDr, and Vero), with an IC_{50} value of 0.16 µg/mL.



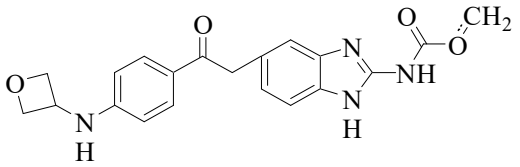
Glycosides

Fig. 10. Structure of steroid glycosides.

FOUR-MEMBERED RINGS WITH OXYGEN HETEROATOM

Oxetane—a four-membered ring containing, one oxygen atom—is also prepared by nucleophilic displacement reactions. Numerous oxetanes, and their synthetic analogs possess antiviral properties (e.g.,. oxetanocin) and are under investigation as anti-inflammatory, antifungal, antiviral and anticancer agents [16].

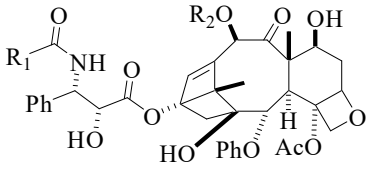
Cheong et al., reported the anticancer activity of a novel benzimidazole containing an oxetane or an amine group to increase solubility [17]. Numerous compounds were synthesized, and it was found that the compound Methyl (5-(4-(methyl(oxetan-3-yl)amino)benzoyl)-1H-benzo[d]imidazol-2-yl)carbamate **(15)** showed significant cytotoxicity against cancer cells, including prostate (PC3, PC3MLN4), lung (H157, Calu1, A549), and ovarian (SKOV3) cancers, with particularly strong activity against highly aggressive cancer lines (IC_{50}: 0.9–3.8 µM). Compound **(15)** has a 361 µM aqueous solubility. Compound **(15)** (30 mg/kg) substantially reduced the development of existing tumours in a mouse xenograft model of highly metastatic human prostate cancer (T/C: 0.36) without causing harm (Figure 11).



(15)

Fig. 11. Benzimidazoles containing an oxetane or an amine group

Taxol (**16a**), which was discovered in the late 1960s in the bark of *Taxus brevifolia*, and its derivative, Taxotere (**16b**), have become the gold standard for the treatment of breast and ovarian cancer. The oxetane, a four-membered D-ring, is one of four structural characteristics thought to be necessary for biological activity (Figure 12). The Taxol-epothilone minireceptor, Ki estimate for microtubule binding, and docking of Taxol analogues into a model of the Taxol-tubulin complex. Oxetane function is thought to be due to two characteristics: (1) rigidification of the tetracyclic Taxol core to create a suitable framework for exposing the C-2, C-4, and C-13 side chains to the microtubule protein, and (2) service as a hydrogen-bond acceptor. The oxetane ring obviously acts by both methods, according to an energy decomposition study of a variety of Taxol analogues [18].



(16)

	R1	R2
Taxol (a)	**Ph**	**Ac**
Taxotere (b)	**t-Bu**	**OH**

Fig. 12. Structure of Taxol and Taxotere

The first complete synthesis of (–)-mitrephorone A, an enttrachylobane diterpene with anticancer and antibacterial action, was reported by Schneider and colleagues in 2020 [19]. A completely substituted oxetane, a tetrasubstituted cyclopropane, a 1,2-diketone, and four quaternary stereogenic centers make up the hexacyclic structure (Figure 13). The late-stage synthesis of the oxetane is enabled by a new oxidative cyclization, resulting in the completion of this powerful natural compound (–)-mitrephorone A which showed antibacterial and antifungal activity as well as

cytotoxicity against different cancer cell lines (MCF-7, H460, SF-268).

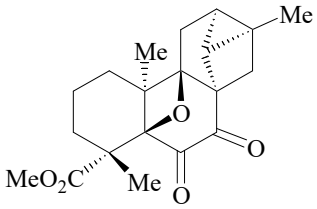
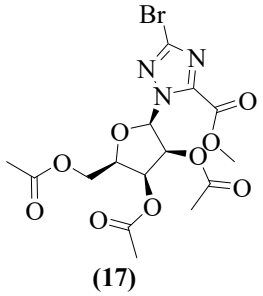


Fig. 13. Structure of Mitrephorone A

FIVE-MEMBERED RINGS WITH OXYGEN HETEROATOM

The parent heterocyclic compound of this class is furan and its saturated derivative is called tetrahydrofuran [20].

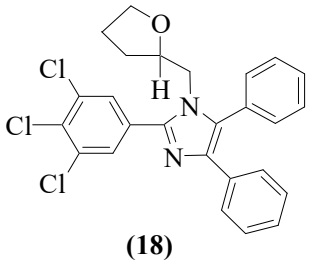
(2R,3S,4S,5R)-2-(acetoxymethyl)-5-(3-bromo- 5-(methoxycar-bonyl)-1H-1,2,4-triazol-1-yl)tetrahydrofuran-3,4-diyl diacetate (**17**), a crucial intermediate in the antitumor nucleosides was synthesized by directly coupling the bromotriazole with the protected ribose sugar by Liu et al. in year 2014 (Figure 14) [21]. These nucleoside analogues can imitate natural nucleosides and, therefore can be used as building blocks or inhibitors to disrupt nucleic acid synthesis or impede biological activities requiring nucleos(t)ides. Compound (**17**) can then stop viruses from reproducing and cancer cells from proliferating uncontrollably, resulting in strong and efficient antiviral and anticancer action.



(17)

Fig. 14. Structure of (2R,3S,4S,5R)-2-(acetoxymethyl)-5-(3-bromo- 5-(methoxycar-bonyl)-1H-1,2,4-triazol-1-yl)tetrahydrofuran-3,4-diyl diacetate,

4,5- diphenyl-1-((tetrahydrofuran-2-yl)methyl)-2-(3,4,5-trichlorophenyl)-1H-imidazole (**18**) was synthesized by Kumar et al, (2020) (Figure 15) [22]. The cytotoxicity of the tetrahydrofuran derivative was evaluated against HepG2 cell lines using MTT assay, and the results showed that the compound had substantial anticancer effects on HepG2 cancer cells for at least 4 hours at 20 µM. The new tetrahydrofuran derivative was shown to be the most effective anti-breast cancer treatment.



(18)

Fig. 15. Structure of compound 4,5- diphenyl-1-((tetrahydrofuran-2-yl)methyl)-2-(3,4,5- trichlorophenyl)-1H-imidazole.

Shi and colleagues in 1995 discovered the powerful anticancer agent mucocin from the leaves of *Rollinia mucosa* (jacq.) Baill (Annonaceae) [23]. Mucocin is the first annonaceous acetogenin with a hydroxylated tetrahydropyran ring to be described, and therefore constitutes a novel skeleton type for this family (Figure 16). With a potency of more than 10,000 times that of adriamycin, this drug showed specific inhibitory actions against A-549 and PACA-2 solid tumor lines, making it a promising therapeutic candidate. By blocking mitochondrial complex I and inhibiting plasma membrane NADH oxidase, annonaceous acetogenins preferentially inhibit malignant cells. This depletes ATP, causing malignant cells to undergo apoptosis (programmed cell death) [24].

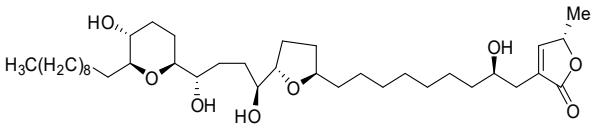
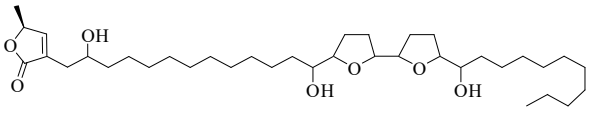


Fig. 16. Structure of compound Mucocin.

Asimicin and bullatacin are two anonaceous adjacent bis-tetrahydrofuran (bis-THF) acetogenins, very powerful cytotoxic compounds (Figure 17). They are said to be hundreds of times more cytotoxic than doxorubicin, especially against multidrug-resistant cell types. Though the specific mechanism of action is not known, these agents are thought to have anticancer properties by blocking complex I, increasing the production of pro-apoptopic genes, and arresting cells in

several stages, including G1 and G2/M. The stereochemistry of the THF core, which includes both THF rings and the central hydroxyl functionalities, is important for the anticancer activity of bis-THF acetogenins [25].



Asimicin: tr-th-tr (16R, 19R, 20R, 23R), (15R,24R),
Bullatacin: tr-th-tr (16R, 19R, 20R, 23R) (15R,24S)

Fig. 17. Structure of asimicin and bullatacin.

Nguyen et al., studied a furanne-like chemical (**19**) produced by *Streptomyces* sp. VN1 that has anticancer efficacy against five different tumour cell lines [26]. This drug inhibited the development of gastric adenocarcinoma (AGS), colon cancer cells (HCT116), melanoma (A375SM), glioblastoma (U87MG), and lung cancer (A549) cells with IC_{50} values of 40.5, 123.7, 84.67, 50, and 58.64µM, respectively. Compound 5-(sec-butyl)−2-ethylfuran-3-carboxylic acid (**19**) suppressed the development of cancer cell lines more efficiently than normal cell lines (267B1 and MRC-5) (Figure 18). Compound (**19**) showed anti-migration and anti-invasion activities against the AGS cancer cell line after 24 hours of exposure. These results confirmed that the compound (**19**) possesses anticancer activity. In cell growth assay the cell viability was 89%. The anti-invasive capabilities of compound (**19**) against cancer cell lines highlight the importance of investigating secondary metabolites and biosynthesis routes for developing clinically useful drugs.

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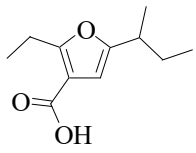
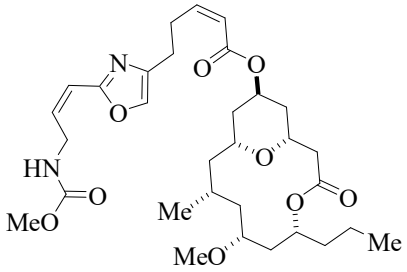


(19)

Fig. 18. Structure of compound (**19**).

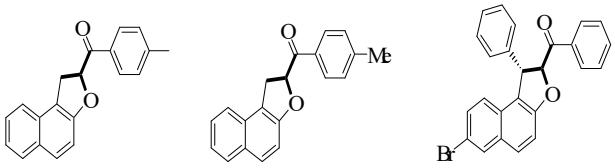
Neopeltolide (**20**) is a macrolide complex, isolated in 2007 by Wright and colleagues in a deep-water sponge of the Neopeltidae family (Figure 19). Neopeltolide was shown to be a very effective anti-proliferative drug against a variety of cancer cell lines, including P388 murine leukemia (IC_{50} = 0.56 nM), A-549 human lung adenocarcinoma (IC_{50} = 1.2 nM), and NCI-ADR-RES human ovarian sarcoma (IC_{50} = 5.1 nM). It also has substantial cytostatic inhibitory effects in the pancreatic cell line PANC-1 and the colorectal cell line DLD-1. The molecular foundation for the strong antiproliferative action of neopeltolide and similar analogues was discovered by Kozmin and coworkers, who discovered that neopeltolide inhibits mitochondrial ATP production and identified the cytochrome bc1 complex as the primary cellular target [27].



(20)

Fig. 19. Structure of Neopeltolide

Islam et al., synthesized a novel series of 1,2-dihydronaphtho[2,1-b]furan derivatives [28]. MTT assays were used to assess the anti-proliferative capability of the synthesized compounds against human triple negative MDA-MB-468 and MCF-7 cells, as well as non-cancerous WI-38 cells. Based on the findings of various biochemical and microscopic studies, three compounds (**21-23**) showed remarkable anti-cancer potential, with compound (**22**) having the highest anti-proliferative properties (Figure 20).

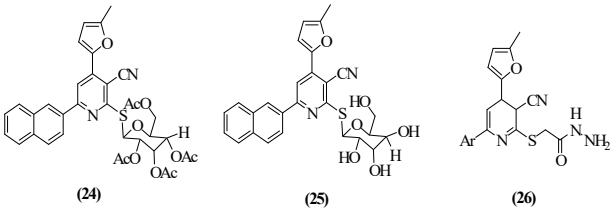


(21) **(22)** **(23)**

Fig. 20. Structure of compounds (**21-23**).

Khalaf et al., synthesized and reported the anticancer activity of new pyridine-furan hybrid compounds, their sugar hydrazone, and glycosyl derivatives [29]. The MTT assay showed that the compound 2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)- thio-4-(5-methylfuran-2-yl)-6-naphthalen-2-ylnicotinonitrile (**24**) had a cytotoxic impact against A549 and

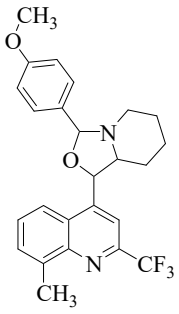
HCT116 cell lines that was similar to that of the reference medication, doxorubicin. Compounds 2-(Galactopyranosylthio)-4-(5-methylfuran-2-yl)- 6-(naphthalen-2-yl)nicotinonitrile (**25**) and (5-Cyano-4-thiophen-2-yl[2,3′]bipyridinyl-6-yloxy)- acetic acid hydrazide (**26**) were extremely active against HCT-116 and A549/PC3 cancer cell line respectively (Figure 21).



(24) (25) (26)

Fig. 21. Structure of compounds (**24-26**).

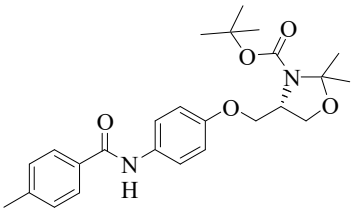
Rodrigues et al., reported a series of 23 racemic mefloquine–oxazolidine compounds against 5 cancer cell lines with excellent cytotoxicity, including SF-295, HCT-116, OVCAR8, HCT-8, and HL60 [30]. Numerous compounds were shown to have high cytotoxic action against the four cancer cell lines. Compounds with aryl groups having strong electron-releasing substituents (e.g., HO and MeO), or electron-rich heteroaryl groups (e.g., imidazol-2-y-l), are active. Compound (**27**) was reported as modestly active among the synthesized compounds (Figure 22).



(27)

Fig. 22. Structure of compound (**27**).

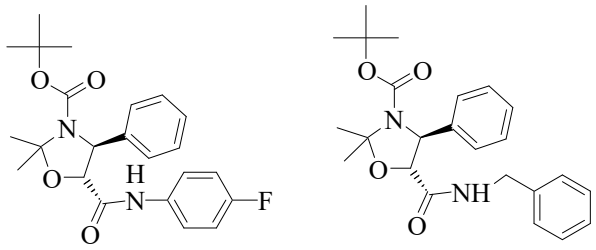
Andrade et al., reported the synthesis and antiproliferative assessment of a targeted library of 30 new oxazolidines created by changing the N-substituent, changing the ring, changing the alkyl, or extending the structure [31]. Carbamate and N,O-aminal groups were shown to be necessary for activity. The substitution of pyridinyl for the phenyl ring was not tolerated. The addition of a second phenyl ring at the 3- or 4-position of the first phenyl ring, together with an adequate spacer, typically improves the cytotoxic profile. Compound 1,1-Dimethylethyl (S)-2,2-dimethyl-4-[[4-(4-methylbenzoylamino)phenoxy]methyl]-3-oxazolidinecarboxylate (**28**) was the most potent molecule in this class, with 4-fold and 10-fold more effective against HL60 and JURKAT cells, respectively, than the lead compounds (Figure 23). In addition, it exhibited significant efficacy against lead-resistant MCF-7 and HCT-116 cells. Furthermore, compound (**28**) had negligible antiproliferative effect against VERO, showing that it was not harmful to normal cells.



(28)

Fig. 23. Structure of compound (**28**).

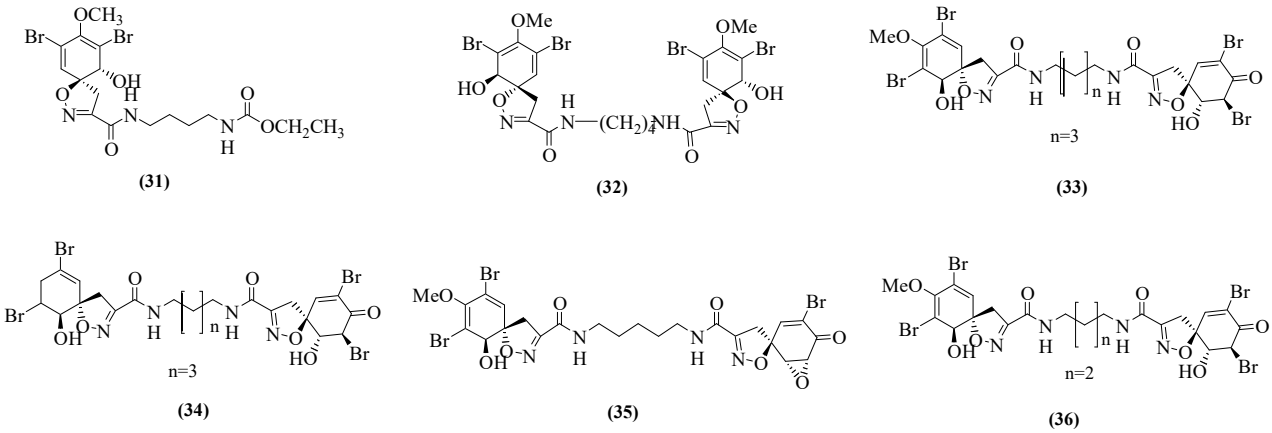
Kumar et al., reported a series of N-substituted 1-N-(tert-butoxycarbonyl)-2,2-dimethyl-4-phenyl-5-oxazolidine carboxamides [32]. Compound 5-N-(40 -Fluoro) phenyl-3-N0 -tert-butoxycarbonyl-2,2- dimethyl-4-phenyl oxazolidine-5-carboxamide (**29**) was prepared via amidation of N-(tertbutoxycarbonyl)-3,3-dimethyl-4-phenyl-oxazolidine5-carboxylic acid with 4-fluoro aniline and showed remarkable cytotoxicity (IC_{50} 14.5.67 mm) in ovarian cancer. While compound 5-N-Benzyl-3-N0 -tert-butoxycarbonyl-2,2-dimethyl-4- phenyl oxazolidine-5-carboxamide (**30**) prepared by the reaction of (N-(tertbutoxycarbonyl)-3,3-dimethyl-4-phenyl-oxazolidine5-carboxylic acid amidated with benzylamine, which showed potential cytotoxicity in ovarian (IC_{50} 14.61 mm) and oral (IC_{50} 14.17 mm) cancer. It has been discovered that di-substituents or electron donating groups in the phenyl ring are ineffective in increasing cytotoxicity. However, N-benzyl-oxazolindine-5-carboxamide (**30**) was shown to have a significant cytotoxic effect against PA-1 (IC_{50} 14 6.1mM) and KB (IC_{50} 144.17 µM) cell lines with a good safety index (Figure 24).



(29) **(30)**

Fig. 24. Structure of compounds (**29**) and (**30**).

Various isoxazoline-containing natural products were reported for their anticancer properties by Kaur et al., [33]. Subereamolline A (**31**), a bioactive dibrominated metabolite isolated from the sponge *Suberea mollis* using methanol, inhibits the migration and invasion of MDA-MB-231 metastatic human breast cancer cells. Their antimigratory action is dependent on the presence of a terminal ethyl carbamate molecule. (+)-Aerothionin (**32**), a tetra bromo chemical with a spirohexadienylisoxazoline pharmacore, was discovered in the acetone extract of *Aplysina aerophoba* and *Verongia thiona* marine sponges. (+)-trans-trans aerothionin (**32**) having spiroisoxazoline unit, with S-configuration at both spirocentres was shown to have modest cytotoxicity against the benchmark HeLa cell line, with an EC_{50} value of 42 mM. The acetone/methanol extract of the sponge *Aplysina gerardogreeni* yielded four dibromotyrosine-derived metabolites known as aplysinones (**33-36**) A-D. Aplysinones (**33**, **34** and **36**), were shown to have substantial growth inhibitory action against all three lines examined, with most GI_{50} values less than 5 mM. Furthermore, compounds (**33**) and (**34**) inhibited total growth of the three cell lines examined with TGI_{50} values less than 5 mM, whereas compound (**35**) inhibited total growth of MDA-MB-231 and HT-29 cell lines. Compound (**34**) primary growth inhibitory impact was discovered in MDA-MB-231 cells. Among these compounds, (**33**) was shown to be a highly effective growth inhibitor with considerable cell killing action, with LC_{50} values ranging from 3.0 to 4.1 mM against all three cell lines. Compound (**33**) had the most cytotoxic potential of all the compounds, which might be related to the presence of a carbonyl group at position 3 rather than a methoxy group as in the other derivatives (Figure 25).



(31) **(32)** **(33)**

(34) **(35)** **(36)**

Fig. 25. Structure of compounds Subereamolline A (**31**), (+)-Aerothionin (**32**) and 11-deoxyfistularin (**33**), 11,19-dideoxyfistularin-3 (**34**), ianthesine E (**35**) and bromotyrosine alkaloid (**36**).

Three bromotyrosine-derived alkaloids, aplysinamisines (**37-39**), have been isolated from a methanol/chloroform extract of the sponge *Aplysina cauliformis* (Figure 26). The compound (**38**) was also obtained from the Australian sponge *Suberea clavata's* dichloromethane/methanol extract. All of the separated products were evaluated against three human tumour cell lines, and compound (**39**) demonstrated cytotoxicity against all three cell lines, with IC_{50} values of 30, 6, and 10 µg/ml for MCF-7, CCRF-CEM, and HCT 116 cell lines, respectively. Aplysinamisines (**38**), on the other hand, showed specific cytotoxicity against the HCT 116 cell line, with an IC_{50} of 14.10 µg/ml. Compound (**37**) with the (2-amino-1H-imidazol-4-yl)allyl group was shown to be totally free of cytotoxicity [34].

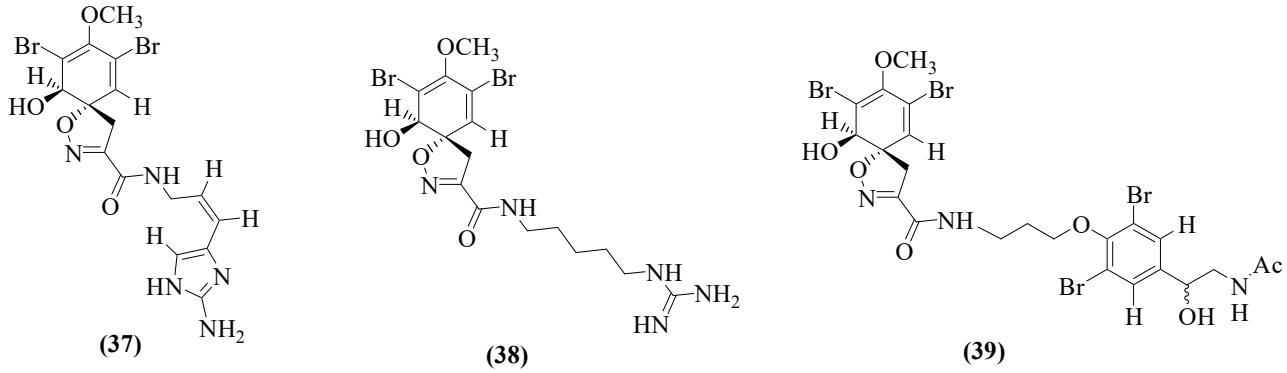


Fig. 26. Structure of Aplysinamisines (**37-39**).

Psammaplysins (**40-43**), are dibromotyrosine-derived metabolites belonging to the Druinella family, were identified from a methanol/chloroform extract of the sponge *Psammaplysilla Purpurea*. *In vitro* cytotoxicity of compounds (**40-42**) were discovered in the human colon tumour HCT 116 cell line, with IC_{50} values of 6, 3 and 3 µg/ml, respectively [35]. Compounds (**42**) and (**43**) have also been obtained from the Guam sponge *Suberea* sp. methanol/ethylacetate extract of *Psammaplysilla Purpurea*, using 95% ethanol extract (Figure 27). Psammaplysin (**43**), another metabolite, was similarly recovered with (**40**) from the methanol extract of the sponge *Pseudoceratina Purpurea*. Compound (**43**) was discovered to have considerable cytotoxic action against KB and LoVo cells at 5µg/ml. Compound (**43**) was also shown to have strong cytotoxicity against P-388 murine leukemia cells, with an IC_{50} value of 2.1 µg/ml. At the isoxazoline connected spirocente, as well as at other chiral centres, the psammaplysins (**40-42**) have an S-configuration. The binding of the 2,5-dioxocyclopent-3-en-1-methylidene moiety to the amide nitrogen of the amide chain might explain (**43**) high cytotoxic impact [36].

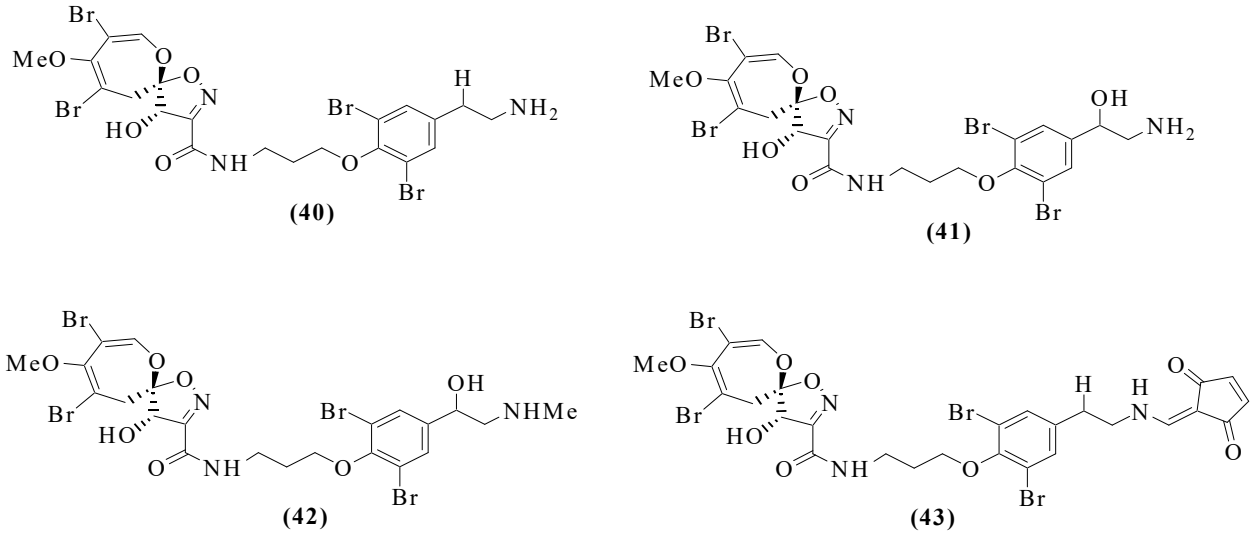
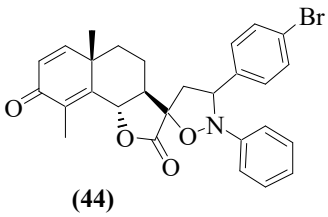


Fig. 27. Structure of Psammaplysin derivatives (40-43).

HCT-1, PC-3, THP-1, MCF-7, Hep-2, and A549 cells were used to evaluate new spiro derivatives of α-santonin for anticancer activity [37]. Reference chemicals included mitomycin, adriamycin, and 5-FU. Spiro-isoxazoline and spiro-isoxazolidine derivatives have been synthesized. Among all, compound (**44**) had shown IC_{50} of 0.01, 0.3 and 0.5 mM against PC-3, MCF-7 and THP-1 cell lines, respectively. Furthermore, flow cytometry analysis revealed that PC-3 cells

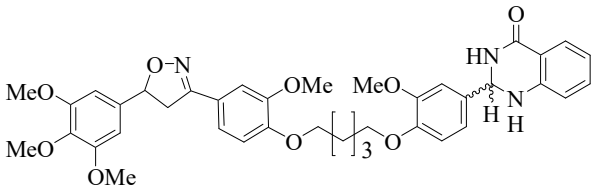
treated with the spiro-isoxazolidine derivative (44) were arrested in the sub G1 phase of the cell cycle in a concentration-dependent manner. The spiro-isoxazolidine derivative (44) demonstrated concentration-dependent inhibitory action against NF-kB and p65, with 57% inhibition in 24 hours at 10 mM (Figure 28).



(44)

Fig. 28. Spiro-isoxazoline derivative of α- santonin.

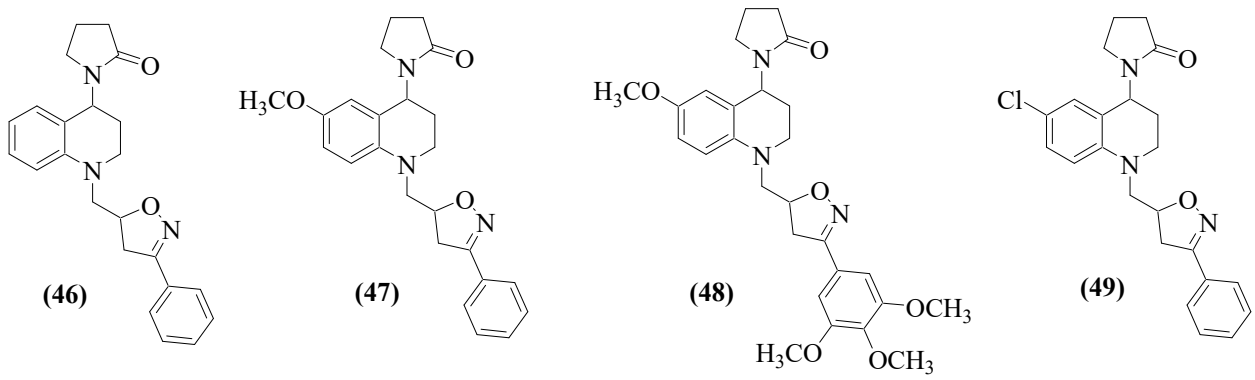
Kamal et al., reported the synthesis and biological assessment of 3,5-diaryl isoxazoline/isoxazole linked 2, 3-dihydroquinazolinone hybrids as anticancer agents [38]. Compound (**45**) showed log GI_{50} values of -7.07 and -6.95, log TGI values of -5.64 and -6.49, and log LC_{50} values of > -4.00 and -6.03 against RPMI-8226 (leukemia) and SKMEL-5 (melanoma) cell lines, respectively. Furthermore, compound (**45**) showed substantial action against 51 cells out of 56 cell lines examined, with log GI_{50} values ranging from -4.22 to -7.07. The compound's mean log GI_{50} value was -5.31 (Figure 29).



(45)

Fig. 29. Structure of compound (**45**).

A new series of tetrahydroquinoline-isoxazoline hybrid derivatives were efficiently synthesised from N-allyl-4-(2-oxopyrrolinidyl-1)-tetrahydroquinolines using a 1,3-dipolar cycloaddition reaction, a click chemistry approach [39]. Compounds (**46**) (CC_{50} = 11.37 M, SI = 5.1) and (**47**) (CC_{50} = 25.59 M, SI > 4.6) demonstrated the highest anticancer activity against murine melanoma cells with significant selectivity. On cervical cancer (HeLa) cells, compound (**48**) had the greatest anticancer activity (CC_{50} = 10.21 M, SI = 4.1), and it was also somewhat more active than the reference medication oxaliplatin. Furthermore, the compounds (**46**) and (**49**) reduce mitochondrial membrane potential and cause apoptosis, suggesting that their lethal actions are dependent on modifications of mitochondrial parameters (Figure 30).



(46) **(47)** **(48)** **(49)**

Fig. 30. Structure of compounds (**46-49**).

Liu et al., synthesized water-soluble 4S-5S/4R-5R-derivatives (**50, 51**) of heptaplatin, cis-{Pt(II)[(4S,5S)-4,5-bis(aminomethyl)-2-isopropyl-1,3- dioxolane]·(3-hydroxyl-cyclobutane-1,1-dicarboxylate)} and evaluated their anticancer activity in human gastric carcinoma NCI-N87 xenografts in nude mice and toxicity by comparing their interaction with DNA [40]. The author reported that whereas both isomers cause DNA condensation to the same extent and have equal cytotoxicity, they have differing anticancer activity and toxicity, most likely due to differences in their pharmacokinetic profiles. The 4S-5S isomer outperforms the 4R-5R optical isomer and the parent heptaplatin in terms of anticancer efficacy while being less hazardous.

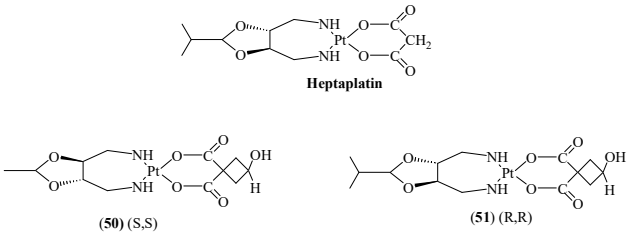


Fig. 31. Chemical structure of heptaplatin and two optical isomers (**50, 51**).

CONCLUSION

Several oxygen-containing three-, four-, and five-membered heterocyclic compounds are discussed in this article. Numerous synthetic oxygen-containing heterocyclic compounds with biological activity and SARs have been reported. These synthetic chemicals exhibit significant anticancer properties. Numerous researchers have employed various cancer cell lines to screen these produced chemicals.

ACKNOWLEDGEMENTS

None

CONFLICT OF INTEREST

NIL

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