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Naphthoquinones&Binaphthoquinones: Future Hope for Medicinal Chemist

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Abstract

Quinones mainly known for Antibacterial, Antimicrobial, Antifungal, Anticancer, Antileishmanial, anti-HIV. The Quinone moieties having special features and pharmacological activity. Some structural modifications make changes in their chemical characters and biological activity. In this paper we thrown light on the naphthoquinones and Binaphthoquinoe and their anti-therapeutic activity

Introduction

Naphtho-1,4-quinones are widely available in nature, mainly in plants, fungi and bacteria. These classes of compounds have various properties and applications, these properties and applications have been extensively reviewed [1,2-3],they can be isolated as yellow, orange, red, or purple solids, and are sparingly soluble in water but readily soluble in most organic solvents.

Naphthoquinones as Privileged Molecules

Naphthoquinones are considered privileged structures in medicinal chemistry due to their biological activities and structural properties. They are present in various families of plants and serve as vital links in the electron transport chains in the metabolic pathway, participating in multiple biological oxidative processes. The fundamental feature of quinone chemistry is its ease of reduction and, therefore, its ability to act as an oxidizing or dehydrogenating agent. This redox property is driven by the formation of a fully aromatic system. In folk medicine, plants containing naphthoquinones are often employed for the treatment of various diseases, and

several quinonoids isolated from traditional medicinal plants are being investigated for their anticancer properties.

The redox cycling of quinones may be initiated by either a one- or two-electron reduction. The one electron reduction of quinones is catalyzed by NADPH-cytochrome P450 reductase, and yields unstable semiquinones. Quinones transfer electrons to molecular oxygen (O_2), and return to their original quinoidal formation, thus generating a superoxide anion radical ($.O_2^-$). Superoxide can be converted to hydrogen peroxide (H_2O_2) via a superoxide dismutase (SOD)-catalysed reaction, followed by the formation of a hydroxyl radical (.HO) by the iron-catalysed reduction of peroxide via the Fenton reaction. All of these highly reactive species may react directly with DNA or other cellular macromolecules, such as lipids and proteins, leading to cell damage.

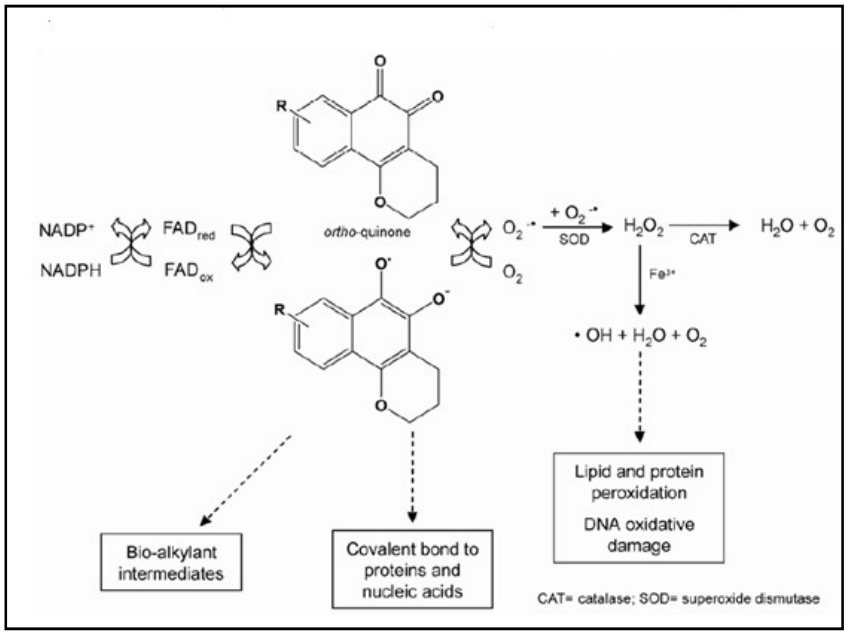


Figure 1. Representation of the redox cycle and metabolites by quinones

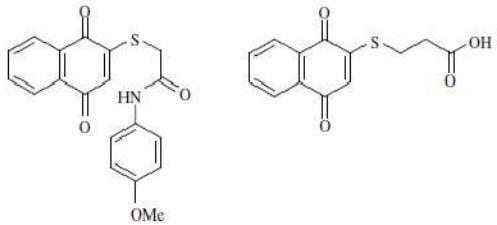
Owing to their molecular structure and their redox properties, they exhibit interesting physical properties, as well as a wide range of biological activities. Extracts from plants containing mixtures of naphtha-1,4-quinone derivatives have been used for centuries not only as dyes or ingredients for cosmetics but also in traditional medicine for the treatment of a great number of diseases [2].Nowadays, a number of naphtha-1,4-quonone, such as phylloquinone (regulation of blood coagulation, bone metabolism and vascular biology), lawsone (natural dye), naphthazarin

(natural dye), atovaquone (antineumococcal) [3] are used as drugs or ointments although the exact mode of action of these compounds has not been completely elucidated, the biological activity is probablydue to their redox properties.

Anti fungal, antimicrobial and anti-bacterial quinones

2-arylamino-3-chloro-1, 4-naphthoquinone derivatives have been prepared and studied for their antifungal and antibacterial activities, chloro, methoxyphenyl and amino derivatives compounds were showing potent antifungal and antibacterial activities [4]. Chloro derivative showed better anti-fungal properties than clinically prevalent anti-fungal drug Fluconazole (MIC50-2.0 g/mL) against *Sporothrixschenckii* (MIC50-1.56 g/mL) potent profile against *Candida albicans* (MIC50-1.56g/mL), *Cryptococcus neoformans* (MIC50-0.78g/mL) and same anti-fungal activity when compared to Amphotericin-B against *C. neoformans* (MIC50-0.78g/mL). Lapacol and its derivatives have two fold greater activities on *Staphylococcus aureus*[5]. In 2-aryl amino naphthalene derivatives at position three showed more potent activity compared to position two. Different compounds have been synthesized for antifungal and antiviral. All the compounds having thiol group showed potent activities. Alpha-amino acid ester, hetero alkyl and aryl substituted 1, 4-naphthoquinone derivatives having antifungal and antibacterial activities whereas amino ester and hetero have potent effect among all for anti-fungal [6]. Naphtho[2,3]isoxazole-4,9-dione have evaluated against ATCC and PYCC strains of candida[7]. This system contains electron withdrawing group at position three.

Sulphur and nitrogen containing napthoquinone also have potent activity against fungal and bacterial stain. C-2 substituted and C-2, C-3 disubstituted derivatives have synthesized with their reaction with amines, thiols and halogen acids and their use for the study of bacterial growth inhibition has also been demonstrated [4]. 2-substituted -3 mercapto-1, 4-naphthoquinones have been evaluated for anti-microbial activities [8]. Morpholino and piperydyno derivatives showed greater antibacterial activity than well knownoxacillin.



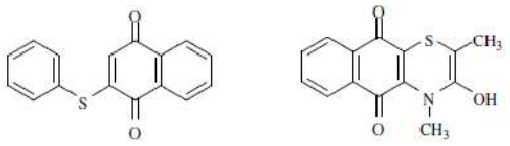


Figure 2. Structures of different sulphur and nirtogen contaning naphthoquinones.

Naphthoquinone and inflammation

Lapachol, a natural organic compound isolated from the lapachol tree (*Tabebuiaavellandedae*) identified as naphthoquinone group and known for its anti-inflammatory, analgesic and antibiotic properties [9]. It is also an anti-tumor agent. *Cipurapaludosa* (Iridaceae) is a plant that forms lapachol and is distributed in the north region of Brazil. Its bulbs are used in folk medicine to treat inflammation and pain. It is having four naphthalene derivatives which have been isolated from the bulbs of the plant. Three of them were identified as naphthalene derivatives,eleutherine, Iso-eleutherine and hongkonin. The structure of the fourth was new and elucidated as 11-hydroxyeleutherine [10] by NMR. In-vivo effect of two major compounds eleutherine and iso-eleutherine, was evaluated in carrageenan-induced hypernociception and inflammation in mice. Eleutherine and iso-eleutherine (1.04-34.92 mol/kg), dosed i.p. (i.p.) or orally (p.o.), decreased the carrageenan-induced paw edema (i.p. - inhibitions of 36 ±7 % and 58 ±14 %, resp.; p.o. - inhibitions of 36 ±7 %and 58 ±14 %, resp.).Iso-eleutherine, but not eleutherine, significantly reduced(inhibitions of 39 ±4 %) the plasma extravasation induced by intradermal (i.d.) injection of carrageenan. Likewise, eleutherine and iso-eleutherine (1.04- 34.92 mol/kg,i.p. or p.o.) were also effective in preventing the carrageenan-induced hypernociceptive response (i.p. - inhibition of 59 ±4 % and 63 ±1 %, resp.; p.o. - inhibitions of 36 ±7 % and 58 ±14 %, resp.). It was also suggested that the anti-inflammatory and anti-hypernociceptive effects of eleutherine or iso-eleutherine partly depend on the interference with the synthesis or activity of mast cell products, kinins, cytokine, chemokines, prostanoids, or sympathetic amines. Two major compounds of *C. paludosa* contain pharmacologically active constituents that possess antinociceptive and anti-inflammatory activity, justifying, at least in part, its popular therapeutic use for treating conditions associated with pain. Vitamin K3, which consists of a quinone component, inhibits the activity of human DNA polymerase [11]. In this study, the inhibitory effects of 1,4-

quinone derivatives, (1,4-benzoquinone (BQ), 1,4-naphthoquinone (NQ), 9,10-anthraquinone (AQ) and 5, 12-naphthacenequinone (NCQ) on the activity of mammalian polymerase has been shown. BQ and NQ potently inhibited the activity of all the polymerase species. NQ was a stronger polymerase inhibitor than BQ. These quinone derivatives could inhibit inflammatory12-o-tetradecanoylphorbol-13acetate (tpa) induced acute responses. BQ and NQ caused a marked reduction in ion in mouse ear. These anti-inflammatory responses of NQwere more potent than those of BQ. In conclusion, this study has identified several quinone derivatives, such as NQ, that are promising anti-inflammatory candidates [12]. A series of 2-substituted 3-chloro-1,4-naphthoquinones were synthesized, and the antiplatelet, antiinflammatory, and antiallergic activities of these compounds were evaluated [13]. The structure-activity relationships in this series were also examined. The title compounds, I [R1, R2 = H, OH; R3 = acyl, etc.; R4 = H, etc.; or NR3R4 = Q1, etc.; r, t = 1 - 3; Y = CH, N, etc.; R10 = alkoxyphenyl, etc.; X = halo] are prepared. The title compd. II (m. p. 214 - 215°) in vitro showed IC_{50} - 0.22 μM against neutrophil expression of CD11b. Naphthoquinone showed potent activities with similar trends in each of the activities evaluated

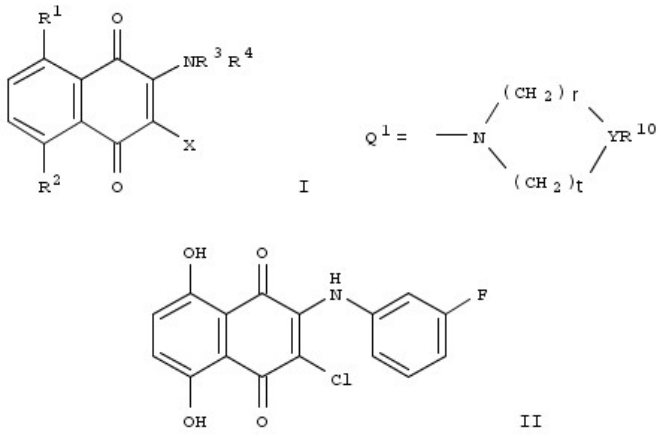


Figure 3.Structures of 2-substitued -3-chloro naphthoquinones.

Novel naphthoquinone and naphthothiazole compounds. I (wherein X and Y are independently halo, (un) substituted aryloxy, (un)substituted aryl, etc.), and methods of treating disorders related to methionine aminopeptidases [14]. The disease or disorder associated with methionine aminopeptidase is selected from: tuberculosis, bacterial infection,

tumor or cancer growth (neoplasia), skin disorders, neovascularization, inflammatory and arthritic diseases, retinoblastoma, cystoid macular edema (CME), exudative age-related macular degeneration (AMD), diabetic retinopathy, diabetic macular edema, or ocular inflammatory disorders.Synthetic procedures for preparation I and related compounds are exemplified. Compound II was prepared by reacting 4-fluorophenol and 2,3-dibromonaphthoquinone.

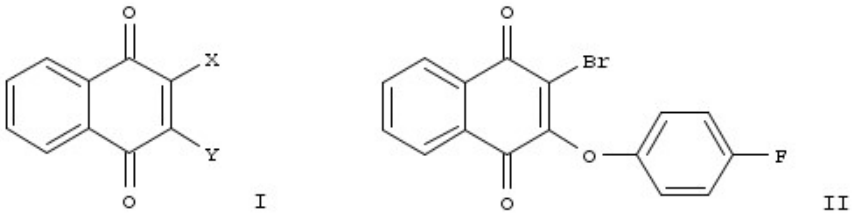


Figure 4.Structure of novel naphthoquinone derivatives.

Three naphthoquinone derivatives, rhinacanthin-C (1), -D (2) and -N (3) were isolated from the leaves of *Rhinacanthusnasutus* extract and were tested for anti-inflammatory activity [15].The result indicated that all three compounds possessed very potent anti-inflammatory activity against lipopolysaccharide (LPS)-induced nitric oxide release with IC_{50} values of 1.8, 6.2 and 3.0 μM, resp.In addn., the effects of rhinacanthin-C, -D and -N on LPS induced release of prostaglandin E2 (PGE2) and tumor necrosis factor (TNF-) were also examined.It was found that rhinacanthin-C exhibited the most potent on PGE2 release with an IC_{50} value of 10.4M, followed by rhinacanthin-D (IC_{50} = 14.4M) and rhinacanthin-N (IC_{50}= 52.1 M).Aethiopinone (I), an o-naphthoquinonediterpene from *Salvia aethiopis* L. roots and two hemisynthetic derivatives (II) and (III) were evaluated for toxicity, anti-inflammatory, analgesic, antipyretic, and hemostatic activities [16]. The compounds tested showed low toxicity and pharmacology profile similar to other NSAIDs on reducing the edema induced by carrageenan and contractions induced by phenyl-p-quinone. On the TPA-induced ear inflammation model, the three compounds showed a moderate reduction of edema.

Compound I and II showed significant inhibition. Compound I produced a significant increase in the reaction time against thermal painful stimuli in the tail immersion test. The results demonstrated strong anti-inflammatory, peripheral and central analgesic properties

for I, as well as antiedema topical action and peripheral analgesic properties for II and III.

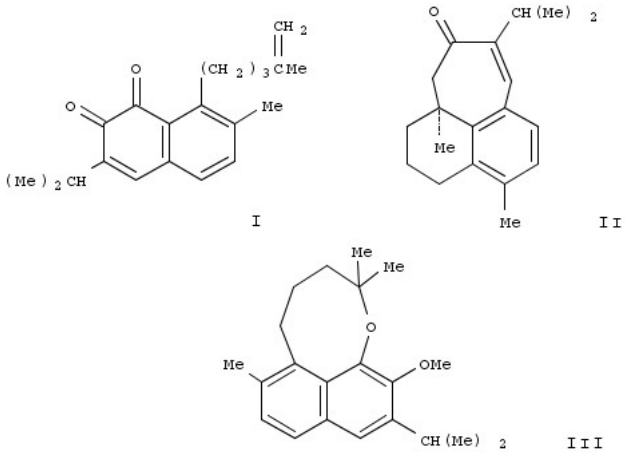
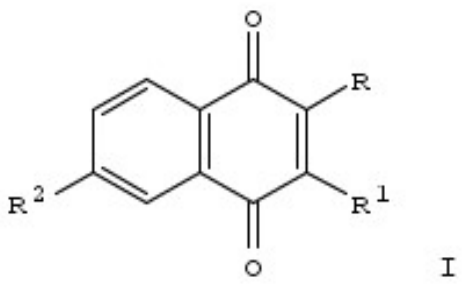


Figure 5.Structure of Aethiopinone (I), an o-naphthoquinonediterpene from *Salvia aethiopis* L. roots and two hemisynthetic derivatives (II) and (III).

Phylloquinone (K1), menaquinone-4 (K2), menadione (K3), 2,3-dimethoxy-1,4-naphthoquinone (DMK) and a synthetic product of vitamin K catabolism, 2-Me-3-(2'-methyl)-hexanoicacid-1,4-naphthoquinone(KCAT). All compounds are inhibiting IL-6 production responsible for inflammation with a rank order of potency: KCAT>K3>DMK>K2>K1.The most potent compound KCAT inhibited IL-6 production with an IC_{50} of 3×10^{-7}µM.The mechanism of action of these naphthoquinones on fibroblast IL-6 production however remains unknown. It was concluded by research that this activity is not essential for the inhibition of IL-6 production and that activity may be related to the redox capacity of these naphthoquinones. The naphthoquinones I [R = alkylamino, AcNH, EtCONH; R1 = H, $MeOCH_2CH_2$, EtO, etc.; R2 = H, H_2NSO_2) are prepared as anti-inflammatory agents [73].Thus, I (R = $NHCH_2CH{:}CH_2$, R1 = H, R2 = SO_2NH_2) (II) was prepd. from 1,4-dioxo-1,4-dihydronaphthalene-6-sulfonic acid by conversion into the sulfamide and reaction with $CH_2{:}CHCH_2NH_2$ in the presence of air.Oral administration of II at 2.5 mg/kg inhibited by 39% the carrageenan-induced edema in rats.



I

Figure 6. Structure of naphthoquinones I [where R = alkylamino, AcNH, EtCONH; R1 = H, $MeOCH_2CH_2$, EtO, etc.; R2 = H, H_2NSO_2]

Anti-leishmanialnaphthoquinones

Naphthoquinones are also having anti-leishmanial activity. A series of naphthoquinones was tested for activity against both extracellular promastigotes and intracellular amastigotesLeishmania major GFP in vitro [17]. In parallel, the compounds were evaluated for cytotoxic effects against bone marrow-derived macrophages as a mammalian host cell control. Most of the compounds inhibited the growth of extracellular parasites (IC_{50} 0.5 to 6 µM) and the intracellular survival of L. major GFP amastigotes (IC_{50} 1 to 7µM), when compared with the antileishmanial drug amphotericin B (IC_{50} of 2.5 and 0.2 µM, resp.). Introduction of a methyl or methoxy group at C-2 of the parent 1,4-naphthoquinone slightly increased the antileishmanial activity against clinical relevant amastigotes, while the presence of a hydroxyl function in this position dramatically reduced the effectiveness. In contrast, hydroxylation at C-5 and dihydroxy substitution at C-5 and C-8 significantly enhanced the antiprotozoal activity. Within the series of naphthoquinones tested, the dimeric mixture of vaforhizin and isovaforhizin showed the highest activity in vitro against the clinicaly relevant intracellular amastigote with an IC_{50} of 1.1 µM. With IC_{50} values mostly in the range of 1-3 µM, the shikonin/alkannin derivatives proved to be similarly considerably leishmanicidal. The mode of action apparently depended on the substitution pattern, associated with the electrophilicity of the naphthoquinone or the efficiency of redox cycling. Pterocarpanquinones and homologous series of derivatives compounds were evaluated on breast cancer cell line and parasites *Leishmaniaamazonesis* and *Plasmodium falciparum* [18]. 2-phenoxy-1,4-naphthoquinone and 2-phenoxy-1,4-anthraquinone derivatives have inhibitory activity towards Trypanosoma or leishmania species. Where three of them were

active against *Leishmaniadonovani*, *Trypanosome cruzi*, *Trypanosomabruceirhodesisence* (IC_{50} = 50 nM, IC_{50} = 0.28 µM, and IC50 = 1.26 µM). The efficacy of different formulations of the naphthoquinonebuparvaquone and two phosphate prodrugs against vivo models of both visceral and cutaneous leishmaniasis is described. Buparvaquone-3-phosphate was shown to be the most effective antileishmanial (P = 0.0003, 50 mg buparvaquone molar equivalent/kg/day five times), reducing the liver parasite burden by ~34% when compared with the untreated control. The introduction of a topical formulation, such as buparvaquone (or its prodrug), would be a significant advance for the treatment of simple cutaneous lesions. Lapachol exhibited an anti-amastigote effect. Monomeric and dimericnaphthoquinones were found active in vitro for treatment of Leishmania infections using a direct cytotoxicity assay against promastigotes of Leishmaniadonovani, L. infantum, L. enriettii and L. major.Somenaphthoquinones was active at in microgram range (EC_{50} 0.9-17.0 µg/mL) [19].

The stem barks of *P. benensis* are employed by the Chimane Indians in the Bolivian Amazonia as treatment of cutaneous leishmaniasis caused by the protozoan *Leishmaniabraziliensis*[20]. The chloroform extracts containing quinones were found to be active against the promastigote forms of leishmaniadonovani and the epimastigote forms of *Trypanosomacruzi* at 10 µg mL-1. The activity guided fractionation of the extract by chromatography afforded active compounds. Their structures were elucidated, by spectral and chemical studies, as known naphthoquinones, plumbagin, 3, 3'-biplumbagin, 8, 8'-biplumbagin, and triterpene, lupeol. The activity in vitro of each compound was evaluated against 5 strains of Leishmania (promastigote), 6 strains of *T. cruzi* (epimastigote) and the intracellular form (amastigote) of *Leishmaniaamazonensis*. The baseline drugs used were Glucantime and pentamidine (Leishmania spp.), nifurtimox and benznidazole (*T. cruzi*). Plumbagin was the most active compound in vitro. This study has demonstrated that *Perabenensis*, a medicinal plant used in folk medicine is an efficient treatment of cutaneous leishmaniasis.

Anti-cancer and tumor quinones

The mannich reaction involving lawsone and certain amines with formaldehyde and acetaldehyde and the condensation product of lawsone with 4-bis(2-chloroethyl) aminobenzaldehyde has been described [21]. Two isomers of naphthoquinones derivatives 6-(1-azidoalkyl)-DMNQ and 2-(1-azidoalkyl-DMNQ exhibited higher cytotoxic activity against

L1210 mouse leukemia cells and stronger inhibition of DNA topoisomerase-I [22]. These molecules contain N- substituted- pyridino [2,3-f] indole-4,9-dione and 6-(α-diethoxy carbonyl methyl)7-substituted amino quinoline 5,8-dione, which contain the active quinoline 5,8-dione moiety. This moiety have been tested against SRB (sulphorodamine B) assay against the cancer cell lines of A-549 (human lung cancer), SK-MEL-2 (human melanoma cancer), SK-OV3 (human ovarian cancer), XF-498 (human brain cancer) and HCT (human colon cancer). This moiety showed higher activity than cis-platin. Rhinacanthone and 1,2-pyranonaphthoquinones were synthesized and showed very potent cyto-toxicity against three cancer cell lines (KB, HeLa and HepG2) with IC_{50} values of 0.92-9.63μM [23].

CDC25 dual-specificity phosphatases are essential key regulators of eukaroytic cell cycle progression and the CDC25A and B isoforms are over-expressed in different tumors. Polyfluoro derivatives of 1,4-naphthoquinones are highly potent inhibitors of Cdc25A and Cdc25B phosphatases and growth of tumor cells and their cytotoxicty in human myeloma, human mammary adenocarcinoma, mouse fibroblasts and primary mouse fibroblast cells as well as their mutagenic and antioxidant properties in a Salmonella tester strain were studied [24]. The β-lapachone based 1,2,3-triazoles showed the best cytotoxicity profile and emerge as promising anti-cancer prototypes.

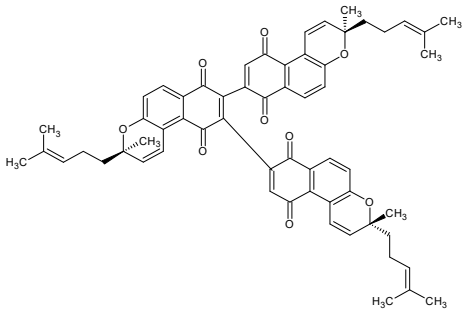
The antitubercular activity and cytotoxocity of juglone derivatives were analyzed with the topological and molecular surface features from a web based server, MODEL(Molecular Descriptor Lab). Novel compounds derived from vitamin K_3 that inhibit CDC25B activity with IC_{50} values in the low micromolar range.Polyamine naphthoquinone conjugates by neuclophilic displacement of 2-methoxy lawsone, 2-methoxy lapachol, 2-methoxynorlapachol with the polyamine N1- Boc- N5- Bn- spermidine 4. 2-methyl-1,4-naphthoquinone derivatives especially vitamin K_3 .Retardation of cytotoxicty and cell proliferation by 2-amino alkyl moiety with terminal bromo, chloro, hydroxyl, mercapto groups were examined on model murine hepatoma cell line-22A. Most active compound were hydroxyl and bromo derivatives [25].

A series of 2-chloro-3-arylsulfanyl-[1, 4] naphthoquinones 2,3-bis-arylsulfanyl-[1,4] naphthoquinones and 12H-benzo [b] phenothiazine- 6,11- diones and their analogs were evaluated for their antiproliferative activity against human cervical cancer (HeLa) cells [26].

Two Compounds were found to possess most potent antiproliferative and cell killing ability. 1, 5-Diazaanthraquinone derivatives were synthesized employing single and double hetero Diels–Alder strategies. Their in-vitro antitumor activity was assayed using three cell lines. Some of these compounds, especially those bearing methyl or ethyl groups at the C-3,7 positions or chloro at C-4 and methyl at C-7, showed IC_{50} values in the 10^{-8} µM range for human lung carcinoma and human melanoma, which makes them attractive candidates for further development as anticancer agents. In order to find a 3,4-dihydro-α-naphtho [1, 2-b] pyran-5, 6-dione more potent than the naturally occurring 2, 2-dimethylderivative [P-lapachone] of the pyran ring orat positions 8 and 9 of the benzene ring.

Bis-naphthoquinones

Bis-naphthoquinones and higher quinone oligomers are a unique group of natural products, which possess a diverse array of biological activities [27]. Their structures are based on two or more quinone units linked together at the quinine double bond. In almost all cases they possess an element of symmetry due to their biosynthetic mechanism of origin, which probably involves oxidative coupling of a common naphthol intermediate in the key step of the oligomerization process [28].One intriguing member of this class is conocurvone isolated from the Western Australian smoke bush [29]. Conocurvone was shown to inhibit the cytopathogenic effects of HIV-1 in human T-lymphoblastic cells over a broad concentration range (ID_{50}=0.02 µM; TD_{50}= 50 µM) [29]. More recently, it was suggested that conocurvone 1 may be a dual inhibitor of both HIV integrase and HIV mediated cell fusion [30]

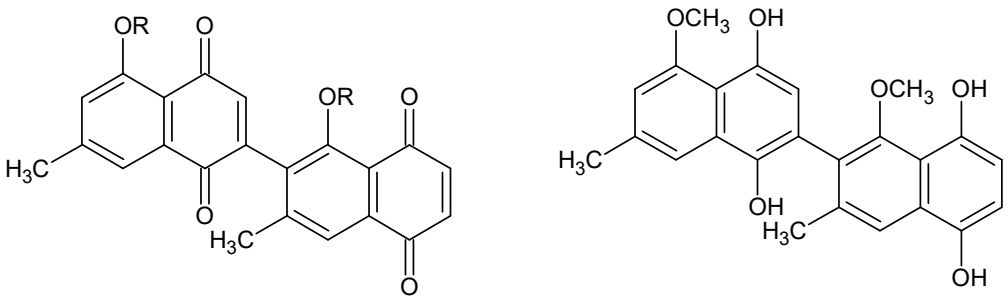


(11)

Figure 7. Structure of Conocurvone

Over the past decade, extensive efforts have been made resulting in the discovery of a large number of molecules that can inhibit replication of HIV [31].An essential step in the HIV life cycle is integration of the viral DNA into the host cell genome. The step is catalyzed by the viral enzyme, HIV integrase, which is absolutely required for productive infection and therefore, inhibition of integrase can half the viral life cycle. Integrasecatalyses two separate steps known as 3'-prossessing and DNA strand transfer. In 3'-prossessing, integrase removes a dinuclotide next to a conserved cytosine-adenine sequence from each 3'-end of the viral DNA. Integrase then attaches the processed 3'-end of the viral DNA to the host cell DNA in the strand transfer reaction. An important result of the structural and biochemical studies on integrace has been the development of practical assays used to identify novel HIV integraseinhibitors. These HIV inhibitors not only represent potential chemotherapeutic lead compounds [32], but as a collection, they are also useful in databases for pharmacophore searching. The most promising inhibitors are proposed to bind to the active site of the integrase enzyme and chelate important metal cofactors such as Mn^{2+} or Mg^{2+}.

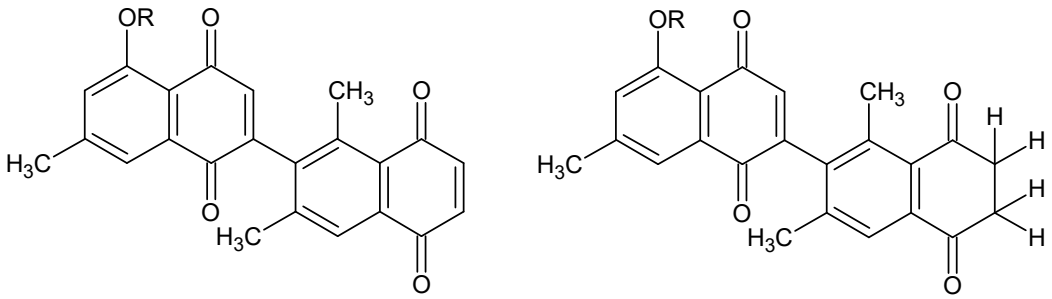
M.Pardhasaradhi and G.S.Sidhu establish the structure of diospyrin, a bisnaphthoquinone with a benzene-quinone linkage [33] .Bisnaphthoquinone may arise either by the oxidation of a bis-naphthol formed by the radical coupling of two naphthol units or by the condensation of a naphthoquinone unit with a naphthol (or quinol) unit and subsequent oxidationDiospyrin, a bis-naphthoquinonoid natural product, and three synthetic derivatives have been tested for their action in four human cancer cells lines: acute myeloblastic leukemia (HL-60), chronic myelogenic leukemia (K-562), breast adenocarcinoma (MCF-7) and cervical epithelial carcinoma (HeLa). Diospyrin was found to show significant tumor inhibitory effect against Ehrilch ascites carcinoma in vivo. Subsequently, synthesis of some derivatives of diospyrin led to the isolation of more potent inhibitors against murine tumors. Cells grown in appropriate media several derivatives elicited cytotoxicity as assessed by Typan Blue dye exclusion, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide reduction and DNA synthesis. Diethyl ether derivative was most effective in this regard while the parent diospyrin was least active.



Diospyrin : R = H Hydroquinonoid derivative
Diospyrin dimethyl ether : R = CH3
Diospyrin diethyl ether : R = C2H5

Figure 8. Structures of Diospyrin and its derivatives

Methyl and ethyl ethers of this compound were prepared by alkylation- the dark red residue with the alkyl iodide and silver oxide in chloroform and separating the ether from the corresponding diospyrin ether by TLC on deactivated silica gel plates with chloroform: methyl ether crystallized from methylene chloride/petroleum ether in brown red hexagonal crystals M.p. 78°C. A comparison of the PMR spectra of this dihydro-diospyrin and its methyl and ethyl ethers with those of diospyrin and its dimethyl and diethyl ethers shows it to have structure II (R=H).



Diospyrin. R=H β' – Dihydroxydiospyrin. R=H

Figure 9. Structures of Diospyrin and β'-Dihydroxydiospyrin

One of these derivatives, (-)-isodiospyrin bearing an unsymmetrical 1, 2'-binaphthoquinonoid chromophore was isolated from the roots of diospyros and Euclea species. 2, 2'-bisnaphthalene derivative and its monomer, 7-methyl-juglone were revealed to have potent anti-tumor activity against human KB epidermic carcinoma, A-549 lung carcinoma, HCT-8 and co-115 colon

carcinoma cells in vitro. Isodiospyrin is also a dual DNA topoisomerase I & II α inhibitor. The inhibition of the catalytic activity of human topoisomerase I by isodiospyrin is 10-fold more potent as compared to camptothecin, a potent anti neoplastic natural product and topoisomerase I inhibitor.

The isomer, diospyrin, was also cytotoxic to several human tumor cell lines in culture. Ray et al. reported that diospyrin significantly inhibited the growth of *Leishmaniadonovani*promastigotes. This agent also inhibited the catalytic activity of DNA topoisomerase I of the parasite and induced DNA Topoisomerase I-mediated cleavage in vitro, suggesting that the bi-naphthoquinonoids derivatives exert their inhibitory effect binding to the enzyme and stabilizing the Topoisomerase-I-DNA cleavable complex. However, diospyrin did not inhibit topoisomerase-II of *L.donovani* and required much concentrations to inhibit calf-thymus topoisomerase-I. Based on the biological properties of isodiospyrin and diospyrin, they can be exploited for rational drug design to develop new anticancer agents or drugs human leishmaniasis. Neo-diospyrin is a structural analogue of diospyrin and isodiospyrin having potent inhibition against mycobacterium tuberculosis as well.

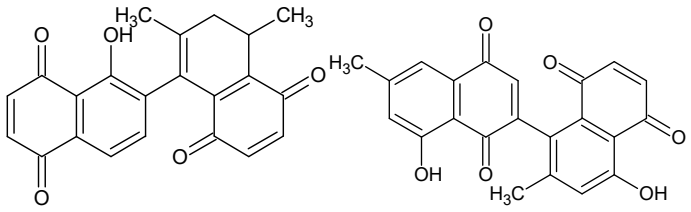
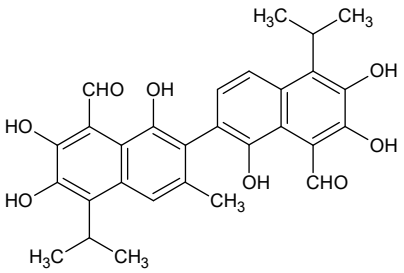
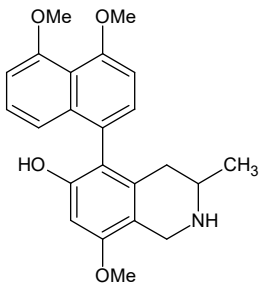


Figure 10. Structures of Isodiospyrin and Neodiospyrin

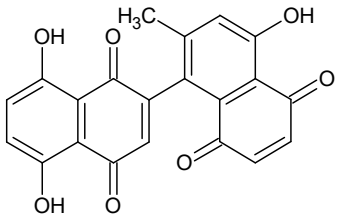
Gossypol (18), was isolated from Gossypium species [33] and has been studied as a male antifertility agent in china. The two representative naphthyl –isoquinoline alkaloids, ancistrocladine were found in lianas of the genera Ancistrocladus and Triphylophyllumpeltatum, respectively. The latter has been found to have fungicidal, insect growth retarding and anti-feedant activity, and in particular activity against malaria parasites.



Gossypol



Ancistrocladine



8'-Hydroxy isodiospyrin

Figure 11. Structure of Naphthoquinone and Bis-naphthoquinone

Conclusion

Naphthoquinones and Bis-naphthoquinones plays imp role for medicinal chemist.both are having different types of biological activity.Here we described different types of synthetic as well as natural naphthoquinones & Bis-naphthoquinone.

Conflict of Interest

The author shows no conflict of interest.

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