Antitumour Quinones

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Abstract: Quinones still comprise one of the largest classes of antitumour agents. For example, the anthracycline antibiotics are among the most utilised anticancer agents ever developed. Many other quinones were tested for their anticancer activity. Though there are general and well-established mechanisms for quinone toxicity, the exact contribution of the quinone moiety to the cytotoxic effect remains frequently uncertain. However, DNA represents the main target for quinoid antitumour agents and most of them belong to the groups of DNA intercalating and/ or alkylating agents. But also other cellular structures such as heat shock protein 90 or telomerase have been identified as targets for quinoid compounds.

Keywords: Quinone, anticancer, anthracycline, aziridinylindolequinone, ansamycin, triptycene, rubromycin, anthracenedione.

1. INTRODUCTION

Quinones are an important class of naturally occurring and synthetic compounds with a great variety of functions. Their fundamental role in the biochemistry of living cells is well established. For example coenzyme Q (**1**) functions as an electron carrier in the respiratory chain. Vitamin K (**2**), a naphthoquinone derivative, is required for blood coagulation and participates in the carboxylation of glutamate to γ-carboxyglutamate. Moreover, many quinones for example, the naphthoquinones juglone (**3**) from Juglans nigra and plumbagin (**4**) from Plumbago rosea, exhibit growth inhibitory effects on bacteria or fungi and are used by plants as defensive compounds.

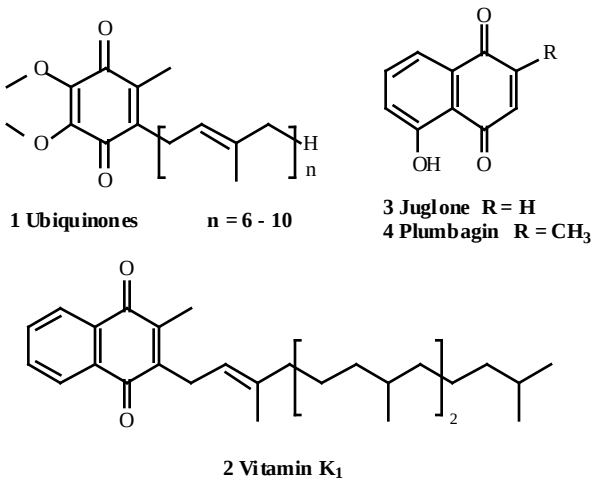
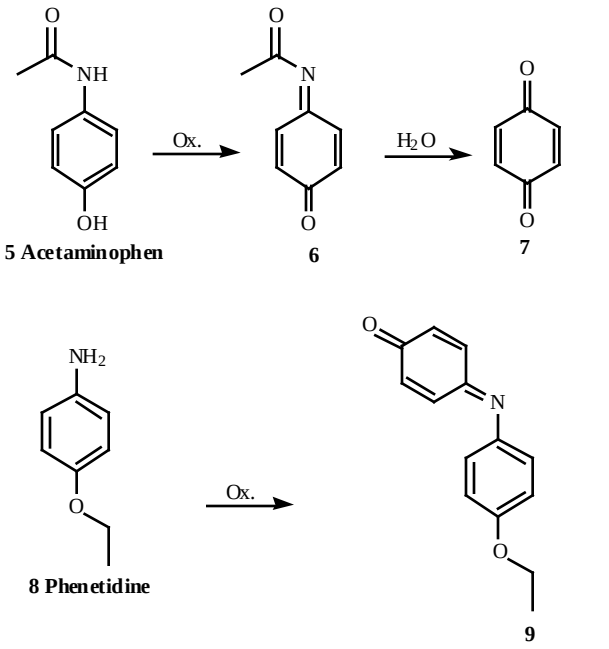


Fig. (1). Natural Quinones.

Apart from these physiological functions of quinones, a number of xenobiotics form toxic quinones by oxidative metabolism. The analgetic acetaminophen (**5**) can cause severe hepatotoxicity in overdose, which is attributed to both a benzoquinoneimine metabolite (**6**) produced by a cytochrome P 450 dependent oxidase reaction and simple p-benzoquinone (**7**) resulting from hydrolysis of (**6**) [1].

Phenetidine (**8**), another analgetic structurally related to acetaminophen (**5**), was even withdrawn due to its strong side effects, nephropathy and pelvic cancer, occurring after long-term treatment. A quinoneimine dimer (**9**) was found to be the toxic metabolite (Scheme 1) [2].



Scheme 1. Toxic quinones of acetaminophen (**5**) and phenetidine (**8**) formed by oxidative metabolism.

Nonetheless, not at last because of this cytotoxic potential quinones today make up an important group of antineoplastic drugs. More than thousand quinoid compounds were tested for anticancer activity and the quinoid anthracycline antibiotics are among the most utilised anticancer drugs ever developed. But though there are general mechanisms for quinone toxicity, such as quinone redox cycling and conjugation reactions with bionucleophiles, the exact contribution of the quinone substructure to their antitumour effect remains often uncertain. The quinones used for anticancer therapy have various chemical structures bearing a number of other functional groups which may possibly be responsible for the cytotoxic activity. This review will focus on the molecular

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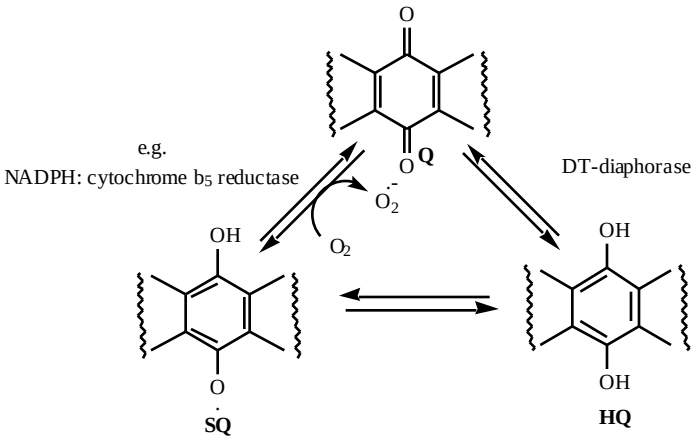


Scheme 2. Quinone redox cycling.

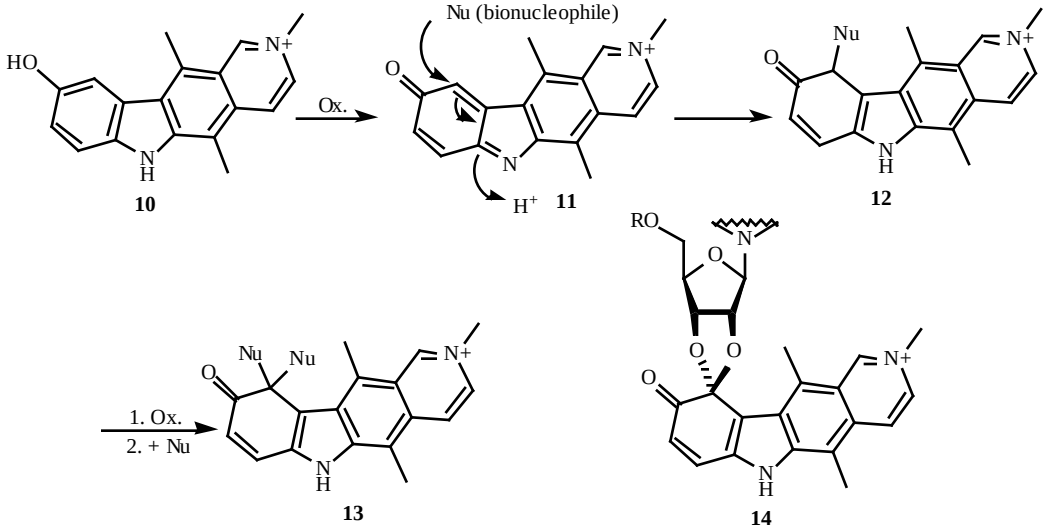
mechanisms of quinone toxicity in cells with a particular view on the quinoid anticancer drugs and their mode of action.

2. GENERAL MECHANISMS OF QUINONE TOXICITY

2.1. Quinone Redox Cycling

The cytotoxic activity of quinones can often be correlated to their chemical behaviour. The striking feature of quinone chemistry is the ease of reduction and therefore their ability to act as oxidising or dehydrogenating agents, the driving force being the formation of a fully aromatic system. They can accept one electron, forming the semiquinone radical, followed by a further electron to give the hydroquinone. It is the reversible reduction process which accounts for the biological activity of quinones: in biological systems quinones can undergo biochemical reductions either by one or two electrons which are catalysed by flavoenzymes using NADPH as electron source. One-electron reducing enzymes are for instance NADPH: cytochrome P 450 reductase, NADPH: cytochrome b_5 reductase and NADPH: ubiquinone oxidoreductase (Scheme 2). The most important two-electron reducing enzyme seems to be the NAD(P)H: quinone oxidoreductase also called DT-diaphorase. The bioreduction of a quinone (Q) leads to the formation of the corresponding semiquinone radical (SQ) or the hydroquinone (HQ). Under aerobic conditions the semiquinone radical can be oxidised to the original quinone by molecular oxygen. This process, the reduction by a reductase followed by autoxidation, yields superoxide anion radicals ($O_2^{\cdot -}$) and is known as “quinone redox cycling". It is oxygen-dependent and continues until the system becomes anaerobic. Hydroquinones resulting from two-electron reductions often have a lower tendency to transfer electrons and can be excreted by the organism after metabolic conjugation reactions with sulfate or glucuronic acid. In general, two-electron reduction leads to detoxification.

This assumption is supported by the fact that blocking of two-electron reduction by a potent inhibitor of DT-diaphorase (e.g. dicoumarol) increases the toxicity of several quinones on hepatocytes. However, in some cases the two-electron reduction of a quinone produces reactive redox-cycling hydroquinone. For some antineoplastic quinones the hydroquinone even represents the biological active form, for example the bioreductive alkylating agent mitomycin C requires DT-diaphorase mediated reduction to develop antitumour activity.

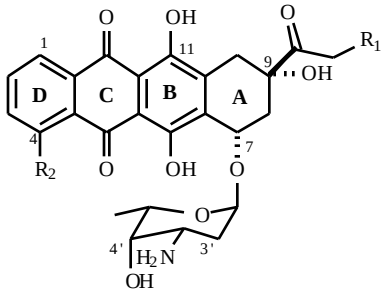


Scheme 3. Alkylating properties of ellipticines after bioactivation.

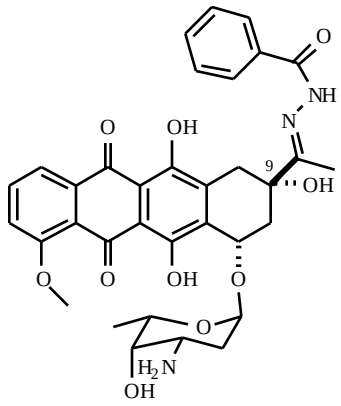
Superoxide radical anions are unstable in aqueous solution and spontaneously dismutase to hydrogen peroxide (H_2O_2) and molecular oxygen. Hydrogen peroxide is particularly harmful because of its reaction with iron (Fenton reaction), which generates extremely toxic hydroxyl radicals ($HO^{\cdot}$). Most of the cytotoxic effects caused by the so-called reactive oxygen species (ROS) can be attributed to these hydroxyl radicals. Although cells continuously generate ROS during normal aerobic metabolism and are therefore equipped with sufficient antioxidative defense systems including antioxidant enzymes such as superoxide dismutase, catalase or glutathione peroxidase and radical scavengers such as ascorbic acid or tocopherol, it is the excessive release of ROS leading to an oxidant-antioxidant imbalance that accounts for the pathological effects produced by these species.

ROS can in principle react with all components of the cell including proteins, carbohydrates, lipids or nucleic acids. Numerous studies showed that the cellular liberation of ROS can overpower the antioxidative defense system and leads to typical fingerprints for oxidative damage in DNA, lipids, proteins and carbohydrates. Therefore, ROS have been implicated in several different human diseases, most notably cancer, neurodegenerative processes and aging. For detailed reviews on quinone redox cycling see [3,4].

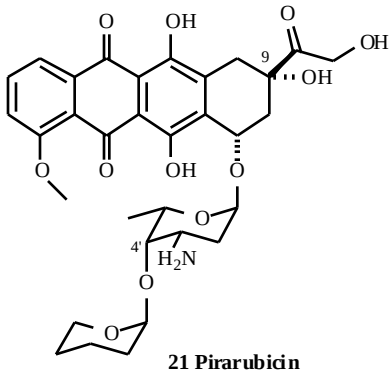
ROS and in particular the hydroxyl radical, produce many different lesions in DNA. Currently, over one hundred oxidative DNA modifications have been characterised [5,6], for example the spontaneous oxidation of guanine residues resulting from an attack of the hydroxyl radical and generating 8-oxo-2-deoxyguanine (8oxodG) [7]. The mutagenicity of 8oxodG results from its ability to mispair



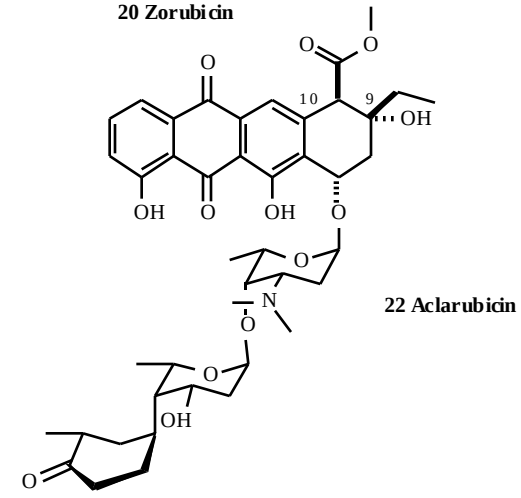
15 Daunorubicin $R_1 = H$, $R_2 = OCH_3$
16 Doxorubicin $R_1 = OH$, $R_2 = OCH_3$
17 Idarubicin $R_1 = H$, $R_2 = H$
18 Epirubicin 4'-epi-doxorubicin
19 Carminomycin $R_1 = H$, $R_2 = OH$



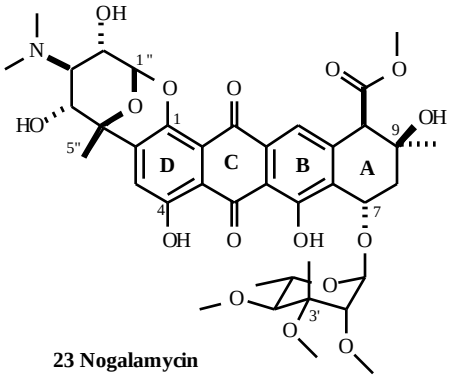
20 Zorubicin



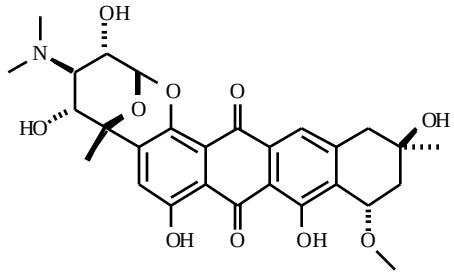
21 Pirarubicin



22 Aclarubicin



23 Nogalamycin



24 Menogaril

Fig. (2). Anthracycline antibiotics.

with adenine during replication, giving rise to G→T transversions [8]. G→T transversions are frequently found in tumour relevant genes and are among the most common mutations in the p53 gene [9].

2.2. 1,4-Reductive Michael-Additions

In addition to their ease of reduction, another main chemical property of quinones which also contributes to their biological activity, is the reaction with O-, N- or S-nucleophiles in a Michael-type 1,4-addition [10]. Due to the high intracellular levels of S-nucleophiles such as the γ-glutamyl-tripeptide glutathione (GSH) the reductive addition of quinones to sulfhydryl groups seems to be particularly important. Quinones can react with glutathione spontaneously or catalysed by glutathione-S-transferases forming hydroquinone-glutathionyl conjugates [11]. Though this reaction is proposed to be a detoxification because of the more hydrophilic character of the conjugate compared to the quinone it was found for different substituted 1,4-naphthoquinones that in some cases redox cycling occurred more rapidly for the glutathionyl conjugates than for the natural quinones [12]. Furthermore, exposure of cells to high amounts of quinones may saturate the detoxification system and often leads to a significant depletion of the reduced thiol form of glutathione by alkylation. Once GSH is depleted, cellular SH-dependent proteins can be alkylated thereby causing irreversible changes and cell death.

Ellipticines are well-known heterocyclic anticancer agents whose precise mechanism of action has not yet been fully understood. It is suggested that the main modes of ellipticine action include DNA intercalation [13,14], inhibition of topoisomerase II activity [13,15,16] and uncoupling of mitochondrial oxidative phosphorylation [17]. Interestingly, it is found that hydroxylated forms of ellipticines such as (**10**) behave as "pro-alkylating" agents, since they can be activated by a biooxidation route which leads to the corresponding quinone imine (**11**) (Michael acceptor) (Scheme 3) [18]. This quinone imine is able to react with bionucleophiles in a 1,4-reductive Michael-addition. Pratviel *et al*. have reported the structure of an ellipticinium ribonucleoside monophosphate adduct (**14**) which was the result of this type of reaction. Additionally, other groups demonstrated the alkylating properties of bioactivated ellipticines, especially towards DNA [19,20,21].

3. ANTHRACYCLINES

Anthracyclines are among the most utilised antitumour agents [22,23]. The most prominent members daunorubicin (**15**) and doxorubicin (**16**) are in widespread clinical use, the former being active mainly against acute leukaemias, whereas doxorubicin possesses a large spectrum of anticancer activity against a variety of solid tumours as well as acute leukaemias [24]. These differences in clinical activity may surprise, since they differ only by one hydroxyl group in the side chain at position 9. Unfortunately, both drugs have shortcomings, most notably their dose-dependent cumulative and often irreversible cardiomyopathy, which may proceed to clinical congestive heart failure even still a long time after completion of the treatment [25,26]. Secondly, it has to be mentioned that many tumour cells show primary or acquired resistances to anthracyclines [27].

Because of their fundamental role in cancer chemotherapy, a number of derivatives of these two naturally occurring anthracyclines have been developed in order to increase their efficacy and to decrease their toxicity, but only a few of them are approved for clinical use: Idarubicin (**17**), the 4-demethoxy derivative of daunorubicin, has acceptable bioavailability *via* the oral route of administration [28]. In epirubicin (**18**) the orientation of the 4'-hydroxyl group is reversed as compared with doxorubicin [29]. Carminomycin (**19**) represents the 4-hydroxy derivative of daunorubicin [30]. In zorubicin (**20**) the side chain at C-9 of daunorubicin is replaced by a benzoylhydrazone substituent [31] and in pirarubicin (**21**) an additional tetrahydropyran is attached to the O-4' of doxorubicin forming an acetal [32]. Aclarubicin (**22**) has several modifications in the aglycone and bears a trisaccharide moiety attached to the C-7 [33].

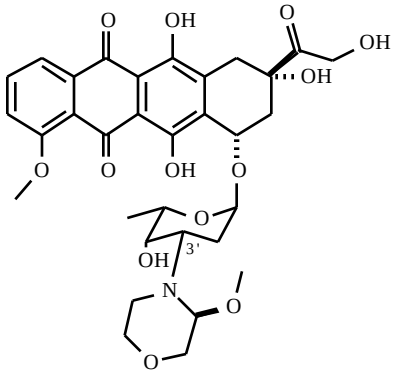
Another interesting natural antitumour anthracycline is nogalamycin (**23**) containing two sugar moieties attached to rings A and D [34]. The amino sugar is attached to the ring D through a glycosidic linkage and a C-C bond. Although the clinical development of nogalamycin was stopped because of its acute toxicity, many natural and semi-synthetic derivatives have been studied. One of them, menogaril (**24**), lacking the acute toxicity of nogalamycin and displaying higher activity has been selected for clinical trials [35,36]. Nogalamycin and menogaril differ by the sugar ring attached to ring A in nogalamycin, which is replaced by a methoxy group in menogaril.

The main target of the anthracyclines remains to be DNA and they all interact with this macromolecule by intercalation. The structural information and the molecular basis of the action, has mainly been probed by X-ray crystallography [e.g. 37-39].

Anthracyclines like daunorubicin share three principal functional components and each of them is important for biological activity: the aglycone intercalator, ring A with its anchoring function and the amino sugar. The intercalator consists of the rings B-D together with the p-quinone substructure in ring C. Although intercalation is a necessary requirement for binding to DNA and even may contribute to their anticancer properties, it is not sufficient on its own. The aglycone itself does not exhibit biological activity. Ring A of the chromophore bears an anchoring function. Thus the 9-hydroxyl forms a key hydrogen bond to DNA anchoring the molecule strongly in the double helix. Additionally, the configuration at the 7-carbon atom is of importance, since the amino sugar is enabled to position in the minor groove of a B-DNA double helix.

Since intercalation was found not to be sufficient for antitumour activity, research was extended to discover the major mode of action of anthracycline antibiotics. There is now consensus that the antitumour activity of anthracyclines such as daunorubicin or doxorubicin mainly results from an inhibition of mammalian topoisomerase II [40,41]. Topoisomerases are nuclear enzymes regulating DNA topology through single- (topoisomerase I) or double-strand breaks (topoisomerase II). They are extensively involved in DNA metabolism including replication and transcription [42]. Anthracyclines convert topo II into an endogenous

toxin by stabilising the topo II-bridged DNA strand breaks in which the enzyme is covalently linked to the 5'-end of the cleaved phosphodiester bond of DNA ("cleavable complex"). They produce persistent cleavable complexes and the treatment of anthracyclines causes an extensive increase in DNA strand breaks, which stimulate various cellular processes including apoptotic events that finally lead to cell death [43]. The anthracycline aglycon seems to represent the DNA-binding domain within the drug-DNA-protein complex, whereas the side chains are supposed to further stabilise contacts with DNA and to act as enzyme-recognition elements [44]. One major disadvantage of topo II inhibitors is their mutagenicity, which may lead to resistance of the drug or to drug-induced secondary cancers [43]. Agents such as daunorubicin stabilising the covalent DNA-topo II complex are traditionally called topo II poisons, while such agents acting on any of the other steps in the catalytic cycle of this enzyme are called catalytic inhibitors. As an example among the anthracyclines one can find aclarubicin used clinically in the treatment of acute myelocytic leukaemia. It is a strong DNA intercalating agent that prevents the binding of topo II to DNA and therefore cleavable complex formation [45]. Thus, aclarubicin is antagonistic to classical topo II poisons [46]. It was also found that aclarubicin is a dual topo I and topo II inhibitor. At biologically relevant concentrations, aclarubicin prevents the binding of topoisomerase I to DNA and is therefore antagonistic to camptothecin [47,48], whereas it stimulates the formation of covalent DNA-enzyme complexes at higher concentrations [49,50].



25 MMRDX

Fig. (3).

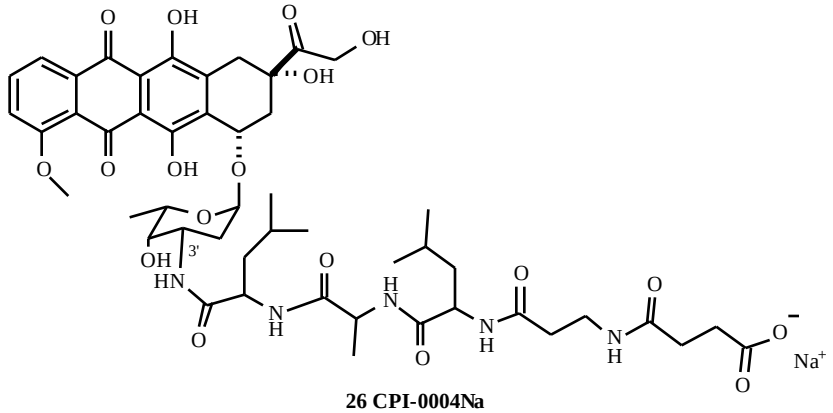
Nogalamycin and menogaril behave differently concerning their topoisomerase inhibitory effects. While nogalamycin poisons topoisomerase I by stabilising cleavage complexes but not topoisomerase II, the situation is opposite with menogaril. The minor groove binding sugar nogalose lacking in menogaril may be responsible for this differential poisoning [51].

Interestingly, formaldehyde can cross-link daunorubicin to DNA using the N-3' atom of the drug and the N-2 of guanine [52]. This finding led to the development of morpholinyl anthracyclines [53].

For example, 2(S)-methoxy-4-morpholinyl doxorubicin (MMRDX) (**25**) is currently undergoing clinical trials [e.g. 54]. It differs from doxorubicin in its mechanism of action, pattern of resistance and metabolism. Contararily to doxorubicin MMRDX inhibits both topo I and topo II leading predominantly to single strand breaks and to a less extent to double strand breaks [55]. Moreover, DNA interstrand cross-links are observed. The most promising result is that this drug shows activity *in vitro* and *in vivo* against multidrug resistant tumour cells [56,57].

Anthracycline cardiotoxicity is a dose-limiting effect. The molecular mechanisms of anthracycline cardiotoxicity seem to be multifactorial [58,59]. There is general consensus that induction of oxidative stress *via* the anthracycline semiquinone radical plays a major role. Normally, the resulting superoxide radical anion is neutralised by superoxide dismutase. Catalase or glutathione peroxidase takes care of hydrogen peroxide. The problem is that, in comparison to other tissues, the heart tissue is poor in catalase. Additionally, glutathione peroxidase is destroyed by the anthracyclines. This leads to an accumulation of hydrogen peroxide, which generates by reaction with superoxide radical anions, increased levels of toxic hydroxyl radicals. But numerous other mechanisms like stimulation of sarcoplasmatic reticulum calcium release, binding to anionic phospholipids or alteration of cardiac gene expression have also been proposed and attributed to anthracycline cardiotoxicity.

One approach to avoid anthracycline-induced cardiotoxicity is to increase the selectivity of the available anthracyclines by delivering them specifically as prodrugs to tumour cells. Tumour-associated enzymes, particularly peptidases, may then release the active anthracycline. It is



26 CPI-0004Na

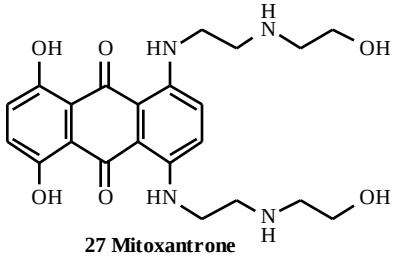
Fig. (4). Anthracycline-peptide conjugate.

understandable that the selective delivery would also allow the use of higher doses of the drug and increased intracellular concentrations of the drug could perhaps overcome resistance. An example of an extracellularly tumour-activated prodrug (ETAP) represents CPI-0004Na (N-succinyl-β-alanyl-L-leucyl-L-alanyl-L-leucyl-doxorubicin) (**24**), a tetrapeptide derivative of doxorubicin. This compound was shown to be stable in blood and unable to enter cells. Extracellular cleavage through enzymes secreted by tumour cells releases N-leucyl-doxorubicin, which freely diffuses into the cells where it is activated into the fully active doxorubicin by an intracellular protease. CPI-0004Na is up to 4.6 times less toxic than doxorubicin after i.v. administration. Additionally, mice treated with equimolar CPI0004Na compared with doxorubicin alone accumulated 2-fold higher doxorubicin in tumour tissue and 1.4-29-fold reduced levels in normal tissue. Tumour xenograft studies in nude mice also indicate a higher antitumour activity against human breast and colon xenografts [60,61].

There are also promising results concerning two other peptidic derivatives of doxorubicin targeting selectively prostate cancer cells through cleavage by prostate specific antigen [62,63].

4. MITOXANTRONE

Anthracyclines can be viewed as substituted anthraquinones and the fact that it is the anthraquinone unit, which is responsible for the intercalation of anthracyclines led to the development of anthraquinones with structural features predicted to favour intercalation [64]. A large number of anthracenediones was synthesised and among them mitoxantrone (**27**) was chosen for clinical trials. Mitoxantrone is a dihydroxyanthracenedione, which contains an ethylene spacer between each two nitrogens and the substituent of the aliphatic amine is hydroxyethyl. It is approved for the treatment of several tumours and has demonstrated clinical efficacy particularly in the treatment of leukaemia, lymphoma and breast cancer [65].



27 Mitoxantrone

Fig. (5).

Mitoxantrone shows strong affinity for nucleic acids and intercalates into DNA [e.g. 66]. But there is also some evidence that its interactions with nucleic acids may also involve nonintercalatory, electrostatic interactions [67]. The antitumour activity of mitoxantrone is attributed to its interaction with topoisomerase II. As well as the anthracycline antibiotics the drug acts as a topo II poison and stabilises the cleavable complex [e.g. 68].

5. SALVICINE

Salvicine (**28**) represents a diterpenoid o-quinone, which was obtained by structural modification of a natural compound isolated from Salvia prionitis [69-72]. It was found to be highly active *in vitro* against lung and gastric tumour cells whereas its inhibitory effects on leukaemia cell lines were moderate [73]. *In vivo* experiments conducted with murine S-180 sarcoma, Lewis lung cancer and human lung adenocarcinoma xenografts A-549 and LAX-83 revealed significant antineoplastic activity [74]. One of the most important features of salvicine is that it effectively kills multidrug-resistant (MDR) cell lines with an average resistance factor of 1.42, which is much lower than that observed for several classical anticancer agents (e.g. vincristine: 344.35, doxorubicin: 233.19, etoposide: 71.22) [75]. This property is mainly related to its ability for down-regulating mdr-1/p-gp expression. These results suggest that salvicine might be a promising novel antitumour agent which is now undergoing clinical trials in China. The cytotoxic activity of salvicine can be associated with its ability to induce tumour cell apoptosis like it is known for most cytotoxic agents. [76]. The mechanism of salvicine-induced apoptosis is not fully understood but in 2001, it was shown by Meng *et al*. that salvicine is a selective Topoisomerase II poison, which traps the Topo II-DNA cleavage complex inducing DNA breaks [77,78]. Like etoposide it belongs to the small class of Topo II poisons which do not intercalate into DNA.

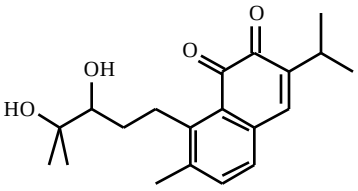
6. β-LAPACHONE

β-Lapachone (**29**) is a pyrano-ortho-naphthoquinone obtained as a minor component from the heartwood of the lapacho tree (Tabebuia avellanedae). It possesses a wide range of pharmacological properties including antibacterial, antifungal, antiviral, antitrypanosomal and antitumour activities [79-85]. The sensitivity of various human tumour cells to β-lapachone with IC_{50}-values at micromolar concentrations illustrates its growth inhibitory properties [86-88]. In combination with taxol, β-lapachone is highly effective against human ovarian and prostate tumours implanted in immunosuppressed mice [89] and it is a radiosensitizer of several human tumour cells [90]. There are many *in vitro* effects of β-lapachone described, but little is known about its key intracellular target and the way it triggers cell death. Topoisomerase I was the first biological target to be discovered [85], but it could be shown that the mode of inhibition is different from other topo I poisons like campthotecin. Instead of stabilising the cleavable complex, β-lapachone is supposed to bind rather to free topoisomerase I than to the protein-DNA complex [85,91] and to prevent topo I-DNA complex formation [92]. Therefore, it is classified as topoisomerase I suppressor. But nevertheless β-lapachone is also reported as a topoisomerase II inhibitor with a novel mode of action inducing the enzyme to religate DNA breaks and to dissociate it from DNA. The inhibition seems to be irreversible so that the catalytic activity stops after dissociation from DNA [93]. This new inhibitory mechanism may be at least partly associated to the ability of quinones to undergo redox-cycling and therefore to oxidise essential cystein residues of topo II [94,95]. Additionally, β-lapachone seems to be a substrate of DT-diaphorase (NQO1) [96-98]. The reduction of β-lapachone appears to be an important determinant for its activity. Pink *et al*. demonstrated that its cytotoxicity against human prostate and breast cancer cells depends on the expression of this

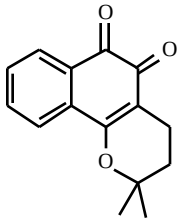
enzyme. The enzyme inhibitor dicoumarol significantly protects NQO1 expressing prostate and breast cancer cells against β-lapachone [99,100]. But anyway the mechanism by which reduction of β-lapachone causes cell death has not yet been resolved. Unlike mitomycin C or E09 it does not cause direct DNA damage [101]. It has been suggested that β-lapachone redox cycling leads to a severe loss of the enzyme co-factors NADH/NADPH, which ultimately leads to the activation of the apoptotic pathway *via* calpain [99]. Another interesting feature of this drug arises from the finding that it causes apoptosis selectively in transformed but not in normal cells accompanied with an increase in E2F1, a regulator of checkpoint-mediated apoptosis. It is supposed that β-lapachone directly activates checkpoint-mediated apoptosis at the step of E2F1 induction unlike other chemotherapeutic agents, which kill cancer cells by indirectly checkpoint-mediated apoptosis [102].

7. STREPTONIGRIN

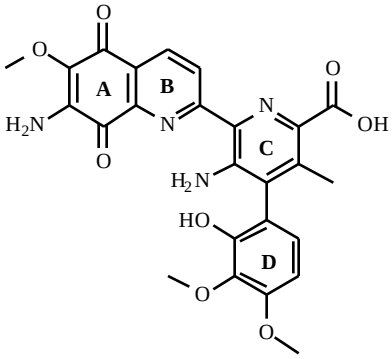
Streptonigrin (**30**), which was isolated from Streptomyces flocculus [103,104], is a functionalised 7-aminoquinoline-5,8-dione that is highly active against a variety of human tumours [105-108]. Due to its severe toxicity it has received only limited use as an anticancer agent [109,110] and at last these side effects resulted in the drug being withdrawn from clinical use [111]. *In vitro* studies suggest that DNA is the main target and that its anticancer activity can be directly related to Streptonigrin-induced DNA strand scission [112-115]. Additionally, there is some evidence that Topoisomerase II is a target of Streptonigrin leading to Topoisomerase II-mediated DNA cleavage. But contrary to many other Topo II poisons like doxorubicin or amsacrine the drug is not supposed to intercalate into the DNA double helix. Instead of that the results indicate that streptonigrin may bind to DNA in a manner similar to that of minor groove binders [116]. Streptonigrin as well as a few other antibiotics like bleomycin or bacitracin called "metalloantibiotics" requires metal ions to function properly [117-120]. But although the drug interacts with metal ions and its DNA binding is clearly enhanced in the presence of metal ions [121-124], the exact function of these species has not yet been fully understood. It has been proposed that they either are implicated in the catalytic formation of DNA-damaging ROS or that they act as delivery agents of streptonigrin or streptonigrin semiquinone to DNA *via* electrostatic interactions [125-127]. The rings A,B and C including the quinone moiety contain the key functional groups required for biological activity. Like mitomycin C Streptonigrin is found to be a substrate for DT-diaphorase [128,129] and there are results indicating the important role for DT-diaphorase and the intermediate semiquinone radical in the cytotoxicity of streptonigrin [130]. The phenolic ring D confers optical activity on streptonigrin but investigations concerning the binding of the two different enantiomers to



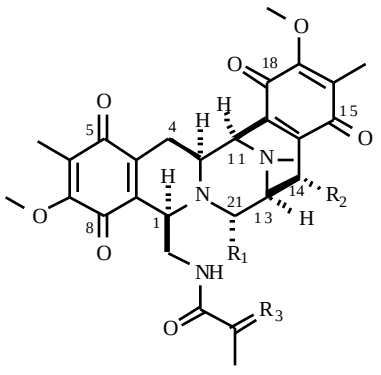
28 Salvicine



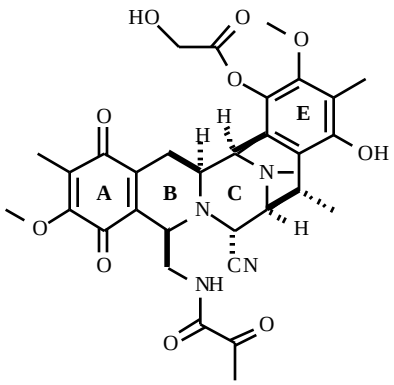
29 β-Lapachone



30 Streptonigrin



31 Saframycin A R_1 = CN, R_2 = H, R_3 = O
32 B R_1 = H, R_2 = H, R_3 = O
33 C R_1 = H, R_2 = OCH_3, R_3 = O
34 S R_1 = OH, R_2 = H, R_3 = O



35 Saframycin R

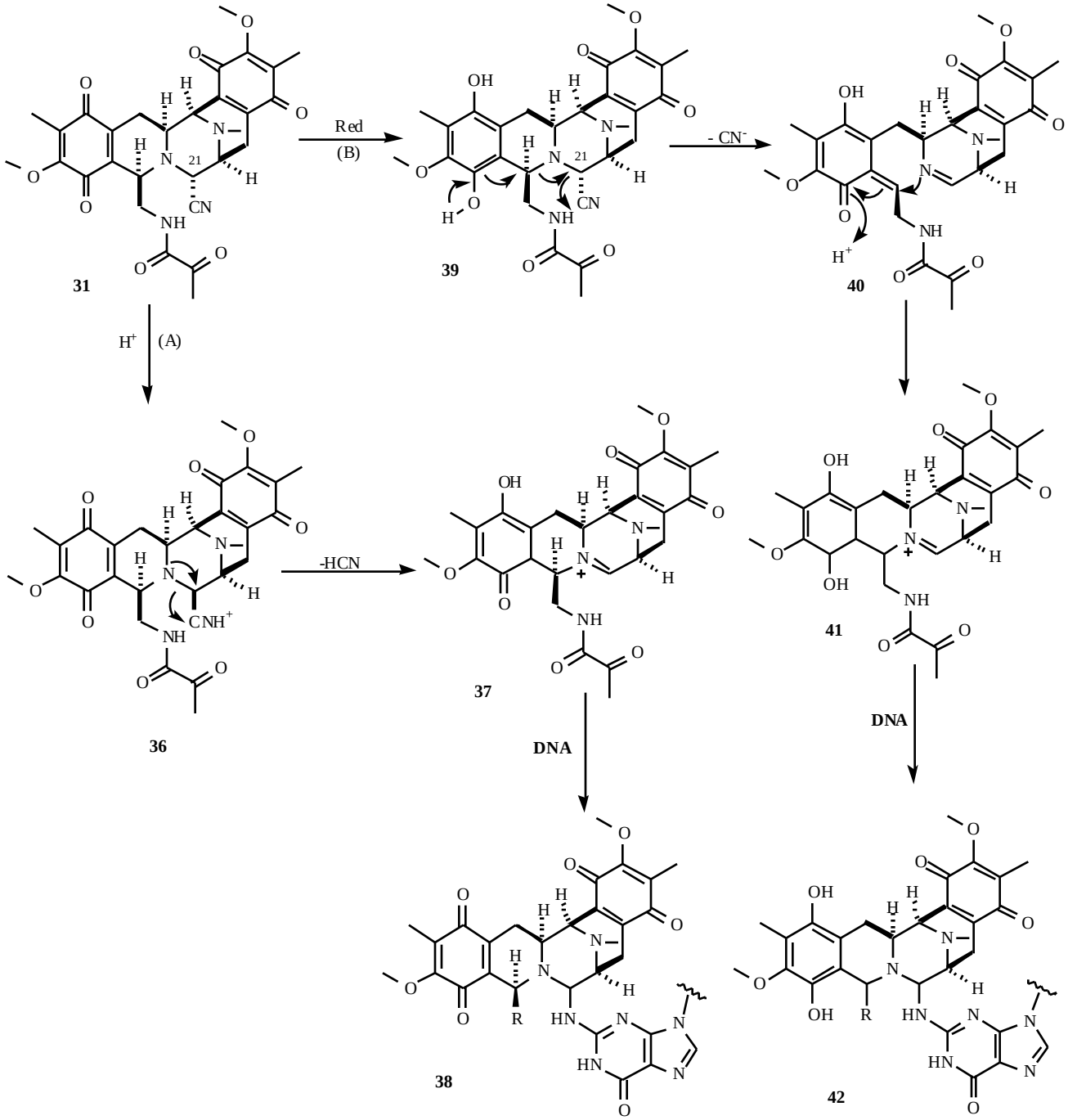
Fig. (6).

calf thymus DNA showed no evidence for selective interaction of the natural (R)-enantiomer [131].

8. SAFRAMYCINS

The saframycins (**31**)-(**35**) belong to the big class of natural tetrahydroisoquinoline antiproliferative agents with DNA alkylating properties. Arai *et al*. isolated the saframycins A (**31**), B (**32**), C (**33**), D and E from Streptomyces lavendulae first in 1977 [131]. Subsequently many other saframycins were isolated [132-136]. They are biosynthetically related to streptonigrin *via* the shikimate-prephenate-tyrosine pathway. Most of the saframycins consist of two units of 7-methoxy-6-methyl-1,2,3,4-isoquinoline-5,8-dione, which are joined through the fifth ring building a pentacyclic dimeric ring system. For saframycin R (**35**) and a few other analogues it was shown that ring E is in the reduced p-hydroquinone and not in the p-quinone form [137].

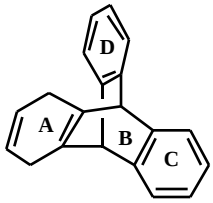
Saframycins containing additionally a labile leaving group at C-21 like the α-cyano group in the case of saframycin A or the α-hydroxyl group in the case of saframycin S (**34**) show the highest antitumour activity [132, 138] and those lacking these groups like saframycin B exhibit much lower antiproliferative activities [131,139,140]. Based on these observations Lown *et al*. derived a



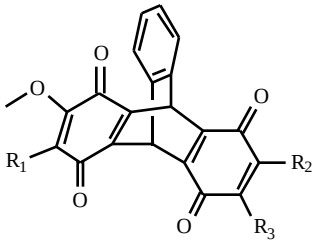
Scheme 4. Mechanism of alkylation by saframycins.

mechanism for the activation of saframycin A and its binding to DNA [141]. They proposed that the carbenium-iminium ion (**36**) resulting from protonation of the 21-nitrile group and subsequent liberation of HCN represents the real alkylating species. The observation that reduction of the quinone substructures to the corresponding hydroquinones (**39**) in saframycin A substantially increases DNA binding [139] led to another mode of action proposed by Hill and Remers [142] in which the phenol facilitates the expulsion of cyanide. The imine (**40**) resulting from this process attacks intramolecularly the reactive o-quinone methide, which leads to the formation of the carbenium-iminium ion (**41**). This ion then alkylates N-2 of a guanine residue of DNA to form the aminal (**42**). Some newer synthetic bishydroquinone saframycin A analogues, which showed up to 20-fold increased activity against the A549 lung carcinoma and the A375 melanoma cell line, support this mechanism of DNA alkylation [143].

There are a number of other naturally occurring compounds belonging to the class of quinoid tetrahydroisoquinoline alkaloids, which exhibit antitumour activity including among others the safracins, the naphthyridinomycins and the bioxalomycins. For a detailed review see [144].



43 Triptycene TTO



44 TT2 $R_1 = R_2 = R_3 = H$
45 TT13 $R_1 = Br, R_2 = R_3 = H$
46 TT24 $R_1 = Br, R_2 = NHMe, R_3 = H$
and $R_1 = Br, R_2 = H, R_3 = NHMe$

Fig. (7). Triptycene quinones.

9. TRIPTYCENE QUINONES

Synthetic triptycene quinones constitute a new class of antitumour agents worth being mentioned here. Contrary to the inactive and unsubstituted tetracyclic triptycene (**41**) (TT0), several functionalised triptycene derivatives containing para-quinone moieties show promising anticancer effects. Among the analogues being synthesised so far, the bisquinones TT2 (**42**), its C-2 brominated derivative TT13 (**43**) and the amino-functionalised TT24 (**44**) exhibit strong antiproliferative activity and they belong to the lead TT compounds.

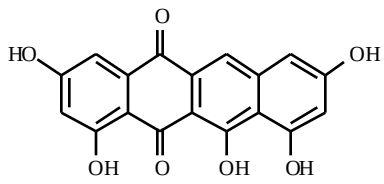
They were shown to inhibit DNA, RNA and protein synthesis, to induce DNA cleavage and to decrease the mitotic index, proliferation and viability of murine L1210 leukaemia cells. TT24 is the most potent compound with IC_{50}-values comparable to daunorubicin in the nM range in L1210 cells *in vitro* [145,146]. But an interesting finding is that, in contrast to daunorubicin, these triptycenes block the cellular transport of nucleosides and they keep their activity in multidrug-resistant tumour cells. In 2003, it was demonstrated by Wang *et al*. that these compounds act as a novel class of dual topoisomerase I and II inhibitors. TT24 is a more potent topo II inhibitor than amsacrine and it possesses the same inhibitory effects on topo I as camptothecin [147]. Due to their ability to inhibit both cellular nucleoside transport and topoisomerase activity, these quinones represent a novel class of bifunctional compounds.

10. SAINTOPIN

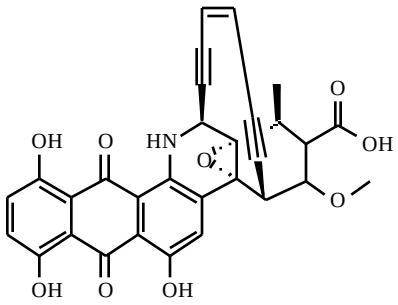
In contrast to the anthracyclines, which are tetrahydro derivatives, the antibiotic saintopin (**47**) isolated from Paecilomyces species comprises a fully aromatised naphthacenequinone. It showed antitumour activity against leukaemia P388 cells. Although it possesses a planar polycyclic chromophore predetermined for intercalation, it was only shown to be a weak intercalator and that the chromophore intercalates only partially [148,149]. Saintopin was reported to induce both DNA topoisomerase I and II mediated DNA cleavage [150,151]. This antibiotic appears to stabilise topo-DNA cleavage complexes and should therefore be named as dual topo I and II poison. However, the DNA cleavage intensity patterns induced by saintopin with topo I and topo II differ from those induced by camptothecin or amsacrine. There are a number of other saintopin-type antibiotics, which possess the naphthacenedione structure, but only saintopin has been identified as a dual inhibitor of topo I and II.

11. DYNEMICIN A

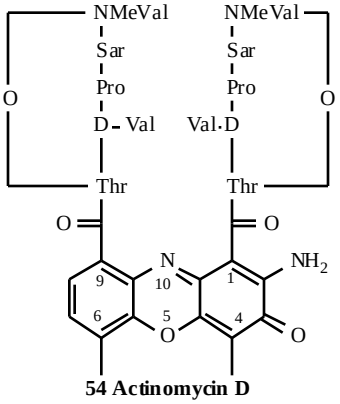
Dynemicin A (**48**) isolated from the fermentation broth of Micromonospora chersina [152,153] belongs to the class of



47 Saintopin



48 Dynemicin A



54 Actinomycin D

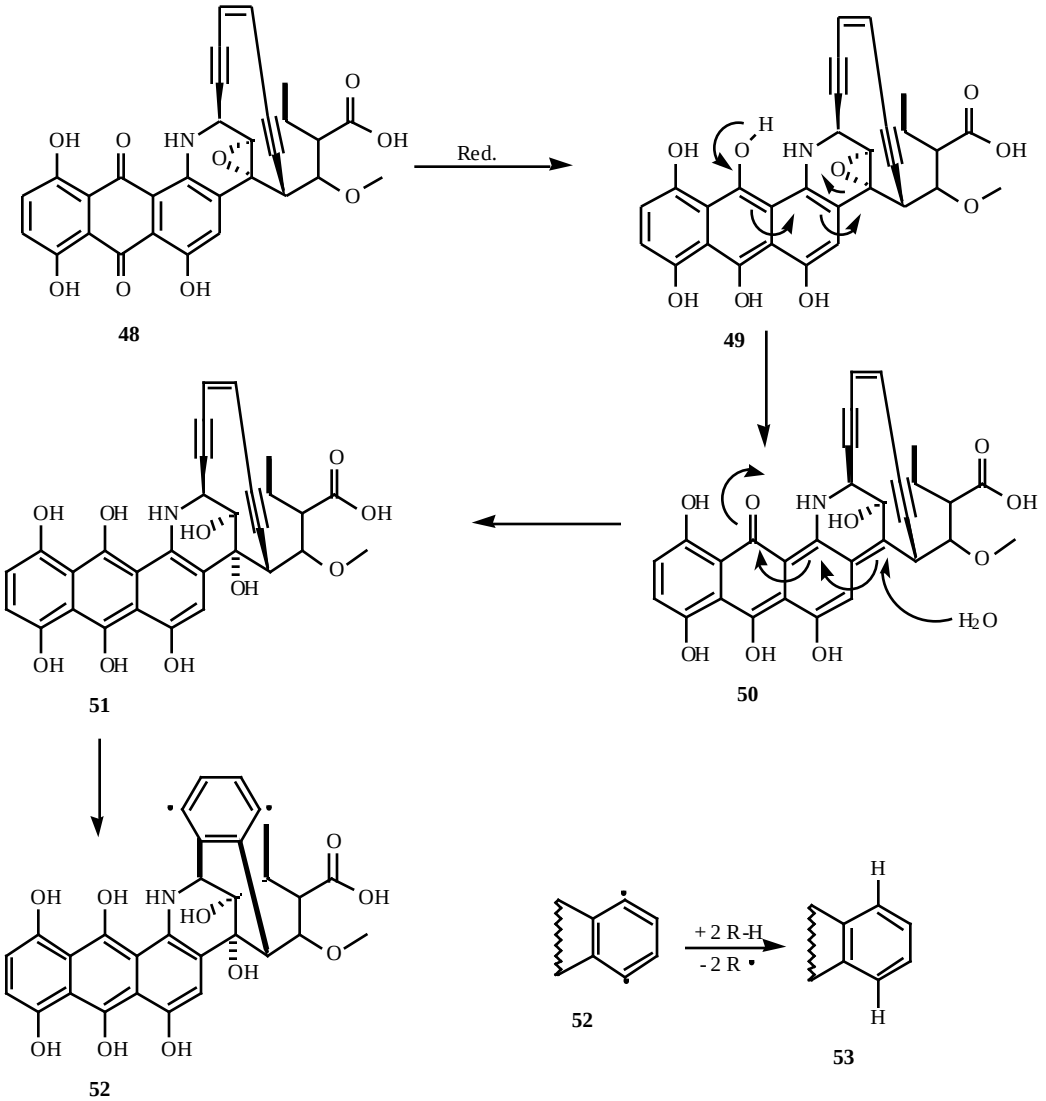
Fig. (8).

highly potent enediyne antibiotics, which bind to specific DNA sequences causing single- and double strand breaks [154]. Although the structures of enediynes such as the neocarzinostatins, the calicheamicins or the esperamicins differ widely, they all share the common feature of a ring with 9 or 10 carbons containing two acetylenic bonds and one olefinic bond (1,5-diyne-3-ene). In dynemicin A this enediyne ring is fused onto an anthraquinone chromophore and proximate to an epoxide ring. The crystal structure reveals that the anthraquinone portion is puckered rather than flat [153].

Dynemicin A shows high activity against a variety of cancer cell lines and significantly prolongs the life span of mice inoculated with P388 leukaemia and B16 melanoma cells. Dynemicin A like the other enediynes constitutes a prodrug and its potency is markedly enhanced by thiols [155]. It has been shown that classical minor groove binders and intercalators inhibit dynemicin A mediated DNA cleavage suggesting both minor groove binding and intercalation for this compound. The drug cleaves DNA preferentially at bases adjacent to the 3'-side of purines upon bioactivation. It is suggested that intercalation of the anthraquinone chromophore *via* the minor groove is the first step in dynemicin A caused DNA damage. A proposed mechanism for its bioactivation is shown in Scheme 5 [155,156]. The p-quinone moiety is reduced to the corresponding hydroquinone (**49**). After opening of the epoxide by electron push, the formed quinone methide (**50**) is trapped by nucleophiles such as water resulting in an overall cis opening of the epoxide. The diol ring system (**51**) undergoes a Bergman-type transformation leading to a 1,4-benzenoid diradical species (**52**), which is located in the minor groove of DNA in the proximity of the sugar phosphate backbones from both strands. This diradical is presumably able to abstract simultaneously two hydrogens from DNA producing compound (**53**) and double strand scissions.

12. ACTINOMYCIN D

Actinomycin antibiotics were first isolated by Waksman and Woodruff [157]. The most important member among the actinomycin family of compounds is actinomycin D (**54**). Its structure was confirmed by total synthesis in 1960 [158]. It



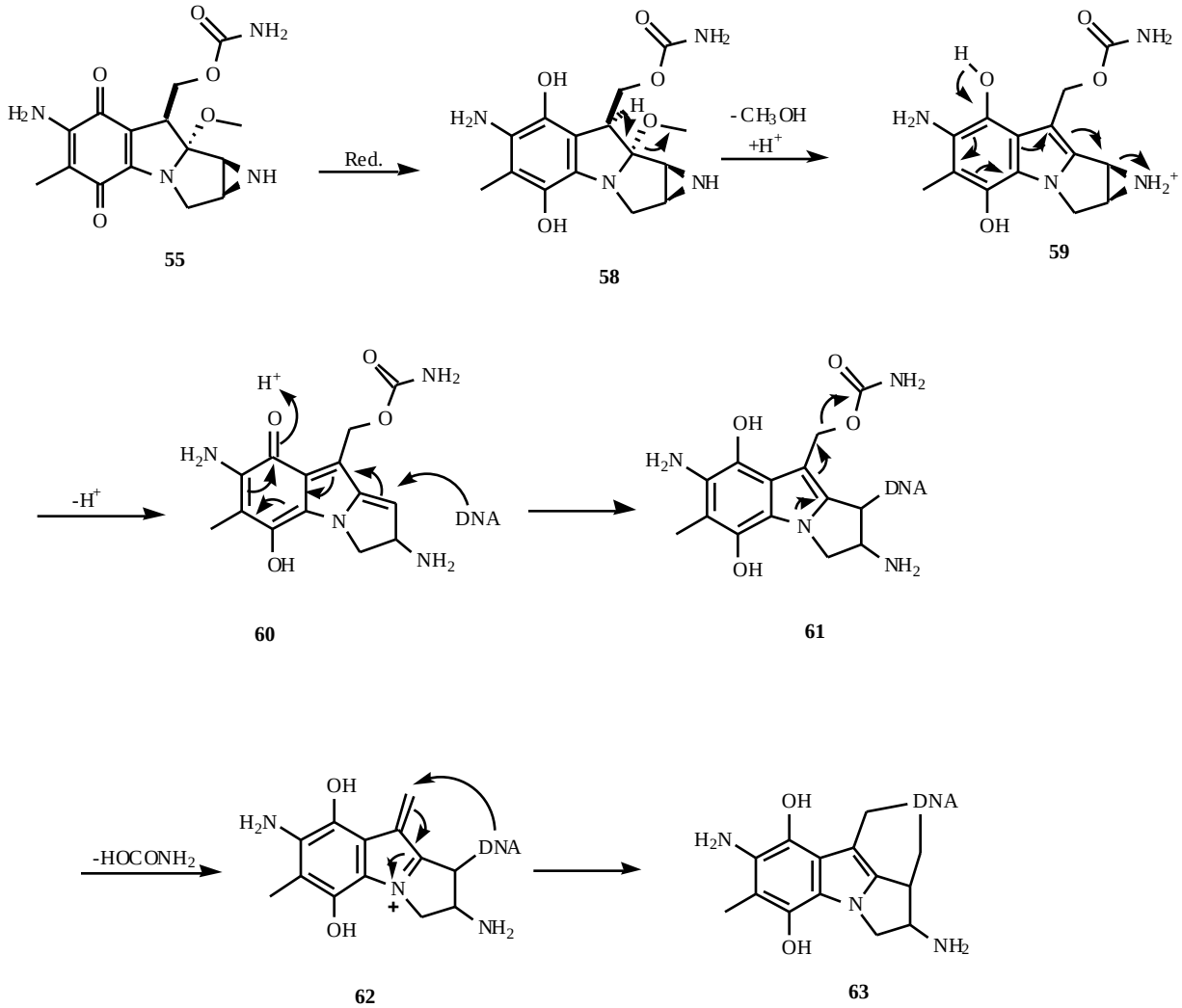
Scheme 5. Bioactivation and DNA damaging of dynemicin A.

represents a chromopeptide, which is composed of two pentapeptide lactone rings and a heterotricyclic chromophore (2-amino-4,6-dimethylphenoxazin-3-one-1,9-dicarboxylic acid) called actinoin, which contains a quinoneimine moiety. The two peptides are attached to the chromophore as amides with the two carboxyl groups. The two pentapeptide residues are identical and consist of the amino acid sequence L-threonine-D-valine-L-proline-sarcosine-L-N-methyl-valine where the terminal carboxyl group is esterified by the hydroxyl group of L-threonine forming a lactone ring. Actinomycin D has clinically been used in the treatment of various cancers especially in children since the mid 1950s, for instance rhabdomyosarcoma, Kaposi's sarcoma or Wilm's tumour [159-161].

The drug binds strongly to DNA duplexes by intercalating its phenoxazone ring at a GpC step with the two pentapeptides located in the minor groove forming hydrogen bonds with adjacent DNA bases, thereby inhibiting DNA-dependent RNA synthesis [e.g. 162-166]. The inhibition of transcript elongation by DNA polymerase is now widely accepted as its major mode of action. Actinomycin D was also found to inhibit topoisomerase I and II, which contributes to its activity [167,168].

13. QUINONES AS BIOREDUCTIVE ALKYLATING AGENTS

Quinoid bioreductive alkylating agents comprise a class of compounds requiring reduction of the quinone substructure for activation of their alkylating properties. In this context the cytosolic DT-diaphorase (NAD(P)H:quinone oxidoreductase), a two-electron reductase and normally an enzyme protecting animals from the toxic effects of quinones and other electrophiles, has received remarkable attention, since it is reported to be noticeably overexpressed in a wide range of tumours and its involvement in the activation of quinones is well established [169-174]. The crystal structure of DT-diaphorase has been confirmed and the rational design of bioreductive agents is ongoing [175,176]. As mentioned above streptonigrin and β-lapachone were found to be substrates for DT-diaphorase. The prototype bioreductive drug is the aziridinylquinone mitomycin C (**55**). It was isolated in 1958 from Streptomyces caespitosus [177] and has been clinically used for the treatment of various types of solid tumours for more than 25 years. It was called the most active single compound for the treatment of non-small cell lung cancer [178] and has been extensively used among others for the treatment of pancreatic and gastric cancer [179]. Although many mitomycin C derivatives have been



55 **58** **59** **60** **61** **62** **63**

Scheme 6. Mechanism for mitomycin cross-linking.

synthesised and tested for their cytotoxic activities *in vitro*, only a few like porfiromycin (**56**) or BMS-181174 (**57**) entered early clinical trials [180-183], but either the response rates were too low or the drugs showed severe side effects during treatment. Thus, mitomycin C remains the only drug being approved for clinical use up to now.

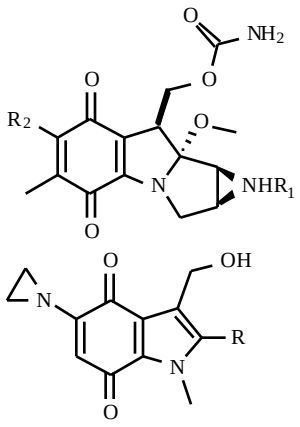
Though the mechanisms of activation and action are complex and still under investigation, it has been proved that mitomycin C bears three potentially active substituents, which all were shown to be utilised during its cytotoxic action. These are the quinone moiety, the aziridine ring and the carbamate side chain. The drug is very stable at physiological pH but becomes unstable on reduction. Scheme 6 shows a generally accepted mechanism for activation and DNA alkylation [184]. The first step is the reduction of the para-quinone to its corresponding hydroquinone (**58**). Afterwards, the hydroquinone forms by spontaneous elimination of methanol the reactive intermediates (**59**) and (**60**). Particularly, the electrophilic quinone methide (**60**) reacts with DNA producing chiefly adducts at the N-2 of guanine residues (**61**). This drug-DNA adduct is now able to form a cross link *via* the N-2 of another guanine (**63**) [185,186]. There is some controversy in the literature on which enzymes are responsible for the reduction of mitomycin C. In early studies it was suggested that mitomycin C is not a substrate for DT-diaphorase and the hydroquinone plays no role in the activation process [187,188]. However, it has now been shown that it is indeed a substrate for this enzyme and its cytotoxic effects can be correlated with intracellular concentrations of the enzyme [189,190].

E09 (**64**) is the best known member of the class of synthetic indolequinoids and has shown pronounced antitumour activity in preclinical trials [191]. Therefore, it seemed to be an ideal candidate for further investigations in clinical trials. However, it showed no antitumour effects in phase II trials of different solid cancers and failed in clinic most probably due to its rapid elimination [192,193]. E09 is a good substrate for DT-diaphorase though this drug can also be reduced by one-electron reductases, especially under hypoxic conditions [194-196]. Based on the structure of E09 and mitomycin C a wide range of analogues have been synthesised and a number of structure-activity relationships have been published for indolequinone prodrugs in general [197-200]. It was found that an aziridine or a methylaziridine ring at the 5-position of the indole skeleton is best to achieve toxic effects and selectivity to DT-diaphorase rich cells. Additionally, a hydromethyl group as potential leaving group at the indole-3-position is favourable. As an example, RB 95629 (**65**) shows up to 200-fold increase in activity under hypoxic conditions when compared to mitomycin C [201,202].

The aziridinylbenzoquinones (**66**)-(**70**) are structurally the simplest bioreductive alkylating drugs but they show significant antitumour activity. In early studies conducted by Nakao *et al*., carboquone (**66**) was identified among a wide range of diaziridinylquinones as very powerful. This benzoquinone is still used in combination therapy for the treatment of prostate and ovarian cancer [203-205]. AZQ (**67**) was designed in the 1970s, as potential intracerebrally active anticancer agent being able to cross the blood brain barrier [206,207]. It is supposed that the main cytotoxic mechanism of aziridinylbenzoquinones is their two-electron reduction by DT-diaphorase to alkylating products. AZQ was shown to be reduced by this enzyme, but in studies concerning AZQ analogues another derivative called MeDZQ (**68**) was found to be a better substrate and to be 100-fold more toxic to DT-diaphorase-rich HT-29 colon carcinoma cell lines than AZQ [208]. Despite this advantage, MeDZQ has some shortcomings due to its low solubility. Therefore, RH1 (**69**), a more water-soluble analogue of MeDZQ, was developed [209]. RH1 is even a better substrate for DT-diaphorase than MeDZQ and shows high selectivity in its cytotoxic effects against DT-diaphorase-rich cells. It is currently undergoing clinical trials [210].

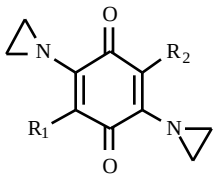
Diaziridinylbenzoquinones are alkylating agents leading to DNA cross-links. In order to reveal the alkylating properties of the aziridine groups, they have to be protonated at the nitrogen. That appears much easier in the reduced hydroquinone form than in the quinone form. Thus, DNA alkylation will only markedly occur after reduction of the quinone and consequently allows selectivity [211].

Another interesting fact is that some of these benzoquinones show sequence selectivities only in the



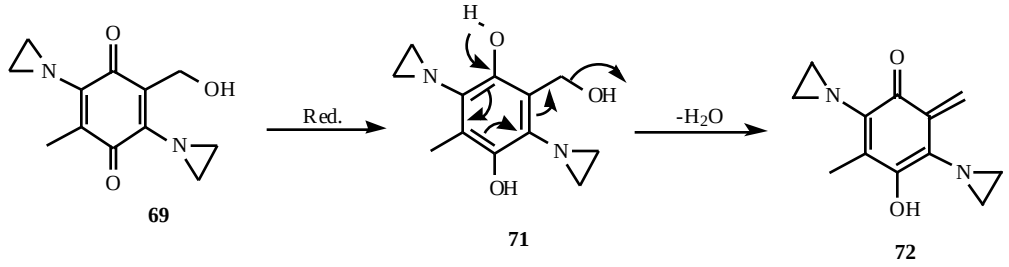
64 EO9 **R = CH=CHCH$_2$OH**
65 RB 95629 R = H

55 Mitomycin C R_1 **= H,** R_2 **=** NH_2
56 Profiromycin R_1 **=** CH_3, R_2 **=** NH_2
57 BMS -181174 R_1 **= H,** R_2 **=** $NH(CH_2)_2SS\text{-}C_6H_4\text{-}NO_2$



66 Carboquone R_1 **=** CH_3, R_2 **=** $CH(OCH_3)CH_2OCONH_2$
67 AZQ R_1 **=** R_2 **=** $NHCOOCH_2CH$
68 MeDZQ R_1**=** R_2 **=** CH_3
69 RH1 R_1 **=** CH_3, R_2 **=** CH_2OH
70 DZQ R_1 **=** R_2 **= H**

Fig. (9). Bioreductive alkylating quinones.



Scheme 7. Quinone methide formation from RH1.

hydroquinone form. For example following reduction of DZQ (**70**) to its hydroquinone, alkylation is not only significantly increased overall, but DZQ hydroquinone alkylates at N-7 of guanine principally at 5'-GC sequences [212-214]. This is explained by a model in which the hydroquinone intercalates between adjacent guanine and cytosine residues with the two protons of the hydroxyl groups forming two hydrogen bonds with functional groups of cytosine. These interactions cannot occur in the quinone form. In this intercalation complex the electrophilic carbon atom of the aziridine ring is in the right position to associate with the N-7 of guanine [212].

Among the aziridine compounds mentioned, RH1 (**69**) shows the highest cytotoxic effects [209]. This enhanced activity may be due to the hydroxymethyl group, which allows formation of a reactive quinone methide intermediate (**72**) after two-electron reduction (Scheme 7) [215,216].

14. QUINONES AS HSP90 INHIBITORS

One of the most interesting targets for the development of novel selective anticancer drugs is the heat shock protein hsp90. This molecular chaperone is critical for the folding, conformational stability and function of many client proteins including oncogenic signalling proteins that promote the growth and the survival of cancer cells. Hsp90 client proteins are for example mutant p53, Her-2/ErbB2, c-Raf-1, v-Src, Bcr/Abl, c-Met and Cdk4 [217]. The inhibition and therefore the loss of function of hsp90 blocks multiple oncogenic pathways leading to the depletion and degradation of a subset of proteins involved in the progression of cancer. Substances inhibiting hsp90 belong to the class of benzoquinone ansamycin antibiotics such as geldanamycin (GA) (**74**) and herbimycin A (**73**), which were first isolated in the 1970s [218]. Although these two antibiotics were extensively tested in preclinical studies, both did not reach clinical trials due to their *in vivo* toxicity and instability. Their mode of action was originally attributed to direct tyrosine kinase inhibition [219], but in 1994, it was shown that hsp90 was the predominant target of these macrocyclic quinones [220-223]. Ansamycin antibiotics exert their biological activity by binding in the ATP-binding site in the N-terminal domain of Hsp90 and therefore inhibiting its folding and ATPase activity leading to cell cycle disruption [224,225]. Crystal structures of hsp90-GA complexes elucidated the binding mode of the ansamycins and provided insights for further developments of derivatives of GA [226]. In spite of extensive research the only improvements over GA could be obtained by modification of the ansa ring hydroxyl group and the methoxy group of the quinone ring. 17-Allylamino-17-demethoxygeldanamycin (17-AAG) (**75**) possesses a lower *in vivo* toxicity and an increased stability than GA [227] and is the first ansamycin currently undergoing phase I clinical trial [228-231]. 17-AAG binds in a similar manner like GA specifically to hsp90 and displays comparable cytostatic effects in SKBR3 and MCF7 cells, even though it was found that 17-AAG binding to hsp90 is weaker.

For a long period of time the molecular basis of the tumour selectivity of hsp90 inhibitors was not understood since hsp90 is present in all cells. Tumour-associated hsp90 has a 100-fold greater affinity for 17-AAG than normal hsp90. This enhanced binding may be because hsp90 is present in tumour cells in a complexed high-affinity form with high ATPase activity which differs from normal cells where it is in a latent uncomplexed low-affinity state as long as there is no significant stress [232].

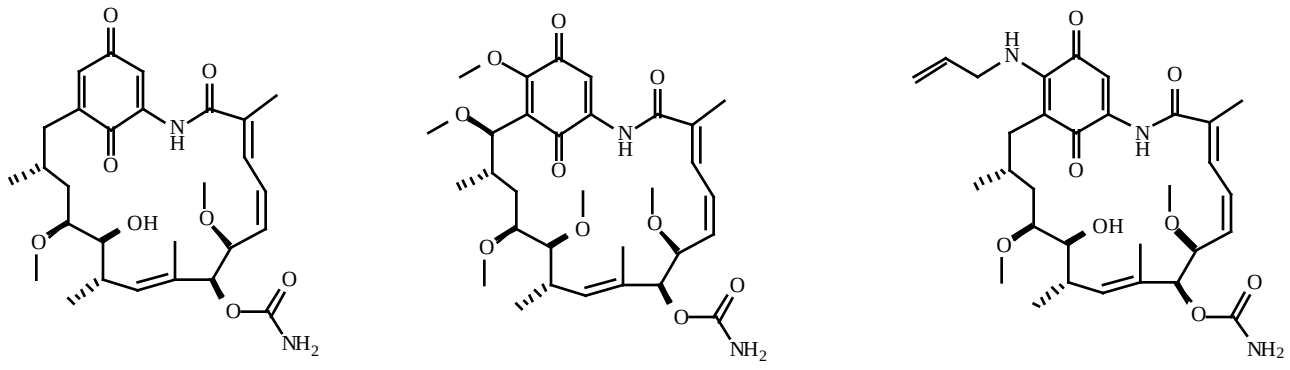
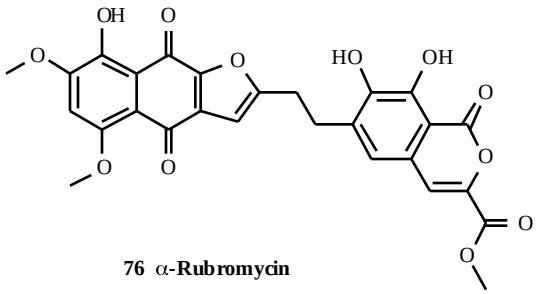


Fig. (10). Quinoid hsp90 inhibitors.

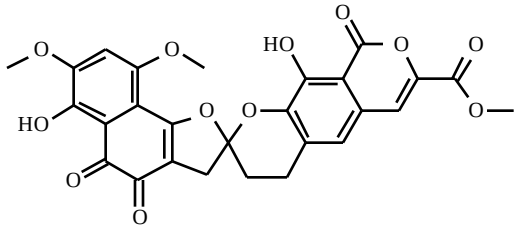
15. QUINONES AS TELOMERASE INHIBITORS

Telomeres are the noncoding ends of chromosomes comprising tandem repeats of short guanine-rich DNA sequences [233]. Human telomeres consist of the sequence 5'-TTAGGG [234]. At each round of cell division telomeres of normal somatic cells are shortened and this shortening ultimately leads to apoptosis. Cancer cells overcome this process by the enzyme telomerase, a ribonucleoprotein with reverse transcriptase activity, which elongates the 3'-end of telomeric DNA. Telomerase activity is therefore strongly associated with cancer progression and cell immortalisation. 85 - 90 % of all known cancers are positive for telomerase. Human telomeres contain guanine-rich sequences, which have the ability to form four-stranded intramolecular guanine quadruplex structures [235,236]. Since telomerase requires a nonfolded telomeric primer in order to cause telomere synthesis, G-quadruplex formation leads to the inhibition of telomerase activity. Because of that these quadruplex structures are considered to be promising targets for drug design [237,238]. The stabilisation of these regions in tumour cells may decrease telomerase activity and at last trigger apoptosis.

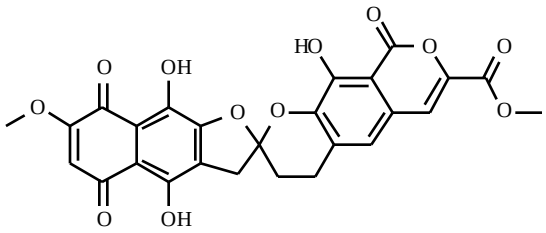
Many different approaches have been undertaken to inhibit telomerase activity up to now, for instance the design of antisense oligonucleotides or nucleoside analogue reverse transcriptase inhibitors [239]. Among the quinones some antibiotics such as streptonigrin and sarkomycin, A were shown to inhibit reverse transcriptase units of retroviral telomerase [240,241]. Interesting structures with strong human telomerase inhibitory effects in a modified telomeric repeat amplification protocol (TRAP) are found among the rubromycins (**76**)-(**79**), quinoid compounds containing benzofuran and benzodipyran rings forming spiroketals [242]. β-and γ-rubromycin (**77**) (**78**) as well as purpuromycin (**79**) have been identified as potent inhibitors of human telomerase (IC_{50} = 3.06 μM rsp. 2.64 μM rsp.3.19 μM at 0.2 μM TS-A) whereas α-rubromycin (**76**), which is formed by spiroketal ring opening from β-rubromycin, revealed clearly



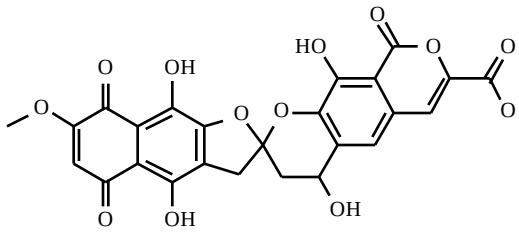
76 α-**Rubromycin**



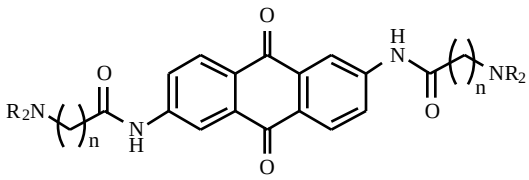
77 β-**Rubromycin**



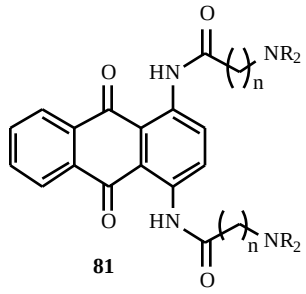
78 γ-**Rubromycin**



79 Purpuromycin



80



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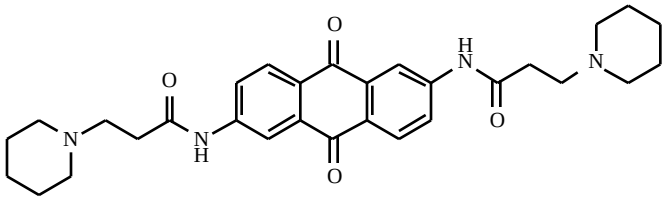

82

Fig. (11). Quiniod telomerase inhibitors.

decreased inhibitory properties (IC_{50} > 200 μM). These findings may contribute to the important function of the spiroketal moiety and one may also suggest that the quinone substructure is not sufficient or even necessary for telomerase inhibition. Additionally, it is worth mentioning that α-rubromycin strongly inhibited rat DNA polymerase α and β (K_i = 0.66 rsp. 0.17 μM) whereas β-rubromycin showed a 10-fold lower potency [243]. Such potencies make these quinones become interesting lead structures for the development of stronger and more selective compounds.

Anthraquinone-based compounds make up the second class of telomerase inhibitors derived from quinones. 2,6- and 1,4-diamidoanthracen-9,10-diones (**80**) and (**81**) exhibit telomerase inhibitory effects [244,245]. These compounds were developed as duplex DNA interacting agents related to the clinically approved 1,4-diamidoanthraquinone mitoxantrone [246,247]. Most of the compounds were found to be less toxic than doxorubicin or mitoxantrone against three human ovarian carcinoma cell lines and members of the 2,6-disubstitued series were generally less toxic than their 1,4-isomers [245]. Their telomerase inhibitory effect is related to a stabilisation of G-quadruplex structures by formation of a binary drug-G-quadruplex complex [248]. Derivatives containing two methylene groups in the side chain and additionally bulky cationic substituents at the end seem to produce the best inhibitory effects. The piperidine 2,6-anthraquinone (**82**) was found to be the most active compound from the TRAP assay (IC_{50} = 4.5 μM) [245]. Its cytotoxic *in vitro* potency against the three ovarian carcinoma cell lines (IC_{50} = 1.3 μM (A2780), IC_{50} = 5.9 μM (CH1) and IC_{50} = 4.0 μM (SKOV-3)) is comparable to that of their inhibitory activity against telomerase which means that it may not cause acute cytotoxicity at concentrations required for telomerase inhibition.

16. QUINONES AS PHOTOSENSITIZERS FOR PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is a medical treatment especially applied against superficially localised tumours, which employs a photosensitising drug in combination with light in the presence of oxygen [249]. PDT has been used for a large variety of solid tumours [250], but the most responsive ones appear to be head, neck, bladder, and skin cancers [251-253]. Promising results were also obtained for oesophagus cancer, locoregional breast cancer and basal cell carcinoma. After administration of the photosensitiser, the tumour becomes exposed to laser light with a wavelength that is maximally absorbed by the drug. The photodynamic effect relates to the excitation of the photosensitiser resulting in the generation of ROS, most notably the strongly electrophilic singlet oxygen. PDT is less toxic than normal chemotherapy, since the utilised drugs lack toxicity in the absence of light and it can also be used for the treatment of recurrent tumours, which have already received normal chemotherapy. Nevertheless, one disadvantage of current PDT remains the lack of selectivity of sensitising agents, which accumulate not only in tumour cells but also in normal cells. This can result in severe tissue damage or skin phototoxicity, which may force the patients to avoid exposure to sunlight for several weeks after completion of the treatment.

The most frequently used photosensitisers in the clinic belong to the class of haematoporphyrins e.g., photofrin, but also naturally occurring perylenequinones such as hypocrellin A (**83**), hypocrellin B (**84**) and hypericin (**85**) have received considerable attention. These compounds have longs been known as excellent photosensitizers producing high yields of singlet oxygen and superoxide radical anions, which is mainly related to an intramolecular H-atom transfer between the peri-hydroxyl group and the quinoid carbonyl group [e.g. 254-257]. Additionally, hypocrellins are also specific and potent inhibitors of protein kinase C, whereas hypericin is a strong inhibitor of both protein kinase C and tyrosine kinase with antiretroviral activity [258-261]. They exhibit only weak dark toxicity, for instance, natural products containing hypocrellin A and B have a long tradition as folk medicine in China. Furthermore, they show high thermo- and photostability and rapid metabolism *in vivo.* However, their low absorption in the photodynamic window (600 - 900 nm) as well as their insolubility in water limit their application in PDT. In order to circumvent these shortcomings a number of derivatives have been synthesized up to now including aminated, sulfonated, thiolated or metal-ioned hypocrellins as well as the use of liposomes as delivery systems [e.g. 257,262-265]. Among them, the aminated hypocrellins seem to possess the highest photodynamic activity. As an example, the introduction of an electron-donating butylamino group into hypocrellin A and B enhanced their photoresponse as well as their ability to generate superoxide radical anions. Promising *in vitro* and *in vivo* results suggest that the 2-butylamino-2-demethoxy-

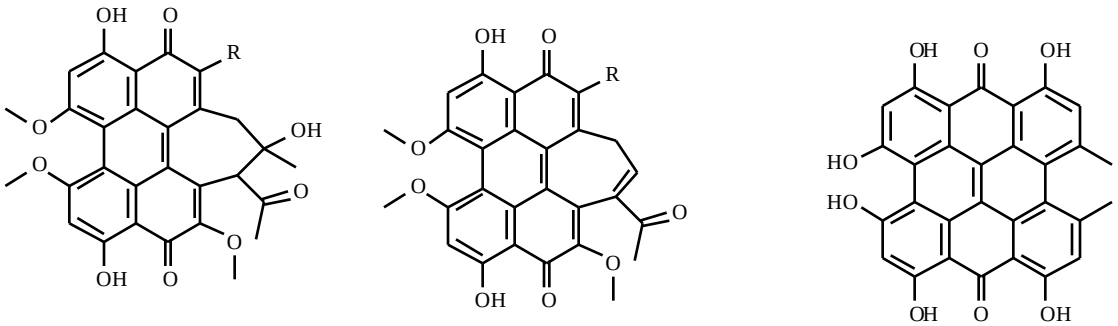

Fig. (12). Quinoid photosensitizers.

hypocrellins A (**86**) and B (**87**) are much more potent photodynamic agents than their corresponding hypocrellins [266].

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