Pakistan Journal of Pharmaceutical Science
Vol. 12(2), July 1999, pp.21-31

ROLE OF QUINONE MOIETY AS ANTITUMOUR AGENTS: A REVIEW

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ABSTRACT:
Quinone antitumour agents with wide spectrum of activity have been extensively used in different fonns of human cancers. Quinones have been isolated either from animals, microorganisms or plants. Extensive research on quinone compounds is going on to discover novel effective antitumour compound. We also discussed the mechanism of action, which have not been fully clarified. In this review we cover all the above mentioned aspects to emphasize the importance of quinone moiety as antitumour agents.

INTRODUCTION

Quinone containing compounds have been widely used for their antitumour and anticancer activity. Problems, such as, toxicity and drug resistance have served to stimulate an intense demand and all out research efforts for the discovery of new and novel anti tumour agents. In the last few decades significant progress has been made in the screening of quinone moiety for antitumour activity.

Nature is an important source of novel compounds useful directly as medicinal agents, as model compounds for synthetic or semisynthetic structure modifications and optimization, Compounds derived from natural sources serve as viable compounds for modem drug development.

QUINONE MOIETY IN NATURE

p-benzoquinone and very simple other alkyl derivatives are arthropod metabolites, which do not occur else where except in reduced form. A rare exception is the presence of *p*-toluquinone and the hydroquinone in the ascomycete *Nectria embescens*. Benzoquinone and its analogues are most widely used as chemical defensive agents by arthropods, millipedes, beetles, arachnids and termites. The actual compounds stored in the inner chamber of defensive glands are hydroquinones and hydrogen peroxide which then passed through another chamber where oxidase enzyme effect an explosive oxidation and as a result benzoquinone discharged as a hot spray, audibly in the case of bombardier beetles [Aneshansely, D.J., 1983].

Almost 350 natural naphthoquinones have been discovered and they constituents the largest group. Now the co-existence of naphthoquinones and anthraquinones in plants is not rare and they have a common precursor. New types include isofuranonaphthaquinones and naphthoquinones linked to coumarine unit while dimers of various kind and benzisochromanquinones form substantial subgroups.

The Anthraquinones are as widely occurring as naphthoquinones. The greater number of anthraquinones has been found in marine animals and in insects and there is substantial group in digitalis plants. Carminic acid, which is an example of anthraquinone, is a coloring pigment of cochineal which contain the dried bodies of cochineal insect *Dactylopius coccus*. It is still used for coloring pork sausage, shrimps, jams and other food and drinks beside medicinal pills and cosmetic products [Lloyed, A.G., 1980].

In the 1950s Brockmann and Brown elucidated the structure of the red-orange pigments isolated from culture of different streptomyces species. The aglycon moieties of these compounds identified as antluacyclinones belonging to the type known as rhodomycinone, isorhodomycinone and pyrromycinone whose color was due to the presence of polyhydroxy-anthraquinone chromophore

Recently number of cyclofarensylated quinines have been isolated from Paluan ascidian and Aplidium longithora [Fu, X., 1997, Davis, R.A., 1999].

Naturally Occuring Quinone Having Antitumour Activity

Asterriquinone obtained from culture of a strain of *Aspergillus terreus* exhibits antitumour activity, other eleven di-indolylbenzoquinones were also isolated [Arai, K., 1981]. Lapachol obtained from heartwood and roots of Haplophragma adenophyllum and Frederieamycin A obtained from Culture of Streptomyces griseus have showed antitumour activity.

Carmine acid is a colouring pigment of cochineal, which contains the dried bodies of cochineal insect *Daclylopius coccus.* It is still used for coloring shrimps, jams and other food and drinks besides medicinal pills and cosmetic products [Lloyed, A.G., 1980]. In rats this pigment revealed antitumour activity and it is a potent feeding deterrent to ants which suggest that its natural function may be to act as a defensive agent against predation specially for males and newly born insects which are not protected by wax covering. Kidamycin and Hedamycinare are other examples of naturally obtained antitumour antibiotics belonging to this class [Kanda, N., 1972].

The Anthracyclines are the important class of antibiotics and great numbers of anthracyclines are being used for the treatment of a range of human cancers. Doxorubicin is the drug against which all other anthracyclines are compared experimentally and clinically, it is first isolated from the culture of Streptomyces strain. Aclacinomycin ‘‘A’’, which is isolated by oki etal. From a culture of *Streptomyces gelilacus* in 1975 is a clinically important antitumour agent which also belong to the anthracycline group [Oki, T., 1975].

The new nortriterpene methylene quinones were isolated from *Maytenus amazonica,* their structure were elucidated by spectroscopic methods and they showed low antitumour activity against four cancer cell lines [Chavez, H., 1999].

Synthetic Approaches Towards New Antitumour Derivatives

Taking Mitomycin C as a model, a number of p- benzoquinone have been synthesized [Khan, A.H., 1976], for example 3,6-diaziridinyl-2, 5-bis- (carbethoxy) amino-1, 4- benzoquinone (Diazoquinone AZQ) and 2, 5, bis (l ,aziridinyl)-3 (-2-carbmoyloxy-1- methoxy ethyl-6- methyl-1, 4-benzoquinone (fig-2) have emerged as clinically useful derivatives as a result of the effort of two different teams.

Another derivative, 4-dialkylamino-5-methoxy-1,2 benzoquinone has also been synthesized

by using a simple and efficient method [Viallen, L., 1995]. Lapachol is reported [Da cansolacao, M., 1975] to be available in Brazil as antitumour drug.

Clinical trials have showed undesirable side effects. Several synthetic analogues have been studied in which only geranyl compound (fig-3) and the dibromoallyl derivative (fig-4) showed activity. Fredericamycin A is a potent antitumour antibiotic [Misra, R., 1982] and its structure was elucidated by using x-ray technique [Misra, R., 1982]. For the signif 10-anthracenedione [Cheng, C.C., 1983].

The molecular modeling studies on the anthraquinone derivatives have been carried out to find out the effect of the different structural features present in the anthraquinone derivatives, i.e. the number of methylene groups (n) in the side chain, the steric bulk of the terminal amines and the presence of hydrophilic hydroxyl groups in the side chain, on their interaction with DNA [Agbandje, M., 1992]. The compound studied presented in fig-5.

Quite a few numbers of Anthracyclines are being used for the treatment of a range of human cancers. Determined efforts have been made to discover new chemotherapeutic agents having less side effects [Aubel-Sadron, G., 1984]. At present among all antineoplastic agents, doxorubicin exhibited the widest spectrum of antitumour activity and is the most utilized antitumour drug worldwide. Due to its cumulative dose-limiting cardiotoxicity, search for new analogues with reduced cardiotoxic potential and a more favorable therapeutic index was carried out. Hundreds of anthracyclines have been synthesized, utilizing new chemical reactions, most of them did not show significant activity as compared to that of doxorubicin [Weiss, G., 1986].

Analogues of daunorubicin possessing a fluorine atom at position C-8 of ring A have been synthesized with the aim of comparing their DNA-drug interaction and antitumour properties with those of the clinically useful anthracyclines doxorubicine and idambicin. The synthesis of (8s)-8-fluoro 4-demethoxydaunorubicin and molecular mechanism and NMR studies led to the synthesis of epimeric (8R)-8-fluoro-4-demethoxydaunorubicin The cytotoxic properties of the two 8-fluoro-anthracyclines analogues were markedly affected by the stereoselectivity of the fluorine substituent [Lomardi, P., 1995].

The fluoro derivatives were synthesized directly from daunorubicin and idarubicin following a non-deglycosidative approach [Pasqui, F., 1996]. In preclinical studies another halogenated anthracycline derivative, 4-deoxy-4-iododoxorubicin has demonstrated significantly reduced levels of cardiotoxicity compared to currently employed anthracyclines. The iodine atom at the 4-position of sugar ring reduces the basically and enhances the lipophilicity of this compound as compared to related anthracycline drugs. The iodine substituent does not alter the geometry of intercalation as compared to previously solved anthracyclines complexes, but appears to markedly effect the solvent environment of the structures. This could have consequences for the interaction of this drug with DNA and DNA binding proteins in cells [Berger, I., 1995].

The search for new antitumour agents having less toxicity, more cytotoxicity potency than their parent compound delivered the morpholino anthracycline. It possesses a morpholino ring incorporating the amino nitrogen of the daunosamine unit at the 3-position. It has been suggested that charged amine at the 3-position of the daunosamine sugar interacts with p-glycoprotein. From morpholinoanthracyclin Methoxy-morpholino-doxombicin and 3-deamino-3-morpholino-13-deoxo-l0-hydroxycarmomycin are under clinical trials [Rpamonti, M., 1992; Watanebe, W., 1988; Ogawa, M., 1989].

Recently a series of indolequinones bearing various functional groups have been synthesized

which exhibited antitumour activity [Beall, H.D., 1998].

Mechanism of Action

There are number of mechanisms by which quinone containing compounds exerts their cytotoxic action, however it is not clear that which of these actions is the most important in inducing cell damage. The main target for their cytotoxic action is DNA.

The best known mechanism is the intercalation between two base pairs of DNA or RNA. The ring of the polycyclic chromophore plays a vital role in the intercalation by binding to DNA and RNA. By a strong electrostatic bond of the positively charged amino sugar portion of the anthracyclines to the sugar sugar-phosphate backbone of DNA the intercalated molecule is stabilized at intercellular pH. This way vital actions such as replication and transcription are blocked [Quigley, G.J., 1980; Wang, A.H., 1987].

Topoisomerase are essential for DNA metabolism by inserting transient breaks into single (topoisomerase 1) or double strand (topoisomerase II) DNA, thus solving mechanical problems caused by the double-helical structure of DNA [Pommier, Y., 1993]. The anthracycline-topoisomerase complex (cleavable complex) form stabilized DNA breaks, thus turning topoisomerase into cellular toxins. The nature of the substiutuent at 3'- position of the daunosamine moiety and of the C-14 position of the chromophore ring A are essential in the formation of cleavable complexes [Capranico, G., 1994; Bodley, A., 1989].

Several 5-alkyl-1, 3-dihydroxy benzene (5-alkylresorcinol) and 6-alkyl-1, 2,4 trihydroxy benzene derivatives were prepared and used to study the mechanism by which such compound effect Cu dependent DNA strand scission Te efficiency of DNA cleavage increased with increasing length of the alkyl substituent. DNA cleavage by the 5-alkylresorcinol appears to involve initial oxygenation of the benzene nucleus. Te resulting trihydroxylated benzene mediated DNA cleavage in a reaction dependent on the presence of both Cu^{2+} and O^{-2} The mechanism appears to involve reduction of Cu^{2+} by the trihydroxy benzene moiety with subsequent formation of reactive oxygen species [Sing, U.S., 1995].

Quinone containing compounds also exert cytotoxicity by radical formation through electron transport with a vital role for the quinone (C) ring. In the absence of oxygen they have the potency to generate aglycone free radicals (by splitting off the amino sugar of the semiquinone radical) that produce DNA and RNA single and double strand breaks. Free oxygen radicals can damage intra as well as extracellular macromolecules (lipids and proteins). Their action cells and mitochondria inhibit swell, other organdies fragmentate, and essential intracellular enzymes.

Quinone moieties can also be cytotoxic by binding to membranes thus altering their functions. Cytotoxicity by membrane interaction in vitro where entrance of free doxombicin was prevented by coupling doxorubicine to an insoluble agarose support has been demonstrated.

Reaction of the anthracyclines, antitumour drugs adriamycin and daunorubicin with the self complementary DNA oligonucleotide $GCGCGCGC(GC)_4$ in the presence of reducing agent dithiothreitol, the oxidizing agent hydrogen peroxide, or the alkylating agent formaldehyde gives a similar mixture of DNA-drug adducts [Dylan, J., 1997].

Mitomycin is a bioreductive alkylating agent of DNA. About DNA-mitomycin ''C'' complex (fig-6) no specific information was available. However it has established that mitomycin binds to

minor groove [Tomasz, M., 1987] not in major groove as believed earlier. Iye, and Szybalski proposed a mechanism [Iycr, V.N., 1964] and that is modified by Moore and Czemiak [Moore, KW, 1981] shown in Scheme A. Quinone moiety in mitomycin C is reduced by one electron to the semiquinone (1.2, R= electron) or by two electrons to hydmquinone (l.2, R= H) and this reduction of quinone converts the heterocyclic nitrogen from a non nucleophlic vinylogons amide nitrogen to an amine nitrogen which can eliminate the β–methoxide ion (1.2). The compound (1.4) is a set up for aziridine ring opening, which is produced by the tautom erization of the immonium ion (1.3) and thus the drug is activates by unmasking the electrophilic site at C-1 which alkylates the DNA (1.5). The cross linking of DNA is result (1.7) by the subsequent reaction of DNA at C-10 (1.6).

Reduction of the quinone is necessary for the covalent reaction of mitomycin C to DNA but there is controversy that whether the semiquinone (1.2, R= electron) or hydroquinonc (1.2, R= H) is the viable intermediate [Frank, R. W., 1990]. Chemical model studies on the mechanism of action of (1.1) indicate that the conversion of 1.1 to 1.7 can occur at the semiquinone stage and conversion of 1.6 to 1.7 occurs at the hydroquinone oxidation state [Kohn, H., 1990].

The bioreductive alkylation method based on quinone reduction to the corresponding hydroquinone was used in the prodrug design. Both mono (scheme B) [Antonini, I., 1982] and bisalkylating agents (scheme C) [Lin, A.J., 1975] were developed. Substituents, which are electron rich, lower the reduction potential of the quinone and make them more reactive. Both monoalkylated and bisalkylated DNA adducts have been identified and the extent of mono and bisalkylation increases as the guanine base composition of DNA increases [Borowy-Borowski, H., 1990]. The attachment site of these adducts is at N-2 of the guanine base [Tomasz, M, 1987),] thus DNA synthesis inhibited. In addition single strand breakage of DNA is caused by reduced mitomycin. In rodents mitomycin is tetratogenic and carcinogenic but the immunosupressive properties of mitomycin are relatively weak.

Scientists are working on quinone compounds because of its potential as effective anticancer agents. Quinones are abundant in nature so, with the help of all relevant structure and chemical information and by understanding how these molecules bind and interact on the molecular level, more new and safe anticancer drugs of the future will most certainly be found in very short time.

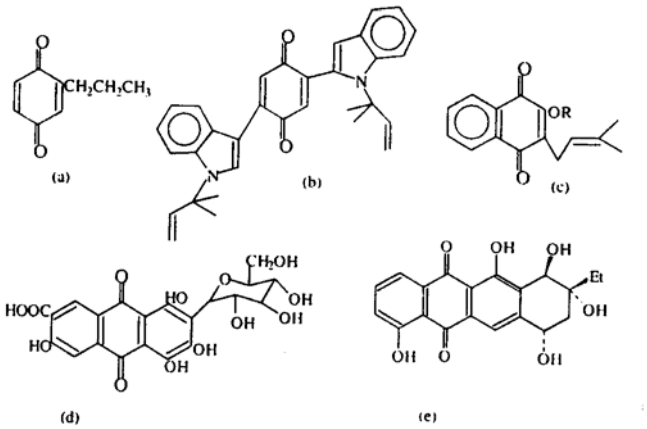
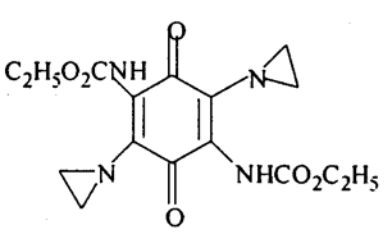
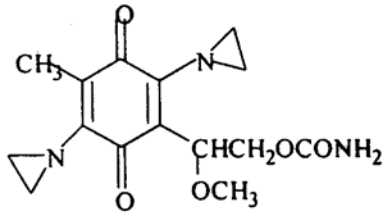


Fig. 1: Some naturally occuring quinone (a) n-propyl-1, 4 hen[oquinone which is a defensive secretion of Pedinini beetles (b) Asterriquinone from the culture of a strain of *Aspergillus terreus* this exhibits antitumour activity (c) Lapachol from the heartwood and roots of *Hoplophyragma* adenopltyllumm (d) Carminic acid from the insect Dactylopiusceylonicus, having antitumour activity. (e) a-citromycinone as a glycoside (cosmocarin) in culture of *St. cosrnasus*.



3,6-diaziridinyl-2,5-bis(carboxy)amino-1,4-benzoquinone



2,5bis(1-aziridinyl)-3-(2-carbamoyloxy)1-methoxy ethyl-6-methyl-1,4-benzoquinone

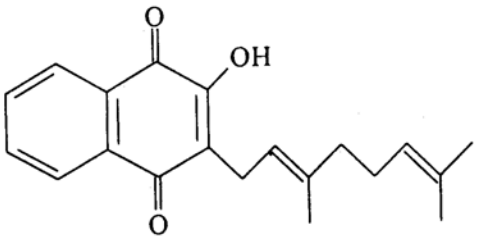


Fig. 3

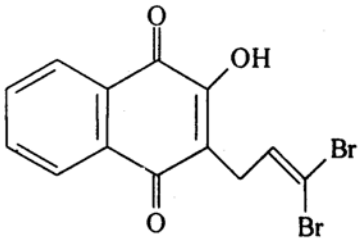


Fig. 4

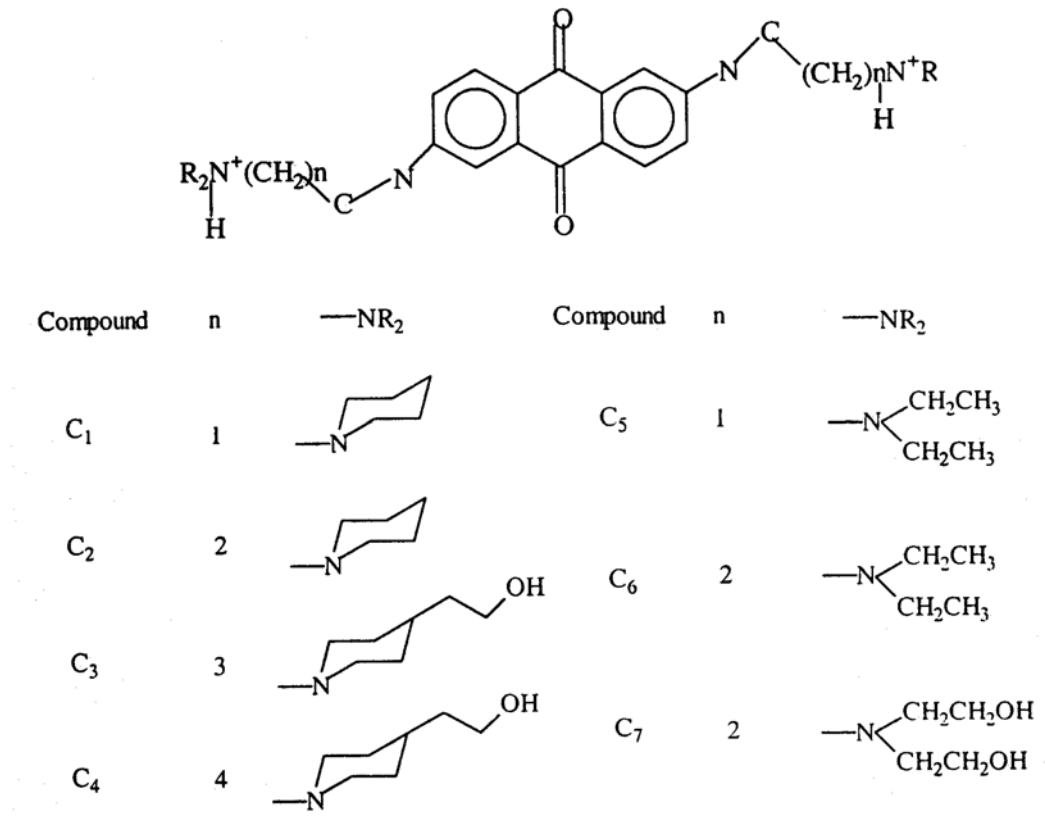


Fig. 5: The strcutural formulae of the compound used in the molecular modeling of the interaction of the interaction of the 2,6-bis(ω-aminoalkanamido)-9, 10 anthracenediones with DNA.

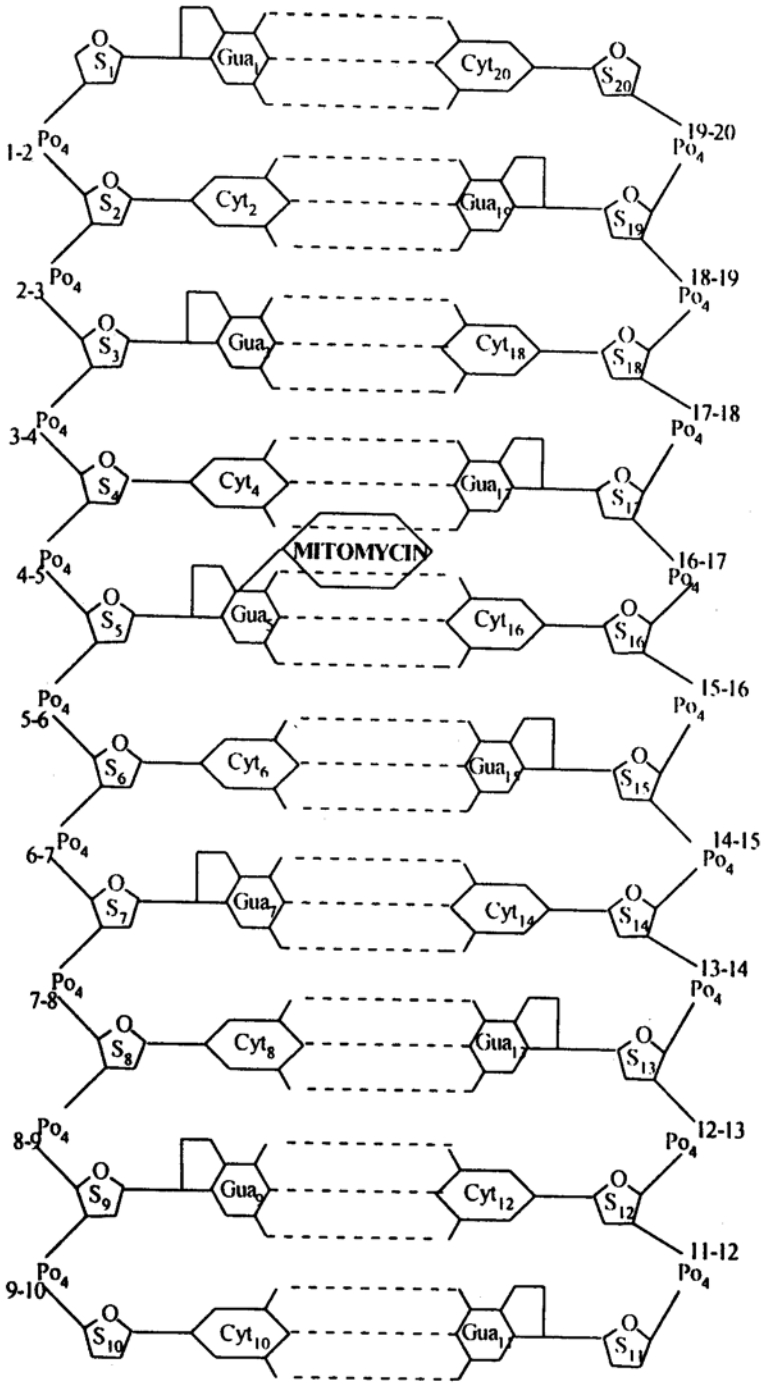
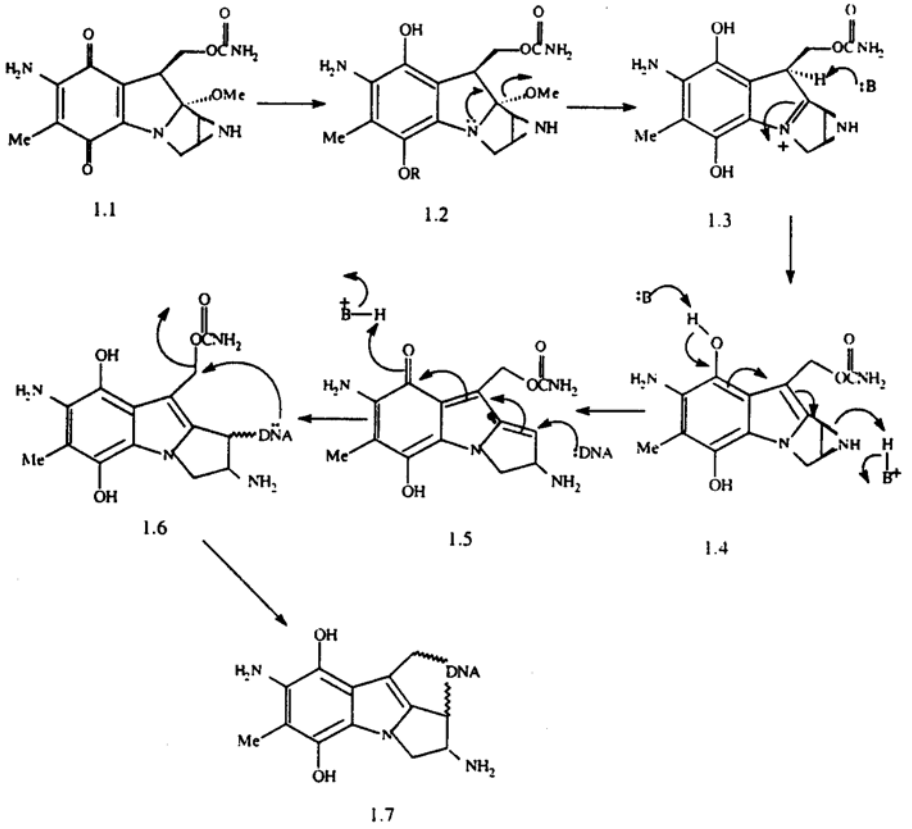
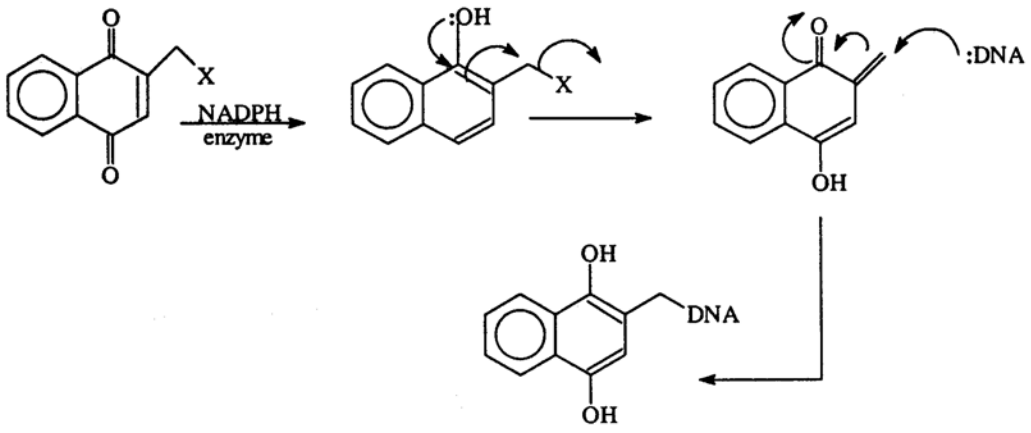


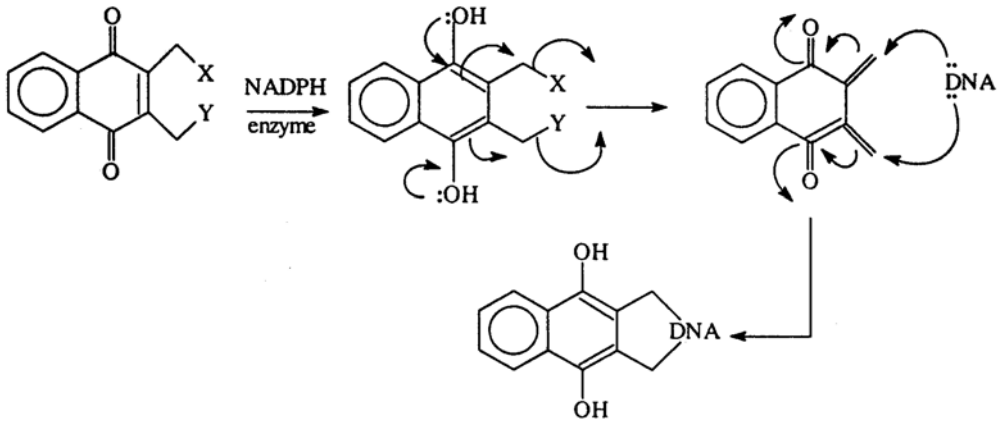
Fig. 6: Schematic representation of d (GCGCGCGCGC)$_2$ (GC$_{10}$) used in the studies on DNA-Mitomycin complex.



Scheme A:Bioactivation of Mitomhycin C.



Scheme B: Bioreductive monoalkylating agents.



Scheme C: Bioreductive bisalkylating agents.

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