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# Structural Variance of Doxorubicin and Anthracycline Analogues as Topoisomerase Alpha and Beta (*Top2a and Top2b*) Inhibitors and Potential Design of Analogue Candidates of Less Side Effects on Cardiomyocytes

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**Doxorubicin that is on WHO's list of essential medicines and other anthracycline analogues, in general, are natural metabolites isolated from Streptomycetaceae, or semi-synthetized derivatives stated as first-generation anticancer agents. The tetracyclic scaffold attached mostly to amino sugar is known to be effective against solid tumors compared to other anticancer agents. The mechanism had been stated as intercalating agent at the minor groove of DNA strands during the step of releasing supercoiled DNA. Along with their anticancer activity, anthracyclines possess antimicrobial effects of notable MIC values. Cardiotoxicity represents the main challenge for both of medical care for treatment of cancers and drug discoverers. This exertion deals with careful structural investigation of the three-dimensional, fully optimized drugs in use. Drug-candidates in clinical studies, and leads failed in last developments. The aim is to find a structural gate to guard against or reduce the cardiac side effects. It deals also, with the topological features differentiating between antibacterial and anticancer agents bearing the tetracyclic scaffold features as well as between the topoisomerases as target molecules.**

**Keywords:** Anticancer Activity; Anthracycline; Cardiac Toxicity; Doxorubicin; Fully Optimized 3D Structure; Gene; Topoisomerase Top2A; Topoisomerase Top2B.

Scaffolds especially those derived from natural sources are of vital biological importance as antineoplastic agents. Anthracyclines dates back to 1960's and their primary isolation revolutionized the treatment modalities for many cancers, namely solid tumors and neoplastic types. Early agents

known were doxorubicin and daunorubicin, categorized as antibiotics having high affinity for Gram-positive bacteria but exhibited significant cytotoxicity which led to their exploitation as anticancer drugs.[1-4]

Anthracyclines are currently used in combination for treatment of breast cancer with the standard CMF (cyclophosphamide, methotrexate, and fluorouracil) regimen[5], as well as other combination.[6,7] The enclosure of an anthracycline has been proved to decrease mortality rates in women. Anthracyclines are also used for different clinical indications.[8,9]

Several anthracyclines obtained via biosynthesis or chemical modifications. An alarming aspect of their clinical use is the toxic risks associated with their accumulation. The aim has always been the development of safer anthracyclines, with broader spectrum of activity against different tumors, as well as enhanced selectivity. Most of the first, second and third generations share an amino-sugar moiety essential for DNA binding and intercalation.[10-12] The main drawback associated with the use of anthracyclines lies in their considerable affinity to the cardiac tissue, lead to cardiotoxicity.[13] In order to avoid and/or minimize the risk of cardiomyopathy and congestive heart failure, this work relates the extent of cardiotoxicity and structural differences in each drug by considering the topology of the fully optimized 3D-structure. The physicochemical data of the optimized structures are also considered. Anthracyclines bind to topoisomerases II and DNA resultant in a ternary complex, and preventing re-ligation.[14,15] The cardiotoxicity involves production of free-radical, which results in damaging DNA, proteins, and lipids and leads to cellular dysfunction.[16] Thorough, investigation of occurrence in cells and organs of topoisomerases mentioned that doxorubicin targets both of topoisomerases namely, alpha (Top2A) and beta (Top2B). Human topoisomerase TOP2A is encoded by the *Top2A*-gene on chromosome-17q21-22, and Top2B is encoded by the *Top2B*-gene on chromosome-3p24. Cardio-myocytes express Top2B but not TopP2A.[15-18]

In area of drug discovery scientists usually locking in the main pharmacophore that fits the pharmaco-dynamic interactions. Derivatization on the skeleton rely on addition, removal, and/or modification of adaptable entities on the skeleton that lead to selectivity and specificity whenever isoforms found. Considering cardiomyocytes that express Top2B but not Top2A and the inhibitor's level of effects and side effects.[19-22] Topoisomerase-2 necessitates ATP to act. It makes a temporary break and rejoin via trans-esterification utilizing phosphate-diester (Figure 1). Thus, inhibition of topoisomerase II preventing DNA repair and causing DNA damage and cell-death.[23]

Several strategies are mentioned for tumor selectivity such as (a) - It can be boosted if aided by specific transporters to malignant tissues in specific organs,[24-27] (b) - Liposomal formulations as well as binding to polymers (31), and (c) - Prodrug preparations that are favorably activated intracellular.[28-33] These tactics were used to increase selectivity and reduce undesirable effects.[34,35] This work is a thorough structural and topological investigation of anthracyclines. Molecular modeling of each selected approved drug or candidate structure studied as fully optimized at full self-consistent field (SCF) levels by using MOPAC[36,37]; a general molecular orbital package implemented with molecular mechanics software MMXPC.[38] This study is to find the structural modalities differentiating between toxic anthracyclines, safer anthracyclines, anthracyclines bearing both antibacterial and anticancer effects, and the related tetracyclines. It is a continuation of our interest in compounds bearing anti-cancer, anti-inflammatory and antimicrobial activities.[24,39-52] The answer for topology differences between approved antimicrobial and antineoplastic tetracyclic structures can be gathered in throughout the article.

**Structural characteristics of drugs approved candidates of anthracyclines**

The structural differences of derivatives in medical use mainly attributed to three substructures in the tetracyclic skeleton namely C-4 (Ring A), C-7 and C-9 (Ring D). The entities involved are amino-sugar (Figure 2, $R^1$), the minor differences of aglycone moiety (Figure 2, $R^2$) and the whole acyl group (Figure 2, R) at C-9.[53-76] The important physicochemical data for these drugs and/or candidates are considered as calculated partition coefficient.[54,55-76]

The calculated partition coefficients of clinically used analogs range from CLogP: 1.734 for the more lipid soluble, like idarubicin to CLogP:

0.648 for the less lipid soluble one like doxorubicin. Lipid solubility is important for effects and side effects as well.[56-76]

**Brief Biosynthesis of anthracyclines**

Biosynthesis of doxorubicin involves many steps reported in conventional articles. It starts by a three carbons unit; propanoyl-CoA; (Figure 3) which combines by a decarboxylation coupling with malonyl-CoA. Malonyl-Co-A is, repeatedly added via carriers after losing carbon dioxide in each step to provide a skeleton of 21 carboxylic acid bearing 10 carbonyl groups.[2,79-81] The poly-carbonyl 21-carbon acid manipulated successively by different enzymes to yield tricyclic; alkanoic acid, then to the aglycone; rhodomycinone. Rhodomycinone undergoes structural modifications and coupling with amino-sugar, *via* several bio-transformations to provide doxorubicin.[82,83]

**Medical importance of anthracyclines in cancer treatment**

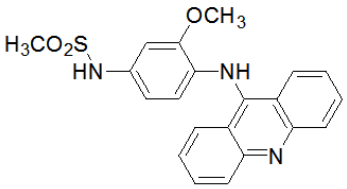
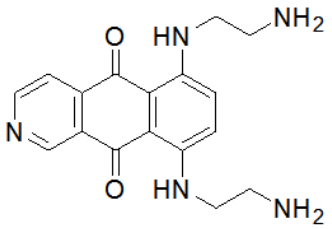
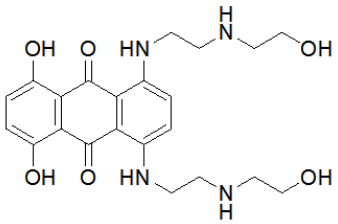
Anthracyclines are still very important for treatment of acute lymphocytic and chronic myelogenous leukemia; the disease in which the bone marrow makes too many white blood cells. Doxorubicin also, succeeded to show a substantial efficacy against solid tumors.[84] Several types of solid tumors are responsive to doxorubicin, as breast carcinoma, small-cell lung carcinoma, and ovarian carcinoma.[85]

**Pharmacological effects and toxicological profiles of anthracyclines**

Not only disrupting topoisomerase-II-mediate DNA repair, anthracyclines also, produce free radicals by reversible quinonoid transformation. Free radicals damaging membrane, DNA and proteins. In addition, reactive oxygen can make epoxidation of fatty acids leading to membrane and DNA damage, oxidative stress, and triggering apoptosis.[86,87] Alternatively, doxorubicin can enter the nucleus and poison topoisomerase-II, also resulting in DNA damage, cell cycle control and cell death.[88-91]

The cumulative dose-dependent cardiac toxicity of doxorubicin represents unwanted health problem from essential medicines. There

**Table 1.** Non anthracycline topoisomerase-2 inhibitors

| Compound Name, Number, cLogP | Chemical Structure | Findings | References |
|---|---|---|---|
| Compound 7: Amsacrine CLogP: 4.69 |  | Amino acridine frequently used in mixtures. It produces consistent but acceptable cardiotoxic effects. | 60,64,65 |
| Compound 8: Pixantrone CLogP: 0.772 |  | Conditional approval was granted by the European Medicines Agency | 60,66,67 |
| Compound 9: Mitoxantrone CLogP: 1.099 |  | Anthraquinone derivative. Approved by FDA. Less cardiotoxic effects. | 60,68-70 |

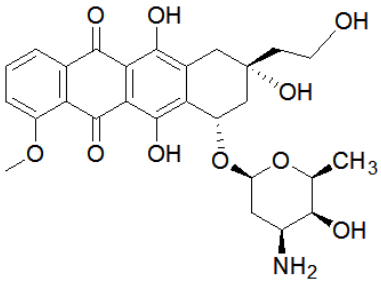
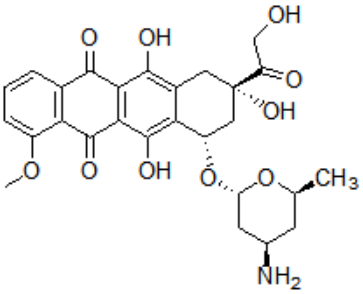
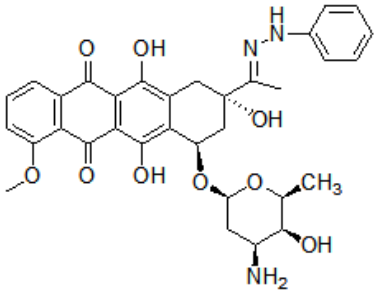
are some differences between the anthracycline's congeners in toxicological profile and upon comparing their ability to induce topoisomerase II-mediated DNA cleavage.[92-94] Cardiac toxicity as reported in several articles attributed to the cellular oxidative stress induced by free radicals. Unfortunately, doxorubicin preferentially interacts with cardiomyocytes, and the side effects resulted as reflection of free radicals on DNA, protein and lipid as reported elsewhere (Figure 4).[95-97]

Oxidative stress resulted as reflection of coordination reactions between metals such as iron and functionalities of the co-planar system at rings B and C (Figure 4). The complex of metal and anthracyclines catch soluble oxygen that accordingly producing superoxide. Superoxide dismutase: the natural cellular antioxidant change catalyzes the disproportionation of superoxide to be converted into two less damaging species.

**Comparative cardiac toxicity and potential chemical modifications to decrease side effects**

The relevant chemical entities involved in oxidative stress-are mentioned on tetracyclic structure of anticancer as well as antibacterial

**Table 2.** Important investigational and experimental anthracyclines

| Compound name, Number, cLogP | Chemical structure | References, Clinical phase, Situation |
|---|---|---|
| Compound 10: 13-deoxy-doxorubicin, natural. CLogP: 1.444 |  | Ref.71 https://clinicaltrials.gov/ct2/show/NCT04704635?rank=1 Clinical Phase II terminated. Reason is the development of heart failure. https://patents.justia.com/patent/5948896 Situation: Investigational candidate |
| Compound 11 Esorubicin; 4'-deoxy-doxorubicin CLogP: 0.879 |  | Ref.72-74 Clinical Phase I/II terminated. Reason toxicological issues. Situation: Investigational candidate National Prostatic Cancer mentioned that this candidate was associated with hematologic toxicity with 50% of patients Further trials do not appear to be warranted in advanced prostate cancer |
| Compound 12 Zorubicin CLogP: 3.0322 |  | Ref.60-75 https://pubmed.ncbi.nlm.nih.gov/9332680/ Situation: Experimental candidate |
| Compound 13 SP1049C | It is doxorubicin in P-glycoprotein-targeting Pluronic. | Ref.60-78 Cardiotoxicity was reduced to 50% |

activities. The group of drugs and candidates realized for elaboration of topology and SAR study (Figure 5). The structural entities responsible for chelation and free radical production are highlighted. Compounds are mentioned by numbers and names (Figure 2 and Table 2). An anthracycline; Compound 14; Mutamycin E (Figure 5) fulfills the features of doxorubicin except the C-9 alpha-hydroxy acetyl group. This compound as active but not considered for further preclinical effects as anticancer. On the other-hand, tetracycline (Figure 5, Compound 15) which has no amino-sugar attachment at C-7 is in use as antibacterial medicine with high safety. The two compounds 14 and 15 are included with anthracyclines to elaborate the important topological differences on biological activity. The differences are important to verify the clinical usefulness of tetracyclic structures as anticancer and/or antibacterial activity.

Doxorubicin (Compound 1, Figure 2) is in wide use especially in solid tumors and used

**Table 3.** Important used drugs, investigational, and experimental tetracyclic structures optimized at full self-consistent field (SCF) levels by using MOPAC

| Compound | % PSA | % UnSA | SE | Str | bnd | DM | HF | CLogP |
|---|---|---|---|---|---|---|---|---|
| Compound 1: Doxorubicin | 37.72 | 14.25 | -97.6 | 1.480 | 9.203 | 7.433 | -383,43 | 0.648 |
| Compound 2: Daunorubicin | 35.26 | 14.25 | -99.2 | 1.422 | 8.306 | 5.598 | -346.62 | 0.959 |
| Compound 3: Epirubicin | 37.84 | 14.35 | -98.5 | 1.509 | 8.875 | 7.52 | -384.24 | 0.648 |
| Compound 4: Idarubicin | 35.72 | 16.02 | -84.4 | 1.373 | 7.091 | 6.595 | -310.49 | 1.734 |
| Compound 5: Amrubicin | 45.36 | 26.55 | -73.4 | 1.688 | 5.960 | 6.245 | -201.03 | 0.113 |
| Compound 6: Annamycin | 37.76 | 14.04 | -110.0 | 1.871 | 8.839 | 5.608 | -369.53 | 1.599 |
| Compound 10:13-deoxy -doxorubicin | 30.66 | 13.30 | -103.1 | 1.290 | 7.265 | 2.758 | -397.34 | 1.444 |
| Compound 11: Esorubicin | 34.89 | 13.88 | -95.6 | 1.394 | 7.440 | 5.655 | -343.02 | 0.879 |
| Compound 12: Zorubicin | 27.45 | 20.97 | -128.6 | 13.850 | 12.000 | 13.886 | -303.78 | 3.032 |
| Compound 14: Mutamycin E | 32.68 | 14.22 | -115.0 | 1.930 | 9.837 | 6.179 | -447.55 | 2.613 |
| Compound 15: Tetracycline | 44.55 | 15.61 | -143.7 | 1.717 | 7.152 | 5.215 | -238.7 | 0.911 |

PSA = Polar Surface Area, UnSA = Unsaturated Surface Area, SE = Standard Entropy, Str = stretching, Bnd = bending, DM = dipole moment, HF = heat of formation, and ClogP = Calculated partition coefficient for n-octanol/water obtained from chemdraw 8 ultra.

**Table 4.** Important used drugs, investigational, and experimental tetracyclic structures calculated in-silico- for pharmacokinetics by Swiss ADME

| No. | Compound | MR | Consensus Log P | Pgp substrate | Bioavail-ability Score | Lead-likeness #violations |
|---|---|---|---|---|---|---|
| 1 | Doxorubicin | 132.66 | 0.52 | Yes | 0.17 | 1 |
| 2 | Daunorubicin | 131.5 | 1.18 | Yes | 0.17 | 1 |
| 3 | Epirubicin | 132.66 | 0.5 | Yes | 0.17 | 1 |
| 4 | Idarubicin | 125.01 | 1.14 | Yes | 0.55 | 1 |
| 5 | Amrubicin | 120.2 | 0.82 | Yes | 0.55 | 1 |
| 6 | Annamycin | 137.59 | 0.99 | Yes | 0.17 | 1 |
| 7 | 13-deoxy-dextrorubicin | 134.18 | 0.95 | Yes | 0.17 | 1 |
| 8 | Esorubicin | 136.2 | 1.76 | Yes | 0.55 | 1 |
| 9 | Zorubicin | 167.5 | 2.24 | No | 0.17 | 2 |
| 14 | Mutamycine E | 132.12 | 0.56 | Yes | 0.17 | 1 |
| 15 | Tetracycline | 110.22 | -0.56 | No | 0.11 | 1 |

MR = Molar refractivity, Consensus Log P = It is method is similar (but not identical) to the ClogP method in Swiss ADME

**Table 5.** Comparative cardiac effects versus doxorubicin and/or each other

| Compound | Comparative cardiotoxicity | References / Findings |
|---|---|---|
| Daunorubicin;<br>Compound 2<br>versus doxorubicin | By contrast, daunorubicin was approximately half as cardiotoxic when compared with doxorubicin. Daunorubicin was less cardiotoxic among survivors of childhood cancer. | Ref (119, 120)<br>1- C-9 acetyl instead of hydroxyl-acetyl<br>2- Sugar at C-7 substituents differently arranged<br>3- Methoxy-substituent at C-7. |
| Epirubicin;<br>Compound 3<br>versus doxorubicin | Clinical trials demonstrated safety comparable to that of doxorubicin in early and advanced breast cancer. Epirubicin has been favored over doxorubicin for lower cardiac toxicity | Ref (92, 121-123)<br>It is the diastereomer of doxorubicin. Sugar C5' alpha-hydroxyl group.<br>1- C-9 acetyl instead of hydroxyl-acetyl.<br>2- Sugar at C-7 substituents differently arranged.<br>3- Methoxy-substituent at C-7. |
| Idarubicin;<br>Compound 4 versus doxorubicin | It is more cytotoxic than doxorubicin, explained by higher hepatic penetration because of high lipophilicity. Orally active.<br>It is less cardiotoxic than doxorubicin in phase II clinical trials. | Ref (124) & Ref. (92, 100, 125-127)<br>1- C-9 acetyl instead of hydroxyl-acetyl.<br>2- Amino-sugar at C-7.<br>3- No substituent at C-4. |
| Idarubicin;<br>Compound 4<br>vesus Epirubicin | A significantly lower accumulation in cardiomyocytes was obtained with epirubicin and idarubicin compared with carminomycin and doxorubicin. | Ref. (126-129)<br>1- C-9 acetyl instead of hydroxyl-acetyl.<br>2- Amino-sugar at C-7.<br>3- No substituent at C-4. |
| Esorubicin;<br>Compound 11<br>(CLogP: 0.879)<br>versus doxorubicin | For human solid tumors in vitro in clonogenic assay appeared to be more potent on a weight basis than DOX. ESO has been reported to have decreased cardiac toxicity in preclinical models as compared to DOX. | Ref. (130-132)<br>Experimental:<br>1- C-9 hydroxyl-acetyl, similar.<br>2- Deoxy-sugar at C-7 substituents (a hydroxyl group is missed from the C-7 entity).<br>3- Methoxy-substituent at C-7, similar |
| Amrubicin;<br>Compound 5<br>versus doxorubicin<br>N.B. Not approved FDA but approved in Japan | There was no significant cardiac toxicity, and concluded that amrubicin has efficacy comparable to doxorubicin. Amrubicin showed lower cardiotoxicity at equivalent dosages. This seems to be due to the restricted distribution of the active metabolite in non-tumor tissues. | Ref (133, 134), (58, 135)<br>1- C-9 acetyl instead of hydroxyl-acetyl.<br>2- No amino group and no methyl group in the sugar at C-7.<br>3- No substituent at C-4. |
| Annamycin;<br>Compound 6<br>versus doxorubicin | Annamycin have little to no cardiac toxicity. It is formulated in a nano-molecular bi-lamellar liposomal system. Side effect (136) Bone marrow toxicity delaying its development. | Ref (137), (62), (63, 136, 137)<br>1- C-9 hydroxyl-acetyl.<br>2- Sugar at C-7 the substituents with iodine and no amino group.<br>3- No substituent at C-7. |
| Zorubicin;<br>Compound 12<br>versus doxorubicin | Toxicity appears high grade granulo-cytopenia, thrombo-cytopenia, Cardiotoxicity appears like DOX. | Ref (138-141)<br>It is the phenylhydrazone of daunorubicin.<br>1- C-9 acetyl instead of hydroxyl-acetyl. |

| | | |
|---|---|---|
| | | 2- Amino-sugar at C-7.<br>3- Methoxy substituent at C-4. |
| Amsacrine;<br>Compound 7<br>versus doxorubicin | Amsacrine in clinical trials it developed occasional instances of acute cardiac arrhythmias and cardiomyopathy. Amsacrine-related cardiac events are less common than those related to anthracycline chemotherapeutic agents. | Ref. (142-146)<br>Acridine derivative |
| Pixantrone;<br>Compound 8<br>versus doxorubicin | It is of reduced cardiotoxic potential compared with doxorubicin and mitoxantrone | Ref. (66, 67, 147, 148)<br>Benzo(g)isoquinoline derivative |
| Mitoxantrone;<br>Compound 9;<br>versus doxorubicin | Active DNA intercalating agent with low cardiotoxic potential. | Ref. (125, 149-151)<br>Aza-anthraquinone derivative |
| SP1049C; Compound 13;<br>doxorubicin in<br>P-glyco-protein<br>versus doxorubicin | P-glycoprotein for increasing cellular uptake, transport, and half-lives of drugs. It is not approved, yet. It reduces the relative cardiotoxity to about half of that of doxorubicin. | Ref. (126, 127, 152, 153) |

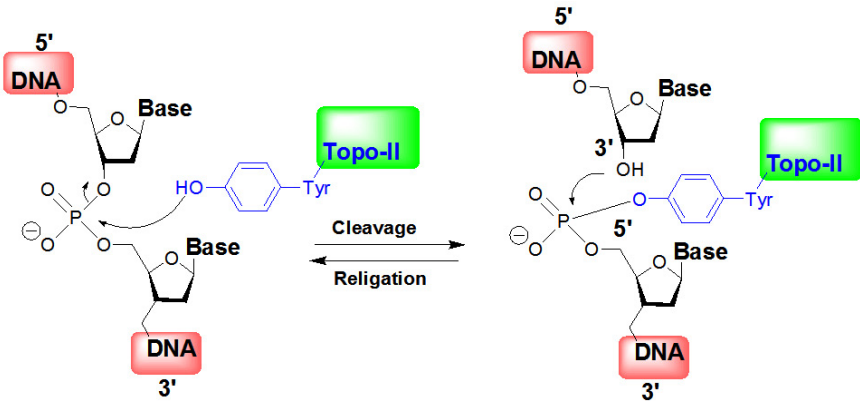



**Fig. 1.** Topoisomerase-II mechanism of releasing the supercoiling and rejoining DNA

admixed with other agents to reduce as possible the side effects on heart (98). In addition to the entities that are highlighted for their contribution in free radical formation (Figure 4), doxorubicin has three main groups represent the differences with congeners. The most important entities are:

i. A coplanar C-4-methoxy group.

ii. Amino-sugar (pyran ring) substituent attached to C-7 of three groups a methyl, a hydroxyl and one amino group.

iii. A hydroxy acetyl group-oriented *beta* as a substituent at C-9.

Daunorubicin has the same structural entities at C-4 and C-7 but having acetyl instead of hydroxyl-acetyl at C-9. This small difference led to a product of less side effect on heart.[98-100]

The (Figure 6) shows a graphical representation of doxorubicin G1 as coplanar four fused rings part C, the substituent at C-7 as part A and the substituent at C-9 as part B. Doxorubicin G2 as optimized at full self-consistent field (SCF) levels by using MOPAC; a general molecular orbital package implemented with molecular mechanics software MMXPC.[36-38] In the general substituted tetracyclic system, the structure part C is planar. Part B (the C-9 substituent) appears perpendicular up with the planar C and the amino-sugar; part A appears perpendicular down to the planar

system. The following monographs are introduced for comparative purposes between tetracyclic structures of anticancer activity concomitant with severe side effect on heart with those having less side effect and with the others bearing antimicrobial activity rather than cytotoxicity.

Candidates of analogs as anticancer compounds, in addition to compd. 14 a natural product (101) bearing antibacterial and cytotoxic activities and tetracycline are studied as 3D-optized structures at full SCF and outlined in (Table 4).[101,102] A very important value gathered from the table is the tetracycline having very high percentage of polar surface area (% PSA, 44.6%). The candidates failed in clinical development like compound 10 and compound 12 bearing the least percentage of polar surface area (% PSA 22.5 and 30.6%). It also indicates the importance of the ketonic-function of substituent at C-9.[103-106]

The methods by which anthracyclines can be prepared are semi synthesis, genetically engineered *Streptomyces peucetius* and from total synthesis.[107-110]

The attempts to reduce the incidence of cardiotoxicity can be made if several modifications can be applied.

First is to remove the methoxy substituent at C-4 of the skeleton. The drugs and candidate such as compounds 4, 5 and 6 are of less cardiotoxic effect. Methoxy group on aromatic systems donates electrons and, in these cases, it may increase the chelation power of the keto-enol systems undergoing the chelation with iron. Other groups can be tried.[111,112]

Second is the ketonic group (C=O) of the C-9 substituent appear of high importance for tumoricidal action (Topoisomerase IIá) but also in the pathogenesis of cardiotoxicity (Topoisomerase

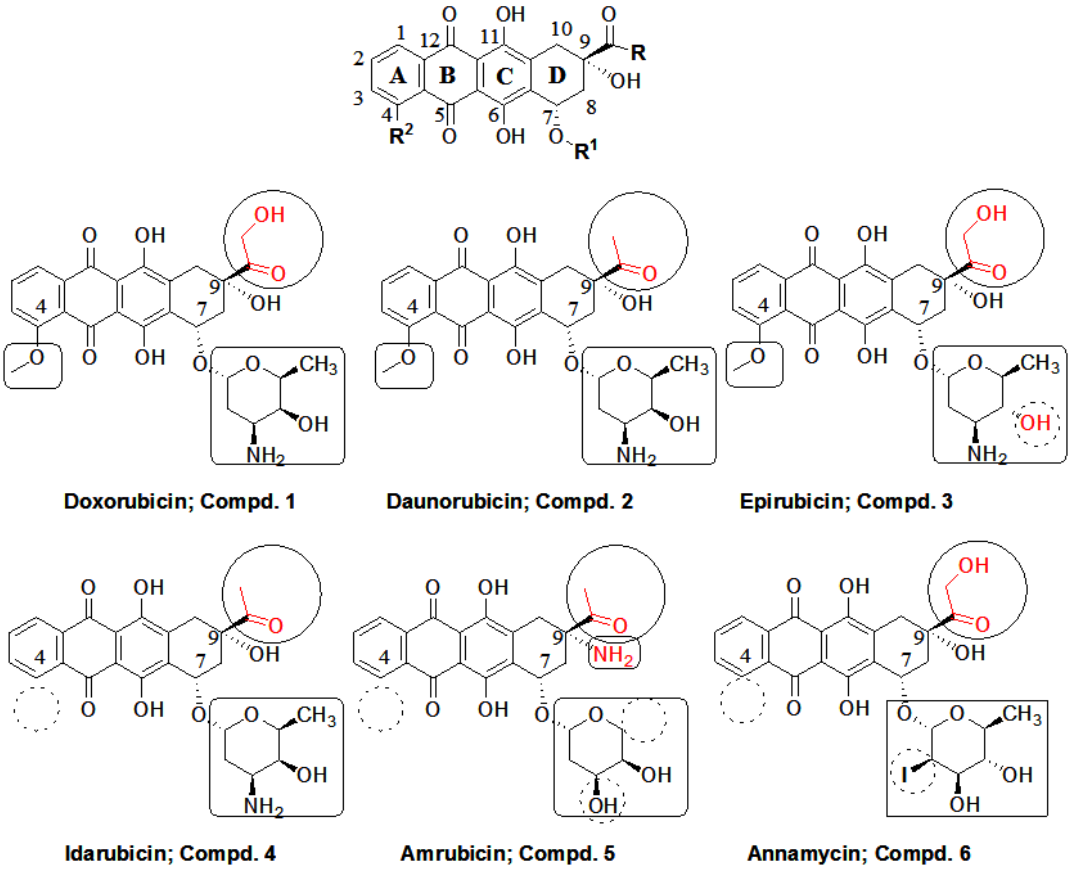



**Fig. 2.** Clinically useful anthracyclines, the orphan drug amrubicin and annamycin

IIâ). Replacement by ($CH_2$) decreases the effect topoisomerase IIá but increases the cardiotoxicity; topoisomerase IIâ. Compd. 10 bears less effects than doxorubicin as anticancer but high side effects on heart. The physicochemical properties of compound 10 appears of less percentage of polar surface area % PSA and less dipole moment than all the clinically useful anthracyclines.[113,114]

Third is the sugar at C-7: In doxorubicin there are three substituents on pyran ring methyl, hydroxyl, and amino groups of specific stereochemistry. Changing the stereochemistry of a single group in pyran provided a potent with less cardiotoxic derivative compound 3. Amino group of pyran at C-7 which has been rigorously mentioned as essential for activity, two derivatives (compound 5 and 6) one of which is orphan drug, compound 5 having no amino group in the C-7 pyran entity. The presence of a powerful hydrogen bond acceptor and donor such as $NH_2$ or OH groups.[115-118]

Fourth is the possible absence of one of the parts at C-7 and C-9 mentioned as A and B in the topology graph (Figure 6) decreases the cytotoxicity relative to all of the anthracyclines considered for developments like compound 14.

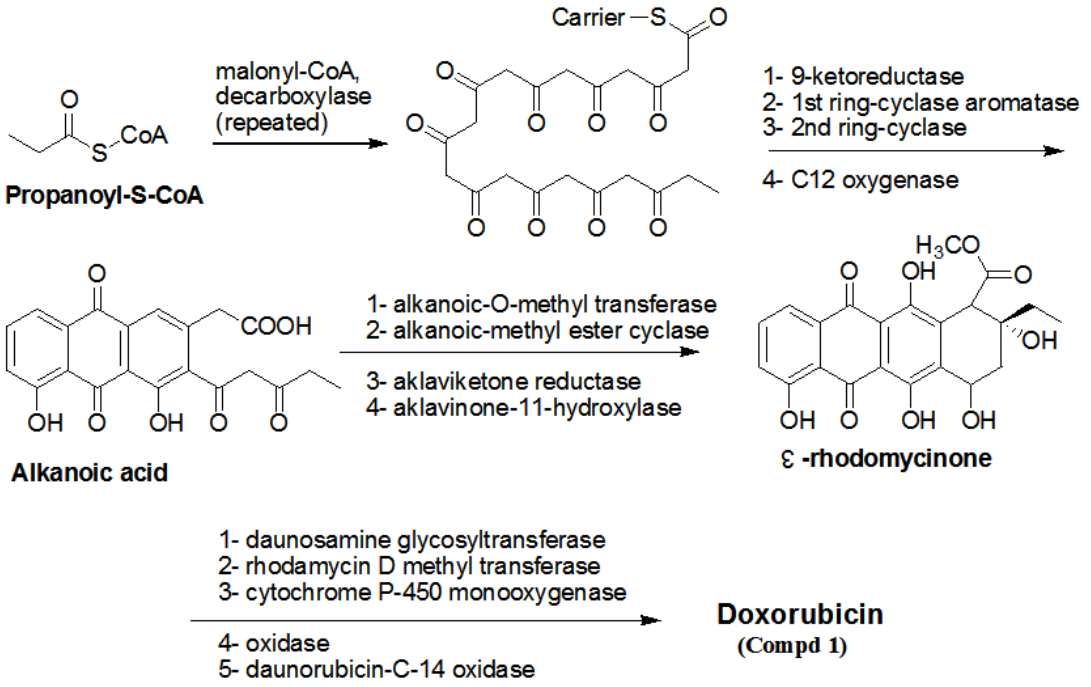



**Fig. 3.** Biosynthesis of doxorubicin

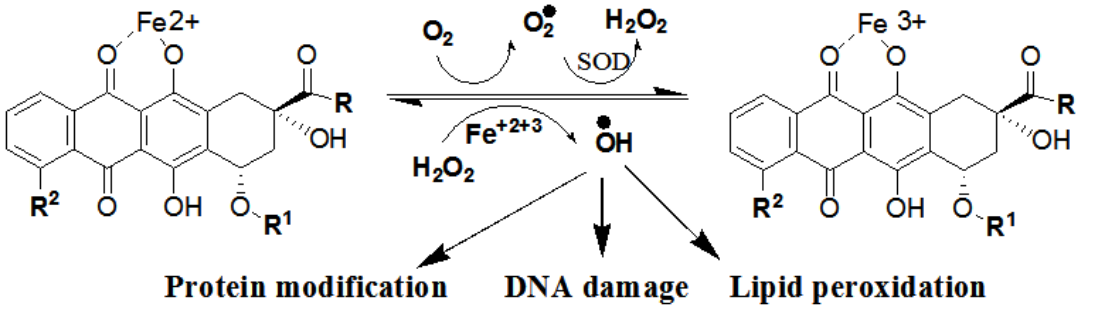



**Fig. 4.** Anthracyclines mediated free radical formation and biological effects.

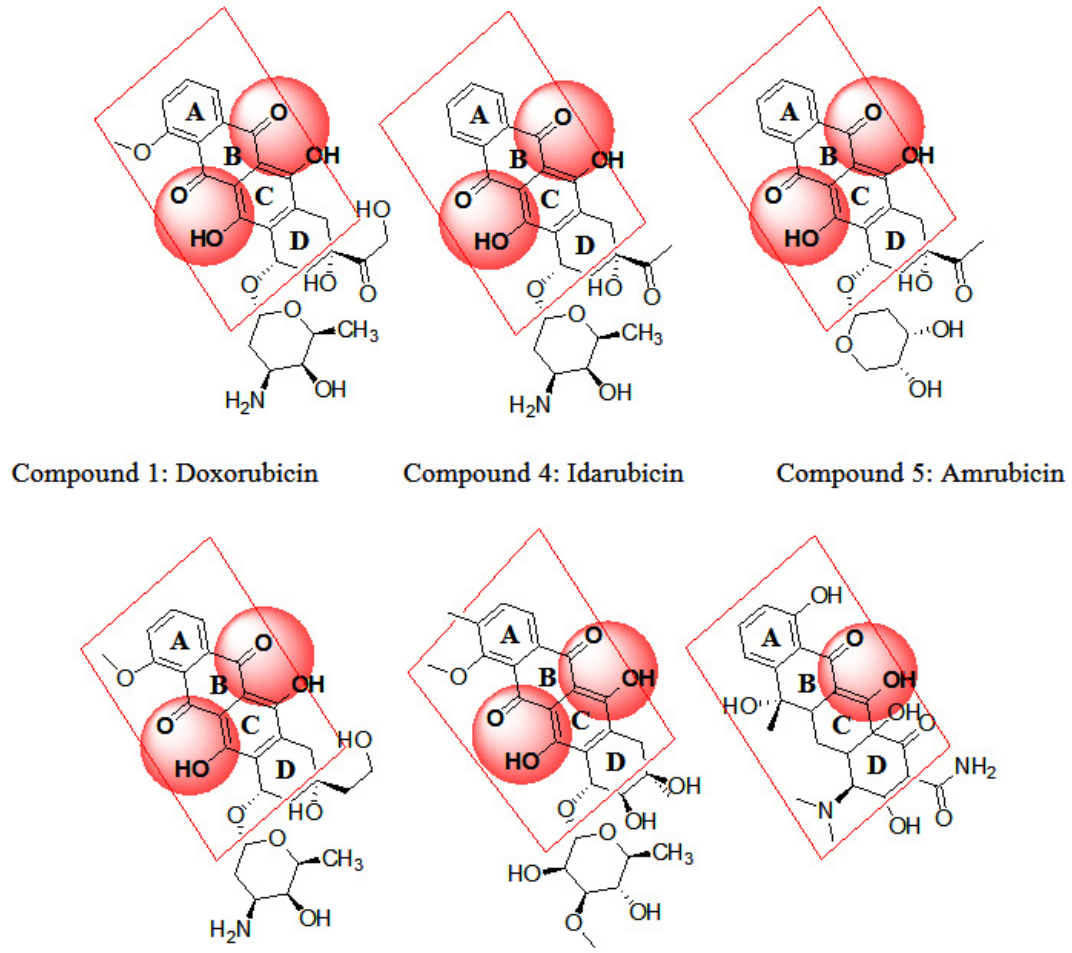



**Fig. 5.** Selected tetracyclic structures of different biological activities

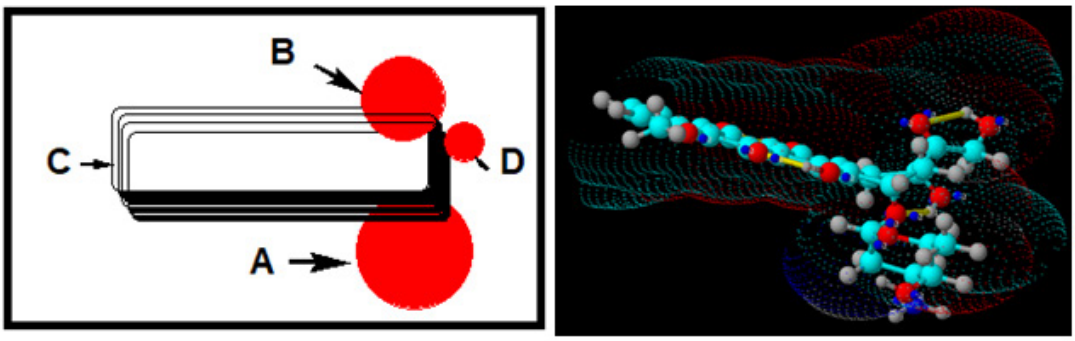



**Fig. 6.** Topology G1 and G2 of doxorubicin bearing the structural units for anticancer activity and 3D-fully optimized structure of doxorubicin

Fifth, is the absence of both parts at C-7 and C-9 mentioned as A and B in the topology graph (Figure 6) abolishing the cytotoxic effect and emerging the antibacterial activity. The compound 15, physico-chemical data in Table 3, demonstrates a high percentage polar surface area of compd. 15 (Table 4) than all the derivatives % PSA exceeding 44%. *In silico* calculation of ADME (Table 4) showed many differences between compound 15 and others in partition coefficient, water solubility, bioavailability score, and even in not being a good substrate for oxidase enzymes.

Sixth is fail in development of the highly potent compound 6. The full output of the *in-silico* calculation of ADME (Table 4) showed that compound 6 has four deviations when investigated for drug-likeness namely being alkyl halide, iodine derivative, the molecular weight, and the bone marrow toxicity.

There are several analogs related to doxorubicin appear with less side effects on heart and Table 5 introduces the comparative data between these derivatives and doxorubicin as well as between each other.[119-152]

## CONCLUSION

Anthracyclines have showed a great deal of cytotoxic activity since their incorporation in cancer treatment protocols, with considerable attempts to ameliorate their structure to overcome their evident cardiotoxicity. The approaches towards making better anthracyclines as anticancer agents are slow. In this work the structures of drugs in clinical use, the orphan drugs, the candidates bearing high cytotoxic activity and examples of tetracyclic structures bearing weak and/or cytotoxicity are collected for investigation. Important findings have been introduced in different points around the topological 3D-feature (Figure 6). Taking in consideration the points mentioned about the substitutions around main tetracyclic structure may help in introducing a selective and potent anticancer with much less cardiotoxicity from anthracycline-scaffold which still very important in treatment of solid tumors.

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**Conflicts of Interest**

The authors do not have any conflict of interest.

**Ethical Approvals**

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

**Authors' Contributions**

All authors made a significant and equal contribution to this work.

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