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Review Article / Derleme Makale

AN OVERVIEW OF CURRENT RESEARCH ON THE DEVELOPMENT OF ANTHRAQUINONES AS ANTICANCER AGENTS

ANTRAKİNONLARIN ANTİKANSER AJANLARI OLARAK GELİŞTİRİLMESİNE YÖNELİK GÜNCEL ARAŞTIRMALARA GENEL BİR BAKIŞ

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ABSTRACT

Objective: *In this study, some scientific studies on anthraquinone compounds that have been synthesized in recent years and have been found to have high in vitro and in vivo anticancer activity are summarized. It is aimed to contribute to the design and development of new anthraquinone derivative drugs that are more effective in cancer treatment and can overcome drug resistance.*
Result and Discussion: *Anthraquinones are a privileged class of compounds that can be obtained from natural and synthetic sources and have anticancer properties with versatile mechanisms. Anthracyclines, which are potent topoisomerase inhibitors, are members of this class that are frequently used in cancer chemotherapy. Literature data suggest that new anthraquinone derivatives developed through structural modifications can exhibit better antiproliferative activity against resistant cancer cells than currently existing anthracyclines and may be more effective antitumor drug candidates.*
Keywords: *Anthracycline, anthraquinone, anticancer activity, chemical modification*

ÖZ

Amaç: *Bu çalışmada son yıllarda sentezlenmiş ve yüksek in vitro ve in vivo antikanser aktivite gösterdiği bulunmuş antrakinon bileşiklerine dair bazı bilimsel çalışmalar özetlenmiştir. Kanser tedavisinde daha etkili ve ilaç direncini aşabilecek yeni antrakinon türevi ilaçların tasarlanması ve geliştirilmesine katkı sunması amaçlanmıştır.*
Sonuç ve Tartışma: *Antrakinonlar, doğal ve sentetik kaynaklardan elde edilebilen ve çok yönlü mekanizmalarla antikanser özelliklere sahip ayrıcalıklı bir bileşik sınıfıdır. Güçlü topoizomeraz inhibitörleri olan antrasiklinler, bu sınıfın kanser kemoterapisinde sıklıkla kullanılan üyelerini oluşturur. Literatür verileri, yapısal modifikasyonlar ile dirençli kanser hücrelerine karşı mevcut antrasiklinlerden daha iyi antiproliferatif aktivite gösteren ve antitümör ilaç adayı olabilecek yeni antrakinon bileşiklerinin geliştirilebileceğini göstermektedir.*
Anahtar Kelimeler: *Antrasiklin, antrakinon, antikanser aktivite, kimyasal modifikasyon*

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INTRODUCTION

Anthraquinones are compounds with the 9,10-dioxoanthracene structure that are widely found in nature and are frequently used especially in traditional Chinese medicine [1]. It is an important member of the conjugated cyclic diketone quinone class and is also referred to as 9,10-dioxoanthracene, anthracene-9,10-dione, anthradione or anthracene-9,10-quinone (Figure 1).

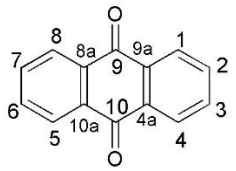


Figure 1. Molecular structure of Anthraquinone

Anthraquinones are found in free or glycosidic forms in various plants such as aloe, rhubarb, and gorse, as well as in certain bacteria, fungi, and animals. Anthraquinones, which constitute one of the largest classes of natural pigments, have been widely used for centuries in various fields, including the food and dye industries and medical applications [2,3]. Anthraquinones have emerged as a significant class of compounds in drug research due to their diverse biological activities, including anticancer [4], antibacterial [5], antifungal [6], antimalarial [7], antidiabetic [8], neuroprotective [9], anti-inflammatory [10]. Rhein, emodin, aloe emodin, chrysophanol, physcion are some examples of anthraquinone derivatives found in nature and have laxative properties. This property is attributed to the hydroxyl groups located at the C-1 and C-8 positions [11] (Figure 2).

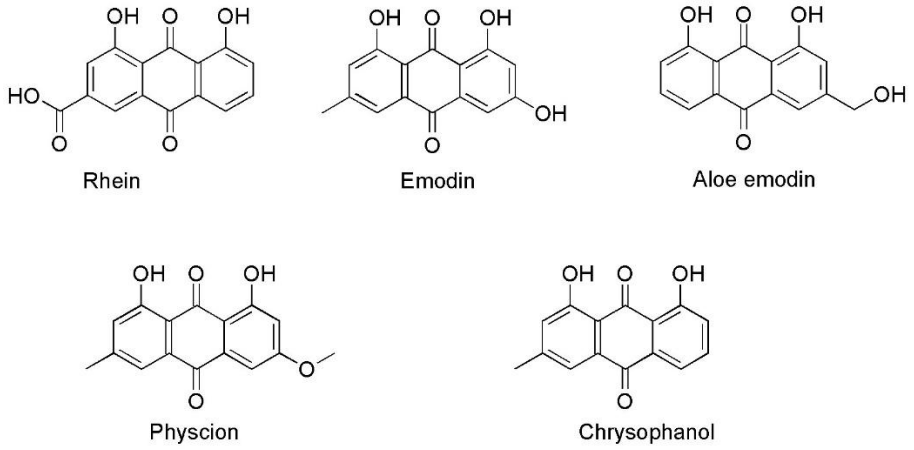


Figure 2. Chemical structures of natural anthraquinones with laxative effects

Marketed drugs with an anthraquinone skeleton include the laxative natural hydroxyanthraquinones (e.g., senna glycosides), the anti-inflammatory and antirheumatic drug diacerein, the anthracyclines (daunorubicin, amrubicin, idarubicin, doxorubicin, epirubicin, valrubicin) which constitute an important class of compounds in cancer chemotherapy, and their synthetic analogs pixantrone and mitoxantrone [12].

Anthracyclines are anthraquinone derivatives with a condensed tetracyclic ring structure joined to an amino-sugar molecule that are highly potent topoisomerase inhibitors [13]. The members of this group used in various cancer chemotherapy in the clinic are given in Figure 3. Daunorubicin and idarubicin are primarily employed for leukemia treatment, whereas doxorubicin and epirubicin are potent against solid tumors. In treating bladder cancer, valrubicin is especially favored. Simplified synthetic analogs of anthracyclines, mitoxantrone and pixantrone lack a D ring. These are bis-substituted

aminoalkylaminoanthraquinones in which amino-substituted alkyl chains have taken the place of the amino-sugar component of anthracyclines. Mitoxantrone is primarily utilized in the management of leukemia, lymphoma, breast cancer and prostate cancer [12]. It also received FDA approval for the treatment of multiple sclerosis in 2000 given its immunosuppressive properties [14]. Pixantrone is utilized in Europe for patients with treatment-resistant and aggressive non-Hodgkin B-cell lymphoma [15].

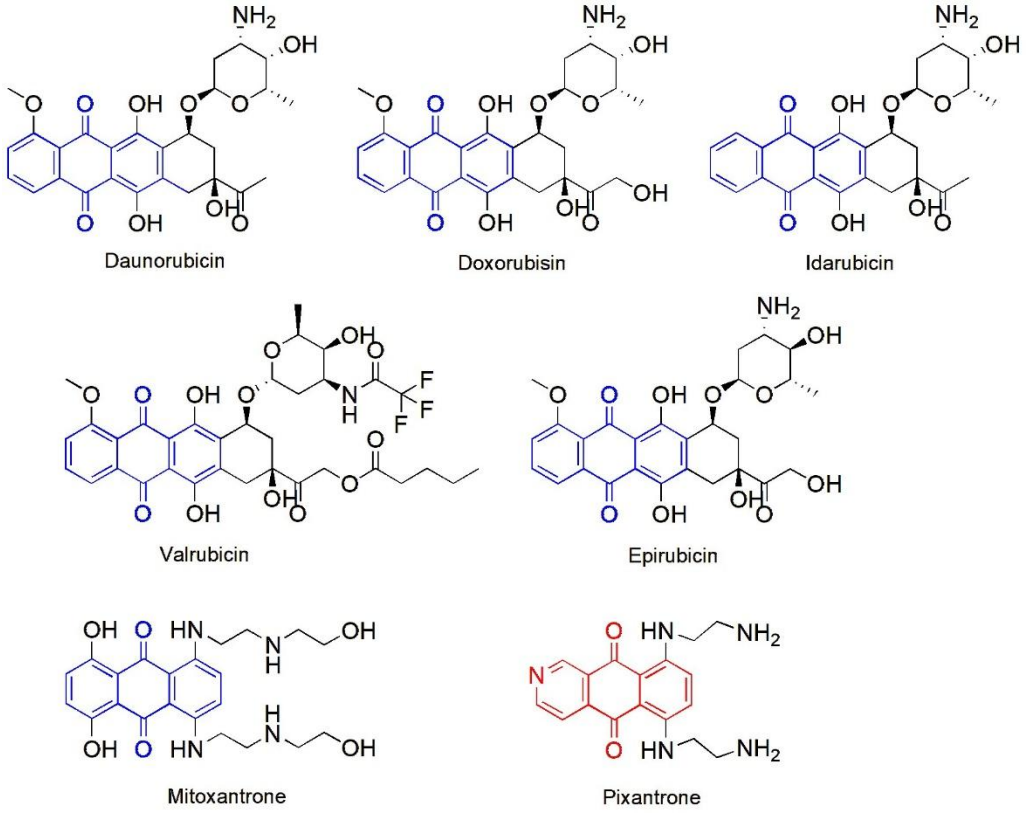


Figure 3. Anthraquinones approved by the FDA and in clinical use for cancer chemotherapy

Cancer threatens life with the uninhibited growth of abnormal cells and dissemination of these cells to other tissues and organs, and is a major cause of death. According to the International Agency for Research on Cancer (IARC), around 20 million new cancer cases were identified globally in 2022, and 9.7 million individuals died from cancer-related causes. More than 35 million new cancer cases are expected by the year 2050 [16]. Clinically used drugs have disadvantages such as high toxicity, low bioavailability, and drug resistance due to their low selectivity. Thus, designing and developing new drug active compounds that are more effective and less toxic is crucial.

In the literature, various anthraquinone compounds have been determined to be cancer growth inhibitors targeting protein kinases [17], topoisomerases [18], telomerases [19], matrix metalloproteinases (MMP) [20] and DNA [21]. Due to its planar tricyclic structure, the anthraquinone structure inserts between DNA base pairs and causes conformational changes in DNA. Thus, it shows cytotoxic activity by causing inhibition of DNA replication and DNA damage [22]. New anthraquinone derivative anticancer drugs continue to be of interest. In the past years, anthraquinone-structured anticancer compounds have been reviewed in several studies based on biological targets [13], [23], [24]. In this review, anthraquinone-structured compounds that have been synthesized in recent years and found to have strong anticancer *in vitro* and *in vivo* activity are discussed and it is aimed to aid in the design and creation of novel anticancer agents derived from anthraquinone.

Anticancer Activity of Anthraquinone Derivative Compounds

In 2021, Lin et al. synthesized 13 new and 1 known anthraquinone derivative compounds and examined their cytotoxicity against prostate (PC3), lung (A549), and bladder (NTUB1) cancer cell lines. Among the synthesized compounds, 1-hydroxy-3[(*E*)-4-bromo-but-2-enyloxy]-9,10-anthraquinone (Compound 1) and 1-hydroxy-3-[(*E*)-4-(piperazine-diium)but-2-enyloxy]-9,10-anthraquinone ditrifluoroacetate (Compound 3) exhibited strongest the antiproliferative activity on NTUB1 and PC3 cells, with IC_{50} values of 1.51 and 2.72 µM, respectively, and were found to be more active than the reference drug cisplatin in these cell lines (Figure 4) [25].

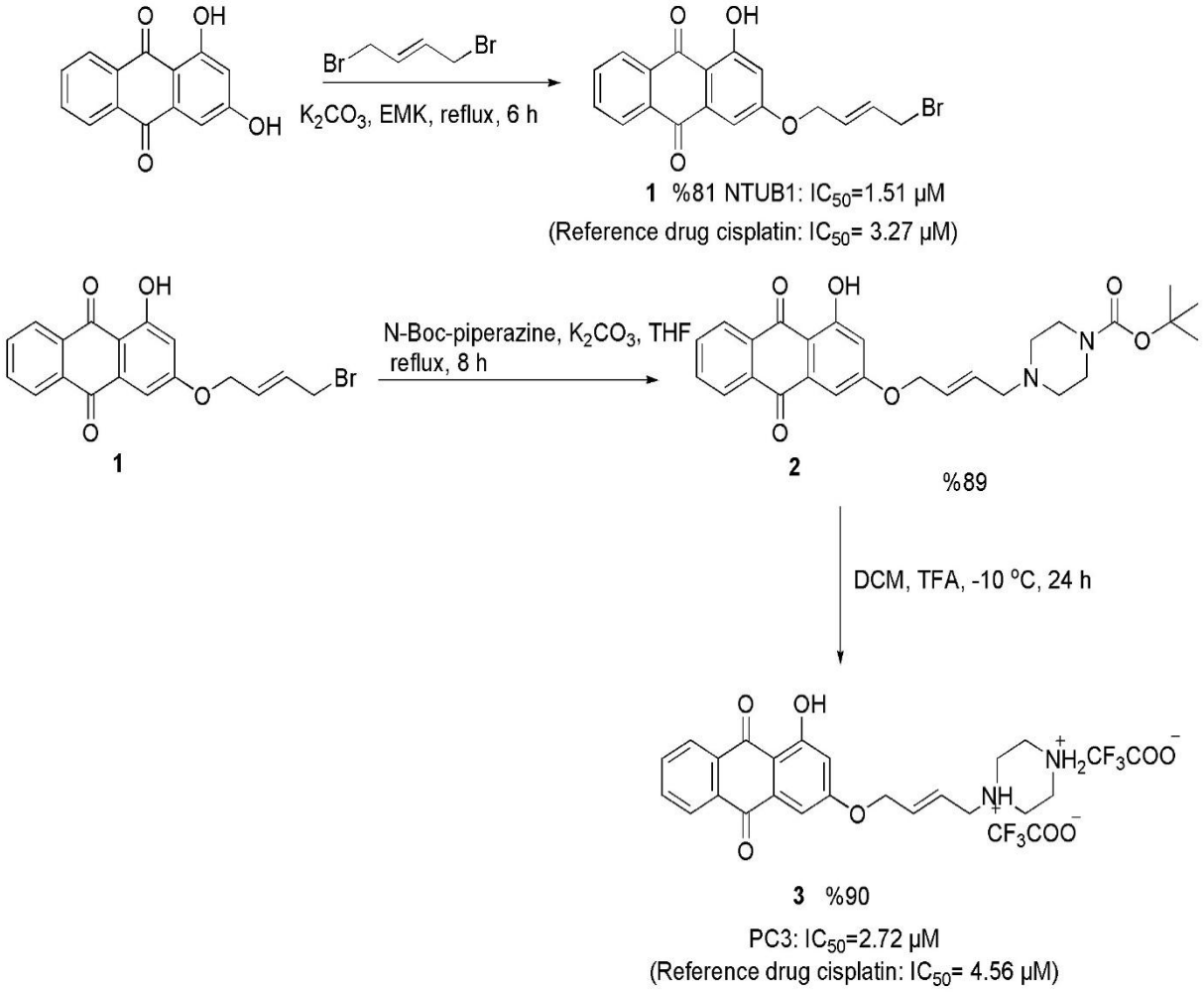


Figure 4. Synthesis of compound 1 and compound 3

In a study conducted by Li et al. in 2020, a group of emodin anthraquinone derivative compounds were prepared and the neuraminidase inhibitory and antitumor activities were examined. The antitumor potentials of the compounds were determined by MTT assay against eight diverse cancer cell lines and one normal intestinal epithelial cell (FHC). Among all the synthesized compounds, 1,3-dimethoxy-5,8-dimethylanthraquinone (Compound 4) was found to exhibit the best anticancer activity against HCT116 cancer cells (IC_{50} = 108.1 µM) without showing cytotoxicity against non-cancerous FHC cells (Figure 5). Furthermore, mechanistic research showed that compound 4 might cause apoptosis in HCT116 cancer cells by raising intracellular reactive oxygen species (ROS) levels and inducing G0/G1 phase cell cycle arrest [26].

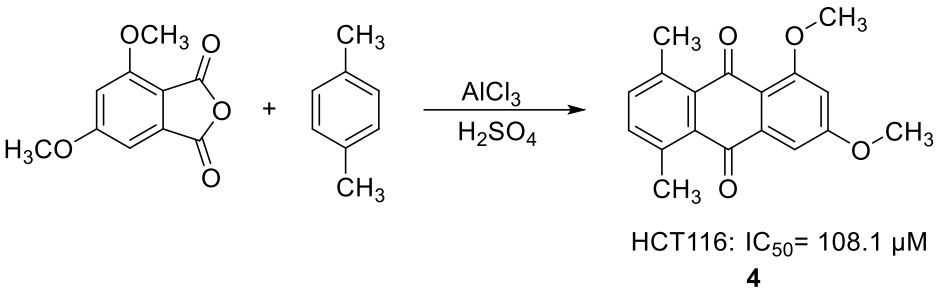


Figure 5. Synthesis of compound 4

Li and coworkers synthesized a range of anthraquinone-amino acid derivatives and investigated their antitumor activities in 2020. The compounds demonstrated potent anti-proliferative properties against various human cancer cell lines (HCT116, MCF-7, EC9708, QBC939, SGC-7901, HeLa, SW480, HEPG2) without significant cytotoxicity against normal cells, and among the compounds, N -[(9,10-dihydro-1-nitro-9,10-dioxo-2-anthracenyl)carbonyl-leucine] (Compound 5) was reported to exhibit significant antitumor activity (IC_{50}=17.80 μg/mL) by promoting apoptosis through the JNK pathway activation in HCT116 cancer cells (Figure 6) [1].

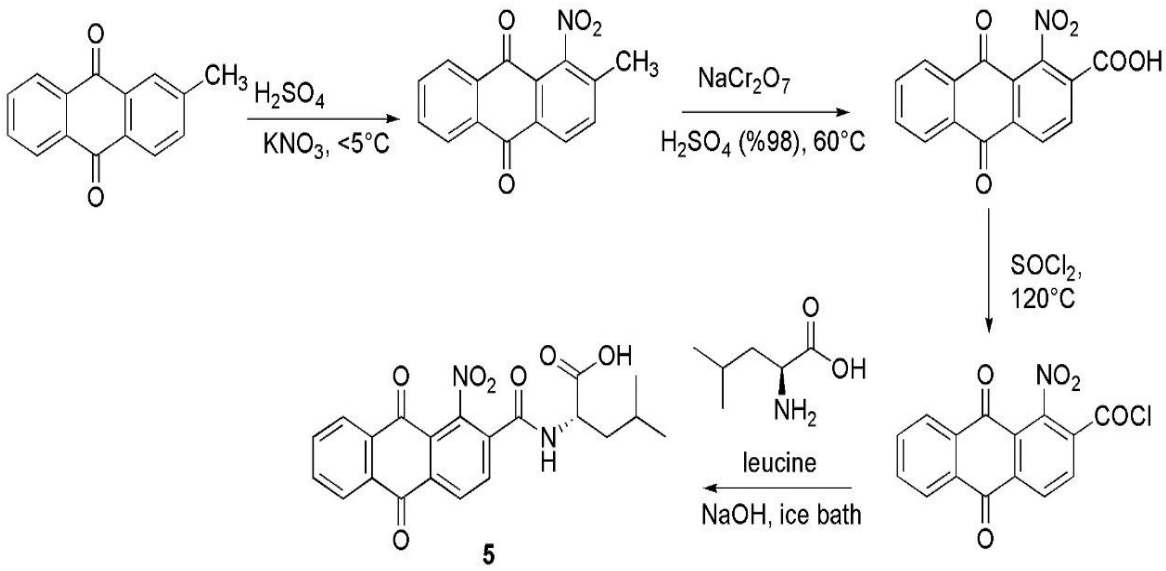


Figure 6. Synthesis of Compound 5

In another study, a range of anthraquinone derivatives were prepared by Sirazhetdinova and colleagues in 2020 by making substitutions at positions 1,2, 1,4 and 1,2,4 and their anticancer activity was evaluated. The cytotoxicity of the prepared compounds was tested on seven different human tumor cell lines (SNB-19, DU-145, MDA-MB-231, U-87MG, T98G, LNCAP, MT-4) as well as hTERT-immortalized lung fibroblast cells by MTT assay. Compounds 6, 7, 8, 9, 10, 11 were found to be more effective than doxorubicin against human glioblastoma SNB-19, prostate cancer DU-145 or breast cancer MDA-MB-231 cells, while showing a relatively safe profile against lung fibroblast cells (Figure 7) [4].

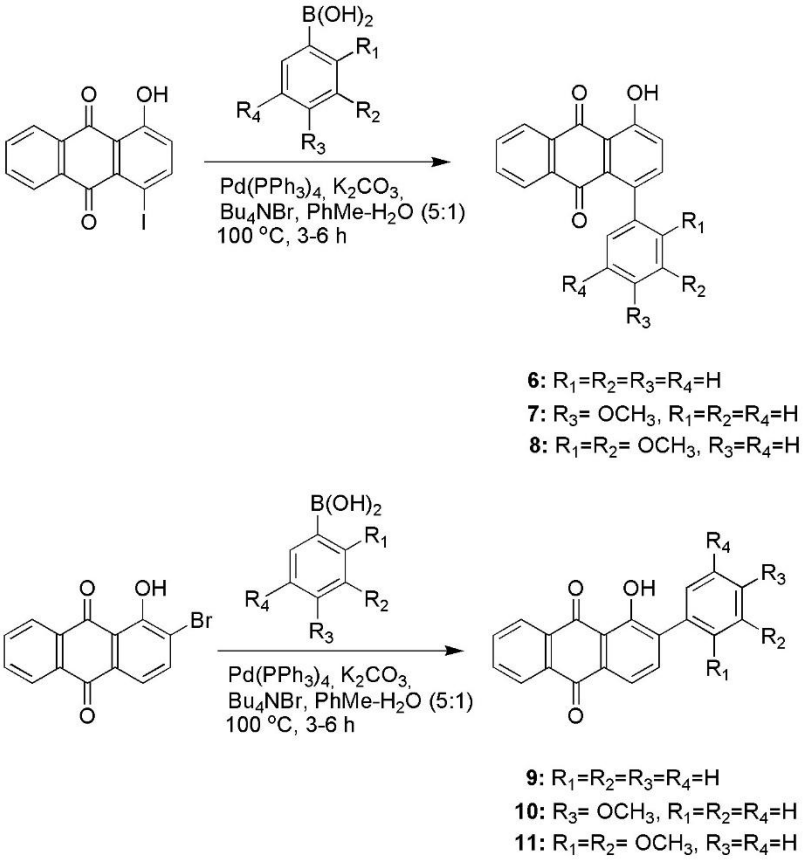


Figure 7. Some aryl substituted-1-hydroxyanthraquinone derivatives showing anticancer activity

In 2020, Oliveira and colleagues developed N-alkylated and O-alkylated anthraquinone derivative compounds with different chain lengths and tested their tumor growth inhibitory activity in various human cancer cell lines (HeLa, MCF-7, M059J). Among the compounds, 1,4-Bis(3'-hexylamino-2'-hydroxypropylamino)anthracene-9,10-dione (Compound 12) was the prominent compound,with an IC_{50} value below 15 µM in all three cancer cell lines, and was reported to show better antiproliferative activity than the reference drug methotrexate (Figure 8) [27].

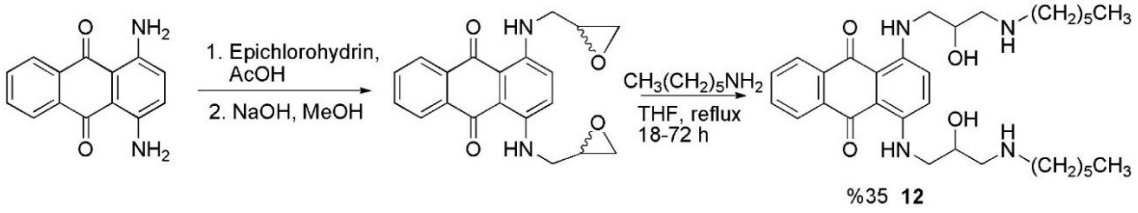


Figure 8. Synthesis of compound 12

In another research, a set of anthraquinone-functionalized imidazolium salts were synthesized and their *in vitro* cytotoxicity against the NCI-60 human cancer cell line panel was evaluated by Stromyer et al., in 2020. 1-((9,10-anthraquinone-2-yl)methyl)-3-(naphthalen-2-ylmethyl)benzimidazolium bromide (Compound 13) was the most potent member of the series, showing an average percent growth inhibition (%GI) of 47.3% across all cell lines, an effect attributed to increased lipophilicity by the presence of naphthalene and benzimidazole. Additionally, compound 13 was reported to exhibit significant *in vitro* activity (IC_{50}=32-50 µM) against selected bladder cancer cell lines (RT112, TCCSUP, J82, UMUC13) after a 1-h exposure time (Figure 9) [28].

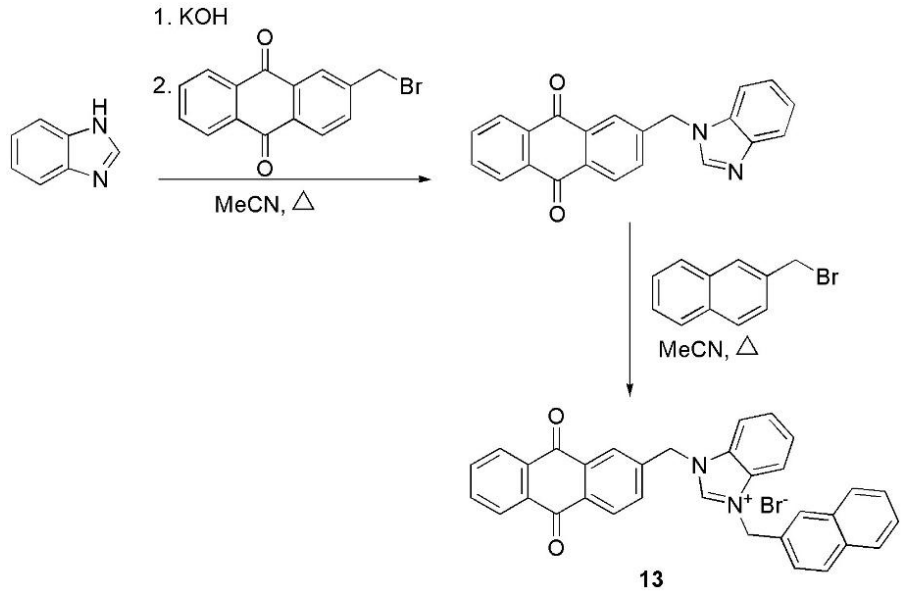


Figure 9. Synthesis of compound 13

In 2019, Liu and colleagues studied the anticancer activities of 1,4-dihydroxyanthraquinones derived from position 2. The *in vitro* cytotoxicity of the compounds against different cancer cell lines (HepG-2, HeLa, A549, CNE-1, MCF-7, MDA-MB-231) and a normal liver cell line (L02) was evaluated by MTT assay. Among the compounds, 2-((2,4-dichlorophenyl)(hydroxy)methyl)-1,4-dihydroxyanthracene-9,10-dione (Compound 14) showed strong antiproliferative activity against human liver cancer HepG2 cells (IC_{50}=12.5μM), while it was reported that it did not show significant cytotoxicity on normal liver tissue cells (Figure 10) [29].

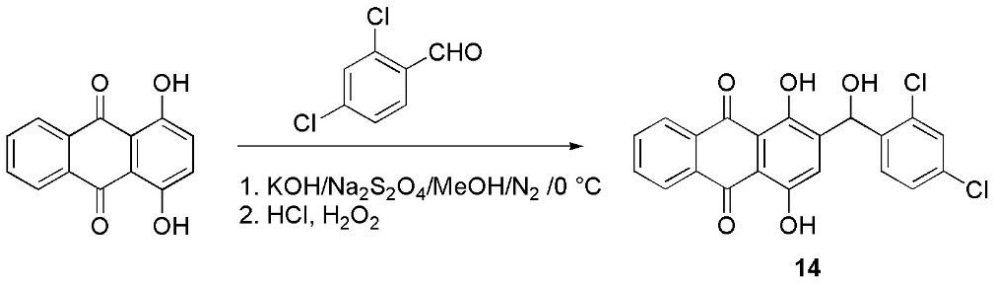


Figure 10. Synthesis of compound 14

In the same year, new 9,10-anthraquinone compounds bearing a piperidine ring were prepared and their *in vitro* antiproliferative activity against several human cancer cell lines (HL-60, LoVo, HL-60/MX2, LoVo/Dx) and BALB/3T3 normal mouse fibroblast cell line was evaluated (Niedziałkowski et al. 2019). The most active derivative, 1-(piperidin-1-yl)-9,10-anthraquinone (Compound 15), was reported to preferentially inhibit the growth of doxorubicin-resistant colon adenocarcinoma cells (Lovo/Dx) by overcoming drug resistance significantly (IC_{50}=2.31μg/mL), and its activity against cancer cells was 5-8 times greater than that of normal fibroblast cells (Figure 11) [30].

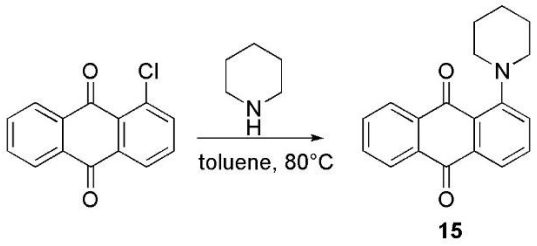


Figure 11. Synthesis of compound 15

Tian and his colleagues synthesized and studied the antitumor activities of 1,8-bis(benzyloxy)-9,10-anthraquinones in 2019. It was reported that 1,8-bis(benzyloxy)-9,10-anthraquinone-*N*-(2-hydroxyethyl)-3-carboxamide (Compound 16) was the most active member of the series, and showed stronger cytotoxicity than cisplatin against all cancer cells in the MTT assay against four tumor cell lines (CNE-1, CNE-2, HepG2 and SMMC-7221) (IC_{50}<5 μM) and caused the death of tumor cells through paraptosis (Figure 12) [31].

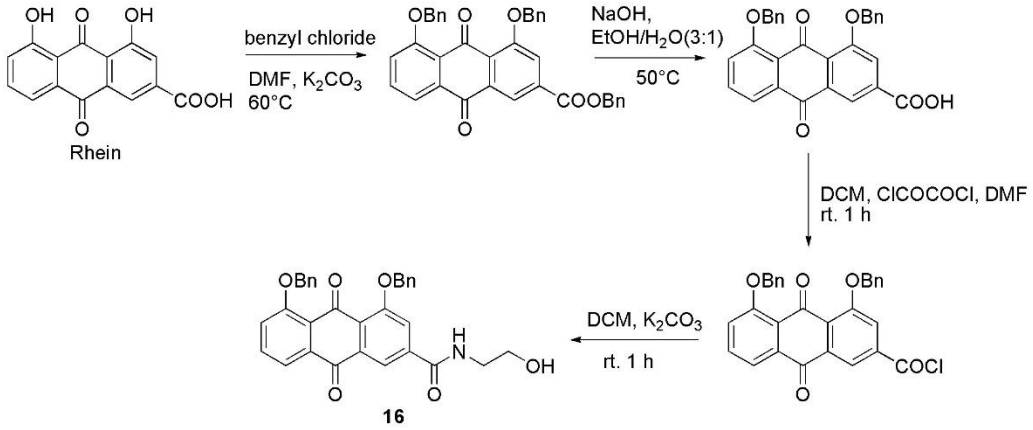


Figure 12. Synthesis of compound 16

Again in 2019, anthraquinone-quinazoline hybrid compounds were designed, synthesized and their anticancer activity was studied by Liang and colleagues. Among these hybrids, 4,5-bis(benzyloxy)-9,10-dioxo-*N*-(4-[4-methylphenylamino]quinazolin-6-yl)anthracene-2-carboxamide (Compound 17), which showed the most potent growth inhibitory activity against human lung cancer A549 cells (IC_{50} = 23.3 μM), exhibited strong EGFR inhibition. The compound was also reported to be a promising anticancer candidate with multi-target biological activities by inducing apoptosis and DNA damage (Figure 13) [32].



Figure 13. Synthesis of compound 17

In another study, a number of hydroxyanthraquinone derivatives containing the alkylating *N*-mustard structure were synthesized and their anticancer activity against four cancer cell lines (MDA-MB-231, HeLa, MCF-7, and A549) was evaluated. Synthesized derivatives exhibited notable *in vitro* cytotoxic activity against human breast cancer cells (MDA-MB-231, MCF-7), among which 2-((bis(2-chloroethyl)amino)(4-fluorophenyl)methyl)-1,4-dihydroxyanthracene-9,10-dione (Compound 18) was found to be more active than doxorubicin against MCF-7 cells, with IC50 values of 0.263 nM and 0.294 nM, respectively (Figure 14) [33].

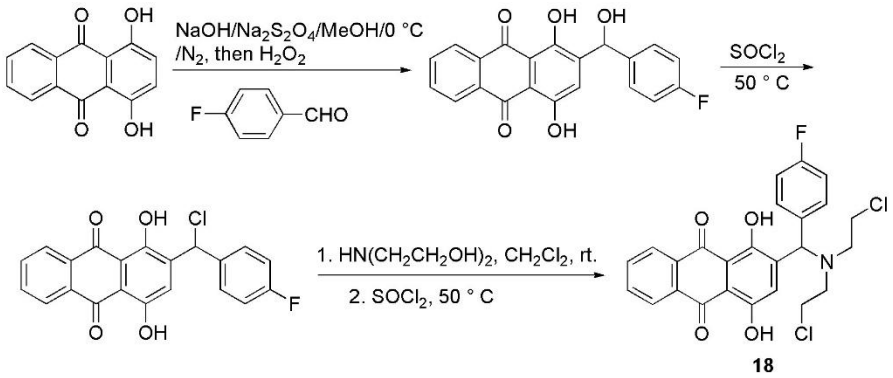


Figure 14. Synthesis of compound 18

In 2024, Wu and his team designed and synthesized anthraquinone-based sulfonamide derivatives and investigated their *in vitro* carbonic anhydrase inhibitory effects on tumor-associated human carbonic anhydrase IX (hCA IX) isoform. The synthesized compounds were found to effectively inhibit hCA IX with IC_{50} values in the range of 30.06–274.81 nM. 9,10-Dioxo-*N*-((4-sulfamoylphenyl)carbamothioyl)-9,10-dihydroanthracene-2-carboxamide (Compound 19) was determined to exhibit moderate antiproliferative effect on MDA-MB-231 (IC_{50}= 48.10 µM), MCF-7 (IC_{50}= 34.33 µM) and HepG2 (IC_{50}= 61.36 µM) cancer cell lines (Figure 15) [34].

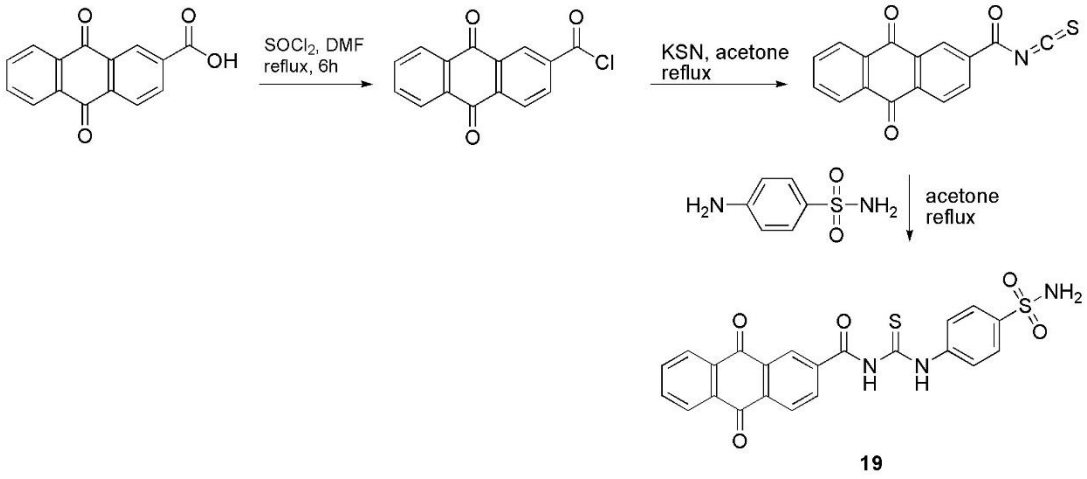


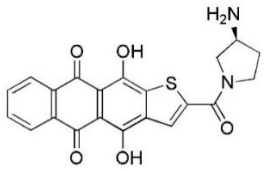
Figure 15. Synthesis of compound 19

Antitumor Activity of Anthraquinone Compounds Fused with Heterocyclic Rings

Although anthracycline anticancer drugs such as doxorubicin have been used effectively for many years in the treatment of various tumors, drug resistance and serious side effects are the main factors limiting the clinical use of these agents. The mechanisms associated with anthracycline resistance

include topoisomerase mutations and P-glycoprotein (P-gp)-mediated multidrug resistance (MDR) [35]. To overcome these problems, various strategies have been investigated, such as various drug delivery systems (liposomes and nanoparticles) [36], combination with P-gp inhibitors or structural modifications. While changing the sugar and hydroxyl groups of anthracyclines generally results in decreased activity [37,38], recent studies show that fusing heterocyclic rings to the anthraquinone structure is a more effective strategy. Such innovations could enable more selective and robust interactions with biological targets, helping to overcome drug resistance and paving the way for new generations of anticancer agents.

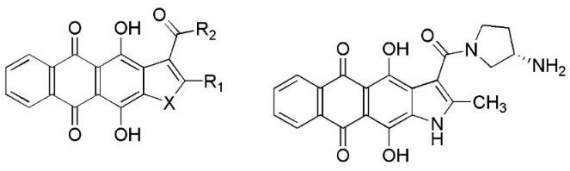
In recent years, cyclic/heterocyclic derivatives of anthraquinones have shown promising activities in the development of new antitumor agents. In 2021, Volodina and colleagues synthesized a series of anthra[2,3-b]thiophene-2-carboxamide derivatives and assessed their antiproliferative activity against a series of human cancer cell lines, including drug-resistant ones. Structure-activity studies showed low micromolar or submicromolar cytotoxicity of anthrathiophene-2-carboxamide derivatives containing aminopyrrolidine and aminopiperidine substituents against Capan-1, NCI–H460, DND-41 and HL60 cancer cell lines. The most active member of the series, (*S*)-2-(3-aminopyrrolidine-1-carbonyl)-4,11-dihydroxyanthra[2,3-b]thiophene-5,10-dione (Compound 20) (Figure 16), showed high activity (IC_{50} = 0.3-0.4 μM) against the K562 chronic myeloid leukemia cell line and the doxorubicin-resistant K562/4 subline after 72 h of exposure. Compound 20 was found to induce apoptotic cell death but did not significantly interact with double-stranded DNA and the DNA-dependent enzyme topoisomerase 1, thus acting through mitochondrial damage and not through DNA targeting. In addition, the bioisostere of compound 20 prepared by replacing the thiophene ring with furan was reported to have a similar cytotoxicity pattern, but lower activity [39].



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Figure 16. Structure of compound 20

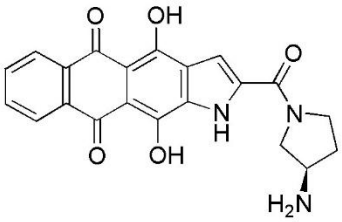
A series of compounds derived from naphtho[2,3-f]indole-3-carboxamide and anthra[2,3-b]thiophene-3-carboxamide (Figure 17) were synthesized by Tikhomirov et al. and they evaluated their *in vitro* antiproliferative activities against five cancer cell lines (Capan-1, HCT116, NCI–H460, HL60, K562) in 2020 [40]. The study found that derivatives carrying naphtho[2,3-f]indole skeleton exhibited higher cytotoxicity than thiophenes. The most active derivative, compound 21, was found to interact with DNA more strongly than furan and thiophene analogs, inhibited topoisomerase 1, and induced ROS-independent apoptosis. *In vivo* study of compound 21 in a P388 lymphoma-bearing mouse model showed that it inhibited tumor growth by up to 79% at tolerable doses and significantly lengthens the mice's lifetime (153%).



21

Figure 17. Naphtho[2,3-f]indole-3-carboxamide and anthra[2,3-b]thiophene-3-carboxamide derivatives

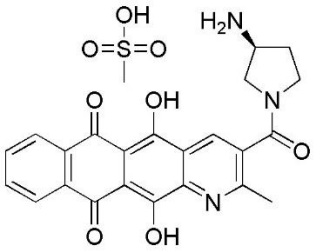
In 2025, Litvinova and colleagues synthesized a new series of naphthoindole-2-carboxamide compounds by shifting the carboxamide group from position 3 to position 2. The most active member of the series, compound 22 (Figure 18), carrying the (*S*)-3-aminopyrrolidine group, accumulated in P-gp-expressing K562/4 leukemia tumor cells and effectively inhibited the growth of the cell line (resistance index = 2.4), while this effect was not observed with the 3-carboxamide analog and doxorubicin. It was reported that compound 22 induced apoptosis in K562 and K562/4 cell lines, interacted with DNA and led to topoisomerase 1 inhibition, and might lead to the demise of tumor cells through the impairment of mitochondria and lysosomes. The study showed that placing the carboxamide group in the 2nd position resulted in increased lipophilicity and P-gp binding [41]. In order to overcome P-gp-mediated drug resistance of anthraquinones, the pharmacophore's location is crucial.



22

Figure 18. Structure of compound 22

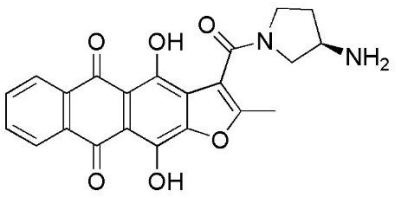
The fusion of anthraquinones with pyridine instead of pyrrole provided compounds with higher anticancer activity against MDR tumor cells. Tikhomirov and colleagues reported that (*S*)-3-(3-aminopyrrolidine-1-carbonyl)-5,12-dihydroxy-2-methylnaphtho[2,3-g]quinoline-6,11-dione methanesulfonate (Compound 23) (Figure 19) accumulated more in K562 and K562/4 cells and had higher P-gp affinity than its five-membered analog, and this compound caused apoptosis at minimal micromolar levels without ROS-mediated organ damage[42].



23

Figure 19. Structure of compound 23

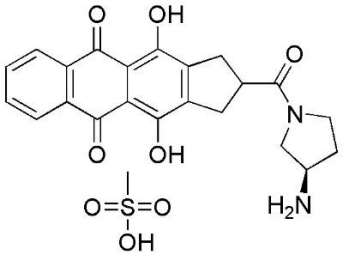
Shchekotikhin et al. designed and synthesized compounds bearing the structure 4,11-dihydroxy-2-methyl-5,10-dioxoanthra[2,3-*b*]furan-3-carboxamide. The antiproliferative potentials of the mesylates of the compounds were studied *in vitro* against L1210, HeLa, K562, K562/4, HCT116 cancer cell lines. (*S*)-3-Aminopyrrolidine derivative compound 24 (Figure 20) was the most active compound of the series by inhibiting the growth of tumor cell lines of the wild type with IC_{50} values of 0.5-1.4 μM. Compound 24 led to apoptosis by causing cell cycle arrest during the G2/M stage, as well as inhibition of topoisomerases (top1 and 2) and protein kinases. Molecular docking studies have shown that 24 forms stable complexes with double-stranded DNA. In *in vivo* studies, 24 was found to significantly increase animal survival (262%) in the P388 mouse leukemia model [43].



24

Figure 20. Structure of compound 24

In 2024, again Tikhomirov's team synthesized a series of novel 4,11-dihydroxy-5,10-dioxocyclopenta[*b*]anthracene-2-carboxamide compounds by designing cyclopentane-fused anthraquinone derivatives. The *in vitro* antiproliferative effect of the compounds was determined by MTT assay in comparison with doxorubicin against Capan-1, HCT-116, LN-229, NCI–H1975, DND-41, HL60, K562, Z138 mammalian cancer cell lines. Most cyclopenta[b]anthracene-2-carboxamides exhibited strong antiproliferative potential, displaying IC_{50} values in the 1–10 μM range. The most active member of the series carrying the (*S*)-3-aminopyrrolidine side chain, compound 25 (Figure 21), was observed to be more active than doxorubicin against Capan-1 and LN-229 cell lines. It was stated that compound 25 inhibited P-gp-mediated drug efflux due to its higher lipophilicity compared to doxorubicin [44].



25

Figure 21. Structure of compound 25

In summary, anthraquinone derivatives combined with cyclic/heterocyclics such as furan, thiophene, pyrrole, pyridine, cyclopentane pose significant potential in the development of anticancer drug candidates. In particular, derivatives containing a carboxamide group at position 2 or 3 have attracted attention with their high anticancer activity in *in vitro* cellular tests and *in vivo* animal experiments. These compounds can suppress tumor proliferation by affecting DNA duplex and topoisomerases I and II. Interestingly, bioisosteric changes in heterocyclic fused anthraquinones can cause unexpected changes in cellular accumulation and binding to P-gp. For example, ring expansion, which occurs by replacing the pyrrole ring with pyridine, increased the efficacy against resistant cells. In addition, it has been observed that the incorporation of cyclic diamine groups into anthraquinones has significant potential in preventing P-gp-mediated drug resistance, especially since the (*S*)-3-aminopyrrolidine group constitutes a privileged structural part.

RESULT AND DISCUSSION

Anthraquinones are an important class of compounds that can be obtained from natural and synthetic sources and may shed light especially on the development of new generation anticancer agents due to their versatile biological effects. The anticancer properties of anthraquinones are mainly achieved through interaction with DNA, inhibition of topoisomerase I and II, cell cycle arrest in G2/M phase, and induction of apoptosis. In addition, some anthraquinone derivatives inhibit targets associated with

cancer cell proliferation, including telomerase, matrix metalloproteinase, and protein kinases, thus inhibiting tumor growth [13,24]. Anthracyclines (doxorubicin, epirubicin, etc.) are anthraquinone compounds used clinically in the chemotherapy of various cancers, but their long-term use is limited due to side effects such as multidrug resistance developed by tumor cells and cardiotoxicity [45]. Therefore, it has become very important to develop new structural derivatives that have increased activity, reduced toxicity and prevent the development of resistance. With structural modifications, anthraquinone compounds have been developed that exhibit superior antiproliferative activity against resistant cancer cells compared to existing anthracyclines and have the potential to serve as antitumor drug candidates. It is important to point out that even bioisosteric alterations in structural modifications can lead to variations in the formation mechanism of cytotoxic effects. To create more effective and targeted cancer treatment drugs, new anthraquinone compounds need to be designed and synthesized, and the effects of structural modifications on antitumor activity should be thoroughly investigated.

AUTHOR CONTRIBUTIONS

Concept: B.K., C.K.K.; Design: B.K., C.K.K; Control: C.K.K.; Sources: B.K., C.K.K.; Materials: - ; Data Collection and/or Processing: B.K.; Analysis and/or Interpretation: - ; Literature Review: B.K.; Manuscript Writing: B.K., C.K.K.; Critical Review: C.K.K.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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