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The Effect Of Aryl And Heteroaryl Conjugation On The Biological Activities Of Naphthalenes: A Review

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Abstract
In medicinal chemistry, there is a great demand to design, develop, and identify novel drug-like agents with the highest therapeutic potentials and lowest side-effects. Naphthalene moiety was found highly in nature, and many reports have been conducted to extract naphthalene-derived products and investigate their biological activities. Synthetic naphthalene-based compounds have been found to possess potent bioactivities such as antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, and cytotoxic effects. In the literature, many studies have been investigated the influence of conjugating various aryl- and heteroaryl-derived moieties with naphthalenes on their biological activities. The results of most of these studies revealed that this type of conjugation could improve the bioactivities of the parent naphthalenes. This systematic review summarized the most important and recent examples of such studies and highlighted the structural features of the resultant conjugates to be considered as promising bioactive scaffolds.

Key words: Naphthalene, Aryl, Heteroaryl, Antibacterial, Antifungal, Antioxidant, Cytotoxicity.

1. Introduction

1.1 Overview

Naphthalene, as shown in Figure 1, is a characteristic member of arenes that is composed of fusing two benzene rings through the ortho positions. Physically, it is found as colorless crystals with significant mothballs' odor [1].

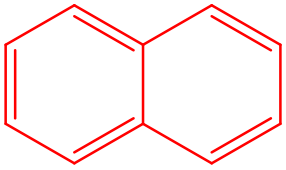

Figure 1: Chemical backbone of naphthalene.

Natural, semisynthetic, and synthetic currently available drugs containing naphthalene or one of its derivatives in their chemical structures have been found to possess distinct biological activities [2]. Examples of these drugs, as shown in Figure 2, are

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included nafacillin, naftifine, tolnaftate, and terbinafine. The first agent is an antibacterial drug while the others are antifungal agents [3].

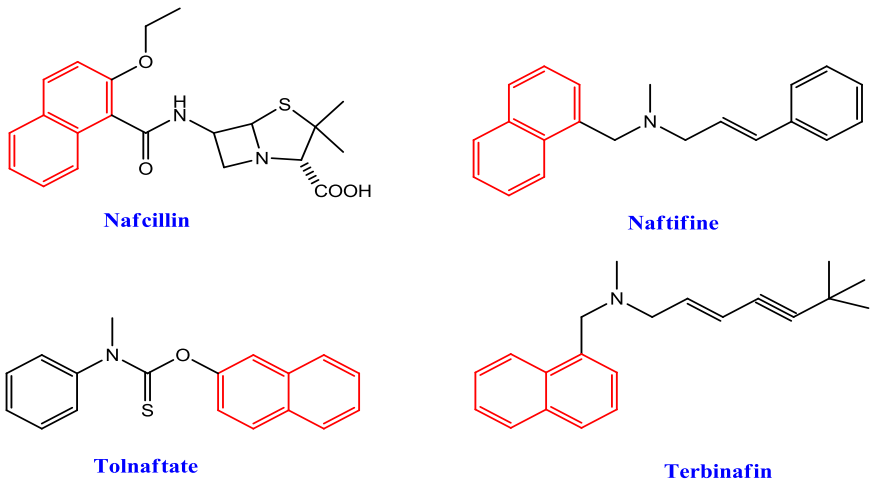

Figure 2: Chemical structures of the currently available naphthalene-based drugs.

1.2 Antibacterial activity

The mounting utilization of antibacterial drugs leads to the upregulation of the antibiotic-resistant bacteria [4,5]. This event necessitates the exploration and efficient development of new antibacterial agents that can combat these resistant bacteria [6]. Many studies have been investigated the positive role of conjugating various aryl- or heteroaryl-based moiety with naphthalene containing compounds on the reported antibacterial action [7-15].

Ashraf *et al.* have synthesized many functionalized indoles that were conjugated with naphthalene nucleus. The *in vitro* biological activity of the synthesized conjugates (Figure 3) as antibacterial agents was investigated against *Staphylococcus aureus* (S. areus) and *methicillin-resistant Staphylococcus aureus* (MRSA). The results showed that the best antibacterial activity correlated to the compounds bearing 5-chloro-, 5-cyano-, and 5-hydroxy-indole in their structures [7].

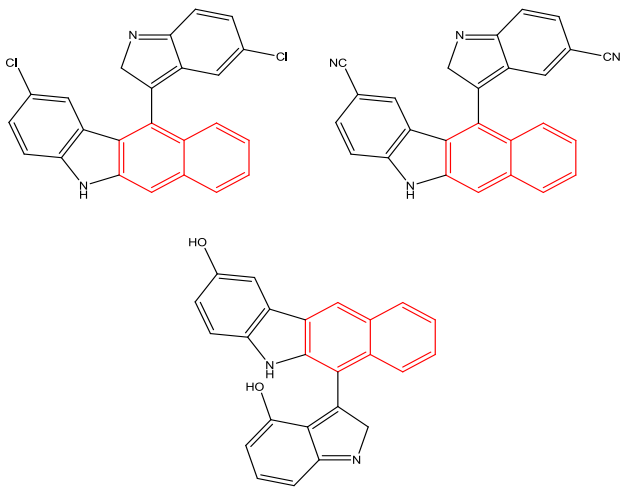

Figure 3: Chemical structures of the naphthalene-based compounds prepared by Ashraf *et al.*

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Chopra *et al.* have synthesized a new series of naphthylamine analogs that were conjugated with substituted azetidin-2-one ring moiety. The antibacterial activity of the resultant naphthalene-based compounds was t examined against *E. coli*, *S. aureus*, *B. subtilis*, and *P. aerogenosa*. Four of the investigated compounds named **4a**, **4e**, **4g**, and **4f** (Figure 4) have revealed good antibacterial activity with inhibition zones ranging between 9-19 mm. The standard antibacterial agent utilized in this study was ampicillin that exhibited the inhibition zones ranging between 15-45 mm versus the test pathogens [8].

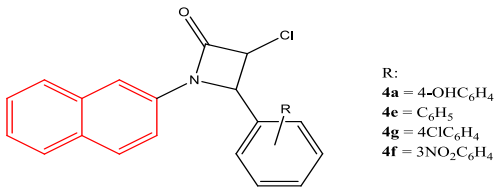

Figure 4: Naphthalene-based compounds with a potential antibacterial effect that were prepared by Chopra *et al.*

Sivasankari and Mary have synthesized a new panel of hydrazine derivatives that were conjugated with naphthalene. The antibacterial activity of these conjugates was investigated via agar-disc diffusion method versus many Gram-positive (*B. subtilis*, *S. pyogen*, and *S. aureus*) and Gram-negative (*E. coli*, and *P. aerogenosa*) bacteria. The results showed that the conjugates termed **3**, **5**, and **6** (Figure 5) were active versus both bacterial phenotypes. Specifically, the best antibacterial effect was found versus *S. aureus* and *E. coli* [9].

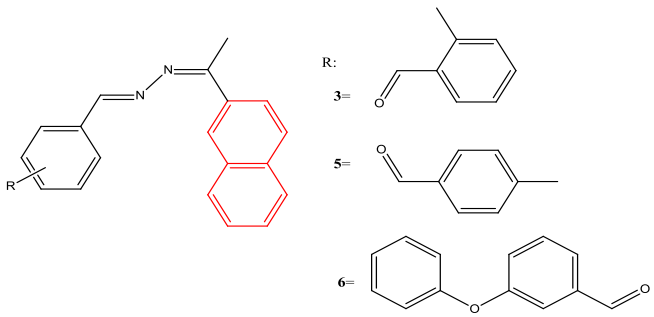

Figure 5: Naphthalene-based conjugates with broad-spectrum antibacterial activity prepared by Sivasankari and Mary.

A series of naphthalene-piperazine conjugates have been synthesized by Kumar *et al.* The antibacterial effect of the synthesized conjugates was tested using cup-plate diffusion technique against both Gram-positive and -negative bacterial strains including *S. aureus*, *E. coli*, *B. subtilis*, and *K pneumonia*). The results showed that the conjugates termed **4b**, **4c**, and **4e** (Figure 6) exhibited the potent effect against the tested bacteria with inhibition zones ranging between 2-6 mm. The standard antibacterial drug used in this study was ciprofloxacin that exhibited the inhibition zones ranging between ranging 10-14 mm [10].

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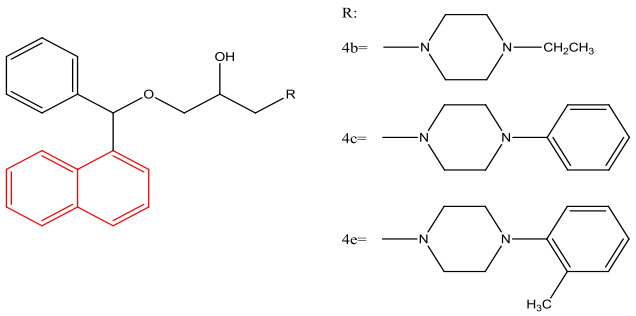

Figure 6: Naphthalene-piperazine conjugates prepared by Kumar *et al.* with characteristic antibacterial effect.

Zangade*et al.* have synthesized a series of naphthalene-flavone conjugates and examined their antibacterial activity against *E. coli* and *S. aureus* via disc-diffusion technique using tetracycline as a golden reference. The results showed that the conjugates termed **IIc** and **IIf** (Figure 7) with a chloride substitution showed a better antibacterial potential than the reference drug [11].

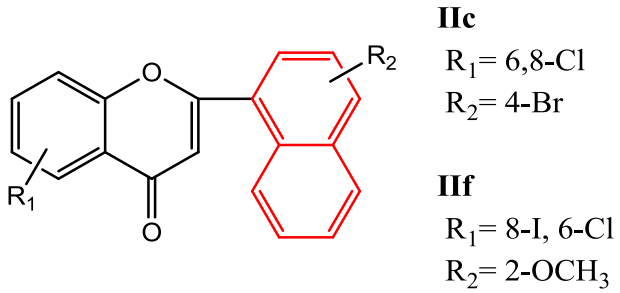

Figure 7: Naphthalene-flavone conjugates prepared by Zangade*et al.* with potent antibacterial effect.

Azarifar and Shaebanzadeh have synthesized a new series of naphthalene-pyrazoline conjugates and examined their activity against six pathogenic bacterial strains included *E. coli*, *S. aureus*, *P. mirabilis*, *K. pneumonia*, *S. dysentery*, and *S. typhi*. This study was conducted by using a well-known technique and the resulted MIC values were compared with those of chloramphenicol that employed as a standard. The results exhibited that the conjugates termed **3cg**, **3eh**, **3ci**, **3di**, and **3ei** (Figure 8) which have hydroxo, chloro, and dimethylamino substituents on the naphthalene rings were the most effective ones compared to the other conjugates [12].

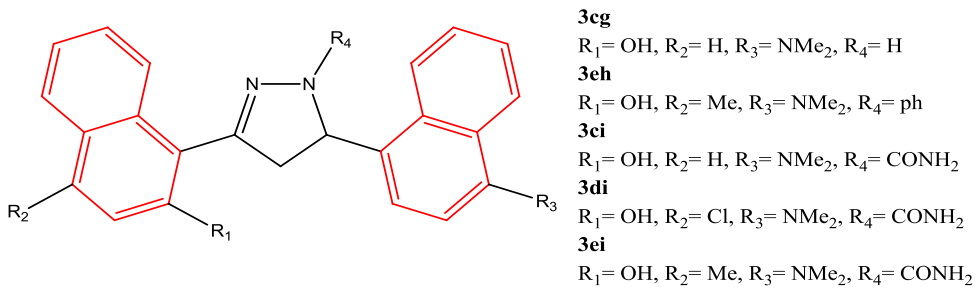

Figure 8: Naphthalene-pyrazoline conjugates synthesized by Azarifar and Shaebanzadeh.

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Many phenylamino-thionaphthaquinone conjugates were prepared by Kara *et al.* and examined their antibacterial effect against several pathogenic bacteria, included *E. coli*, *S. aureus*, *S. epidermidis*, *E. faecalis*, *P. aerogenosa*, *P. mirabilis*, and *K. pneumonia*). The results showed that the conjugates termed **5a** and **5b** (Figure 9) were the most effective against *S. aureus* with MIC values of 1.22 and 19.53 µg/ml respectively compared with the cefuroxime MIC value of 1.2 µg/ml. These results suggested that further study may be conducted on these conjugates to define their functionality as potent antibacterial agents [13].

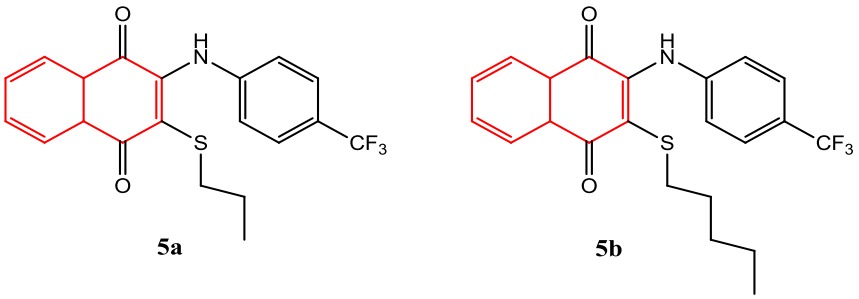

Figure 9: Phenylamino-thionaphthaquinone conjugates prepared by Kara *et al.* with promising antibacterial activity.

A similar study to the previous one was conducted by Shakh*et al*. who synthesized a series of 1,4-naphthoquinone conjugated with various 1,2,4-triazole-3-thiones. The antibacterial potential of these conjugates was examined against *E. coli* and *S. aurous* using the agar-diffusion technique and vancomycin as a reference drug. The results showed that the conjugates termed **5** and **7** (Figure 10) were highly effective versus *S. aurous* with inhibition zones of 10.4 mm and 10.7 mm, respectively compared with vancomycin's inhibition zone equaled to 11.3 mm [14].

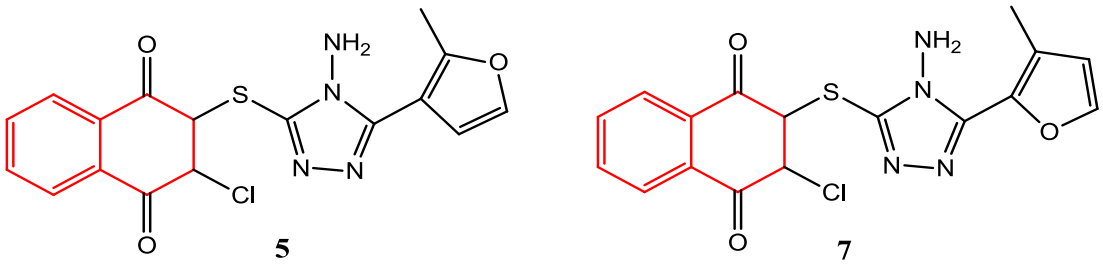

Figure 10: 1,4-Naphthoquinone conjugates prepared by Shakh*et al.* with good antibacterial activity.

Novel congeners have synthesized by conjugating naphthalene moiety with arylcoumarins and investigated their antibacterial activity against Gram-positive and -negative pathogenic bacteria, included *B. subtilis*, *S. aurous*, *E. coli*, *P. vulgaris*. The results showed that the congeners termed **2b** and **2e** (Figure 11) were the most effective compared to the standard drug, streptomycin. The authors were found that the substitution at the 8th position of coumarin with the methoxy group exerted a significant positive impact on the antibacterial activity of these congeners [15].

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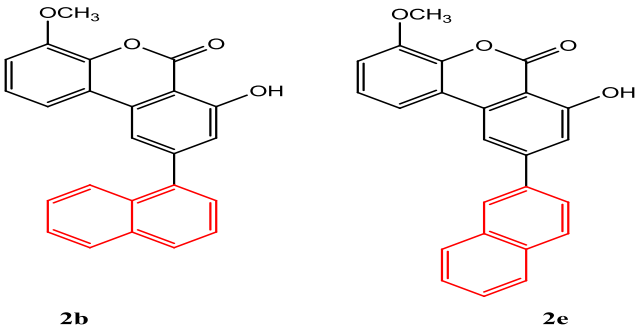
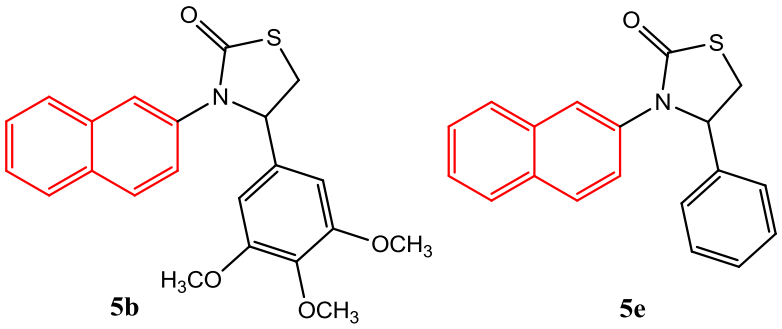


2b **2e**

Figure 11: Naphthalene-arylcoumarin conjugates with potent antibacterial potential.

1.3 Antifungal activity

Chopra *et al*. have synthesized a series of naphthalene-thiazolidinone conjugates and examined their antifungal activity against *Candida albicans* (*C. albicans)* using agar-plate diffusion technique besides amphotericin B as a reference drug. The results showed that the conjugates termed **5b** and **5e** (Figure 12) were significantly effective with inhibition zones of 9 mm and 13 mm, respectively, while the reference exhibited an inhibition zone of 16 mm. These outcomes indicated that the hybridization of N-heterocyclic moiety with naphthalene may result in the creation of a promising scaffold for developing potential antifungal agents [8].



5b **5e**

Figure 12: Nnaphthalene-thiazolidinone conjugates prepared by Chopra *et al.* with potent anti-candida effect.

Ghiya and Joshi have synthesized a novel series of naphthalene conjugates via a one-pot green synthetic method. The synthesis of these conjugates was carried out under the influence of microwave irradiation by mixing various substituted aromatic carbonyl compounds with naphthalene-1-sulfonhydrazide. The antifungal potential of these conjugates was examined against *Aspergillusniger* (*A. niger)* and *C. albicans* using potato-dextrose agar and fluconazole as nutrient medium and standard drug, respectively. The outcomes revealed that the synthesized conjugates possessed a good to excellent antifungal activity, specifically the conjugates termed **3h** and **3i** (Figure 13). The reported inhibition zones against *A. niger* and *C. albicans* for conjugate **3h** were 10 mm, 12 mm; 12 mm, 12 mm for conjugate **3i**; while for the standard drug were 20 mm, 18 mm, respectively [16].

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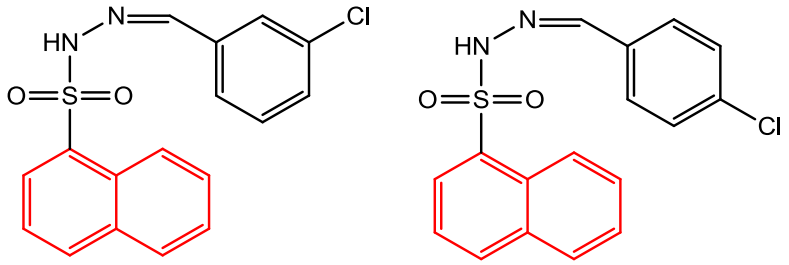
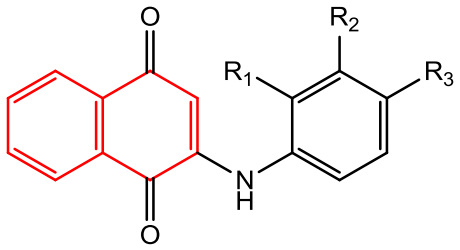


3h **3i**

Figure 13: Naphthalene-based conjugates prepared by Ghiya and Joshi with a characteristic antifungal effect.

Ryu and Chae have synthesized three series of naphthalene-based compounds included 2-arylamino-5-hydroxy-naphthalene-1,4-diones (series I), 2-arylamino-3-chloro-5-hydroxy-naphthalene-1,4-diones (series II), and 3-arylamino-5-methoxy-naphthalene-1,4-diones (series III). The antifungal activity of these conjugates was tested by utilizing a broth-dilution technique and flucytosine and ketoconazole as standard drugs. The fungal strains involved in this study were *C. albicans*, *Candida tropicalis(C. tropicalis)*, *Candida krusei (C. krusei)*, and *A. niger*. The outcomes showed that the conjugates of the series III named **5a**-**5h** (Figure 14) were the most active with MIC values ranged between 0.8-12.5 µg/ml, while those of the standard drugs ranged between 3.2-12.5 µg/ml. The authors have attributed the improved activity of the series III conjugates to the positive roles exerted by the arylamine and methoxy functional groups [17].



	R_1	R_2	R_3
5a=	H	H	GH_3
5b=	H	H	Br
5c=	H	H	F
5d=	H	H	Cl
5e=	F	F	F
5f=	H	F	F
5g=	F	H	H
5h=	F	H	F

Figure 14: Series III conjugates that were prepared by Ryu and Chae.

Many attempts have been conducted to isolate naphthalene-based products from different natural resources and investigate the potential of these products as bioactive agents [18-19]. Elansary*et al*. have isolated a secondary metabolite named bis-naphthoquinone (Figure 15a) from *Ceratostigmaplumbaginoides*(hardy blue-flowered leadwort, Figure 15b)and examined its antifungal activity against *C. albicans*. The results showed that the isolated product has a significant activity with MIC value of 0.09 µg/ml compared to the MIC values of the standard positive controls, fluconazole and ketoconazole, which were 0.1 µg/ml and 0.18 µg/ml, respectively [20].

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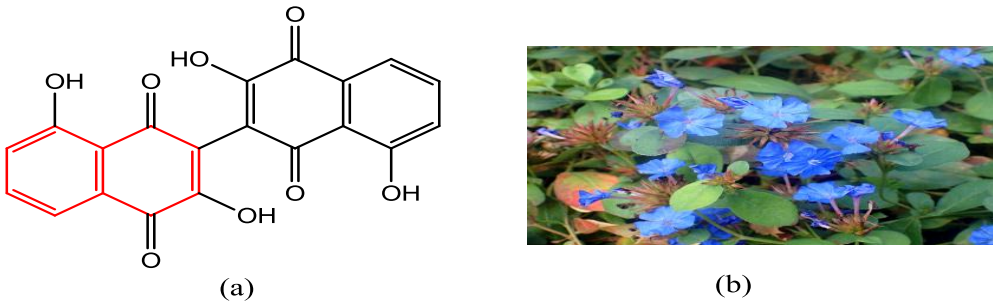

Figure 15: (a) The chemical structure of the natural product named bis-naphthaquinone. (b) The natural resource termed *Ceratostigmaplumbaginoides.*

On the same side, the natural product (Figure 16a) represented by conjugating naphthoquinone with anthraquinone was isolated from the bark of *Newbouldialaevis* (Figure 16b). The antifungal activity of this naphthalene-based product was examined against *C. albicans*, *C. glabrata*, and *C. krusei*. The outcomes showed that this product has a more potent effect against *C. glabrata* by 13-fold than nystatin, which was employed as a standard drug [21].

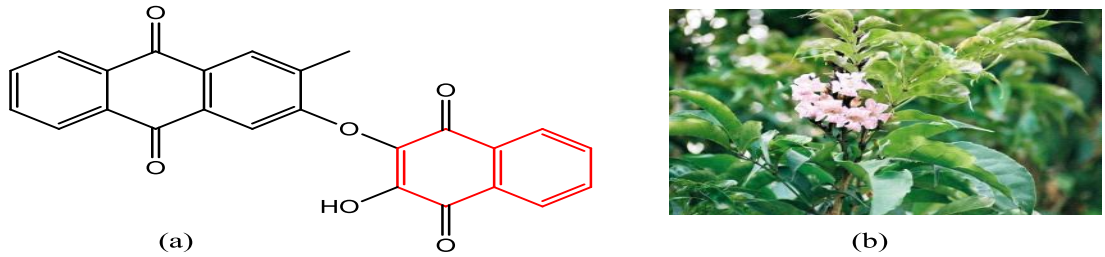

Figure 16: (a) The natural product isolated from *Newbouldialaevis* (b).

Campo *et al*. have isolated and identified three pyrano-naphthoquinones from *Cipurapaludosa*bulbs (Figure 17a), which were eleutherine, isoeleutherine, and eleutherol. The antifungal activity of the isolated products was examined using a broth-dilution technique against *C. albicans, C. tropicalis, Saccharomyces cerevisiae,* and *Cryptococcus neoformans*. The results showed a potent antifungal activity of these products, particularly eleutherine (Figure 17b). This product has a MIC value of 7.8 µg/ml compared to the MIC of the positive control amphotericin B of 0.25 µ/ml. The authors attributed the traditional use of *Cipurapaludosa*bulbs for treating superficial fungal infections to the presence of these naphthalene-based products [22].

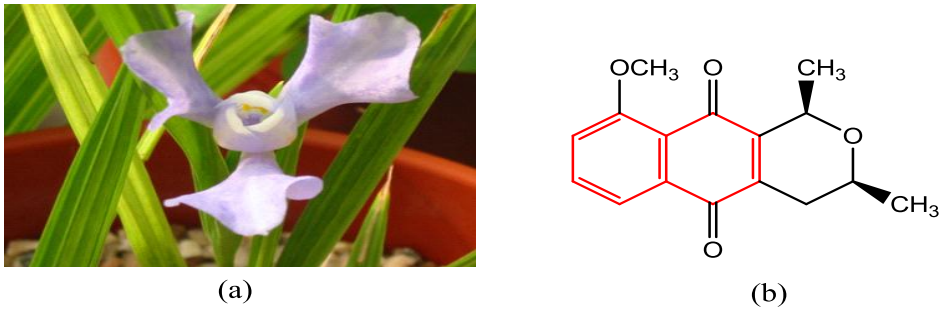

Figure 17: (a) *Cipurapaludosa*bulb from which eleutherine (b) was isolated.

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1.4 Anti-inflammatory activity

Inflammation is a normal immune response to protect the body from tissue injury. However, the excessive inflammatory response that is manifested by overexpression of pro-inflammatory cytokines (e.g. interleukins and necrotic factors) and inflammatory factors (e.g. nitric oxide and prostaglandin E_2) may lead to cell damage and progress to inflammatory diseases such as arthritis, neurodegenerative disorders, and inflammatory bowel diseases [23]. Hence, the inhibition of these mediators and factors is the principal target for treating inflammatory diseases.

Naphthalene and its conjugates have been highly investigated for their anti-inflammatory action [24-29]. Muralidharan*et al*. have synthesized and characterized a novel series of naphthalene-pyrimidine conjugates. Their anti-inflammatory effect was assayed via the HRBC-membrane stabilization technique, which is applied to detect the hypotonicity-induced RBC membrane lysis as a detector of the anti-inflammatory potential. The results showed that the naphthalene-based conjugates termed **2a**, **2c**, **2d**, and **2f** (Figure 18) have a significant anti-inflammatory action compared to diclofenac as a standard [24].

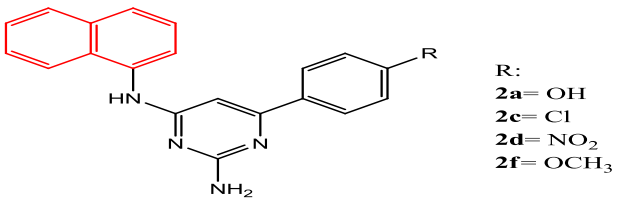

Figure 18: Naphthalene-pyrimidine conjugates prepared by Muralidharan*et al*. with a significant anti-inflammatory action.

Naproxen is an important member of the propionic acid group of NSAIDs. This member has a naphthalene moiety in its chemical structure and can effectively block the cyclooxygenase (COX) enzymes reducing pain and inflammation. Many attempts have been conducted to minimize the GIT side effects of naproxen and improve its anti-inflammatory activity. El-Husseiny*et al*. have conjugated different aryl and heteroaryl moieties with naproxen-scaffold and examined the influence of such conjugation on the anti-inflammatory effect. The results showed that the conjugation of naproxen with oxadiazole- or triazole-based derivatives resulted in a marked inhibition of cyclooxygenase isozymes (COX-1/COX-2). Besides, the conjugates termed **6c** and **10c** (Figure 19) showed a high selectivity for inhibiting COX-2 isozyme [25].

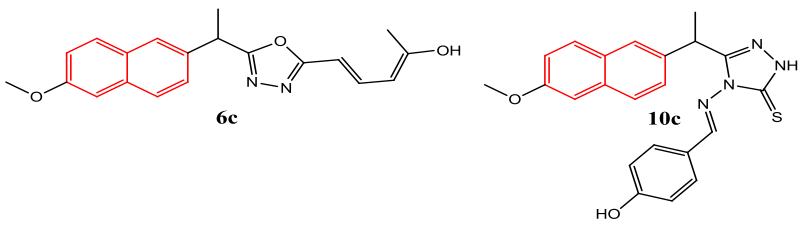

Figure 19: Conjugates of oxadiazole- and triazole-based derivatives with naproxen-scaffold that were prepared by El-Husseiny*et al*.

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Gangwar*et al*. have synthesized, characterized, and examined the anti-inflammatory activity of a novel series of thiazolidinone derivatives conjugated with naphthalene. The outcomes showed that two of the naphthalene-based conjugates termed **TB1** and **TB2** (Figure 20) exhibited a significant anti-inflammatory effect compared to diclofenac as a standard. This effect was assayed by using the Carrageenan-induced paw edema technique, in which, the paw volume after 60 minutes was 0.32 ml and 0.3 ml for **TB1** and **TB**2, respectively, compared to 0.34 ml of paw volume afforded by the standard [26].

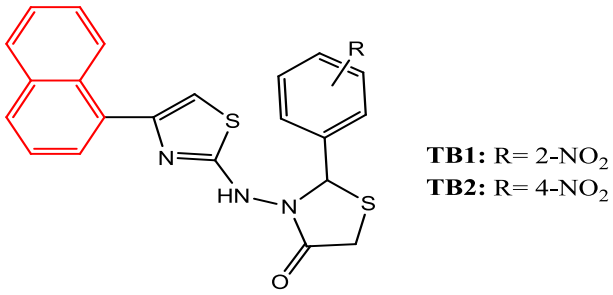

Figure 20: Chemical structures of TB1 and TB2 prepared by Gangwar*et al.*

Naturally, naphthalene-based products are highly investigated for their biological activities including the anti-inflammatory effect. Tan *et al*. have isolated and characterized seven new spiro-bis-naphthalene conjugates from Phyto-endophytic fungus named *Edeniagomezpompae*. The authors have examined the anti-inflammatory effect of these natural conjugates by detecting the nitric-oxide production in LPS-induced-RAW264.7 macrophagic cells. The results showed a potent inhibitory impact on the production of this inflammatory factor exerted by the conjugates termed **8** and **13** (Figure 21) with IC_{50} values of 2.61 and 1.32 µmol/l, respectively [27].

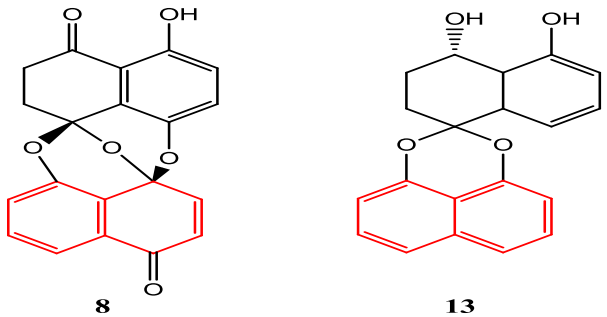

Figure 21: Natural naphthalene-based conjugates with an anti-inflammatory activity isolated from *Edeniagomezpompae.*

Jin *et al*. have synthesized, characterized, and evaluated the anti-inflammatory activity of new naphthalene-chalcone conjugates. The evaluation was conducted by monitoring the acetic acid-induced abdominal writhing and xylene-induced ear-edema assays in mice. The results exhibited a significant anti-inflammatory effect of the conjugates termed **2f**, **2i**, and **2u** (Figure 22) with inhibition percentages of writhing

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as 58.5%, 50.0 %, and 59.8 %, respectively, compared to the inhibition percentage of indomethacin 76.9 % that employed as a reference drug [28].

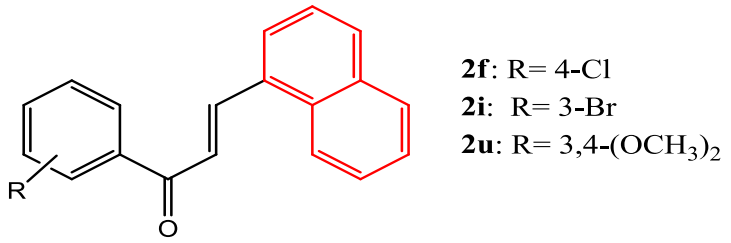

Figure 22: Naphthalene-chalcone conjugates with a characteristic anti-inflammatory potential synthesized by Jin *et al.*

Pandya*et al.* have synthesized several naphthalene-pyrazole conjugates and evaluated their anti-inflammatory activity utilizing the Carrageenan-induced-paw edema technique in rats and indomethacin as a standard. The outcomes revealed that the conjugates termed **7a**, **7b**, **7c**, and **7d** (Figure 23) were significantly active compared to the standard. The authors proposed that the predicted mechanism of action regarding these conjugates is similar to that of the pyrazolone-derived NSAIDs [29].

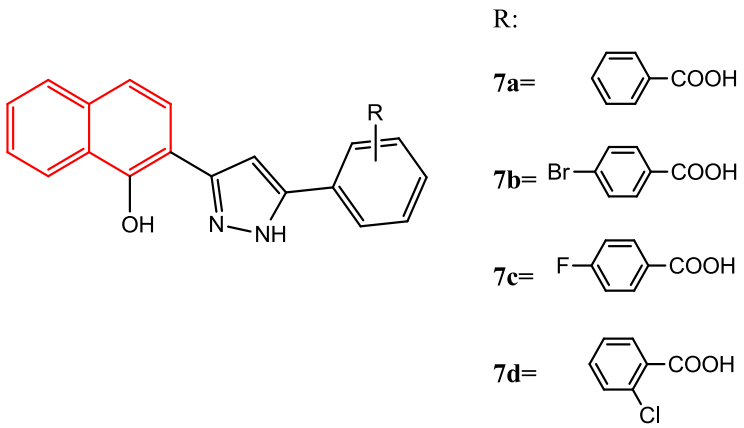

Figure 23: Naphthalene-pyrazole conjugates with a characteristic anti-inflammatory potential that were prepared by Pandya*et al*.

1.5 Antiviral activity

Viral infections constitute a large percentage of infectious diseases affecting humans worldwide. So, many efforts have been performed to fight such infectious viruses [30]. Naphthalene and its derivatives have been used widely as a scaffold for developing effective antiviral agents [31-35]. Barman *et al*. have conjugated naphthalene-based compound with tetrahydronaphthalene via a carbohydrazide linker. These conjugates were investigated for the anti-influenza A activity by monitoring their capacity to inhibit NS1 (non-structural protein 1) in MDCKCs (Madin-Darby Canine Kidney cells) model. The results showed that the substitution of the linker imine's carbon with senior electron-donating group like the phenyl or cyclohexyl group could result in a high potentiating of activity. Accordingly, the conjugates termed **15** and **18** (Figure 24) that have such groups in their structures showed an antiviral effect similar to that of Oseltamivir [31].

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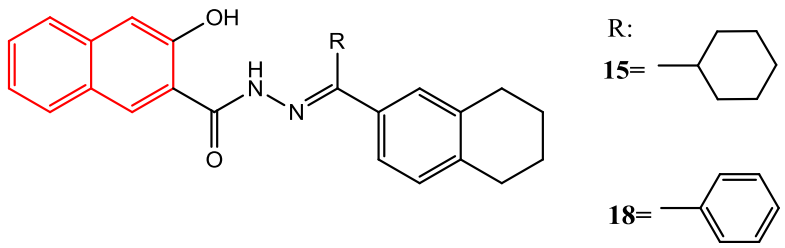

Figure 24: Naphthalene-tetrahydronaphthalene conjugates with a potent anti-influenza virus synthesized by Barman *et al.*

The stabilization of G-quadruplex (G4) through the multiplication of the HIV-1 virus is a novel target for the newly-developed antiviral agents. Based on that, Perrone*et al*. have synthesized a new class of legends composed of naphthalene-based derivatives conjugated with an aromatic core depending on the unique structural features of the targeted G4 protein. The results showed that the conjugate numbered **2** (Figure 25) in the synthesized series exhibited a potent antiviral activity against HIV-1 by the selective interaction with the G4 loop. This interaction was followed via the mass spectroscopy operated in an electrospray ionization mode [32].

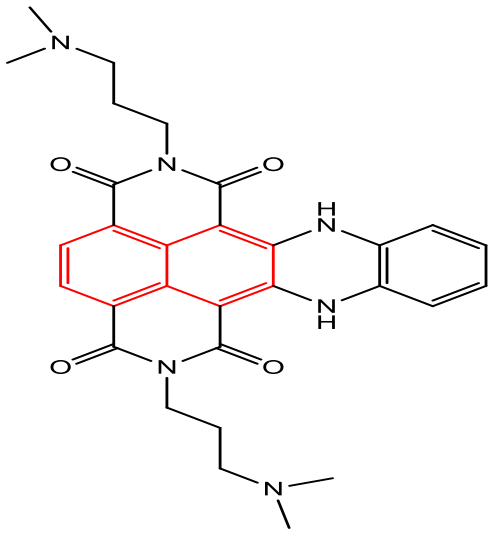

Figure 25: Naphthalene-based derivative synthesized by Perrone*et al.* to target G4 protein.

Zika virus represents a serious public health problem particularly in the tropical and subtropical regions because this virus can be transmitted to humans through an infected mosquito. In response to this health issue, Gonzaga *et al*. have synthesized many bis-naphthoquinone-based compounds and measured their anti-Zika virus effect. Five of the synthesized compounds exhibited a characteristic antiviral activity, which are **10o**, **13e**, **13h**, **13j**, and **13k** (Figure 26) with EC_{50} values of 1.38, 0.65, 1.11, 0.62, and 0.91µM, respectively. These results may maximize the hope for the development of a potent antiviral drug to face the infection with Zika virus [33].

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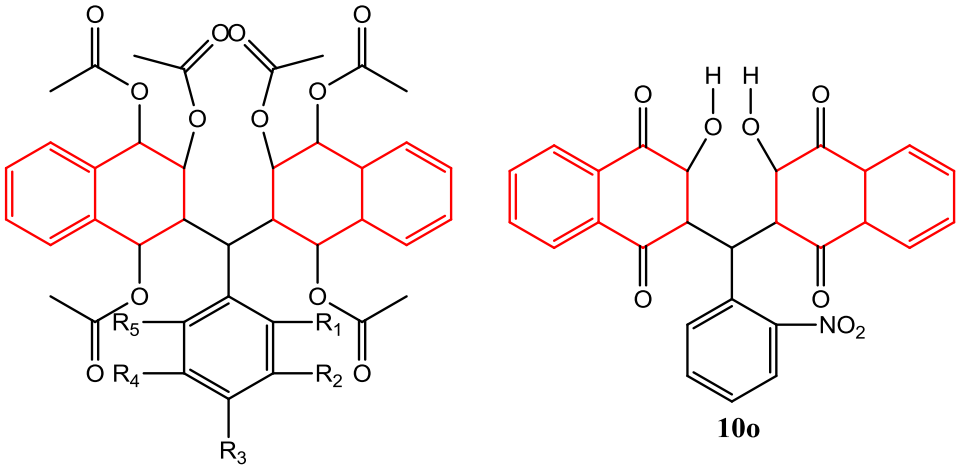
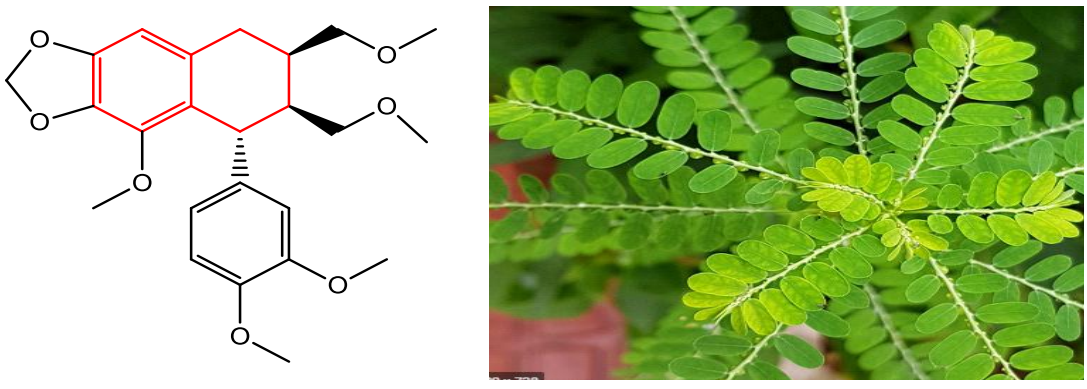


13e: $R_1=R_2=R_4=R_5=H$, $R_3=Cl$
13h: $R_1=R_2=R_4=R_5=H$, $R_3=CH_3$
13j: $R_1=R_3=R_4=R_5=H$, $R_2=OH$
13k: $R_1=R_2=R_3=R_4=R_5=F$

Figure 26: Effective bis-naphthoquinone derivatives as anti-Zika virus.

Wei *et al*. have isolated a novel natural aryltetrahydronaphthalene product named nirtetralin-B from *Phyllanthusniruri*leaves (Figure 27) and examined its anti-hepatitis B virus (HBV) activity. The study showed that this product was effectively suppressed the virus antigens with IC_{50} values of 69.3 µM and 16.7 µM for HBeAg and HBsAg, respectively. Besides, This product revealed a significantly better inhibition rate for HBV than acyclovir, which was applied as a control [34].



Nirtetralin-B **Phyllanthus niruri leaves**

Figure 27: Chemical structure of the natural product named nirtetralin-B isolated form *Phyllanthusniruri*leaves.

1.6 Cytotoxic activity

Globally, cancer is considered as the second prime issue of death worldwide through reporting 18.1 million cases and 9.6 million deaths from this disease in 2018 [35,36]. In the term of mortality incidence, the top three cancer-phenotypes are the lung, breast and colorectal cancers [37,38]. Many efforts have been conducted to restore humanity stock to face this type of mortal disease [39-47]. Naphthalene and its derived conjugates are among many synthetic compounds that have been synthesized and

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examined against various kinds of cancer. For instance, naphthoquinone is the core structure of three important natural cytotoxic drugs including daunorubicin, doxorubicin, and mitoxantrone (Figure 28). These natural killers of tumorous cells operated their impact by inhibiting the DNA topoisomerase I and II leading to apoptosis [39].

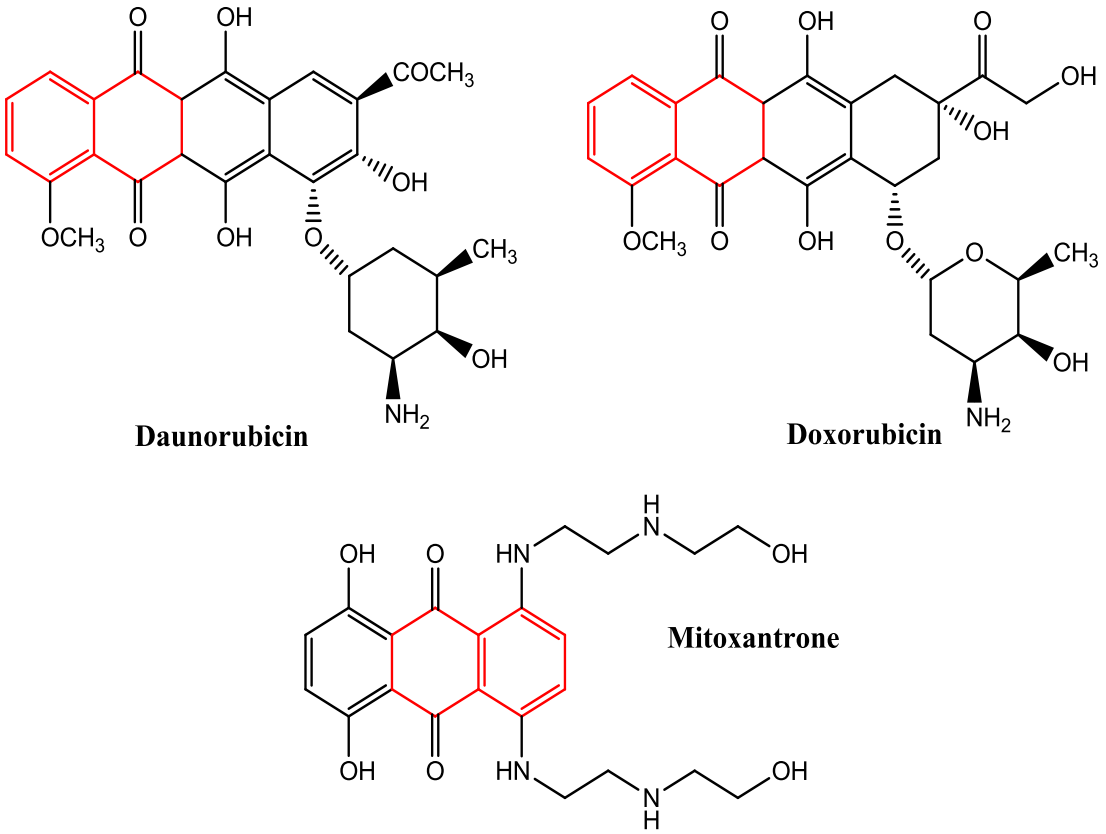

Figure 28: Chemical structures of the naphthoquinone-based cytotoxic drugs.

Budhiraja*et al*. have synthesized a series of naphthalene-chalcone compounds that were conjugated with a substituted phenyl group. The resultant conjugates were tested as cytotoxic agents against prostate (PC-3), ovarian (OVACAR), neuroblastoma (IMR-32), and liver (HEP-2) cancerous-cell lines. The outcomes revealed that the compound numbered **9** (Figure 29) possessed the most potent activity with inhibition percentages of 81%, 88%, 75%, and 72% versus the aforementioned cell lines, respectively. The structure-activity relationship (SAR) of these conjugates revealed that the replacement of naphthalene group with another heterocycle may minimize the cytotoxic activity indicating the significance of this group for the titled activity [40].

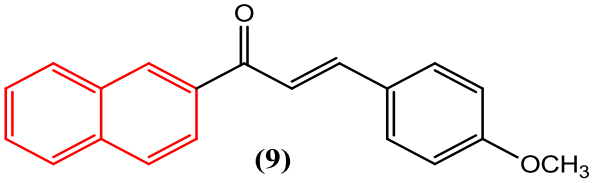

Figure 29: Chemical structure of compound 9 that synthesized by conjugating naphthalene-chalcone product with *p*-methoxy phenyl ring.

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Rajabi*et al.* have prepared a series of compounds by conjugating naphthalene with butyrolactone-based products. The *invitro* cytotoxicity of the resultant conjugates was examined against HCT-15 (colon) and MCF-7 (breast) cancerous-cell lines. The results showed that the conjugate numbered **4** (Figure 30) was the most effective versus the test cancerous lines with IC_{50} values ranged between 64-66 µM [41].

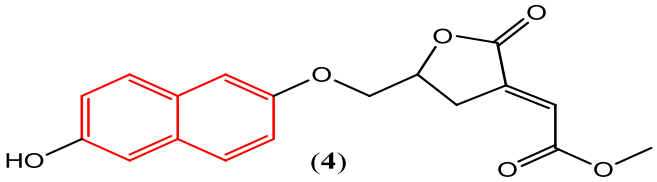

Figure 30: Chemical structure of the conjugate numbered 4, which was prepared by Rajabi*et al.*

Spaczyńska*et al*. have designed and synthesized many naphthalene-based conjugates and tested there *in vitro* cytotoxicity on human colon-carcinoma cell lines. The outcomes showed that the most significant effects were attributed to the conjugates (Figure 31) with Cl, Br, CF_3, NO_2, or OCH_3 substituent with IC_{50} values ranged between 6.25-25 µM compared to the IC_{50} of 5-fluorouracil that was 4.42 µM. The author suggested that the intercalation of these conjugates with DNA may represent the possible mechanism of action [42].

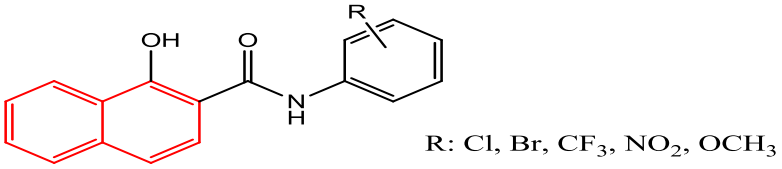

Figure 31: Effective 1-hydroxynaphthalene-2-carboxamides

A new panel of naphthalene-pyrazole conjugates was synthesized by Karakurt*et al*. The cytotoxicity of these conjugates was investigated *in vitro* utilizing the mouse fibroblast- and human neuroblastoma-cell lines. The outcomes revealed that most of the synthesized conjugates exhibited the inhibition ratios ranged between 50-60% against the test cancerous lines without detected effect on the healthy fibroblasts. Besides, conjugates termed **7a** (Figure 32) was the most effective among the synthesized conjugates with an IC_{50} value of 85.94 µM compared to vincristine, as a control, with an IC_{50} value of 25.52 µM [43].

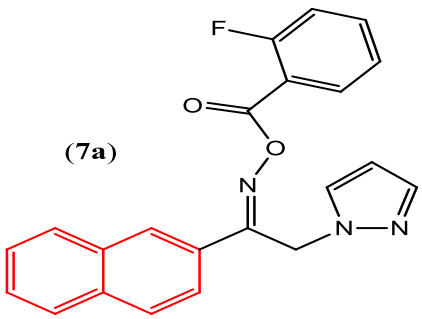

Figure 32: Chemical structure of the naphthalene-pyrazole conjugate termed 7a.

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Yuan *et al*. have synthesized a series of naphthalene-thiazole-pyrazole conjugates and investigated their cytotoxicity on HeLa cell line. The results showed that the conjugate termed **7d** (Figure 33) was the most effective with an IC_{50} value of 0.12 µM compared to gefitinib with an IC_{50} value of 2.67 µM as a control. The SAR study revealed that the cytotoxic effect of this conjugate was highly related to the substitution on the ring A. Besides, the docking simulation showed that the naphthalene ring of the targeted conjugate could form two *p-π* bonds with LYS721 of the active site of EGFR (epidermal growth factor receptor), which may explain the high activity of this conjugate [44].

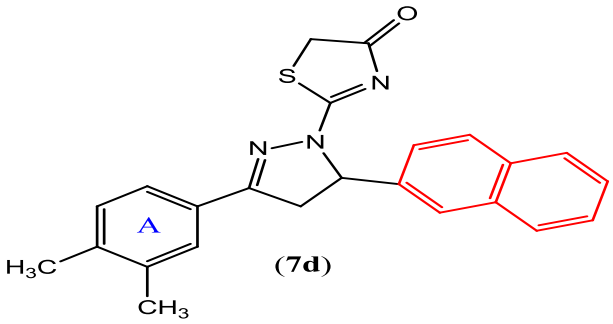

Figure 33: Chemical structure of the naphthalene-thiazole-pyrazole conjugate that termed 7d.

A series of naphthoquinone O-glycosides derivatives have been synthesized and investigated for their *in vitro* cytotoxicity on mouse Ehrlich carcinoma cell line and results showed that the glycosylated naphthoquinones were highly effective with compound 42 as the most effective one with an IC_{50} of 5.1 µM comparing to cisplatin IC_{50} of 50.1 µM as a control. Such results may indicates the importance of glycosylation on the cytotoxicity of their conjugates [45].

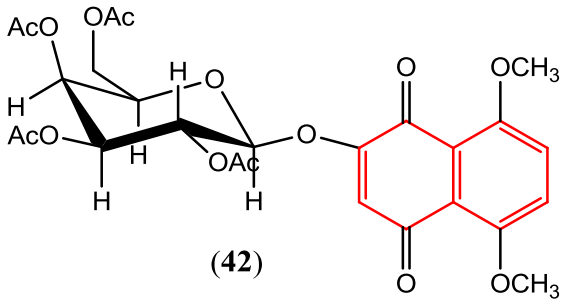

Figure 34: Glycosylated naphthoquinone (42)

Many naphthalene-based products conjugated with indole via a chalcone linker were synthesized by Wang *et al*. The *in vitro* cytotoxicity of the synthesized conjugates was examined against three human cancerous-cell lines, included hepatocellular carcinoma (HEPG2), breast adenocarcinoma (MCF-7), and colon carcinoma (HCT116). The results showed that the conjugate numbered **7** (Figure 35) was the most effective with an IC_{50} value of 1.13, 0.65, and 0.82 µM against HCT116, HEPG2, and MCF-7, respectively. The mechanism study conducted on this conjugate revealed its ability to inhibit the tubulin polymerization and subsequently arrest the G2/M phase of the cell cycle [46].

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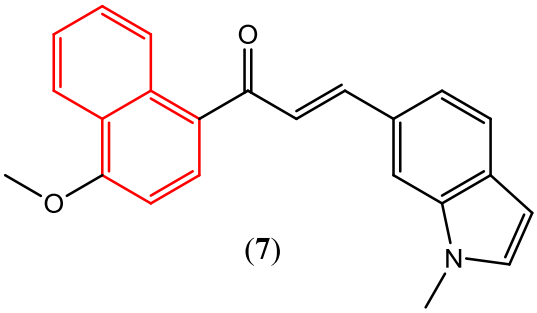
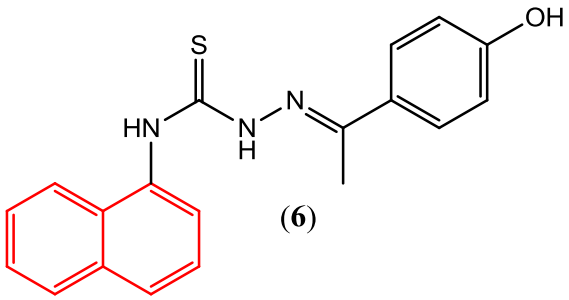


(7)

Figure 35: Chemical structure of the compound number 7, which was synthesized by Wang *et al*.

Altintop*et al.* have synthesized many naphthalene-based semicarbazones and evaluated their in vitro cytotoxic effect against human prostate cancer cells (LNCaP). The outcomes revealed that the conjugate numbered **6** with a phenol substitution (Figure 36) was the most effective among the other conjugates with an inhibition percentage up to 83% [47].



(**6**)

Figure 36: Chemical structure of the conjugate number 6, which was synthesized by Altintop*et al*.

1.7 Antioxidant activity

The oxidative stress generated from the elevated levels of the damaging free radicals may correlate with many human diseases such as atherosclerosis, stroke, ischemic cardiac, inflammation, and cancer [48,49]. Reactive-oxygen species (ROS), superoxide anion, peroxyl radicals, and nitric oxide are the familial examples of the free radicals that could interact with lipids, proteins, and DNA leading to characteristic health problems [50,51]. The trapping of free radicals became an important field of investigation in order to protect the body from their harmful potentials [52].

Ateş-Alagöz*et al*. have synthesized many derivatives of 6-fluoro-5-substituted benzimidazole, in which, the 1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene moiety was grafted to the position 2 of the benzimidazole ring. All synthesized compounds possessed good superoxide-anion scavenging activity at 10^{-3} M concentration. Besides, the compound numbered **5** (Figure 37) exhibited the most significant trapping effect that reached 98% compared with superoxide dismutase, which showed a trapping activity of 76% [53].

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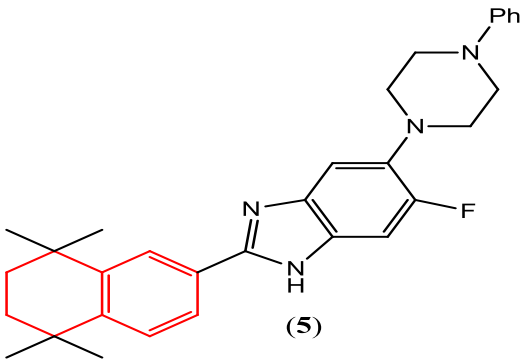

Figure 37: Chemical structure of the conjugate number 5, which was prepared by Ateş-Alagöz*et al*.

Shirinzadeh*et al*. have synthesized and developed many melatonin bio-isosteres (Figure 38) by replacing the indole moiety with naphthalene rings of various aryl-substituted side chains. The synthesized compounds were *in vitro* investigated for their radical trapping activity. The results showed that these compounds were highly effective as antioxidant agents. The authors contributed this improved activity to the replacement of the indole ring with that of naphthalene and the absence of the 6-methoxy substituent [54].

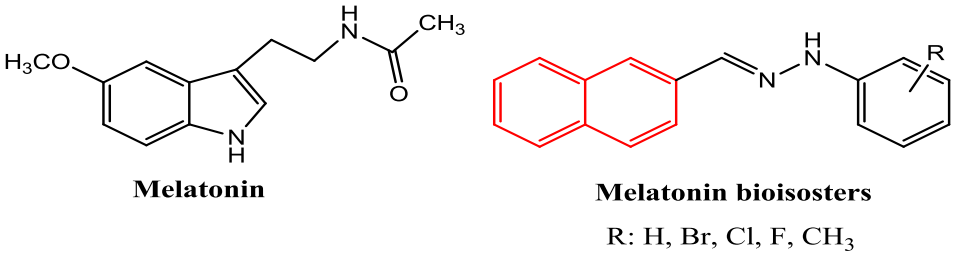

Figure 38: Chemical structures of the melatonin and its synthesized bio-isosteres.

Hamdy*et al*. have synthesized many naphthalene-pyrazolopyridine conjugates and investigated their trapping capacity via DPPH assay employing vitamin C as a reference agent. The outcomes showed that the conjugate termed **5a** (Figure 39) was more effective as an antiradical agent than the other synthesized conjugates and reference [55].

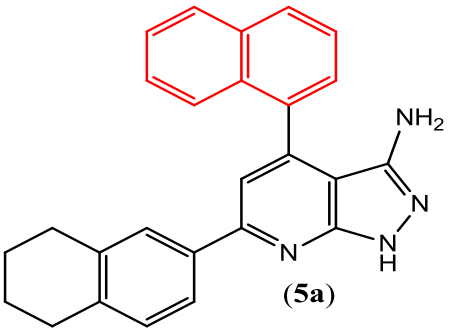

Figure 39: Chemical structure of the conjugate number 5a, which was prepared by Hamdy*et al* as an antioxidant.

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Somashekara B *et al*. have synthesized many naphthalene-imidazole conjugates and examined their antioxidant capacity via DPPH-radical scavenging assay. The outcomes showed that the conjugates termed **2d**, **2g**, and **2K** (Figure 40) exhibited good trapping capacity compared to the control, butylatedhydroxyanisole (BHA). The authors contributed the improved activity to the naphthalene moiety and substitution on positions 4 and 5 of the imidazole ring with good electron-donating groups [56].

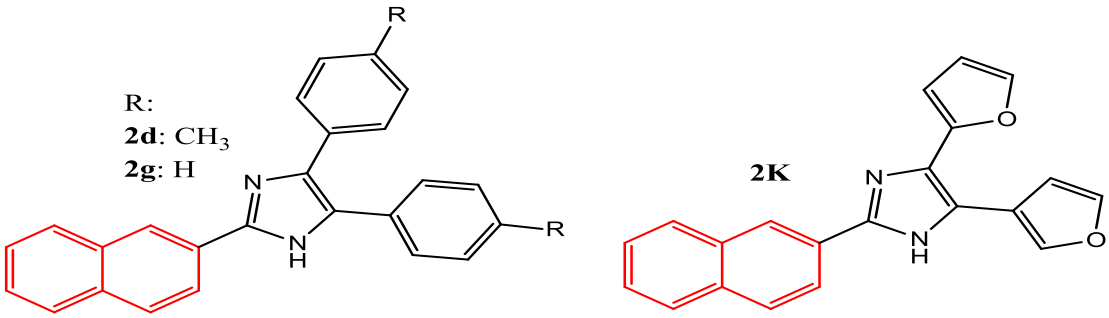

Figure 40: Naphthalene-imidazole conjugates with a potent antioxidant effect.

A novel series of naphthalene functionalized by (*E*)2,3-dihydrofuro[3,2-*c*] coumarin has been synthesized and investigated for their *in vitro* antioxidant activity using a H_2O_2-trapping assay. All the synthesized compounds possessed a comparable antiradical activity compared to BHA as a control. Besides, the compound termed **4f** (Figure 41) showed the best activity compared with the control even at the lowest concentration (10µM/ml). The authors concluded that the antiradical activity of such compounds may be enhanced by the presence of an electron-withdrawing group on the aryl moiety linked to the dihydrofuran ring [57].

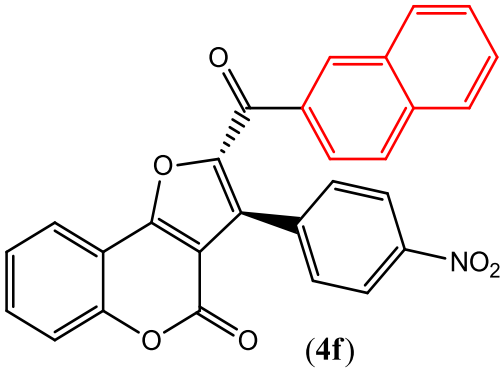

Figure 41: Chemical structure of the naphthalene functionalized with dihydrofurocoumarin (4f), which has a potent antioxidant potential.

Gouda *et al*. have synthesized many benzothiophene-naphthoquinone conjugates and investigated their*in vitro* antiradical effect using ABTS-screening assay. The results possessed that the conjugate termed **9a** (Figure 42) was the most effective with an inhibition percentage of 95.97% compared with the vitamin C's inhibition percentage of 89.87%. Also, this study showed that these synthesized conjugates can protect DNA from the injury induced by the cytotoxic drug named bleomycin [58].

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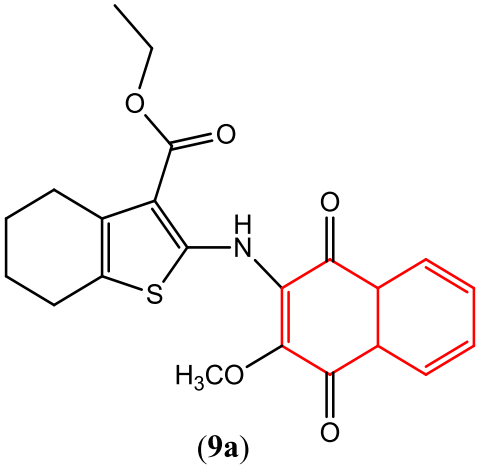

(**9a**)

Figure 42: Chemical structure of the naphthoquinone-benzothiophene conjugate termed 9a, which has a potent antiradical potential.

Ozen*et al*. have synthesized twelve naphthalene-based compounds having a Schiff-base linker. The antioxidant capacity of these conjugates was examined through several methods included phosphomolybdenum-, metal chelating-, lipid peroxidation-, reducing power-, and H_2O_2 scavenging activity-assays [59]. The compounds termed **NAPH5**, **NAPH10**, and **NAPH12** (Figure 43) were the most effective at 10 and 50 mM concentrations compared to the control. The results of this report may open a new field for developing effective antioxidants that can be useful for medicinal and industrial purposes [60].

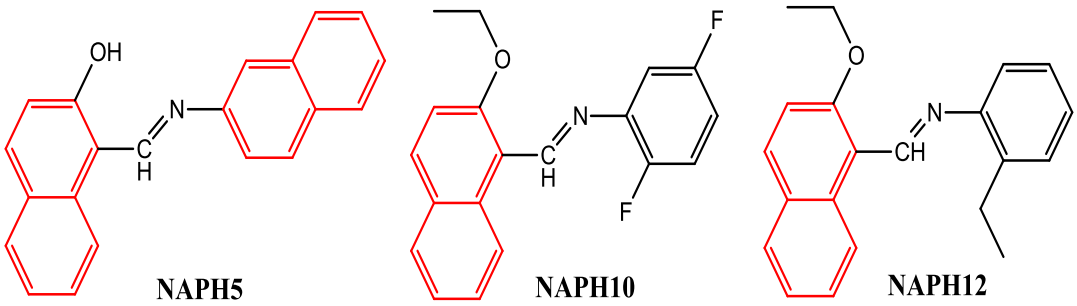

Figure 43: Naphthalene conjugates with imine linkage

2. Conclusion

The conjugation of naphthalene-based compounds with various aryl- or heteroaryl-moieties became a characteristic motive for the investigation to discover new lead compounds in various pharmacological fields. Based on the previously discussed studies, this conjugation-phenotype has resulted in the improvement of the bioactivities of the synthesized conjugates compared to the parent naphthalenes. This conclusion may be contributed to the enhanced lipophilicity of the resultant conjugates. This feature could improve the penetration of these conjugates into the targets and intensify the drug-target interactions by generating more Van der Waals forces.

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