Review Article :

Study 1,4- Naphthoquinone Derivative and Biological Activity: A Review

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Abstract:

In this work, we focused on studying 1,4-naphthoquinones and their derivatives, and knowing the methods of preparing them using different auxiliary agents and forming derivatives containing heterocyclic rings, active groups and saturated rings containing heterogeneous elements . In addition, due to their strong antibacterial, antifungal and anticancer activity, 1,4-naphthoquinone compounds biological importance and are considered a source of various pharmaceutical compounds.

Keywords: 1,4- Naphthoquinone, Biological Activity, antibacterial activity, antifungal activity, Anticancer activity.

دراسة مشتقات 4,1- نفثوكوينون و النشاط البايولوجي: مراجعة

نبراس مظفر جميل بسمة جعفر احمد مائدة حميد سليم
قسم الكيمياء / كلية التربية للعلوم الصرفة (ابن الهيثم) / جامعة بغداد

الخلاصة :

يركز البحث, على دراسة4,1 – نفثوكوينونات و مشتقاتها, و معرفة طرق تحضيرها باستخدام عوامل مساعدة مختلفة وتكوين مشتقات تحتوي على الحلقات غير المتجانسة ومجاميع فعالة وحلقات مشبعة تحتوي على عناصر مغايرة كما تتمتع مركبات4,1 –نفثوكوينون بأهميتها البايولوجية و يعد مصدراً للعديد من المركبات الصيدلانية نظرا لنشاطها القوي كمضاد للجراثيم و الفطريات و السرطان.

الكلمات المفتاحية: 4,1 – نفثوكوينونات, فعالية البايولوجية, مضاد للجراثيم,مضاد للفطريات,مضاد للسرطان.

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1.Introduction

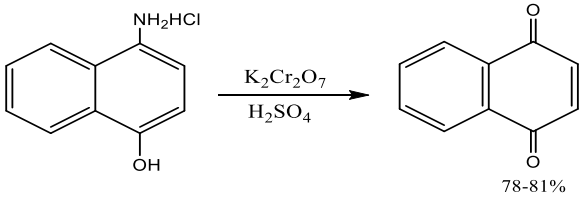
Quinones compounds are unsaturated cyclic diketones and its widespread in nature and include important kind of natural active compounds in plants, fungi, and bacteria and it has important role in cellular breathing and photosynthesis [1] Quinones compounds are chromatic because it has high conjugation and in general it is yellow and solid crystals, [2] A kinds of naphthoquinone compounds have biological activity, such as vitamin potassium and in cell metabolism[3]. Naphthoquinones are considered natural organic compounds with high reactivitye, that intensively studied as promising bioactive agents [4,5], mediators in oxidation processes [6] and dyes. [7] The formation of 1,4-Naphthoquinone [8] occurs when two benzene rings in the α- -position are oxidized during the preparation of a 1,4-quinoid nucleus., the quinone ring system alternates with the carbonyl groups and It is affected by various factors:(reducing, oxidizing, and adding O-, N-, and S nucleophiles.), It reduces and obtained 1,4-dihydroxy naphthalene using different agents.

1,4- naphthoquinone derivatives hydroxyl Natural of lawsone [9] and juglone [10] ,the hydroxyl groups is in position α- and β- from naphthalene obtain salts and complexes by reaction with various metals used for dyeing such as 1,4-naphthoquinone (Naphthazarin) is derived from 5,8-Dihydroxy derivative.[11].

It is clear that 1,4-naphthoquinones derivatives are of great importance because dichlone and its derivatives or equivalents have taken a prominent place in the quinone family. [12] Amino acid derivatives derived from 1,4-naphthoquinone possess strong bactericidal, [13-18] antiviral, antiphthisic, antibiotic[19-24], antimalarial[25,26], antihypoxic, antiplatelet activities [27,28] Antiplasmodial [29], antianginal, anti-ischemic [30,31], and antitumor activity [32-37]. Pharmacological drugs in medicine and fungicides and insecticides are among the uses for them. [38-41]

2. Synthesis

1,4- naphthoquinone Prepared by oxidation of 1,4-diamino-, dihydroxy- or amino hydroxyl naphthalene The formation of a yellow solid at 125 ^{o}C is achieved by the direct oxidation of naphthalene in glacial acetic acid using dichromate, sulfuric acid, or chromium trioxide. [2]

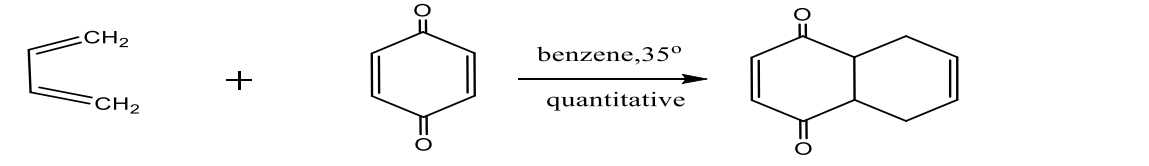


1 2

Scheme(1)

Synthesis of naphthoquinone derivatives

t is highly probable that a one-step mechanism is involved; both new carbon-carbon bonds are partially formed in the same transition state but not necessarily to the same extent. The most important is the Diels-Alder reaction example of cycloaddition, which is advantageous because it generates a ring and can be carried out easily for a wide variety of reactants. Electron-withdrawing substituents in the dienophile are a favourable factor in the reaction, but simple alkenes can also react. [42]

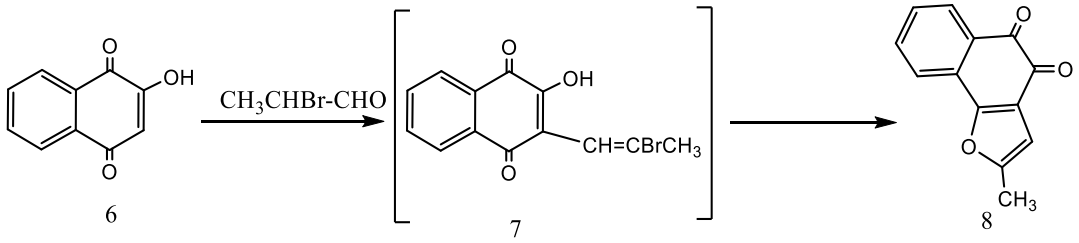


1,3-Butadiene p-Benzoquinone 5,8,9,10-Tetrahydro-1,4-naphoquinone

3 4 5

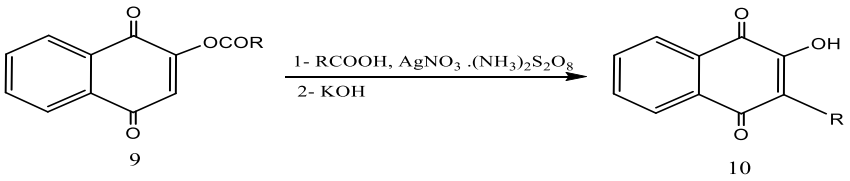
Scheme(2)

While, reaction of Lawsone with 2-bromo propanal to Cyclization ortho-quinone furan derivatives. [1]



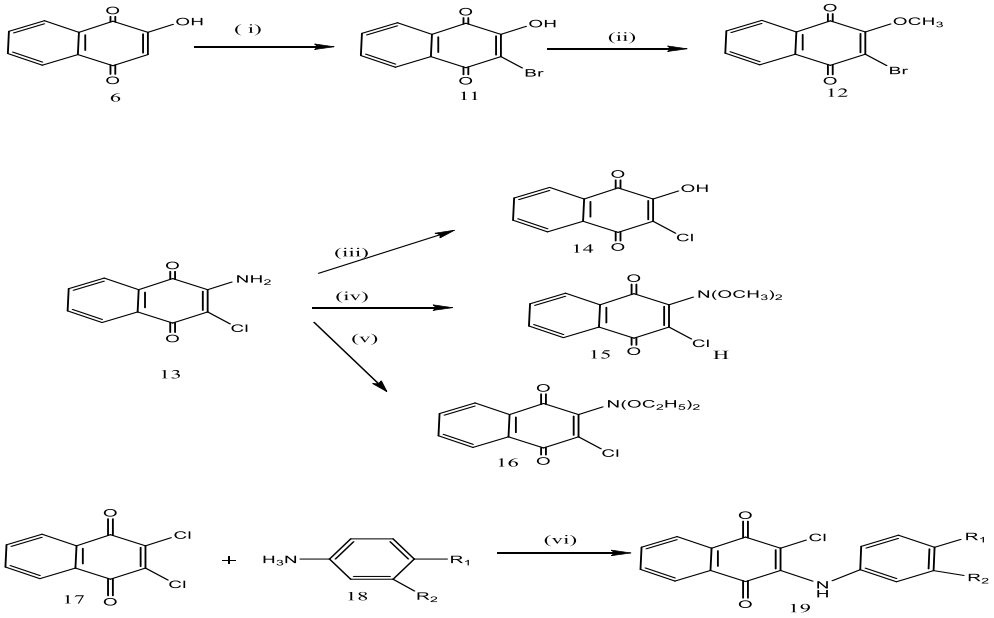
Scheme(3)

The peroxysulfate-mediated radical decarboxylation reaction [43] resulted in better results when acylated lawsone reacted with carboxylic acid.



Scheme(4)

Synthesis of novel halogen substituted 1,4-naphthoquinones [44]

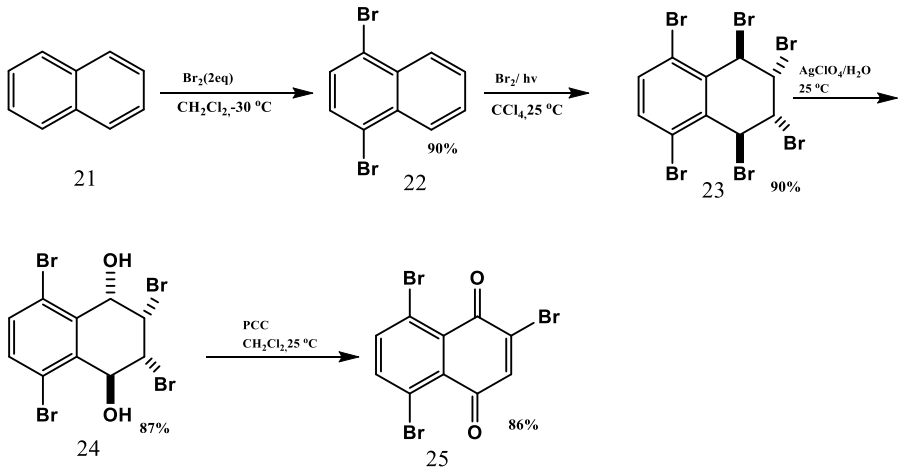


(i):Br_2, H_2O_2, H_2SO_4, 2N, 20°C
(ii):$(CH_3)_2SO_4$, K_2CO_3, aceton,60°C
(iii):$NaNO_2$, HCl- AcOH-H_2O, 0-5°C-> 50°C;
(iv):$(CH_3CO)_2O$, AcOH, H_2SO_4,70°C;
(v):$(C_2H_5CO)_2O$, C_2H_5COOH, H_2SO_4,70°C;
(vi):abc.MeOH, 50-60 °C

5a: R_1=H ; R_2=H
5b: R_1=F ; R_2=H
5c: R_1=Cl ; R_2=H
5d: R_1=Br; R_2=H
5e: R_1=H ; R_2=CF_3
5f: R_1=CH_3 ; R_2=H

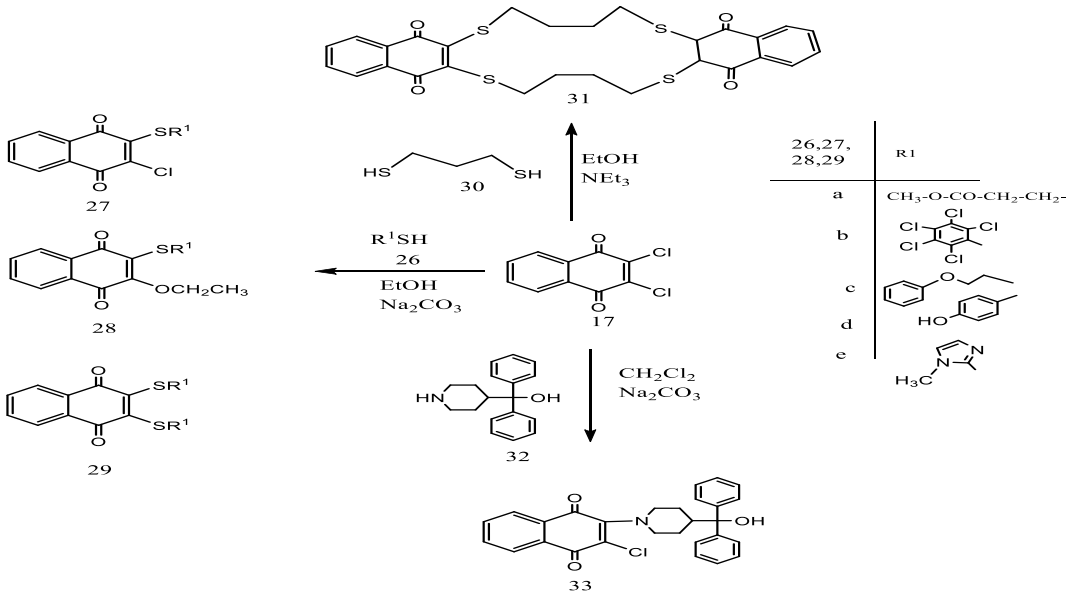
Scheme(5)

Either by naphthalene reaction in four steps [45] ,obtained on 2,5,8-tribromonaphthoquinone



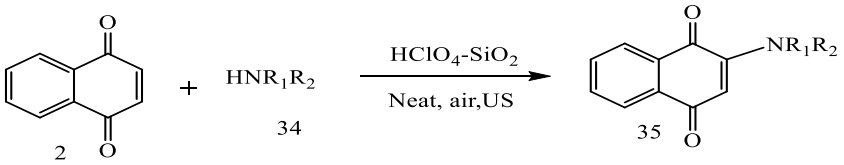
Scheme(6)

The preparation of 1,4-naphthoquinone derivatives.[46] of 1,4-naphthoquinone with [26], [30], and [33].

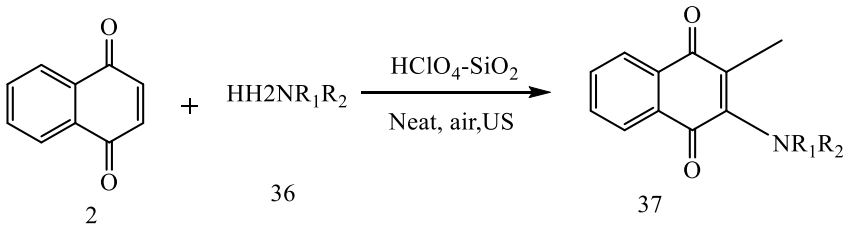


Scheme(7)

the method synthesis 1,4- naphthoquinone derivatives of primary and secondary amines with 1,4-naphthoquinone by catalyst $HClO_4$-SiO_2.[47]



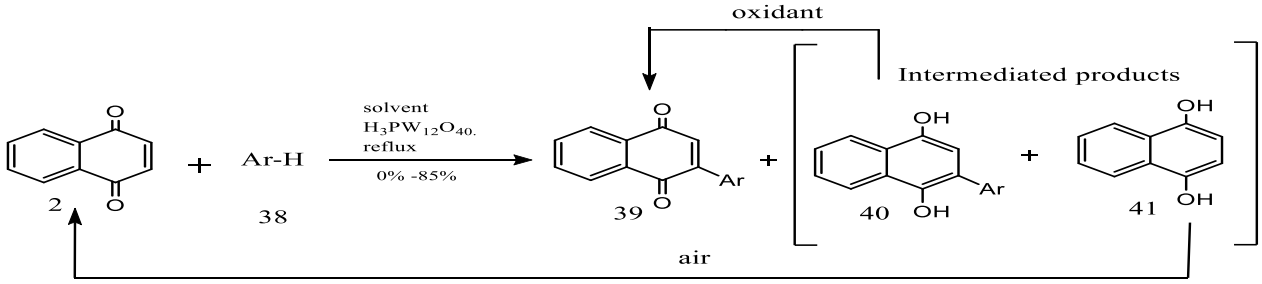
NR_1R_2=Methylamine,Ethylamine,*tert*,Butylamine,aniline,o-Toluidine,p-Toluidine,3,5-Dimethylaniline,,p-Anisidine,Benzylamine,Tyramine,Morpholine,Cyclohexylamine,*N*-Ethylamin emorpholine,4-Amino-*N*-benzyl piperidine,Pyrolidine,*m*-Bromoaniline,*N*-Ethylamine piperidine

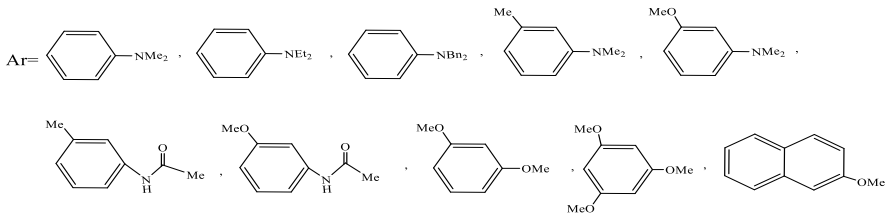


NR_1R_2=Methylamine, Aniline

Scheme(8)

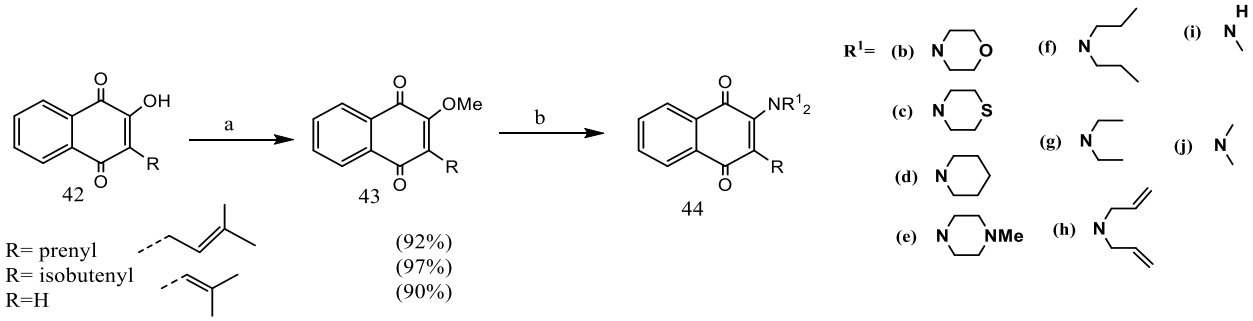
The optimal method for making N,N-dimethylaniline involves reacting it with twice the amount of excess [2] in DMSO and catalyzing it with $H_3PW_{12}O_{40}$ (on air after 24 h) of stirring was 100 ^oC and 35% yield (Scheme9), Comparing [39], it is structurally simple and has a low yield. $CH_3COOH$was not useful in terms of yield, but it prevented naphthoquinone from decomposition observed in basic medium. That reaction did not require the addition of oxidants because the intermediates [40] and [41] were spontaneously oxidized by air to produce.[48]





Scheme(9)

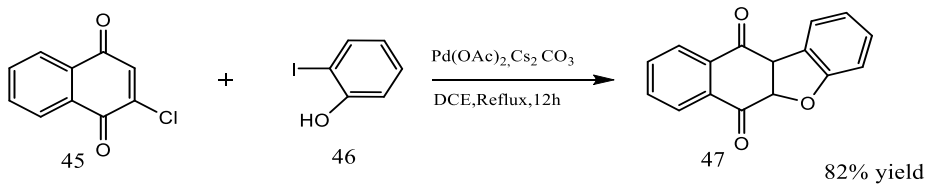
Synthesis of 2-dialkylamino-naphthoquinones derivatives of [43] and amines2^o.[49]



Reagents and conditions: a) Me2SO4, K2CO3, acetone; b) secondary amine (excess)

Scheme(10)

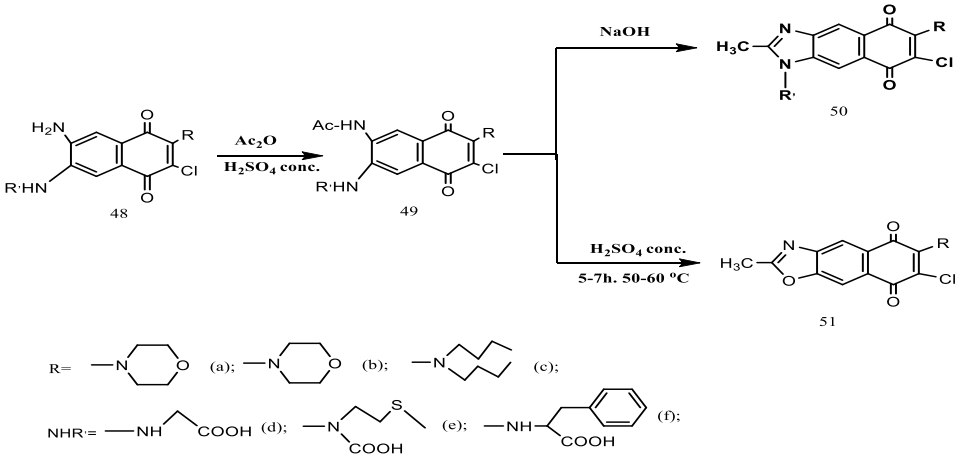
The ring-closed product [50] that was reacted with chloronaphthoquinone and 2-iodophenol resulted in a 82% yield with palladium as the catalyst.



45 46 47

Scheme(11)

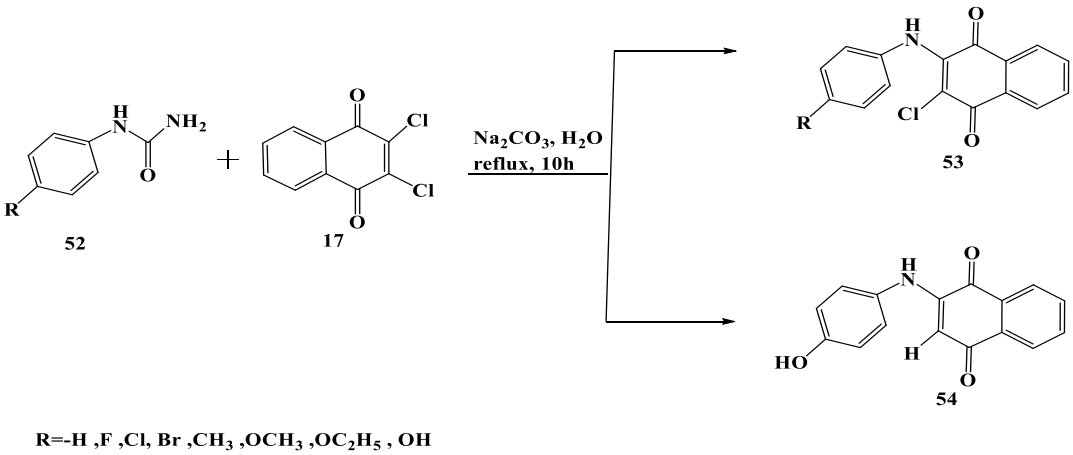
Our method for synthesizing a new imidazole ring with 1,4-naphthoquinone involved using [49], which was derived by acyl ting [48] with acetic anhydride in catalytic H_2SO_4 exposed to Heat in ethanol in the presence NaOH lead to cyclization in imidazole derivatives [51] (Scheme 12). Oxazoles of this type were synthesized by synthesizing 48 in the presence of acetic anhydride with catalytic H_2SO_4 and heating at (50-60°C) for 5-7 hours. [52, 53]



48 49 50 51

Scheme(12)

The synthetic pathway to generate naphthoquinone derivatives,[54] have high antimicrobial activity including S. aureus, E. coli, and C. tenuis,



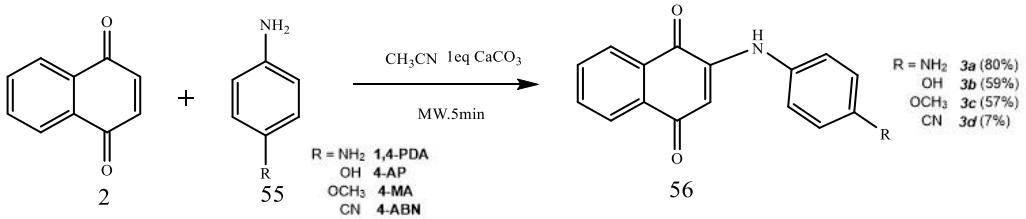
52 17 53 54

R=-H ,F ,Cl, Br ,CH_3 ,OCH_3 ,OC_2H_5 , OH

Scheme(13)

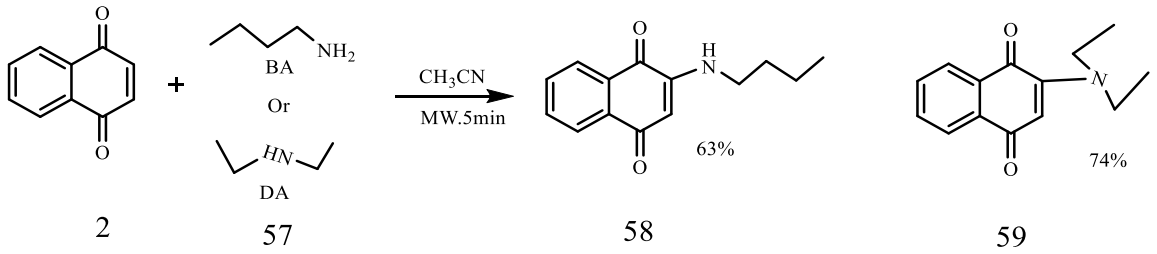
By using microwaves to assist with the synthesis of [56],[58],[59] with middle base, the end product was average to excellent. [55]

a)Arylamino couplers



2 55 56

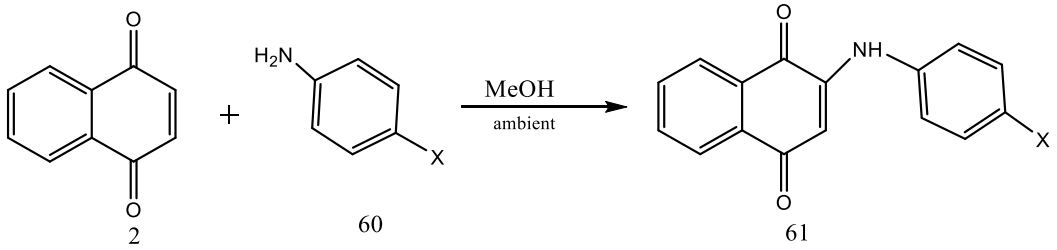
b)Alkylamino couplers



2 57 58 59

Scheme(14)

Composite 2-(phenylamino)-1,4-naphthoquinones (PAN) form of 1,4-naphthoqinone and p-substituted anilines[56] in Methanol and stirred at 200 rpm for variable and reflux at 70 °C, Then mixture was cooled and filtered.



2 60 61

X= Cl, NO_2 ,Me ,Br

Scheme(15)

Biologically Active 1,4-Naphthoquinone Derivtives

These compounds are of pharmaceutical importance due to their biological activities; among these compounds are: Lavendamycin [57], Doxorubicin [58], Adriamycin [59], Mitoxanthrone [60], Menadione [61], Plumbagin [62], Lapachol [63], Streptonigrin [64], Juglone [62] (Fig.1) 2,3-dichloro-1,4-naphthoquinone is the source of many compounds that contain both biological and pharmaceutical actives.

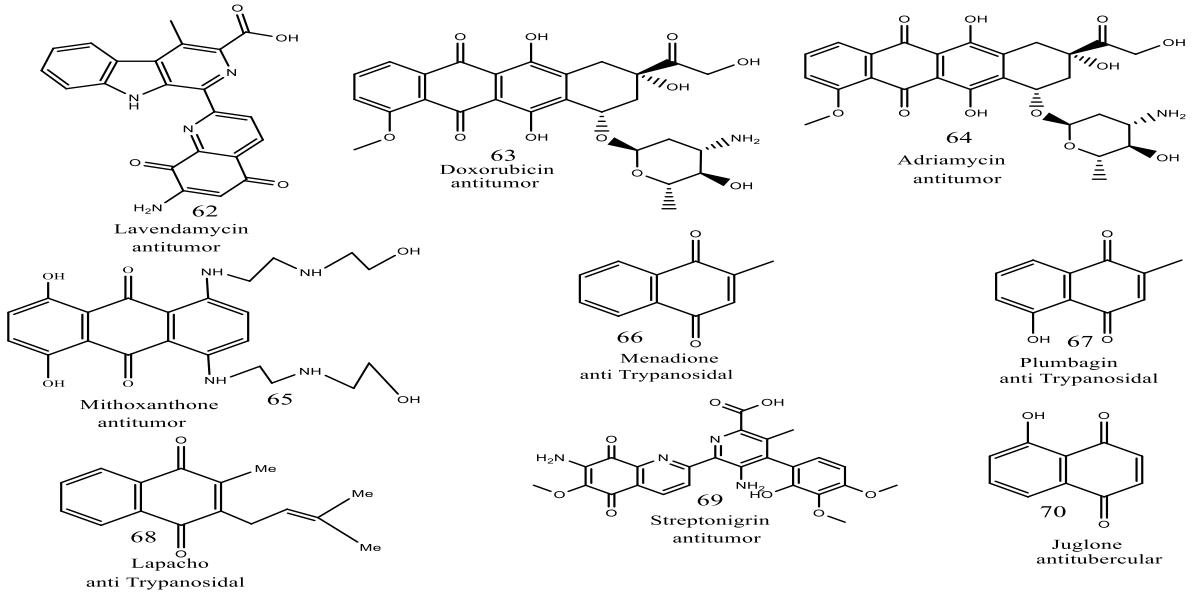


Figure (1) : Naturally biologically active1,4-naphthoquinone derivatives

The derivates of 1,4-Naphthoquinone have a bigger interest for science due to their strong biological activity [65]. From this family of quinones, juglone, plumbagin and lawsone are the most widely spread ones, and so, the most studied as well. [66]

Juglone, or 5-hydroxy-1,4-naphthoquinone (Figure2), can be found in black walnut (Juglans nigra L.) [67]. Plumbagin is present in the roots of the plant Plumbago zeylanica L [68] and has already been proved to have an excellent antimicrobial activity for S. aureus and C. albicans infections [69]. Lawsone (Fig.2) is an orange dye found in the leaves of Lawsonia inermis (also known as henna plant). [70]

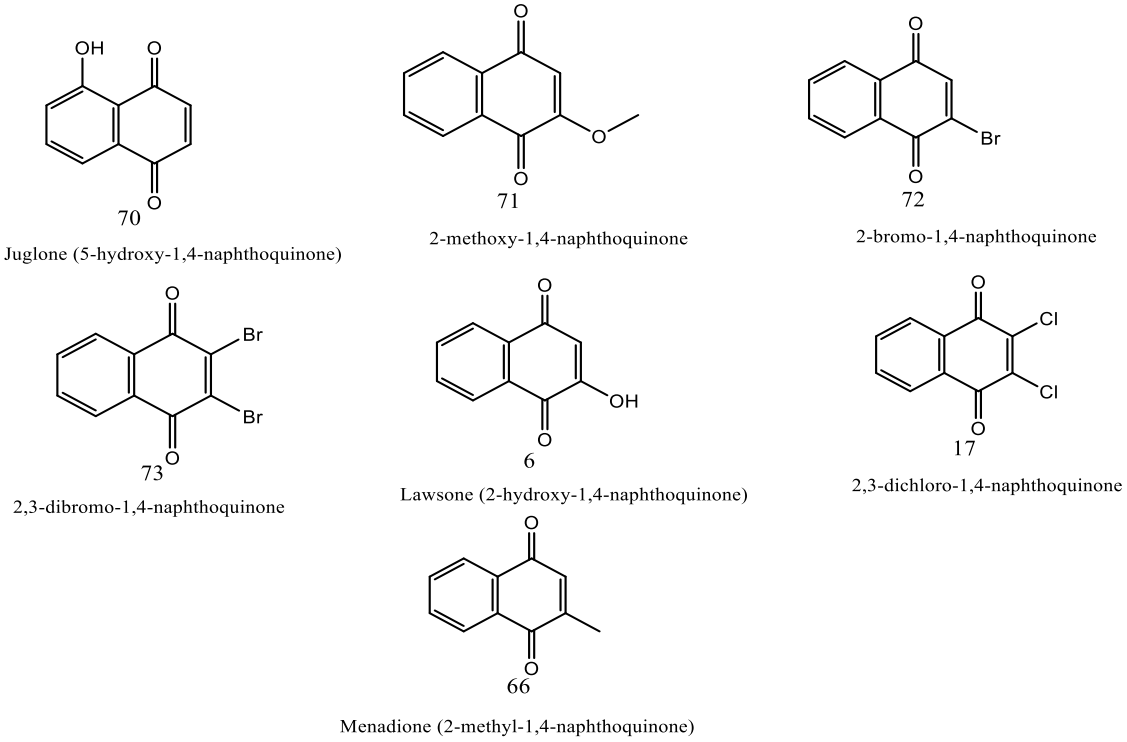


Figure (2) : Chemical structure of the eight naphthoquinones

Antibacterial Activity

The compounds in Fig. 3 [71,72] have antibacterial activity, as shown in [76] of various bacterial pathogens. They also have antibacterial activity against (E. Coli, and Staphylococcus aureous) respectively Figure 3 and activity against (K. pneumonia and S. aureus). [73] As for the compound [79], it has antibacterial activity against M. Luteum. [74]

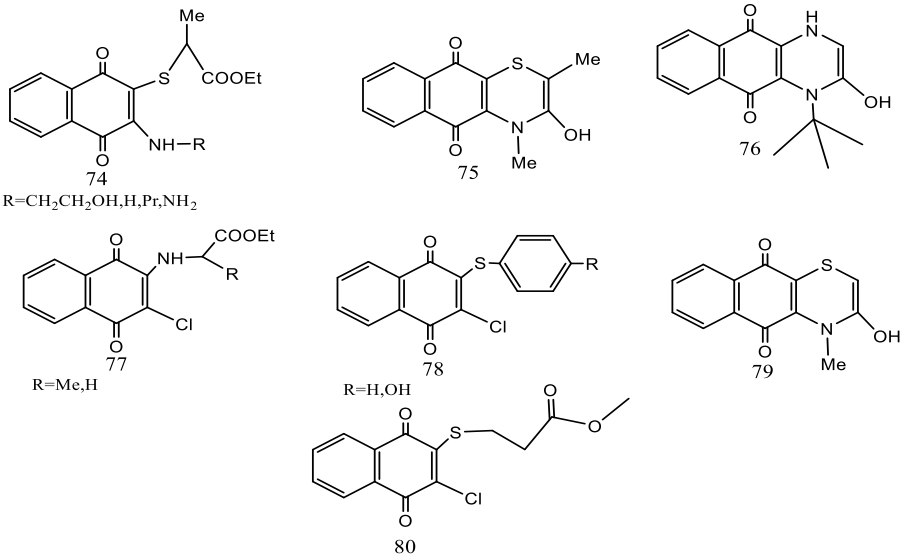


Figure (3) : The antibacterial and antifungal activity is potent

[81]and [82] Figure4 were shown to have antibacterial properties against Staphylococcus aureous, Serratia (marcesens, and Bacillus cereeus). [75]

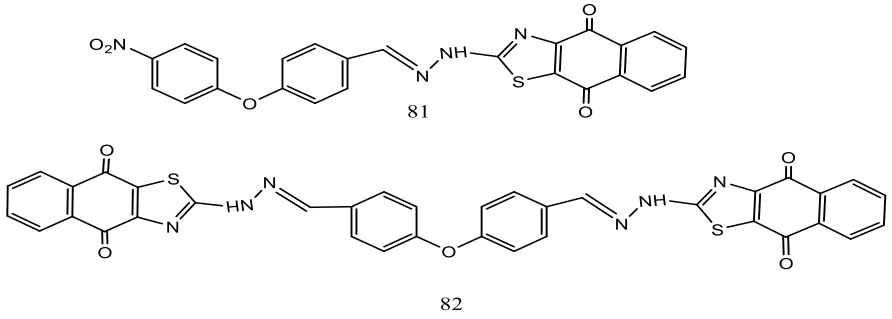


Figure (4) : Antibacterial activity

The compound Natural Antitubercular Juglone Derivatives[76] and exhibited broad spectrum and higher Antibacterial activity. [47]

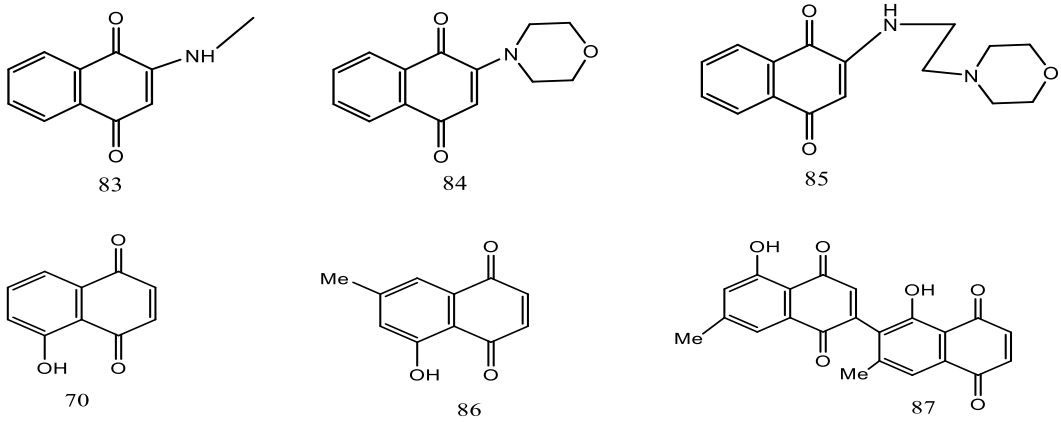


Figure (5) : Antitubercular and Antibacterial activity

Antimicrobials

The substitution of [88] and [89] (Figure6) were effectively on some fungal and against bacteria growth. [17]

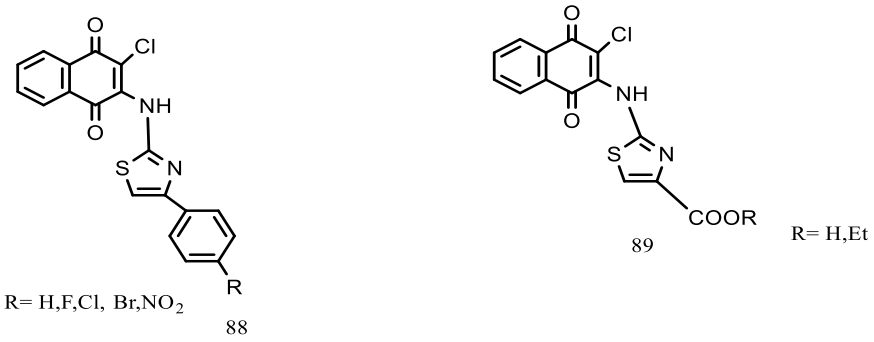


Figure (6) : Synthetic naphthoquinone as an antimicrobial agent

These compounds (Fig.7) containing phenylamino- phenylthio moieties have antimicrobial activity (Staphylococcus aureus, Listeria monocytogenes, E. coli, P. aeruginosa, Salmonella bongori and Klebsiella pneumonia) [14,34,77] and naphthoquinone derivatives (Figure7) antimycobacterial activity against three Mycobacterium tuberculosis (strains, isoniazid and rifampicin) development of new therapeutic strategies against tuberculosis.[78] Two novel heterocyclic [93](Figure7). [79]

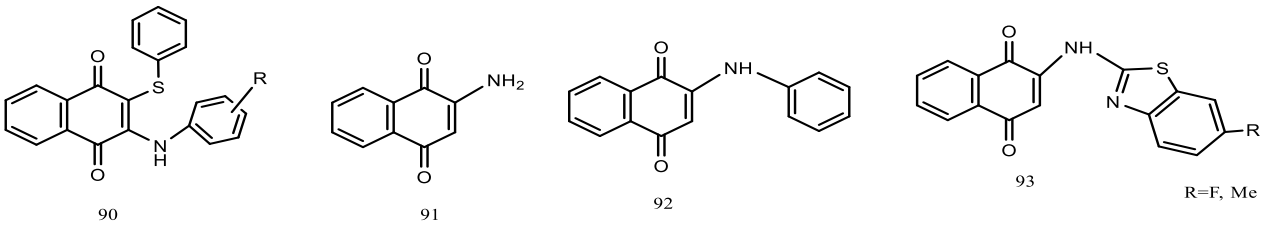


Figure (7): Aminonaphthoquinones as Antimycobacterials activity

The medication Malarone is used, which is a derived substance [6]-[94] [80-82] active antimalarial and natural antileishmanial.

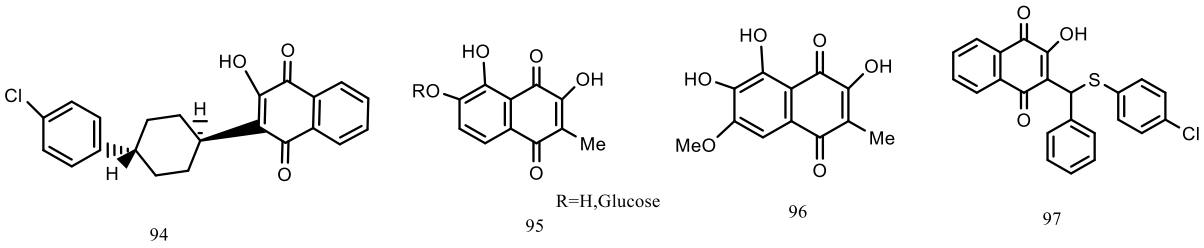


Figure (8) : 1,4-Naphthoquinone derivatives antimalarial and natural antileishmanial

4.2. Antifungal Activity

The Compounds Aryl naphthoquinone ethers [71, 72] [83,84] have reported significant antifungal activity, found to be very effective Antifungal properties for S. schenckii and T. mentagraphytes (fig.9).[85]

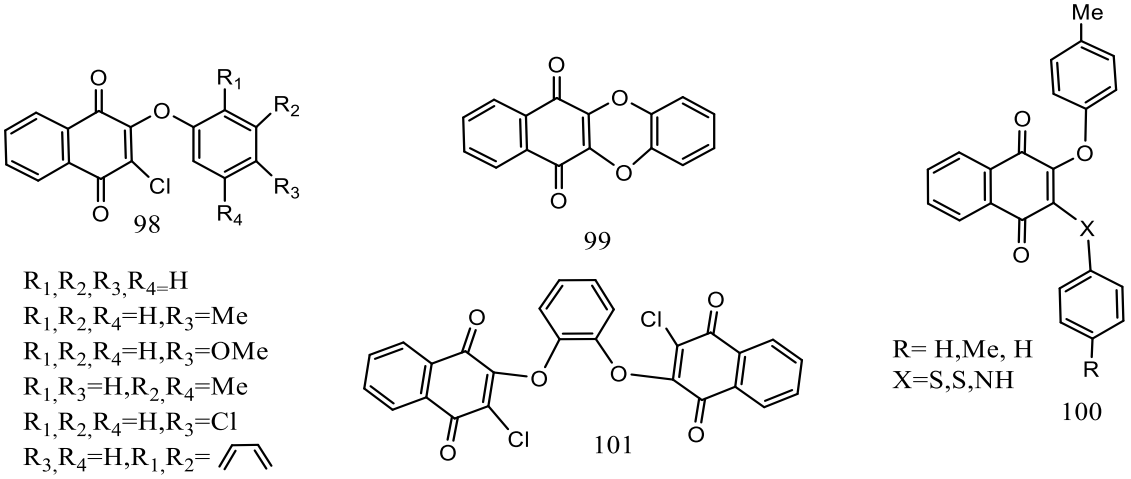


Figure (9) : Antifungal activity

Santos et. al. showed that [102-103] [86] were antifungal. Additionally [104] showed strong antifungal activity, as shown in (Fig. 10) [73], As for Tandon et. Al reported on [105] that has favorable antifungal activity [87] and is also similar to [106] and the last compound in (Fig.10). [88]

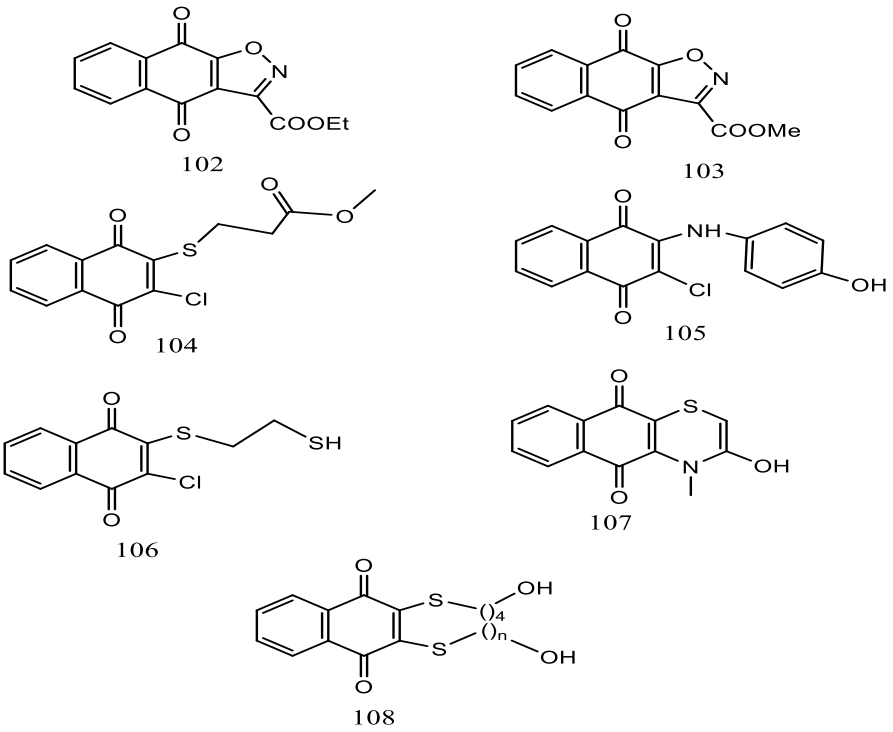
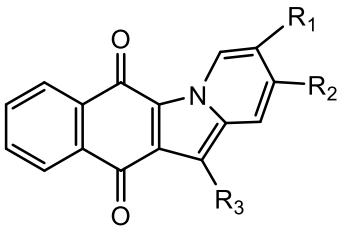


Figure (10) : Potent Antifungal activity

We also note that Ryu et. al [89] tested the effect of 109 due to its growth inhibitory activity against antifungal (Fig.11).



a R^1=OAc, R^2=R^3=H
b R^1=OAc, R^2=H, R^3=Me
c R^1=OAc, R^2=H, R^3=$(CH_3)_2$NMe
d R^1=OH, R^2=H, R^3=Me
e R^1=$O(CH_3)_2$NMe, R^2=H, R^3=Me
f R^1=$O(CH_3)_2N[CHMe_2]_2$, R^2=H, R^3=Me etc

Figure (11) : inhibitory Antifungal activity

3. Anticancer Activity

Cytotoxic effects of phenylamino-1,4-naphthoquinone derivatives were observed in cancer cells and healthy fibroblasts, and it was concluded that the cytotoxicity of phenylamino naphthoquinones is influenced by the phenyl and quinone groups. [90]

Tandon et. al elucidate the effectiveness naphthoquinone in killing cancer cell in human cervix and causing disruption in both microtubules and actin filaments,[74] However [113] showed activity against the proliferation of cancer. [63]

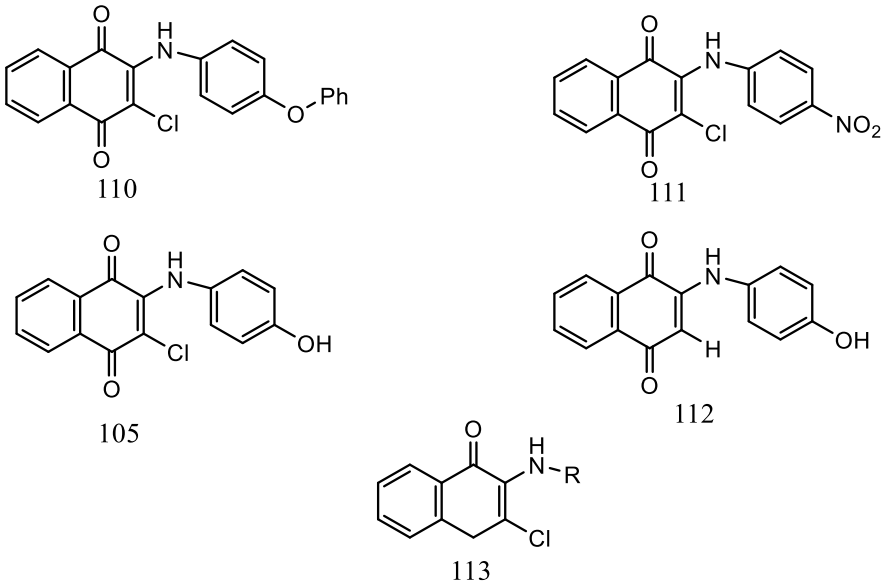


Figure (12) : anti-cancer agents

The anti-tumor activity of several compounds (Fig.13) created by Cheng et al. was demonstrated by demonstrating their activity. [91, 92]

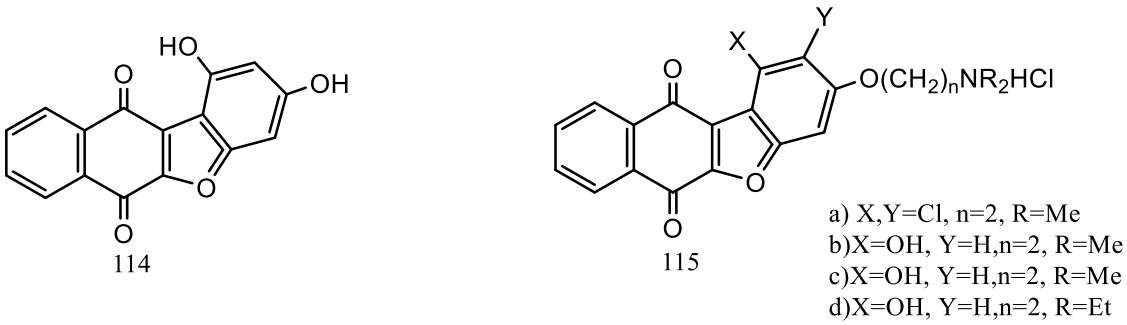


Figure (13) : anti-tumor activity

Luo et. al. noted that Indolylquinone derivatives in humans have activity against human tumor cells[93] (Against cancer).

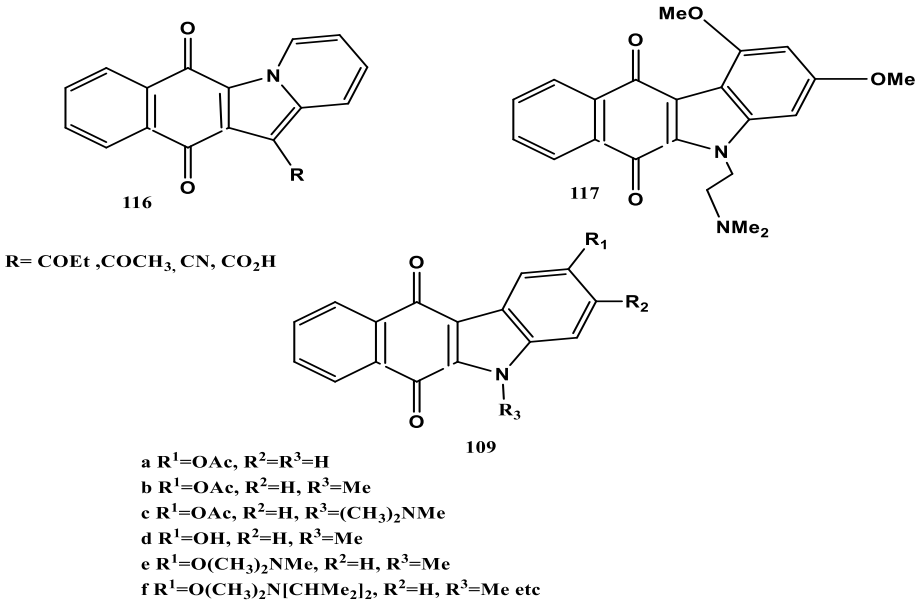


Figure (14) : Indoly quinone as anticancer agents

Compounds derived from 5-hydroxy-1,4-naphthoquinone were effective in treating various types of cancer, including colon adenocarcinoma, breast ductal carcinoma, and chronic myelogenous leukemia. The derivatives were found to have moderate to excellent activity against cancer, as was found in [118]. [94]

A N(H)-, S- and S,S-substituted-1,4-naphthoquinones naphthaquinone compound with biological activity has been manufactured. It has been shown that naphthaquinone derivatives have activity against human cervical cancer (HeLa) but the more effective [119]. [36] While those substituted with halogens and alkyl are considered to have activity against acute myeloid leukemia, Leukemia cells were successfully treated with [120] (Fig.15). [95]

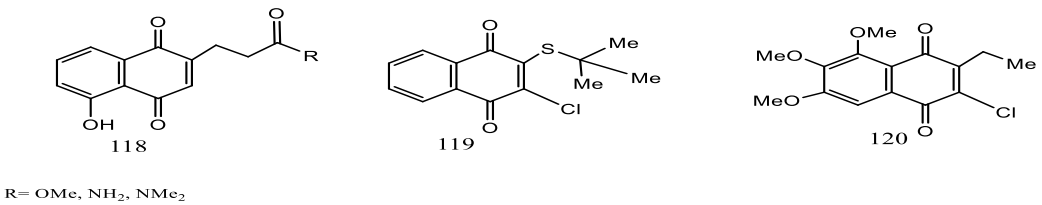


Figure (15) : 1,4-Naphthoquinone Derivatives cancer against

Myeloma cells are inhibited by the compound [121] (Figure 16). [96] Aromatase inhibition is present in 2-amino (chloro)-3-chloro-1,4-naphthoquinone derivatives, but not in [17]and[122], which are also active, As well as the 2,3-disubstitution of the1,4-naphthoquinone ring with halogen atoms, it is more effective in inhibiting aromatase, [97] (Fig 16) shows that [123] has an effect on stomach cancer cells. [98, 99]

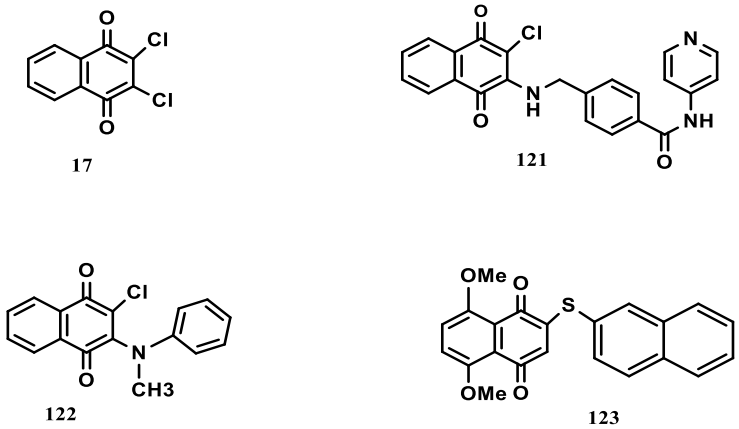


Figure (16) : 1,4-naphthoquinones derivatives are effective in combating cancer and fungal infections.

Recent studies have shown the activity of [124-126] against three human cancer cell lines (Fig. 17),where they cause protein and genetic cell death.[14]

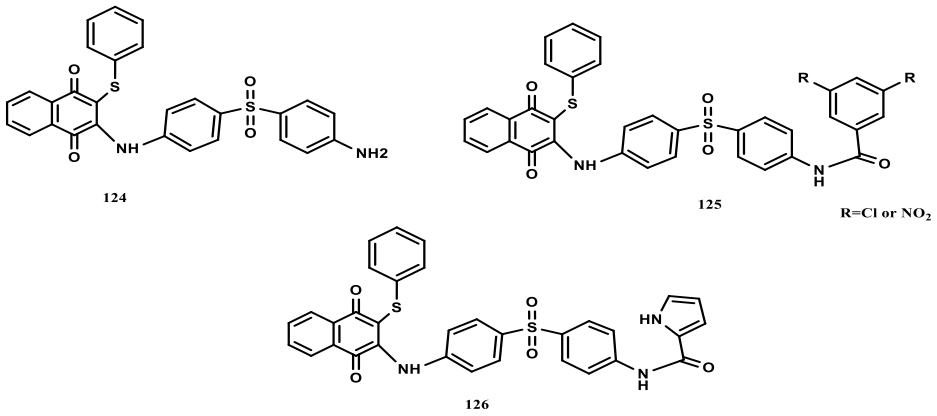


Figure (17): Derivatives of sulfanyl-phenylamino-1,4-naphthoquinone are effective against cancer

While pancreatic cancer cells [100] can inhibit the compound of 2-chloro-3-((2-hydroxyethyl)amino)naphthalene-1,4-dione[127], skin cancer cells [(101)]can only inhibit it through 2,3-bis(naphthalen-2-ylthio)naphthalene-1,4-dione [128] (Fig. 18).

Figure (18) : Anticancer agents include[127],[128].

Two compounds [129] were nominated as outside the cell suppressors, and the first compound (Fig.19) showed activity against 9 types of tumors. [102] 1,4-naphthoquinones derivatives were prepared, replacing position2 with cyclic amines and aliphata [130] (Fig.19), which work against triple-negative breast cancer. [103]

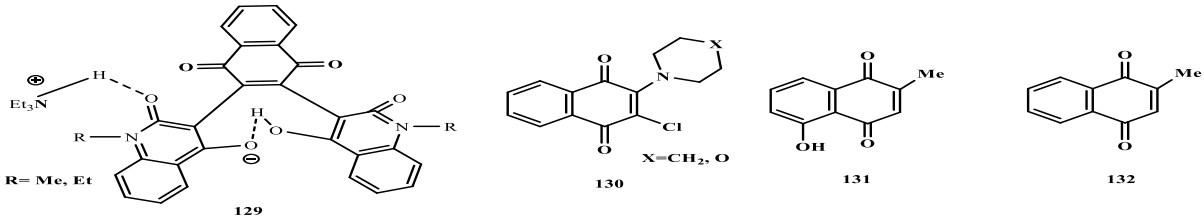


Figure (19) : 1,4-Naphthoquinones substituted and salt Anticancer

CONCLUSION

1,4-naphthoquinone formation of two benzene rings in the α- -position carbonyl, It is consider naphthoquinone basic chemical structure of natural compounds, especially Vitamin K 1,4-naphthoquinone.derivatives prepared with various auxiliary factors, and these compounds have a wide biological scope include: antibacterial, antifungal and anticancer activity.

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