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SYNTHETIC AND BIOLOGICAL UTILITY OF 2,3-DICHLORO-1,4-NAPHTHOQUINONE: A REVIEW

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Abstract

2,3-Dichloro-1,4-naphthoquinones (dichlone) have attracted considerable attention for the construction of biologically active tricyclic and tetracyclic 1,4-quinones and other derivatives. A diversified reaction of 2,3-dichloro-1,4-naphthoquinones such as cycloaddition, condensation, photo induced and nucleophilic substitution reactions with suitable nucleophiles viz. carbon, nitrogen, oxygen, sulfur, selenium etc have been explored. Various synthesized compounds have also explored for their biological activity such as antifungal, antibacterial, anticancer, antiplatlet, anti-inflamentry, anti-allergic and anti HIV. This review describes the chemistry and biological activity of compounds synthesized from 2,3-dichloro-1,4-naphthoquinones during the last three decades.

Keywords: 2,3-Dichloro-1,4-Naphthoquinones($C_{10}H_4Cl_2O_{20}$); Dichlone; Naphthoquinone; Quinone; Antifungal; Antibacterial; Anticancer.

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1. Introduction

The naphthoquinone skeleton is found in a wide variety of natural products that have broad range of biological activity for example awamycin, damavaricin, kanamycin [1], streptovaricins [2], rifamycins, vitamin K2, lapachol [3], juglone and their derivatives (Figure 1) have been applied as key intermediates for construction of biologically active compounds associated with anticancer [4], antineoplastic [5], antifungal [6], antibacterial [7], antiviral [8], antimalarial [9] and antitrypanosomal [10] activity. The electron donating or withdrawing substituents present in quinone play significant role in quinones to accept or donate electrons and responsible for various biological activity [11] such as its mechanism study shown that it act as topoisomerase inhibitor [12, 13]. Amongst the 1,4-naphthoquinones, an important derivative of reactive quinone is 2,3-

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dichloro-1,4-naphthoquinone (dichlone) (1) and its analogs. The reaction of 2,3-dichloro-1,4-naphthoquinone or their equivalents has gained a prominent position in quinone family.

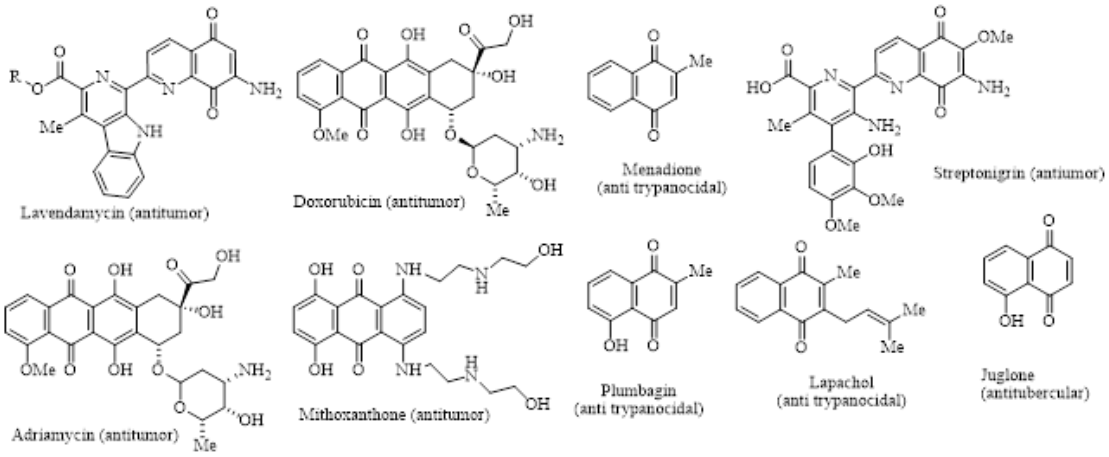


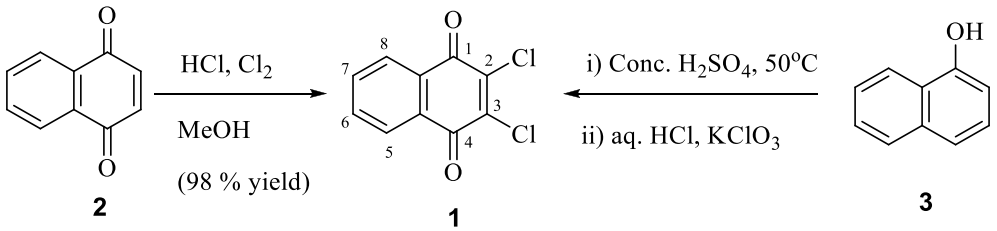
Figure 1: Quione and naphthoquinone containing naturally occurring and biologically active compounds.

2,3-Dichloro-1,4-naphthoquinone (1) work as precursor in various reaction which have been discussed in detail in this review. 2,3-Dichloro-1,4-naphthoquinone (1) is highly reactive towards nucleophilic attack of oxygen, carbon, nitrogen, sulfur and selenium nucleophiles at C-2 and C-3 position (Scheme 1) thus a variety of biologically active heterocyclic quinones have been synthesized from 2,3-dichloro-1,4-naphthoquinones (1) and its analogs.

A review available on the chemistry of 2,3-dichloro-1,4-naphthoquinone was reported by Sartori [14] in 1963 which had covered synthesis of various heterocycle analogs. Extensive research has been carried out after 1963 on the chemistry of 2, 3-dichloro-1,4-naphthoquinone. The present review describes the chemistry of 2,3-dichloro-1,4-naphthoquinone and their biological applications.

2. Synthesis

A general synthetic route to synthesize 2,3-dichloro-1,4-naphthoquinone (1) was reported by Katsurayama [15] by the chlorination of 1,4-naphthoquinone with Cl2 and HCl in methanol in high yields and in other method 2,3-dichloro-1,4-naphthoquinone (1) was synthesized by the oxidation of α-naphthol with conc. sulphuric acid followed by chlorination with aq HCl and $KClO_3$ [16]; Scheme 1.



Scheme 1: Synthesis of 2,3-dichloro-1,4-napthoquinone.

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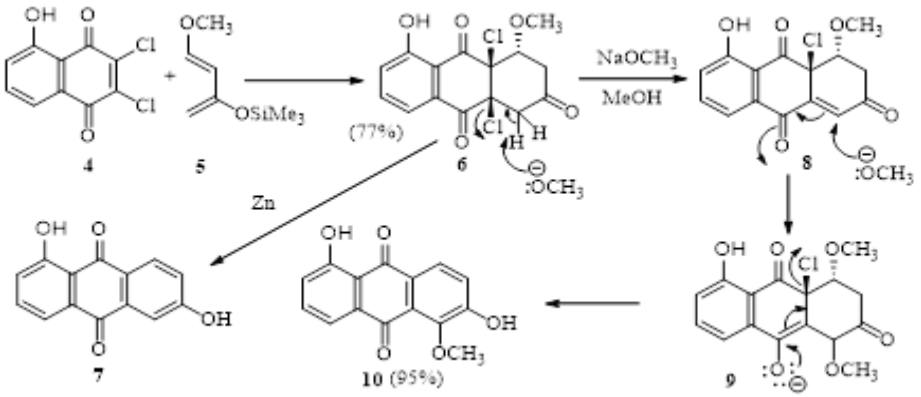
3. Reactions

3.1. Addition Reactions

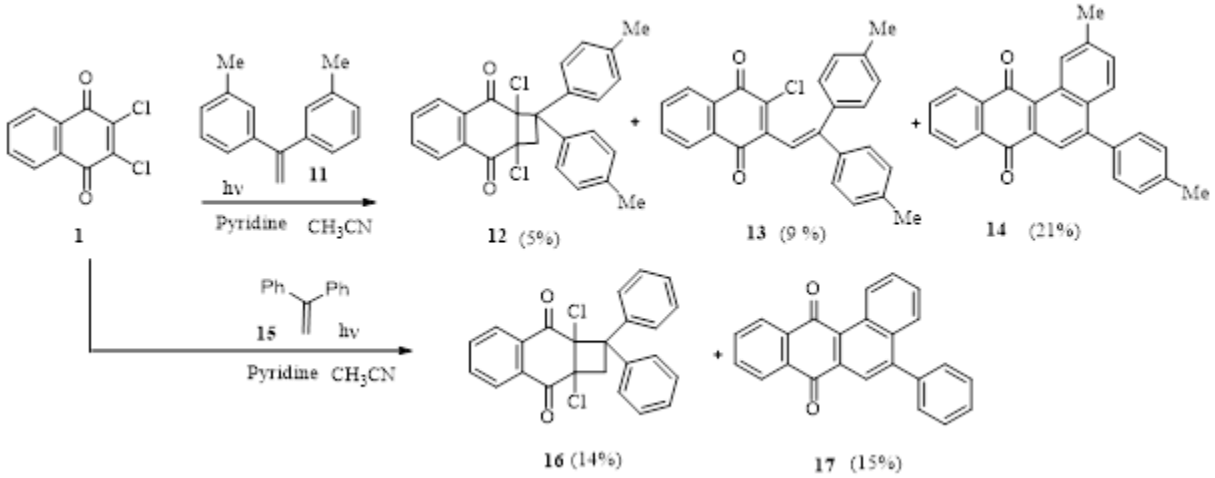
3.1.1. Cycloaddition Reactions

2,3-Dichloroquinone (4) on reaction with diene (5) produced cyclo adduct (6) [15]. Reduction of 6 with Zn and subsequent aromatization yielded 6-hydroxyanthraquinone (7) while 6 on treatment with NaOMe in methyl alcohol resulted in the formation of 1,2-dioxyanthraquinone (10) in 95% yields; Scheme 4.



Scheme 2: Cycloaddition reaction of 2,3-dichloro-1,4-napthoquinone (4).

Photochemical reaction of 2,3-dichloro-1,4-naphthoquinone (1) with alkene (11) in acetonitrile reported cyclobutane adduct (12), ethylene adduct (13) and 5-tolylbenz[a]anthracene-7,12-dione (14). Similarly reaction with 1,1-diphenylethylene (15) gave a mixture of cyclobutane adduct (16) and 5-phenylbenz[a]anthracene-7,12-dione (17); Scheme 3 [17]. Formation of 12 and 16 produced by (2π+2π) cycloaddition while 14 and 17 produced by (4π+2π) cycloaddition followed by dechlorination and aromatization.



Scheme 3: Photochemical reaction of 2,3-dichloro-1,4-naphthoquinone (1) with alkenes (11, 15)

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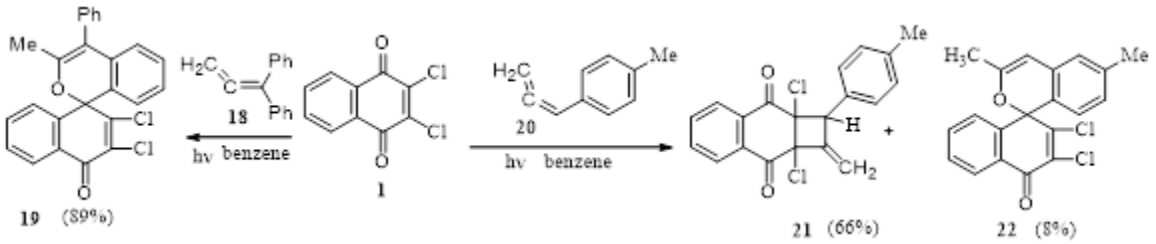
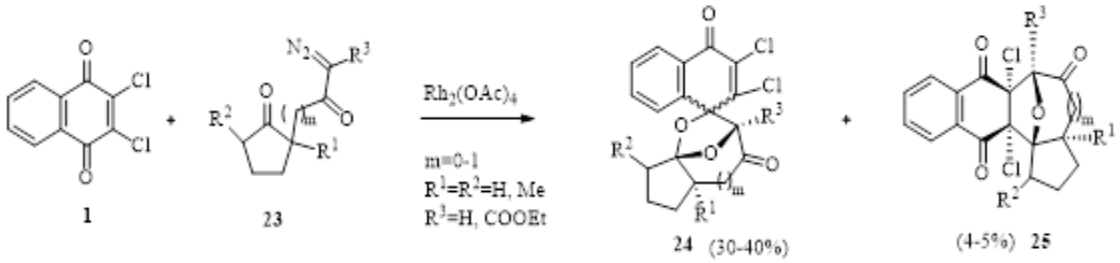


Scheme 4: Photochemical reaction of 2,3-dichloro-1,4-naphthoquinone (1) with 1,1-diphenyl allene (18)

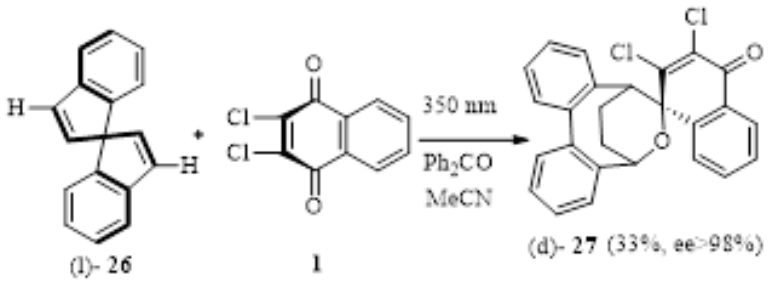
The photochemical reaction of 2,3-dichloro-1,4-naphthoquinone (1) and 1,1-diphenyl allene (18) in benzene produced 19 in 89% yield [18]. However, photochemical reaction of 1 with 1-(4-methyl) phenylallene (20) gave (2+4)cycloaddition adduct (21) in 66 % yield with a miner spiro adduct (12) [19]; Scheme 4.

Cycloaddition reaction of 2,3-dichloro-1,4-naphthoquinone (1) with α-diazo compounds (23) in benzene using catalyst $Rh_2(OAc)_4$ formed cycloadducts 24 and 25; Scheme 5 [20].



Scheme 5: Cycloaddition reaction of 2,3-dichloro-1,4-naphthoquinone (1) with α-diazo compounds (23)

2,3-Dichloro-1,4-naphthoquinone (1) with optically pure l-isomer of 26 at 350 nm irrediation in presence of benzophenone formed (4+2) adduct d isomer d-isomer of 27 as a enantiospecific excess product; Scheme 6 [19].



Scheme 6: Photochemical reaction of 2,3-dichloro-1,4-naphthoquinone (1) with 1,1'-spirobi[indene] (26).

A three component reactions of 1,4-quinone (1), aromatic aldehydes (28) and dicarbomethoxy carbene obtained by 29 produced spiro-dioxolanes (30) regio and stereo selectively; Scheme 7 [21].

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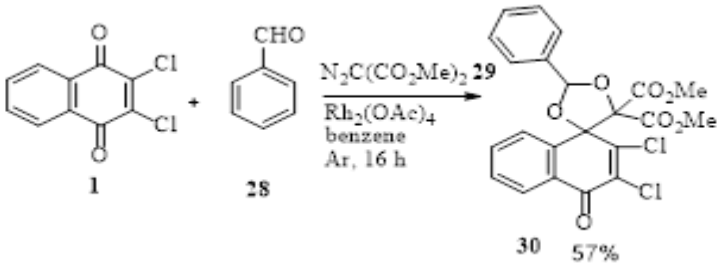
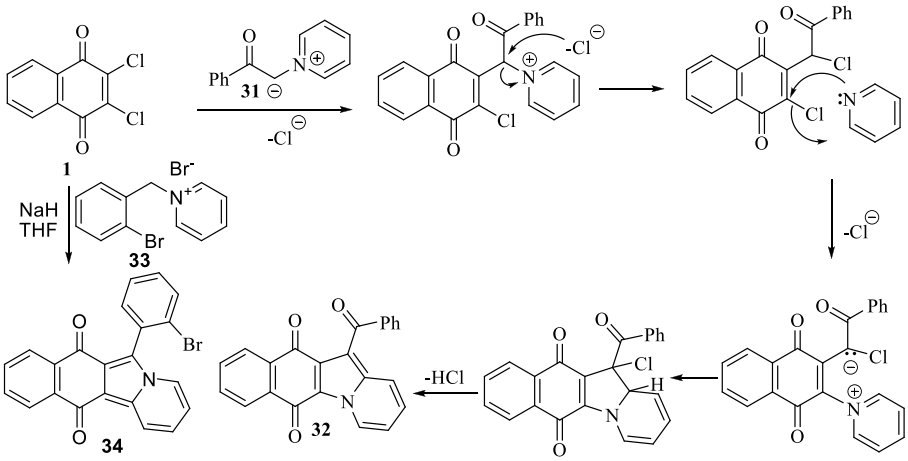
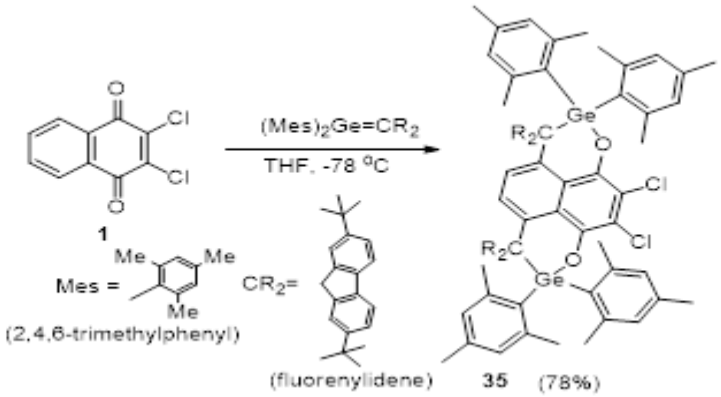


Scheme 7: A three component reactions of 2,3-dichloro-1,4-naphthoquinone (1).



Scheme 8: Reaction of *N*-ylide (31) derived from pyridinium salt with 2,3-dichloro-1,4-naphthoquinone (1).

The reaction of *N*-ylide (31) derived from pyridinium salt with 2,3-dichloro-1,4-naphthoquinone (1) resulted in the formation of 32 [22].



Scheme 9: Cycloaddition reaction of 2,3-dichloro-1,4-naphthoquinone (1) with dimesityl (fluorenylidene) germane

An other polycyclic indolizine derivatives (34) was synthesized from the reaction of 1 with 1-(2-bromobenzyl) pyridinium bromide and elucidated x-ray structure by Hu and Ma [23]; Scheme 8.

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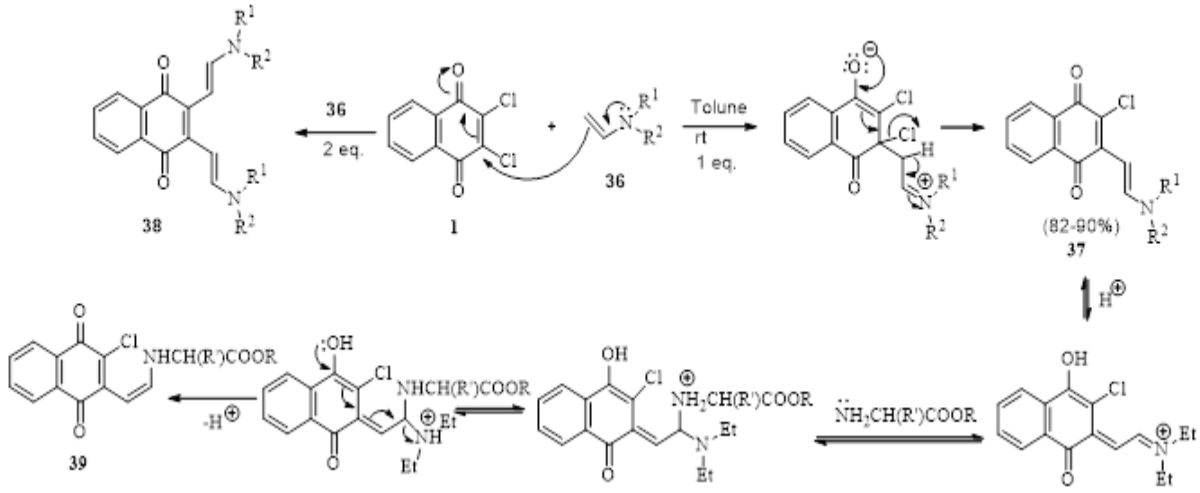
Ghereg et. al. had been explored the cyclo addition reaction of 2,3-dichloro-1,4-naphthoquinone (1) with organometallic compound dimesityl (fluorenylidene)germane and synthesized geranium containing tetracyclic organometallic adduct (35) by a double [2+4] cycloaddition between the Ge=C double bond and the conjugated system O=C–CH=CH; Scheme 9 [24].

3.2. Nucleophilic Substitution Reactions

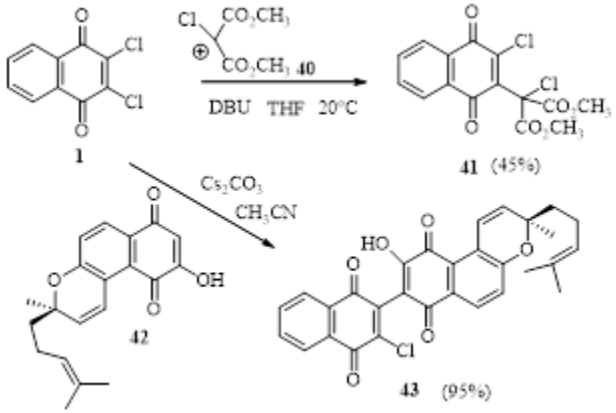
3.2.1. With Carbon Nucleophiles



Scheme 10: Reaction of 2,3-dichloro-1,4-naphthoquinone (1) with enamines (36).

2,3-dichloro-1,4-naphthoquinone (1) reacted with enamines (36) and formed mono quinone enaminones (37). The use of 2 equivalents of enamine (36) resulted bis derivatives (38) [25]; Scheme 10. The diethylaminonaphthoquinone enaminone (37; R^1=R^2=Et) on reaction with hydrochlorides of amino acids or their salts yielded the conjugates 39; Scheme 10 [26].

The additions of carbanions of dimethyl 2-chloromalonate (40) with 2,3-dichloro-1,4-naphthoquinone (1) in DBU/THF produced nucleophilic substitution product 41 in 45% yield; Scheme 11[27].



Scheme 11: Reaction of dimethyl 2-chloromalonate (40) and teretifolione-B (42) with 2,3-dichloro-1,4-naphthoquinone (1).

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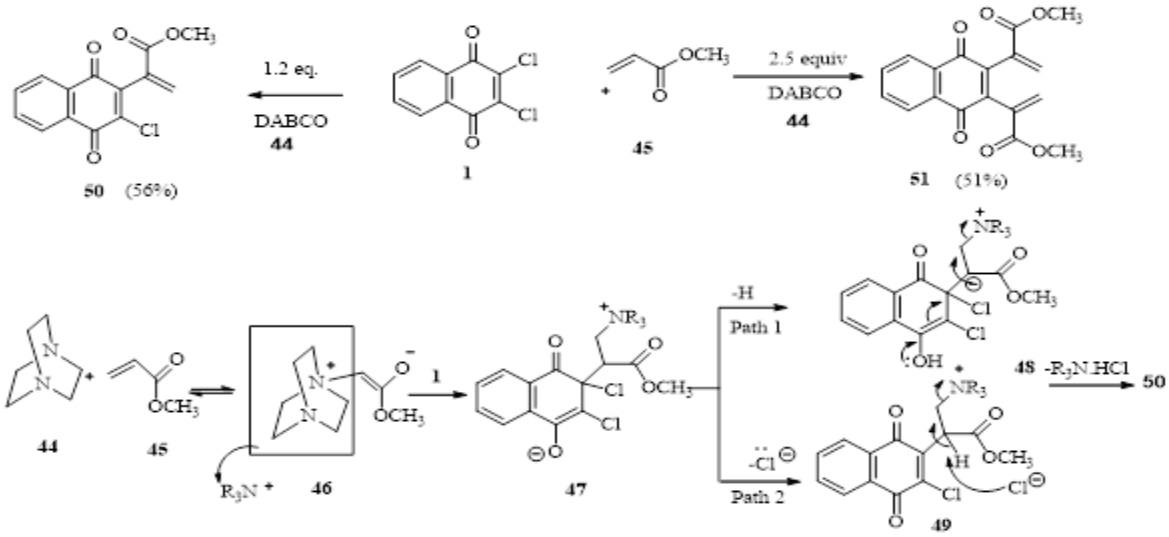
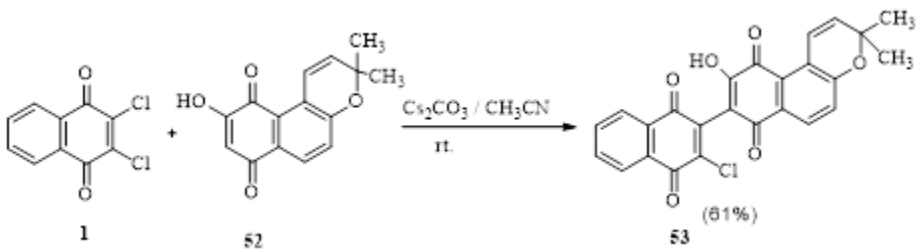
The reaction of 2,3-dichloro-1,4-naphthoquinone (1) with Teretifolione-B (42) in presence of methyl cynide and Cs_2CO_3 produced bisquinone (30); Scheme 11 [28].

The reaction of 2,3-dichloro-1,4-naphthoquinone (1) with methyl acrylate (44) and DABCO (45) formed mono (50) and di (51) α-vinylnaphthoquinones in 56% and 51% yields respectively. The reaction proceed through zwitter ion enolate (47) formation which attack as a nucleophile onto the 2,3-dichloro-1,4-naphthoquinone (1) to generate the zwitter ionic intermediate (48 or 49). A subsequent migration of H+ and extrusion of DABCO and HCl gave product 50 [29]; Scheme 12.



Scheme 12: The reaction of 2,3-dichloro-1,4-naphthoquinone (1) with methyl acrylate (44)

Reaction of hydroxyquinone (52) with 2,3-dichloro-1,4-naphthoquinone (1) in presence of Cs_2CO_3 undergoes nucleophilic substitution reaction and produced 8-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-9-hydroxy-3,3-dimethyl-3H-benzo[f]chromene-7,10-dione (53) in 61% yield; Scheme 13 [30].



Scheme 13: Reaction of hydroxyquinone (52) with 2,3-dichloro-1,4-naphthoquinone (1).

3.2.2. With Nitrogen Nucleophiles

2,3-Dichloro-1,4-naphthoquinone (1) undergoes nucleophilic substitution with pyrazole, pyridine, pyridine-4(1*H*)-one and 2,3-diamino-1,4-naphthoquinone and produced 2,3-disubstituted-1,4-naphthoquinones (54-58); Scheme 14 [31].

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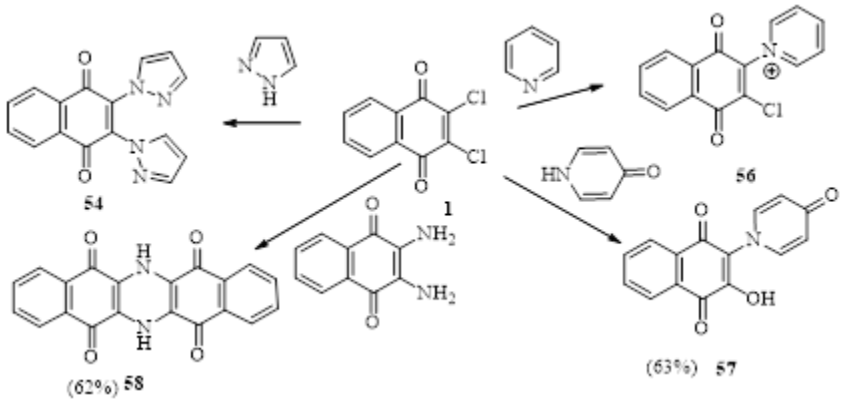
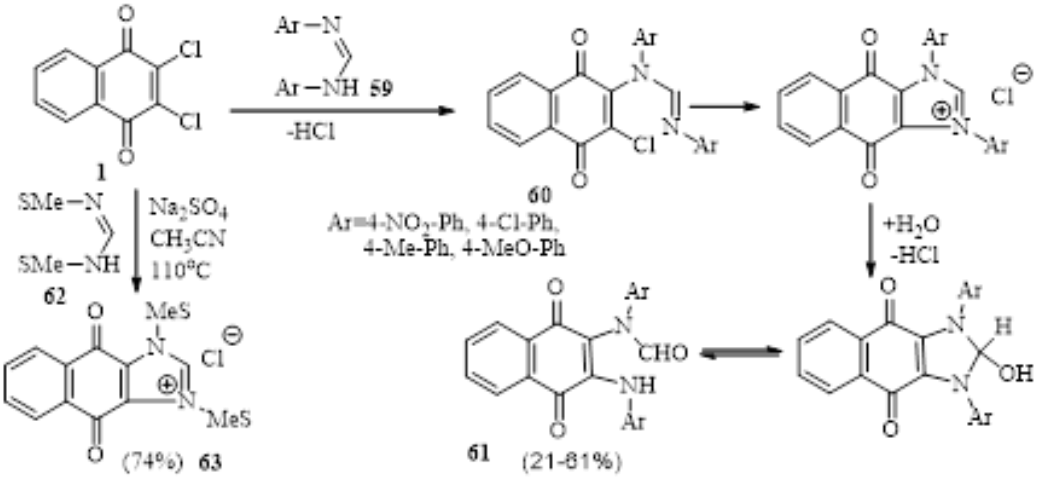


Scheme 14: Nucleophilic substitution reaction of 2,3-dichloro-1,4-naphthoquinone with nitrogen nucleophiles.

When N1, N2-diaryl formimidamide (59) was reacted with 2,3-dichloro-1,4-naphthoquinone (1), both chlorine atoms are successively substituted by nitrogen atoms resulting in the formation of 2-(arylamino)-3-(*N*-formylarylamino)-1,4-naphthoquinones (61) via intermediate formation of 60 [32]. Novel imidazolium salt (63) was synthesized in 74% yield by reacting 2,3-dichloro-1,4-naphthoquinone (1) with *N,N*-dimesitylformimidamide (62) under mild basic conditions; Scheme15 [33].



Scheme 15: Reaction of N^1, N^2-diaryl formimidamide (59) with 2,3-dichloro-1,4-naphthoquinone (1).

Reaction of 2,3-dichloro-1,4-naphthoquinone (1) with benzylideneanilines (64) gave 2-aryl-amino-3-chloro-1,4-naphthoquinone (65). The azomethines such as 64 were thus used for arylamination of 1,4-naphthoquinone derivatives (1). These reactions indicate that benzylideneanilines (64) react like amines by a Michael addition-elimination mechanism through a nucleophilic attack of the imino nitrogen atom on the double bond of conjugated system; Scheme 16 [34].

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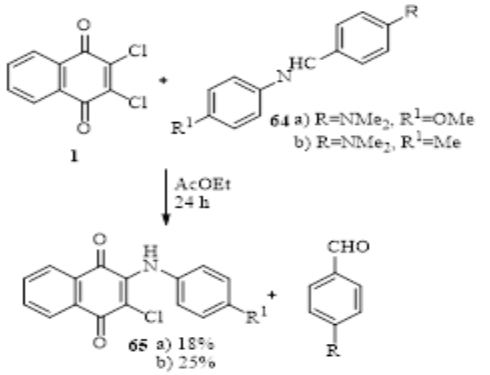
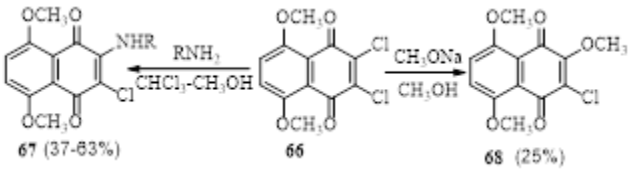


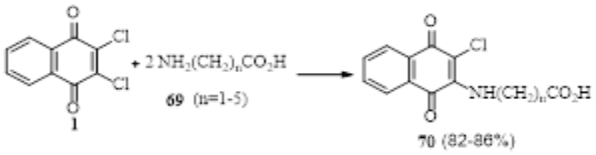
Scheme 16: Reaction of 2,3-dichloro-1,4-naphthoquinone (1) with benzylideneanilines (64)

Nucleophilic substitution reaction of 5,8-dimethoxy-2,3-dichloro-1,4-naphthoquinone (66) with primary amines and alkoxide formed of 2-alkylamino derivative (67) and 2-alkoxy substituted-1,4-naphthoquinone derivative (68); Scheme 17 [35].

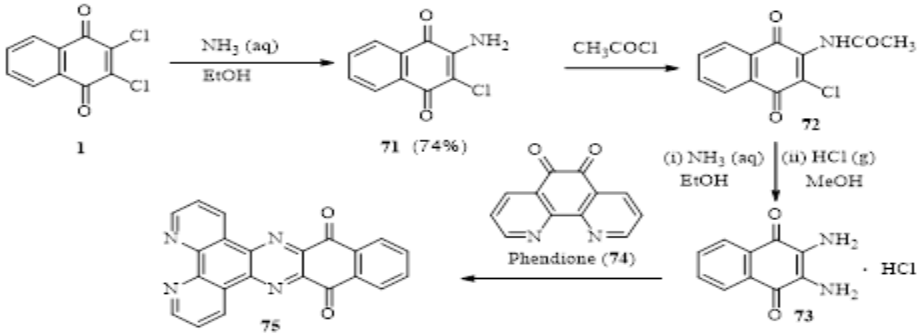


Scheme 17: Nucleophilic substitution reaction of 5,8-dimethoxy-2,3-dichloro-1,4-naphthoquinone (66) with primary amines and alkoxide

2,3-Dichloro-1,4-naphthoquinone (1) reacted with ω-amino carboxylic acids (69) produced *N*-quinonyl amino acids (70). The reaction resembles a substitution process by displacement of one of the chlorine atoms involving elimination of HCl. No displacement of second chlorine atom takes place; Scheme 18 [36].



Scheme 18: Reaction of 2,3-Dichloro-1,4-naphthoquinone (1) with ω-amino carboxylic acids (69)



Scheme 19: Synthesis of Nqphen (75).

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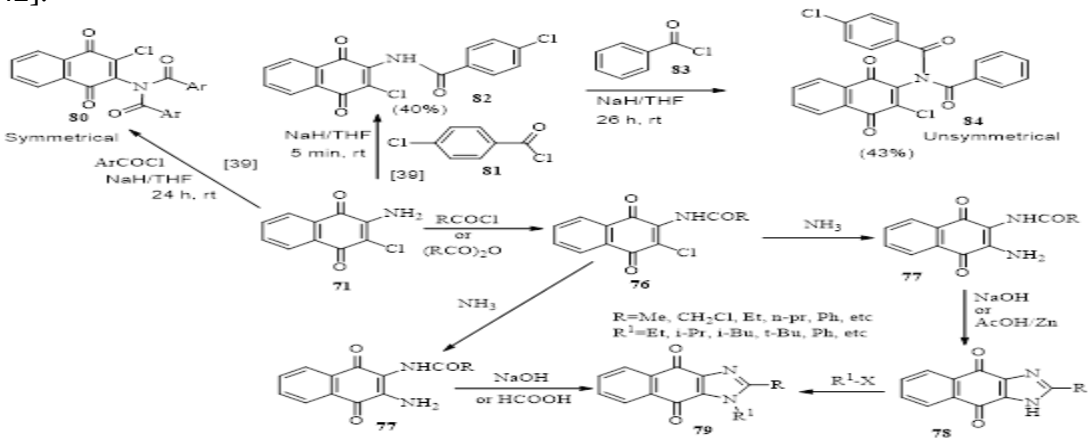
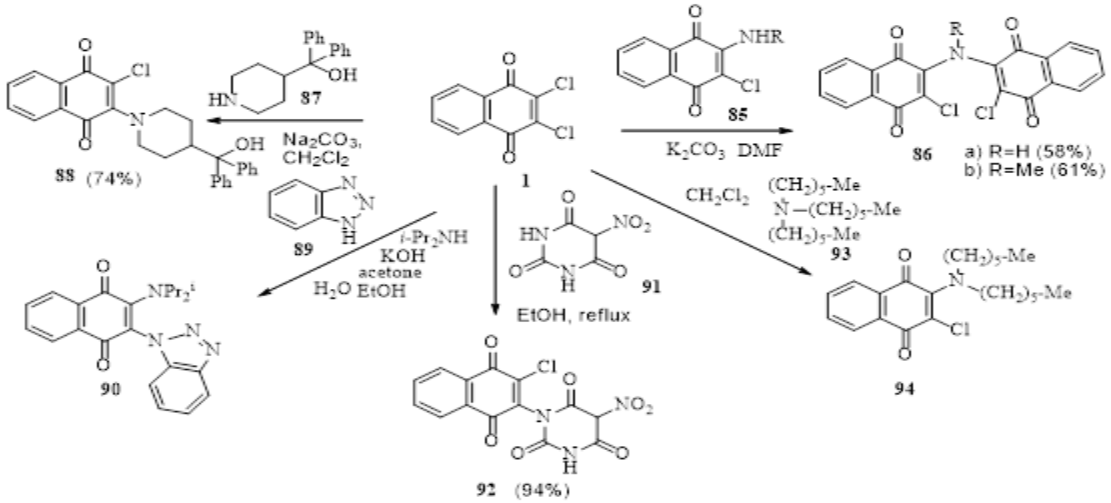
The reaction of 2,3-dichloro-1,4-naphthoquinone (1) with ammonia (aq) in ethanol produced 2-amino-1,4-naphthoquinone (71). Following substitution by protection of amino group and deprotection led to the formation of 2,3-diamino-1,4-naphthoquinone (73). Further condensation with Phendione (74) resulted in the formation of Nqphen (dipyrido[3,2-a:2′,3′-c]-benzo[3,4]-phenazine-11,16-quinone) (75); Scheme 19 [37]. While 2-amino-1,4-naphthoquinone (71) on further reaction with different acid chlorides or anhydrides gave compounds 76 which on further reaction with amines produced imidazoles (79) [38] and Symmetrical (80) and unsymmetrical (84) acetamide quinone [39]; Scheme 20.

The formation of diquinonylamines (86) [40] and an amine substituted analog (88) [41] were reported while 2,3-dichloro-1,4-naphthoquinone (1) reacted with benzotriazole (89) and aliphatic or aromatic amines to give the corresponding 2-amino-3-(benzotriazol-1-yl)-1,4-naphthoquinones (90) [42].



Scheme 20: Various reactions of 2-amino-1,4-naphthoquinone (71).

2,3-dichloro-1,4-naphthoquinone (1) also reacted with tertiary amines in CH2Cl2 resulting in the formation of N:N-dialkyl-2-chloro-1,4-naphthoquinone (94) [43] and when it reacted with dilituric acid (91) produced 2-dilituro-3-chloro-1,4-naphthoquinone (92, 94%) [44]; Scheme 21.



Scheme 21: Nuclophilic reactions of 2,3-dichloro-1,4-naphthoquinone (1).

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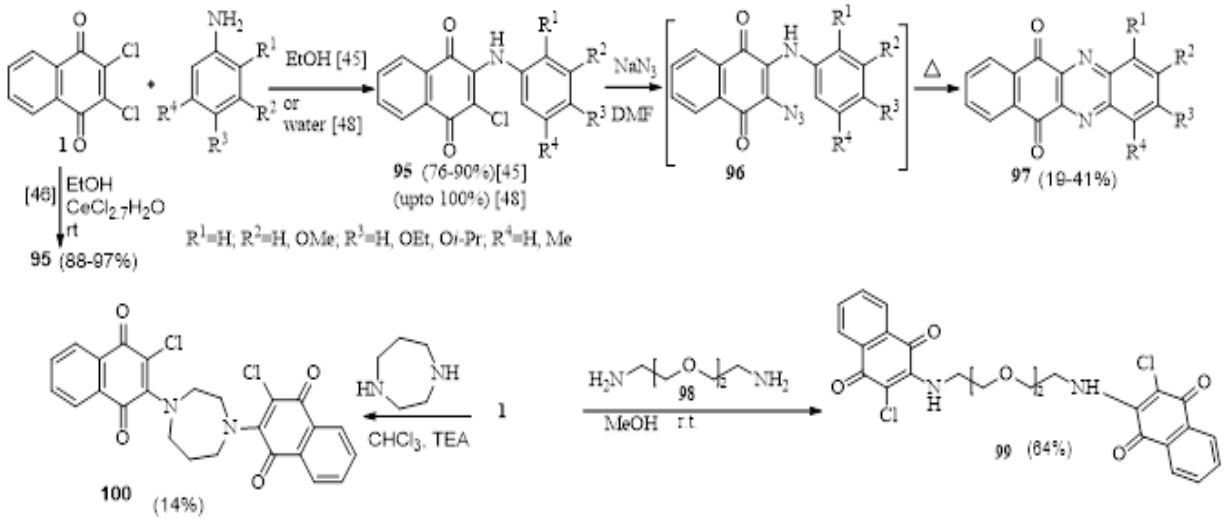
2,3-Dichloro-1,4-naphthoquinone (1) on reaction with aryl amines in ethanol [45-47] or in water [48] gave 2-arylamino-3-chloro-1,4-naphthoquinones (95) according to Scheme 22. 95 on further nucleophilic displacement reaction with NaN_3 in DMF resulted in the formation of 2-arylamino-3-azido-1,4-naphthoquinones (91) which on further heating at 100 ^oC resulted in formation of benzophenazinediones (92); Scheme 22 [45].

Several 2-phenylamino-1,4-naphthoquinone-based dyes and two related benzo[2,3-b]–phenazines were resynthesized by Szymczak *et. al.* and found to be capable photosensitizers for radical (reducible/oxidisable) and cationic polymerizations [49].



Scheme 22: Synthesis of benzophenazinediones (92), α, ω-bis(quinonyl)amine (99) and bis (3-chloro-1,4-dinaphtho quinone) (100

Reaction of 2,3-dichloro-1,4-naphthoquinone (1) with α,ω-diamino derivatives of polyalkenylenoxides (98) resulted in the synthesis of α,ω-bis(quinonyl)amine (99) [50] and reaction with 1,4-diazepane produced 2,2-(1,4-Diazacycloheptane-1,4-diyl)-bis(3-chloro-1,4-dinaphthoquinone) (100) [51]; Scheme 22.

Aminothiazole derivatives (101) and (102) on treatment with 2,3-dichloro-1,4-naphthoquinone (1) in presence of K_2CO_3 resulted in the formation of 2-[(3-chloro-1,4-naphthoquinonyl)amino]-1,3-thiazoles(104) and (105); Scheme 23 [52]. Analogous reaction of 2,3-dichloro-1,4-naphthoquinone (1) with 103 in refluxing toluene in the presence of Et3N gave aminoquinone (6106) in poor yield [53].

Reaction of 2,3-dichloro-1,4-naphthoquinone (1) with NaNCO or KNCO proceeded smoothly resulting in the formation of 2-chloro-3-isocyanato-1,4-naphthoquinone (107) via Michael-type addition reaction. Further reaction of 107 with primary amine gave the ureido derivative (108) which spontaneously undergoes nucleophilic substitution and cyclization leading to formation of tricyclic imidazolove (109) as exhibited in Scheme 23 [54].

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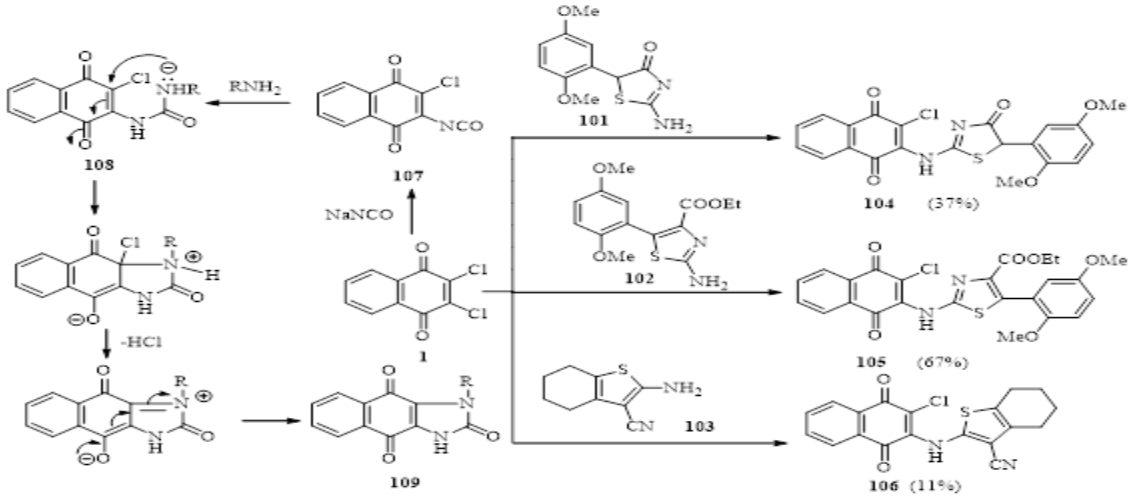
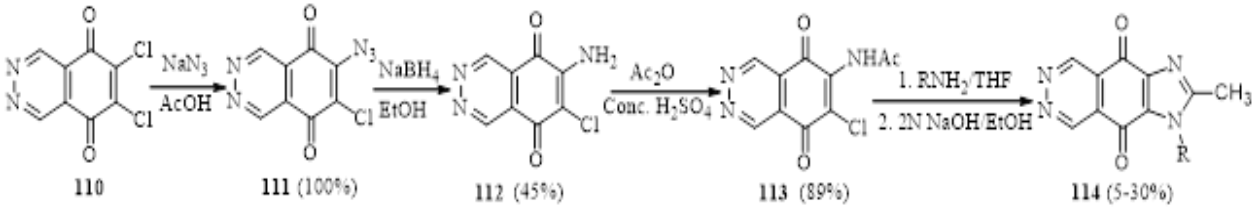


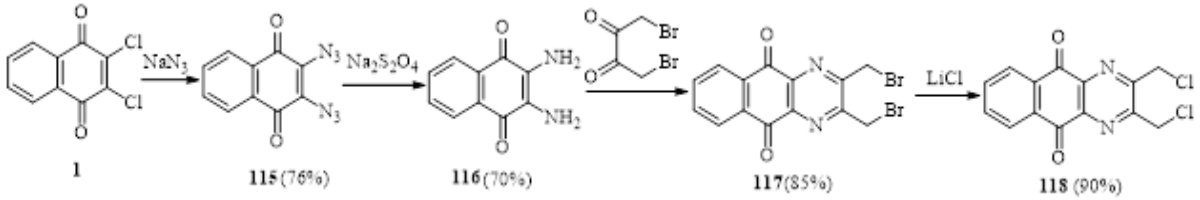
Scheme 23: Nucleophilic reaction of 2,3-dichloro-1,4-naphthoquinone (1) with various amino heterocycles.

Diaza analog of 2,3-dichloro-1,4-naphthoquinone (110) on treatment with NaN3 in AcOH at room temperature resulted in the formation of 6-azide-7-chloro-phthalazine-5,8-dione (111) which was further reduced and acetylated with $NaBH_4$ and Ac_2O in H_2SO_4 to yield 112 and 113. Further treatment with alkylamine resulted in the formation of imidazoline derivatives (114); Scheme 24 [55].



Scheme 24: Nucleophilic reaction of diaza analog of 2,3-dichloro-1,4-naphthoquinone (110).

2,3-Dichloro-1,4-naphthoquinone (1) on nucleophilic substitution reaction with NaN_3 lead to formation of diazido derivative (115) which on further reduction with $Na_2S_2O_4$ gave 2,3-diamino-1,4-naphthoquinone (116). The condensation of 116 with 1,4-dibromobutan-2,3-dione gave 2,3-bis(bromomethyl)benzo[g]quinoxaline-5,10-dione (117) which was converted into dichloro derivative (118) on reaction with LiCl; Scheme 25 [56].



Scheme 25: Synthesis of 2,3-bis(chloromethyl)benzo[g]quinoxaline-5,10-dione (118) from dichlone (1)

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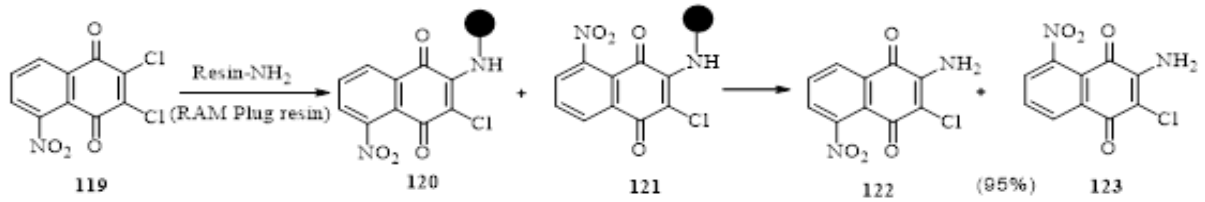
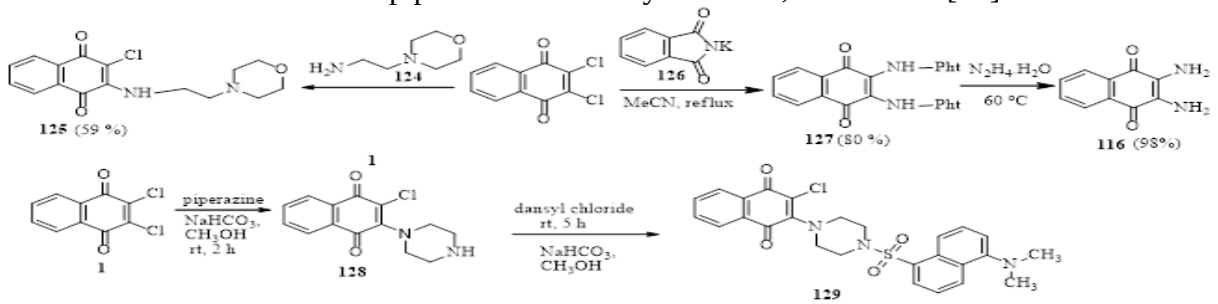
2,3-Dichloro-5-nitro-1,4-naphthoquinone (119) on treatment with resin-bound primary or secondary alkyl and arylamino bead led to rapid formation of dark coloured red beads (120-121). The mixture of 2-amino-3-chloro-5-nitro (122) and 8-nitro-1,4-naphthoquinones (123) were easily obtained from acidification; Scheme 26 [57].



Scheme 26: Reaction of 2,3-dichloro-5-nitro-1,4-naphthoquinone (119) with resin-bound primary or secondary alkyl and arylamino bead.

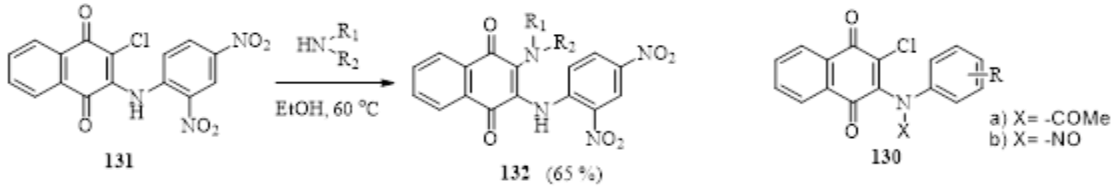
2,3-Dichloro-1,4-naphthoquinone (1) on reaction with *N*-morpholinoethylamine (124) in Et_3N resulted in the formation of *N*-morpholino derivative (125) [58]. The reaction of 2,3-dichloro-1,4-naphthoquinone (1) with potassium salt of phthalimide (126) in MeCN resulted in the formation of N:N′-diphthally-1,4-naphtho- quinone (127) which on further treatment with hydrazine hydrate led to formation of 2,3-diamino-1,4-naphthoquinone (116); Scheme 27 [59].

A quinone analog (129) containing molecular switching property was synthesized by nucleophilic substitution reaction of 1 with piperazine and dansyl chloride; Scheme 27 [60].



Scheme 27: Reaction of 2,3-dichloro-1,4-naphthoquinone (1) with heterocyclic nucleophiles 124, 126 and piperazine

It was generally found that if one chlorine atom had been replaced than it was difficult to replace second chlorine atom in 2,3-dichloro-1,4-naphthoquinone. Win et. al. studied that nitrogen nucleophile were facilitated by replacement of first chlorine atom in 1 by: a) *N*-acylation (X=COMe) b) *N*-nitrosation (X=NO) 130 or substitution of one chlorine atom by pyridine nucleus leading to formation of pyridinium salts and synthesized various 2,3-disubstiuted analogs (132); Scheme 28 [61].



Scheme 28: Effect of nitro group on nucleophilic reaction of 2,3-dichloro-1,4-naphthoquinone

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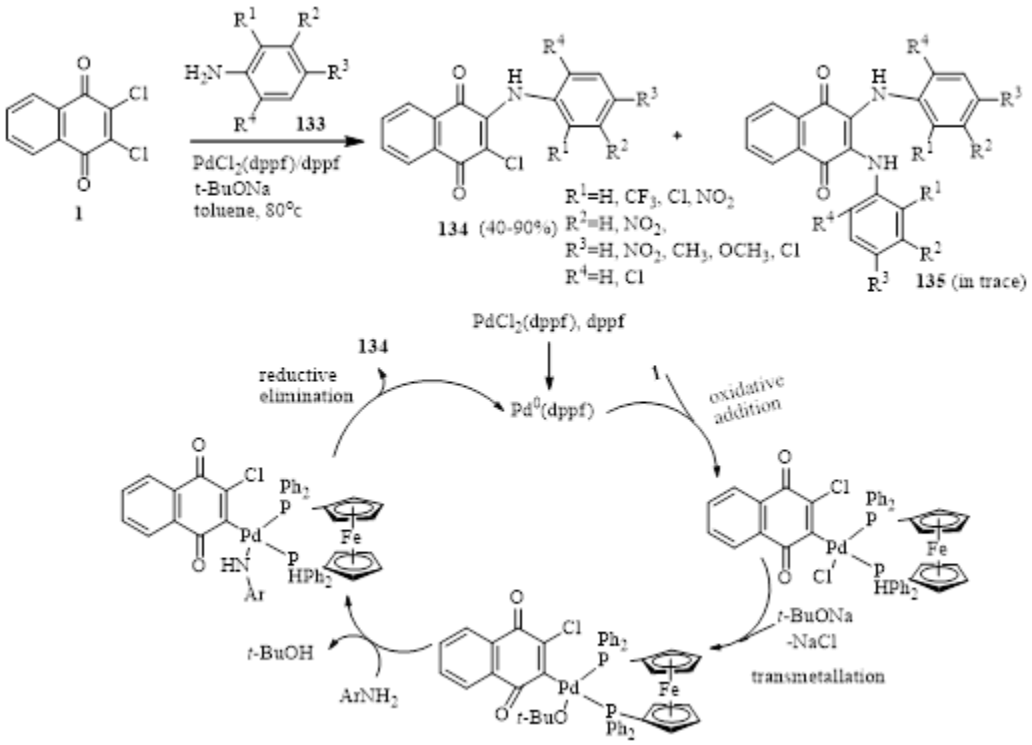
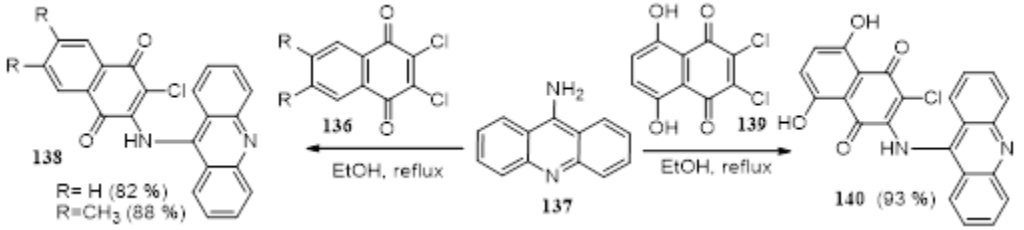
The reaction of 2,3-dichloro-1,4-naphthoquinone (1) with nitro-substituted aryl amines (133) catalyzed by $PdCl_2$(dppf)/dppf in the presence of base t-BuONa produced of 2-[(nitroaryl)amino]-3-chloro-1,4-naphthoquinone (134) and 2,3-di[(nitroaryl)amino]-1,4-naphthoquinone (135) as trace. The mechanism for the formation of 134 proceeded by oxidative addition, transmetallation and reductive elimination respectively Scheme 29 [62].



Scheme 29: Mechanistic approach of palladium based nucleophilic substitution reaction of dichlone (1).

Gellerman et. al. explored the reaction of chloronaphthoquinones (136 and 139) with 9-aminoacridine (137) and synthesized novel antiproliferative agents (138 and 140) in high yields, Scheme 30 [63].



Scheme 30: Synthesis of antiproliferative agents (138 and 140).

2-anilino-3-chloro-1,4-naphthoquinones (141) obtained from 2,3-dichloro-1,4-naphthoquinone (1) on further reaction with halo substituted anilines undergo nucleophilic substitution in presence of catalyst $PdCl_2$(dppf) with *t*-BuONa leading to formation of 2,3-diamino substituted-1,4-naphthoquinones (142) [64]; Scheme 31.

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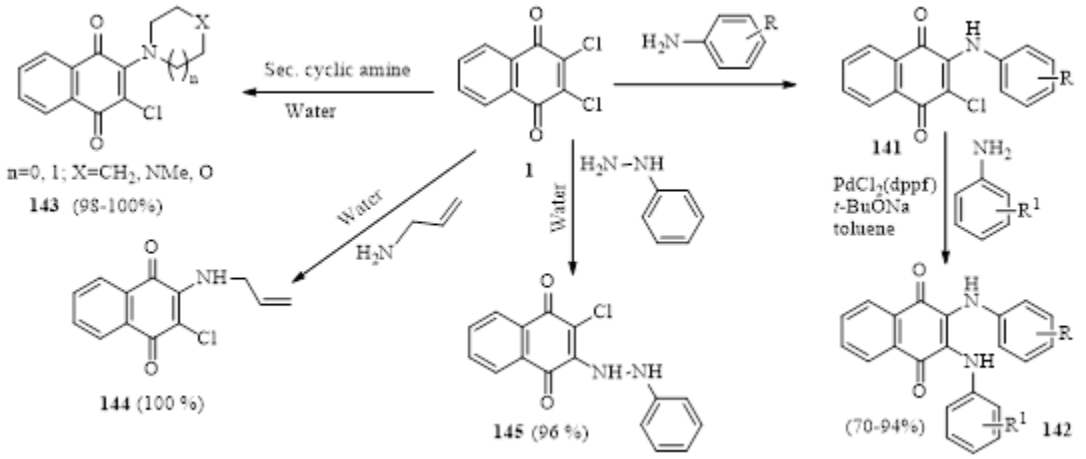
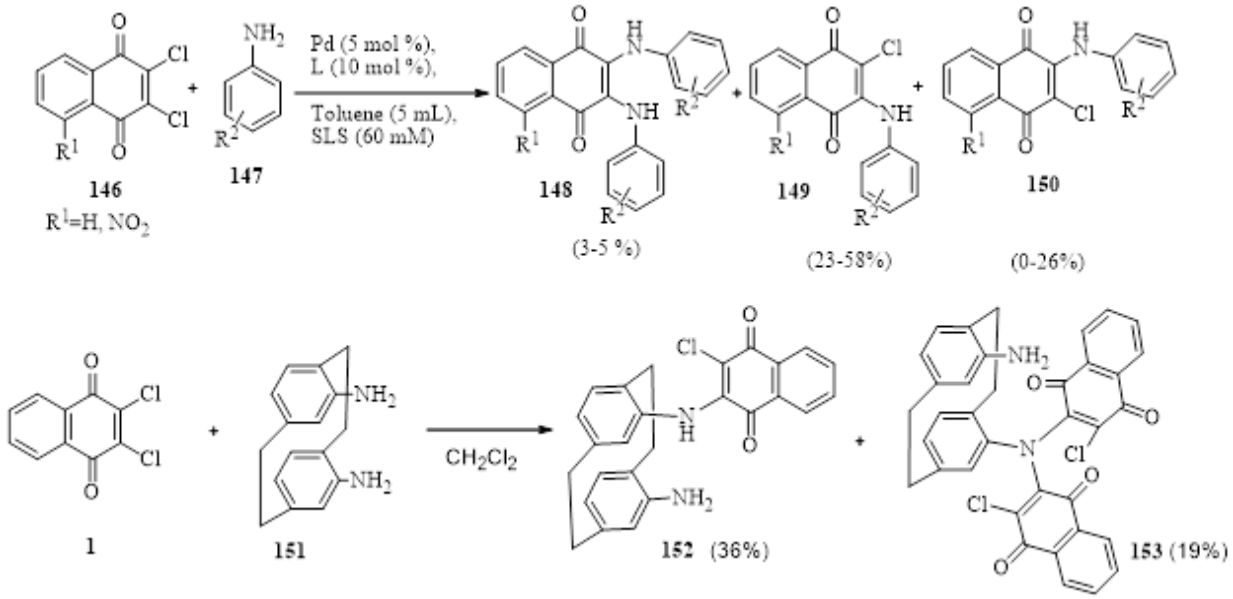
When 2,3-dichloro-1,4-naphthoquinone (1) was stirred with different secondary heterocyclic amines viz. 1-methylpiperazine, pyrrolidine, piperidine and morpholine at room temperature/50oC using water as solvent, mono substituted products (143); were obtained respectively in 98-100% while nucleophilic substituted products (e.g. (144 and 145) were also reported [65, 66]; Scheme 31.



Scheme 31: Synthesis of biologically active hetero analogues of naphthalene-1,4-dione.

2,3-Dichloronaphthalene-1,4-diones (146) and anilines (147) using NaOH, L (10%), and [cinnamylPdCl]$_2$ (5%), in surfactant (sodium lauryl sulphate, SLS)-toluene as the reaction media were further studied by Samant et al. [49b] and observed a high percentage conversion but also enhancement in the selectivity towards mono derivative products. The selectivity was very surprising because substitution of the activating group NHR was expected to enhance the rate of formation of di-coupled product. [67]; Scheme 32.



Scheme 32: Study of Pd and surfactant as well as only solvent based reaction of dichlones

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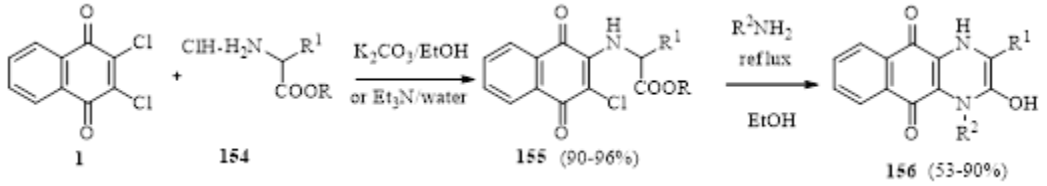
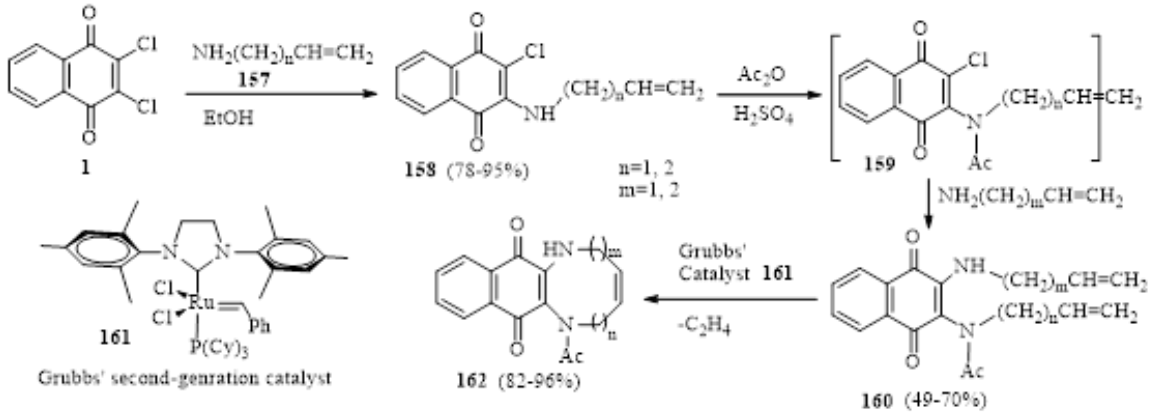
2,3-Dichloro-1,4-naphthoquinone (1) on reaction with donor 4,13-diamino[2,2]paracyclophane (151) produced 2-*N*-[4′(13′-amino[2.2]paracyclophanyl)]amino-3-chloro-1,4-naphthoquinone (152) and 4-amino-13-*N*,*N*-bis-2′-(3′-chloro-1,4-naphthoquinonyl) amino[2.2]paracyclophane (153) in 36% and 19% respectively; Scheme 32 [68]

The reaction of 2,3-dichloro-1,4-naphthoquinone (1) with enantiomerically pure L-α-amino acid ethyl ester hydrochlorides (154) yielded *N*-[3-chloro-1,4-naphthoquinon-2-yl]- α-amino acid ethyl ester (155) in EtOH [7] as well as in water [65, 66]. Further reaction of 1 with primary aliphatic and aromatic amines resulted in the formation of 1,2,3-trisubstituted-1,4-dihydrobenzo[g]quinoxaline-5,10-diones (156) in 53-90% yields; Scheme 33 [7].



Scheme 33: Reaction of 2,3-dichloro-1,4-naphthoquinone with amino acid esters.

2,3-dichloro-1,4-naphthoquinone (1) reaction with allylamines (157) yielded only mono substituted derivative 2-allylamino-3-chloro-1,4-naphthoquinones (158). Thus the reaction of 158 with acetic anhydride, in the presence of sulfuric acid, afforded the acylated products (159) which facilitate the substitution of the second chlorine atom and 2,3-diallylamino-2-homoallylamino derivatives (160) could be obtained as shown in Scheme 34 [51].On further reaction of 160 with Grubbs' catalyst (162), a second generation catalyst undergoes ring-closing olefin metathesis (RCM) leading to formation of eight, nine and ten-membered nitrogen containing quinone fused heterocycles (162); Scheme 34 [69].



Scheme 34: Grubb's catalyst based ring-closing olefin metathesis in the synthesis of quinone fused heterocycles.

2,3-Dichloro-1,4-naphthoquinone (1) on nucleophilic substitution with 163 produced 3-(3-chloro-1,4-dioxonaphthylamino-4-(chlorophenyl)-6-(4,6-dimethoxybenzofuran-5-yl) pyrimidin-2-imine (164); Scheme 35 [70].

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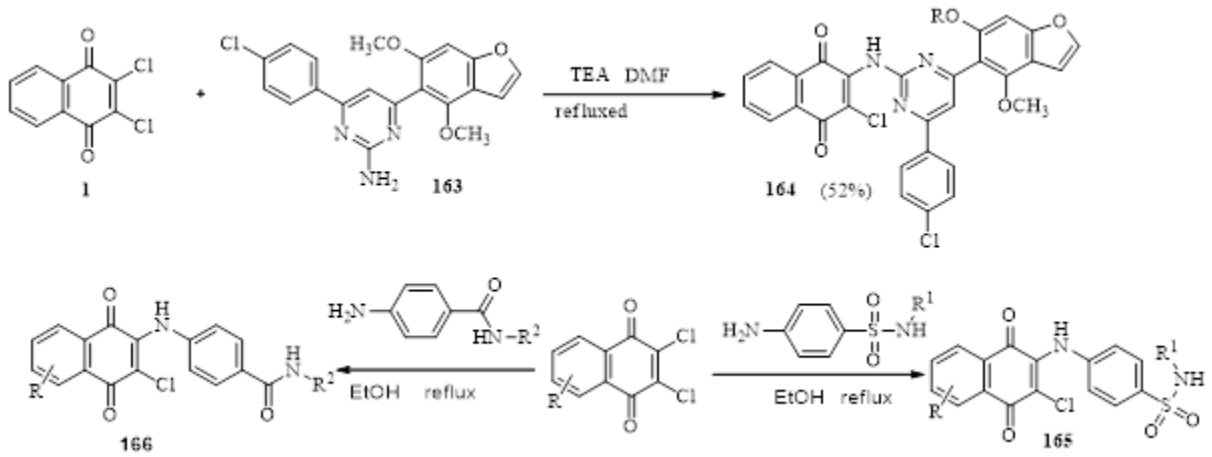
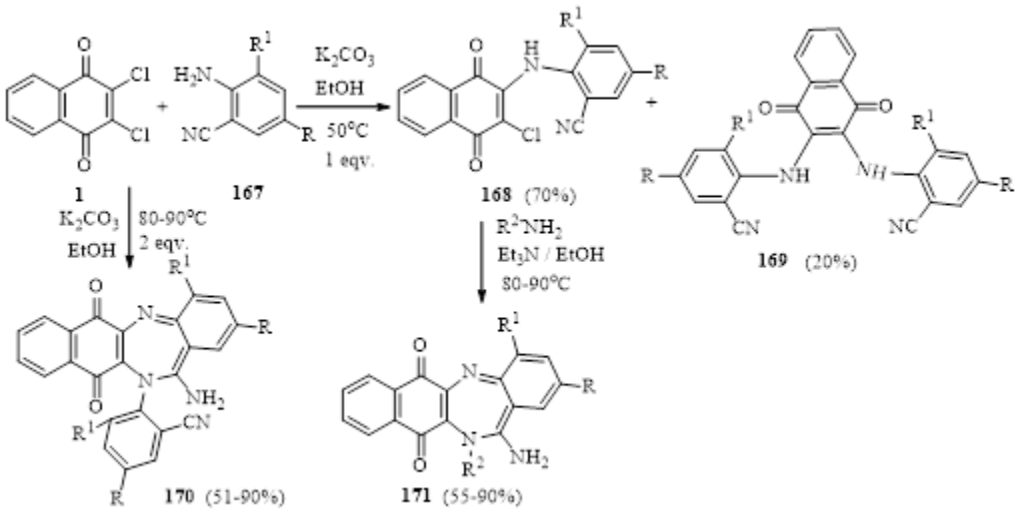
Screening of selective proteasome inhibitor for cancer over normal cells, a library of novel compounds (165) based on chloronaphthoquinone and sulfonamide moieties were synthesized by Lawrence et. al. to gain a better understanding of the structure-activity relationship responsible for chymotrypsin like proteasome inhibitory activity [71]. Xu et. al had been investigate the effect of substituting a carbonyl group for the sulfonyl group in PI-083, and R_2 was also replaced with different tailing groups to explore the effect of these molecular (166) region on antiproliferative activity [72]; Scheme 35.



Scheme 35: Synthesis of proteasome inhibitors (165).

While reaction of 2,3-dichloro-1,4-naphthoquinone (1) with aryl amine (167) gave 2-(3-chloro-1,4-dioxo-1,4-dihydro-naphthalen-2-yl-amino)-benzonitriles (168) and 2-[3-(2-cyno-phenylamino)-1,4-dioxo-1,4-dihydro-naphthalen-2-ylamino]benzonitriles (169) at 50ºC while at 80-90 ºC produced 12-alkyl derivatives of 12-substituted aryl derivatives of 13-amino-12*H*-5,12-diaza-substitutedbenzo[4,5]cyclo-hepta[1,2-b] naphthalene-6,11-diones (170) and further reaction of 168 with amines gave 13-amino-12*H*-5,12-diaza-substitutedbenzo[4,5] cyclohepta[1,2-b]naphthalene-6,11-dione (171); Scheme 36 [73].



Scheme 36: Synthetic route of diazepines (170, 171).

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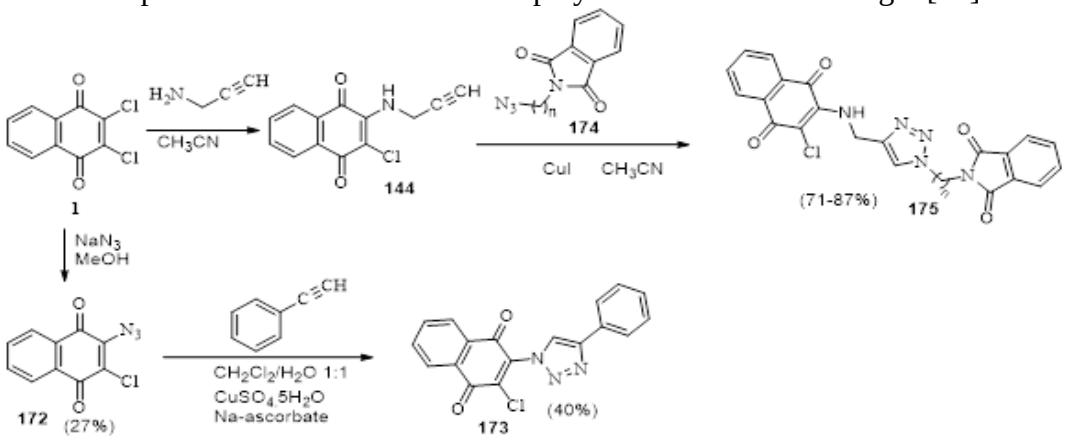
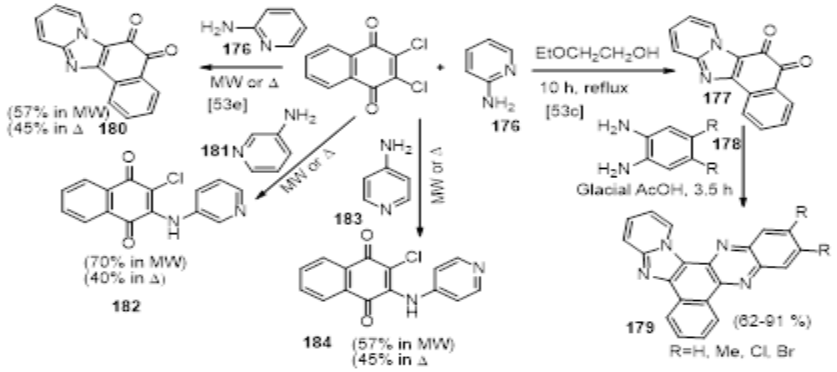
In the continued search for novel trypanocidal compounds, Camara et. al. synthesized naphthoquinones coupled 1,2,3-triazoles (173) through Cu-catalyzed azide-alkyne cycloaddition reaction; Scheme 37 [74]. A other methodology was also established to synthesized a trypanocidal triazole compound 175 [75]. Several benzophenazine dyes containing a diazobenzo[a]fluorene moiety (178-180) have been synthesized from 1 in two step (Scheme 38) and shown that these dyes are efficient photoinitiators for free radical polymerization in visible light [76].



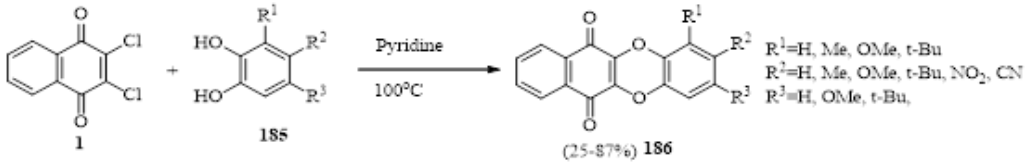
Scheme 37: Synthesis of naphthoquinone coupled 1,2,3-triazoles (173, 175)

The synthesis of pyridylamino naphthoquinones (182, 184) by microwave-assisted reaction of 2,3-dichloro-1,4-naphthoquinone with aminopyridines is also explored with the increasing yields 12-20% under Microwave irradiation reaction (in 15-60 min) as comparison with conventional heating (15 h, 78 ^{o}C) [77]



Scheme 38: Synthesis of benzophenazine dyes containing a diazobenzo[a]fluorene moiety (178-180) and pyridylaminonaphthoquinones (182, 184).

3.2.3. With Oxygen Nucleophiles



Scheme 39: Reaction of 2,3-dichloro-1,4-naphthoquinone (1) with oxygen nucleophiles.

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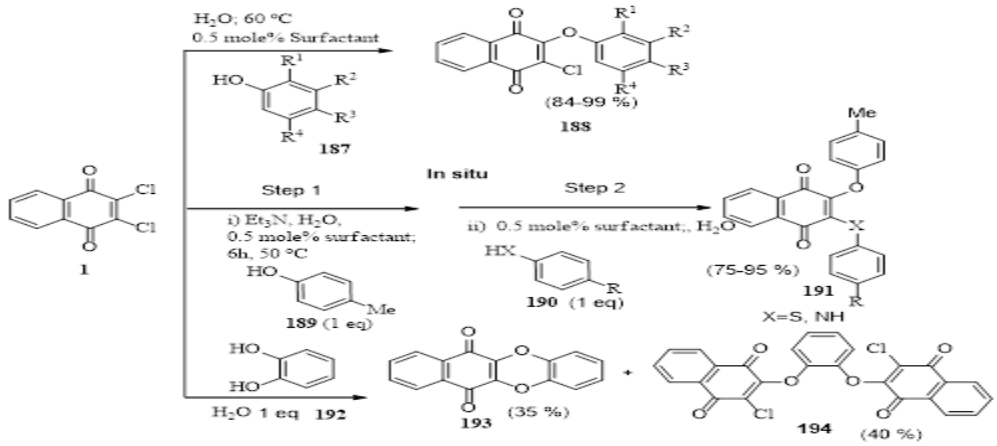
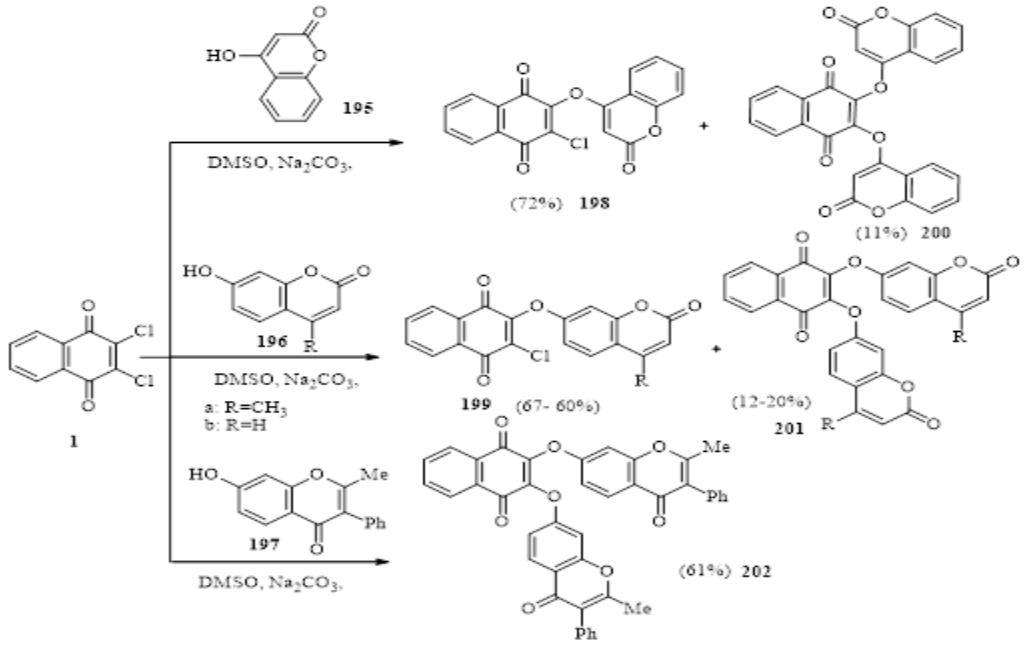
Compound 186 was synthesized in 25 to 87% yield by condensation of 2,3-dichloro-1,4-naphthoquinone (1) with catechol and its derivatives (185) in the presence of pyridine as both base and solvent as shown in Scheme 39 [78].

Tandon et. al. [79, 80] have been optimize various reaction condition and synthesized various oxygen containing 1,4-naphthoquinone derivatives (188, 191, 193, 194) chemoselectively by an economical, viable green methodology approach using water as solvent with or without surfactants such as SDS as well as LD (laundry detergent) in high yields (< 99%), Scheme 40.



Scheme 40: Optimization and synthesis of oxygen containing 1,4-naphthoquinone derivatives in aqueous medium.

2,3-Dichloro-1,4-naphthoquinone (1) reacts readily with hydroxyl chromanes (195-197) and produced mono 198-199 and di 200-202 substituted derivatives of 1,4-napthoquinone respectively as shown in Scheme 41 [73].



Scheme 41: Reaction of hydroxy chromenes.

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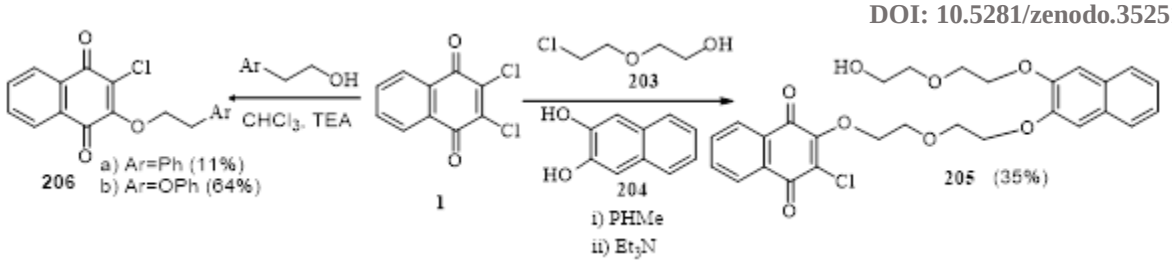
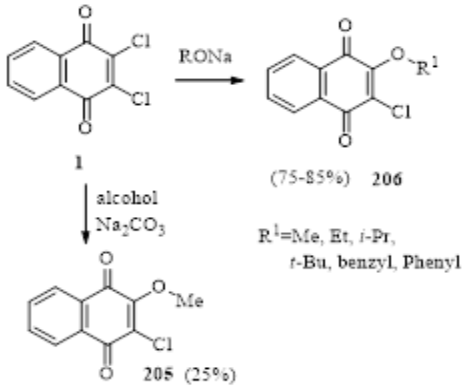


Scheme 42: Nucleophilic substitution reaction of hydroxy ethers.

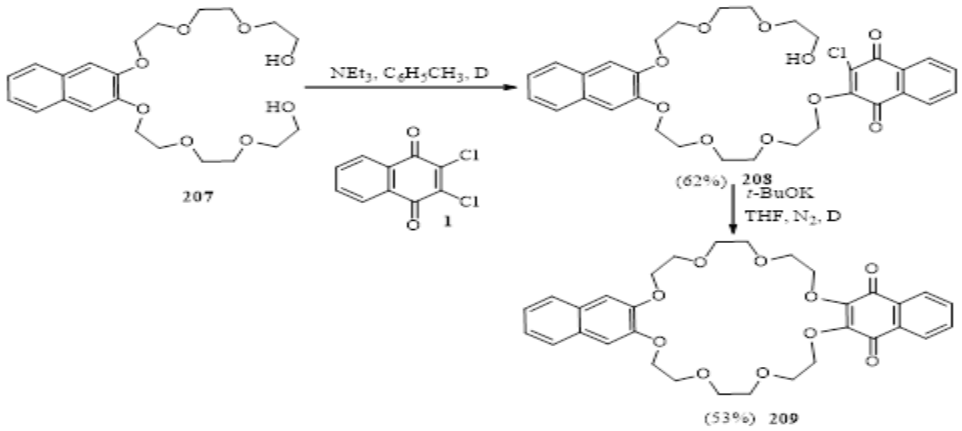


Scheme 43: Synthesis of 2-alkoxy-3-chloro-1,4-naphthoquinone (205, 206)

The bichromophoric ether (205) was synthesized in three steps from readily available starting material 1, 203 and 204 [92] and ethers were synthesized from corresponding alcohols in the presence of TEA/CHCl3 [53] as shown in Scheme 42.

The target compounds 2-alkoxy-3-chloro-1,4-naphthoquinone (205, 206) were synthesized from 2,3-dichloro-1,4-naphthoquinone (1) using different bases as shown in Scheme 43 [81,82].

2,3-Dichloro-1,4-naphthoquinone (1) on reaction with diol (207) gave quinone 208 in the presence of Et_3N in 62% yield. Further reaction of 208 with *t*-BuOK in THF under N_2, crown ether (209) was obtained in 52% yield as outlined in Scheme 44 [83].



Scheme 44: Synthetic route of naphthoquinone fused crown ether (209).

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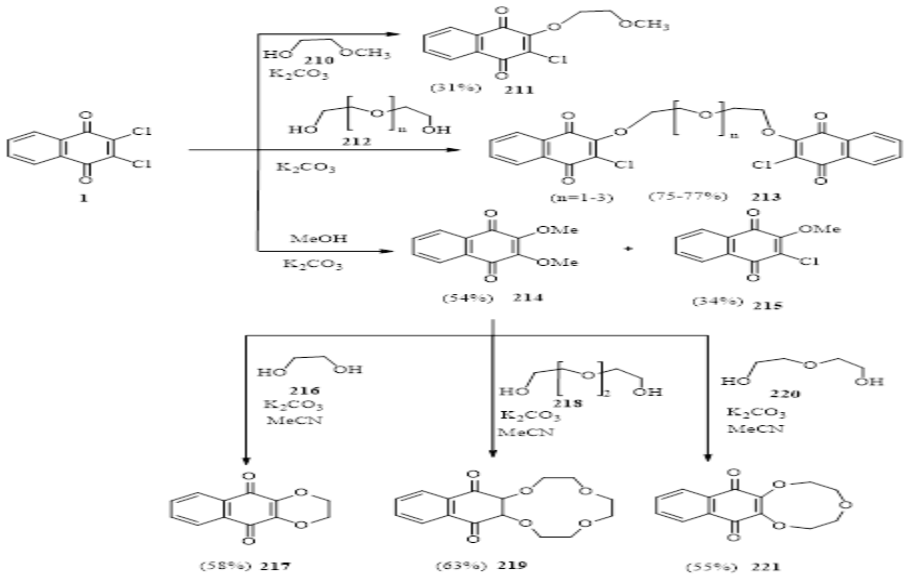
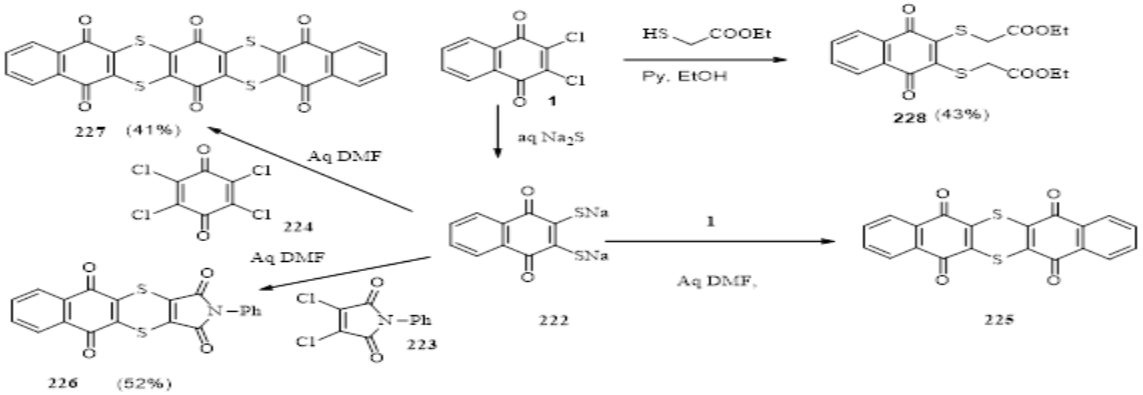


Scheme 45: Synthesis of various naphthoquinone fused crown ether (209) from 2,3-dichloro-1,4-naphthoquinone (1).

Treatment of 2,3-dichloro-1,4-naphthoquinone (1) with 2-methoxyethanol (210) and glycols (212) produced 211 and 213 respectively in 31% and 75-77% yields as shown in Scheme 45. The reaction with methanol at room temperature in the presence of potassium carbonate gave a mixture of the substitution products 214 and 215 in 51% and 34% yield. Further reaction of 214 with 216, 218 and 220 produced products 217, 219 and 221 in 58, 63 and 55% yield respectively [84]; Scheme 45.

3.2.4. With Sulfur Nucleophiles

2,3-Dichloro-1,4-naphthoquinone (1) reacted with a large excess of sodium sulfide in aqueous solution to give a deep green solution 222 which on further reaction with 1, 2,3-dichloro-N-phenylmaleimide (223) and 2,3,5,6-tetrachloro-1,4-benzoquinone (224) yielded 5,7,12,14-tetraoxodibenzo[*b*,*i*]thianthrene (225) and dithiins (226) and tetrathiins (227) respectively as outlined in Scheme 46 [85]. While the treatment of 2,3-dichloro-1,4-naphthoquinone (1) with methyl mercaptoacetate produced bis(methoxycarbonyl methylthio) naphthoquinone (228) [86].



Scheme 46: Reaction of 2, 3-dichloro-1,4-naphthoquinone (1) with sulfur nucleophiles.

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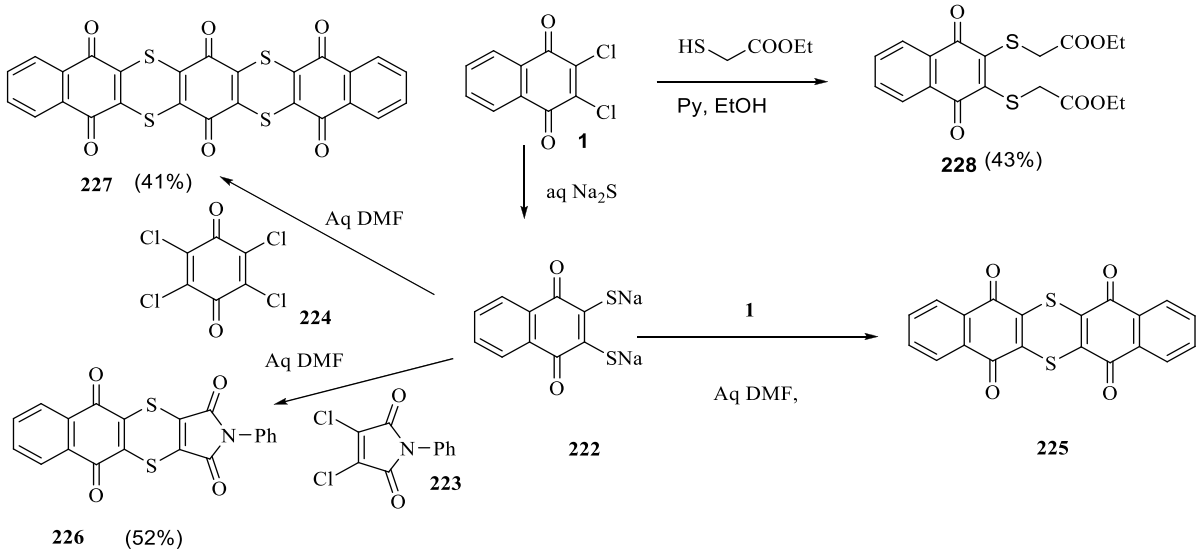
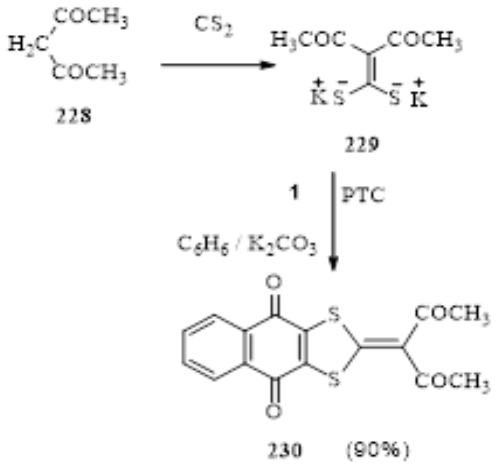


Scheme 47: Synthesis of naphthoquinone thiol-crown ethers (227).

The naphthoquinone thiol-crown ethers (227) were prepared from 2,3-dichloro-1,4-naphthoquinone (1) as outlined in Scheme 47 [87], in which a double nucleophilic 1,4-addition-elimination of 1 to β,β′/dimercaptodiethyl ether (226) under basic condition (Ce_2CO_3 in DMF) yielded crowned naphthoquinones (227) in moderate yield (35-57%).

2-(1-Acetyl-2-oxopropylidene)naphtha[2,3-*d*][1,3] dithiole-4,9-dione (229) was obtained via reaction of pentane-2,4-dione (228), carbon disulphide and 2,3-dichloro-1,4-naphthoquinone (1) in one pot reaction using phase transfer catalysis condition [K_2CO_3/benzene/ tetrabutylammonium bromide (TBAB)] in 90% yield as shown in Scheme 48 [88].



Scheme 48: Synthesis of naphtha[2,3-*d*] [1,3]dithiole-4,9-dione

Michael type addition reaction of 1 with alkyl thiols optimized and synthesize alkyl chain containing mercapto-1,4-naphthoquinones (231-238) and explore their dyes properties, Scheme 49 [89, 51]

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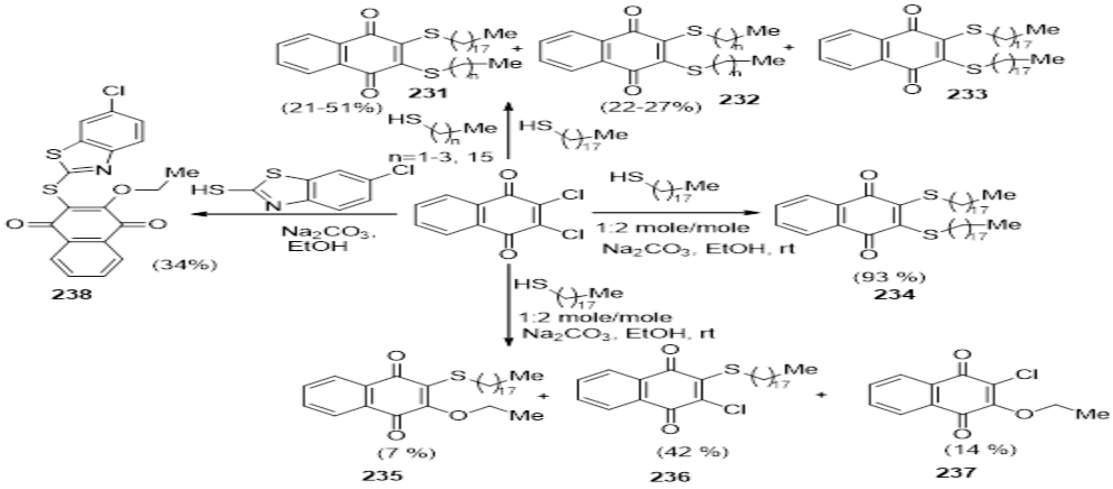


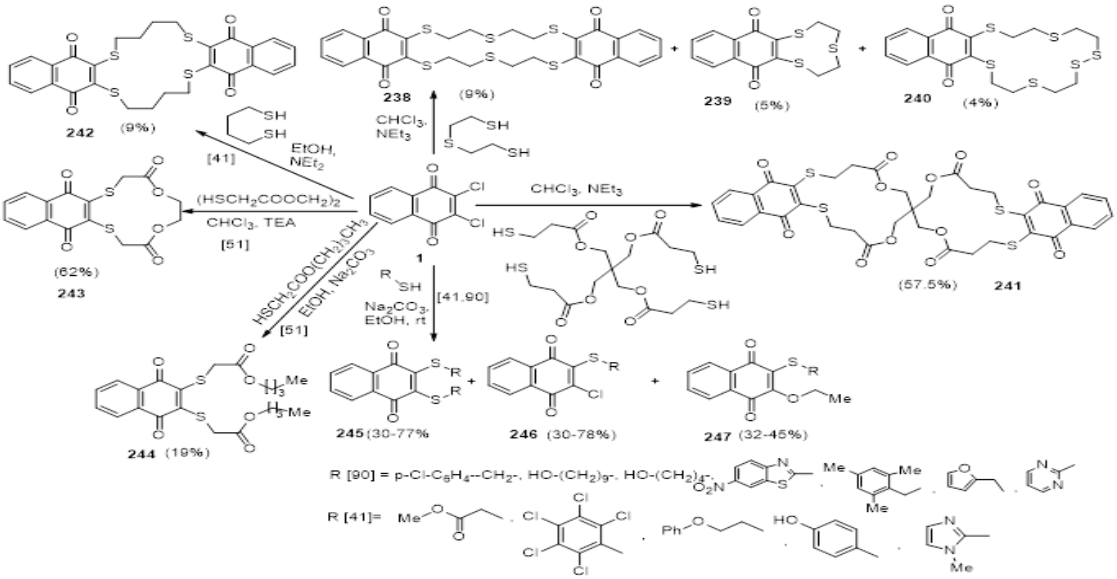
Scheme 49: Synthesis of various sulfur containing naphthoquinones.

Further work extended, towards the synthesis of heterocyclic and non-heterocylic (238-247) transformations of sulfur continuing 1,4-naphthoquinones for pharmacological purpose as depicted in Scheme 50 [90, 41, 51].

3.2.5. With Selenium Nucleophiles

2,3-Dichloro-1,4-naphthoquinone (1) reacted with sodium selenide in the presence of acetonitrile as a solvent to give a red coloured compound dinaphtho[2,3-b;2′,3′-e]-[1,4]diselenine-5,7,12,14-tetraone (248) in 42% yield as shown in Scheme 51 [91].

2,3-Dichloro-1,4-naphthoquinone (1) reacted with selenium in the presence of magnesium produced 249 in 59% yield while the reaction with PhSeSePh in presence of NaBH4 gave 249 in 70% yield as outlined in Scheme 52[92].



Scheme 50: Synthesis of naphthoquinone fused sulfur containing crown ethers.

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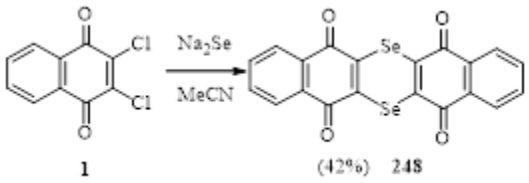
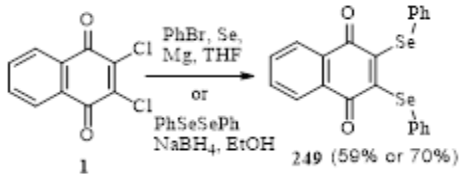


Scheme 51: Reaction of 2, 3-dichloro-1,4-naphthoquinone with selenium nucleophiles



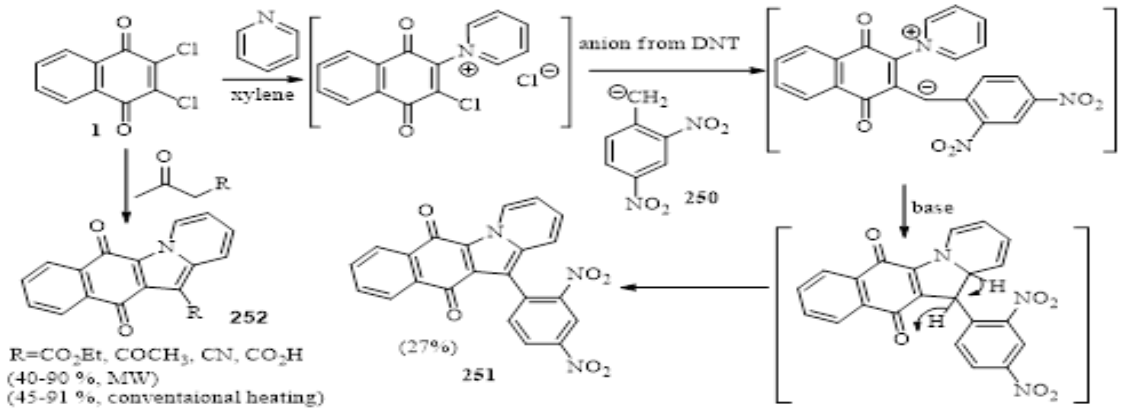
Scheme 52: Synthesis of 2,3-bis(phenylselanyl) naphthalene-1,4-dione

3.2.6. With Carbon and Nitrogen Nucleophiles

Reactions of 2,3-dichloro-1,4-naphthoquinone (1) with anion of dinitrotoluene (DNT) (250) and pyridine in different solvents like DMF, DMSO, EtOH, benzene, toluene, chlorobenzene and xylene were studied and best results were obtained to yield 27% compound 251 as described in Scheme 53 [93].

Indolizino[1,2-*b*] quinoline derivatives, were prepared in a one-pot reaction of 2,3-dichloro-1,4-naphthoquinone with ketones under microwave irradiation (40-90% yields); Scheme 53 [94].

However, Cheng et. al., [95] and Defant et. al. [96] have also synthesized a series of indolizinoquinoline-5,12-dione derivatives (253-256, 258-261) as shown in Scheme 54. Compound 254, 256 were efficiently synthesized by aminolysis of the ester obtained as a single regio-isomer by a one-pot three-component procedure involving metal-assisted cyclization under microwave irradiation conditions [96]. It was reported that complex of 6,7-dichloroquinoline-5,8-dione with the eco-friendly salt $MgCl_2$ was able to induce a highly regio-selective production of the *N,N*-anti ester 261, whereas the *N,N*-syn isomer 259 was obtained by the most convenient procedure [96].



Scheme 53: Synthesis of indolizino[1,2-*b*] quinolines

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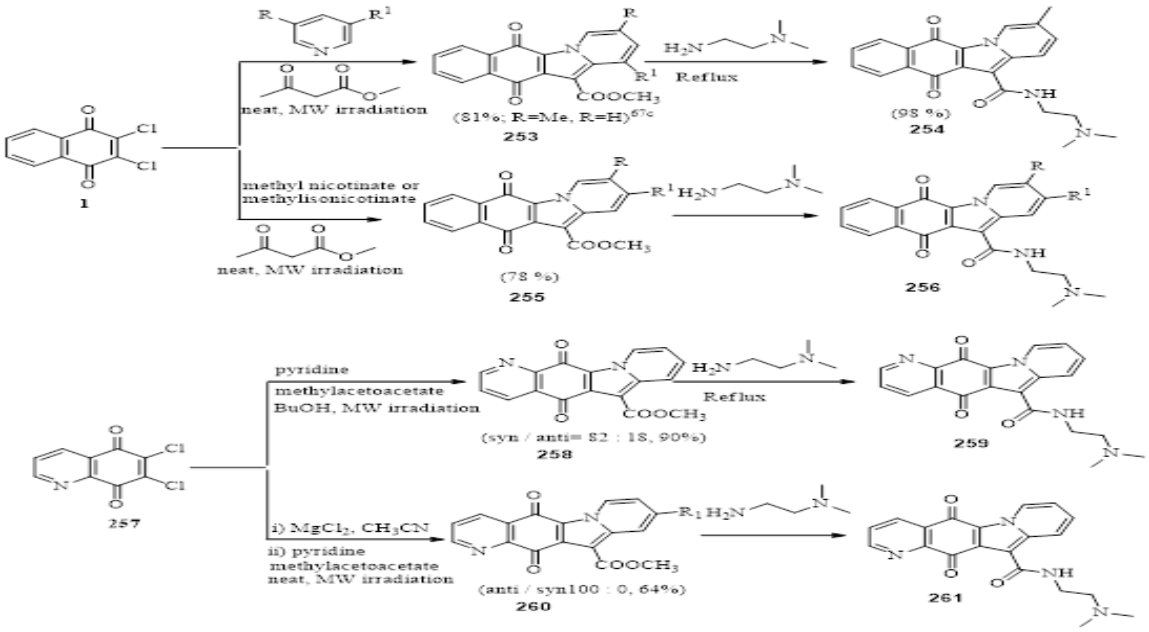
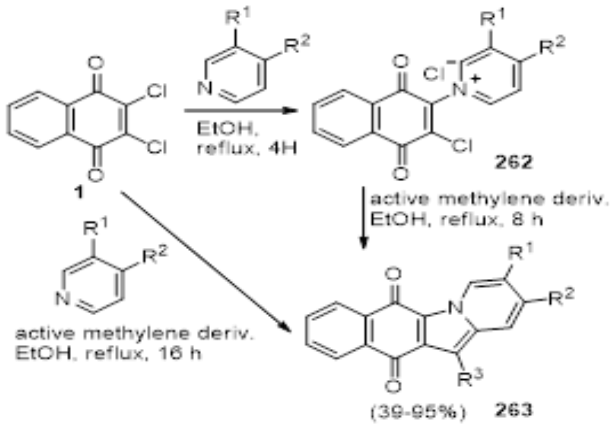


Scheme 54: Synthesis of indolizinoquinoline-5,12-dione derivatives



Scheme 55: Synthesis of benzo[*f*]pyrido[1,2-*a*] indole-6,11-diones (263)

A convenient method for synthesis of benzo[*f*]pyrido[1,2-*a*] indole-6,11-diones (263) were also explored by Ryu et. al. [97] with minor modification as shown in Scheme 55 and 1,4-dioxo-(1,4-dihydronaphthalen-2-yl)-4-methyl-pyridinium chlorides (262) were also synthesized by nucleophilic substitution of compound (1) with appropriate pyridines.

Consequently, benzo[*f*]pyrido[1,2-*a*] indole-6,11-diones (263) were synthesized by nucleophilic substitution and cyclization of compounds 262 with 1 equiv. of appropriate active methylenes in EtOH with overall yields 39–95%.

Buccini et. al. have been reported the synthesis of benzo[*c*]pyrrolo[4,3,2-mn] acridines (267) starting from 1. They have explored the reaction 1 with 2-(2-nitrophenyl) acetonitrile (264) in water as well as in ethanol. However, reaction with indolin-2-one (268) in DMF has been explored for the synthesis of 271; scheme 56 [98].

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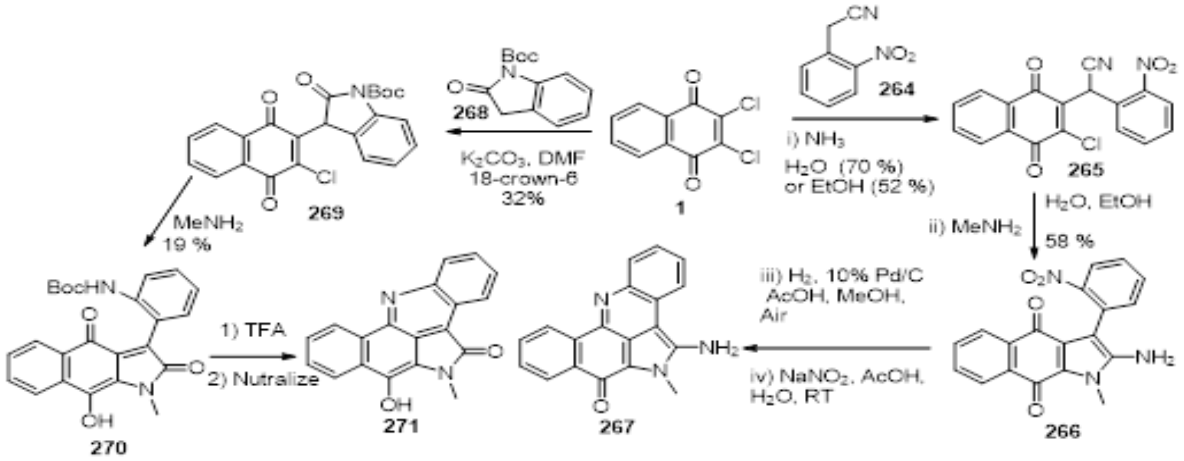
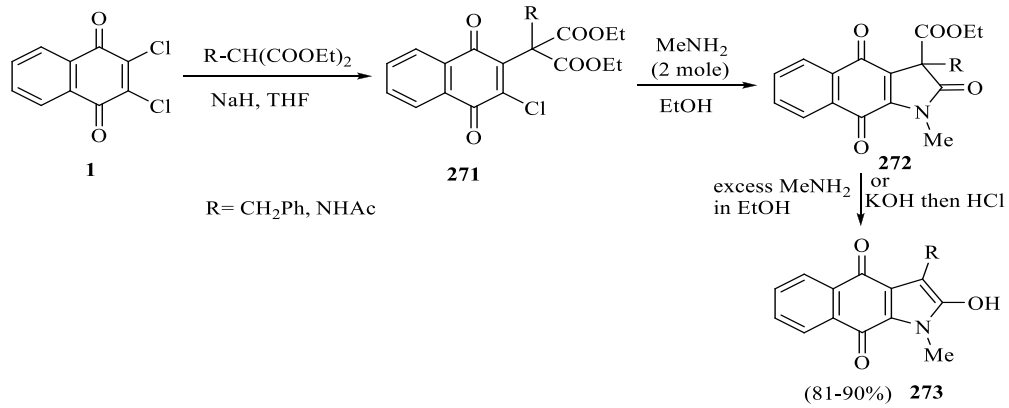


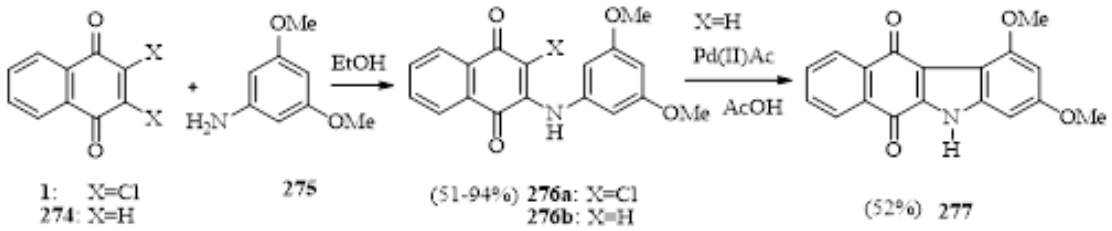
Scheme 56: Synthesis of benzo[c]pyrrolo[4,3,2-mn] acridines (267).



Scheme 57: Synthesis of 1H-benzo[f]indole-4,9-dione

Sodium salts of diethyl benzylmalonate and diethyl acetamidomalonate, obtained from corresponding esters by the reaction with NaH in THF, reacted with 2,3-dichloro-1,4-naphthoquinone (1) to give 271, which cyclized to lactams (272) upon reaction with $MeNH_2$. Lactams were converted to indole (273) on treatment with excess of methyl amine in EtOH or KOH as described in Scheme 57 [99].

Quinones (1) and 274 on reaction with 3,5-dimethoxyaniline (275) yielded 276. 276b on further treatment with Palladium (II)acetate in glacial acetic acid under N2 produced 277 in 52% yield as reported in Scheme 58 [100].



Scheme 58: Synthesis of 1,3-dimethoxy-5H-benzo[b]carbazole-6,11-dione (277).

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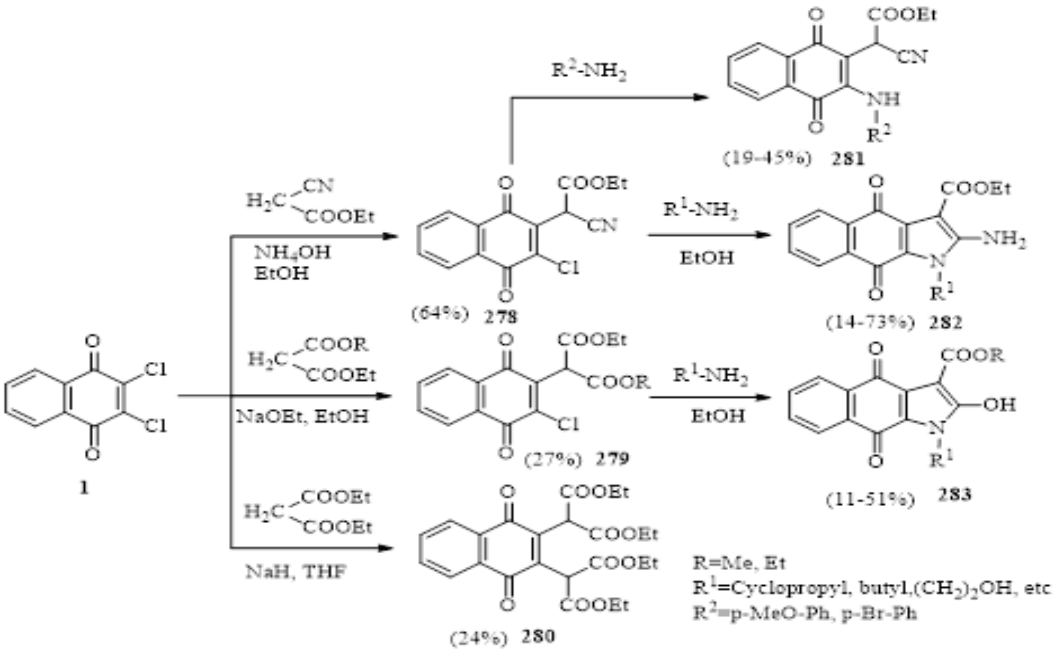
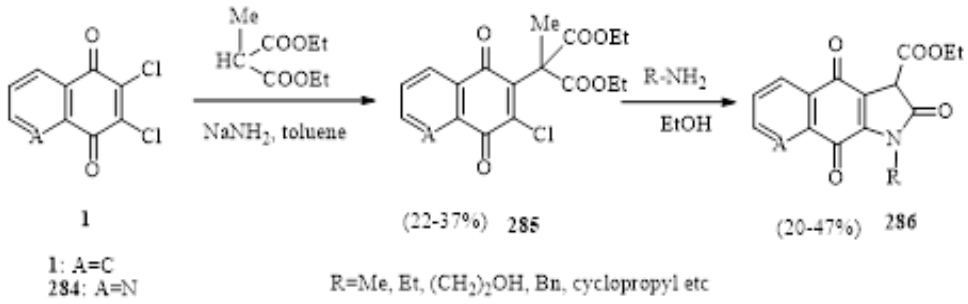


Scheme 59: Reaction of 2,3-dichloro-1,4-naphthoquinone (1) with ethyl cyanoacetate or diethyl malonate under different conditions.

Reaction of 2,3-dichloro-1,4-naphthoquinone (1) with ethyl cyanoacetate or diethyl malonate under different conditions gave 2-chloro-3-(α-cyano-α-ethoxycarbonyl-methyl)-1,4-naphthoquinone (278), 2-chloro-3-(diethoxycarbonyl-methyl)-1,4-naphthoquinone (279) or 2, 3-di(diethoxycarbonyl-methyl)-1,4-naphthoquinone (280). When the compound 278 and 279 were reacted with various amines, nuclephilic substitution occurred, followed by intramolecular cyclization to give the 2-amino-3-ethoxycarbonyl-*N*-substituted-benzo[*f*]indole-4,9-dione derivatives (282) or 2-hydroxy-3-ethoxycarbonyl-*N*-substituted-benzo[*f*]indole-4,9-dione derivatives (283) respectively, while 278 gave uncyclized product 281 when reacted with p-anisidine or p-bromoaniline as outlined in Scheme 59 [101].



Scheme 60: Synthesis of indole derivatives (286).

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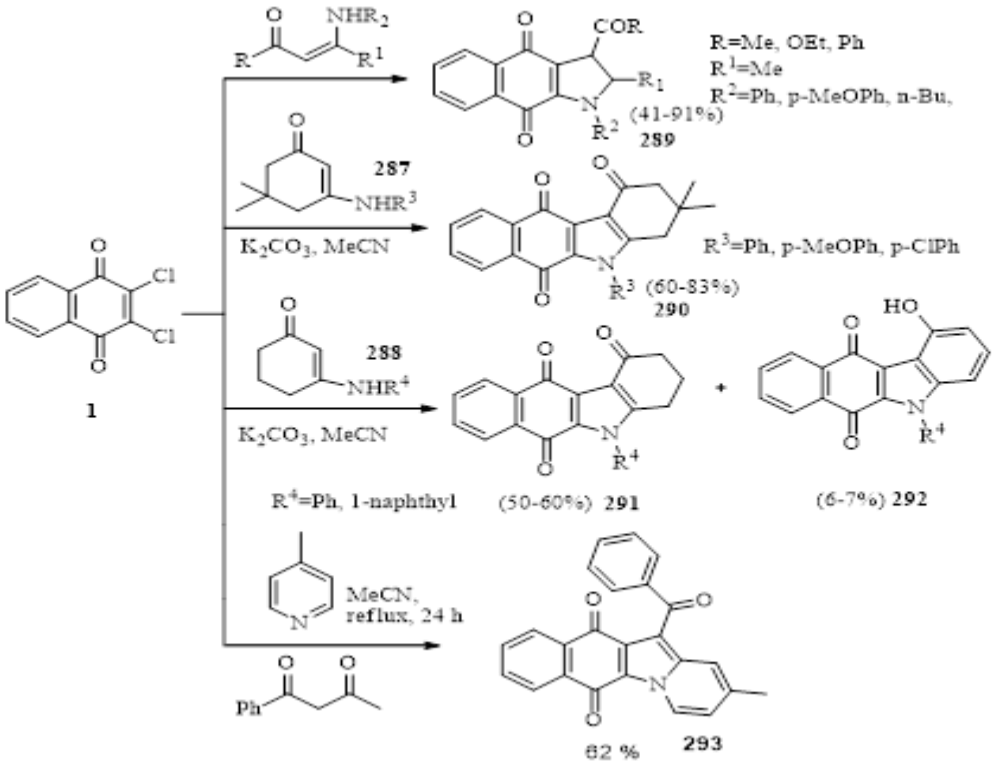

Scheme 61: Synthesis of various indole derivatives

The reaction of either 2,3-dichloro-1,4-naphthoquinone (1) or 6,7-dichloro-5,8-quinolinedione (285) with diethyl methymalonate gave the products 286 which on further nucleophilic substitution and intramolecular cyclization with various amines produced various indole derivatives 287 as described in Scheme 60 [102].

While Hu et al. reported one pot synthetic route to synthesize indole derivatives (289-292) from reaction of 2,3-dichloro-1,4-naphthoquinone (1) with β-enaminones, dimedone (287) and cyclohexadione monoenamines (288) respectively; Scheme 61 [103]. Liu et. al. has synthesized and explored crystallographic study of 12-Benzoyl-2-methylnaphtho[2,3-*b*]indolizine-6,11-dione (293) from 1; Scheme 61[104].

3.2.7. With Carbon and Oxygen Nucleophiles

2,3-Dichloro-1,4-naphthoquinone (1) on condensation with phloroglucinol (294) gave 1,3-dihydroxybenzo[b]naphtha[2,3-*d*] furan-6,11-dione (295a) [68]. Hejaz et al. has reported the synthesis of 3-hydroxybenzo[b]naphtha[2,3-*d*] furan-6,11-dione (295*b*) [105] from the parent compound 1 by reacting with resorcinol in ethanolic sodium ethoxide as well as Rhee et. al. [106] 295a-c synthesized using Na in EtOH or KOH in MeOH. while methylation of 2,3-dichloro-1,4-naphthoquinone (1) with CH_3I and Ag2O in $CHCl_3$ gave a mixture of 2,3-dichloro-5,8-dimethoxy-1,4-naphthoquinone (296) and 6,7-dichloro-5,8-dimethoxy-1,4-naphthoquinone (297).

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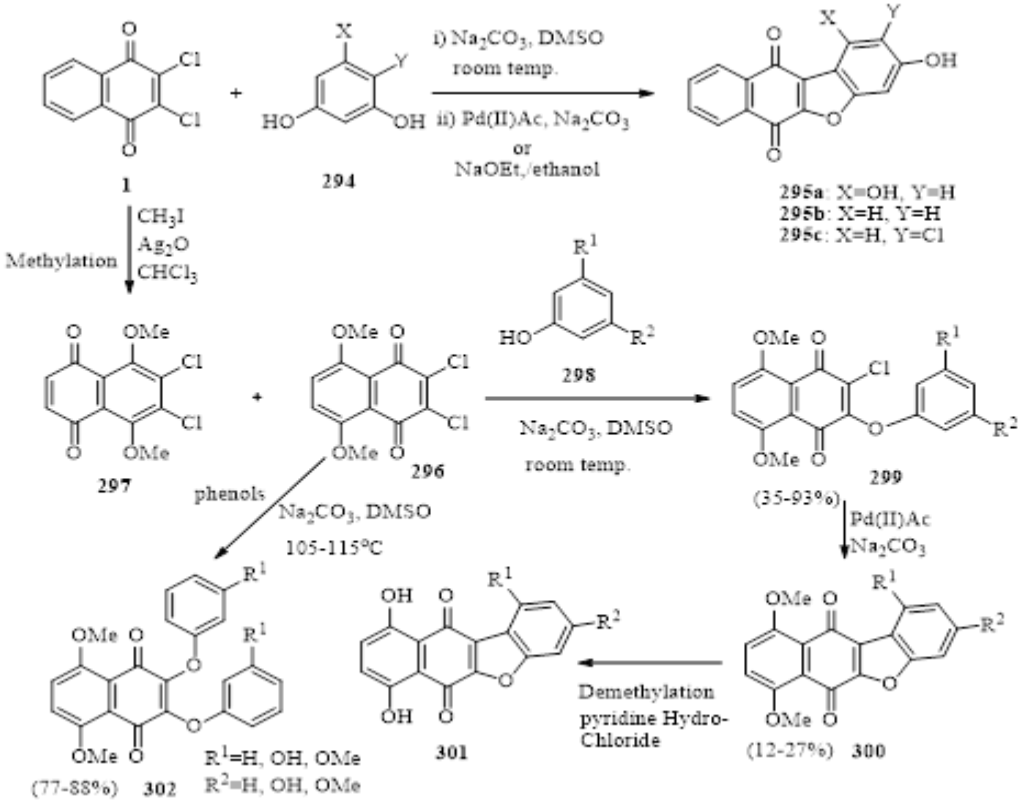

Scheme 62: Synthesis of benzo[b]naphtha[2,3-d] furan-6,11-dione

Further reaction of 296 with phenols (298) and Na2CO3 in DMSO at elevated temperature resulted in the formation of 302 and room temperature to yield 2-chloro-5,8-dimethoxy-3-phenoxy derivatives of 1,4-naphthoquinone (299) which on further treatment with palladium(II)acetate and Na2CO3 led to cyclization to yield benzo[*b*]naphtha[2,3-*d*]furan-6,11-dione (300) which on demethylation produced analogs of 1,3-dihydroxybenzo[b]naphtha[2,3-*d*]furan-6,11-dione (301)[107]; Scheme 62.

Dinaphtho[1,2-b;2′3′-d]furan-7,12-dione (304) was synthesized by the base-promoted condensation of 2,3-dichloro-1,4-naphthoquinone (1) with methyl 1,4-dihydroxy-2-naphthoate (303) in the presence of K_2CO_3 in refluxing pyridine and provided 64% product as shown in Scheme 63 [108].

While further reaction of 2,3-dichloro-1,4-naphthoquinone (1) and 257 with phenolic derivatives (305) produced benzofuroquinolinediones (306) in 24-31% yields using Na or KOH as base; Scheme 63 [109,110].

Base–prompted (Na_2CO_3, K_2CO_3) reaction of acyclic and cyclic β-dicarbonyl compounds (308) with 2,3-dichloro-1,4-naphthoquinone (1) and 4a,6,7,8a-tetrachloro-1,4-methanonaphthalene-5,8-dione (307) resulted in one pot C,O-dialkylation of 308 produced 2,3-disubstituted naphtha[2,3-*b*]furan-4,9-diones (309) and 5,8-methanonaphtho[2,3-*b*]furan-4,9-diones(310) respectively in variable yields 11-99% in different solvents like MeCN, DMSO, Toluene, *i*-PrOH, *t*-BuOH and acetone, Scheme 64 [111].

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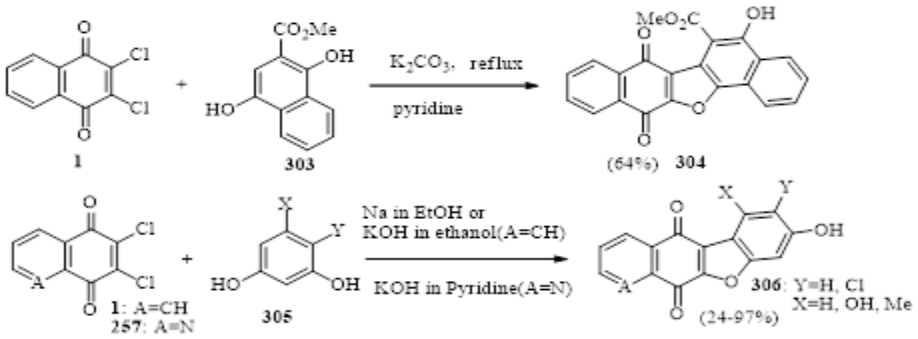
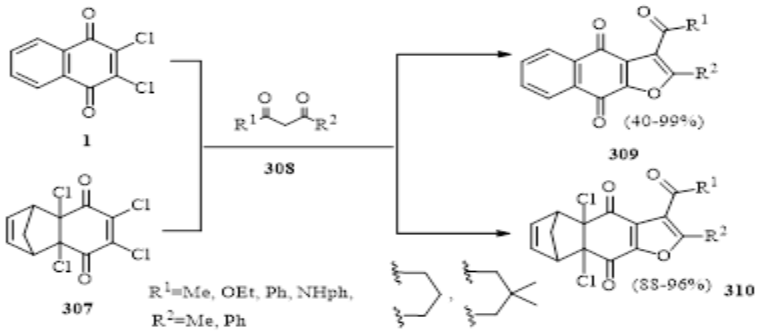
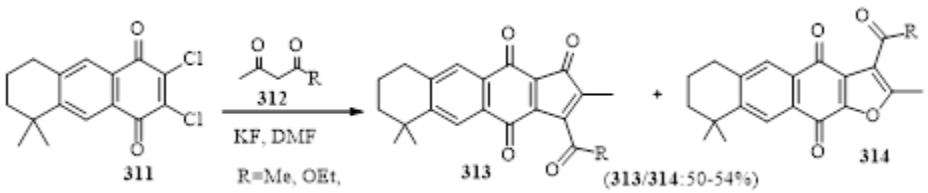


Scheme 63: Synthesis of benzofuroquinolinediones (306).

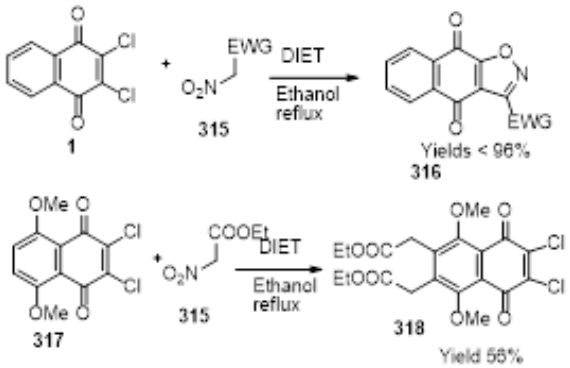


Scheme 64: 2,3-disubstituted naphtha[2,3-*b*] furan-4,9-diones (309) and 5,8 methanonaphtho[2,3-*b*] furan-4,9-diones (310).



Scheme 65: Synthesis of furo-1,4-naphthoquinones.

2,3-Dichloroquinone (311) on condensation with acetylacetone and ethyl acetoacetate (312) in DMF in the presence of KF, yielded the furo-1,4-naphthoquinones (314) and 314; Scheme 65[112].



Scheme 66: Synthesis of naphtho[2,3-*d*] isoxazole-4,9-diones

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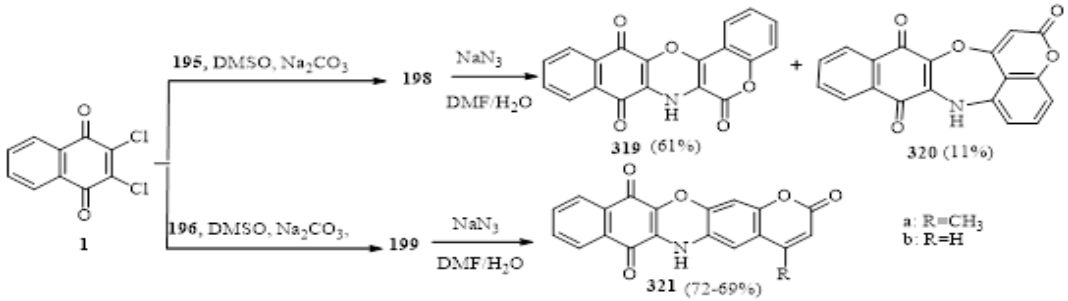
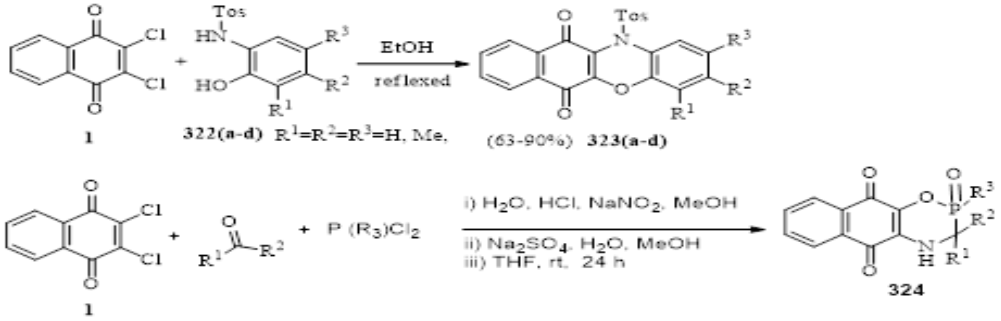
Santos et. al. optimize various reaction condition and reported an efficient procedure for the synthesis of naphtho[2,3-d]isoxazole-4,9-diones (316) (yields up to 96%) using 2,3-dichloro-1,4-naphthoquinones (1) and nitromethyl derivatives in the presence of base DIEA in refluxing ethanol. When they used 2,3-dichloro-5,8-dimethoxy-1,4-naphthoquinone (317) as starting materials, after 1.5 h at reflux in ethanol in the presence of 2 equiv of DIEA and molecular sieves, they isolated compound 318 in 56% yield; Scheme 66 [113].

3.2.8. With Nitrogen and Oxygen Nucleophiles

2,3-Dichloro-1,4-naphthoquinone (1) reacted readily with 195 and 196 and produced 198 and 199 respectively. Further reaction of 198 and 199 with sodium azide gave 319, 320 and 321 respectively as reported in Scheme 67 [114]. 2,3-Dichloro-1,4-naphthoquinone (1) reacted with *N*-tosyl-2-aminophenols (322) to give product 323 as outlined in Scheme 68 [115]. However, Wang et. al. reported the naphthoquinone fused cyclic aminoalkylphosphonates (324) from the reaction of 1 through mannich type condensation reactions; Scheme 68 [116].



Scheme 67: Synthesis of oxazine (319, 321) and oxazepine (320).



Scheme 68: Synthesis of benzo[b]phenoxazine.

3.2.9. With Nitrogen and Sulfur Nucleophiles

The reaction of 2,3-dichloro-1,4-naphthoquinone (1) with NH_4OH in ethanol afforded 2-amino-1,4-naphthoquinone. Successive substitution by Na2S in water gave 2-mercapto-3-amino-1,4-naphthoquinone (325). 2-mercapto-3-amino-1,4-naphthoquinone (325) reacted with aldehydes (328-331) to give 1,4-thiazine (337-340) in 65-82% yield. Similarly 325 reacted with 1, 326 and 327 affording 334, 335 and 336. 2,3-dichloro-1,4-naphthoquinone (1) produced 341 and 342 when reacted with 332 and 333 respectively; Scheme 69 [85].

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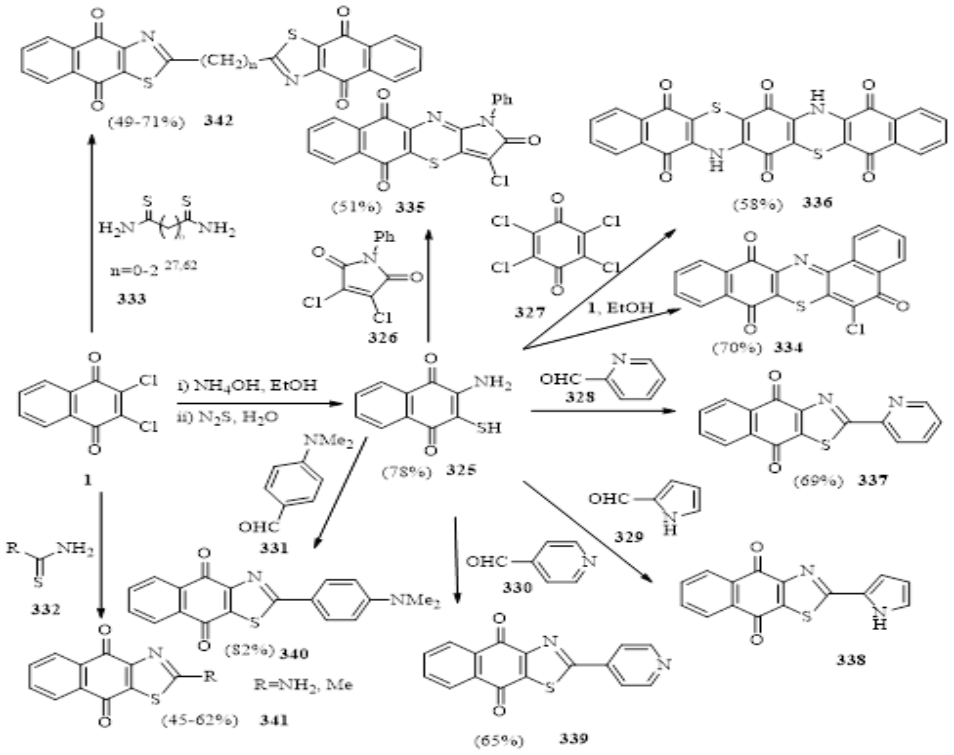
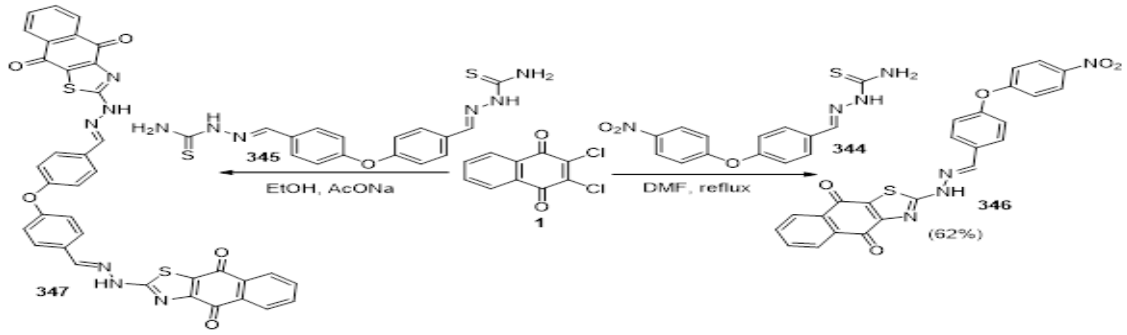


Scheme 69: Synthesis of various nitrogen and sulfur containing heterocyclic quinones.

Biologically active thiazole (346) and bisthiazole (347) derivative were prepared from the reaction of 1 with thiosemicarbazone (344) and 4,4'-bis thiosemicarbazone) diphenyl (345) ether respectively; Scheme 70 [86].



Scheme 70: Synthesis of biologically active thiazole (346) and bisthiazole (347) derivative

Treatment of 2,3-dichloro-1,4-naphthoquinone (1) with 2-(methylthio)aniline (348) produced 349 in 15% yield as shown in Scheme 72 [115] While the quinone 1 reacted with arylthiols (350) to produce 351 and 352 which on further reaction with sodium azide gave phenothiazine and related compound 349 and 353 in 78-79% yields [117]. However, Tandon et al. reported the synthesis of 2-anilino-3-thioaryl-1,4-naphthoquinone (354, 356) in methanol [47] in 60-99% yields as well as Tandon et. al. also explored various reaction of 1 with aryl amine followed by arylthiol in aqueous micelle and synthesized various biologically active compounds 354, 356 in 76-98% yield [48].

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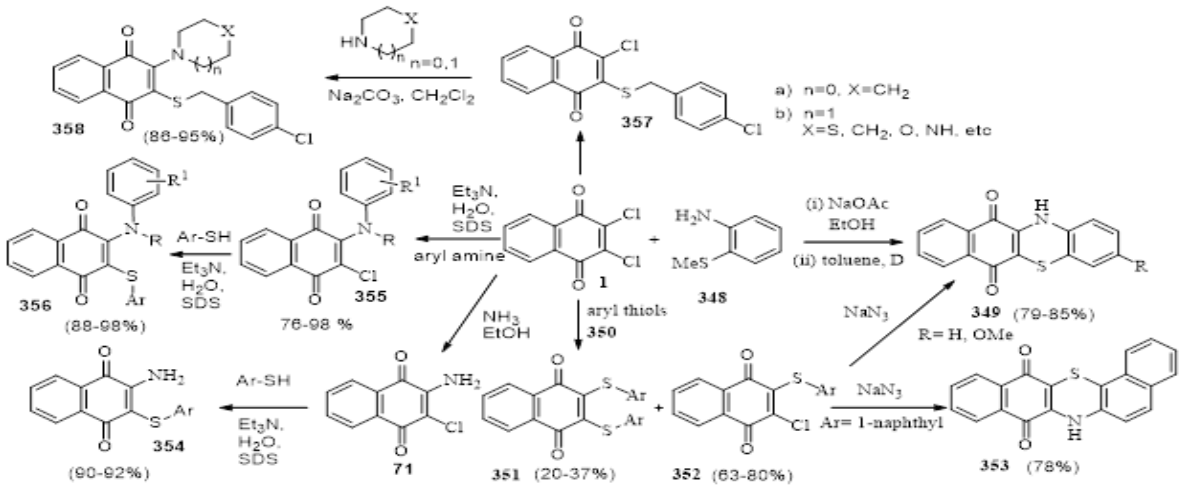
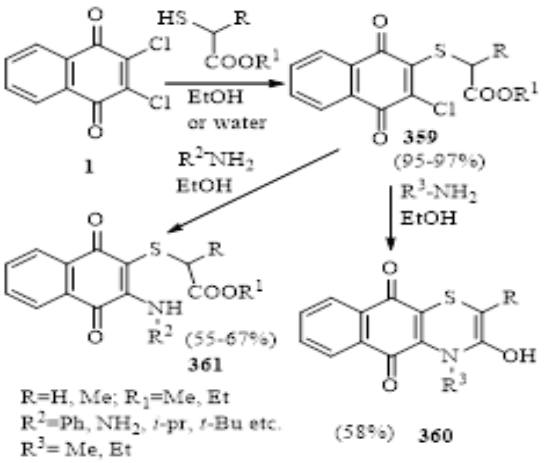
Ibis et. al. also reported sulfur 357 and nitrogen 358 containing analogues respectively [41]; Scheme 71.



Scheme 71: Synthesis of biologically active nitrogen and sulfur containing heteroquinones.



Scheme 72: Synthesis of biologically active naphthothiazine derivatives

The reaction of 2,3-dichloro-1,4-naphthoquinone (1) with thioalkanoic acid methyl and ethyl esters in EtOH [6] or in water [65,66] afforded 359 which on further reaction with primary amines produced naphthothiazine derivatives 360 or 3-substituted thioalkanoic acid methyl and ethyl ester derivatives of 1,4-naphthoquinone (361)in 55-67% yields; Scheme 72 [6].

3.2.10. With Nitrogen and Selenium Nucleophiles

2-Amino-3-chloro-1,4-naphthoquinoe (71) which was synthesized from 2,3-dichloro-1,4-naphthoquinone (1), on treatment with Na_2Se gave a green solution 362, which on further reaction with an aromatic aldehyde afforded 2-aryl-4,9-dioxonaphtho[2,3-*d*]selenazoles (363). The reaction of 362 with RX produced 364 and 365; Scheme 73 [81].

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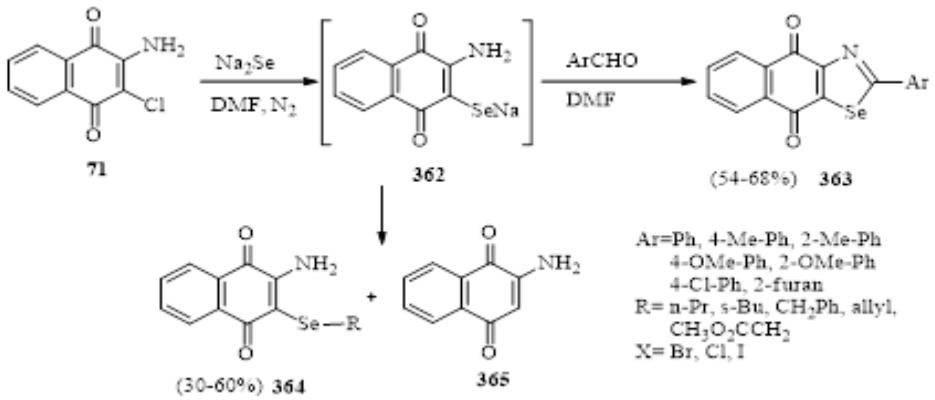
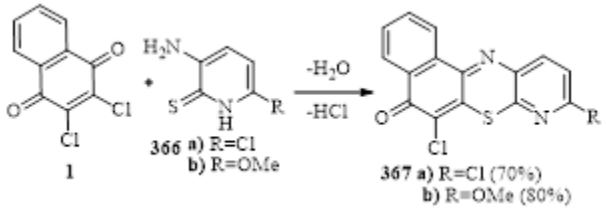


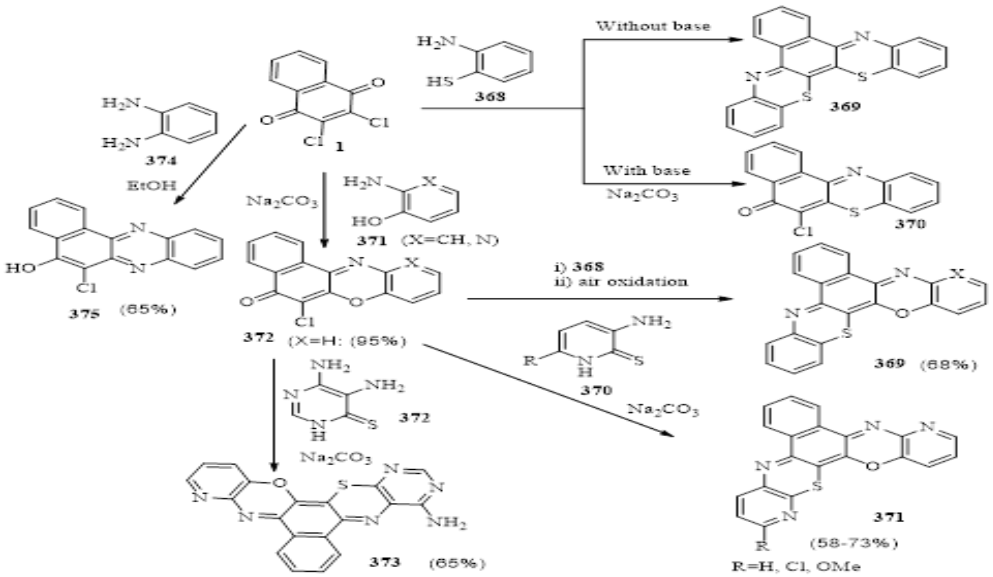
Scheme 73: Synthesis of naphtho[2,3-d] selenazoles.

3.3. Condensation Reactions of Carbonyl Group Of 2,3-Dichloro-1,4-Naphthoquinone



Scheme 74: Acid–catalysed reaction of 2,3-dichloro-1,4-naphthoquinone (1) with o-aminoheterocyclic thiones.

The acid–catalysed reaction of 2,3-dichloro-1,4-naphthoquinone (1) with o-aminoheterocyclic thiones (366a-b) in ethanol afforded 6,9-dichloro-5*H*-benzo[a]-8-azaphenothiazin-5-one (367a) and 9-methoxy-6-chloro-5*H*-benzo[a]-8-azaphenothiazin-5-one (367b) in 75 and 80% yield respectively; Scheme 74[118].



Scheme 75: Condensation reaction of aminothioles with 2,3-dichloro-1,4-naphthoquinone.

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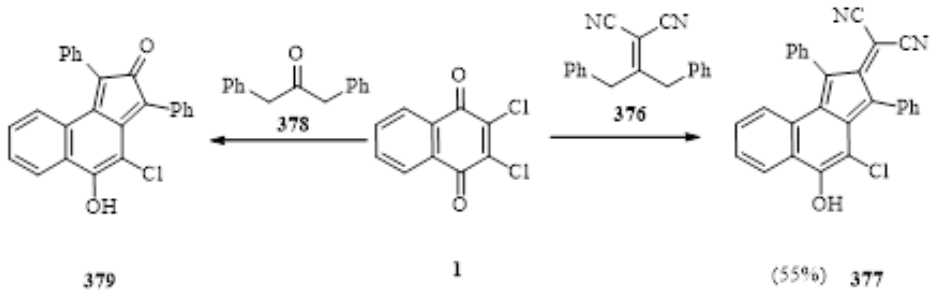
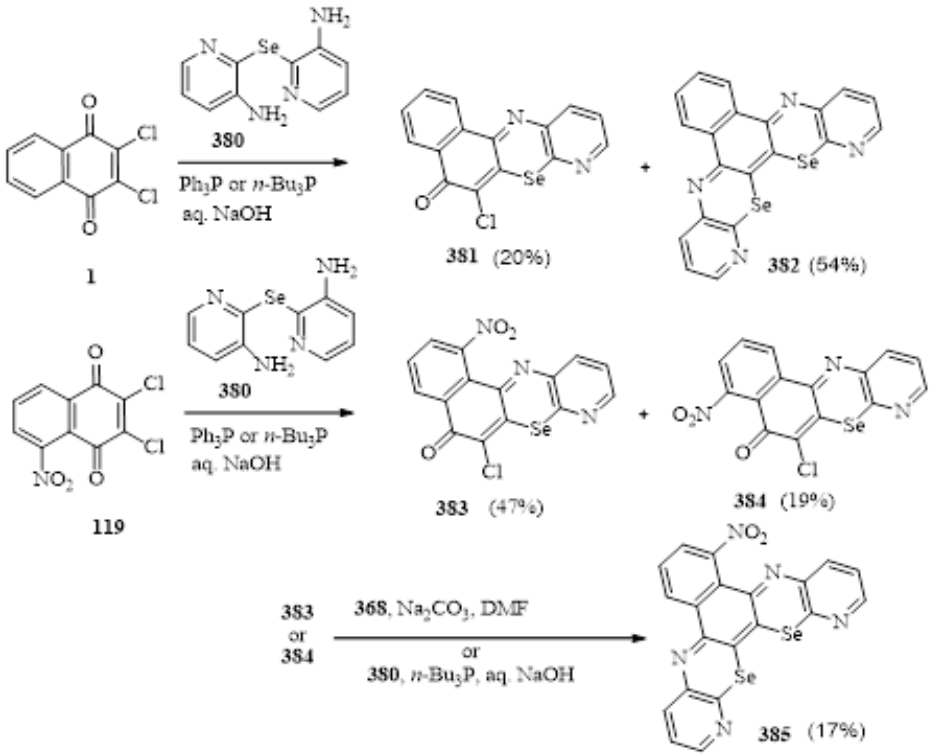
2,3-Dichloro-1,4-naphthoquinone (1) undergoes double condensation with 2-aminothiophenol (368) in the absence of a base to produce 369. However, in the presence of a base, mono condensation product 370 was formed. Reaction of 1 with aminophenols (371), with or without base produced only mono condensation product (372) which on further reaction with 368, 370 and 372 produced 369, 371 and 373 respectively; Scheme 75 [119]. The reaction of 1 and 2-phenylenediamine (374) in ethanol produced 6-chloro-5-hydroxybenzo[*b*]phenazine (375) in 65% yield [31].

The reaction of 2-dicyanomethylidene-1,3-diphenylpropane (376) with 2,3-dichloro-1,4-naphthoquinone (1) gave the 6,6-dicyanofulvene derivative (377) in 55% yield. The structure of 377 was found similar to 379 as compared with the model reaction of 1 with 1,3-diphenylacetone (378), Scheme 76 [120].



Scheme 76: Synthesis of fulvenes.



Scheme 77: Synthesis of selenium based heterocycles.

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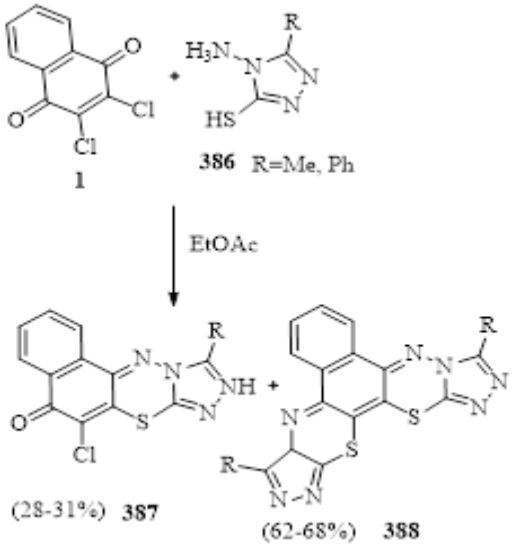
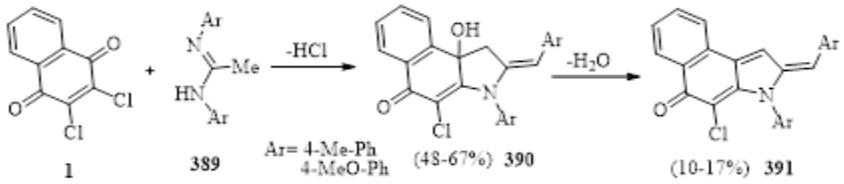
The reaction of 2,3-dichloro-1,4-naphthoquinone (1) with 3-amino-2-pyridineselenolate ion generated by 380 and triphenylphosphosphine afforded 381 and 382 in 61 and 18% yield respectively. Using tributylphosphine instead of Ph3P 381 and 382 was formed in 20 and 54% yield due to higher reducing property of Bu3P.



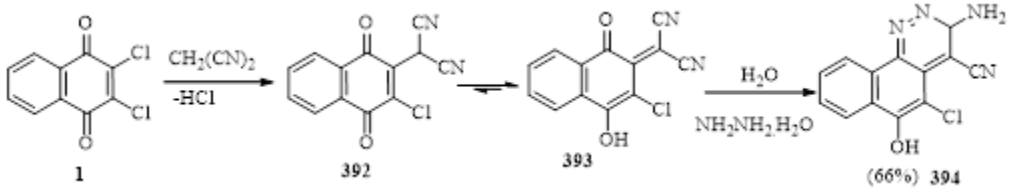
Scheme 78: Synthesis of naphthotriazolothiadiazinones

Treatment of 119 with 3-amino-2-pyridineselenolate ion (380) gave two regioisomer 383 and 384 in 47 and 19% yield respectively in the presence Ph3P and 30, and 18% in the presence of Bu3P. Further reaction of 383 and 384 with 2-aminothiophenol (368) or 3-amino-2-pyridineselenolate ion produced double condensed product 385; Scheme 77 [118]. In a similar manner, 1,2,4-triazole-3-thiols (386) condensed with 1 gave two products naphthotriazolothiadiazinones (387) and 388; Scheme 78 [121]. The mechanism of the formation of condensation products may be explained by elimination of HCl followed by cyclocondensation.

The condensation reaction of 2,3-dichloro-1,4-naphthoquinone (1) with acetamidine (389) afforded 390, which on further dehydration gave 391; Scheme 79 [32].



Scheme 79: Condensation reaction of 2,3-dichloro-1,4-naphthoquinone (1) with acetamidine



Scheme 80: Synthesis of cinnoline derivative.

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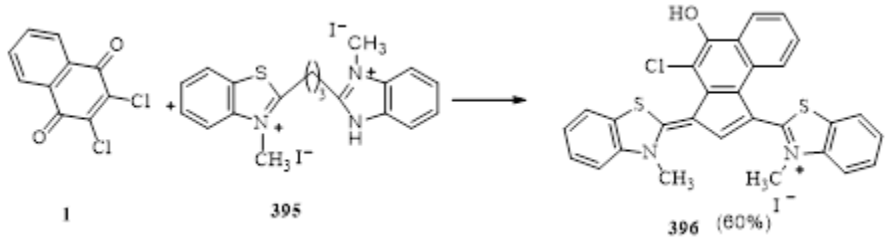
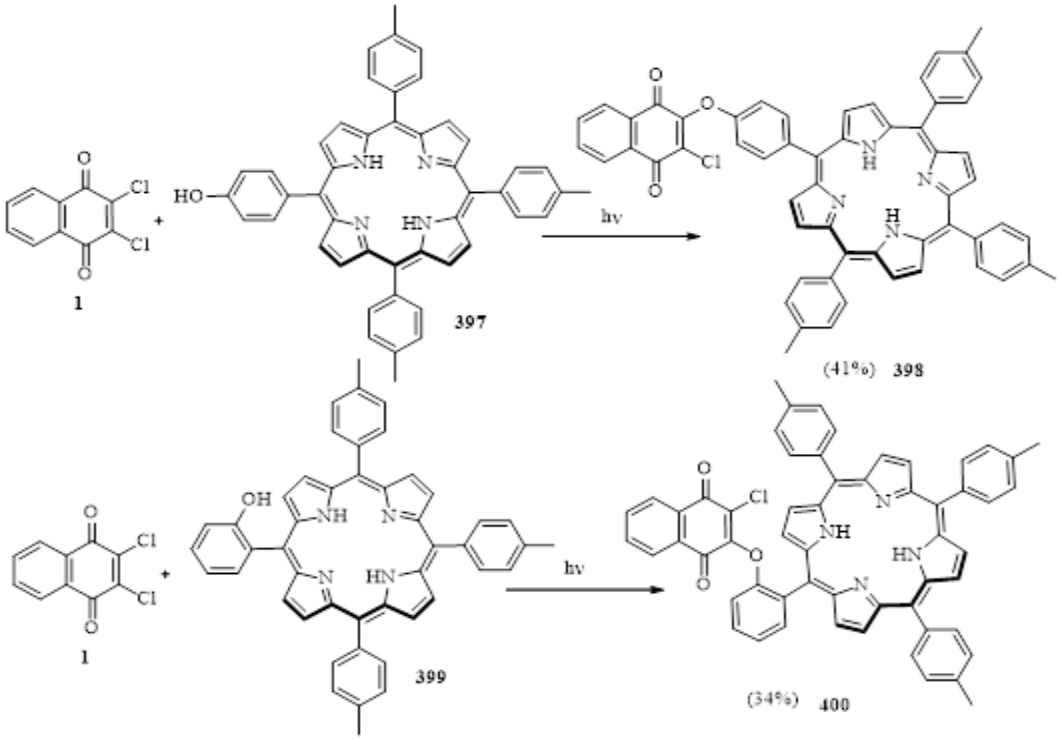


Scheme 81: Reaction of 2,3-dichloro-1,4-naphthoquinone with 1,3-bis(*N*-methyl-2-benzothiazolyl) propanediiodide (395).

When equivalent amounts of ylidene (392) (prepared by reaction of 1 with malononitrile) and hydrazine hydrate was mixed in ethanol and wormed for 5 minutes the cinnoline derivative (394) was formed; Scheme 80 [122].

2,3-Dichloro-1,4-naphthoquinone (1) reacted with 1,3-bis(*N*-methyl-2-benzothiazolyl) propanediiodide (395) to produce 396 in 60% yield; Scheme 81 [123].

3.4. Photo Induced Reaction of 2,3-Dichloro-1,4-Naphthoquinone



Scheme 82: A photo induced reaction of 2,3-dichloro-1,4-naphthoquinone with porphyrin.

A typically, irradiated (λ>590 nm) chloroform solution of porphyrin 397 and 399 in the presence of 2,3-dichloro-1,4-naphthoquinone (1) under argon gave the quinone-substituted porphyrin 398 and 400 in 41 and 34% yield respectively; Scheme 82 [124].Further photo induced reaction of quinone (1) with porphyrins (401) at >590 nm radiation in benzene produced 402; Scheme 83[125].

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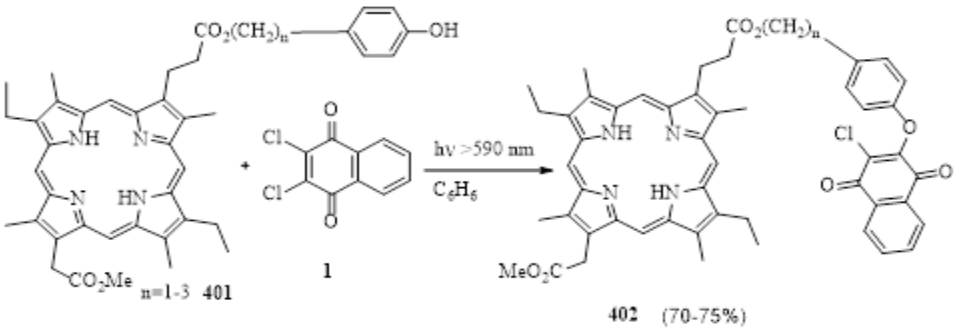
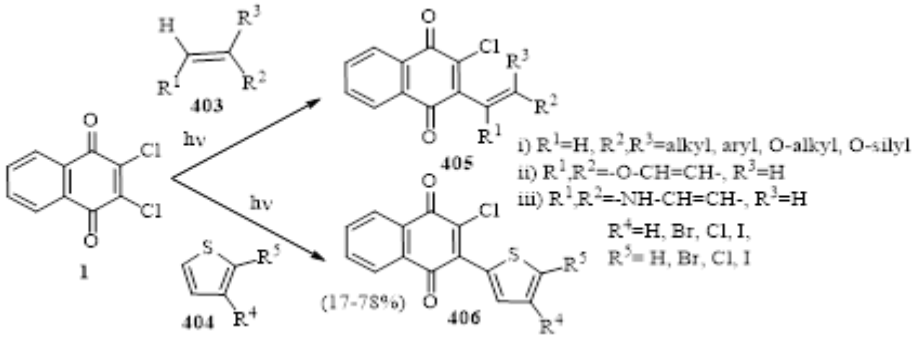


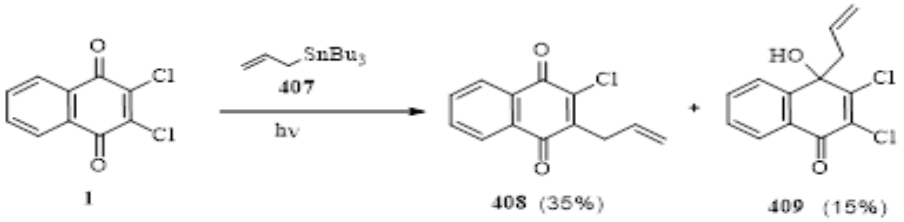
Scheme 83: Photoinduced synthesis of porphrin-napthoquinone combined product 402.



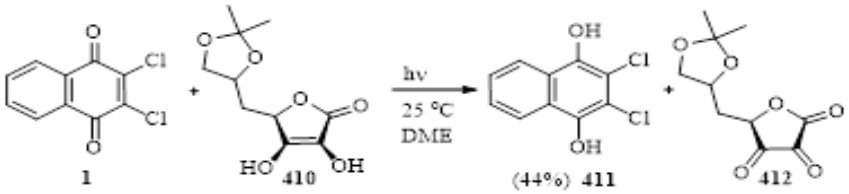
Scheme 84: Photochemical reaction of 2,3-dichloro-1,4-naphthoquinone (1) with olefins (403) and thiophenes (404)

Photochemical reaction of 2,3-dichloro-1,4-naphthoquinone (1) with olefins (403) and thiophenes (404) produced 405 and 406 respectively; Scheme 84 [126].

Photochemical reaction of 2,3-dichloro-1,4-naphthoquinone (1) with allyltributylstannane (407) in benzene gave 408 and 409 in 35 and 15% yields respectively while in acetonitrile were formed in 12 and 26% yields; Scheme 85 [127].



Scheme 85: Photochemical reaction of 2,3-dichloro-1,4-naphthoquinone (1) with allyltributylstannane (407)



Scheme 86: Photoinduced reduction of 2,3-dichloro-1,4-naphthoquinone (1)

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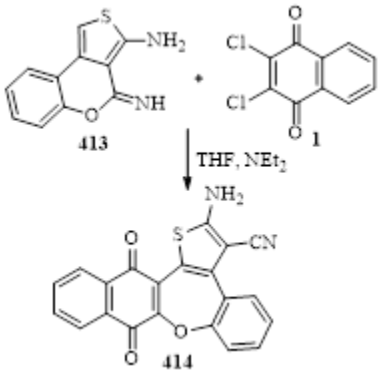
Upon irradiation with UV light, instead of the Paterno-Buchi reaction, 5,6-O-isopropylidene-L-ascorbic acid (410) reduced 2,3-dichloro-1,4-naphthoquinone (1) in hydroquinone (411) in 44% yield; Scheme 86 [128].

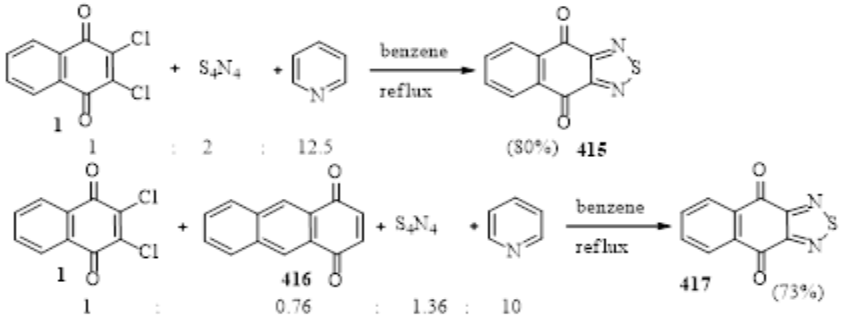
3.5. Miscellaneous Reactions of 2,3-Dichloro-1,4-Naphthoquinone

The thienocoumarin (413) and 2,3-dichloro-1,4-naphthoquinone (1) in refluxing THF in the presence of triethylamine produced 414; Scheme 87 [53].



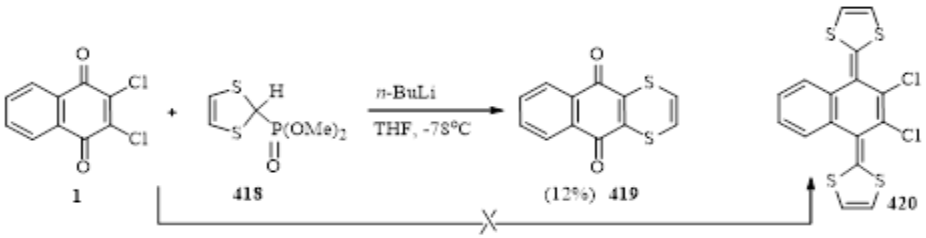
Scheme 87: Synthesis of benzo[f]naphtho[2,3-b]thieno[2,3-d]oxepine.

2,3-Dichloro-1,4-naphthoquinone (1) (1 mmol) on fusion with S_4N_4 (2 mmol) in the presence of pyridine (12.5 mmol) gave 415 in 80% yields while adding 416 produced compound 417 in 70% yields; Scheme 88 [16].



Scheme 88: Synthesis of naphtho[2,3-*c*] [1,2,5]thiadiazole-4,9-dione

The reaction of 1,3-dithiol-2-ylphosphonate esters (418) with 2,3-dichloro-1,4-naphthoquinone (1) produced 1,4-dithiin (419) in 12% instead of 420 as outlined in Scheme 89 [129].



Scheme 89: Synthesis of 1,4-dithiin (419).

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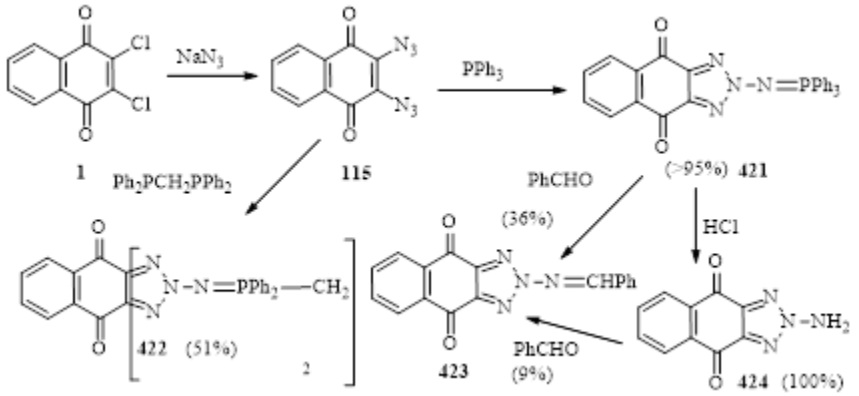
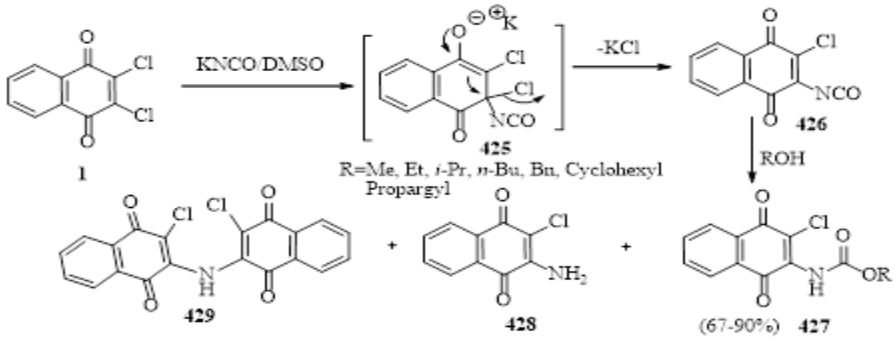
Triphenylphosphine was reacted with 2,4-naphthoquinone diazide (115) to form phosphorane of 2-amino-1,2,3-triazole derivative (421). Which undergoes an aza-Wtting reaction with benzaldehyde to form 423 and hydrolyzed to form 2-amino-1,2,3-triazole (422). While diazide (115) reacted with bis(diphenylphosphine)methane to form (421); Scheme 90 [130].

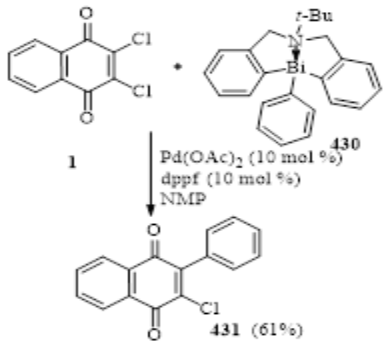


Scheme 91: Synthesis of 2-(benzylideneamino)-2*H*-naphtho[2,3-*d*] [1,2,3]triazole-4,9-dione

The reaction of potassium cyanate with 2,3-dichloro-1,4-naphthoquinone (1) in DMSO or DMF afforded the unstable naphthoquinonyl isocyanate (426), for stabilization alcohol was added which gave product 427 in 67-90% yields and byproducts 428 and 429. The naphthoquinonyl isocyanate (426) was proceeds via Michael addition of the isocyanate anion with the quinone (1) followed by KCl elimination and rapid reaction with alcohol lead to the formation of carbamate (427); Scheme 91 [131].



Scheme 91: Michael addition of the isocyanate anion with the quinone (1).



Scheme 92: Cross coupling reaction of 2,3-dichloro-1,4-naphthoquinone (1)

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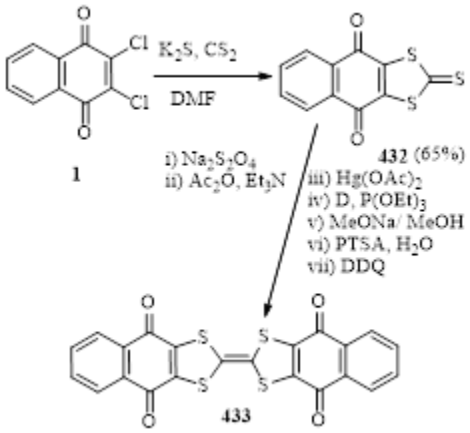

Scheme 93: Synthesis of tetrathiafulvalene.

Cross coupling reaction of 2,3-dichloro-1,4-naphthoquinone (1) with hypervalentorgano- bismuth compound 6-tert-butyl-5,6,7,12-tetra- hydrodibenz[*c,f*][1,5]azabismocine (430) was efficiently catalyzed by the $Pd(OAc)_2$/dppf and produced 431 in 61% yields; Scheme 92 [132].

Dumur et al. reported the synthesis of tetrathiafulvalene (433) from 432 in seven steps; scheme 93 [133]. Compound 432 was synthesized from 1 by reaction with CS2 in presence of K_2S.

4. Biologically Active Compounds Synthesized from 2,3-Dichloro-1,4-Naphthoquinone and Analogs

Quinone is an important pharmacophore for various well established drugs and biologically active compounds such as Lavendamycin (434) [134], Doxorubicin (435) [135], Adriamycin (436) [136], Mitoxanthrone (437) [137], Menadione (438) [138], Plumbagin (437) [139], Lapachol (440) [140], Streptonigrin (441) [141], Juglone (442) [142] (Figure 2) etc. A large number of biological active compounds were

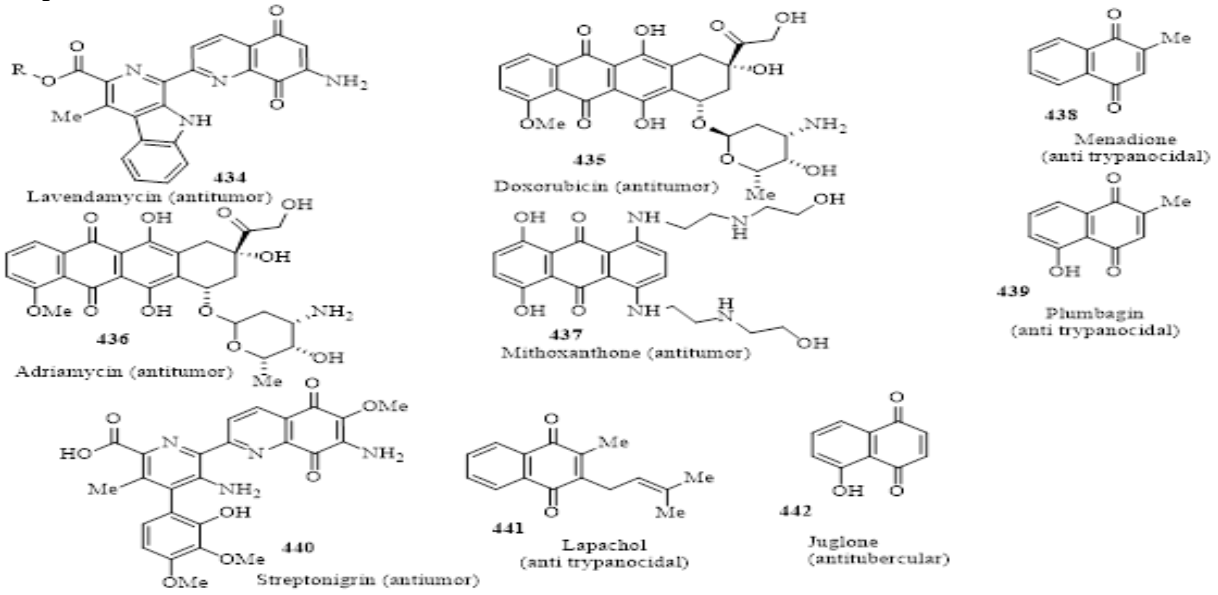

Figure 2: Naturally occurring biologically active quinone analogs

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synthesized from 2,3-dichloro-1,4-naphthoquinone (1) as reported above (Scheme 1-93). We have summarized in this review potent biologically active compounds synthesized from 2,3-dichloro-1,4-naphthoquinone (1), as a versatile pharmacohore.

4.1. Antibacterial Agents

Compound 443-447 [6] and 448 [7] have been found to possess marked antibacterial activity against various bacterial pathogens. Compound 444 (IC_{50} =1.18 μg/mL) and Compound 447 (IC_{50} =1.92 μg/mL) have been found to possess potent antibacterial activity against E. Coli, and Staphylococcus aureous respectively (Figure 3) and compound 453 possessed 3.00 μg/mL activity against K. pneumonia and S. aureus [66] while compound 454 reported 7.8 μg/mL antibacterial activity against M. Luteum [41].

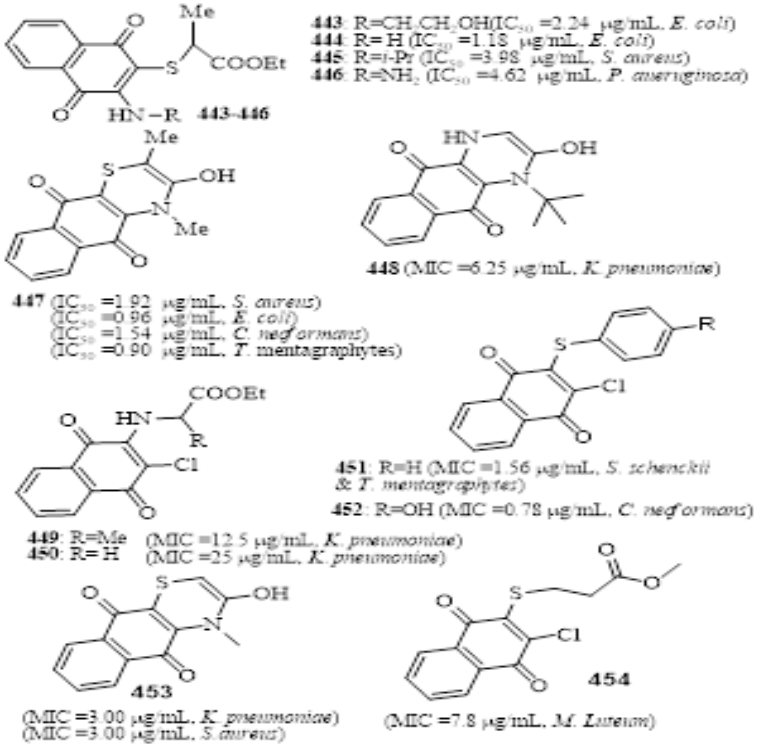

Figure 3: Potent antibacterial and antifungal agents.

Bisthiazole and thiazole derivative (455, 456) showed moderate antibacterial activity (0.6-2.4 cm) towards Staphylococcus aureous bacillus (NCTC-14579), Serratia marcesens (IMRU-70) and Bacillus cereeus (NCTC-14579) [86c], Figure 4.

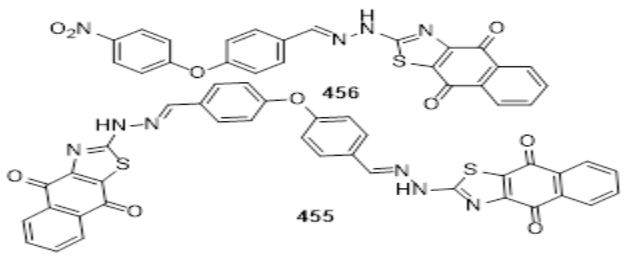

Figure 4: Antibacterial agents

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4.2. Antifungal Agents

Compound 443-452 [6, 7, 47, 117,] have reported significant antifungal activity. Compound 447 has been exhibited potent antifungal activity against Cryptococcus neoformans (IC_{50}=1.54 µg/mL) and Trichophyton mentagraphytes (IC_{50}=0.90 µg/mL). Compound 449 [75,103] has been found to possess potent antifungal activity against Sporothrix schenckii (MIC= 1.56 µg/mL) and Trichophyton mentagraphytes (MIC= 1.56 µg/mL) and compound 450 [47] has been also shown potent antifungal activity against Cryptococcus neoformans (MIC= 0.78µg/mL), Figure 3.

Aryl naphthoquinone ethers (457-462) have found to posses potent antifungal activity against S. schenckii and T. mentagraphytes (MIC=0.78-3.12 µg/mL) [112]; Figure 5.

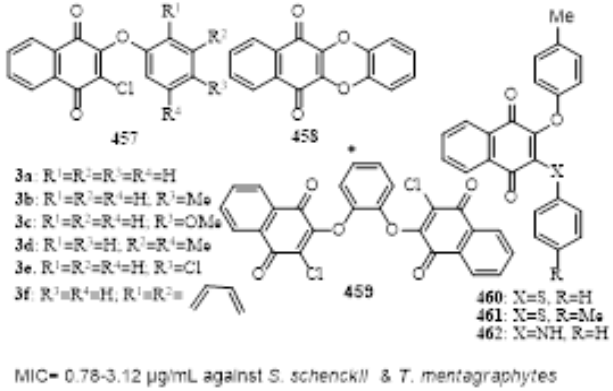

Figure 5: Antifungal agents.

Santos et. al. evaluated antifungal activity of naphtho[2,3-d]isoxazole-4,9-diones (463-464) against various ATCC and PYCC reference strains of Candida and reported MIC value upto 0.2 µg/mL [113] and compound 454 exhibited potent antifungal activity against C. tenuis (MIC 1.9 µg/mL) [41]; Figure 6.

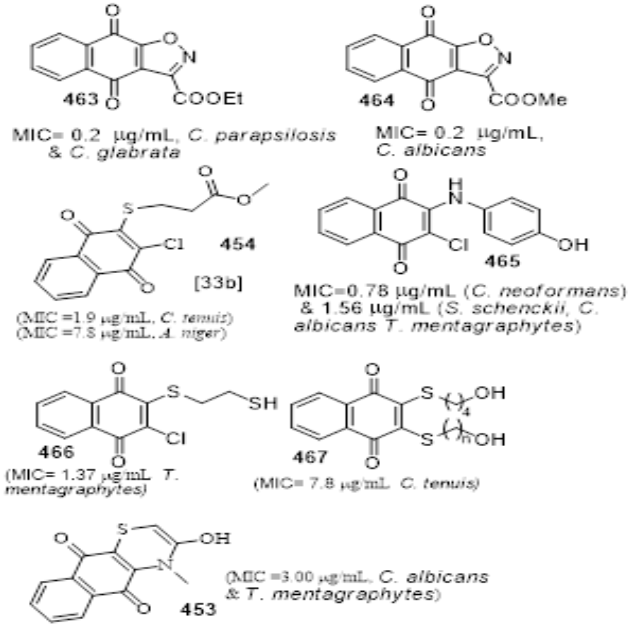

Figure 6: Potent Antifungal agents

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While Tandon et. al. reported 2-Chloro-3-(4-hydroxyphenylamino)naphthalene-1,4-dione (465) as promising antifungal agent against C. neoformans (MIC50=0.78 µg/mL), S. schenckii (MIC50 1.56 µg/mL), C. albicans (MIC50 1.56 µg/mL), T. mentagraphytes (MIC50 1.56 µg/mL) and A. fumigatus (MIC50 3.12 µg/mL) [92] while compound 453 found 3.00 µg/mL activity against T. mentagraphytes as well as compound 466 found 1.37 µg/mL activity against T. mentagraphytes [140] and compound 467 shown 7.8 µg/mL activity against C. tenuis [90].

Ryu et. al [97] were tested in vitro growth inhibitory activity of benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones (468) in against pathogenic fungi C. albicans, C. tropicalis, C. krusei, C. neoformans, A. niger, A. flavus and found MIC up to 3.2µg/mL, Figure 7.

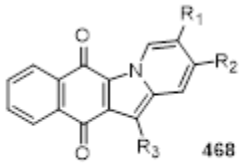

Figure 7: Growth inhibitory antifungal study.

4.3. Anti-Platlet, Anti-Inflammatory and Anti-Allergic Agents

Compounds 469 were reported promising antiplatlet (10-20 µg/mL), anti-inflammatory (0.03-0.1 µg/mL) and antiallergic activities (0.03-0.1 µg/mL). The structure activity relationship explored by Lien et al. to investigate compound 470 [100]. Hung et al. synthesized compound 471-473 which were found to possess antiplatlet, anti-inflammatory and antiallergic activities [148], In which compound 472 was lead compound at 20 µg/mL and completely inhibited the platelet aggregation induced by thrombin (0.1 unit/mL), arachidonic acid (AA) (100 FM), collagen(10 µg/mL) and platelet activating factor (PAF) (2ng/mL), Figure 8.

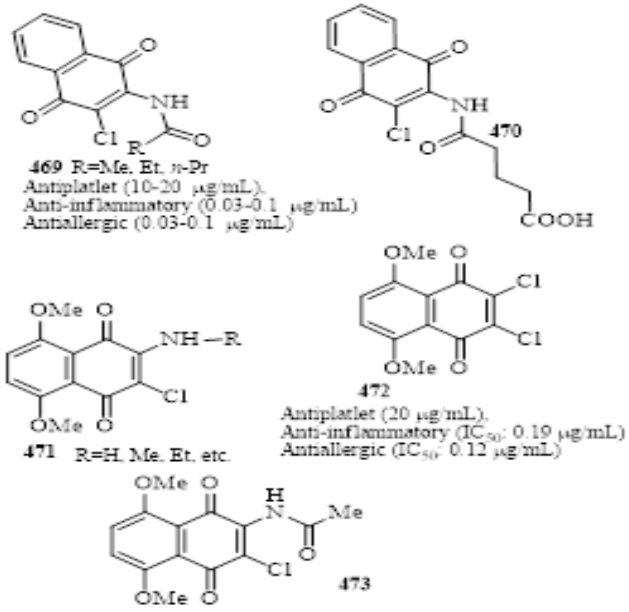

Figure 8: Anti-platlet, anti-inflammatory and anti-allergic agents

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4.4. Anticancer Agents

Lawrence et. al. synthesized chloronaphthoquinone and sulfonamide moieties containing naphthoquinone derivative (474) and studied CT-L, T-L and PGPH inhibition. In which compound was found to possess pronounced CT-L activity 1.0 μM and docking study displayed their binding side, Figure 9 [71].

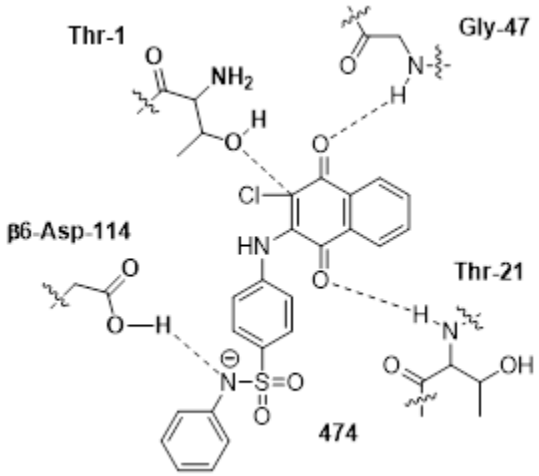

Figure 9: Binding side of quinine 474

Xu et al. [52c] have modified PI083 (Figure 9) and found anticancer activity (IC 50= 1.30 μM) against Kbvin cell line of compound 475 while compound 476 shown inhibition of the chymotrypsin-like activity of 20S proteasome (IC50= 3.65 μM) [72].

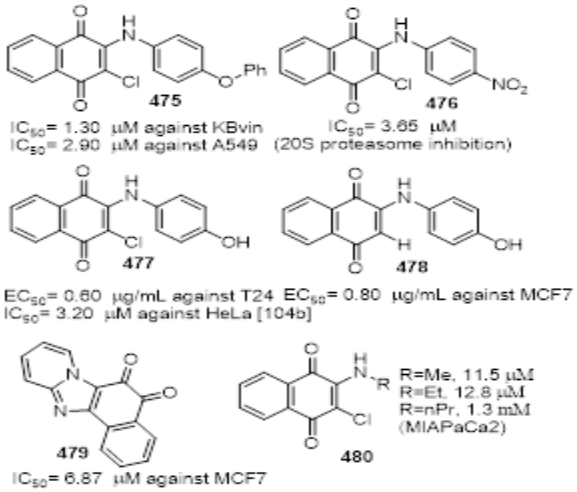

Figure 10: Selected anti-cancer agents

Several members of the phenylamino-1,4-naphthoquinones were explored cytotoxic effects of the aminoquinones (EC_{50}) against cancer cell lines MCF7, DU145, T24 cells and healthy fibroblasts (BALB/3T3) with the EC_{50} upto 0.6 μg/mL and observed that cytotoxicity of phenylamino naphthoquinones (477, 478) depends upon the nature of the donorphenyl and the acceptor quinone groups [46].

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Tandon et. al identified an active naphthoquinone 477 that potently induce apoptosis in human cervical carcinoma (HeLa) cells and perturbed both microtubule and actin filaments [66]. 4a,11-Diazabenzo[3,2-a] fluorene-5,6-dione (479) showed (IC50= 6.87 μM) against MCF7 cell line [77], Figure 10. While 2-alkyl-3-chloro-1,4-naphthoquinone (480) were showed anti-proliferative activity 1.3 mM to 12.8 μM against carcinoma cell line MIAPaCa2 [140].

Cheng et al. synthesized several benzo[*b*]naphtha[2,3-*d*]furan-6,11-dione (481-482) and studied marked antineoplastic activity against HL-60, SCLC and CDDP cell line [106, 110]; Compounds 482b and 482c were found to possess pronounced activity IC_{50} =0.046 and 0.045 μM against HL-60 cell line. Figure 11.

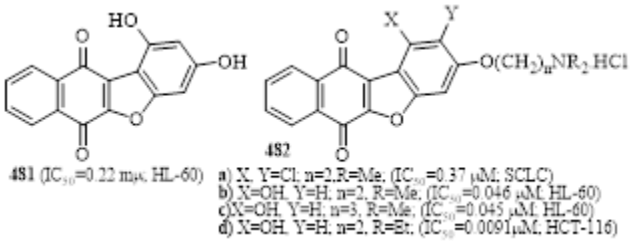

Figure 11: Benzo[b]naphtha[2,3-d] furan-6,11-diones as anticancer agents.

Indolylquinone derivatives (483) in human gastric (AGS), lung (SK-MES-1), bladder (J82) cancer cell lines shown IC50 value upto 20.3 μM [93]; Figure 12.

Luo et. al. reported antineoplactic activity of compound 484-485 against human promyelocytic leukemia cells (HL-60). Compound 485b was found to possess promising activity (IC_{50}=0.17μM) in the entire series of compounds [100]; Figure 12. The various derivative of compound 485 were further explored the anticancer activity against cancer cell line lung (A549), stomach (SNU-638), colon (HCT116), fibro sarcoma (HT1080) and myeloid leukemic (HL-60) by SRB assay method with IC50 value up to 0.0091 μM. and all the tested compounds showed very low topo I inhibitory activity. At 5 μM concentration, most of compounds showed over 50% inhibitory activity against topo II compound 485d and two other derivative shown topo II inhibition at 5 μM better than clinically useful drug doxorubicin (5 μM, 78% inhibition) [106].

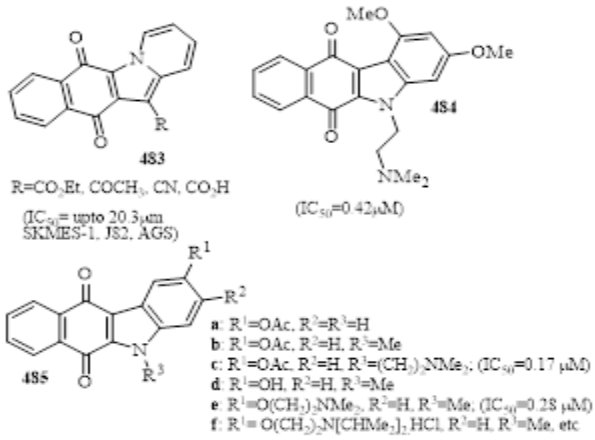

Figure 12: Indolylquinone as anticancer agents

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1-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl) pyrrolidine-2,5-dione (486) exhibited MeK1 inhibitory activity (IC50=0.38μg/mL) better than PD098059 487 (IC_{50}=3.8μg/mL) [141]. Compounds 79a-e were found to possess potent anticancer activity (IC_{50} range= 0.001-1.03μM) better than ellipticine (IC50 range= 1.88-5.80 μM) against human lung (A549), human colon (Co12), human stomach (SNU-638), human fibrosarcoma (HT1080) and human myeloid (HL-60) cancer cell lines. Compound 79a, 79d and 79f also shown potent cytotoxicity (IC_{50} range=0.003-0.34 μM) better than doxorubicin (IC_{50} range= 0.20-0.39 μM) against human ovarian (SK-OV-3), human melanoma (SK-MEL-2), human CNS (XF-498) and human colon (HCT 15) cancer cell lines [55]; Figure 13.

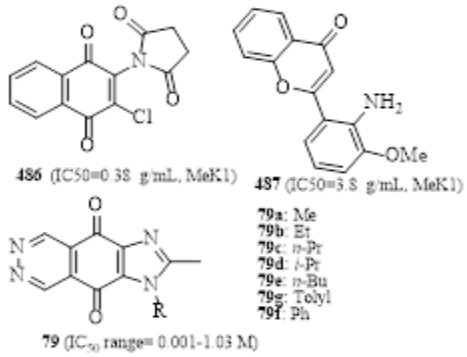

Figure 13: Cytotoxicity against MeK1, A549, CO12, SNU638, HT1080, HL60 carcinoma cell line.

Compound 337 (IC_{50}=0.049 μM) and 338 (IC_{50}=0.067μM) exhibited promising antineoplastic activity against HL-60 cancer cell line [56]; Figure 14.

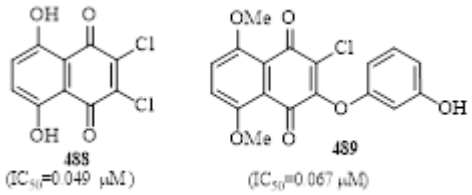

Figure 14: Cytotoxicity against HL-60 cancer cell carcinoma cell line.

Based on the structure of the Kinamycin, active against a broad range of tumor, the cytotoxicity of benzo[*f*]indole-4,9-dione derivatives and related compound towards several human carcinoma cell lines was studied. Compound 490 and 491 were found to possess promising antitumor activity (ED_{50} range=0.04-0.27 μg/mL) against A549, SK-OV-3, SK-Mel-2, XF-498 and HCT 15 carcinoma cell lines [101]; Figure 15.

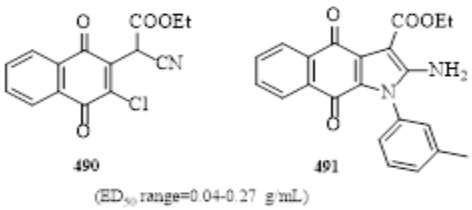

Figure 15: Cytotoxicity against A549, SK-OV-3, SK-Mel-2, XF-498 and HCT 15 carcinoma cell lines.

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Based on the antitumor activity of Streptonigrin Kim et al. synthesized and studied cytotoxicity of compounds 492 and 493 against various cancer cell line (A 549, SK-OV-3, SK-MEL-2, XF 498, HCT 15). Compound 493d (IC_{50}=0.16 μM) and 493f (IC50=0.20 & 0.06 μM) showed in vitro antitumor activity comparable to doxorubicin against human ovarian tumor cells (SK-OV-3) and CNS cells (XF 498) [45]; Figure 16.

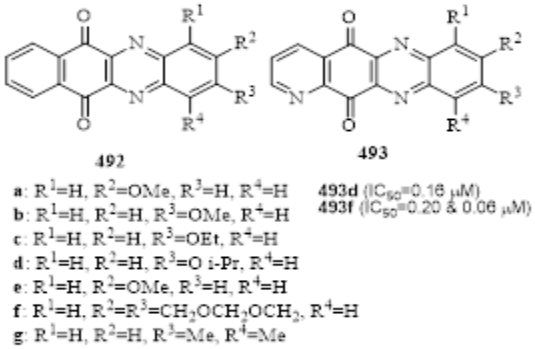

Figure 16: Cytotoxicity against human ovarian tumor cells (SK-OV-3) and human CNS cells (XF 498) carcinoma cells.

Lee et al. synthesized and evaluated antitumor activity of compounds 494. Compound 494 (a-i) shown cytotoxic activities against the variety of human tumor cell lines. compound 494h (ED_{50} range=0.01-0.02 μg/mL) against A549, SK-OV-3, SK-MEL-2 and HCT 15 cancer cell lines were found better than doxorubicin (ED50 range=0.02-0.18 μg/mL) [102]; Figure 17. Compound 495-500 were synthesized and also explored for their in vitro enzymatic inhibition using recombinant fused MBP-CDC25B3. Compound 495 was found to possess better activity [IC_{50}=1.75 μM] amongst all studied compounds [58]; Figure 17.

Bis(methoxycarbonylmethylthio)naphthaquinone (501) was shown 1.17 μM inhibitory activities against CDC25 cancer cell line [86b] while 2,3-bis-arylsulfanyl- [1,4] naphthoquinones (502) found 100 % inhibitory activity towards HeLa cell line at 20 μM concentration [117].

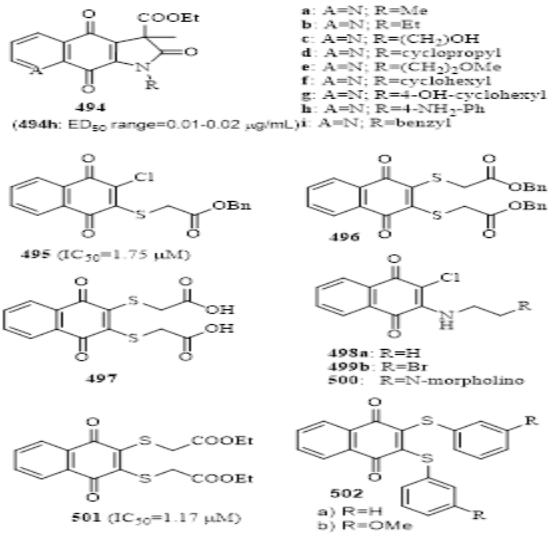

Figure 17: Cytotoxicity against various carcinoma cell lines.

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A series of dinaphtho[1,2-b;2'3'-*d*] furan-7,12-dione derivatives were synthesized and explored inhibitory activity against receptor tyrosine kinases. The compound 503 (IC_{50}=2.8 μM) showed better activity than tyrphositn A51 (IC_{50}=4.1 μM) against epidermal growth factor receptor (EGFR) [108]; Figure 18.

Several benzofuroquinolinediones were synthesized and evaluated for in vitro cytotoxic activities against various human tumor cell lines (lung; A549, stomach; SNU-638, colon; HCT116, fibro sarcoma; HT 1080, myeloid leukemic; HL-60, ovarian; SK-OV-3, melanoma; SK-MEL-2 and CNS; XF-498). Compound 504d (IC50=0.02 □M) was shown to posses seven fold better activity than doxorubicin (IC_{50}=0.15 μM) against A549 cancer cell line and compound 504c-d (IC_{50} range=0.07-0.08 μM) were shown ten fold better activity than doxorubicin (IC_{50}=0.62 μM) against HCT 116 cancer cell line [110]; Figure 18.

Wang et. al. [116] synthesized naphthoquinone fused cyclic α-aminophosphonates (505) and evaluated for in vitro cytoxic activity against cell lines HeLa, Hep2, and LoVo IC_{50} value upto 0.018 μM and found catalytic inhibitors of topoisomerase II, Figure 18.

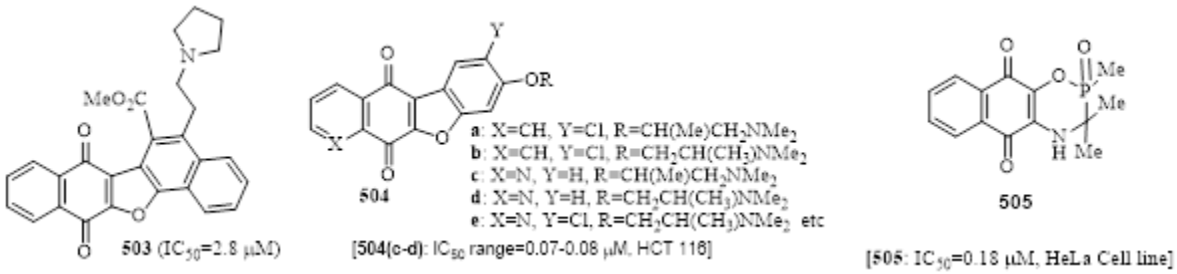

Figure 18: Cytotoxicity of benzofuroquinolinediones.

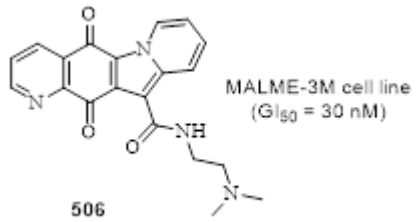

Figure 19: Selective inhibition against the melanoma MALME-3M cell line.

Defant et. al. [96] explored anticancer activity against human tumor cell lines panel (59 cell lines) and reported *N,N*-anti compound 506 as a higher activity than its *N,N*-syn isomer, exhibiting the best selective inhibition against the melanoma MALME-3M cell line (GI_{50} =30 nM) corresponding to a 330-fold increase in activity compared to the corresponding deaza-analogue, Figure 19.

4.5. Anti HIV Agents

Several pyranylated binapthoquinones (507) and simple binaphthoquinones (508) were synthesized and studied for their anti HIV activity using MTT assay. Compound 507a (ID_{50}=0.62 μM) was shown better anti HIV activity than other derivatives [30]; Figure 20.

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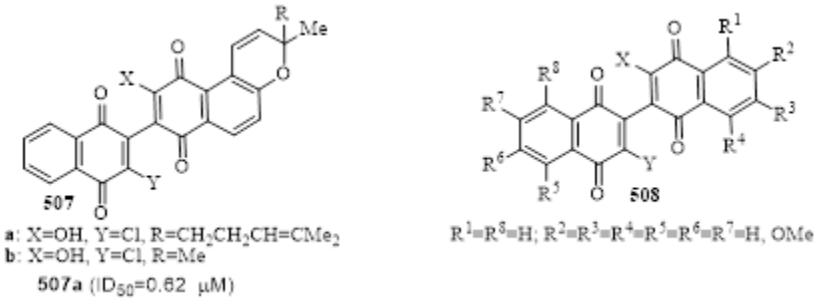


Figure 20: Anti HIV study of pyranylated binapthoquinones.

4.6. Anti Trypanosidal

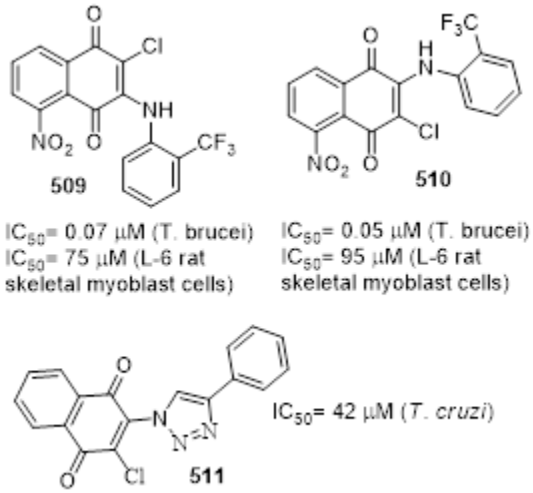
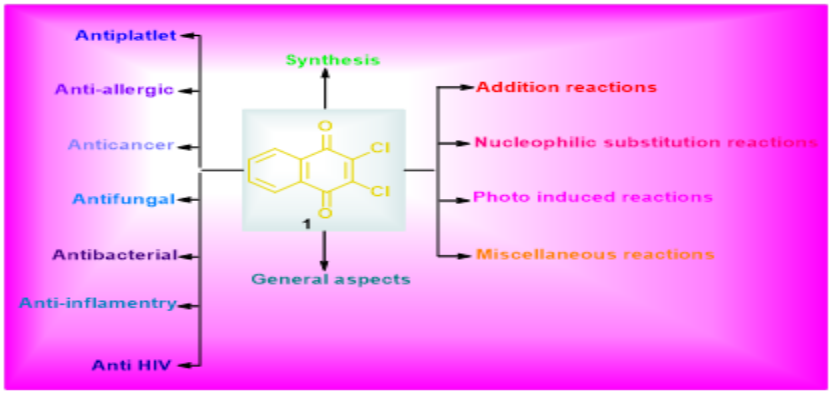


Figure 21: Anti trypanosidal naphthoquinones.

Compounds 509-510 showed excellent Trypanosoma brucei inhibitory activity with low cytotoxicity and found that electron withdrawing group such as NO2,CF3 and Cl and electron density rich groups (phenylamine ring and aromatic ring) at particular positions on the naphthoquinone as the backbone structure are important to *T.* brucei inhibitory activity [67] while trizole compound 511 have shown 42 μM activity against *T.* cruzi. [74]; Figure 21.



Graphical abstract

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5. Conclusion

A variety of hetero-1,4-naphthoquinones have synthesized through nucleophilic substitution, cycloaddition, condensation and photo induced methods and were found to posses good to excellent biological activity as antifungal, antibacterial, anticancer, anti HIV, anti trypanosidal etc and exploring regularly in the search of more potent biological active naphthoquinone derivative.

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This review dedicated to Prof. Vishnu K. Tandon, Ex Head & Dean, Department of Chemistry, Lucknow University, Lucknow, India.

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