Aminonaphthoquinones in Heterocyclization

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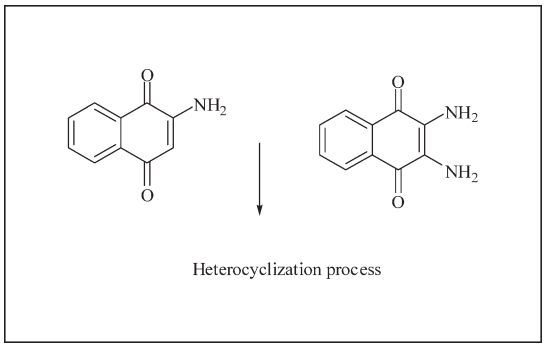

Because of the interesting biological activities of aminonaphthoquinones, in this review we survey two classes of amino-1,4-naphthoquinones: 2,3-diamino-1,4-naphthoquinone and 2-amino-1,4-naphthoquinone. The review includes synthetic methodologies for these classes in addition to their heterocyclization processes.

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Contents

1. INTRODUCTION

Naphthoquinones are widely distributed in plants, fungi, and some animals. Their biological activities have been studied including their effects on prokaryotic and eukaryotic cells [1,2]. Plumbagone, juglone, and lawsone are naturally occurring naphthoquinones of plant origin that have antibacterial effects on several species of both aerobic and anaerobic organisms [3], and toxins derived from naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) are produced by *Fusarium solani* and attack plants, other fungi, and bacteria [4]. The natural naphthoquinone products alkannin and shikonin and their derivatives, in general, are active against Gram-positive bacteria such as *Staphylococcus aureus*, *Enterococcus faecium*, and *Bacillus subtilis*, but are inactive against Gram-negative bacteria [5]. 2,3-Diamino-1,4-naphthoquinone itself was found to act as an antibacterial agent against *S. aureus*, with IC_{50} values ranging from 30 to 125 μg/mL. 2,3-Diamino-1,4-naphthoquinone presented a minimal bactericidal concentration higher than 500 μg/mL, indicating that its effect was bacteriostatic [6].

Carnivorous plants have evolved special mechanisms for trapping insects and consuming their components when grown under harsh conditions [7]. Carnivory is also characterized by the synthesis of secondary metabolites in the insect-trap tissues, which contain the aminonaphthoquinone moiety [8]. The synthesis of protecting secondary metabolites is very common in many plants and occurs in response to chemical, biotic or physical stress [8–10].

Aminonaphthoquinones, considered to be potential antifungal drugs, are also produced by many plants that belong to the Caryophyllales families [8], including Nepenthaceae [11], Droseraceae [12], Plumbaginaceae [13], Drosophyllaceae [14], and Ebenaceae [15]. *In vitro* assays showed that several 2,3-di-substituted 1,4-naphthoquinones are as effective as the clinically used antifungal drugs fluconazole and amphotericin-B [16].

In addition, the 4-aminoquinolines (chloroquine [CQ] for adults/amodiaquine for children) have been used as the first-line antimalarial drugs for many years. However, the therapeutic efficacy of the 4-aminoquinolines, particularly of CQ, has declined over the years [17] since the mid-70s [18].

Malaria is a major tropical disease, which kills 2 million people annually. As antimalarials are the major arsenal for treatment of the disease, there is an urgent need for newer drugs with novel mechanisms of action, which will be effective against all strains of the parasite. Several synthetic and natural naphthoquinones as potential antimalarial agents have identified aminonaphthoquinones, as a class of antimalarial compounds with antimalarial activity against *Plasmodium falciparum*. Among these compounds, 2-amino-3-chloro-1,4-naphthoquinone is the most potent. It had an IC_{50} of 0.18 μ*M* (37.3 ng mL^{-1}) against the W2 clone, and is more potent than CQ, which had an

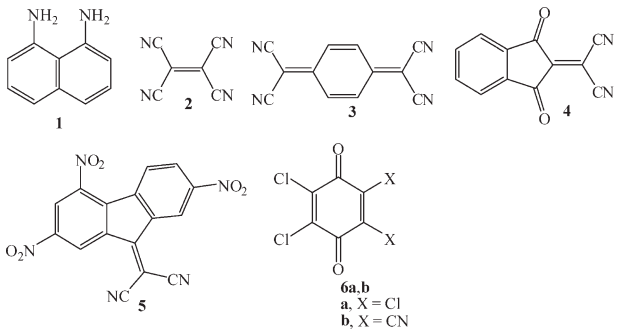


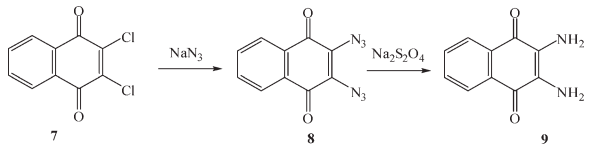
Figure 1. Reactions of 1,8-diaminonaphthalene (**1**) (as a structural resembled analogous) with π-acceptors.

IC_{50} of 0.23 μ*M* (72 ng mL^{-1}). It was also active against the D6 clone. In general, 2-amino-1,4-naphthoquinone analogs and the 4-amino-1,2-napthoquinone analog showed promising antimalarial activity in the bioassay. In contrast, a number of 2-hydroxy-1,4-naphthoquinones and dimeric quinones were less active [19].

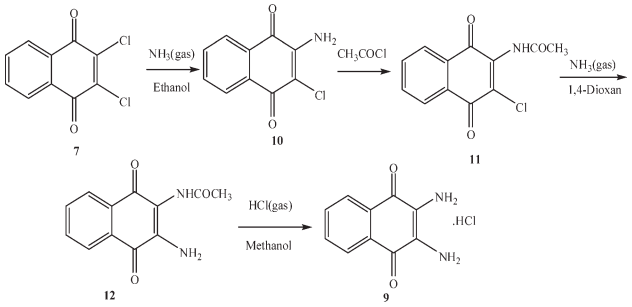
The synthesis and investigation of tumor-inhibitory activity of a series of aminonaphthoquinone derivatives of diospyrin (a bisnaphthoquinone), which was isolated from *Diospyros montana* Roxb., have been reported [20]. An aminoacetate derivative showed the maximum (~93%) increase in life span *in vivo* against murine Ehrlich ascites carcinoma (EAC) at a dose of 1 mg kg^{-1} day^{-1} (ip; five doses), and the lowest IC_{50} (0.06 μ*M*) *in vitro*. Further, the same analog also exhibited considerable enhancement in antiproliferative activity when evaluated against human cell lines, *viz*., malignant skin melanoma and epidermoid laryngeal carcinoma (IC_{50} = 0.06 and 0.92 μ*M*, respectively) in comparison to the natural precursor, diospyrin (IC_{50} = 0.82 and 3.58 μ*M*, respectively). Moreover, diospyrin and all its derivatives were found to show significantly greater (~17- to 1441-fold) cytotoxicity against the tumor cells as compared with normal human lymphocytes. All these quinonoids generated substantial amounts of reactive oxygen species in EAC cells, more or less commensurate to their respective IC_{50} values [20].

Previously, Aly and El-Shaieb [21] investigated the reaction of 1,8-diaminonaphthalene (**1**) (as a structural resembled analogous to 2,3-diamino-1,4-naphthoquinone) with π-acceptors. Various heterocyclic compounds were obtained during the addition of compound **1** to 1,1,2,2-tetracyanoethylene (TCNE, **2**), 7,7′,8,8′-tetracyanoquinodimethane (TCNQ, **3**), 2-dicyano-methyleneindane-1,3-dione (CNIND, **4**), 2-(2,4,7-trinitro-9*H*-fluoren-9-ylidene)propane-dicarbonitrile (DTF, **5**), 2,3,5,6-tetrachloro-1,4-benzoquinone (CHL-*p*, **6a**), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, **6b**) (Fig. 1) [21]. Although most of the examples herein involve cyclization reactions of aminonaphthoquinones, a few of these expected novel syntheses of heterocycles have been reported. So, it is of interest to report on the vital target class of compounds [21].

Scheme 1



Scheme 2



2. DISCUSSION

In the light of the aforementioned interesting biological activities of aminonaphthoquinones, our attention is turned to investigate the routes of synthesis of 2,3-diamino-1,4-naphthoquinone and 2-amino-1,4-naphthoquinone. In additon, we report on the utility of these two substances in heterocyclization.

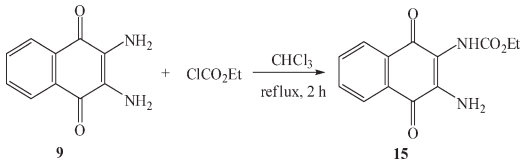
2.1. 2,3-Diamino-1,4-naphthoquinone.

2.1.1. Synthesis. Reaction of 2,3-dichloro-1,4-naphthoquinone (**7**) with 2 equiv of sodium azide produced in good yield the diazido derivative **8** [22], which was reduced with $Na_2S_2O_4$ to give the compound **9** (Scheme 1) [23,24].

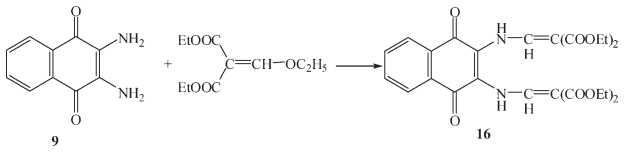
Díaz *et al*. used the published procedure [25] of the synthesis of intermediated compounds **10–12** (Scheme 2) [25]. Thereafter, addition of hydrochloric acid gas in methanol to **12** produced the corresponding salt of compound **9** as shown in Scheme 2 [25].

Winkelmann [26] reported that reaction of compound **7** with 2 equiv. of potassium phthalimide proceeded to afford diphthalimido naphthoquinone **13**, which was allowed to react with hydrazine hydrate to give compound **9** (Scheme 3) [26].

Scheme 5



Scheme 6



2.1.2. Reactions.

2.1.2.1. Substitution reaction. Treatment of 2,3-diaminonaphthalene-1,4-dione (**9**) with benzoyl chloride in chloroform afforded *N*-(3-amino-1,4-dioxo-1,4-dihydronaphthalen-2-yl)benzamide (**14**; Scheme 4) [27].

Similarly, reaction of compound **9** with ethyl chloroformate afforded ethyl 3-amino-1,4-dioxo-1,4-dihydronaphthalen-2-ylcarbamate (**15**, Scheme 5) [28].

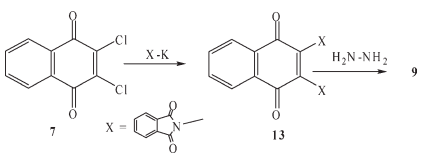
Reaction of compound **9** with diethyl 2-(ethoxymethylene)-malonate gave in good yield tetraethyl 2,2′-(1,4-dioxo-1,4-dihydronaphthalene-2,3-diyl)bis(azanediyl)bis-(methan-1-yl-1-ylidene)-dimalonate (**16**) as shown in Scheme 6 [29].

Heating of compound **9** in acetic anhydride for 2 h produced 1,4-dioxo-1,4-dihydro-naphthalene-2,3-diyl)-diacetamide (**17**) as shown in Scheme 7 [28].

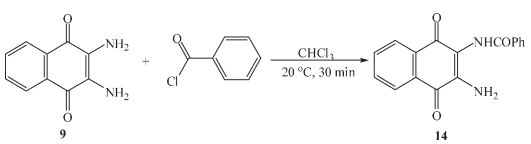
Benzoylation of compound **9** was achieved by refluxing **9** with 2 equiv. of benzoyl chloride in *p*-xylene for 2 h. The dibenzoyl product of **9**, identified as *N*,*N*′-(1,4-dioxo-1,4-dihydronaphthalene-2,3-diyl)dibenzamide (**18**), was obtained in good yield (Scheme 8) [30].

2.1.2.2. Synthesis of imidazoles. Compound **9** reacted with potassium xanthogenate to give 2-thioxo-2,3-dihydro-1*H*-naphtho[2,3-*d*]imidazole-4,9-dione (**19**). Various

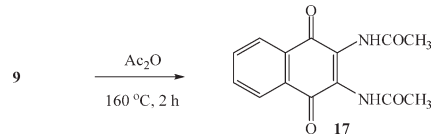
Scheme 3



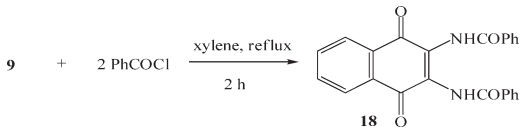
Scheme 4



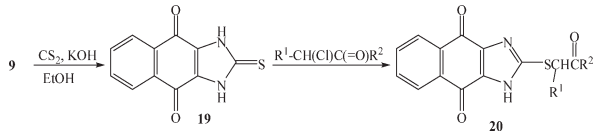
Scheme 7



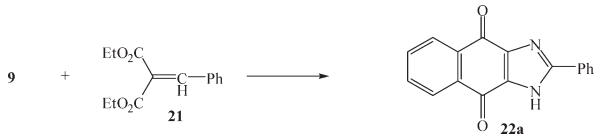
Scheme 8



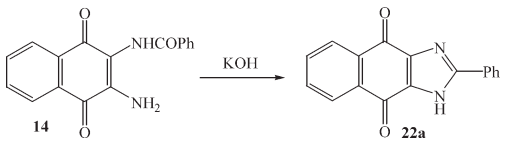
Scheme 9



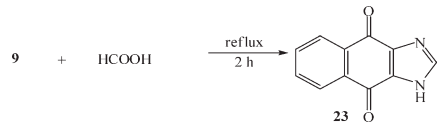
Scheme 10



Scheme 11



Scheme 12



2-(2-oxoalkylthio)-1*H*-naphtho[2,3-*d*]-imidazole-4,9-diones **20** were obtained by the reaction of **19** with α-halo carbonyl compounds as shown in Scheme 9. Eleven examples were described [30].

Reaction of compound **9** with diethyl 2-benzylidenemalonate (**21**) afforded 2-phenyl-1*H*-naphtho[2,3-*d*]imidazole-4,9-dione (**22a**) as shown in Scheme 10 [29].

Imidazole **22a** was also obtained *via* the reaction of 2-amino-3-benzoylamino-1,4-naphthoquinone (**14**) with alcoholic KOH for 3 h (Scheme 11) [30].

On refluxing a mixture of compound **9** in formic acid for 2 h, the reaction afforded in poor yield 1*H*-naphtho[2,3-*d*]imidazole-4,9-dione (**23**) as shown in Scheme 12 [30].

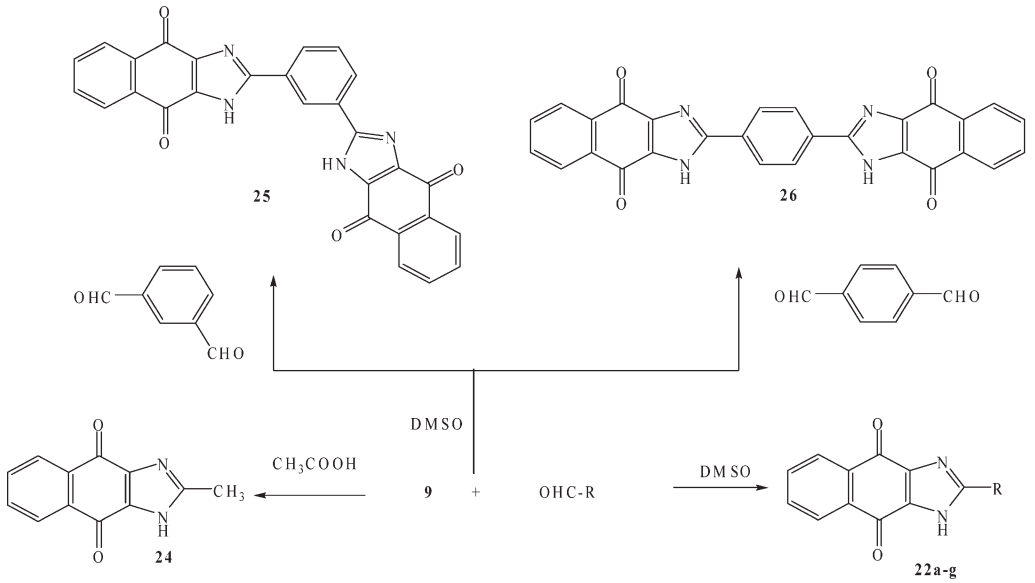
Aly *et al*. [31] have recently reported that imidazoles derived from compound **9** were easily directly prepared by addition of stoichiometric quantities of the appropriate aldehydes in dimethyl sulfoxide as a solvent as shown in Scheme 13 [31]. The reaction proceeds in few hours to give mono- and bis-imidazoles **22a–g**, **25**, and **26**. That procedure can be generalized to different classes of aldehydes. 2-Methyl-1*H*-naphtho[2,3-*d*]imidazole-4,9-dione (**24**) was also obtained, by refluxing in acetic acid [31].

2.1.2.3. Synthesis of thia- or selena-diazole derivatives. Compound **9** reacted with thionyl chloride or selenium oxychloride to afford the corresponding thia- or selenadiazole derivatives **27a**,**b** as shown in Scheme 14 [32]. Either compound **27a** and/or **27b** can then be condensed with substituted hydrazines and/or hydroxylamine hydrochloride to give compound **28a**,**b** and/or **29** (Scheme 14) [32].

2.1.2.4. Synthesis of fused pyridine derivatives.

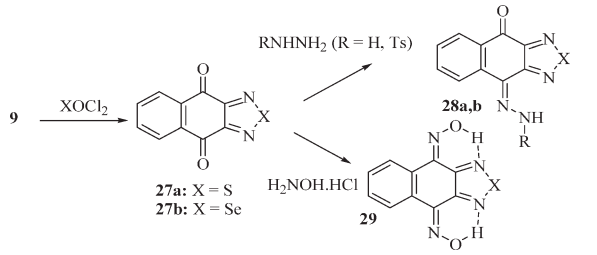
2.1.2.4.1. Synthesis of Discorhabdin C. A model study designed for the total synthesis of Discorhabdin C (**30**) is presented (Fig. 2). The key reaction is the para alkylation of the phenolate derived from the dibromomesyloxy

Scheme 13



a: R = C_6H_5- (85%); **b**: R = 4-H_3C-OC_6H_4- (90%), **c**: R = 4-Cl-C_6H_4- (80%); **d**: R = 3,4-O-CH_2-OC_6H_3- (94%); **e**: R = 2-Furyl (76%) and **f**: R = 4-[2.2]Paracyclophanyl (74%)

Scheme 14



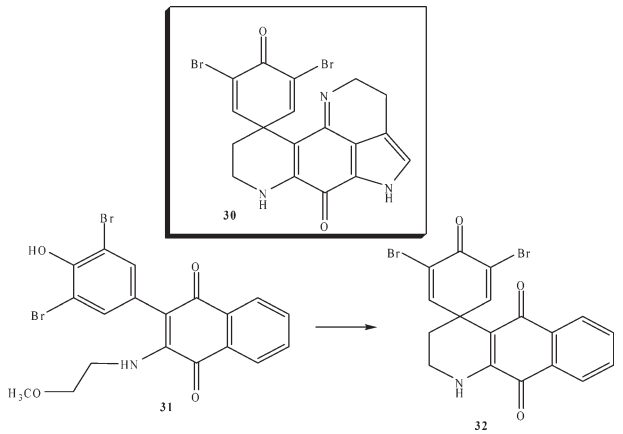


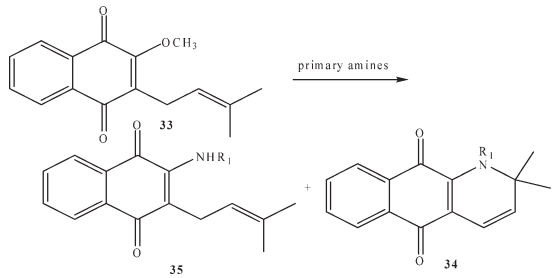
Figure 2. Synthesis of Discorhabdin C.

phenol **31**. The desired product **32** (Fig. 2) contains the tetracyclic aza-spirobicyclic system present in this class of marine alkaloids [33].

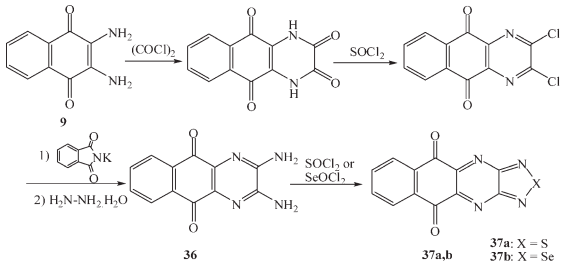
2.1.2.4.2. Synthesis of 1-aza-anthraquinones. A series of 1-aza-anthraquinones **34** were characterized, besides the expected *N*-alkylamino derivatives **35**, from the substitution reactions of 2-methoxylapachol (**33**) with primary amines. An investigation of the reaction conditions allowed reasonable selectivity in the products distribution (Scheme 15) [34].

2.1.2.5. Synthesis of quinoxalinediones. Interestingly, reaction of **9** with oxalyl chloride afforded the tetralone, which directly reacted with thionyl chloride to give the dichloride followed by Gabriel reaction to obtain compound **36**, which was directly reacted with thionyl chloride, to yield compound **37a**. The reaction of **36** with

Scheme 15



Scheme 16



selenium oxychloride produced compound **37b** as shown in Scheme 16 [35].

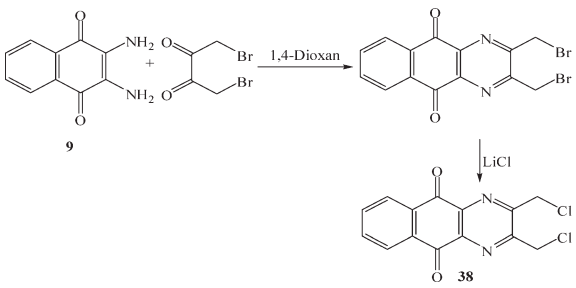
Condensation of compound **9** with 1,4-dibromobutane-2,3-dione led to 2,3-bis(bromo-methyl)-benzo[*g*]quinoxaline-5,10-dione [36], which was converted to compound **38** by classical chlorination using lithium chloride as illustrated in Scheme 17 [36].

Reaction of compound **9** with α-dicarbonyl compounds afford 2,3-disubstituted benzoquinoxaline-5,10-diones **39** as shown in Scheme 18 [36].

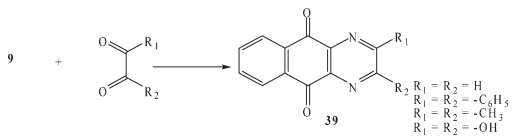
It was reported that refluxing of compound **9** with 1,2-di(1*H*-pyrrol-2-yl)ethane-1,2-dione (**40**) in glacial acetic acid for 12 h afforded 2,3-di(1*H*-pyrrol-2-yl)-benzo[*g*]-quinoxaline-5,10-dione (**41**) as illustrated in Scheme 19 [37]. Refluxing of **9** with naphthalene-1,2-dione (**42**) in 10% acetic acid for 2-3 h gave dibenzo[*a*,*i*]phenazine-8,13-dione (**43**, Scheme 19) [37]. Similarly reaction of **9** with phenanthrene-9,10-dione (**44**) produced tribenzo[*a*,*c*,*i*]phenazine-10,15-dione (**45**, Scheme 19) [37]. Benzo[*i*]dipyrido[3,2-*a*:2′,3′-*c*]phenazine-10,15-dione (**47**) can be obtained from the reaction of **9**.HCl with 1,10-phenanthroline-5,6-dione (**46**) in refluxing ethanol for 1.5 h (Scheme 19) [37–39].

It was indicated that different aromatic aldehydes can react with 2,3-diamino-naphthalene-1,4-diol to yield 2,3-

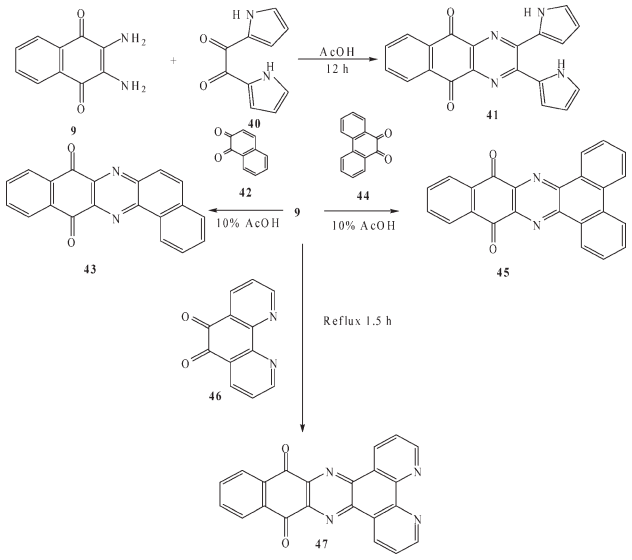
Scheme 17



Scheme 18



Scheme 19



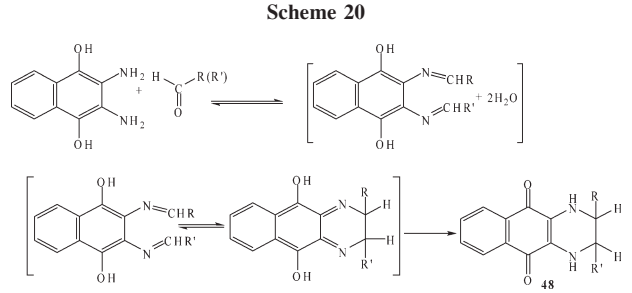
disubstituted 1,2,3,4-tetrahydrobenzo[*g*]-quinoxaline-5,10-diones **48** as shown in Scheme 20 [40].

Katritzky [41] and his group reported that the reaction of compound **9** with 2,3-dichloro-naphthalene-1,4-dione (**7**) in absolute ethanol afforded dibenzo[*b*,*i*]phenazine-5,7,12,14(6*H*,13*H*)-tetraone (**49**) as shown in Scheme 21 [41].

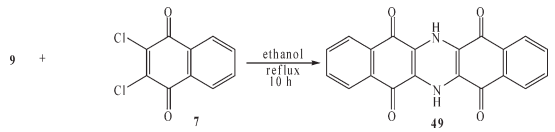
2.1.2.6. Synthesis of diazepine derivatives. Compound **9** reacted with various derivatives of diethyl malonate to afford condensed products, which in the presence of potassium hydroxide gave 3-substituted 1*H*-naphtho[2,3-*b*][1,4]diazepine-2,4,6,11(3*H*,5*H*)-tetraones **50** as illustrated in Scheme 22 [27].

A rapid route to a series of naphthoquinone-fused indole derivatives **51** (Fig. 3) *via* irradiation in a modified commercial domestic microwave was reported [42]. The desired products were produced in high yields and short reaction times. The naphthoquinone-fused indole derivatives **51** were evaluated for their proinflammatory cytokines responses using lipopolysaccharide (LPS)-stimulated RAW264.7 marine macrophages. The results showed that most of the tested compounds inhibit the production of nitric oxide (NO), prostaglandin (PG)E_2,

Scheme 20



Scheme 21

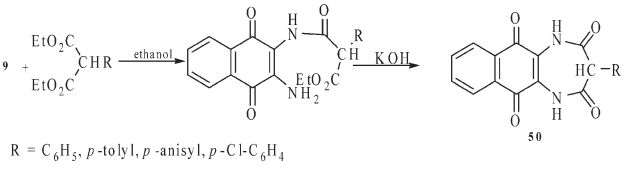


tumour necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1β in RAW264.7 cells treated with LPS [42].

Reaction of 2,3-bis(arylamino)naphthalene-1,4-diones **52** (1 equiv.), aldehydes (1.1 equiv.) and $BF_3.Et_2O$ (2 equiv.) in acetonitrile afforded the diazepine derivatives **53** and **54** (Scheme 23) [43]. The reaction involves the formation of iminium ion intermediates, followed by cyclization to produce seven-membered rings (Scheme 23). Thirteen examples were described [43].

2.2. Chemistry of 2-amino-1,4-naphthoquinone. It was previously reported that the nucleophilicity of the amino group in **55** is greater than expected for its vinylogous amide structure. Thus, 2-amino-1,4-naphthoquinone (**55**) reacts as an *N*-nucleophile with some bis-electrophiles [44]. On the other hand, Michael addition between **55** and activated unsaturated bonds is differed from those generally found in β-imino-α,β-unsaturated carbonyl compounds [45]. These results indicate that the mesomeric interaction between the nitrogen lone pair and the C=O group in **55** is not very important and, consequently, *C*-alkylations proceeding on the enol tautomer **55′** (Fig. 4) through the electronic interaction of the lone pair on the nitrogen atom with the quinoid structure, are less favored than in related systems. The mesomeric effect explains the shift of the $E_{1/2}$ value of **55** (at pH 7.0) of *ca*. 225 mV to more negative potential, as compared with unsubstituted naphthoquinone [46]. However, this value might be also explained by a

Scheme 22



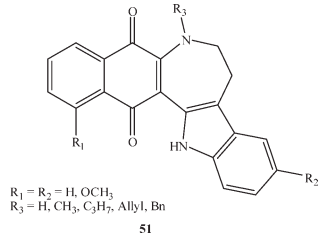
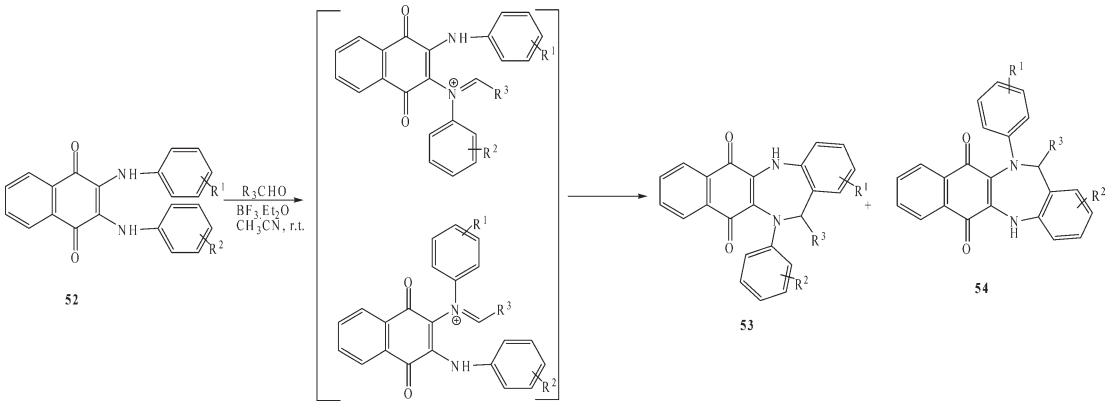


Figure 3. Structure of naphthoquinone-fused indole derivatives **51**.

Scheme 23



hydrogen bond interaction between the C^1=O and NH_2 groups, stabilizing the quinoid form (**55**″, Fig. 4) [47].

For instance, the intramolecular *N*-acylation of some aminoquinones has required their prior reduction to the more basic aminonaphthohydroquinone derivatives [48,49]. Lately, 2-amino-1,4-naphthoquinone (55) has been shown to have some reactivity with some electrophiles such as β-dielectrophiles [50], and methyleniminium salts (Fig. 5) [50]. In these reactions, the principal product was found to be that of *N*-alkylation. The reaction of **55** with electrophiles follows the general sequence outlined in Figure 5. The reaction follows path ''a'' leading to *N*-alkylated product **57** or path ''b'' leading to *C*-alkylated product **58**. In these reactions, the principal product was found to be that of *N*-alkylation. The reaction of **55** with electrophiles follows the general sequence outlined in Figure 5 [51].

2.2.1. Synthesis. 2-Amino-1,4-naphthoquinone (**55**) can be prepared by the reaction of naphthoquinone (**59**) with hydrazoic acid at 0°C for about 5–15 min. Compound **59** is first reduced by hydrazoic acid to the corresponding hydroquinone **60** (Scheme 24). The obtainable 2-azidohydroquinone **61**, which is in equilibrium with its keto form (**61a** ↔ **61b**), is unstable and is converted to 2-aminonaphthoquinone (**55**) or 2-azidonaphthoquinone (**62**), depending on the reaction conditions as shown in Scheme 24 [52]. The mechanism of the formation of 2-amino-naphthoquinone is illustrated in Scheme 25 [52].

2.2.2. Reactions.

2.2.2.1. Substitution reactions. Reaction of formaldehyde with 2-amino-1,4-naphthoquinone (**55**) in chloroform at rt gives exclusively *N*-(hydroxymethyl)aminoquinone (**63**) in 64% yield (Scheme 26) [51]. There is no observed product corresponding to nucleophilic substitution at C-3 (compound **64**). This means that **55** did not act as an enamine compound and the reaction follows path ''a'' in Scheme 26 [51].

Reaction of **55** with simple aldehydes and ketones under neutral conditions gave *N*-(alkenyl)-aminoquinones **65a–d** in 45–56% yield (Scheme 27). Four examples were described [51].

Reaction of 2-dimethylamino-1,4-naphthoquinone (**66a**) with 2 equiv. of cyanomethylenetriphenylphosphorane afforded the adduct **67**, which was obtained through an internal elimination of triphenylphosphine from the intermediate (B) (Scheme 28) [53].

Previously, Bestmann and Lang reported that the reaction of 2-anilinophenyl-1,4-naphthoquinone (**66b**) with benzylidenetriphenylphosphorane (**68a**) yielded the respective quinonemethide **69** and triphenylphosphine oxide (TPPO) (Scheme 29) [54].

2.2.2.2. Synthesis of pyrroles. Reaction of 1 equiv. of 2-substituted amino-1,4-naphthoquinones **66b**,**c**,**d** with 2

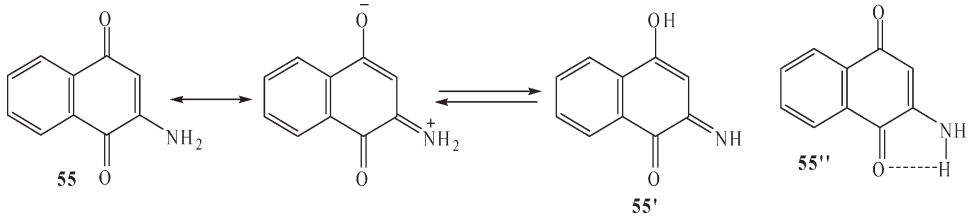


Figure 4. Hydrogen bond interaction between the C=O and NH_2 group in 2-amino-1,4-naphthoquinone (**55**).

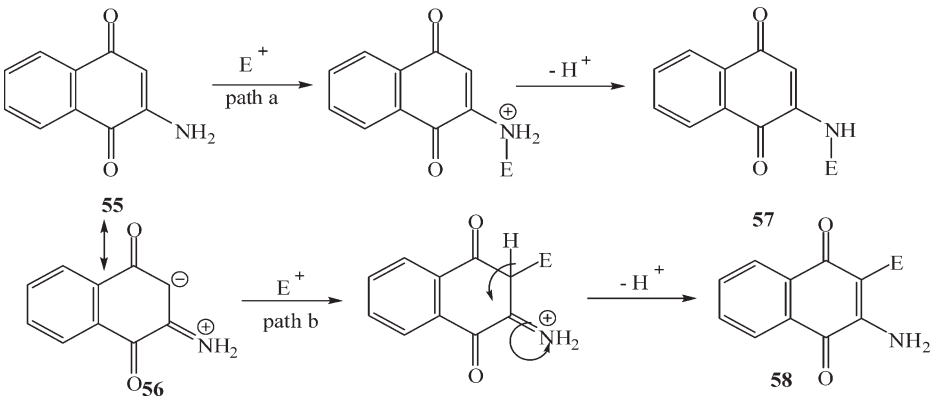
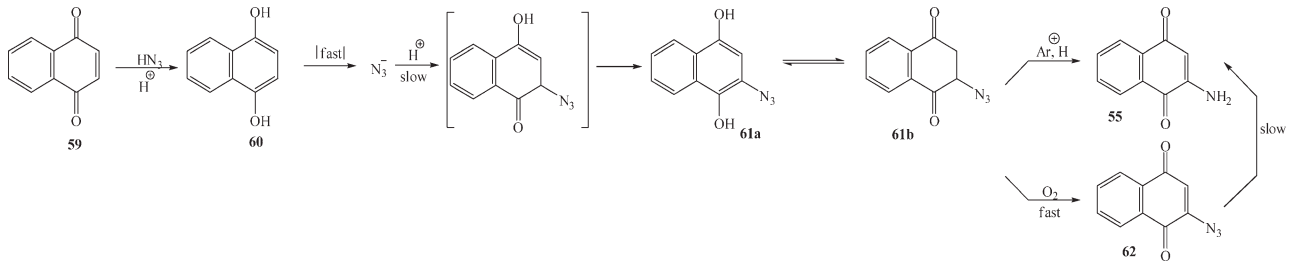


Figure 5. Various electrophilic substitution types in **55**.

Scheme 24



equiv. of the phosphonium ylide **68b**,**c** afforded the phosphorane adduct **70a–f** in good yield along with TPPO (Scheme 30) [53].

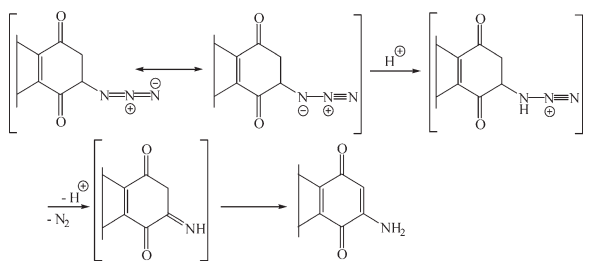
Mechanistically, quinone **66b–d** reacted with 1 mol of ylide **68** to give TPPO and the reactive olefinic intermediate (A) *via* a 1,2-addition, which reacted with another molecule of ylide **68** to afford the cyclic phosphorane adduct B, through loss of a suitable moiety (*i.e.*, R). That was followed by autoxidation to attain the aromaticity and therefore compounds **70a–f** were formed (Scheme 31) [53].

Reaction of 2-aminonaphthoquinones **66a–d** with active methylene compounds (2 equiv.) in the presence of manganese (III) acetate in acetic acid for 2 h afforded compounds **71** in not bad yields (Scheme 32) [54].

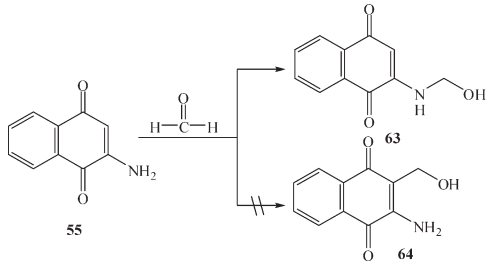
The proposed mechanism for the formation of **71** is outlined in Scheme 33. The addition of malonyl radical **72** to quinone ring followed by oxidation gives **73**, which undergoes lactamization to produce **71** (Scheme 33) [55].

Jiang and Chuang indicated that upon treatment of 2-(ethylamino)-1,4-naphthoquinone (**66d**) with 2,4-pentanedione and manganese (III)acetate under similar conditions, compound **76a** was obtained in 65% yield and other by-cyclized products **77** and **78** (Scheme 34) [56]. Oxidation of the β-keto ester by manganese (III) acetate gives radical **79**. Addition of the radical intermediate to the quinone ring, followed by oxidation, gives **80** (Scheme 35) [56]. Compound **80** underwent condensation to produce **76** (path a). With larger R^5, **80** undergoes either

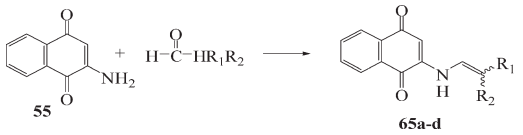
Scheme 25



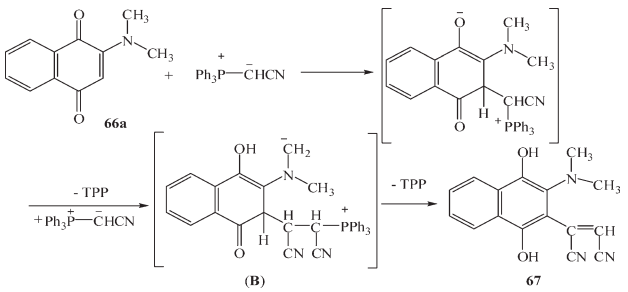
Scheme 26



Scheme 27

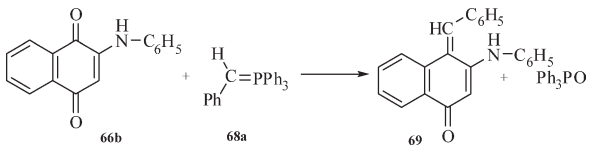


Scheme 28

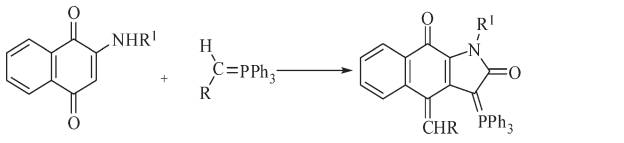


condensation to generate **76** (path a) or oxidation to produce radical **81**. Radical **81** undergoes either cyclization with (R = H, Me, *i*-Pr) to give **82**, followed by alkyl group migration and oxidation to produce **77** (path b) or oxidation (with R = *p*-tolyl) by manganese (III) acetate to produce imine **84**. Imine **84** underwent further intramolecular nucleophilic addition followed by retro-Claisen condensation and oxidation to produce **78** (Scheme 35) [56]. The free radical mechanism might here explained the rather difficulty arises in Scheme 35, where an ethyl group on the nitrogen in **81** somehow becomes a propylidene group (in **84**), thereafter becoming entangled with the incoming diacylmethyl group, the ethyl group eventually winding up on C(2) (**85** → **78**) (Scheme 35) [56]. The proposed free radical mechanism can describe unexpected products formation such as those **77** and **78** (Scheme 35).

Scheme 29



Scheme 30

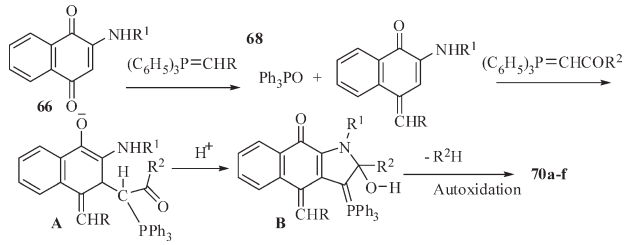


66b: $R^1 = C_6H_5$
66c: $R^1 = CH_3$
66d: $R^1 = C_2H_5$

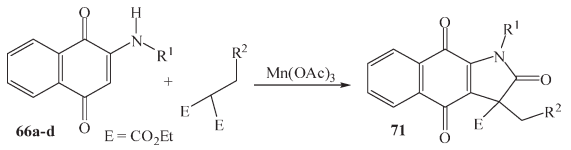
68 b, $R = R^2CO$, $R^2 = CO_2CH_3$
c, $R = R^2CO$, $R^2 = CO_2C_2H_5$

70a, $R = CO_2CH_3$; $R^1 = C_6H_5$
b, $R = CO_2C_2H_5$; $R^1 = CH_3$
c, $R = CO_2CH_3$; $R^1 = C_2H_5$
d, $R = CO_2C_2H_5$; $R^1 = C_6H_5$
e, $R = CO_2CH_3$; $R^1 = CH_3$
f, $R = CO_2C_2H_5$; $R^1 = C_2H_5$

Scheme 31



Scheme 32

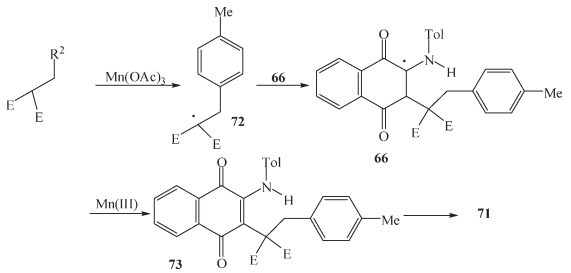


Upon reaction of 2-(substituted-amino)-1,4-naphthoquinone **66a–d** with substituted acetones and manganese (III) acetate in acetic acid at 45°C, compounds **86** was obtained in good yields (Scheme 36) [57].

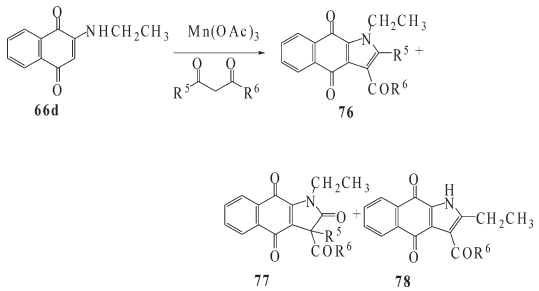
Similarly and as mentioned before, initiation occurs with the manganese (III) acetate oxidation of acetone to produce its radical. This radical intermediate underwent intermolecular addition to the quinone ring followed by oxidation process. Most indicative is the high chemoselectivity of that reaction, which was observed in different solvents [57a,b].

Treatment of *N*-substituted 2-amino-1,4-naphthoquinones **66a–d** with 1,3-dione derivatives and manganese

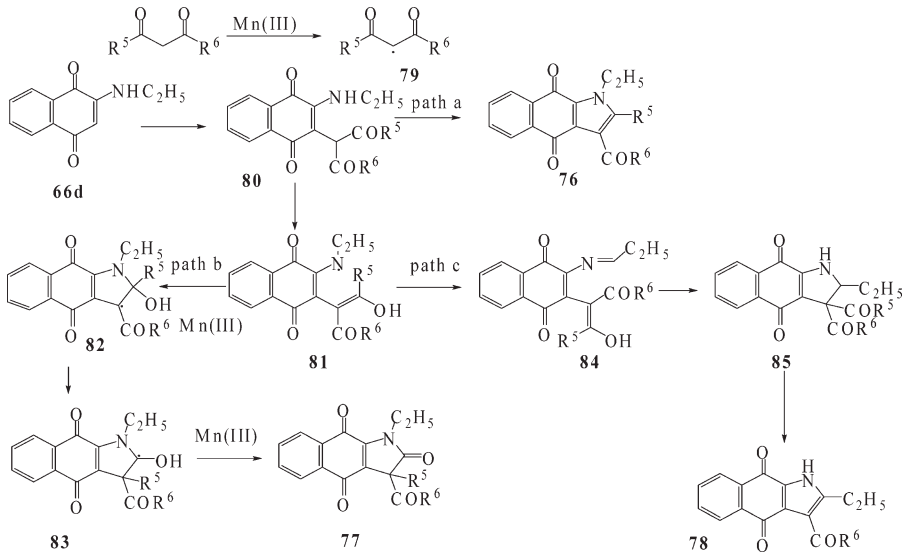
Scheme 33



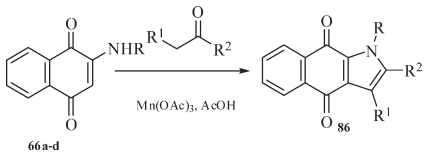
Scheme 34



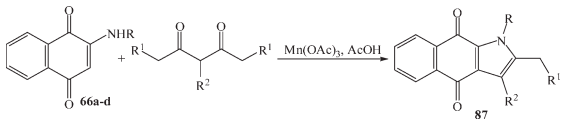
Scheme 35



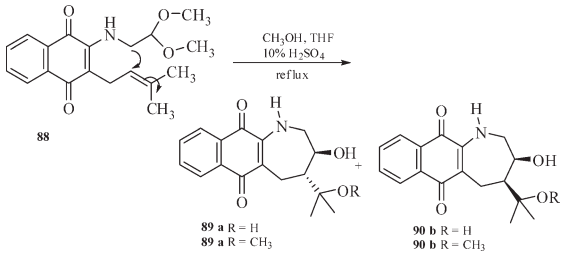
Scheme 36



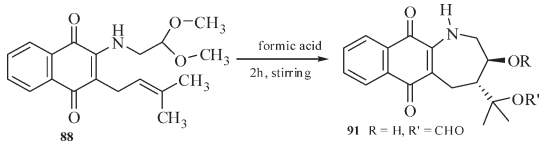
Scheme 37



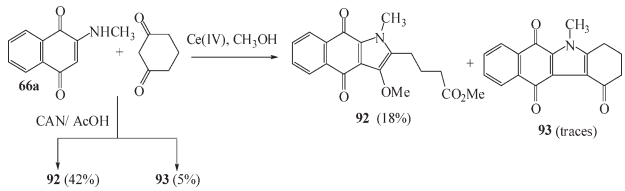
Scheme 38



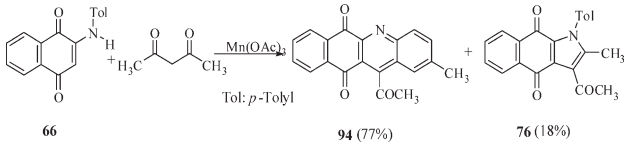
Scheme 39



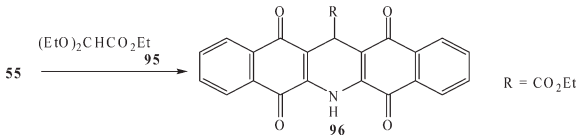
Scheme 40



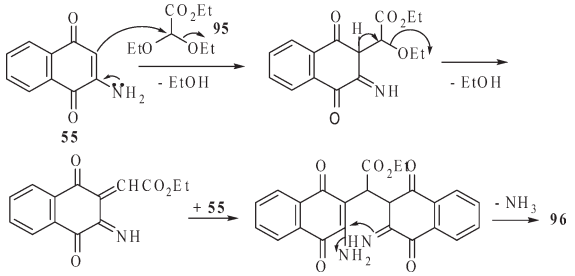
Scheme 41



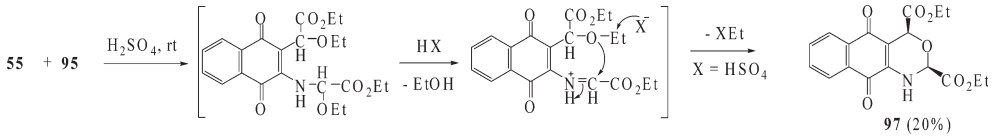
Scheme 42



Scheme 43



Scheme 44



(III) acetate at rt gave only one compound **87**, the structure of which is shown in Scheme 37 [58,59].

2.2.2.3. Synthesis of azepine derivatives. Vargas′s group reacted 2-(2,2-dimethoxyethylamino)-3-(3-methylbut-2-enyl)-naphthalene-1,4-dione (**88**) with a mixture of tetrahydrofuran and 10% H_2SO_4 in methanol for 1 h. An intramolecular Prins pathway proceeded, to afford compounds **89a**,**b** and **90a**,**b** (Scheme 38) [60].

The same group also reported that compound **88** reacted with formic acid at room temperature for 2 h, to afford regioselectively compound **91** (Scheme 39) [60].

2.2.2.4. Synthesis of indole derivatives. Reaction of 2-(methylamino)-1,4-naphthoquinone (**66a**) with 1,3-cyclohexanedione and cerium (IV) sulfate in methanol at room temperature gave **92** in 18% yield and no trace of the desired product **93** could be found. A better yield of compound **92** (42%) was obtained when CAN was used (Scheme 40) [61].

2.2.2.5. Synthesis of quinoline derivatives. Reaction of 2-(*p*-toluidino)-1,4-naphthoquinone (**66f**) with 2,4-pentanedione in presence of manganese (III) acetate in acetic acid at room temperature afforded compounds **94** and **76** in 77% and 18% yields, respectively (Scheme 41) [56].

2.2.2.6. Synthesis of 1,4-dihydropyridines. Upon thermal cyclization of **55** with ethyl 2,2-diethoxyacetate (**95**), 6*H*-dibenzo[*b*,*i*]carbazole-5,13:7,12-diquinone (**96**) was obtained. This transformation constitutes a new example of Huntzsch synthesis of 1,4-dihydropyridines [62] and has to involve a nucleophilic substitution of **48** at C-3 [57b]. This means that **48** is acting here as an enamine compound (Scheme 42) [57b].

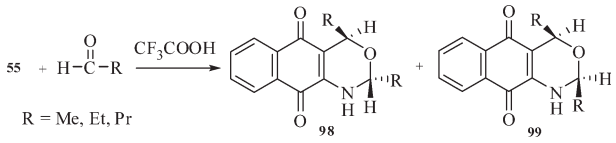
A plausible reaction mechanism involves C-3-alkylation, ethanol elimination, Michael addition of a second molecule of **55** and cyclization with elimination of ammonia to give **96** as illustrated in Scheme 43 [62].

2.2.2.7. Synthesis of oxazine, terahydrobenzo[g]chinazoline and pyridoacridines derivatives. Reaction of **55** with **95** catalyzed by H_2SO_4 afford (±)-*cis*-diethyl-5,8-dioxo-1*H*-2,4-dihydronaphtho[2,3-*d*]1,3-oxazine-2,4-dicarboxylate (**97**) after 6 d (Scheme 44) [62].

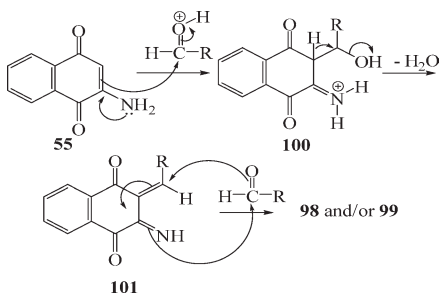
Reactions of compound **55** with aldehydes in the presence of a catalytic amount of trifluoroacetic acid at rt produce substituted 1*H*-2-dihydronaphtho-[2,3-*d*]1,3-oxazine-5,10-diones (**98** and **99**) in 54-70% yield as illustrated in Scheme 45 [51].

A plausible reaction mechanism for the formation of the products **98** and **99** involves C-3 alkylation, followed by water elimination to produce the azadiene intermediate (**101**; Scheme 46). This intermediate is reactive enough to produce the cyclized product by trapping another aldehyde molecule, most likely by Diels-Alder reaction [51].

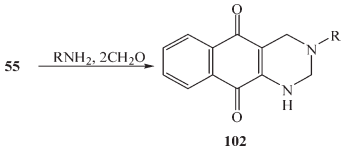
Scheme 45



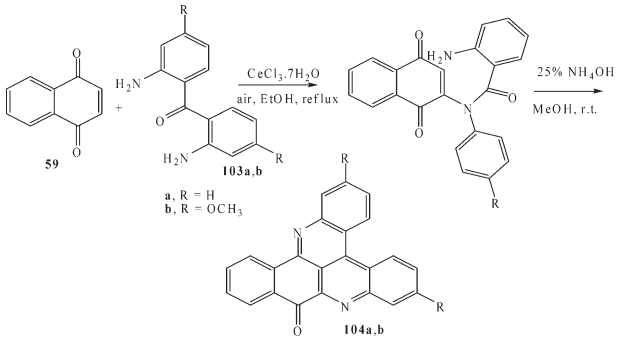
Scheme 46



Scheme 47



Scheme 48



2-Amino-1,4-naphthoquinone (**55**) behaves as a bidentate nucleophile with primary amines and formaldehyde to give 3-substituted 1,2,3,4-terahydrobenzo[*g*]chinazoline-5,10-diones **102** in poor to moderate yields (Scheme 47) [50].

Several pyridoacridines **104** were synthesized in a two-step reaction of β,β′-diaminoketones (**103a**,**b**) with 1,4-naphthoquinone (**59**) (Scheme 48). The prepared pyridoacridines showed moderate effect *in vitro* cytotoxicity against P-388 mouse lymphoma cells [63].

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