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Mannich bases derived from lawsone and their metal complexes: synthetic strategies and biological properties

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Lawsone (2-hydroxynaphthalene-1,4-dione) is a natural product which shows significant biological activity. Aminomethylnaphthoquinone Mannich bases derived from lawsone constitute an interesting class of naphthoquinones and/or their metal complexes have demonstrated a series of important biological properties. So, this review aimed to document the publications concerning the synthesis of aminomethylnaphthoquinone Mannich bases from lowsone, aldehydes and amines and their metal complexes using different conditions, and investigation of their applications.

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1. Introduction

Molecules with the quinoid structure bearing a hydroxy group on the quinone ring constitute one of the most interesting classes of synthetic compounds in organic chemistry and they are widely distributed in nature. Specifically, naphthoquinone structures receive great attention because of their pharmacological activities such as antibacterial, antiviral and antifungal activities.[1–3] 2-

Hydroxy-1,4-naphthoquinone, or lawsone, or hennotannic acid, has been known for the past 4000 years, is one of the simplest naturally occurring naphthoquinones. It is a red-orange dye, classified as Natural Orange 6 (C.I.75480), present in the leaves of the henna plant (*Lawsonia* spp., family Lythraceae) as well as in the flower of water hyacinth (*Eichhornia crassipes*) and in jewelweed *Impatiens balsamina.*[4,5] It is traditionally used for coloring hair and dying nails, skin, wool and cotton.[6–10] Besides it has several other uses including antiaging additive to vulcanized natural rubber ,[11] skin protection from ultraviolet radiation,[12,13] oxidation of chlorinated compounds,[14,15] corrosion inhibition for steel,[16,17] and sensitive colorimetric and electrochemical sensor for anions.[18] Extracts of henna are widely used in folk medicine to treat burn

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Mahdieh Sadeghpour Associate professor Dr Mahdieh Sadeghpour was born in Qazvin, Iran, in 1978. She received his B.Sc. degree in pure chemistry in Alzahra University, Tehran, Iran in 2001. And her M.Sc. in 2004 in organic chemistry under supervision of Associate Professor Nikoo Sedighi in Tehran University, Tehran, Iran. She graduated from PhD in 2009 in organic chemistry under supervision of professor Abbas Shokravi and associate professor Abolfazl olyaei, in organic chemistry in Kharazmi University, Tehran, Iran. Now she is an Associate Professor in Islamic Azad University of Takestan. Her research interests include organic synthesis, green chemistry and application of materials and nanomaterials in different sciences.

wounds infected by microorganisms[19] due to its antibacterial properties[20] as well as headaches, lumbago, bronchitis, ophthalmia, syphilis, sores and amenorrhoea.[21] The classical Mannich reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis because of its atom-economy advantages and application in biologically active molecule syntheses. However, a three-component condensation between structurally diverse substrates containing at least one acidic hydrogen atom, an aldehyde component and an amine reagent leads to Mannich bases. This multicomponent reaction usually occurs under acid catalysis, although catalysis is not mandatory.

3-(Aminomethyl)-2-hydroxy-1,4-naphthoquinones known as aminonaphthoquinone Mannich bases, constitute an interesting class of naphthoquinones and/or their metal complexes have demonstrated a series of important biological properties such as anticancer,[22] antimalarial,[23] antimolluscicidal,[24] antibacterial,[25] cholinesterase inhibitors,[26] leishmanicidal,[27] antiviral,[28] antifungal,[29] anti parasitic[30] activities and they have also been employed as fluorescent compounds and dyes.[31] Because of their prevalent applications, several methods have been reported for the synthesis of these important compounds and their metal complexes. This review will summarize the reported methods for the synthesis of aminonaphthoquinone Mannich base derivatives by multicomponent reactions of lawsone with a non-enolizable aldehyde and a primary or secondary amine *via* the Mannich reaction and their metal complexes using different conditions, and applications of these compounds.

2. Synthesis of aminomethylnaphthoquinone Mannich bases

2.1. Uncatalyzed reactions

The first synthesis of 2-hydroxy-3-aminomethyl-1,4-naphthoquinones **1** by the Mannich reaction has been reported

by Leffler and Hathaway in 1948. The reaction mixture of lawsone (**2**), amine and 37% formalin (**3**) in absolute ethanol was allowed to stir at room temperature for one hour was warmed on the steam-bath for an additional hour, and was then left at room temperature overnight gave the corresponding aminonaphthoquinone **1** in 66–98% yields. In this study diethylamine failed to react, on the other hand, primary amines, such as butylamine, gave especially good yields (Scheme 1).[32]

However, two mechanisms may be operating in the formation of the aminomethylnaphthoquinone derivatives (**4**), depending on the reaction conditions: the first mechanism is preformation of the imine *via* the reaction of amine and aldehyde followed by nucleophilic attack of lawsone (**2**) to the activated imine or iminium species, and/or the second mechanism is Knovenagel-type condensation of lawsone with aldehyde followed by Michael-type 1,4-addition of amine to the alpha, beta-conjugated carbonyl species formed. Apparently, mechanism (1) operates mostly in catalyzed transformations while mechanism (2) will probably be the one operating for uncatalyzed transformations (Scheme 2).

In 1949, Dalgliesh demonstrated that Mannich bases **5** were prepared by the reaction of lawsone, aldehydes and primary aliphatic amines or 2-aminopyridine in EtOH at room temperature for 3–24 h. The mechanism of the Mannich reaction is still obscure, it being uncertain whether the primary reaction is that of formaldehyde with the amine or with the active hydrogen component (Scheme 3).[33] It has been suggested that the formation of aminonaphthoquinine **5** was occurred through the second mechanism as shown in Scheme 2.

Hydroxynaphthoquinones **1** and **6a–d**[24] were synthesized as previously described methods (Fig. 1).[32,34] They have been submitted to molluscicidal bioassays against the snail *Biomphalaria glabrata*, intermediate host of *Schistosoma mansoni*. Several of the quinones **1** and **6a–d** assayed showed significant molluscicidal activities, and correlation of their activities and electrochemical parameters showed that the first wave reduction potential is an important parameter. The easily reduced quinones ($>E_{p1c}$) were more active against adult snails and against their egg masses, whilst the 3-methylamino-2-hydroxy derivatives presented higher negative reduction potentials and were not active as molluscicides.

Mehdi Khalaj Associate Professor Dr Mehdi Khalaj was born in Karaj, Iran in 21/03/1982. He received his PhD in 2014 in Inorganic chemistry under the supervision of Professor Sadegh Salehzadeh in Bu-Ali Sina University in Hamedan one of the oldest cities in the world. In 2019 he was awarded a best researchers prize in Qazvin province. He was an Assis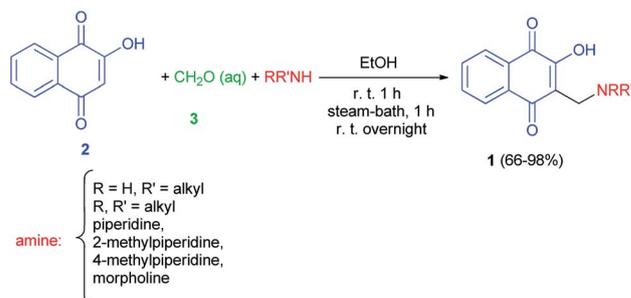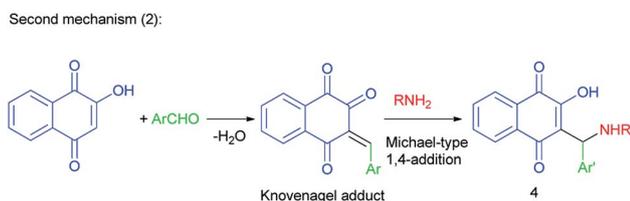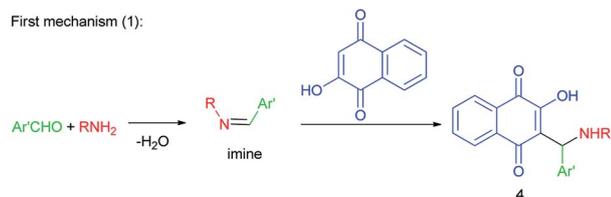tant Professor in Islamic Azad University of Buinzahra Branch from 2014 and now has become to Associate Professor in that University. His research interests include organic and inorganic synthesis, porous coordination polymers based on phosphonates, synthesis, complexation and structural studies of some diimine ligands, nanocomposite green chemistry and so on.

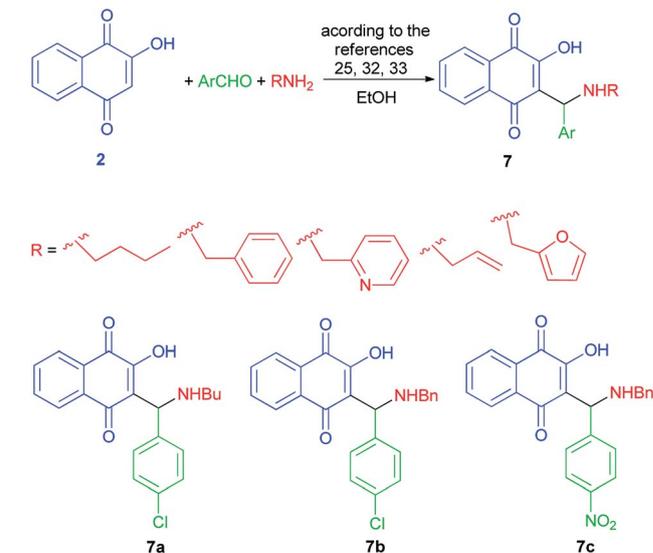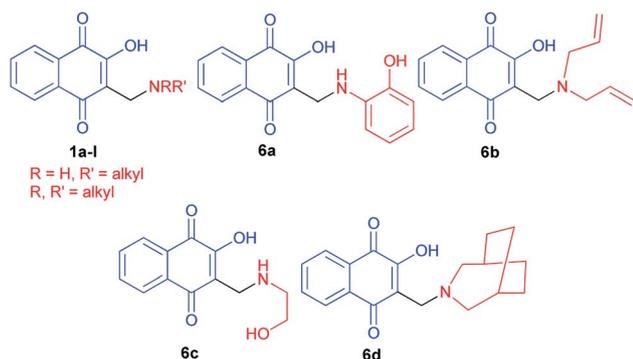**Scheme 1** Synthesis of 2-hydroxy-3-aminomethyl-1,4-naphthoquinones **1**.
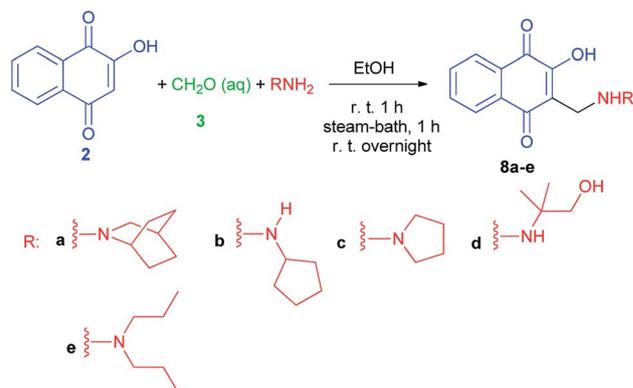
Scheme 2 Proposed mechanisms for the synthesis of amino-methylnaphthoquinones 4.

Scheme 3 Synthesis of aminonaphthoquinines 5.

Fig. 1 Structures of the synthesized hydroxynaphthoquinones 1 and 6a–d.

Scheme 4 Synthesis of aminomethylnaphthoquinone derivatives 7.

Scheme 5 Naphthoquinones 8 obtained by Mannich reaction from lawsone.

Aminomethylnaphthoquinones 7 were synthesized from the Mannich reaction of lawsone (2) with the desired substituted benzaldehydes and primary amines in ethanol as described previously,[32,33] with some modifications (Scheme 4).[25] Although AMNQs 7a–c exhibited similar antiviral activities against BoHV-5, AMNQ 7c was at least 50-fold less cytotoxic than the other two compounds.[3]

2-Hydroxy-3-substituted-aminomethyl naphthoquinones 8a–e,[35] Mannich adducts, were obtained in high quantities by the classic reaction of lawsone (2), using amine and formaldehyde in alcoholic solution (Scheme 5), as previously reported by the Pinto group,[24,36,37] based on the procedure described by Leffler and Hathaway.[32] Compounds 8 exhibit molluscicidal activity[24,36,37] against the snail *Biomphalaria glabrata*, the
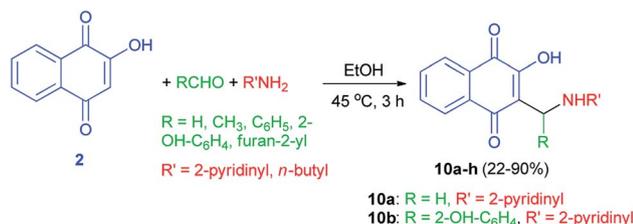
causative agent of schistosomiasis. Compound 8e, the most active member of this group, was two times less effective than benznidazole (IC_{50}/24 h = 103.6 $\pm$ 0.6 μM), the standard anti-*T. cruzi* drug, and 2.6 times more active than crystal violet (IC_{50}/24 h = 536.0 $\pm$ 3.0 μM), which is recommended by WHO to hemotherapeutic centers in endemic areas for eliminating the parasite in blood used for transfusions.[35]

Krettli *et al.* noted that the naphthoquinones derived from lawsone (compounds 8a and 8e) showed the highest activity against *P. falciparum* chloroquine-resistant blood-stage parasites (clone W2), indicated by their low inhibitory concentration for 50% (IC_{50}) of parasite growth. The therapeutic potential of the compounds was evaluated according to the selectivity index, which is a ratio of the cytotoxicity minimum lethal dose which eliminates 50% of cells and the *in vitro* IC_{50}. Naphthoquinones 8a and 8e, with activities similar to the reference antimalarial chloroquine, were also active against malaria in mice and suppressed parasitaemia by more than 60% in contrast to Nor-lapachol (9) which was inactive (Fig. 2).[38]
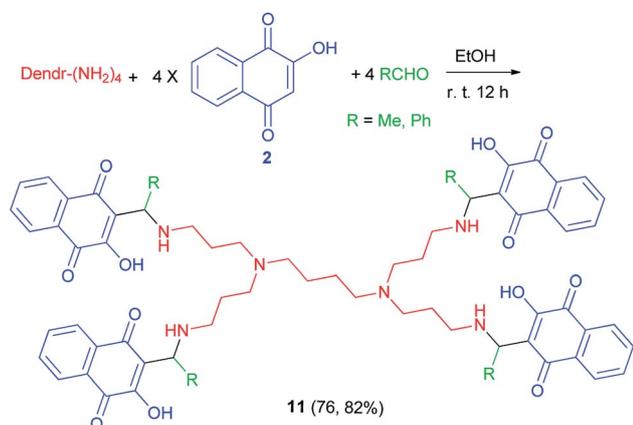
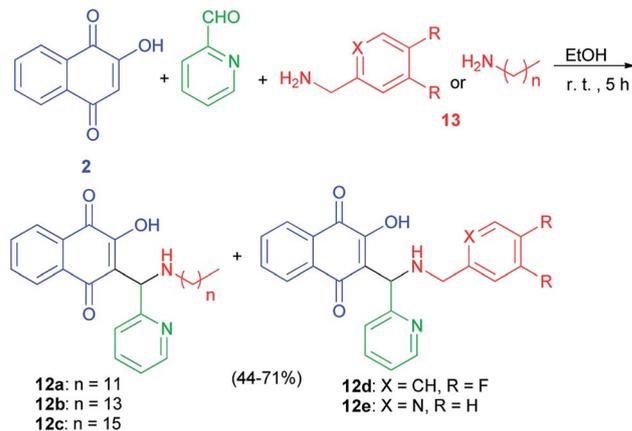**Fig. 2** Structure of the naphthoquinones derived from lawsone (**8a,e** and **9**).

Scheme 6 Synthesis of 2-hydroxy-1,4-naphthoquinones **10**.

R = H, CH₃, C₆H₅, 2-OH-C₆H₄, furan-2-yl
R' = 2-pyridinyl, n-butyl

10a–h (22–90%)
10a: R = H, R' = 2-pyridinyl
10b: R = 2-OH-C₆H₄, R' = 2-pyridinyl

A series of substituted derivatives of 2-hydroxy-1,4-naphthoquinones **10** were prepared by a Mannich reaction from lawsone (**2**), aryl/alkyl aldehydes and 2-aminopyridine/n-butylamine in EtOH at 45 °C for **3** h in 22–90% yields (Scheme 6). Minimum inhibitory concentration (MIC) of the synthesized compounds was measured against *Mycobacterium tuberculosis* (MTB) H37Ra strain. Among them, two compounds **10a,b** showed antibacterial activity within the MIC range of 20–50 μg mL⁻¹ while the other compounds did not show antibacterial activity. It was found that compound **10a** showed the high activity anti-tuberculosis among other compounds, although cytotoxicity issues have been observed when evaluated on Ver-ocells for further concerns.[39]

The synthesis of two new PPI-G1 dendrimers containing lowsone **11** as pharmacophoer is reported by Ndiaye and co-workers. The compounds were synthesized in course of Man-nich reaction involving lawsone (**2**), the commercial PPI-G1(polypropyleneimine-G1) dendrimer with functional amino groups on the exterior and acetaldehyde or benzaldehyde in
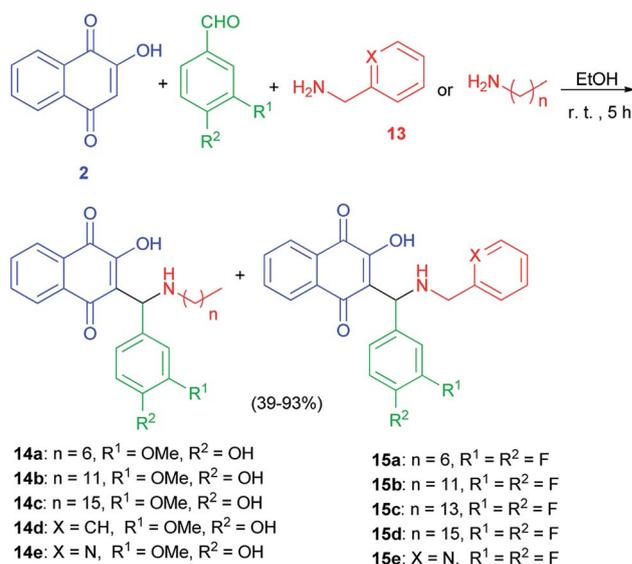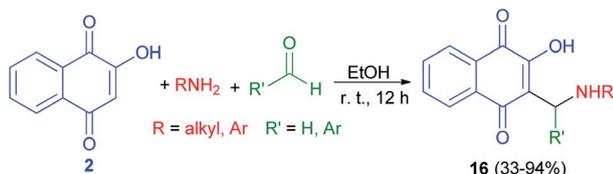
4 : 1 : 4 molar ratio in absolute EtOH at room temperature for overnight in the dark (Scheme 7). The reaction mechanism could be explained briefly in a few words, *i.e.* condensation of the amino with the acidified aldehyde to give the imine followed by protonation and addition of lawsonate anion (mechanism (1)).[40]

The Mannich bases **12a–e** were prepared in 44–71% yields *via* Mannich reaction of lawsone, 2-pyridylcarboxaldehyde and the corresponding amines **13** in detail, dodecyl amine, tetra-decyl amine, hexadecyl amine, 3,4-difluorobenzylamine and 2-pyridylmethylamine in EtOH at room temperature for 5 h (Scheme 8). In addition, closely related vanillyl and 3,4-difluorophenyl derivatives **14a–e** and **15a–e** were prepared. Analogously to the synthesis of compounds **12a–e**, the Mannich reaction of lawsone with vanillins and the corresponding primary amines in EtOH gave the Mannich bases **14a–e** as orange-red solids. In addition, reaction of lawsone with 3,4-difluorobenzaldehyde and various primary amines led to
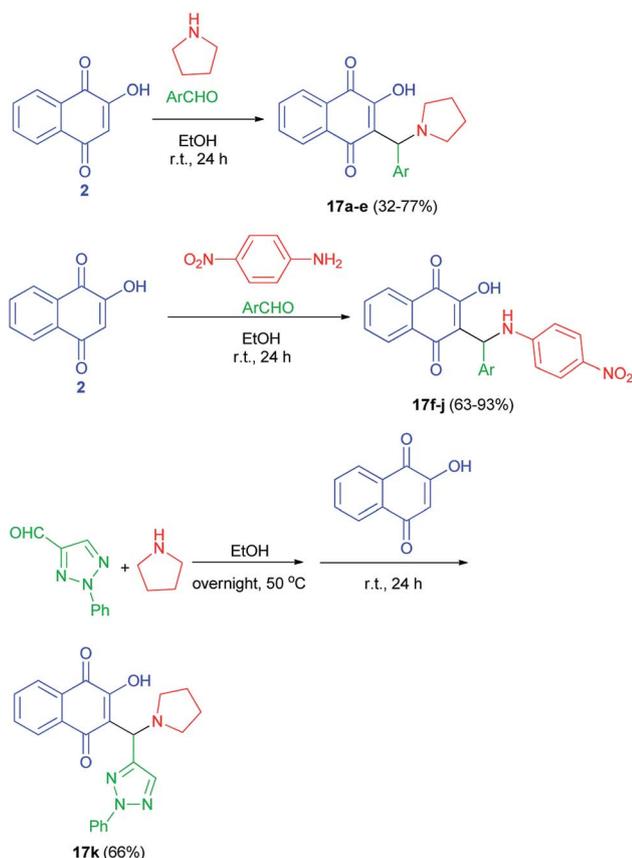
Scheme 8 Synthesis of Mannich bases **12a–e**.

12a: n = 11
12b: n = 13
12c: n = 15
(44–71%)
12d: X = CH, R = F
12e: X = N, R = H

Scheme 7 Synthesis of PPI-G1 dendrimers containing lowsone **11**.

Dendr-(NH₂)₄ + 4 X + 4 RCHO → EtOH, r. t. 12 h
R = Me, Ph
11 (76, 82%)

Scheme 9 Synthesis of Mannich bases **14** and **15**.

14a: n = 6, R¹ = OMe, R² = OH
14b: n = 11, R¹ = OMe, R² = OH
14c: n = 15, R¹ = OMe, R² = OH
14d: X = CH, R¹ = OMe, R² = OH
14e: X = N, R¹ = OMe, R² = OH
(39–93%)
15a: n = 6, R¹ = R² = F
15b: n = 11, R¹ = R² = F
15c: n = 13, R¹ = R² = F
15d: n = 15, R¹ = R² = F
15e: X = N, R¹ = R² = F

Scheme 10 Synthesis of 3-(aminomethyl)naphthoquinones **16**.

compounds **15a–e** (orange-red solids). These target compounds were obtained in EtOH at room temperature in moderate to high yields (39–93%) (Scheme 9). Substituted lawsone Mannich bases **12a–e**, **14a–e** and **15a–e** tested for their biological activities. The new fatty alkyl substituted compounds **12a–c** exhibited strong and selective growth inhibitory activities in the low one-digit micromolar and sub-micromolar range against a panel of human cancer cell lines associated with ROS formation. In addition, compounds **12a–c** revealed sub-micromolar anti-trypanosomal activities against parasitic *Trypanosoma brucei* cells *via* deformation of the microtubule cytoskeleton. The *N*-hexadecyl compound **12c** was also highly active against locally isolated *Entamoeba histolytica* parasite samples exceeding the activity of metronidazole.[30]
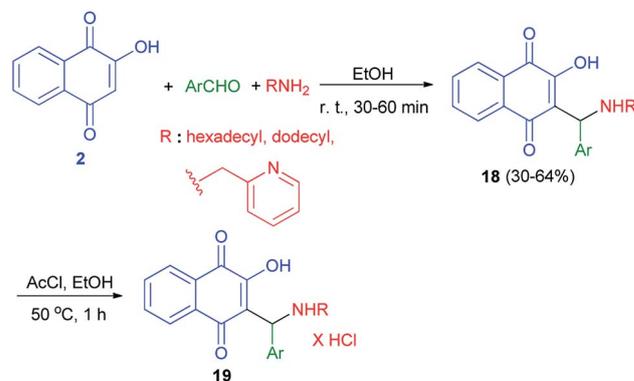
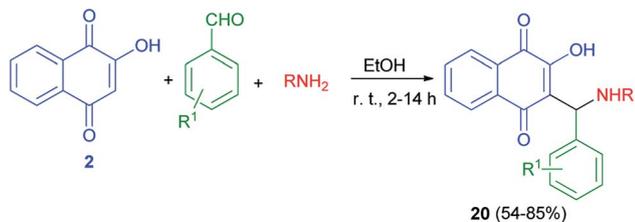The synthesis of 3-(aminomethyl)-2-hydroxy-1,4-naphthoquinones **16** was carried out following a procedure described previously.[25] The products were isolated as analytically pure orange powders with yields ranging from 33–94% (Scheme 10). In general, the compounds **16** have shown high to moderate activity against the HL-60 (promyelocytic leukaemia) cell line with IC_{50} = 1.1–19.2 μM. The results suggest that the nature of the aryl moiety introduced in the structure of products by the aldehyde component is crucial to the cytotoxicity, and although the group originated from the primary amine has a lesser influence, aromatic ones were found to suppress the activity.[41]

Greco *et al.* succeeded in preparation of amino-naphthoquinone derivatives **17** from lawsone (**2**), aldehydes and amines in EtOH at room temperature in the dark for 24 h. Also, for the synthesis of the lawsone derivative **17k**, a mixture of 2-phenyl-2*H*-1,2,3-triazole-4-carbaldehyde and pyrrolidine in ethanol was stirred overnight at 50 °C. After this time, lawsone was added and the mixture was allowed to react for 24 h in the dark (Scheme 11). Among the synthetic lawsone derivatives, 2-hydroxy-3-((2-hydroxyphenyl)(pyrrolidin-1-yl)methyl) naphthalene-1,4-dione, 2-hydroxy-3-(((4-nitrophenyl) amino)(phenyl)methyl)naphthalene-1,4-dione and 2-hydroxy-3-((2-hydroxyphenyl)((4-nitrophenyl)amino)methyl)naphthalene-1,4-dione showed high activity against *Candida albicans* ATCC 10231, with minimal inhibitory concentrations (MICs) and minimal fungicidal concentrations (MFCs) ranging from 20 to 330 and from 80 to 330 μg mL^{-1}, respectively. Moreover, they also showed a mechanism of action on exogenous ergosterol.[29]

Biersack *et al.* have been prepared a series of new lawsone Mannich bases **18** in 30–64% yields from lawsone (**2**), salicylaldehydes or nitrofurfural and dodecylamine or hexadecylamine or 2-aminomethylpyridine in EtOH at room temperature for 30–60 min. Compounds **18** were converted to the hydrochloride salts **19** by reaction with acetyl chloride in ethyl alcohol at 50 °C for 1 h (Scheme 12). These compounds tested for activities against *Leishmania major*, *Toxoplasma gondii*, and *Trypanosoma brucei* parasites. The hydrochloride salts **19** of the Mannich bases **18**, derived from unsubstituted salicylaldehyde and long chained alkyl amines, were selectively and strongly active against *T. gondii* cells and appear to be new promising drug candidates against this parasite. Also, Some of them

Scheme 11 Synthesis of aminonaphthoquinone Mannich bases **17**.

Scheme 12 Synthesis of lawsone Mannich bases **18** and their hydrochloride salts **19**.

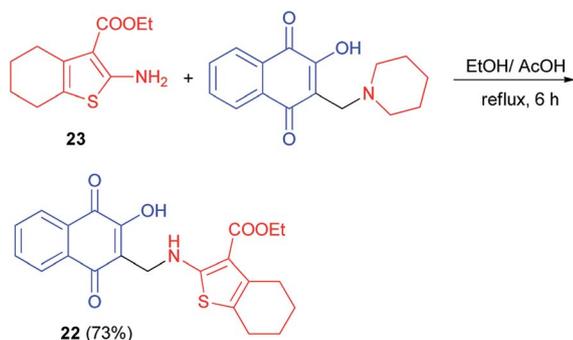**Scheme 13** Synthesis of aminonaphthoquinone derivatives **20**.
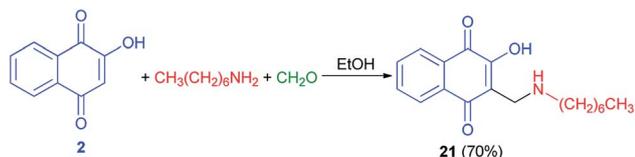
Scheme 14 Synthesis of 3-(N-(1-heptyl)aminomethyl)-2-hydroxynaphtoquinone **21**.

proved active against *L. major* promastigotes and up to four times more efficacious against *L. major* amastigotes.[42]

Thakore *et al.* described synthesis of Mannich bases of lawsone **20** by the reaction of lawsone, aromatic aldehydes and aliphatic amines in EtOH at room temperature for 2–14 h in 54–85% yields. It primarily forms the iminium ion by condensation of amine and aldehyde. Subsequently, the nucleophile lawsonate attacks iminium ion (analogous to the enolate) to give a Mannich base **20**. Overall, the compounds with aliphatic substituent at R position and hydroxyl substituted phenyl ring at R^1 position are associated with the highest activities. The effective IC_{50} concentration for compounds are 1.68–4.64 μM. These compounds showed higher anticancer potential against HepG2 cells (Scheme 13).[43]

Moreover, compound **21** was obtained in 70% yield using a direct condensation of *n*-heptylamine on 2-hydroxynaphthoquinone (**2**) in the presence of formaldehyde in EtOH (Scheme 14). This novel atovaquone derivative **21** was tested for their *in vitro* activity against two apicomplexan parasites of medical importance, *Toxoplasma gondii* and *Plasmodium falciparum*, including resistant strains to atovaquone (*T. gondii*) and chloroquine (*P. falciparum*).[44]
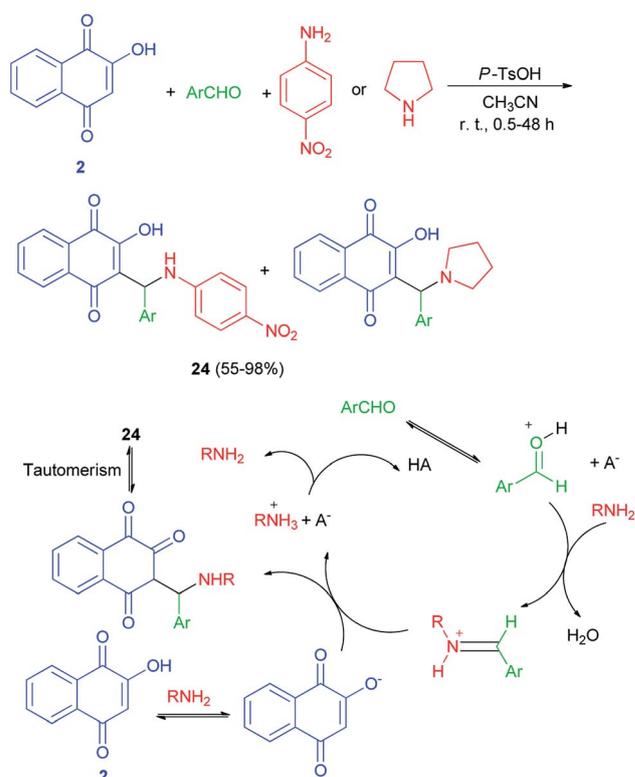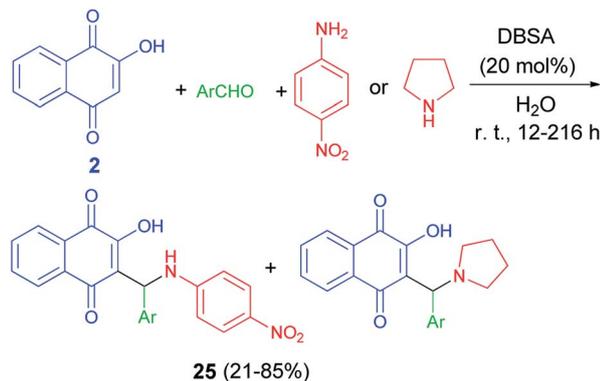

Scheme 15 Synthesis of aminonaphthoquinone **22**.

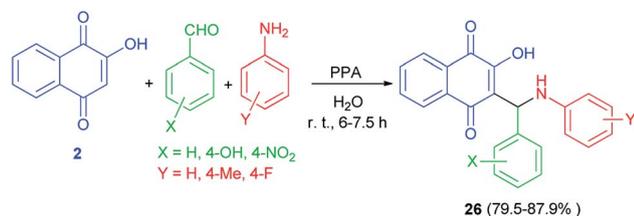## 2.2. Acid catalyzed reactions

Synthesis of aminonaphthoquinone **22** in 73% yield has been carried out by the reaction of ethyl 2-amino-4,5,6,7- tetrahydrobenzo[*b*]thiophene-3-carboxylate **23** with 2-hydroxy-3-((piperidin-1-yl)methyl)naphthalene-1,4-dione in a mixture ethanol/acetic acid under reflux for 6 h (Scheme 15). It was screened for antioxidant activity. Calculation of the inhibition ratio (%) showed clearly that compound **22** exhibited moderate activity (63.17%) compared with ascorbic acid (89.87%) as a standard antioxidant. Also, it was selected for bleomycin-dependent DNA-damage testing. If the sample to be tested is able to reduce the bleomycin–Fe^{3+} to bleomycin–Fe^{2+}, DNA degradation in this system will be stimulated, resulting in a positive test for pro-oxidant activity. The results showed that compound **22** has an ability to protect DNA from the induced damage by bleomycin. Thus, it would appear generally that introducing of naphthoquinone moiety enhances the antioxidant properties of 2-aminothiophene compounds.[45]

Greco *et al.* demonstrated that one-pot protocol was developed for the synthesis of a series of new aminonaphthoquinones **24** in 55–98% yields from 2-hydroxy-1,4-naphthoquinone (**2**), aldehydes and 4-nitroaniline or pyrolidine by three-component Mannich reaction using catalytic amount of *p*-TsOH in CH_3CN at room temperature for 0.5–48 h. A reasonable mechanism possibility is shown in Scheme 16. First, the catalyst protonates the carbonyl oxygen of the aldehyde favoring the formation of the iminium ion which reacts

Scheme 16 *p*-TsOH catalyzed synthesis of aminonaphthoquinones **24**.

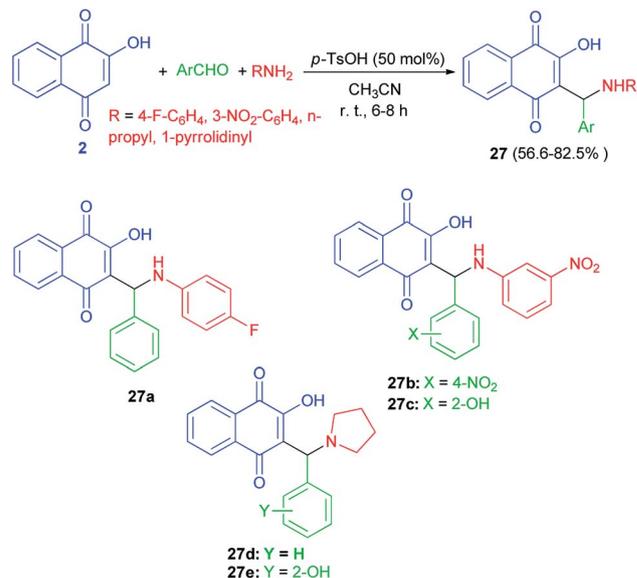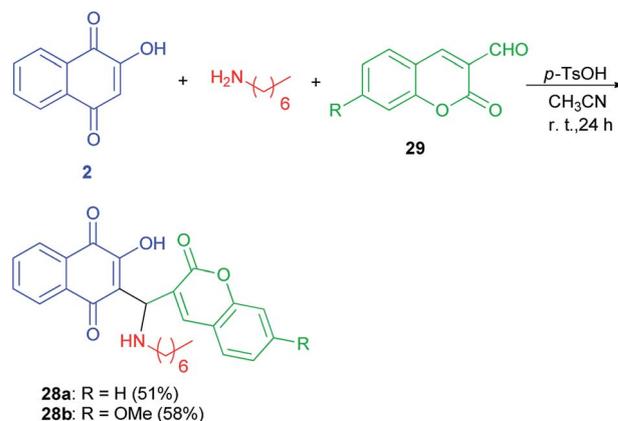Scheme 17　DBSA catalyzed synthesis of aminonaphthoquinones 25.

Scheme 18　PPA catalyzed synthesis of hydroxylnaphthalene-1,4-dione derivatives 26.

Scheme 19　p-TsOH catalyzed Mannich bases of lawsone 27.

Scheme 20　Synthesis of Mannich bases 28a–b.

with the nucleophilic species, that may be the ion formed from deprotonation of lawsone by the amine. Finally, the product is obtained after tautomerism and the catalyst is regenerated.[46] Environmentally friendly one-pot protocol was developed for the first synthesis of aminonaphthoquinones 25 in 21–85% yields derived from lawsone (2) via a multi-component Mannich reaction in aqueous media using a catalytic amount of dodecyl benzenesulfonic acid (DBSA) (20 mol%), exploring a Brønsted acid-surfactant catalyst (BASC) concept, at room temperature for 12–216 h. Most likely, all of the reaction steps, from the iminium salt formation to the final Mannich adduct, occur inside of the surfactant micelles due to the affinity of the medium for reactants/intermediates (Scheme 17). In this context, DBSA enhances the chemical yield and decreases the reaction time by building a colloidal dispersion system and protonating electrophilic species, the aldehyde and imine, increasing its reactivity towards the nucleophile at the same time.[47]

An efficient one-pot synthesis of lawsone derivatives 26 in 79.5–87.9% yields is accomplished by a three-component reaction of 2-hydroxynaphthalene-1,4-dione (2), aromatic aldehydes and amines carrying electron-donating or electron-withdrawing substituents in water under ambient temperature catalyzed by phenylphosphinic acid for 6–7.5 h (Scheme 18). It should be noted that aliphatic aldehyde reacted poorly under the same conditions. The proposed mechanism for the formation of the compounds 26 is shown in Scheme 2 (mechanism (1)).[48]

A series of Mannich bases of lawsone as 3-alkyl/aryl/heteroaryl substituted aminonaphthoquinones 27 were synthesized in 56.6–82.5% yields from lawsone (2), amines and aromatic aldehydes in CH_3CN at room temperature in presence of p-TsOH (50 mol%) for 6–8 h (Scheme 19). Among synthesized compounds, five compounds (27a–e) showed good antimalarial activity against both chloroquine (CQ)-sensitive (3D-7) and -resistant (RKL-2) strains of P. falciparum, which, however, was considerably less than that of the standard reference drug, CQ. The antimalarial activity of these five compounds was found better against sensitive (IC_{50} = 0.411–0.502 µg mL^{-1}) strain than the resistant (IC_{50} = 1.391–2.394 µg mL^{-1}) one.[23]

Mannich bases 28a–b derived from lawsone, heptylamine and 3-formylcoumarins (29) have been synthesized in the presence of p-TsOH (20 mol%) in CH_3CN at room temperature for 24 h in the dark in 51 and 58% yields, respectively (Scheme 20). The cyclic voltammetry data of these compounds showed a charge transfer (CT) process from the coumaryl to the naphthoquinonoid group, in spite of the absence of conjugation between these two fragments, with the nitrogen atom playing an important role.[49]
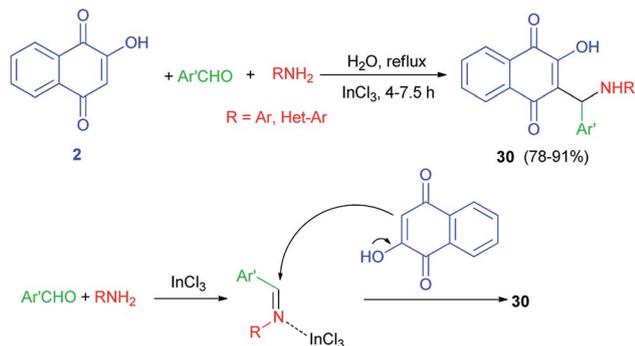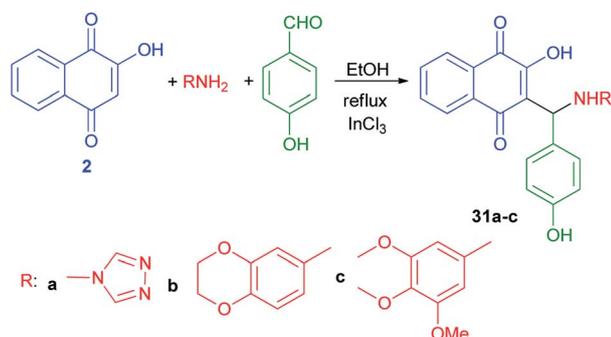
Scheme 21 InCl$_3$ catalyzed synthesis of aminonaphthoquinones 30.

2.3. Metal catalyzed reactions

An efficient one-pot synthesis of fluorescent hydroxyl naphthalene-1,4-dione derivatives 30 in 78–91% yields by atom-economical and three-component reaction of 2-hydroxynaphthalene-1,4-dione (2), aromatic aldehydes and heterocyclic or carbocyclic amines in the presence of a catalytic amount of InCl$_3$ in refluxing water for 4–7.5 h is reported. The products were fluorescent in methanol solution emitting at green light (546–560 nm). Possible mechanism for the formation of products 30 as shown in Scheme 21.[31]

Ghodsi *et al.*[50] have published synthesis of 2-arylaminonaphthoquinone derivatives 31a–c from lawson (2), 4-hydroxybenzaldehyde and aryl amines in the presence of InCl$_3$ in refluxing EtOH according to the previously reported procedure (Scheme 22).[31]

Aminonaphthoquinone derivatives 32 have been prepared in 88–93% yields by one-pot three-component condensation
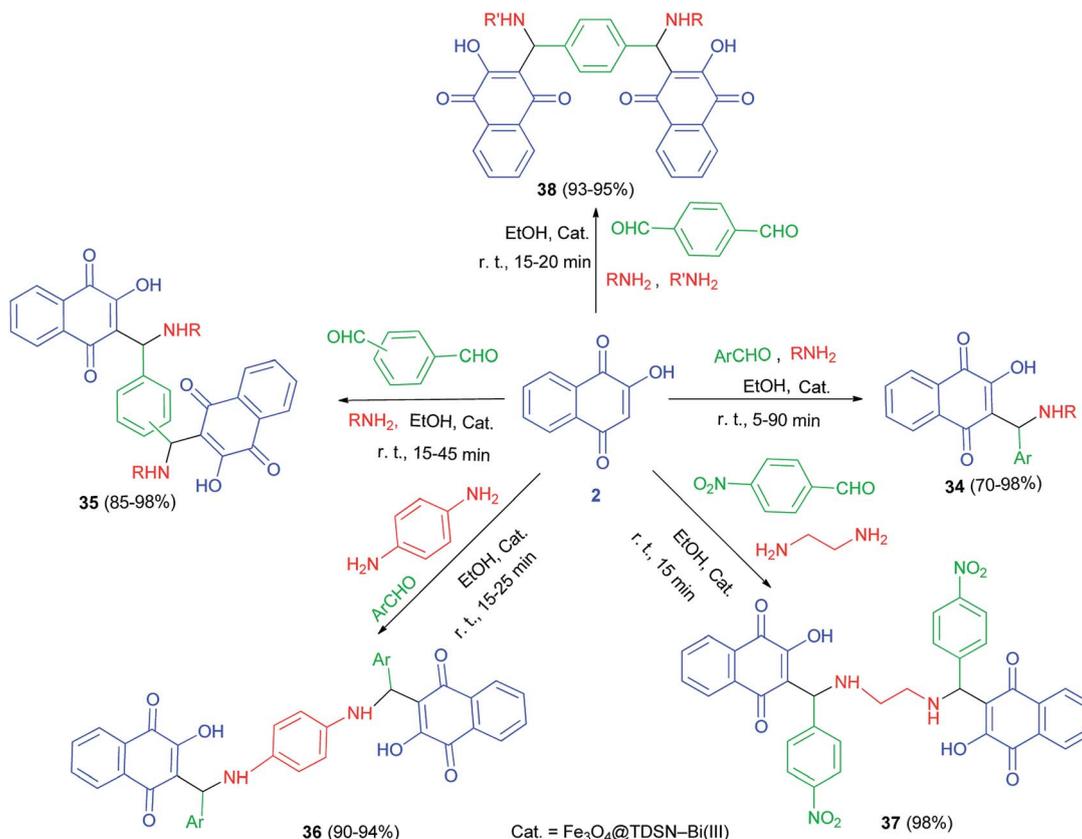

Scheme 22 InCl$_3$ Catalyzed synthesis of 2-arylaminonaphthoquinones 31a–c.

Scheme 23 Nano CuO catalyzed synthesis of aminonaphthoquinone derivatives 32.
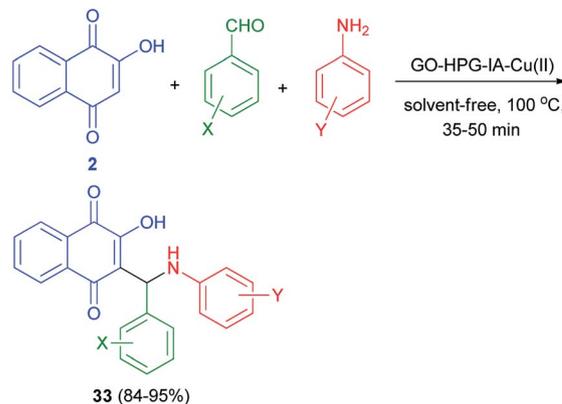
Scheme 24 Synthesis of aminonaphthoquinone derivatives 33 using Cu(II) immobilized on graphene oxide.

reaction of aromatic aldehydes, aromatic amines, and 2-hydroxynaphthalene-1,4-dione (2) in the presence of nano-copper(II) oxide (8 mol%) as catalyst under mild, ambient and solvent-free conditions for 10–13 min. The proposed catalytic mechanism for the preparation of 32 using nano-copper(II) oxide as the catalyst is described in Scheme 23.[51] The proposed mechanism is similar to the first mechanism as shown in Scheme 2.

Cu(II) immobilized on hyperbranched polyglycerol (HPG) functionalized graphene oxide catalyzed synthesis of aminonaphthoquinones 33 in 84–95% yields *via* one-pot three-component condensation reaction of lawsone (2), benzaldehyde and aniline derivatives at 100 °C for 35–50 min under solvent-free conditions (Scheme 24). According to the plausible mechanism, firstly, the aldehyde is activated by the GO–HPG–IA–Cu(II) catalyst which upon nucleophilic attack of amine to form imine. Subsequently, lawsone attacks to imine in the presence of the GO–HPG–IA–Cu(II) catalyst and undergoes tautomeric proton shift to generate the aminonaphthoquinone derivative 33 and releases the catalyst for the next run.[52]

Synthesis of mono-aminonaphthoquinone derivatives 34 catalyzed by Bi(III) immobilized triazine dendrimer-stabilized magnetic nanoparticle Fe$_3$O$_4$@TDSN–Bi(III) (3 mol%) *via* a one-pot three-component reaction of lawsone, aldehydes containing electron with-drawing or electron-donating groups and amines (anilines, 4-methylaminopyridines, *i*-butylamine, pyrolidine and piperidine) in EtOH as a green solvent at room temperature for 5–90 min in 70–98% yields. This catalytic system also showed excellent activity in the synthesis of symmetric and unsymmetric bis-aminonaphthoquinones 35–38 from dialdehyde (terephthaladehyde and isophthalaldehyde) and/or diamines (benzene-1,4-diamine and 1,2-ethylenediamine) in EtOH at room temperature for 15–45 min in high yields (85–98%) and purity *via* an easy work-up procedure (Scheme 25). A plausible mechanism for the Fe$_3$O$_4$@TDSN–Bi(III) catalyzed synthesis of aminonaphthoquinones is depicted in Scheme 26. First, the aldehyde is activated by the catalyst to give 39 which upon nucleophilic attack of amine forms imine 40. Then, 2-hydroxynaphthalene-1,4-dione attacks imine 40 in

**Scheme 25** Synthesis of mono-and bis-aminonaphthoquinone derivatives **34–38**.
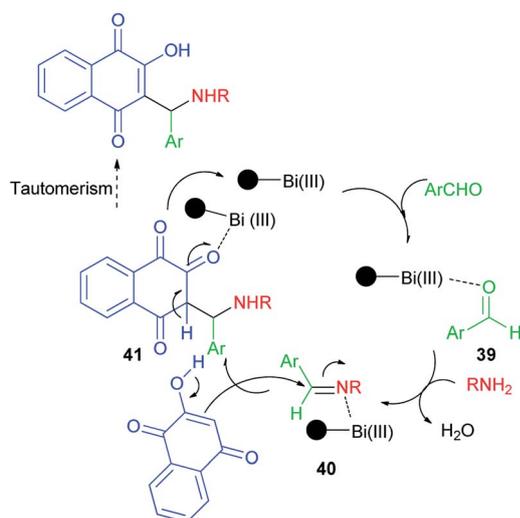
Scheme 26 Plausible mechanism for the Fe$_3$O$_4$@TDSN–Bi(III) catalyzed synthesis of aminonaphthoquinones **34–38**.

the presence of the catalyst to furnish intermediate **41** desired products and releases the catalyst for the next run.[53]

2.4. Other-types of catalyzed reactions

Enantioenriched naphthoquinone Mannich base **42** by organocatalyzed nucleophilic additions of 2-hydroxy-1,4-

naphthoquinone (**2**) to *in situ* formed imines has been reported by Westermann and Ayaz. In this process, lawsone (**2**) to preformed imine **43** using Takemoto's catalyst **44** (10 mol%) afforded the Mannich base **42** in only 40% yield and a very low
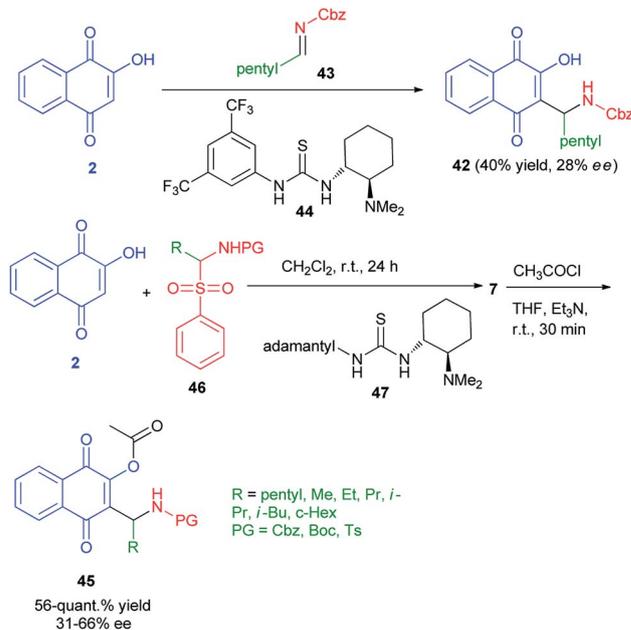
Scheme 27 Preparation of Mannich bases **42** and **45**.
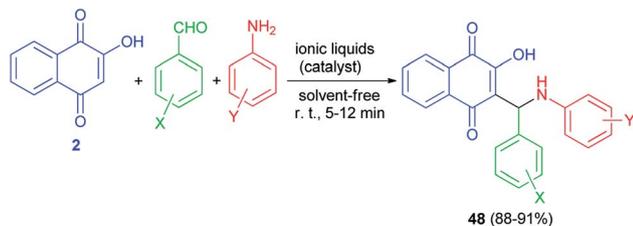
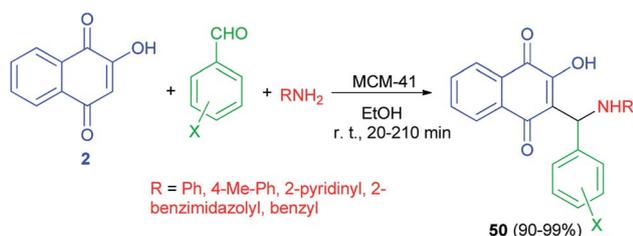**Scheme 28** Ionic liquid catalyzed synthesis of amino-naphthoquinones **48**.

Scheme 29 Task-specific ionic liquid catalyzed synthesis of naphthoquinone-urazole hybrids **49**.

Scheme 31 Montmorillonite K-10 catalyzed synthesis of amino-naphthoquinones **51**.

enantioselectivity of 28% ee. Also, enantioenriched naphthoquinone Mannich bases **45** have been synthesized by the reaction of **2** with α-amidosulfone **46** in the presence of organocatalyst **47** in CH_2Cl_2 at room temperature for 24 h. Then, the reaction of title product with acetyl chloride in the presence of Et_3N in THF at room temperature for 30 min gave the corresponding products **45** in 56-quant.% yield and 31–66% ee (Scheme 27).[54]

Condensation of 2-hydroxynaphthalene-1,4-dione (**2**), anilines, and aromatic aldehydes in the presence of the mild basic ionic liquids, (A) DBU [CH_3COO] (10 mol%), (B) Pyrr [CH_3COO] (15 mol%), (C) Pyrr[HCOO] (15 mol%), (D) Pip [CH_3COO] (10 mol%), (E) Pip[HCOO] (10 mol%), (F) [Hmim] [HCOO] (15 mol%) and (G) 3-HPAA (15 mol%) as the most efficient catalysts with respect to the reaction time and yields under solvent-free and ambient conditions for 5–12 min afforded the corresponding aminonaphthoquinones **48** in high to excellent yields (Scheme 28).[55] The proposed mechanism for the preparation of compounds **48** is similar to the first mechanism as indicated in Scheme 2.

Khurana et al.[56] described synthesis of naphthoquinone–urazole hybrids **49** in high yields (82–92%) via one-pot condensation of lawsone (**2**), various aromatic aldehydes having electron with-drawing and electron-releasing groups and 4-phenylurazole using task specific ionic liquid (bmim[HSO_4])

(10 mol%) at 60 °C for 1.5–2.5 h (Scheme 29). A mechanistic rationale portraying the probable sequence of steps is similar to the second mechanism as shown in Scheme 2. All newly synthesized compounds were screened for in vitro antioxidant and anticancer activities against human breast (T47D), colon (HCT-15), lung (NCI-H522), liver (HepG-2) and ovary (PA-1) cancer cell lines. The in vitro antioxidant and anticancer activity of these compounds revealed that all of the synthesized naphthoquinone-urazole hybrids **49** have a significant activity. 3-Bromophenyl, 2-methylphenyl, 2-naphthyl and 3-methyl-phenyl derivatives were more active among all the naphthoquinone–urazole hybrids.

Naimi-Jamal et al. succeeded in preparation of 2-hydroxy-1,4-naphthoquinone derivatives **50** from 2-hydroxynaphthalene-1,4-dione (**2**), aromatic aldehydes and heterocyclic or carbocyclic amines using MCM-41 nanoporous as catalyst in EtOH at room temperature for 20–210 min. The aromatic aldehydes carrying both electron-withdrawing and electron-releasing substituents were converted to their corresponding products in high yields (90–99%) (Scheme 30).[57]

An efficient one-pot protocol for the synthesis of 2-((substituted amino)(4-phenyl)methyl)-3-hydroxy-naphthalene-1,4-diones **51** has been developed by the three-component reaction of 2-hydroxynaphthalene-1,4-dione (**2**), aromatic

Scheme 30 MCM-41 catalyzed synthesis of amino-methylnaphthoquinones **50**.
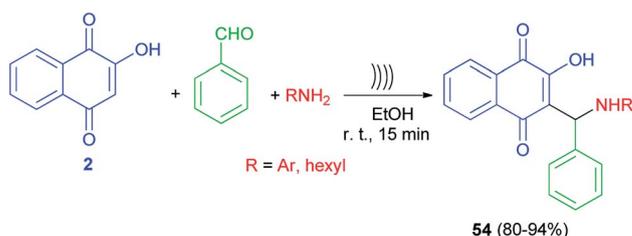
Scheme 32 Synthesis of Mannich bases **54** derived from lawsone under ultrasonic irradiation.
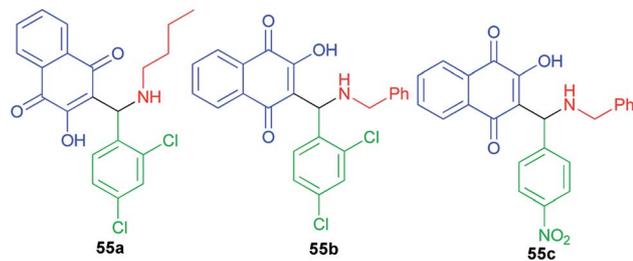
Fig. 3 Structures of 3-aminomethylnaphthoquinones 55a–c active against HSV-1.

Scheme 33 Synthesis of ferrocenyl aminohydroxynaphthoquinones 57.

Scheme 34 Synthesis of ferrocenyl aminohydroxynaphthoquinones 59.

aldehydes and anilines/heterocyclic amines using montmorillonite K-10 (10 mol%) as a catalyst in EtOH at room temperature for 8–10 h. Benzaldehydes and aromatic amines carrying both electron-donating and electron-withdrawing substituents and heterocyclic amines displayed high reactivity under this optimized conditions to afford the desired products in 81–93% yields. A speculative mechanistic explanation for this reaction is provided in Scheme 31. In the first step, aromatic amines attacked the activated benzaldehydes to form activated imines 52. The latter compounds reacted with lawsone, to give an intermediate 53 that underwent tautomerization to yield the products. Montmorillonite K-10 is likely to enhance the rate of Mannich reaction.[58]
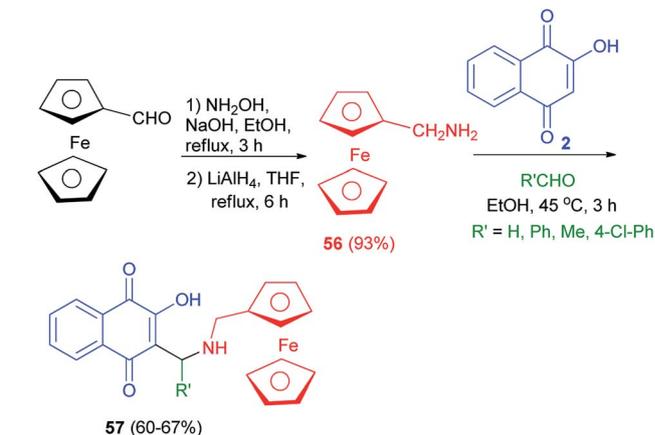
Lopez-Lopez et al. developed a non-catalytic effective procedure to prepare Mannich base lawsone derivatives 54 in 80–94% yields using one-pot three-component reaction of lawsone (2), amines and benzaldehyde promoted by ultrasound irradiation at room temperature for 15 min (Scheme 32).[59] A possible mechanism for the formation of 54 is proposed according to the first mechanism as indicated in Scheme 2.

A small series of 3-aminomethylnaphthoquinones 55a–c active against HSV-1 with low in vitro and in silico toxicity profile has been evaluated by Paixao and co-workers. In spite of the highest antiviral activity against HSV-1 of compound 55b, the most promising molecule is probably compound 55a due to its grater SI value (SI = CC_{50}/EC_{50}). All compounds exhibited L-phase of lytic replication. Compounds 55a–b also inhibited IE and E phases to different degrees and they affect gD protein expression (L-phase). Structural features, such the nature of the substituent on the nitrogen atom (benzyl versus n-butyl) the conformation and LUMO distribution and energy profiles seem to modulate the antiviral activity of these compounds (Fig. 3).[28]
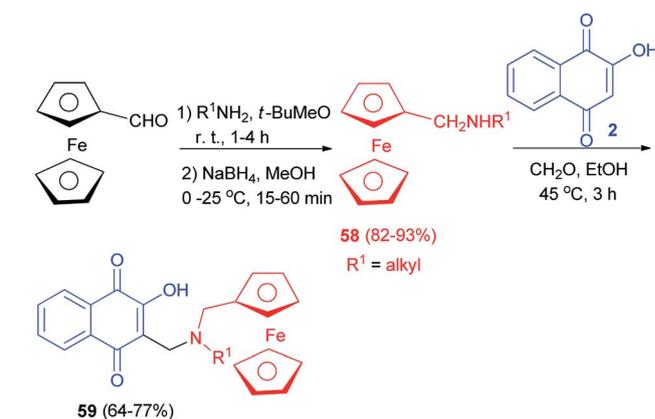
3. Synthesis of aminomethylnaphthoquinone Mannich base–metal complexes

3.1. Complexes derived from ferrocenylalkanamines

Ferrocenylmethylamine 56 was first synthesized from ferrocene carboxaldehyde by condensation of hydroxylamine on the aldehyde function followed by a reduction with LiAlH4. The amine 56 was obtained in 93% global yield. Ferrocenyl aminohydroxynaphthoquinones 57, analogues of atovaquone, were synthesized from 2-hydroxyquinone, ferrocenyl amines 56 and aldehydes in EtOH at 45 °C for 3 h in 60–67% yields (Scheme 33).[60]

Condensation of commercial amines on ferrocene carboxaldehyde followed by reduction with NaBH4 led to secondary ferrocenyl amines 58 in high global yield (82–93%). The ferrocenyl derivatives 59 were then prepared by condensation of lawsone (2) with the formaldehyde in the presence of the corresponding ferrocenylmethylamines 59 in EtOH at 45 °C for 3 h. Compounds 59 were obtained in 64–77% yields (Scheme 34).[60] Ferrocenic atovaquone derivative 59 composed of the hydroxynaphthoquinone core plus an amino-ferrocenic group and an aliphatic chain with 6–8 carbon atoms were found to be significantly active against T. gondii. Moreover, this novel compound were also effective against the atovaquone-resistant strain of T. gondii (AtoR).[44]

Following the procedure described in the literature,[60] the diamine 60 was prepared from commercially available N,N-dimethylaminomethylferrocene (61). The treatment of compound 60 with 2-hydroxynaphthoquinone (2) in the presence of acetaldehyde in EtOH at room temperature for 5 h afforded the compound 62 as a mixture of diastereomers in 55/
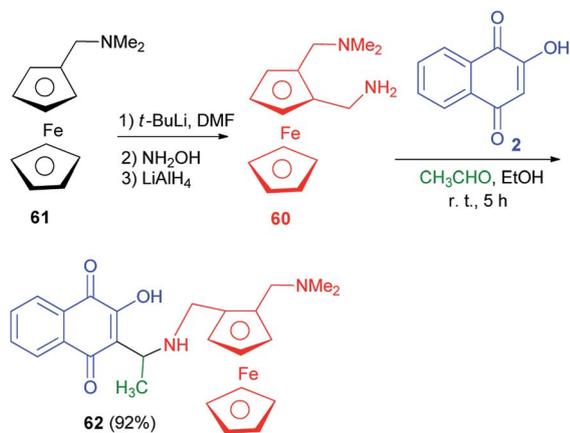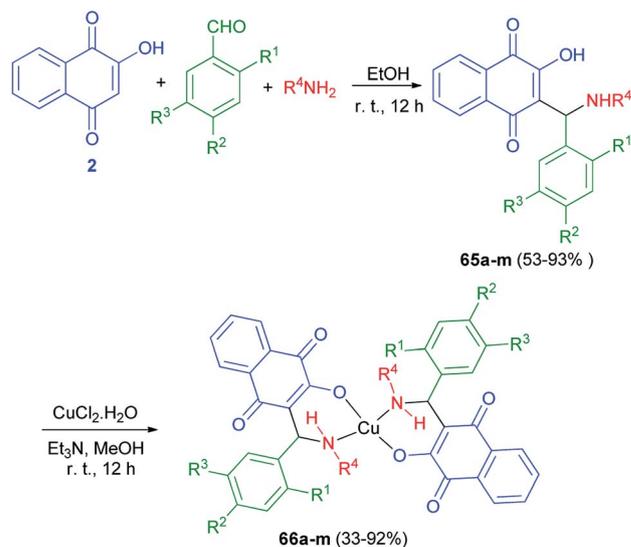
Scheme 35 Synthesis of 3{*N*-(2-(*N,N*-dimethylaminomethyl)ferrocenylmethyl)-1-aminoethyl}-2-hydroxynaphthoquinone **62**.

Scheme 37 Synthesis of Mannich bases of **65** and their copper complexes **66**.

45 ratio (92% yield) which cannot be separated by silica gel column chromatography (Scheme 35).[60]

The new Mannich bases **63a–c** were prepared in 57–98% yields *via* Mannich reaction of lawsone (**2**), aryl carboxaldehyde (2-pyridylcarboxaldehyde) for **63a**, 4-pyridylcarboxaldehyde for **63b**, and 3,4-difluorobenzaldehyde for **63c** and ferrocene-1-ylmethylamine (**64**) in EtOH at room temperature for 5 h. Analogously, compound **63d** was obtained in 25% yield from the reaction of **2** with ferrocene-1-yl carboxaldehyde and heptylamine in EtOH at room temperature for 5 h (Scheme 36). The 2-pyridyl derivative **63a** was distinctly more active than its analogs **63b–d** in breast, prostate and pancreatic cancer cells. Compound **63a** also exhibited greater antiproliferative effects in the androgen-receptor negative PC-3 prostate and Pgp-expressing KB-V1/Vbl cervix carcinoma cell lines. Compound **63a** reached sub-micromolar activities in these aggressive

cancer cells and, thus, features a promising drug candidate for the efficient treatment of hormone- or multidrug-resistant cancer types.[22]

3.2. Copper complexes

A series of novel Mannich bases **65a–m** derived have been synthesized in 53–93% yields from 2-hydroxy-1,4-naphthoquinone (**2**), substituted benzaldehydes and various primary amines (NH$_2$R^4, R^4 = *n*-butyl, benzyl, allyl, 2-furfuryl) in EtOH at room temperature for 12 h in the dark. Followed, their Cu^{2+} complexes **66a–m** have been prepared in 33–92% yields from the reaction of the compounds **65a–m** with CuCl$_2$.2H$_2$O in
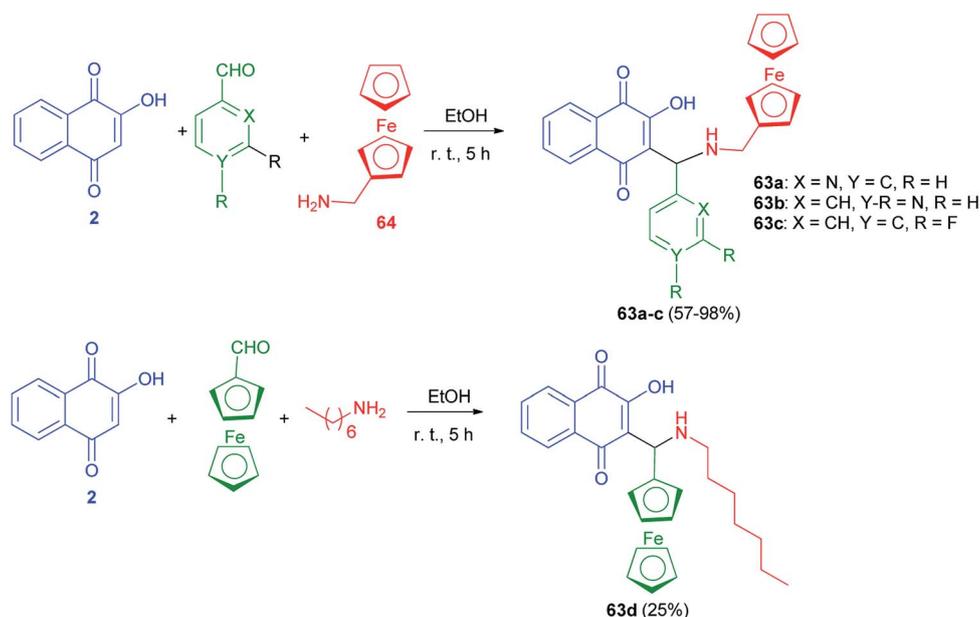
Scheme 36 Ferrocene modified lawsone Mannich bases **63**.
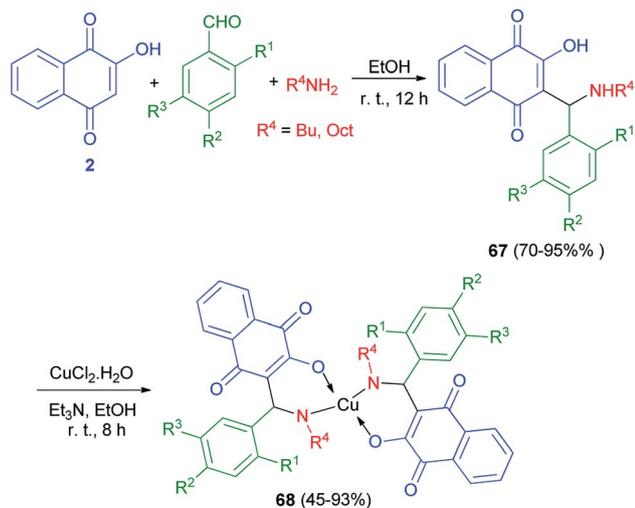
Scheme 38 Synthesis of Mannich bases **67** and their copper complexes **68**.

MeOH in the presence of Et₃N in the dark for 12 h at room temperature (Scheme 37). The antimicrobial activity of all compounds has been tested. In general, Mannich bases were more active than complexes, **65k** ($R^1 = OH$; $R^2 = H$; $R^3 = Me$; $R^4 = Bn$) and **65m** ($R^1 = OH$; $R^2 = H$; $R^3 = Br$; $R^4 = Bn$) being the most potent inhibitors. The MIC for the most active compound **65k** against *S. Coli* was 20 μmol L⁻¹ (8 μg mL⁻¹), better than chloramphenicol (90 μmol L⁻¹) and well below most values reported for other naphthoquinones.[25]

A new series of Mannich bases **67** derived from 2-hydroxy-1,4-naphthoquinone (**2**), substituted benzaldehydes and two primary amines, and their Cu²⁺ complexes **68** were synthesized by Cardoso and co-workers. At the first stage, 2-hydroxy-1,4-naphthoquinone (**2**) undergo an amino alkylation with butyl-amine or octylamine and benzaldehydes in EtOH at room temperature for 12 h, which led to lawsone derivatives **67** in high yields 70–95%. Complexes **68** were obtained by addition of triethylamine to an ethanolic suspension of compounds **68** and CuCl₂·2H₂O under stirring at room temperature for 8 h, with yields varying from 45 to 93% (Scheme 38). Compounds **68** evaluated for their potential as selective cholinesterase inhibitors (ChEIs). Eight copper complexes were identified and characterized as potent reversible and selective ChEIs with inhibitory potencies (IC₅₀) and constants of inhibition (K_i) ranging from 1.24 to 11.5 μmol L⁻¹. One of the compounds was particularly promising, showing IC₅₀ and K_i values of 1.24 ± 0.01 and 1.06 ± 0.01 μmol L⁻¹, respectively, for huAChE.[26]

A novel versatile tridentate 3-(aminomethyl)naph-thoquinone proligand, 3-[*N*-(2-pyridylmethyl)aminobenzyl]-2-hydroxy-1,4-naphthoquinone (**69**), was obtained from the Mannich reaction of 2-hydroxy-1,4-naphthoquinone (**2**) with 2-aminomethylpyridine and yielded a polymeric compound **70** in 57% yield. When the reaction mixture was left stirring under the same conditions for over 5 h benzaldehyde in EtOH at 22 °C for 5 h in 68% yield. The reactions of **69** with CuCl₂·2H₂O in the presence of Et₃N in MeOH at 30 °C yielded a polymeric compound **70** in 57% yield. When the reaction mixture was left
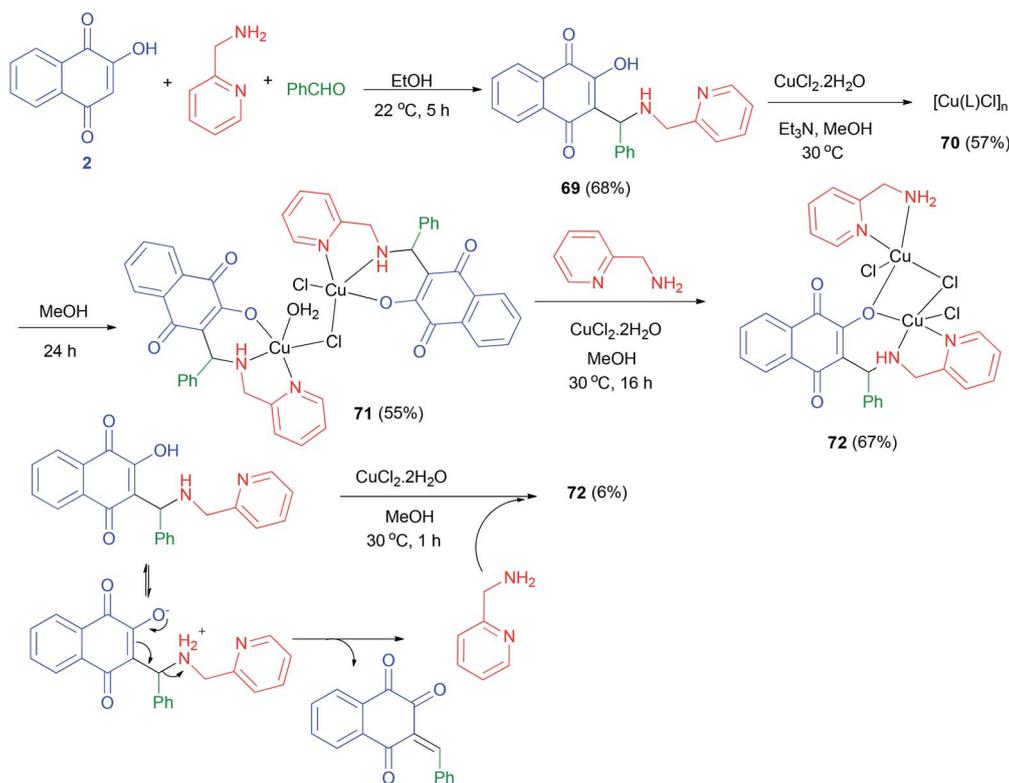
Scheme 39 Synthesis of Mannich base **69** and their complexes **71** and **72**.
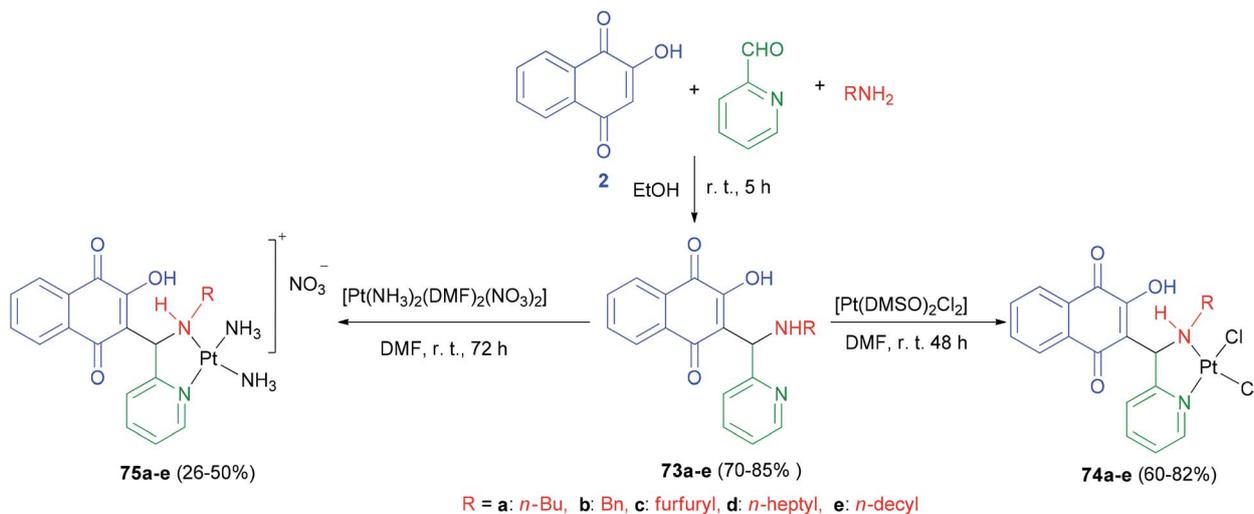
Scheme 40 Synthesis of 3-(aminomethyl)naphthoquinones **73** and their Pt-complexes **74** and **75**.

stirring under the same conditions for over 5 h darkening was observed. Dark green solid **71** isolated after 24 h in 55% yield. The reaction of complex **71** with 2-aminomethylpyridine in using CuCl$_2$·2H$_2$O in MeOH at 30 °C for 16 h in afforded complex **72** in 67% yield. Complex **72** could also be obtained in 6% yield from decomposition of **69** in methanol using CuCl$_2$-·2H$_2$O at 30 °C for 1 h (Scheme 39).[61]

3.3.   Platinum complexes

The first examples of platinum(II) complexes of 3-(aminomethyl) naphthoquinone Mannich bases **73** have been synthesized by Vargas and coworkers. Proligands 3-[(R^1-amino)(pyridin-2-yl) methyl]-2-hydroxy-1,4-naphthoquinones (R = *n*-Bu, **73a**; Bn, **73b**; furfuryl, **73c**; *n*-heptyl, **73d** and *n*-decyl, **73e**) were synthesized in 70–85% yields from the Mannich reactions of lawsone (**2**) with the respective primary amines and 2-pyridinecarboxaldehyde, in ethanol, under stirring, at room temperature for 5 h. The reactions of equimolar amounts of **73a–e** and *cis*-[Pt(DMSO)$_2$Cl$_2$] in dimethylformamide (DMF) at room temperature for 48 h in the dark yielded the chlorido complexes *cis*-[Pt(**74a–e**)Cl$_2$] **74a–e** in 60–82% yields as yellow solids (Scheme 40).

The amino complexes *cis*-[Pt(**75a–e**)(NH$_3$)$_2$]NO$_3$ **75a–e** were obtained as orange powders in 26–50% yields from the reactions of the solid proligands **73a–e** with a solution of *cis*-[Pt(NH$_3$)$_2$(DMF)$_2$](NO$_3$)$_2$ in DMF at room temperature in the dark for 72 h (Scheme 40). The cytotoxic activities of all compounds have been tested for different cancer cell lines. Proligands **73d** and **73e** have exhibited high activity against the tested cell lines, although they were only moderately active against the PC-3 cell line (IC$_{50}$ = 29.9 and 15.6 mmol L^{-1}, respectively). In general the compounds with the longest carbon chains (R = *n*-heptyl and *n*-decyl) have exhibited the highest activities.[62]

2-Hydroxy-3-(aminomethyl)-1,4-naphthoquinones **73a,d,e** derivatives, chlorido **74a,d,e** and amino **75a,d,e** Pt^{2+} complexes

were synthesized as described in the literature.[44] The DMF solutions of compounds [Pt(**73a,d,e**)(DMF)$_2$](NO$_3$)$_2$ were obtained by reacting a solution of AgNO$_3$ with **73a,d,e** in DMF at 50 °C for 24 h. [Pt(**76a,d,e**)(H$_2$O)$_2$](NO$_3$)$_2$ **76a,d,e** were obtained by dilution of the DMF solutions with water to a final concentration of 95 : 5 (H$_2$O : DMF). The water solution of [Pt(**68a**)(H$_2$O)$_2$](NO$_3$)$_2$ **76a** was also prepared using the same procedure above, except for the use of H$_2$O instead of DMF, for the gel mobility shift assays (Fig. 4). Several chlorido and amino Pt^{2+} complexes of 2-hydroxy-3-(aminomethyl)-1,4-naphthoquinone Mannich bases **73a,d,e** exhibiting moderate to high cytotoxicity against cancer cell lines were studied in order to investigate their modes of DNA binding, *in vitro* DNA strand breaks, mechanism of topoisomerase (Topo I) inhibition and cellular accumulation. DNA model base studies have shown that complex **74a** was capable of binding covalently to 9-ethylguanine (9-EtG) and 5′-GMP. The chlorido Pt^{2+} complexes **74a,d,e** highly accumulate in prostate (PC-3) and melanoma (MDA-MB-435) cell lines, being able to induce DNA strand
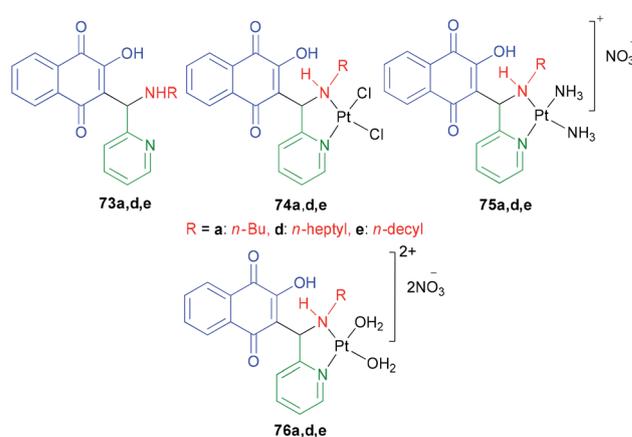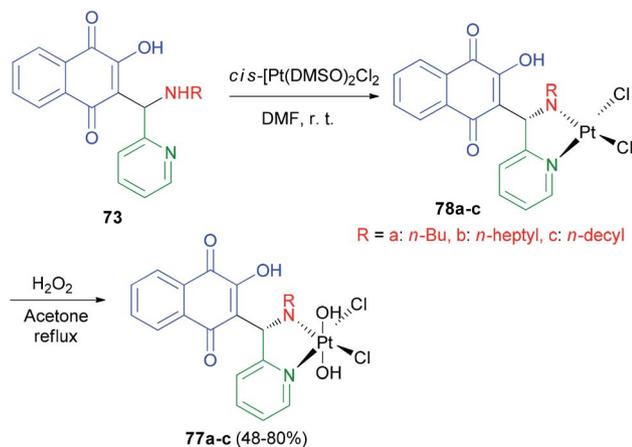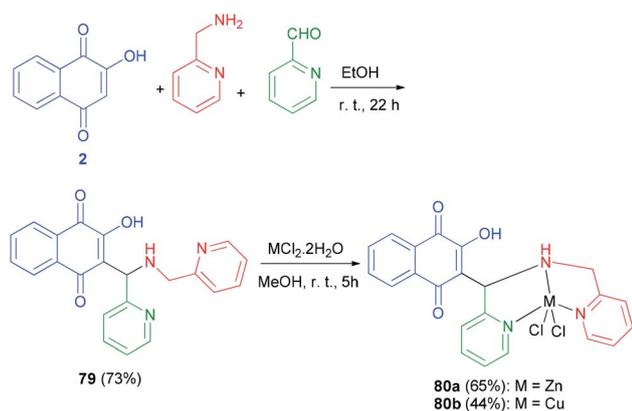

Fig. 4 Structures of 2-hydroxy-3-(aminomethyl)-1,4-naphthoquinones **73** and their Pt^{2+} complexes **74**, **75**, **76a,d,e**.

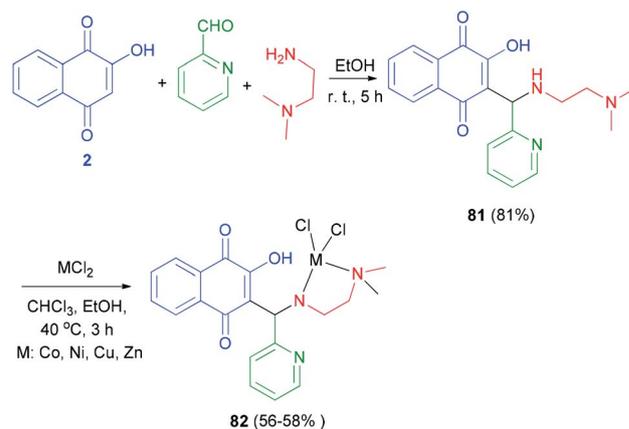**Scheme 41** Synthesis of Mannich base–platinum(IV) complexes **77a–c**.

Scheme 42 Synthesis of Mannich base **79** and complexes **80a–b**.

Scheme 43 Metal(II) complexes of Mannich base derived from lawsone **82**.

breaks *in vitro* and inhibit Topo I by a catalytic mode. On the other hand, the free 2-hydroxy-3-(aminomethyl)-1,4-naphthoquinones **73a,d,e** and the amino Pt^{2+} complexes **75a,d,e** neither cause DNA strand breakage nor exhibit strong DNA interaction, nevertheless the latter were also found to be catalytic inhibitors of Topo I at 100 μM. Thus, coordination of the Mannich bases **73a,d,e** to the "PtCl$_2$" fragment substantially affects the chemical and biophysical properties of the pro-ligands, leading to an improvement of their DNA binding properties and generating compounds that cleave DNA and catalytically inhibit Topo I. Finally, the high cytotoxicity exhibited by the free (uncomplexed) 2-hydroxy-3-(aminomethyl)-1,4-naphthoquinones **73a,d,e** might be associated with their decomposition in solution, which is not observed for the Pt^{2+} complexes.[63]

Vargas *et al.* described synthesis of three novel platinum(IV) complexes *cis,cis,trans*-[Pt(**77a–c**)Cl$_2$(OH)$_2$] **77a–c** (77 = 2-hydroxy-3-[(R-amino)(pyridin-2-yl)methyl]-1,4-naphthoquinone, R = *n*-butyl, **77a**; *n*-heptyl, **77b** and *n*-decyl, **77c**). In this process, the yellow-orange complexes **77a–c** were obtained by selective oxidation of **78a–c** with H$_2$O$_2$ (30%) in refluxing acetone for 7 h in 48–80% yields (Scheme 41). The cytotoxicity studies against

four human cancer cell lines have shown that in general the platinum(IV) and platinum(II) derivatives exhibit the same cytotoxic profile and are all more active than cisplatin. The lowest *in vitro* IC$_{50}$ values have been observed for **77b–c**, which bear ligands with the largest R groups being the most lipophilic. Furthermore similar IC$_{50}$ values for platinum(II) and platinum(IV) complexes of the same ligands have been associated with rapid *in vitro* reduction of the latter complexes to afford **77a–c**.[64]

3.4. Other-types metal complexes

Tridentate Mannich base **79** derived from lowsone, pyridine carboxyaldehyde and 2-aminomethylpyridine, have been synthesized in EtOH at room temperature in the dark for 22 h in 73% yield. Dichloro{3-[N-(2-pyridylmethyl)aminomethyl-2-pyridyl]-2-hydroxy-1,4-naphthoquinone}zinc(II) **80a** was obtained from the reaction of **79** with 1 equiv. ZnCl$_2$·2H$_2$O in methanol at room temperature in the dark for 5 h in 65% yield. The analogous dichloro 3-[N-(2-pyridylmethyl)aminomethyl-2-pyridyl]-2-hydroxy-1,4-naphthoquinone copper(II) complex **80b** was obtained from equimolar amounts of **79** and CuCl$_2$·2H$_2$O in methanol at room temperature for 5 h in 44% yield (Scheme 42).[65]

The Mannich base ligand **81** has been synthesized in 81% from lawsone, pyridine-2-carbaldehyde and N,N-dimethylethylenediamine in EtOH at room temperature for 5 h. Ligand **81** was dissolved in chloroform and then corresponding metal chloride (Co(II), Cu(II), Ni(II) and Zn(II)) dissolve in ethanol was added drop wise and stirred at 40 °C for 3 h afforded metal(II) complexes of Mannich base **82** in 56–58% yields (Scheme 43).[66]

4. Conclusions

Aminomethylnaphthoquinone Mannich bases derived from lawsone and their metal complexes belong to an important class of organic/organometallic compounds and exhibit a wide range of biological properties and due to their potent activities, thus thesynthesis of Mannich bases derived from lawsone is an area

of current interest. Several multi-component reactions for the synthesis of aminomethylnaphthoquinones have been reported from lawsone, aldehydes and amines using green solvents, Bronsted and Lewis acid catalysts, ionic liquids, ultrasound irradiation under room temperature, reflux and solvent-free conditions. Also, Metal complexes of 3-(aminomethyl)naphthoquinone Mannich bases have been synthesized from lawsone, aldehydes and organometallic amines or the reaction of Mannich bases with metal cations under different conditions. This review summarizes the most multi-component strategies in the synthesis of aminomethylnaphthoquinone Mannich bases derived from lawsone and their metal complexes and applications.

Conflicts of interest

There are no conflicts to declare.

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