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Novel naphthoquinone derivatives: Synthesis and activity against human African trypanosomiasis

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ABSTRACT

A series of naphthoquinone derivatives has been synthesized and tested for its biological activity against human African trypanosomiasis. The use of reverse micellar medium not only enhanced the conversion rate, but also showed selectivity towards mono-coupled product in aryl chloride–aniline coupling reactions. Two derivatives of naphthoquinone (**9b** and **9c**) exhibited potent activity against *Trypanosoma brucei* in vitro with low cytotoxicity.

The Human African trypanosomiasis (HAT), normally known as sleeping sickness, is a perilous and neglected parasitic disease. It is prevalent in at least 36 sub Saharan Africa countries. Most (96%) cases of HAT are caused by the *Trypanosoma brucei gambiense* protozoa, which is transmitted from infected animals to humans by bites of blood sucking tsetse flies (*Glossina* genus).[1–3] The medications currently used for treatment are unsafe and inefficient; for example, treatment with melarsoprol (a trivalent arsenical derivative) often results in fatal encephalopathy, agranulocytosis, and myocardial damage.[4,5] There is a dearth of effective treatment regimens to fight against HAT. The negligence towards this disease engenders a demand for new research projects to produce drugs which are effective against the disease as well as safe for human use.

During research conducted on the chemical genetics of *Plasmodium falciparum*, potential anti-malaria agents, such as naphthoquinones, were discovered through use of screening techniques such as high through-put screening (Scheme 1).[6]

A process development study of transition metal catalyzed coupling reactions is one of the most important areas for organic scientists because of the applications of these reactions in pharmaceuticals;[7] especially in synthesizing bioactive compounds to fight against various diseases such as parasitic diseases. One such class of drugs is naphthoquinones which has shown anti-malarial, anti-cancer, anti-diabetic, anti-fungal, anti-bacterial and anti-inflammatory activities since 1969,[8–10] until recently, where epoxy-1,4-naphthoquinones have also been used as inhibitors of human leukemia (THP1) cell proliferation.[11] Atovaquone is an example of a naphthoquinone that is in use as an antimalarial agent. It is believed that it interferes with the mitochondrial respiratory chain of the *Plasmodium* sp.[12] Because of their positive antimalarial activities; we tested the naphtaquinones against HAT and performed a structural activity relationship study. In a continuation of our ongoing research focused on novel chemical entities with antimalarial or antitrypanosomal activities we aim on synthesizing various bioactive compounds; examples include derivatives of hydroxypyrid-2-ones,[13] febrifugine,[14] and fexinidazole,[15]. Our previous structure–activity relationship study[13] revealed the following requirements for bioactivity against *T. brucei*: an electron withdrawing moiety, an aromatic ring (good source of electrons), an electronegative halogen and its position in the molecule. We decided to design a molecule which included a halogen at the 2nd position and an electron donating and/or withdrawing substitution on the aromatic rings (X, R^1 and R^2, respectively in Scheme 1). In the proposed molecule, substitution of R^1 and R^2 on various positions aid in our understanding of the effect of substitution on activity against *T. brucei*. Hence, we decided to synthesize a series of substituted naphthoquinone derivatives (Scheme 1).

Mital et al. synthesized various 2-substituted 1,4-naphthoquinone derivatives by using 2-bromonaphthalene as the starting material in a Heck coupling reaction followed by oxidation.[10] Similarly, some scientists used palladium catalyzed Suzuki cross coupling reaction of aryl chlorides and Boronic acids.[16] Tandon et al. have done exceptional work in chemoselective coupling reactions by using water as a solvent.[17–19] However, coupling reaction in water (Tandon process) has limitation of substrate specificity.[18] The catalytic amination of aryl halides, called as Buchwald–Hartwig reaction, has been proved to be an useful method for preparing a variety of arylamines.[20–25]

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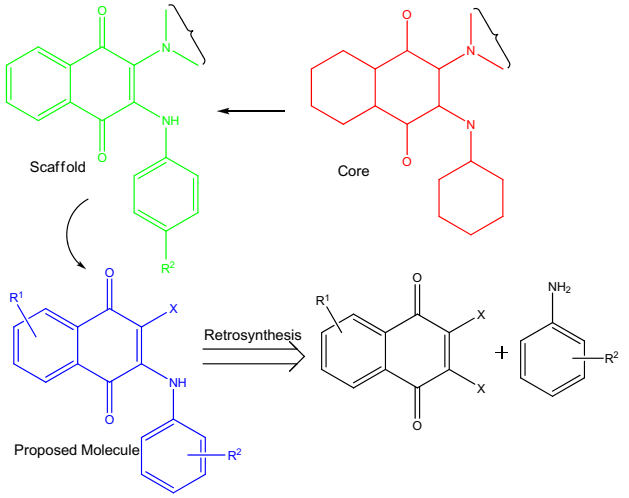


Scheme 1. Retrosynthetic approach for naphthoquinone derivatives. R^1 and R^2 = electron withdrawing or donating functional groups; X = halogen.

The design of novel, eco-friendly and cost effective synthetic processes for use in industry is an important goal. One of the best approaches involves the use of micellar micro-reactors, which possess a controlled balance of amphiphilicity and the ability to affect selectivity towards particular products.[26–32] In this study, we present the catalytic coupling reaction of anilines and aryl halides (Buchwald–Hartwig reaction) for synthesizing substituted naphthoquinones using reverse micellar micro-reactors.

We coupled 2,3-dichloronaphthalene-1,4-dione (RCl) and aniline ($R'NH_2$) using NaOH, L (10%), and $[cinnamylPdCl]_2$ (5%), in surfactant (sodium lauryl sulphate, SLS)–toluene as the reaction media and we not only observed a high % conversion but also enhancement in the selectivity towards **1b** (Table 1, entry 3).[33] The selectivity towards **1b** was very surprising because substitution of the activating group NHR on **1b** was expected to enhance the rate of formation of di-coupled **1a** product.

The above reaction suggest that in the presence of reverse micellar media (60 mM SLS surfactant) gave good yield of coupling reaction between aniline and 2,3-dichloronaphthalene-1,4-dione with reduced quantities of Pd catalyst and L (5 mol % Pd and 10 mol % L). It was also observed that the presence of surfactant micelles enhanced the % conversion and the selectivity towards the mono-coupled **1b** product of the reaction. Gas chromatography technique was employed to determine the exact % conversion to product **1**, and results were further confirmed by using ^1H and ^{13}C NMR spectroscopy.

The application of the process to derivatives of 2,3-dichloronaphthalene-1,4-dione with different substituted anilines is shown in Table 2, in which electron withdrawing and donating groups on aniline and electron withdrawing group (NO_2) on 2,3-dichloronaphthalene-1,4-dione gave good yields. The substitution pattern (2nd, 3rd and 4th position) on aniline does not appear to affect the yield.

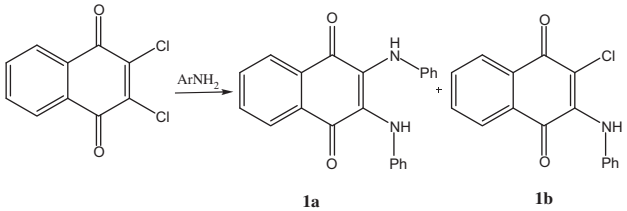
The synthesized compounds were evaluated on the basis of their ability to inhibit cell proliferation of *T. brucei* rhodesiense in culture.[34] The growth inhibitory activity against L-6 rat skeletal muscle myoblast cells was determined to establish a cellular therapeutic index.[35] The relationship between toxicity of naphthoquinone derivatives and substituted functional groups on the structure is still unknown and perplexing. Some naphthoquinone derivatives have shown to possess haemolytic activity and cause nephrotoxicity.[36,37] Hence, before proposing naphthoquinone derivatives as biologically active compounds, along with activity determination, in vitro toxicological studies becomes a prerequisite.

Compounds with mono-substitution (**b** and **c**) showed higher *T. brucei* rhodesiense inhibitory activity compared to di-substituted isomers (**a**). The presence of an electron-withdrawing chlorine group and phenyl amine ring with high electron density at two adjoining carbon atoms in the structure seems to be the main reason for this activity. This also showed the importance of selectivity towards mono-substituted product in coupling reaction. Compounds **1a** and **1b** showed effective *T. brucei* inhibitory activity and low cytotoxicity (Table 2, entry 1). However, compounds **2–4** showed lower inhibition activity compared to **1** but had low cytotoxicity (Table 2, entries 3–8). The decrease in the *T. brucei* inhibitory activity was attributed to the presence of an electron-donating group (Me) on the phenyl amine ring.

On comparing the *T. brucei* inhibitory activity of compounds **2–4** and **5–7** there is no correlation between the activity and the position of electron-donating group on phenyl amine ring (Table 2, entries 3–8 and 9–17).

To study the effect of electron withdrawing groups (NO_2 and CF_3) on the *T. brucei* inhibitory activity, we tested compounds **5–11** (Table 2, entries 9–27). We found that the presence of electrophile NO_2 on naphthalene-1,4-dione ring (with electron donating Me group on phenyl amine ring) in compounds **5–7** increased *T. brucei* inhibitory activity with a slight increase in cytotoxicity compared to compounds **2–4**. Surprisingly, compounds **8a** and **8b** with a CF_3 (electron withdrawing group) at the 2nd position on phenyl amine ring (without the presence of Me group on phenyl amine ring) showed *T. brucei* inhibitory activity with average cytotoxicity (Table 2, entries 18 and 19). Also the presence of NO_2 on naphthalene-1,4-dione ring and CF_3 on phenyl amine ring in compounds

Table 1
Synthesis of 2-chloro-3-(phenylamino)naphthalene-1,4-dione



1a **1b**

Entry	Reaction conditions	% Total conversion[a] (% selectivity)	Isolated yield (%)
1	Pd (10 mol %), L (20 mol %), THF (5 mL), 24 h, 70 °C	35, **1a** (90), **1b** (10)	**1a** (27), **1b** (5)
2	Pd (10 mol %), L (20 mol %), Toluene (5 mL), 24 h, 110 °C	2	—
3	Pd (5 mol %), L (10 mol %), Toluene (5 mL), SLS (60 mM), 5 h, 20 °C	62, **1a** (7), **1b** (93)	**1a** (3), **1b** (55)

[a] Determined by gas chromatograph. Each experiment was done three times.