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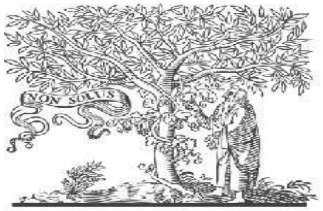

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A STUDY OF SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SUBSTITUTED 1, 4-NAPHTHOQUINONES AND THEIR BYPRODUCTS

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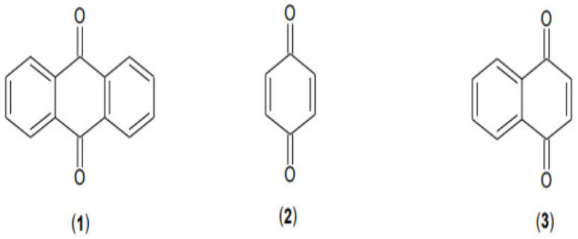
ABSTRACT
Innovative synthetic methodologies are enabling the creation of tailored quinone derivatives, driving progress in drug development, catalysis, and materials science. Furthermore, the medicinal potential of quinones, particularly as anticancer agents and antimicrobial compounds, is gaining prominence, with ongoing studies focusing on their mechanisms of action and therapeutic applications. In materials science, quinones are finding utility in the design of conductive polymers, organic photovoltaics, and molecular switches, owing to their tunable electronic properties. Additionally, quinones continue to play pivotal roles in environmental chemistry, impacting processes such as pollutant degradation and redox cycling in aquatic ecosystems. Finally, their biochemical significance remains paramount, with ongoing investigations into their roles in enzymatic reactions, respiratory chains, and electron transport chains. This abstract offers a concise overview of these emerging facets of quinone chemistry, highlighting their potential to reshape our understanding of these compounds and their practical applications across various scientific disciplines.

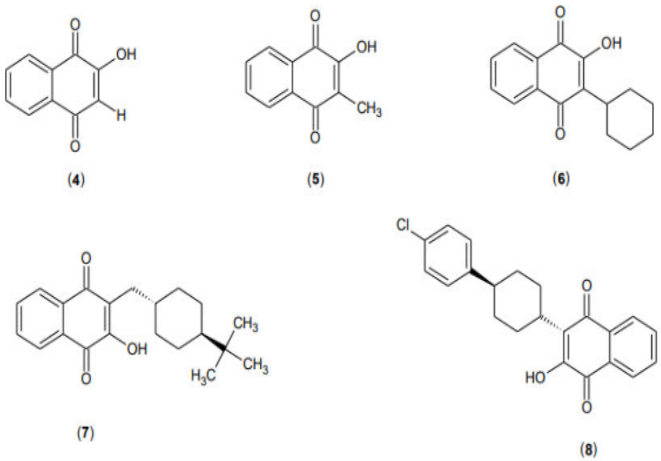
KEYWORDS: Biological Evaluation, Naphthoquinones, quinone derivatives, organic photovoltaics

INTRODUCTION

Synthesis of substituted quinones has received considerable attention in medicinal chemistry. Numerous studies of anthraquinones (1), benzoquinones (2) and naphthoquinones (3) have demonstrated biological potency as antibiotics1, antitumor agents2, vitamin E and K analogs and radical scavengers.



Hydroxy naphthoquinones are well known for their chemical and biological properties4. The hydroxy naphthoquinones like lawsone5 (4), phthiocol6 (5), parvaquone (6), buparvaquone (7) and atovaquone (8) have gained large interest due to their presence in natural products and their pharmacological properties as antitumoral, antiprotozoal, antiinflammatory, antiviral and antifungal agents.



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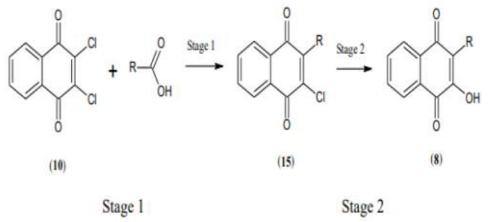
Atovaquone (8) is approved and marketed as a prescription drug for the treatment of Pneumocystis carinii pneumonia (PCP), a common parasitic lung infection of immunocompromised patients. It also displays potent activity as an antimalarial agent and has been used in the treatment of toxoplasmosis and babesiosis. The mechanism of action for Atovaquone (8) involves the inhibition of the mitochondrial electron transport in cytochrome complex-bc, which is linked to pyrimidine biosynthesis.

General procedure for synthesis of Atovaquone

2,3-Dichloro-1,4-naphthoquinone (10), substituted carboxylic acid derivatives, silver nitrate and acetonitrile were stirred at 25-300C for 15 min. Heated the mass to 75-80 0C. Added ammoniumpersulfate solution in water dropwise to the reaction mass. Maintained the reaction mass at 75-800C for 2-5hrs. Reaction progress was monitored by TLC. Cooled the reaction mass to 25-300C, filtered and extracted the product to dichloromethane. Filtered again to isolate the inorganic salts. To the filtrate (organic layer) sodium bicarbonate solution (10%) wash was given. Distilled off dichloromethane to isolate the intermediate trans-chloro derivative (15). It is later hydrolyzed using potassium hydroxide in aqueous methanol under reflux conditions to isolate the product Atovaquone (8), scheme 1.

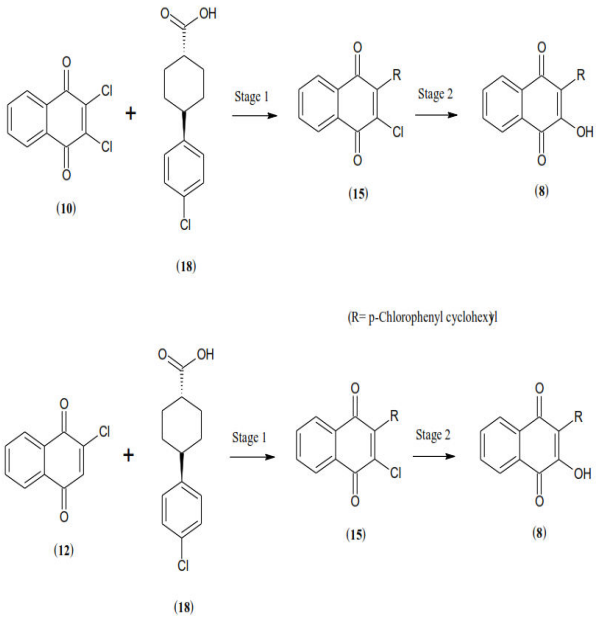
General reaction Scheme



(15), R= p-Chrorophenyl cyclohexyl (8), R = p-Chrorophenyl cyclohexyl (15a), R= Cyclohexyl methyl (8a), R= tert-butyl cyclohexyl (15b), R= Propyl (8b), R= Cyclohexyl (15c), R= tert-butyl cyclohexyl (15d), R= Cyclohexyl (15e), R= Phenyl

Scheme 1: Synthesis of 2-hydroxy-3-substituted-1,4-naphthoquinone derivatives by decarboxylative coupling (stage 1) and their subsequent hydrolysis (stage 2).

Selection of 2,3-dichloro-1,4-naphthoquinone (10)



Scheme 2: Reaction scheme for the synthesis of Atovaquone (8) using raw materials (10) and (12)

Literature search reveals that majority of the routes available for the synthesis of transchloro derivative (15) involves the use of 2-chloro-1,4-naphthoquinone (12). There are no reports on the use of 2,3-dichloro-1,4-naphthoquinone (10) for the preparation of trans-chloro derivative (15). The prohibiting cost of 2-chloro-1,4naphthoquinone (12) and its scarce availability, we explored the usage of 2,3dichloro-1,4-naphthoquinone (10) in

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place of 2-chloro-1,4-naphthoquinone (12). Apart from the usage 2-chloro-1,4-naphthoquinone (12) alone, we also tried to use the mixtures of these two raw materials in different proportions to find out its impact on the quality and quantity of the product.

In order to improve the raw material efficiency and also to minimize the effluent load, efforts are put on recovery of silver metal, subsequently converted to silver nitrate and also the solvents recovery for reuse. The results of these studies are discussed below. Preparation of Atovaquone (8) as per scheme 2 starting from of 2,3-dichloro1,4naphthoquinone (10) alone and combination of 2,3-dichloro-1,4-naphthoquinone (10) with 2-chloro-1,4-naphthoquinone (12) in various proportions has been studied. Intermediate trans-chloro derivative (15) is further hydrolyzed to get Atovaquone (8). Up to 4.0% of 2,3-dichloro-1,4-naphthoquinone (10) as contamination in trans-chloro derivative (15) allows us to go for hydrolysis of trans-chloro derivative (15) to get Atovaquone (8) without further purification and there was no much impact on the quality and quantity of Atovaquone (8). The detailed data of the study is summarized in Table 1.

Table 1 Selection of 2,3-dichloro-1,4-naphthoquinone (10)

Sl. no.	Quantity (10)	Quantity (12)	Ratio (w/w)	Yield (15)	Yield (8)	Purity (8)
1	5.0g	Nil	100:0	1.5g	0.9g	99.98%
2	4.5g	0.5g	90:10	2.0g	1.3g	96.98%
3	3.5g	1.5g	70:30	2.0g	1.3g	97.77%
4	2.5g	2.5g	50:50	2.1g	1.4g	96.15%
5	1.5g	3.5g	30:70	2.0g	1.3g	97.38%
6	0.5g	4.5g	10:90	2.0g	1.3g	97.54%
7	Nil	5.0g	0:100	1.2g	0.8g	99.93%

As per the tabulation, better yield was obtained when we use a mixture of 2, 3dichloro1,4-naphthoquinone (10) and 2-chloro-1,4-naphthoquinone (12) in equal ratios. For obtaining a product of required quality we need to purify Atovaquone (8) by recrystallization. It has been observed that the removal of impurities from Atovaquone (8) was always difficult. Purification involves repeated recrystallization which results in considerable loss of yield and also increase in the effluent load. It is also clear from the table that the purity of the product is good when 2,3-dichloro-1,4-naphthoquinone (10) alone was used instead of the mixture of (10) and (12). If we use 2,3-dichloro-1,4- naphthoquinone (10) alone, we get much purer material even though the yields are relatively lower, but much higher than using 2-chloro-1,4-naphthoquinone (12). If we consider the overall yield of the purer material, the yield is on the higher side, with minimum process steps. Further 2,3-dichloro-1,4-naphthoquinone (10) being a significantly cheaper and abundantly available raw material, it is advisable to use this as starting material rather than 2-chloro-1,4-naphthoquinone (12).

Majority of the prior arts have used the reaction of trans-4-(4-chlorophenyl) cyclohexane carboxylic acid (18) with 2-chloro-1,4-naphthoquinone (12) in presence of silver nitrate, ammoniumpersulfate, acetonitrile and water to get transchloro derivative (15) which upon hydrolysis in the presence of aqueous methanol and potassium hydroxide yielded Atovaquone (8). Use of 2,3-dichloro-1,4naphthoquinone (10) for the synthesis of Atovaquone (8) is not

reported so far. We are the first for reporting the use of 2,3-dichloro-1,4-naphthoquinone (10) for the preparation of Atovaquone (8). Hence this invention becomes novel and also patent non-infringing route for the synthesis of Atovaquone (8)28. Study of 2,3-dichloro-1,4-naphthoquinone (10) in the synthesis of Atovaquone (8) and the reaction optimization Atovaquone (8): {2-[trans-4-(4-chlorophenyl) cyclohexyl]- 3-hydroxy-1,4naphthoquinone} The reaction of Atovaquone (8) synthesis was split into two stages as stage 1 and stage 3. Stage 1 involves the use of 2,3-dichloro-1,4-naphthoquinone (10) in the synthesis of intermediate trans-chloro derivative (15) and stage 2 involves hydrolysis reaction to yield Atovaquone (8).

The main areas of the study for the improvement of yield, reagent efficiency and solvent efficiency in individual stages are given below. To get insight of the reaction, some of the byproducts formed in the reaction were isolated and characterized. These results are also discussed below.

Stage 1

1. Change in the sequence of addition of reagents
2. Variation in decarboxylative coupling agents
3. Variation in reaction solvents
4. Recovery and reuse of silver metal
5. Recovery and reuse of acetonitrile
6. Byproducts isolation/characterization
7. Preparation of analogues

Stage 2

1. Impact of use of dichloromethane addition for isolation.
2. Impact of different acids during acidification.
3. Recrystallization method development to prepare Atovaquone form I
4. Byproducts isolation
5. Preparation of analogues

CONCLUSION

In the present invention, naphthoquinone derivatives and few of their geometric/structural isomers were synthesized by a novel process using 2,3dichloronapthoquinone and characterized. The novel process has been optimized by varying different process parameters to get better yield and purity. Recovery and reuse of acetonitrile from mother liquors, since the above process uses large quantity of acetonitrile which is an expensive solvent and has become scare now a days, has been studied. The study also involved recovery and reuse of silver salt by further conversion to silver nitrate, since silver nitrate is also an expensive material and contribute significantly to the cost. The fate of silver from the above reaction is not known in any of the literatures, as we have found out for the first time the nature of silver salt and conversion to silver nitrate and reuse of the same in the reaction. During isolation of Atovaquone (8) from the reaction mass, acetic acid has been introduced instead of dilute hydrochloric acid, which resulted in the enhanced purity with removal of polar impurities. The present study focused on to provide Atovaquone form I of atleast 99% purity by using a combination of solvents. It is reported in the literature use of large quantity of acetonitrile for the recrystallization of Atovaquone to get form I. commercially this is not viable and large quantity of the solvent usage is a bottleneck in manufacturing. Surprisingly we have found that considerably small

quantity of combination of solvents produce form I and the output from the reactor can be enhanced significantly. All the objects are met in part or whole by the current process wherein 2,3-dihalo naphthoquinone compounds are used to prepare naphthoquinone derivatives, which may be further used to prepare 2-cyclohexyl-1,4-naphthoquinone derivatives such as Atovaquone, Parvaquone, tert-butyl Atovaquone. Industrially feasible, economical and environmentally benign process has been developed for the preparation of above products.

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