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A Systematic Study towards the Synthesis, Isolation, and Recrystallization of Atovaquone, an Antimalarial Drug: A Sustainable Synthetic Pathway

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Abstract

In the present work, studies were conducted towards the synthesis of 2-[trans-4-(4-chlorophenyl) cyclohexyl]-3-hydroxy-1 ,4-naphthoquinone 5 with systematic reaction and recrystallization condition optimization to isolate 5 in high yield with better purity. Synthesis of 5 was done by the hydrolysis of 2-[trans-4-(4-chlorophenyl) cyclohexyl]-3-chloro-1, 4-naphthoquinone 4, which was isolated by the decarboxylative condensation of trans-4-(4-chlorophenyl) cyclohexanecarboxylic acid 3 with naphthoquinone moiety. After the hydrolysis of 4, isolation of crude 5 was done by the use of acetic acid instead of dilute hydrochloric acid, product 5 was isolated in good purity with very less polar impurities. The study

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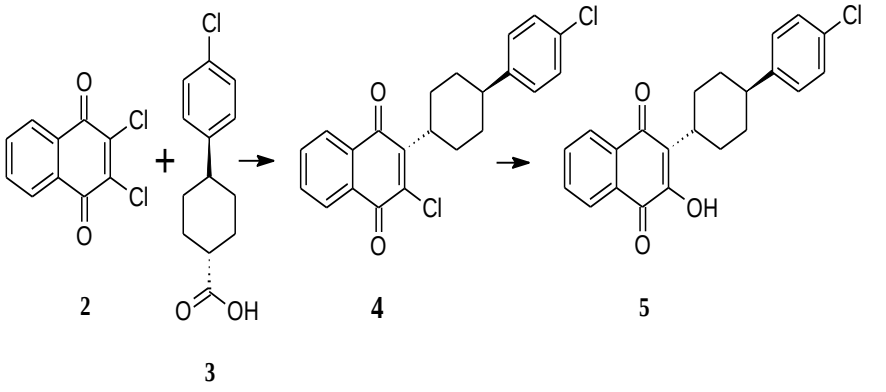
extends to provide the polymorphic form I of 5 by the use of solvent combination for the recrystallization, prior art reports the use of a large volume of solvent for the isolation of polymorphic form I of 5. The use of a large volume of solvent becomes a bottleneck for the commercial synthesis of 5. Our efforts towards optimization of hydrolysis reaction and recrystallization of 5 with the use of the small volume of solvent combination had made the process to be more cost-effective and commercially viable for large-scale manufacturing.



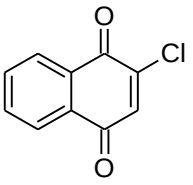
EMPHASIS: SYNTHESIS, OPTIMIZATION OF REACTION AND RECRYSTALLIZATION CONDITIONS

Keywords: 2-[trans-4-(4-chlorophenyl) cyclohexyl]-3-hydroxy-1, 4-naphthoquinone (Atovaquone), reaction optimization, isolation, recrystallization.

1. Introduction

Synthesis of substituted quinones had received considerable attention in the field of medicinal chemistry. Numerous studies on anthraquinones, benzoquinones, and naphthoquinones have demonstrated their biological potency as antibiotics [1] (Thomson, R. H.), antitumor agents [2] (Patai, S., & Rappoport, Z.), Vitamin E, and K analogs and radical scavengers [3] (Patai, S.). Hydroxy naphthoquinones are renowned for their pharmacological features [4] (Spyroudis, S.), compounds like Lawsone [5] (Sauriasari, R., et al.,), Phthiocol [6] (Lira, A., et al.,), Parvaquone, Buparvaquone and

Atovaquone [7] (Kessl, J. J., et al.,) 5 have gained large interest due to their biological activities as antitumoral, antiprotozoal, anti-inflammatory, antiviral and antifungal agents. [8] (Teimouri, M. B., et al.,). Clinically, 5 as such or its combination with Proguanil was found to be highly effective for the prevention of Plasmodium falciparum malaria. In combination with Proguanil, the ability of 5 to inhibit parasitic mitochondrial electron transport had got enhanced remarkably [9, 10, 11](Bakshi, R. P., et al., Tse, E. G., et al., and Tisnerat, C., et al .,).



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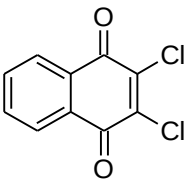

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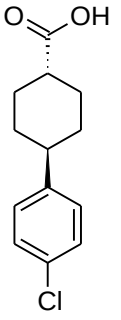

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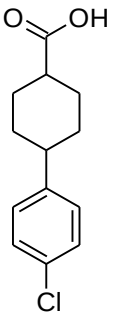

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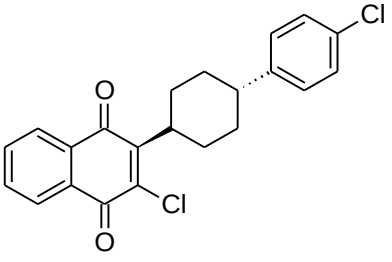

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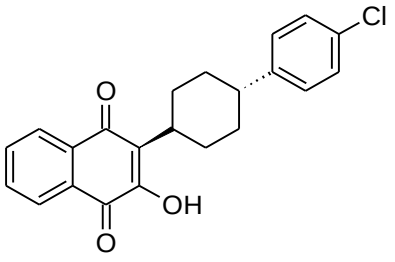

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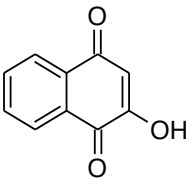
Prior art search discloses the extensive use of 2-chloro-1, 4-naphthoquinone 1 for the synthesis of 5 in relatively low yield. Hudson, A. T., et al., [12, 13] had reported the condensation of 1 and 3 in the presence of silver nitrate and ammonium persulfate to prepare 4. Potassium hydroxide mediated hydrolysis of 4 in presence of methanol had resulted in the formation of 5 in very low yield (4-5%). Williams, D. R., et al., [14] reported the condensation of 1 with 3a in presence of silver nitrate, ammonium persulfate,

dichloromethane, acetonitrile, and water, 4 was isolated in moderate yield (14%). Furthermore, phase transfer catalyst (Adogen 464) was used for the decarboxylative coupling of 1 with trans-1, 4-substituted cyclohexyl oxalate acid had resulted in significant-high yield (43%) with a 1.3 to 1.0 ratio of trans/cis isomers. Intermediates isolated were hydrolyzed in presence of potassium hydroxide and methanol to isolate crude 5 in good yield (94%), it was further recrystallized in acetonitrile to obtain pure 5.



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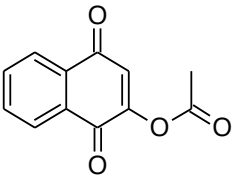

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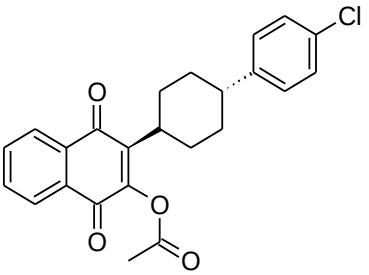

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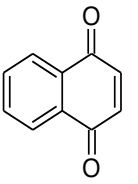
Antonio, N., et al., [15] had reported the use of Lawsone 6 to convert it to acetyl derivative 7, which in turn was decarboxylatively coupled with 3a to isolate the intermediate 8 as the mixture of trans/cis isomers (41.7% yield). Epimerization and deprotection of 8 to isolate 5 was done using sulfuric acid at different temperatures with varied yields, at 0-5^{0}C (67%), +15^{0}C (76%), and +5^{0}C (81%) respectively. Furthermore, work reports the direct conversion of 6 to 5 by oxidative decarboxylation with a poor conversion rate of (5-10%) by HPLC analysis with the formation of numerous byproducts.



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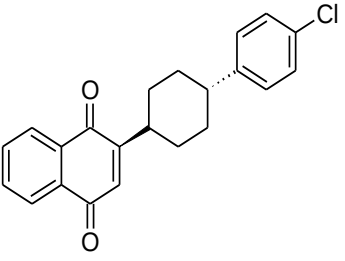

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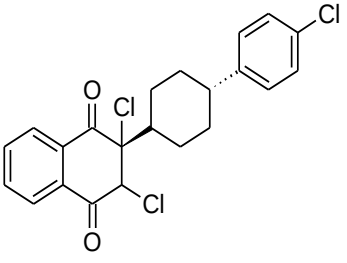

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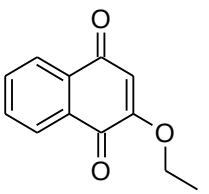
Kumar, A., et al., [16] treated 9 with 3 to isolate the intermediate 10 (20% yield) which later was halogenated 11 (85-95% yield), dehydrohalogenated 4 (70-89% yield), and hydrolyzed to isolate 5 (70-86% yield). Verma, S. S., et al., [17] reported the coupling of 1 with 3a to isolate the intermediate as a racemic mixture (47% yield) and further hydrolyzed to isolate 5 (67% yield). The work extends to report the conversion of cis isomer to trans isomer using xylene.



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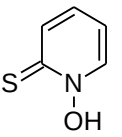

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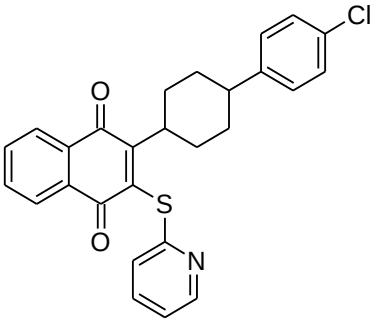

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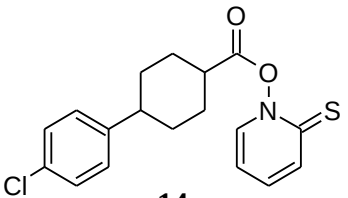

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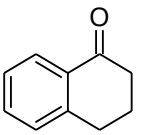
Wang, Yu.,et al., [18] reported a simple process with a one-step reaction to isolate 5 using 12 and 3a by the decarboxylative coupling pathway. Sanjay, S. S., et al., [19] reported the use of 2 and 3 for the synthesis of 4 by decarboxylative coupling (40% yield), and subsequent hydrolysis of 4 to isolate 5 (90% yield). Gui, H., et al., [20] reported the synthesis of 4 (40-50% yield) by coupling 1 and 3 using the solvents such as acetonitrile and dichloromethane for the oxidative decarboxylation. Various peroxides were used like sodium persulfate, potassium persulfate, sodium percarbonate, and potassium peroxy carbonate. Hydrolysis of 4 was done by using methanolic KOH solution and neutralization by aqueous HCl to isolate 5 (60-70% yield) after recrystallization in acetonitrile. Zhu, F., et al., [21] reported a process for the synthesis of 5 by the reaction of 3 with 13 to give 14 (87% yield), it was further condensed with 1 by irradiation using a 400W halogen lamp to give 15 (80% yield as a racemic mixture). Hydrolysis of 15 and its

subsequent isomeric separation was done to isolate 5 (12-80% yield). Vyas, J. R., et al., [22] reported the condensation of 1 and 3 to isolate 4 (16-19% yield), it was further hydrolyzed using KOH to isolate 5 (70-95% yield). Furthermore, recrystallization of 5 was reported in various solvents like isopropyl alcohol, acetone, acetonitrile, ethyl acetate, etc.



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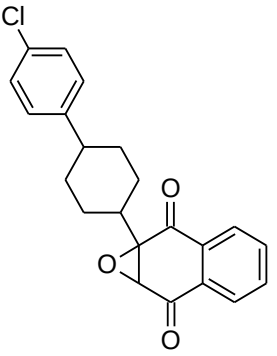

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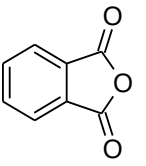

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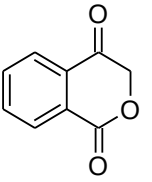
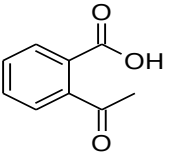


19

Roy, B. N., et al., [23] reported a multistep pathway for the synthesis of 5 using 16. The racemic mixture of 5 was isolated by the sulphuric acid treatment to 17. Work also reports the conversion of cis-isomer to trans-isomer by the impact of Lewis acid. Britton, H., et al., [24] reported the use of cheap and readily available 18, which was converted to 19 and then to 5 by the reaction with 3 through bromination, Rosenmund reduction, and rearrangement pathways.



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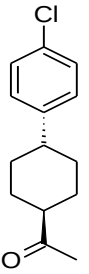

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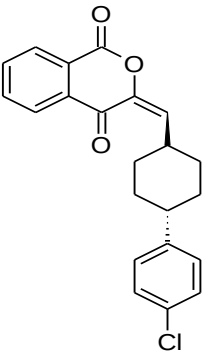
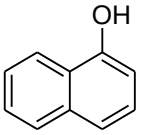


22

Dwyer, A. N., et al., [25] reported the reaction of 18 with malonic acid to form 20, further converted 19 by bromination and hydrolysis. Compound 22 was isolated by the reaction of 19 and 21, which in turn was converted to 5. Dike, S. Y., et al., [26] reported the single-pot synthesis of 5 (42% yield) using 9 and 3a (racemic mixtures) by decarboxylation followed by chlorination, dehydrohalogenation, hydrolysis, and epimerization in an acidic medium.



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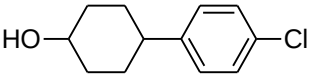

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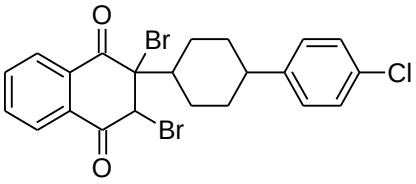

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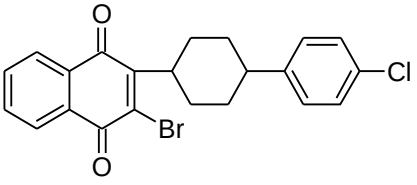

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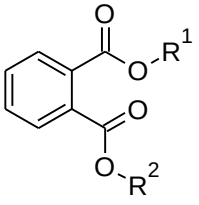
Dong, M., et al., [27] reported the multistep process for the synthesis of 5 by the condensation of 23 and 24. Further, the process carries on with the formation of a few intermediates to generate 25, which upon dehydrohalogenation will form 26, and its subsequent hydrolysis would isolate 5. Zhang, J., [28] reported the direct synthesis of 5 by the condensation of 12 and 3a, purification of crude 5 was done using chloroform and recrystallization in acetonitrile.



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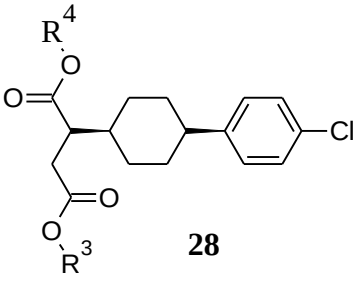

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Cui, Q., et al., [29] reported a method that uses 27 and 28 as raw materials, reaction pathway passes through alkali condensation, hydrolysis, and decarboxylation to obtain 10 and it was halogenated to isolate the dihalo intermediate, 4 will be isolated by the release of hydrogen halide. Furthermore, hydrolysis of 4 will result in the formation of 5.

The prior arts disclosed for the synthesis of 5 are not commercially viable due to various collective reasons such as, use of expensive starting materials, multi-step processes, issues related to static nature of crude 5, use of large volume of expensive solvent for the recrystallization and low yield. In the present work, 5 was prepared by a novel method with the use of cheaper key starting material 2 in high yield and purity. Hydrolysis of 4 to isolate 5 and its subsequent recrystallization pathways were optimized for the sustainability and commercial viability.

2. Materials & Methods

Present work involves the use of key starting materials 1 and 2, which were procured from DL Intrachem, and another starting material 3 was procured from Sigma-Aldrich. Reagents like silver nitrate, nitric acid, and acetic acid were procured from Rankem, ammonium persulfate, sodium bicarbonate, and potassium hydroxide from Sd fine chem and solvents (acetonitrile, dichloromethane, methanol, and N-methyl pyrrolidine) were procured locally in commercial grades. These key starting materials, reagents, and solvents were used in the experiments without further purification.

Melting points (m.p) of 4 and 5 were recorded by the open capillary method and are uncorrected. ^{1}HNMR spectra were recorded (in DMSO-d6/$CDCl_3$) on a 400 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Coupling constants *J* are in Hz and multiplicities are represented as a singlet (s), doublet (d), triplet (t), broad singlet (bs), and multiplet (m). Progress of the reaction, purity of intermediate, and product, were preliminarily evaluated by thin-layer chromatography (TLC) using precoated silica TLC plates (Merck $^{60}F_{254}$). Purity of the intermediate and product were established specifically by HPLC (Agilent, 1260 Infinity II LC System).

2.1. Synthesis & Recrystallization

2.1.a. Procedure for the synthesis of 4

Synthesis of 4 was done by the novel pathway with the use of 2 (100.00 g, 0.44 mol), 3 (105.14 g, 0.44 mol), silver nitrate (74.74 g, 0.44 mol), ammonium persulfate (301.23 g, 1.32 mol) and 1.0 L of acetonitrile were taken in the reactor. The reaction mixture was stirred at room temperature (RT) for 10-15 min. Added 1.3 L of DM water to the reaction mass at RT, heated to 70-75^{0}C, and maintained at the same temperature for 4-5 h. Product isolation along with recovery and reuse of essential reagent/solvents was done as per the method disclosed by us [19] (Sanjay, S. S., et al.,). Yield: 42% (71.27 g). $C_{22}H_{18}Cl_2O_2$, m.p. 186-188^{0}C.

2.1.b. Procedure for the synthesis of 5

4 (37.40 g, 0.097 mol) and 673.2 ml of methanol was taken in the reactor. Potassium hydroxide (37.40 g, 0.667 mol) was dissolved in 374 ml of DM water and added to the reaction mixture under stirring over a period of 15-20 min. The reaction mixture was then refluxed for 6-7 h and the reaction completion was monitored by TLC. After the reaction completion, the dark red colored reaction mixture was cooled to 10-15^{0}C and then acidified with acetic acid to get a yellow solid, which was filtered and washed thoroughly with DM water until neutral p^H. It was then dried under reduced pressure for 4-5 h at 50-55^{0}C to isolate 5. Yield: 95.5% (34.00 g). Purity: 99.0% (Area%).

2.1.c. Optimized/improved procedure for the synthesis of 5

4 (30.00 g, 0.078 mol), 150 ml of DM water, and 540 ml of methanol were taken in the reactor. Potassium hydroxide (30.00 g, 0.535 mol) was dissolved in 150 ml of water and added to the reaction mixture under stirring over a period of 15-20 min. The reaction mixture was then refluxed for 4-5 h and the reaction completion was monitored by TLC. After the reaction completion, the dark red colored reaction mixture was cooled to 25-30^{0}C and 150 ml of dichloromethane was added. The reaction mixture was further cooled to 10-15^{0}C and acidified with 75 ml of acetic acid to get a yellow solid, which was filtered and washed thoroughly with DM water until neutral p^H. It was then dried under reduced pressure

for 4-5 h at 50-55^{0}C to isolate 5. Yield: 96.7% (27.62 g), m.p. 217-219^{0}C.

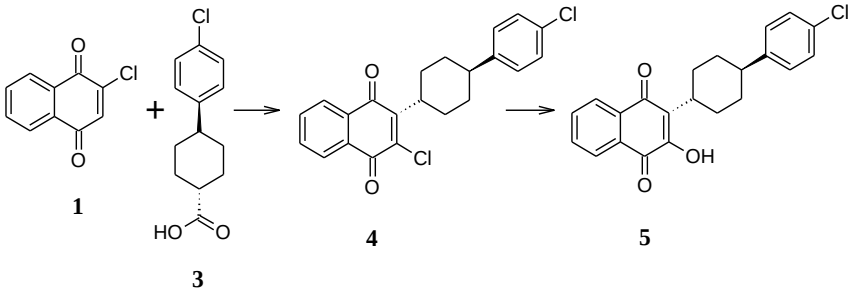
2.1.d. Procedure for the recrystallization of 5 using N-methylpyrrolidone and acetonitrile

Crude 5 (20.00 g) and 100 ml of N-methylpyrrolidone was taken in the reactor. Heated the mixture to 40-45^{0}C for about 30 min to get a clear solution and clarity filtration was done using hyflosupercel. The clear filtrate was taken into the reactor and cooled to 25-30^{0}C under stirring, 400 ml of acetonitrile was added to the solution over a period of 15-20 min. The resultant mass was cooled to 0-5^{0}C, under stirring for 30-45 min, filtered and washed with 50 ml of acetonitrile. It was then dried under reduced pressure for 4-5 h at 50-55^{0}C to isolate pure 5. Yield: 85.0% (17.00 g), m.p. 219-222^{0}C,IR (KBr, γmax, cm^{-1}): 3378.05 (OH group), 1656.71 (C=O group), ^{1}HNMR (400 MHz, $CDCl_3$): 8.12-8.14 (1H, d, *J*=7.68Hz), 8.06-8.09 (1H, d, *J*=7.52Hz), 7.70-7.76 (1H, t, *J*=7.6Hz), 7.66-7.68 (1H, t, *J*=7.52Hz), 7.50 (1H, s), 7.26-7.28 (2H, d, *J*=8.0Hz), 7.17-7.19 (2H, d, *J*=8.0Hz), 3.12-3.19 (1H, m), 2.60-2.66 (1H, m), 2.13-2.21 (2H, m), 1.95-1.98 (2H, m), 1.74-1.78 (2H, m), 1.52-1.62 (2H, m).^{1}HNMR (400 MHz, DMSO-d6): 10.87 (1H, s), 7.96-7.98 (2H, m), 7.74-7.84 (2H, m), 7.28-7.32 (4H, m), 3.05-3.31 (1H, m), 2.48-2.60 (1H, m), 2.11-2.19 (2H, m), 1.82-1.85 (2H, m), 1.60-1.63 (2H, m), 1.47-1.51 (2H, m). MS (m/z): 366.23.0 (M^+), 367.32 (M^+ +1), 365.31 (M^+ -2).

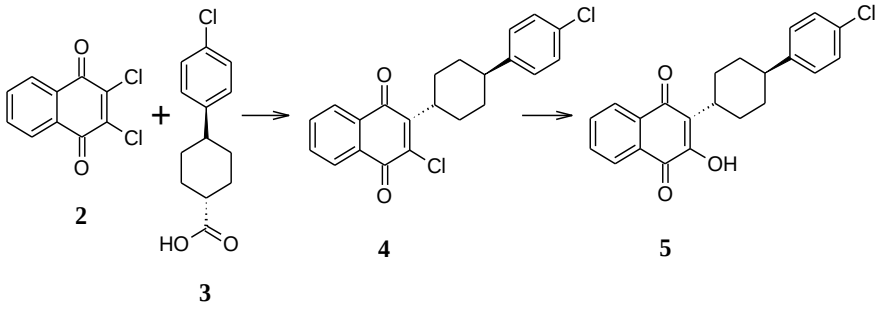
3. Results and discussion

3.1. Reasons behind the selection of 2 for the synthesis of 5

In the course of our investigations on the synthesis of 5, surprisingly we found that the condensation of 3 with the abundantly available, commercially inexpensive 2 in presence of silver nitrate and ammonium persulfate gave a reasonable yield (42%) of 4 which upon hydrolysis in presence of potassium hydroxide resulted in the formation of 5. Position 3 in 2 was occupied by a chlorine atom, it was not anticipated that it would be displaced by a bulky substituted cyclohexyl group. This unexpected finding had led us towards the systematic study of reactions using pure 1 (Scheme 1), its different mixtures with 2 and also with exclusive pure 2 (Scheme 2) for the synthesis of 5.



Scheme 1: Synthesis of 5 using 1



Scheme 2: Synthesis of 5 using 2

Distinct experiments were carried out (Table 1) and the quantitative and qualitative aspects were considered for the key starting material finalization to synthesize 5.

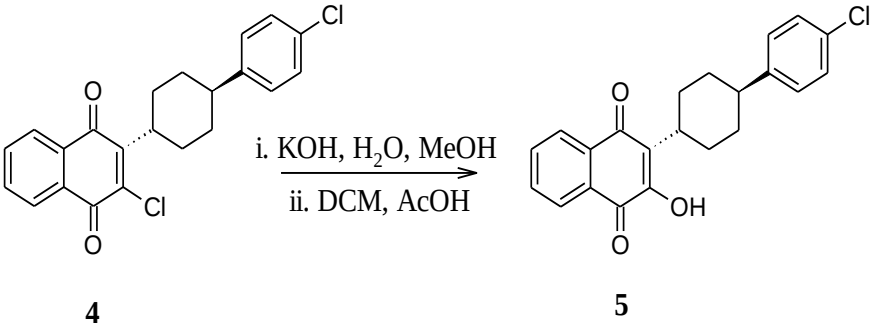
Table 1: Results of experiments conducted to select the key starting material for the synthesis of 5

Exp. No.	Input of 2	Input of 1	Yield of 4	Yield of 5	Purity of 5 by HPLC
1.	5.00 g	Nil	1.50 g	0.99 g	99.98%
2.	4.50 g	0.50 g	2.00 g	1.33 g	96.98%
3.	3.50 g	1.50 g	2.00 g	1.33 g	97.77%
4.	2.50 g	2.50 g	2.10 g	1.40 g	96.15%
5.	1.50 g	3.50 g	2.00 g	1.33 g	97.38%
6.	0.50 g	4.50 g	2.00 g	1.33 g	97.54%
7.	Nil	5.00 g	1.20 g	0.83 g	99.93%

The experimental results clearly show that the mixtures of 1 and 2 (Exp. No: 2-6, Table 1) gave better yields of 4 and 5 when compared to the yield obtained from either 1 (Exp. No: 7) or 2 (Exp. No: 1) alone. The preparation of pure 1 goes through a crude product that contains at least 10-12% of 2, our present work allows the direct use of this crude mixture based on the experimental findings. Furthermore, 5 isolated by the use of 2 had very less impurities compared to the variables used in other experiments. It had >90% of trans–isomer and <2% of cis-isomer along with the least impurities, whereas 5 isolated by the use of 1 had composed of 55-75% of trans-isomer and 3-7% of cis-isomer along with considerably high impurities. As per the experimental results, commercially viable key starting material 2 becomes an excellent source for the synthesis of 5 with an improved purity profile.

3.2. Optimization of isolation and recrystallization methods

3.2.a. Evaluation of acetic acid impact on the isolation of crude 5



4 **5**

Scheme 3: Hydrolysis of 4 to isolate 5

As per the prior art disclosure, hydrolysis of 4 was done by the use of potassium hydroxide solution in methanol and after the reaction completion, the mixture was acidified with hydrochloric acid to isolate crude 5. The product 5 so isolated had a lot of impurities, comprising more of polar impurities. It was very difficult to eliminate these impurities without significant yield loss, which was achieved by crystallizing from excess acetonitrile. Surprisingly, it was observed that acidification of the reaction mass (Scheme 3) by acetic acid had removed most of the major impurities and the purity of 5 was found to be not less than 99% (Table 2).

Table 2: Impact of acids on the quality of 5

Criteria	Rt (by HPLC) in min	AcOH impact (% Area)[a]	HCl impact (% Area)[b]
Impurity#1	4.50	0.09	0.12
Impurity#2	5.28	0.35	0.32
Impurity#3	10.64	0.08	0.10
Impurity#4	13.52	0.15	1.55
Impurity#5	17.46	0.26	0.03
5	20.23	99.00	97.80

Rt=Retention time, AcOH=acetic acid, HCl=hydrochloric acid

a. HPLC result of 5 isolated by the use of AcOH for the neutralization of reaction mixture.
b. HPLC result of 5 isolated by the use of HCl for the neutralization of reaction mixture.

3.2.b. Evaluation of dichloromethane impact on precipitation and filtration of crude 5

After the reaction completion (Scheme 3), the dark red colored reaction mixture was cooled to 25-30^{0}C, and dichloromethane was added. The reaction mixture was further cooled to 10-15^{0}C and acidified with acetic acid to get a yellow solid, which was filtered and washed thoroughly with DM water until neutral p^H. In the absence of dichloromethane, noticeable slow filtration was observed and the resulting crude 5 was too dusty and static in nature to handle. The addition of dichloromethane to the reaction mass prior to product precipitation helps in the formation of slightly crystalline/granular particles of 5 during acidification which eventually contributes to rapid filtration and drying process since the isolated crude 5 was nondusty and crystalline in nature.

3.2.c. Optimization of recrystallization method

As per the prior art disclosure, excess acetonitrile was used for the recrystallization of 5 to get the polymorphic form I. The method was not commercially viable due to the use of the large volume of solvent, hence it will be a certain bottleneck in large-scale manufacturing. We have done some experiments using different solvents and their combinations in relatively lower volumes to crystallize 5 in high yield and good purity (Table 3) to recommend

a feasiblere crystallization method. Surprisingly, we have found that, considerably small volume of combination of solvents to recrystallize 5 in good yield along with all the impurities well within the desired limits (Exp. No: 3, Table 3). Crude 5 was dissolved in N-methylpyrrolidone and added acetonitrile as an anti-solvent to precipitate 5 quantitatively. Optionally a few crystals of polymorphic form I of 5 (crystallized from acetonitrile alone) can also be added just prior to crystallization as a seeding material, to avoid the polymorphic contamination while large scale manufacturing of 5.

Table 3: Results of experiments conducted towards recrystallization of 5

Exp. No.	Input of 5	Solvent/s used	Method	Output
1.	1.00 g	80 mL of acetonitrile	Heated to dissolve and cooled gradually to RT.	0.72 g
2.	1.00 g	10 mL of N,N-dimethylformamide	Heated to dissolve and cooled to RT and then cooled further to 0-5^{0}Cfor 30 min.	0.44 g
3.	2.00 g	10 mL of N-methyl pyrrolidone and 40 mL of acetonitrile	Added N-methyl pyrrolidone, heated to dissolve, clarity filtered, added acetonitrile and cooled to 0-5^{0}C for 30 min.	1.66 g

3.3. Characterization of 5

The structure of 5 was established based on the ^{1}HNMR, mass, and IR spectrum reports. The 400MHz ^{1}HNMR spectrum (Figure S1a and S1b, Supplementary Information) of 5 in $CDCl_3$ showed a doublet (J=7.68Hz) in the range δ 8.12-8.14ppm was assigned for one proton attached to C5. The doublet (J=7.52Hz) in the range δ 8.06-8.09ppm was assigned for the one proton attached to C8. The triplet (J=7.6Hz) in the range δ 7.70-7.76ppm corresponds to one

proton attached to C6. The triplet (*J*=7.52Hz) in the range δ 7.66-7.68ppm was assigned for one proton attached to C7. The sharp singlet at δ 7.50ppm corresponds to the proton of the OH group being attached to C3. The protons attached to C18, C19, C20, and C21 were resonated as 2 doublets (*J*=8.0Hz) in the range δ 7.17-7.28ppm, integrated for 4 protons. The multiplet in the range δ 3.12-3.19ppm was assigned for a proton attached to C11. The multiplet in the range δ 2.60-2.66ppm was assigned to a proton attached to C16. The remaining 8 protons attached to C12, C13, C14, and C15 resonated as multiplets in the range δ 1.52-2.21ppm.

The 400MHz ^{1}HNMR spectrum (Figure S2a and S2b, Supplementary Information) of 5 in DMSO-d6 showed a sharp singlet at δ 10.87ppm corresponding to the proton of the OH group being attached to C3. The multiplet in the range δ 7.96-7.98ppm was assigned for 2 protons which are attached to C5 and C8. The multiplet in the range δ 7.74-7.84ppm was assigned for 2 protons which are attached to C6 and C7. The multiplet centered at δ 7.28-7.32ppm was assigned for 4 protons which were attached to C18, C19, C20, and C21. The multiplet in the range δ 3.05-3.31ppm was assigned for a proton attached to C11. The multiplet in the range δ 2.48-2.60ppm corresponds to a proton attached to C16. The remaining 8 protons which are attached to C12, C13, C14, and C15 were resonated as multiplets in the range δ 1.47-2.19ppm.

The IR spectrum (Figure S3, Supplementary Information) of 5 showed a characteristic absorption band at 3378.05 cm^{-1}, which was assigned for the OH group. The absorption band at 1656.71 cm^{-1} corresponds to the C=O group of the naphthoquinone ring.

The mass spectrum (Figure S4, Supplementary Information) of 5, showed (m/z): 366.23.0 (M^{+}), 367.32 (M^{+} +1), 365.31 (M^{+} -2). This would match to molecular formula $C_{22}H_{19}ClO_3$ with a molecular weight of 366.83.

4. Conclusion

In the present work, studies were conducted towards the synthesis and characterization of 5 along with systematic optimization studies towards reaction and recrystallization conditions. A novel synthetic procedure was adopted by the use of cheaper key starting

material 2 and it was condensed with 3 to generate 4. It was further hydrolyzed and recrystallized to isolate 5 in high yield and purity. The use of dichloromethane and the impact of acetic acid during neutralization were established by the experimental results, which had a direct influence on the qualitative aspects of 5. Our efforts towards optimization of hydrolysis reaction to isolate crude 5 and its effective recrystallization with a relatively lower volume of solvent combination had made the synthetic pathway cost effective and commercially viable for large-scale manufacturing.

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Supplementary information (SI)

The spectral details which are supportive to characterization aspects of 5 are available in the supportive information file (Figure S1a to S4, from page no. 4 to 9).

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