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REVIEW article

A progressive review on the synthesis of Atovaquone (an anti-malarial drug), empowered by the critical examination of prior-art disclosures

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Abstract: In this article, a systematic flow of contents was provided about the synthesis of Atovaquone **1a** on a critical examination of the prior arts. Several patents and study articles were published, disclosing different synthetic methods for the preparation of Atovaquone **1a** at various scales. Based on the starting materials used, there are a few one-step, two-step and multi-step synthetic routes were reported with varied yields. In this work, we have put in our sincere effort to collect all the synthetic routes of Atovaquone **1a** in detail with distinct and elaborate reaction schemes for better and collective process clarity. From this review, global researchers will get a platform to re-design or re-work the synthetic approach of Atovaquone **1a** with better atom economy and purity. In addition, the drug commercialization angle could also be looked at during the design stage itself alongside green chemistry concepts. We have done a chronic analysis of study articles to highlight the commercial feasibility of the disclosed synthetic methods. A special emphasis was given to the synthetic routes with process development initiatives towards, recovery/reuse of costly starting materials/ reagents/solvents and their feasibility for large-scale manufacturing of drug Atovaquone **1a**.

Introduction

Atovaquone (**1a**) is a popular anti-malarial drug, it belongs to the category of hydroxy-1,4-naphtho-quinones. Some essential details of **1a** are tabulated in **Table 1**, to have its brief outline. Other popular drugs falling under a similar category are Parvaquone and Buparvaquone. It is proven to be effective in the treatment of Pneumocystis jirovecii pneumonia and Plasmodium falciparum malaria [1, 2]. It is administered with the drug Proguanil, for a better therapeutic efficacy [3-5]. It is popular even as an effective anti-cancer, anti-viral, anti-protozoal, anti-inflammatory and anti-fungal agent [6-12]. The poor water solubility of **1a**, had enforced to build of a few of its prodrugs for better bioavailability [13]. The synthesis of substituted 2-hydroxy-1,4-quinones has received considerable attention in medicinal chemistry over the past few decades [14-16]. The drug under focus **1a**, has the hydroxyl (-OH) group attached to the naphthaquinone ring at position 2 and the substituted cyclohexyl group attached to position 3. Several patents and study articles were reviewed in detail for the disclosed synthetic strategies of **1a** with elaborate reaction schemes.

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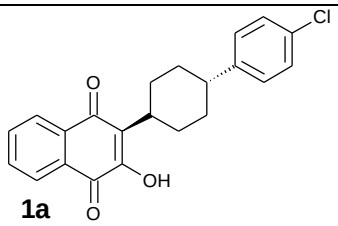
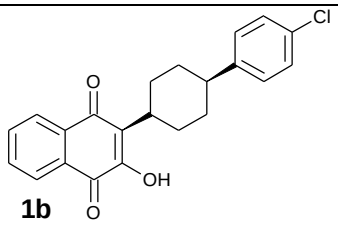
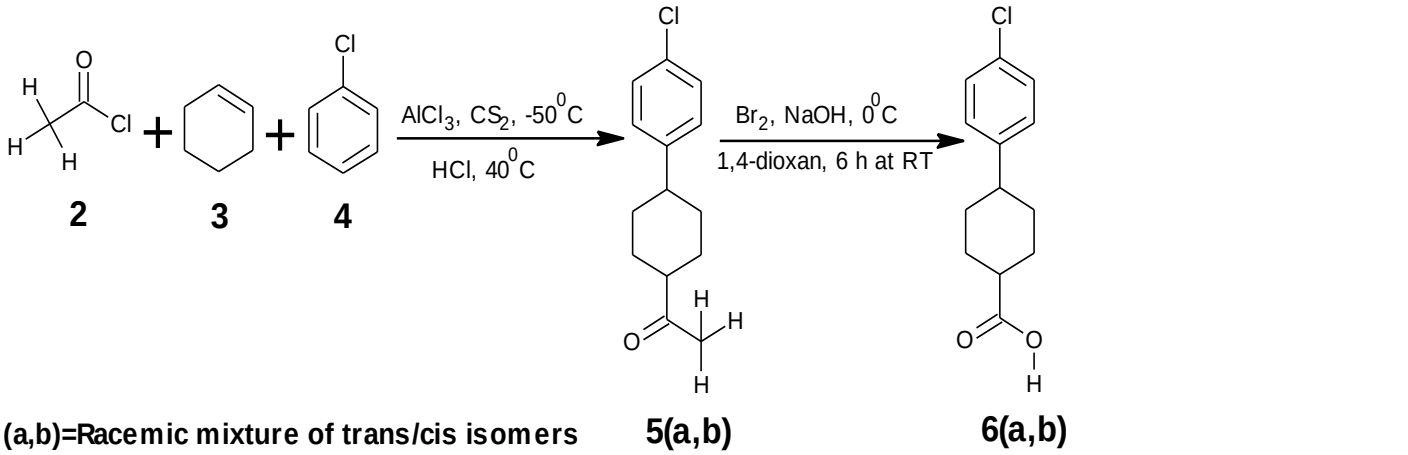
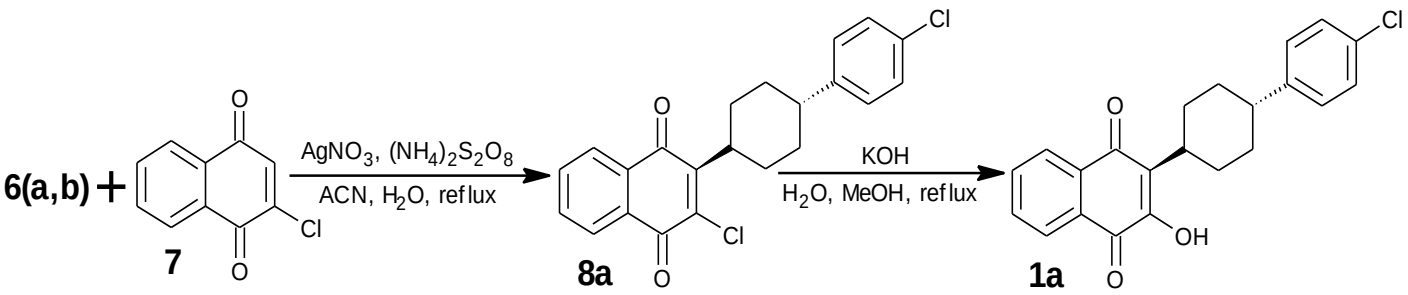
Table 1: Basic details about the drug, **1a**

Category	**Details**
Generic name	Atovaquone
Class	Naphthoquinones
Analogue of	Ubiquinone and Lawsone
Pharmacological activity	Anti-microbial
Brand/Trade name	Mepron, Malarone
Molecular formula	$C_{22}H_{19}ClO_3$
Molecular weight	366.84
Melting point (m.p.)	216 - 219°C
IUPAC name	*trans*-2-[4-(4-Chlorophenyl) cyclohexyl]-3-hydroxy-1,4-naphthalenedione
CAS registry number	95233-18-4
Drug bank accession number	DB01117
FDA approval	1999
The chemical structure of the drug, *trans*-Atovaquone	 **1a**
Chemical structure of *cis*-Atovaquone	 **1b**





Scheme 1: Synthesis of **1a** from **2**, **3**, **4** and **7**

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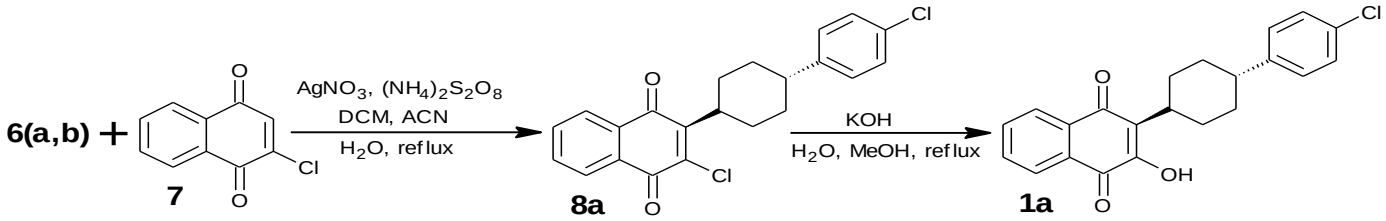
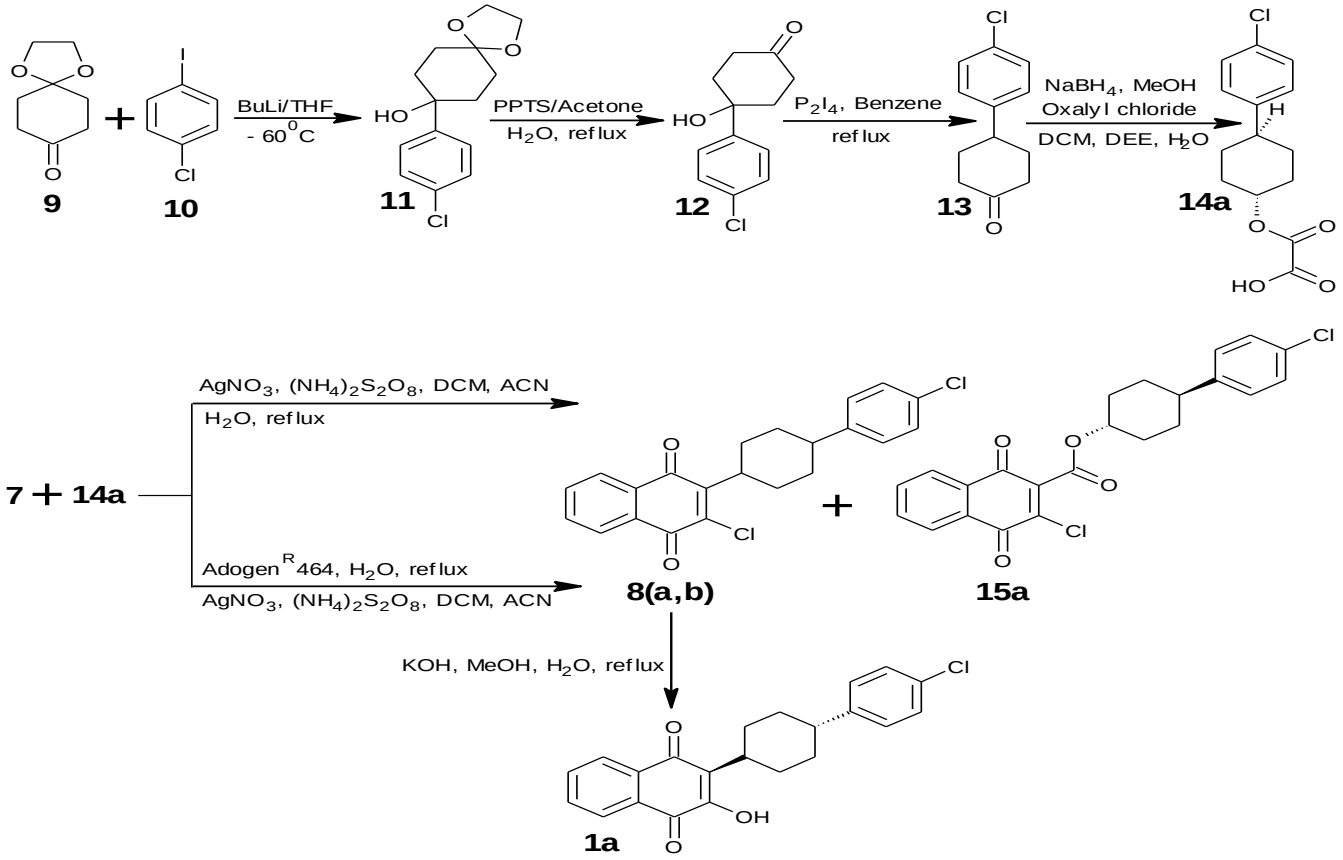
In 1989, Hudson et al. [17, 18] reported the reaction of acetyl chloride **2** and cyclohexene **3** at a low temperature in the presence of anhydrous aluminum chloride ($AlCl_3$) using carbon disulphide (CS_2). To the reaction mixture, added chlorobenzene **4** (as the reagent and solvent) at room temperature and maintained at 40ºC for 3 hr. It was quenched to cold hydrochloric acid (HCl) and the organic layer was retained for the acid wash, alkali wash, water wash, and solvent evaporation. The oily mass has finally been subjected to fractional distillation to obtain 1-[4-(4-chlorophenyl) cyclo-hexyl] ethenone **5**(**a**, **b**). The fraction boiling at 140-154ºC, which was enforced out under the reduced pressure of 0.1 mm Hg was collected as **5**(**a**, **b**). Bromine (Br_2) in an alkaline medium was reacted with **5**(**a**, **b**) in 1,4-dioxan for 6 hr., later acidified, filtered, washed, dried and recrystallized from ethanol to get 4-(4-chlorophenyl) cyclohexane-carboxylic acid **6**(**a**, **b**) with a m.p. of 254-256ºC. 2-Chloro-naphthalene-1,4-dione **7** and **6**(**a, b**) were coupled under the joint mediation of finely powdered silver nitrate ($AgNO_3$) and ammonium persulfate {$(NH_4)_2S_2O_8$} in acetonitrile and water under reflux, to get 2-chloro-3-[*trans*-4-(4-chloro-phenyl) cyclohexyl] n-aphthalene-1,4-dione **8a** with a m.p. of 172-175ºC. Hydrolysis of **8a** using potassium hydroxide (KOH) in aqueous alcohol, followed by acidification, filtration and recrystallization from acetonitrile gave **1a** with a m.p. of 216-219ºC (yield: 3.98%, as from **7**), (**Scheme 1**). Due to poor yield, the disclosed process is not suitable for the large-scale manufacturing of the drug.



Scheme 2a: Synthesis of **1a** from **6**(**a**, **b**) and **7**



Scheme 2b: Synthesis of **1a** from **7**, **9**, **10** and **14a**

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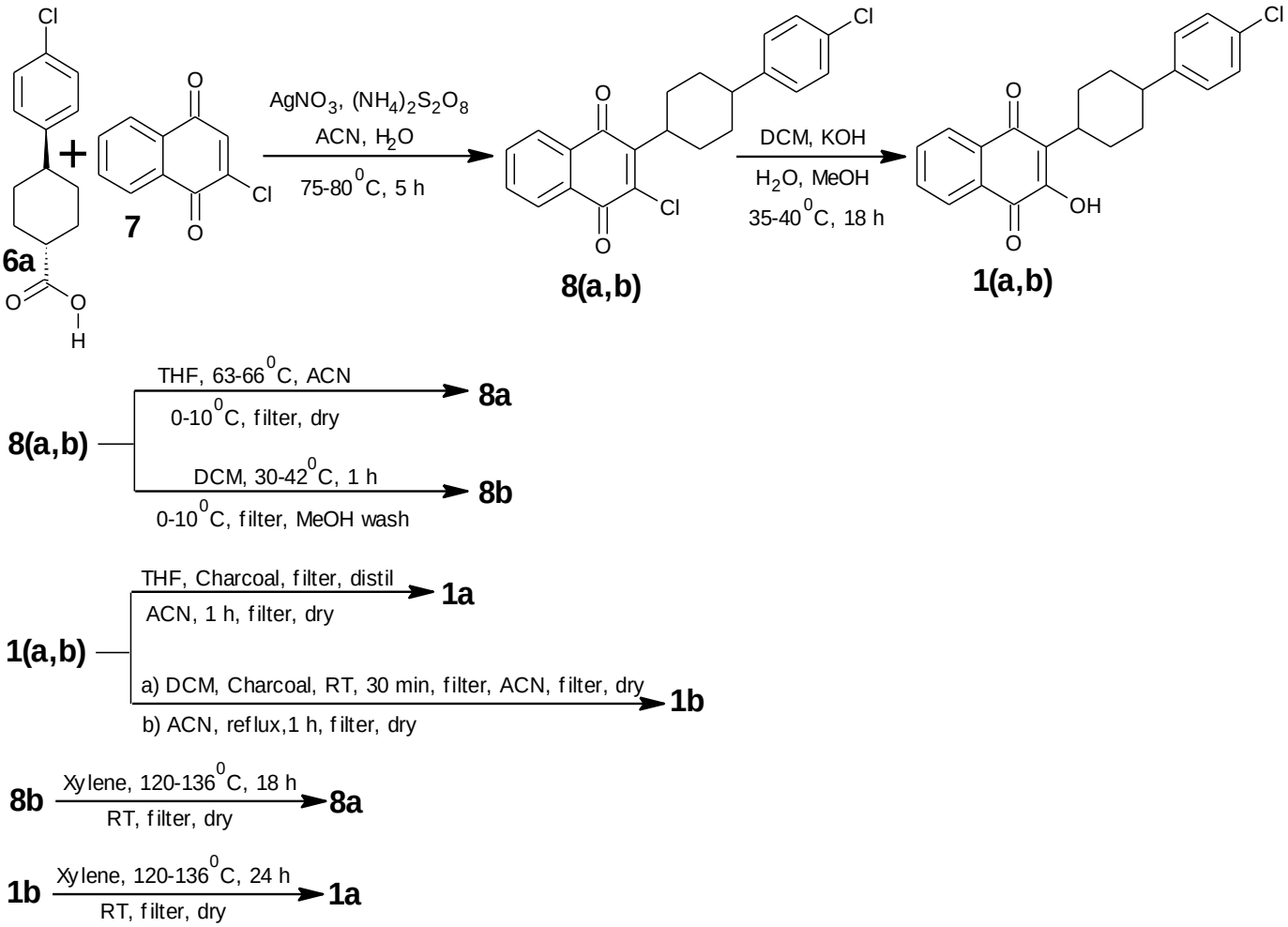
Inspired by the initiatives of Coppa et al. [19], in 1998, Williams et al. [20] demonstrated the condensation of **6**(**a**, **b**) and **7** under the catalytic influence of $AgNO_3$ in the presence of $(NH_4)_2S_2O_8$ using a bi-phase solvent system comprising dichloromethane and aqueous acetonitrile to get **8a** (yield: 14%). Hydrolysis of it by KOH solution in methanol, followed by acidification and recrystallization from hot acetonitrile gave **1a** (yield: 14.01%, as from **7**). Substantial yield improvement was observed by the use of the aqueous bi-phase solvent system for the process (**Scheme 2a**). Further, 1,4-dioxaspiro[4.5]decan-8-one **9** and 1-chloro-4-iodobenzene **10** have been reacted in the presence of butyl-lithium (BuLi) in tetrahydrofuran (THF) at -60ºC to get 8-(4-chloro-phenyl)-1,4-dioxaspiro[4.5]decan-8-ol **11**. Hydro-lysis of it using pyridinium-*para*-toluene sulfonate (PPTS) and aqueous acetone gave **12**. Diphosphorous tetraiodide (P_2I_4) mediated de-oxygenation of **12** in benzene had led to the formation of 4-(4-chloro-phenyl) cyclohexanone **13**. It was subjected to reduction using sodium borohydride ($NaBH_4$) in methanol, followed by acylation using oxalyl chloride in dichloromethane and water quench gave {[*trans*-4-(4-chlorophenyl) cyclo-hexyl]oxy} (oxo)acetic acid **14a** (yield: 65%, as from **9**). **7** and **14a** were reacted under the above said bi-phase solvent system to get the mixture of **8**(**a**, **b**) (yield: 5%) along with *trans*-4-(4-chloro-phenyl) cyclohexyl 3-chloro-1,4-dioxo-1,4-dihydr-onaphthal-ene-2-carboxylate **15a** (yield: 15.0%). The introduction of a phase transfer catalyst (Adogen®464) for the above reaction showed a drastic rise in the conversion rate to generate the mixture of **8**(**a**, **b**) (yield: 43.0%) along with **15a** (yield: 38.0%). Interestingly, the reaction of **7** and **14a** under silver nitrate mediation in the presence of $(NH_4)_2S_2O_8$ using acetonitrile had failed to go for the conversion, to form either **8**(**a**, **b**) or **15a** (**Scheme 2b**). The multi-step pathway, relatively low yield and the formation of isomeric mixtures had made this process to be fine-tuned further to suit for a large-scale manufacturing of the drug.



Scheme 3: Synthesis of **1a** from **6a** and **7**

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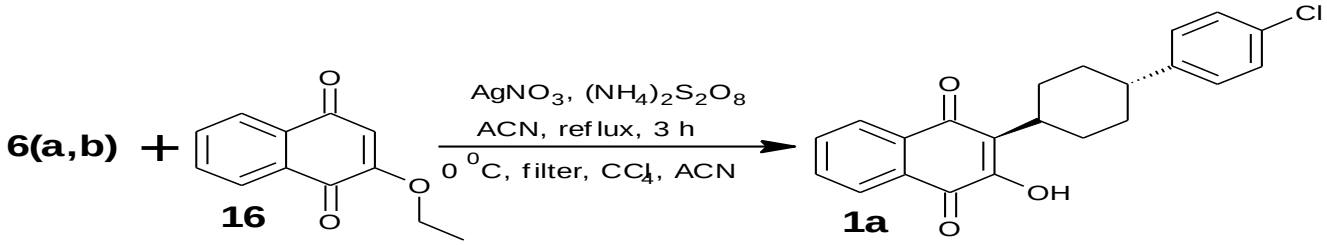
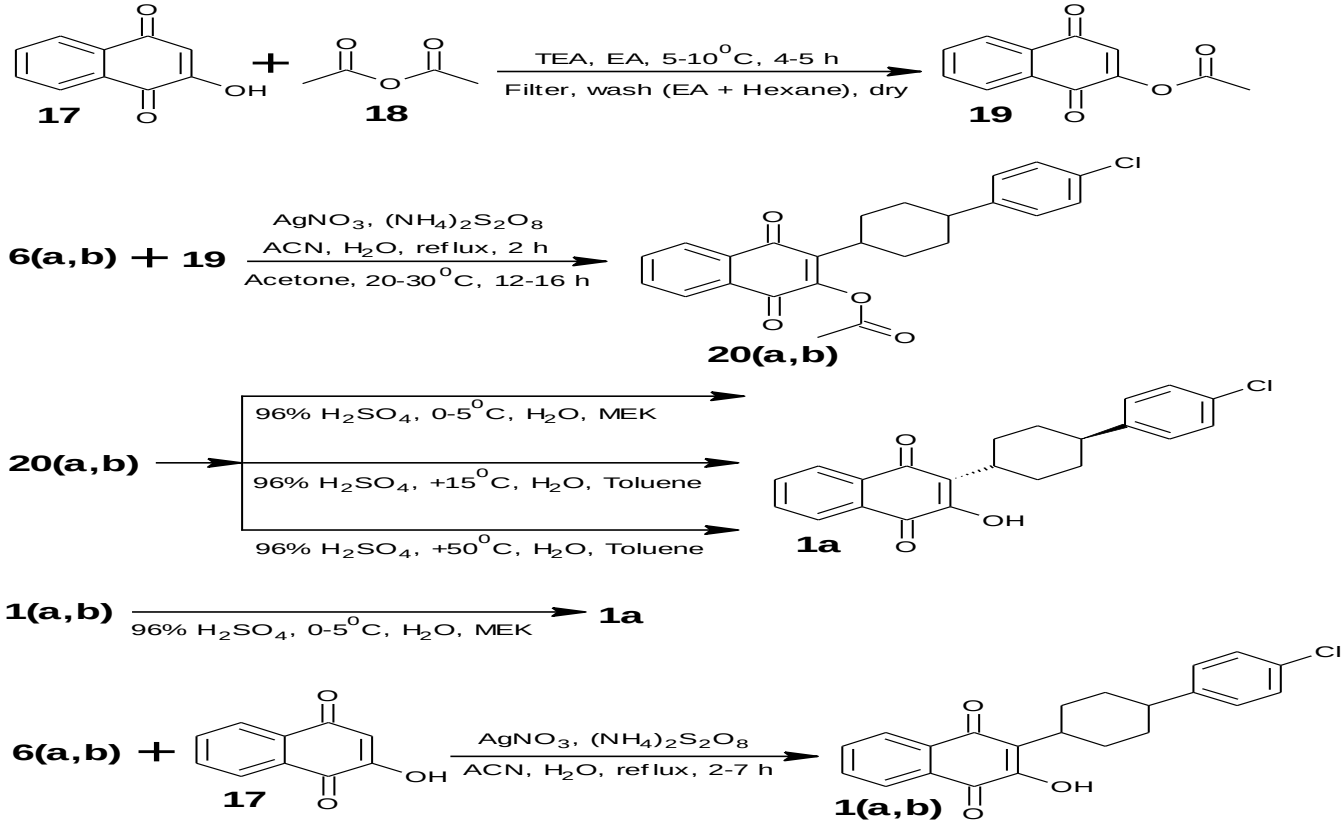
In 2008, Verma et al. [21] illustrated the $AgNO_3$ and $(NH_4)_2S_2O_8$ mediated condensation of **6a** and **7** in acetonitrile and water at 75-80°C for 5-6 hr., followed by distillation, cooling, water wash and drying to get **8**(**a**, **b**) (yield: 47.0%). Dichloro-methane was added to the mixture, stirred at RT for 1.0 hr. and filtered. The filtrate obtained was directly taken up for alkali (KOH) mediated hydrolysis in aqueous methanol at 35-40°C for 18-20 hr. Post reaction completion, added HCl to adjust the acidity to pH: 2 before the filtration to get **1**(**a**, **b**) (yield: 67.0%). It was subjected to charcoal treatment in THF, followed by solvent evaporation, acetonitrile addition and filtration to get **1a** (yield: 22.0%-23.0%, as from **8**). In addition, the work emphasizes the solvent/temperature-mediated inter-conversion of racemic mixtures (intermediate or crude final product) to their respective pure isomeric forms (**Scheme 3**). This process was executed in a substantial-high scale with moderate yield, thus gaining the feasibility for large-scale manufacturing with isomeric inter-conversion capability.

In 2008, Wang et al. [22] reported the condensation of **6**(**a**, **b**) with 2-ethoxynaphthalene-1,4-dione **16** in the presence of $AgNO_3$ by the varied input of $(NH_4)_2S_2O_8$ in aqueous acetonitrile medium under reflux for 3-4 hr. gave **1**(**a**, **b**). The reaction mixture was cooled to RT, added carbon tetrachloride and filtered to remove the insoluble. Furthermore, the solvent evaporation and recrystallization from acetonitrile gave **1a** with a m.p. of 216-219°C (yield: 7.0%-8.0%, as from **16**). This process (**Scheme 4**) could effectively be taken up for large-scale manufacturing since it is a feasible one-step process with a moderate yield.



Scheme 4: Synthesis of **1a** from **6 (a, b)** and **16**



Scheme 5: Synthesis of **1a** from **6** (**a**, **b**) from **17** and **18**

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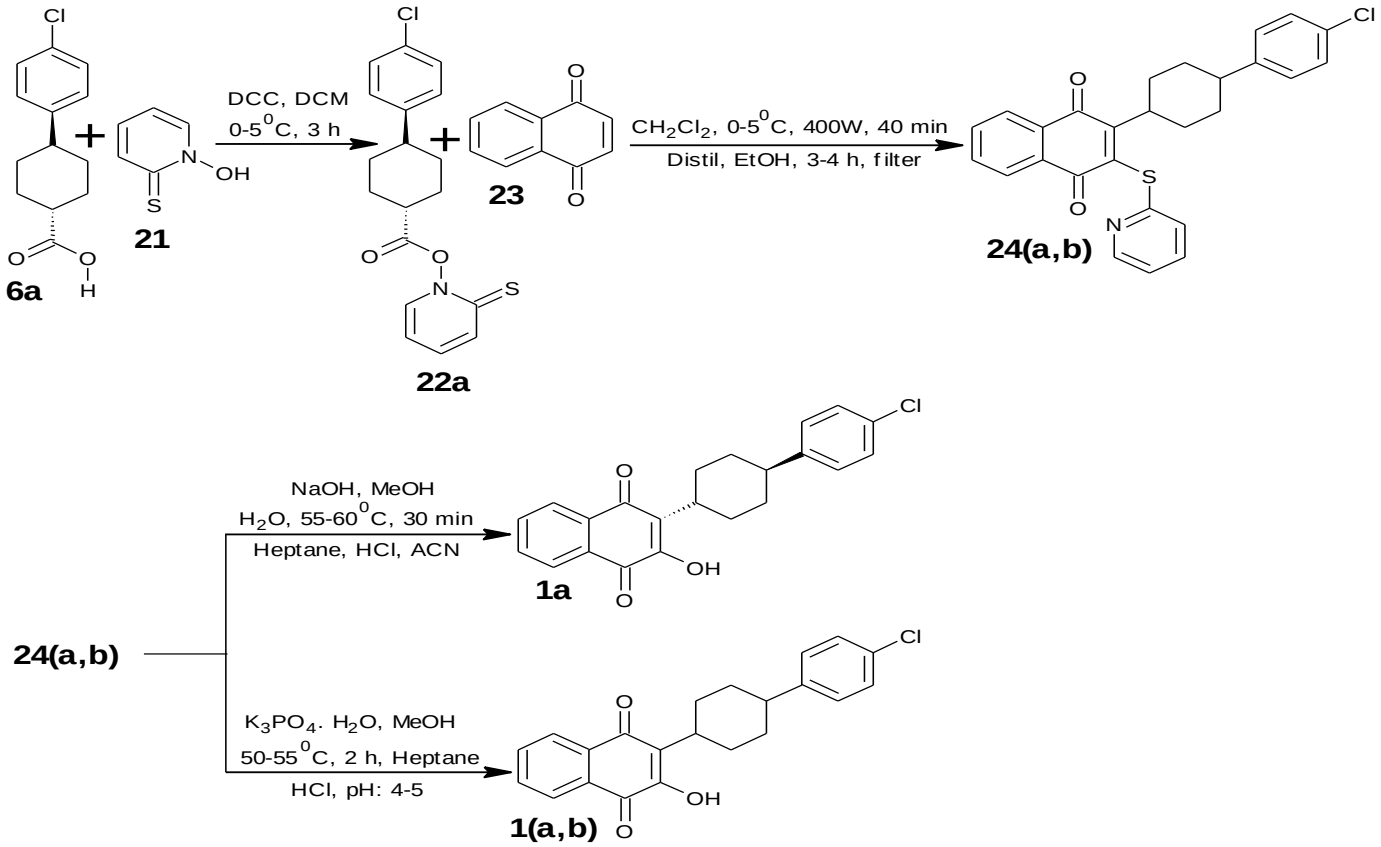
In 2008, Antonio et al. [23] demonstrated the acylation of 2-hydroxynaphthalene-1,4-dione **17** by acetic anhydride **18** under the mediation of triethylamine (TEA) in ethyl acetate at 05-10^{o}C for 4-6 hr. to get 1,4-dioxo-1,4-dihydronaphthalen-2-yl acetate **19** (yield: 80.0%). The condensation of **6**(**a**, **b**) and **19** was done in the catalytic presence of $AgNO_3$ using $(NH_4)_2S_2O_8$ in acetonitrile and water for 2-3 hr., followed by the sequential steps like toluene addition, phase separation, sodium chloride (NaCl) solution wash, water wash, distillation, cooling, filtration, drying and the parallel product isolation from the filtrate gave **20**(**a**, **b**) (yield: 41.7%). The solid isolated by direct filtration gave **20b** (Ist crop-major) with a m.p. of 197-200^{o}C and the solid isolated from the filtrate had **20a** (IInd crop-minor) with a m.p. of 150-155^{o}C. The epimerization and de-protection of **20**(**a**, **b**) were done by using concentrated sulfuric acid (H_2SO_4) at different temperatures. At 0-5^{o}C for 30 min, water quenching and the use of methyl ethyl ketone (MEK) gave **1a** (yield: 67.0%) with a m.p. of 220-223^{o}C. A similar pathway at 15^{o}C and the use of toluene instead of MEK, gave **1a** (yield: 76.0%). Furthermore, a similar attempt at 50^{o}C, gave **1a** (yield: 25.0%). An isomeric mixture of **1**(**a**, **b**), having 58.0% of **1b** and 48.0% of **1a** was subjected to concentrated H_2SO_4 treatment at 5^{o}C, followed by water quenching and MEK influenced isolation gave **1a** (yield: 81.0%). An attempt has also been made to condense **17** with **6**(**a**, **b**) under silver and persulfate mediated pathways to achieve a below-par conversion rate of only 10.0% (**Scheme 5**). A large volume of solvent utility and isomer separation issues are key factors that form a setback for the scalability of the disclosed synthetic pathway.



Scheme 6: Synthesis of **1a** from **6a**, **21** and **23**

In 2008, Zhu et al. [24] reported the coupling of *N*-hydroxypyridine-2-thione **21** with **6a** under the catalytic mediation of dicyclohexylcarbodiimide (DCC) in dichloromethane at 0-5^{o}C for 2 hr. to isolate *trans*-2-thioxopyridin-1 (2*H*)-yl-4-(4-chlor-ophenyl)-cyclohexane carboxylate **22a** (yield: 87.8%) with a m.p. of 153-156^{o}C. It was condensed with naphthalene-1,4-dione **23** in dichloromethane at 0-5^{o}C under the irradiation of 400W halogen lamp for 40 min, followed by distillation and ethanol slurry gave 2-[4-(4-chloro-phenyl)cycloh-exyl]-3-(2-pyridin-2-yl-thio)-naph-thalene-l,4dione **24**(**a**, **b**) (yield: 80.2%), comprising 48.0% of **24b** and 38.0% of **24a**. Purification of **24**(**a**, **b**) was done by the use of various solvents through slurry wash or

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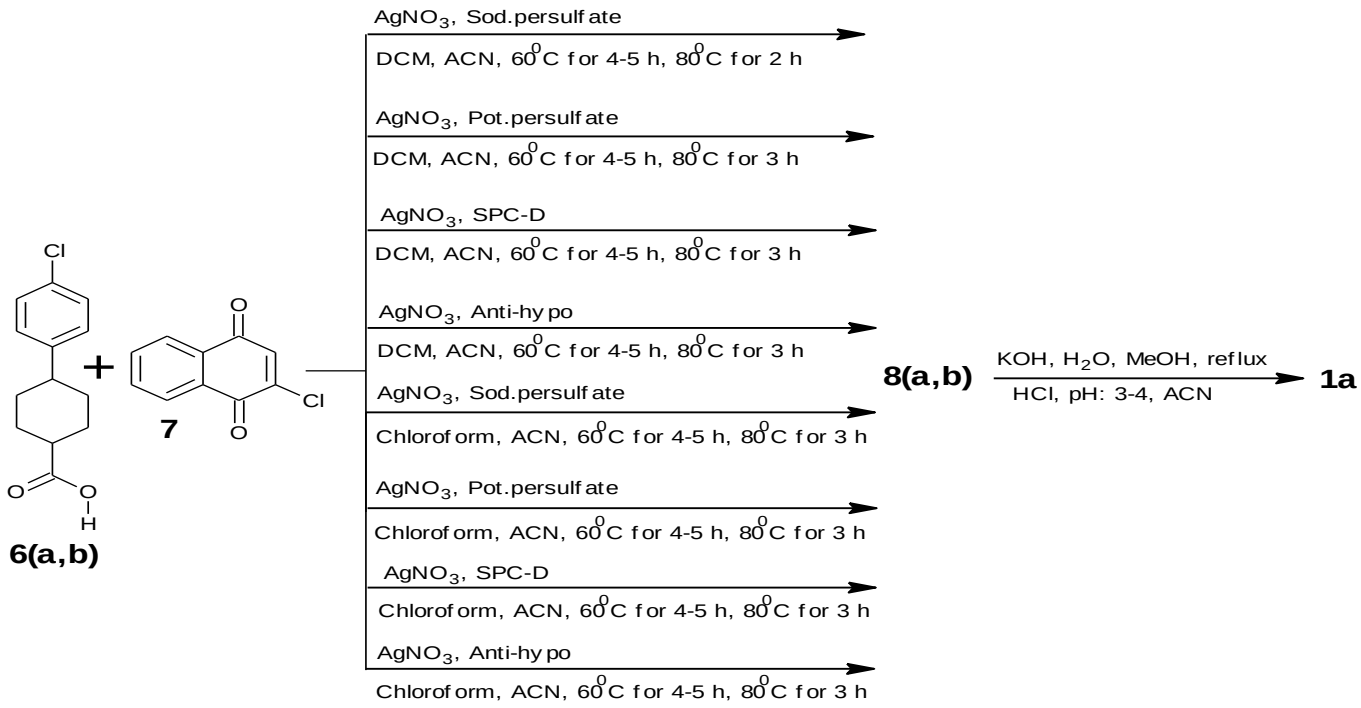
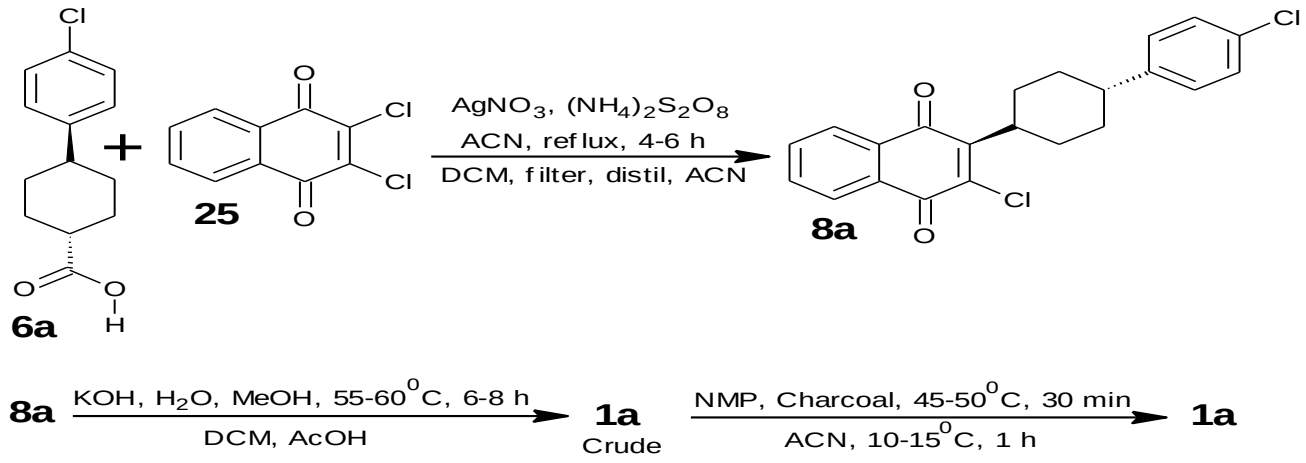
recrystallization techniques to get the isomeric purity in the range of 92%-96% with a recovery of 50-85%. Hydrolysis of **24**(**a**, **b**) using sodium hydroxide (NaOH) in aqueous methanol at 55-60^{o}C for 30 min, followed by n-heptane addition, acidification and recrystallization from acetonitrile gave **1a** (yield: 12.0%) with 99.35% of purity. Similarly, hydrolysis of **24**(**a**, **b**) using tri-potassium phosphate trihydrate (K_3PO_4. $3H_2O$) in aqueous methanol at 50-55^{o}C for 2 hr., followed by n-heptane addition and acidification to pH 4-5 gave **1**(**a**, **b**) (80.0% yield), comprising 48.0% of **1b** and 41.5% of **1a** (**Scheme 6**). The process successfully avoids the use of expensive reagent silver nitrate, and thus becomes commercially viable for scalability.

In 2009, Gui et al. [25] illustrated the condensation of **6**(**a**, **b**) with **7** under the catalytic presence of $AgNO_3$ in an aqueous bi-phase solvent system with the use of different oxidizers to get **8**(**a**, **b**), its hydrolysis, acidification and crystallization in acetonitrile gave **1a** (yield: 24.0%-35.0%, as per **7**). Along-with acetonitrile, dichloromethane or chloroform was used for the reaction and four different oxidizing agents were used in distinct experiments (**Scheme 7**) to get **8**(**a**, **b**) and later **1a** with the purity of around 98.2%-99.3%. This two-step process provides a moderate yield with good purity, it will suit large-scale manufacturing.



Scheme 7: Synthesis of **1a** by the condensation of **6**(**a**, **b**) and **7**



Scheme 8: Synthesis of **1a** from **6**(**a**, **b**) and **25**

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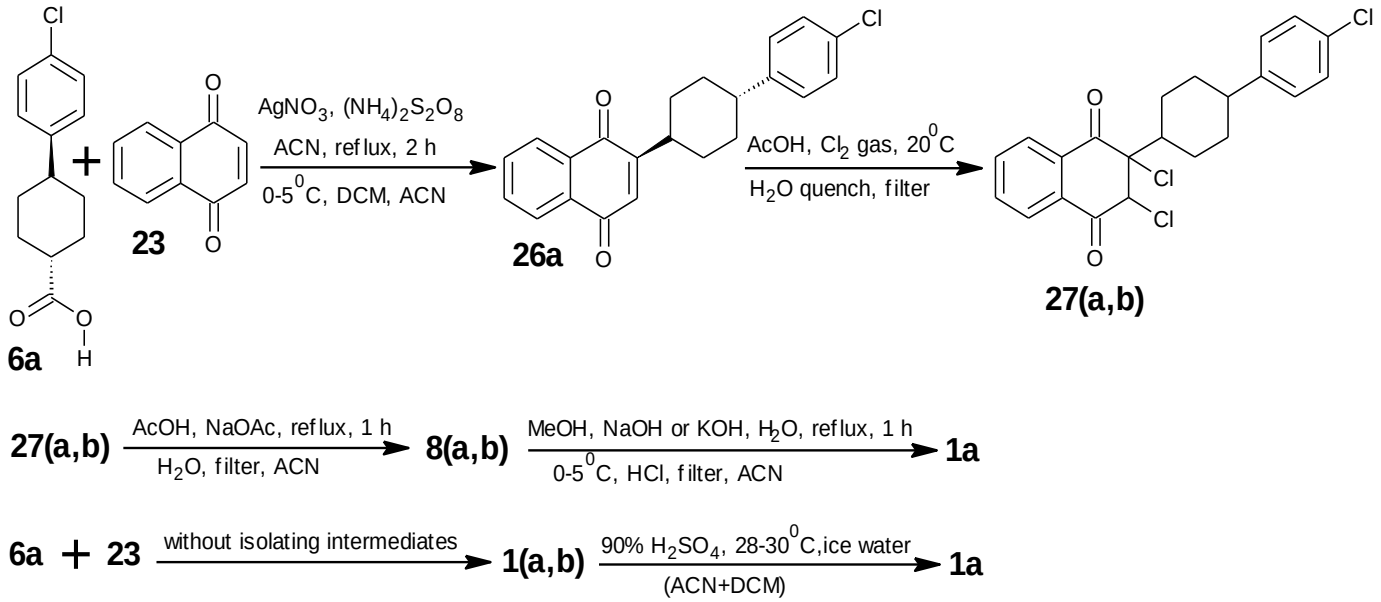
The past disclosed method was refurbished in 2009/2022 by Saralaya et al. [26-28] to condense **6a** with 2,3-dichloronaphthalene-1,4-dione **25** under the influence of $AgNO_3$ and $(NH_4)_2S_2O_8$ in aqueous acetonitrile under reflux for 4-6 hr. to get **8a** (yield: 40.0%-42.0%). Significant process optimization studies were conducted to achieve better atom economy and good purity. The recovery and reuse of expensive silver salt was achieved along with solvents such as acetonitrile and dichloromethane. The hydrolysis of **8a** was done using KOH solution in methanol under reflux for 4-6 hr. To the dark red reaction mass at RT, dichloromethane was added, acidified by acetic acid (AcOH), filtered and crystallization was done by the solvent mixture (acetonitrile and *N*-methyl pyrrolidone) to isolate **1a** (yield: 90.0%-95.0%). Hydrolysis and recrystallization steps were optimized to achieve the reduction in alkali addition, acidifier acid selection, and use of solvent combination in reduced volume for the crystallization of crude **1a** to get better yield and purity (**Scheme 8**). This process involves the use of abundant and cheaper raw material **25** giving the best output in terms of product yield and purity. The process was empowered with recovery and reuse studies, it avoids column chromatography for the product isolation and involves an optimized input of solvents and reagents. The process fits well for the large-scale manufacturing of the drug.



Scheme 9: Synthesis of **1a** from **6a** and **23**

In 2009, Kumar and others [29] disclosed the silver and persulfate driven reaction pathway to condense **6a** and **23** in acetonitrile and water medium under reflux for 2 hr. to get 2-[*trans*-4-(4-chlorophenyl) cyclohexyl] naphthalene-1,4-dione **26a** (yield: 20.0%) with a m.p. of 146-149^oC (as recrystallized from acetonitrile). Chlorine gas (Cl_2) was passed to **26a** in glacial AcOH at 20^oC and later quenched to water to get 2,3-dichloro-2-[4-(4-chlorophenyl) cyclohexyl]-2,3-dihydronaphthalene -1,4-dione **27**(**a**, **b**) (yield: 95.0%). It was then been taken in glacial acetic acid and refluxed with anhydrous sodium acetate (NaOAc) for 1 hr., followed by recrystallization in acetonitrile to isolate **8**(**a**, **b**) (yield: 70.0%). An alkali (NaOH or KOH) driven hydrolysis of **8(a**, **b**) in aqueous methanol under reflux, followed by acidification and acetonitrile recrystallization gave **1a** (yield: 70.0%-86.0%). A similar process pathway (**Scheme 9**) was followed and the intermediates were not isolated to get **1**(**a**, **b**). Further, its epimerization by 90.0% H_2SO_4 at 28-30^oC and recrystallization by the solvent mixture (acetonitrile and dichloromethane) gave **1a** (yield: 28.5%) with a purity of 99.8%. The disclosed process was empowered with an acid-mediated epimerization pathway and a solvent-driven recrystallization technique to isolate the intermediates and the product in good yield and purity. Hence, the process will suit the large-scale manufacturing of the drug.

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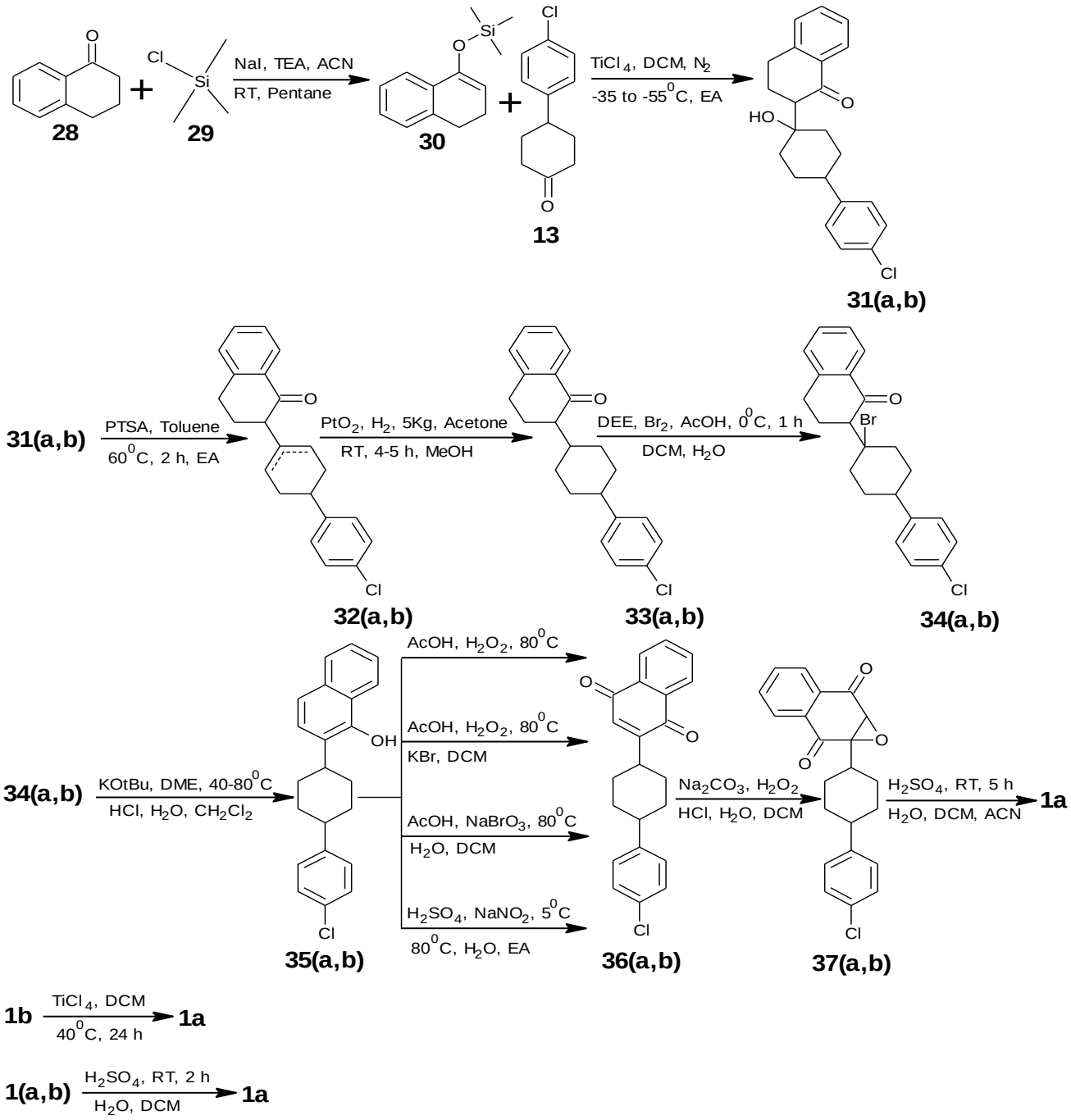
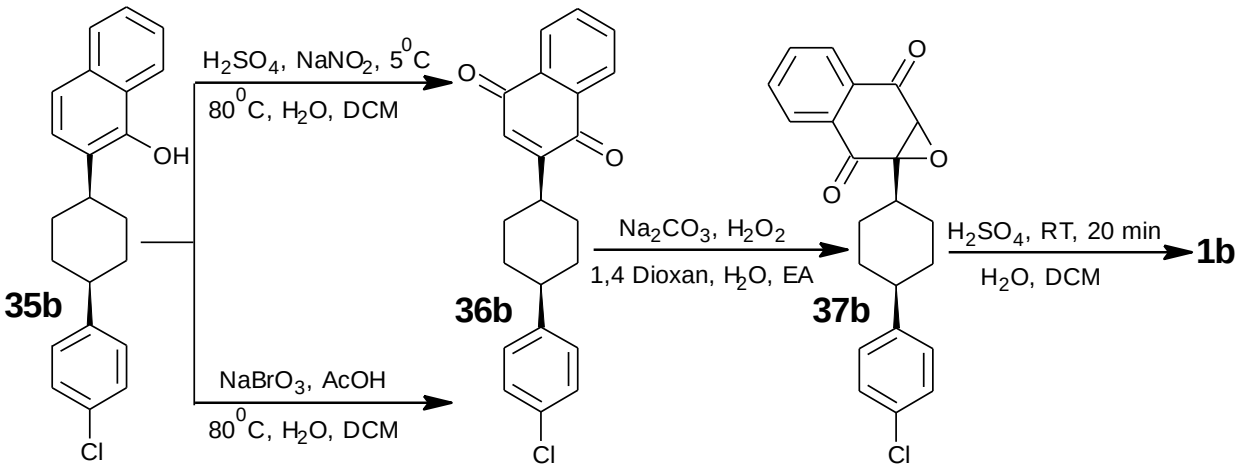


Scheme 10a: Synthesis of **1a** from **13**, **28** and **29**



Scheme 10b: Synthesis of **1b** from **35b**

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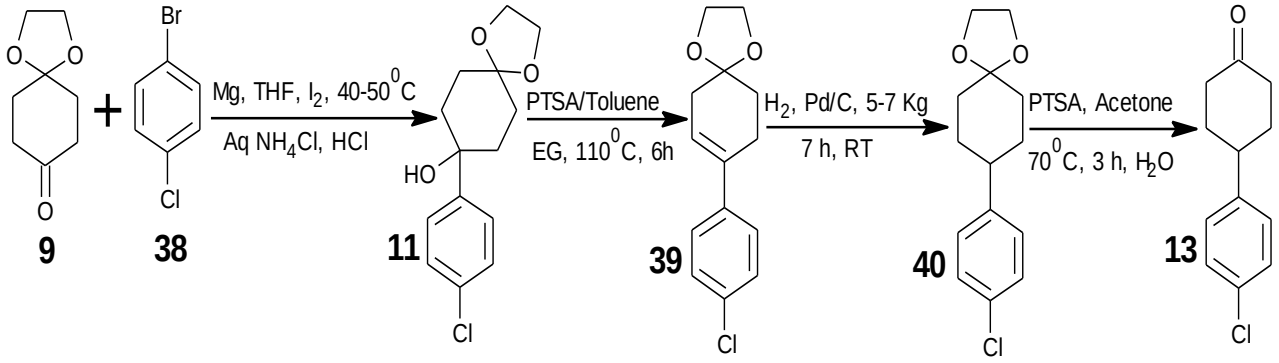

Scheme 10c: Synthesis of **13** from **9** and **38**

In 2011, Roy et al. [30] demonstrated the condensation of 3,4-dihydronaphthalen-1(2*H*)-one **28** and trimethylsilyl chloride **29** in the presence of triethylamine (TEA) and sodium iodide (NaI) in acetonitrile, followed by quenching to water and n-pentane extraction gave (1, 2-dihydronaphthalen-4-yloxy) trimethyl silane **30** (yield: 90%-97%). The reaction of **13** and **30** under the catalytic influence of titanium tetrachloride ($TiCl_4$) in dichloro-methane at -55^oC, followed by quenching to ice water, bicarbonate wash, ethyl acetate slurry and filtration gave 2-[4-(4-chlorophenyl)-1-hydroxy-cyclohexy-l]-3,4-dihydronaphthalen-1(2*H*)-one **31**(**a**, **b**) (78%-85%). It was treated with *para*-tolune sulfonic acid (PTSA) in toluene at 60^oC for 2 hr., followed by the addition of ethyl acetate, bicarbonate wash, brine wash, solvent evaporation and recrystallization in methanol gave 2-(4-(4-chlorophenyl) cyclohex-l-enyl)-3,4-dihydrona-phthalen-l 2H)-one **32**(**a**, **b**) (yield: 45%-56.0%). Its reduction under the catalytic influence of platinum oxide (PtO_2) in autoclave, followed by spent catalyst filtration, solvent evaporation and methanol recrystallization gave 2-[4-(4-chlorophenyl) cyclohexyl]-3,4-dihydronaphthalen-1(2*H*)-one **33**(**a**, **b**) (yield: 85%-95%). Its bromination by Br_2 in diethyl ether (DEE) and AcOH at 0^oC, followed by dichloromethane addition, water wash, 5.0% sodium thiosulphate solution wash and solvent evaporation led to the isolation of 2-[1-bromo-4-(4-chlorophenyl) cyclohexyl]-3,4-dihydronaph-thalen-1(2*H*)-one **34**(**a**, **b**) (yield: 95%-99%). The influence of potassium *tert*-butoxide (KOtBu) in dimethoxy ethane (DME) on **34**(**a**, **b**), followed by the addition of 10.0% aqueous HCl, dichloromethane extraction and solvent evaporation gave 2-[4-(4-chlorophenyl) cyclohex-yl] naphthalen-1-ol **35**(**a**, **b**) (yield: 70%-80%). It was converted to 2-[4-(4-chlorophenyl) cyclohexyl] naphthalene-1,4-dione **36**(**a**, **b**) (yield: 32%-70.0%) by the use of four different reagents with varied outputs. The reagents used are hydrogen peroxide (H_2O_2) in AcOH (yield: 32.0%), H_2O_2 and potassium bromide (KBr) in AcOH (yield: 50.0%), sodium bromate ($NaBrO_3$) in AcOH (yield: 66.0%) and sodium nitrite ($NaNO_2$) in H_2SO_4 (yield: 70.0%). In the above experiments isolation of **36**(**a**, **b**) was done by column chromatography using eluents with suitable polarity. The impact of sodium carbonate (Na_2CO_3) and hydrogen peroxide (H_2O_2) in 1,4-dioxan on **36**(**a**, **b**), ethyl acetate extraction and solvent evaporation gave 1a-[4-(4-chloro-phenyl) cyclohexyl]-1a,7a-dihydrona-phtho[2,3-*b*] oxirene-2,7-dione **37**(**a**, **b**). Its exposure to H_2SO_4 at RT, followed by dichloro-methane extraction, solvent evaporation and recrystallization from acetonitrile gave **1a** (yield: 74.0%). Present work had given a method for the conversion of **1b** to **1a** under $TiCl_4$ mediation at 40^oC for 24 hr. (**Scheme 10a**). **35b** was converted to **36b** under $NaNO_2$ mediation or by $NaBrO_3$ mediation (yield: 55%-65%). It was reacted with Na_2CO_3 and H_2O_2 in 1,4-dioxan had led to the formation of **37b** (yield: 90.0%). It was exposed to H_2SO_4, followed by water quenching, dichloro-methane extraction and distillation gave **1b** (**Scheme 10b**). Magnesium turnings and iodine (I_2) mediated reaction to couple **9** and 1-bromo-4-chlorobenzene **38** in THF at 40-50^oC, followed by quenching to NH_4Cl solution, acid treatment and filtration gave **11** (yield: 93.0%). It was treated with PTSA in toluene and ethylene glycol (EG) at 110^oC for 6.0 hr., followed by solvent evaporation, 1.0% bicarbonate slurry wash and filtration gave 8-(4-chlorophenyl)-1,4-dioxaspiro [4.5] dec-7-ene **39** (yield: 90%-97%). Its reduction by palladium/carbon (Pd/C) in autoclave with H_2 pressure of 5-7 kg/

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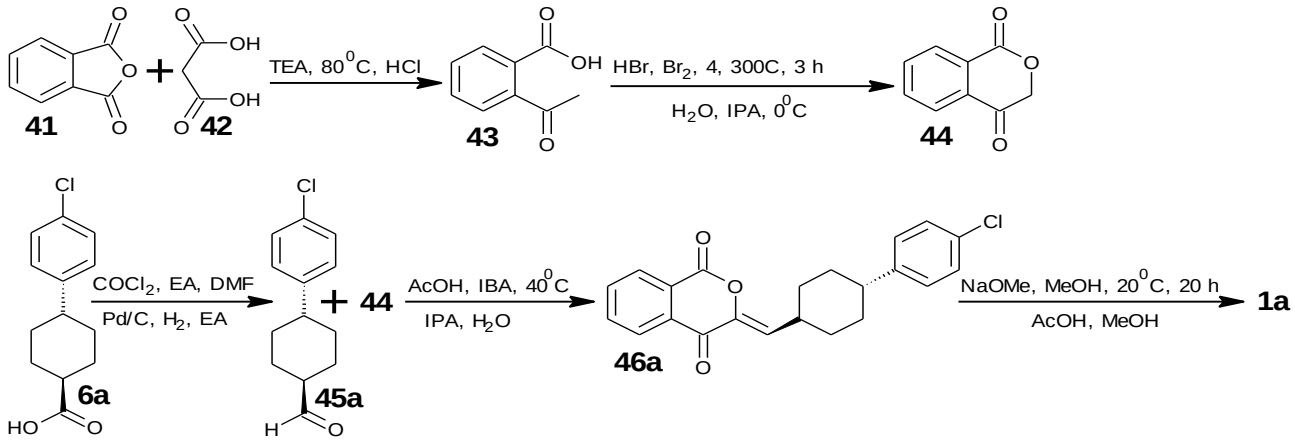
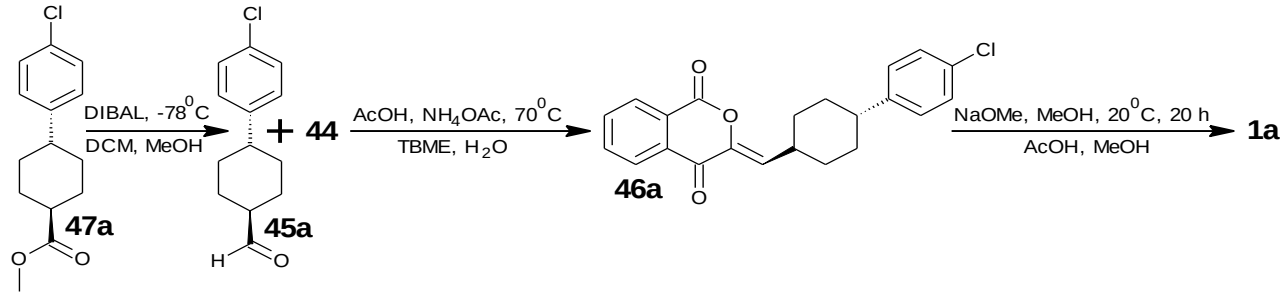
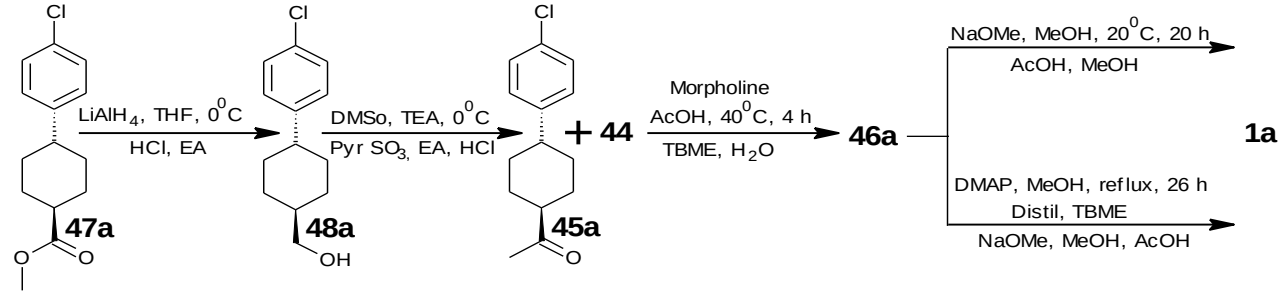
cm^2 gave **40**, it was treated with PTSA in acetone at 70ºC for 3 hr., followed by acetone evaporation, sodium carbonate slurry wash and filtration gave **13** (yield: 80%-90%) (**Scheme 10c**), the disclosed multi-step process has a moderate yield, column chromatography-based isolation and the formation of racemic intermediates/ product. These parameters would form a certain bottleneck for the industrial production of the drug.



Scheme 11a. Synthesis of **1a** from **6a**, **41** and **42**



Scheme 11b. Synthesis of **1a** from **44** and **47a**.



Scheme 11c. Synthesis of **1a** from **44** and **47a**

In 2011, Dwyer et al. [31] reported the reaction of phthalic anhydride **41** and malonic acid **18** in the presence of TEA at 80ºC, followed by acid (HCl) quench and filtration to get 2-acetyl benzoic acid **43** (yield: 68.0%). The solution of **43** in chloro-benzene **4** (as solvent) was treated with hydro-bromic acid (HBr) in AcOH and Br_2, followed by slow addition of water extraction, solvent extraction, solvent evaporation, isopropyl alcohol addition and filtration gave 1*H*-isochromene-1,4(3*H*)-dione**44** (yield: 75.0%). To the solution of **6a** in ethyl acetate with a few drops of dimethyl-l formamide (DMF, as catalyst), oxalyl chloride ($COCl_2$) was added, and heated to 55ºC till a clear solution. It was later taken up for reduction using Pd/C in H_2 atmosphere under pressure with suitable solvents to get *trans*-4-(4-chloro-phenyl)cyclo-hexane carbaldehyde **45a**. Isobutyl-amine (IBA) mediated condensation of **44** and **45a** in AcOH at 40ºC for 3 hr., followed by water addition, filtration and cake wash by the solvent mixture (isopropyl alcohol & water) gave (3*Z*)-3-{[*trans*-4-(4-chloro-

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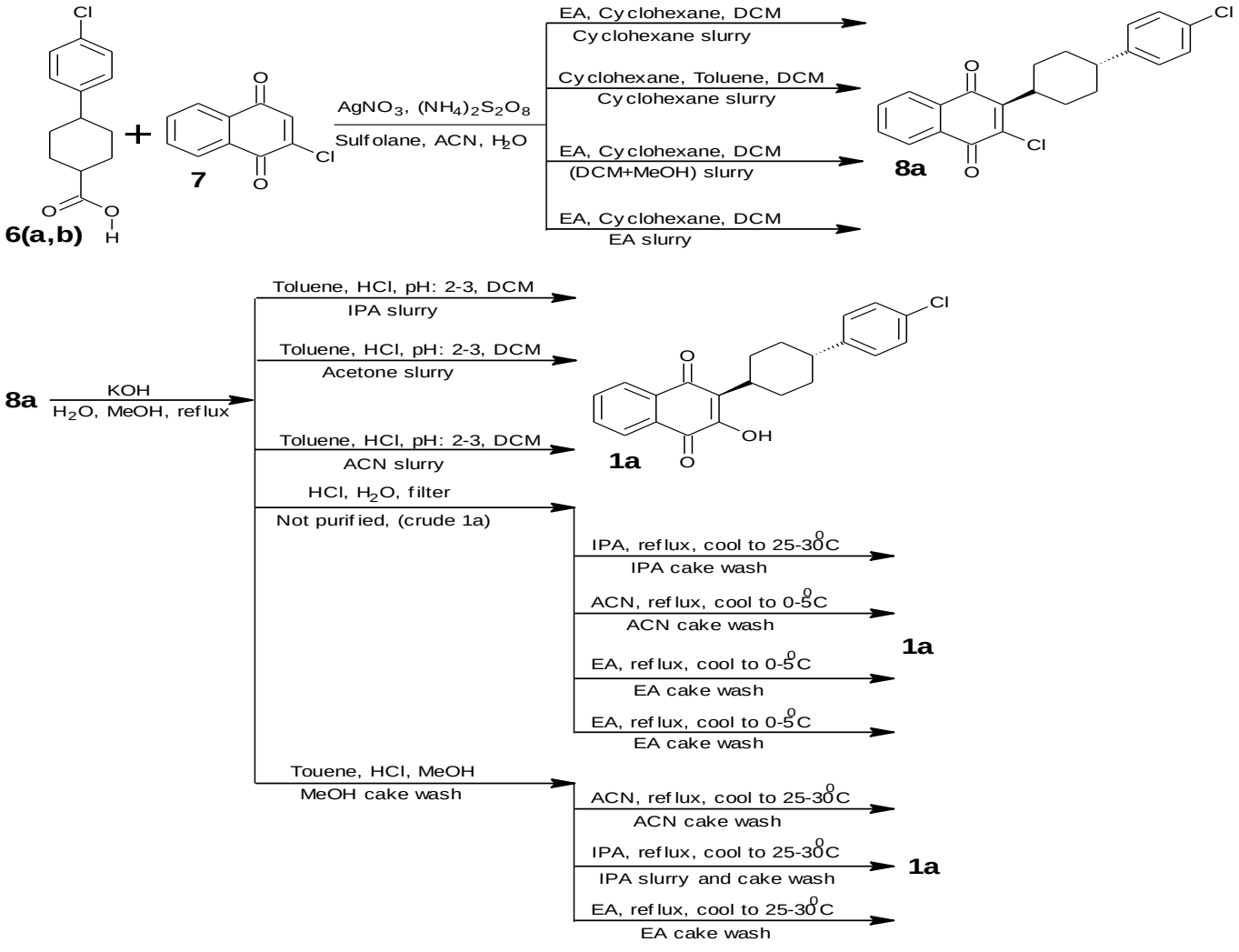
phenyl)cyclohexyl]methy-lid-ene}-1*H*-isochrom-ene-1,4(3*H*)-dione**46a** (yield: 76%-78%). The impact of sodium methoxide (NaOMe) in methanol on **46** for 18-20 hr. at 20°C, followed by dilute AcOH addition and filtration gave **1a** (yield: 91.0%) (**Scheme 11a**). The solution of methyl *trans*-4-(4-chlorophenyl)-cyclohexane carboxylate **47a** in dichloromethane at -78°C in an inert atmosphere, was treated with di-iso-butyl ammonium hydride (DIBAL). After the reaction completion, methanol addition, acidification, extraction, water wash, solvent evaporation, ethyl acetate addition and filtration gave **45a**. Ammonium acetate (NH_4OAc) driven coupling of **44** and **45a** in AcOH at 70°C for 2 hr., followed by water addition, filtration, cake wash by *tert*-butyl methyl ether (TBME) gave **46a**. Further, NaOMe impact on **46a** in methanol gave **1a** (**Scheme 11b**). Lithium aluminum hydride ($LiAlH_4$) mediated reduction of **47a** in THF at 0°C for one hour, followed by acidification, ethyl acetate addition, extraction, water wash and solvent evaporation gave [*trans*-4-(4-chlorophenyl) cyclo-hexyl] methanol **48a**, which was not isolated, instead taken to dimethyl sulfoxide (DMSo) for next step. It was taken in DMSo and treated with TEA, pyridine sulfur trioxide (pyr-SO_3) at 0-20°C for 2 hr., followed by ethyl acetate addition, acidification, extraction and solvent evaporation to get **45a**, which was not isolated, instead taken to AcOH for next step. Morpholine mediated condensation of **44** and **45a** in AcOH at 40°C for 4 hr., followed by water addition, filtration and cake wash by TBME gave **46a**. It was converted to **1a** under the influence of NaOMe or dimethyl amino-pyridine (DMAP) in good yield and purity through phosphoric acid (H_3PO_4) or AcOH neutralization (**Scheme 11c**). The disclosed process does not involve column chromatography for the isolation of intermediates or products. Hence it can be adopted with minor modifications for the large-scale manufacturing of the drug.



Scheme 12. Synthesis of **1a** from **6**(**a**,**b**) and **7**.

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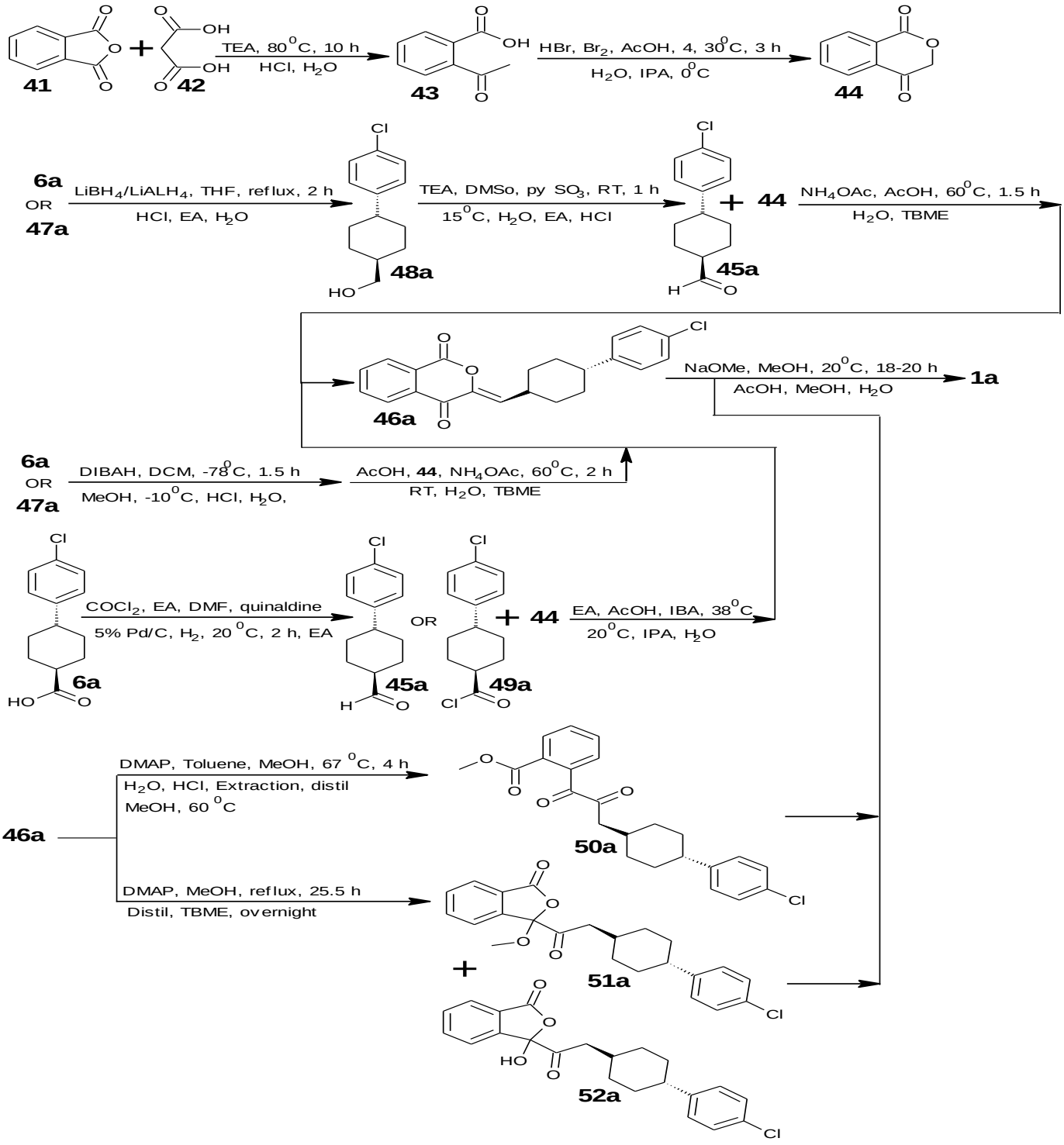
In 2011/2012, Vyas et al. [32, 33] reported the use of an aqueous bi-phase solvent system mediated coupling of **6**(**a**, **b**) and **7** under the influence of $AgNO_3$ and $(NH_4)_2S_2O_8$. It was followed by four different workup procedures were followed to isolate **8a** (yield: 16%-19%). An alkali mediated hydrolysis of **8** in aqueous methanol and its acidification gave crude **1a** (95%-97%). A few different recrystallization methods were followed to obtain **1a** by the use of solvents such as isopropyl alcohol (yield: 84.0%), acetone (yield: 71.0%), acetonitrile (yield: 80.0%), ethyl acetate (yield: 70-75%) etc. (**Scheme 12**). The disclosed process reports a known pathway to condense **6**(**a**, **b**) and **7**, followed by the solvent driven pathway for the isolation of intermediates and the product with good yield and better purity. The disclosed process was empowered with optimization initiatives; hence, the synthetic pathway will suit for large-scale manufacturing of the drug.



Scheme 13: Synthesis of **1** from **6a**, **41**, **42** and **47a**

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Inspired by the initiatives of Parikh et al. in 1967 [34], Rylander et al. [35] in 1967, and Barcia et al. [36] in 2002, a readily available and commercially affordable **41** was used for the synthesis of **1a** in 2012 by Britton et al. [37]. It was treated with **42** in the presence of TEA at 80^{o}C for 10 hr., followed by quenching to dilute HCl, filtration and water wash to get **43** (yield: 67.0%). It was reacted with 5.5 M HBr and Br_2 in AcOH at 30^{o}C for 3 hr., followed by water addition, reflux for 3 hr., extraction by **4** (as solvent), solvent evaporation, isopropyl alcohol addition and filtration gave **44** (yield: 73.0%). The borohydride driven reduction of **6a** or **47a** in THF under reflux for 2 hr., followed by quenching to aqueous HCl, ethyl acetate extraction, water wash and solvent evaporation gave [*trans*-4-(4-chlorophenyl) cyclohexyl] methanol**48a** (yield: 90%-96%). Impact of TEA, DMSo and py-SO_3 on **48a** at RT for 1 hr., followed by the addition of water, ethyl acetate, extraction, water/brine wash and solvent evaporation gave **45a** (yield: 95.0%). NH_4OAc mediated condensation of **44** and **45a** in AcOH at 60^{o}C for 1.5 hr., followed by cooling to RT, water addition, filtration and cake wash by the mixture of water and TBME gave **46a** (yield: 72.0%). NaOMe in methanol was used to convert **46a** to **1a** at 20^{o}C for 18-20 hr., followed by acidification with aqueous AcOH, methanol addition and filtration gave **1a** (yield: 85.8%). Di-isobutylaluminium hydride (DIBAH) mediated reaction of **6a** or **47a** in dichloromethane at -78^{o}C for 1.5 hr., followed by methanol addition, acidification by HCl solution, water wash, ethyl acetate addition and solvent evaporation gave **45a**, which was not isolated. It was dissolved in AcOH and condensed with **44** at 60^{o}C for 2 hr., followed by water addition, filtration and cake wash by TBME gave **46a** (yield: 68.0%). The addition of $COCl_2$ to the solution of **6a** in ethyl acetate with a few catalytic drops of DMF at 55^{o}C until clear solution, followed by the addition of quinaldine at 20^{o}C, hydrogenation in the presence of Pd/C with H_2, filtration and ethyl acetate addition gave **45a** or *trans*-4-(4-chlorophenyl) cyclohex-anecarbonylchloride**49a**, which are not isolated. To the solution of **45a** or **49a** in ethyl acetate, **44** in AcOH and IBA were added at 38^{o}C, followed by filtration and cake wash by isopropyl alcohol gave **46a** (yield: 81.0%). A mixture of **46a** and dimethyl aminopyridine (DMAP) in toluene and methanol was heated to 67^{o}C for 4 hr., followed by HCl addition, water wash, solvent evaporation, methanol addition and filtration gave the *trans*-isomer of methyl-2-{3-[4-(4-chlorophenyl) cyclo-hexyl]-2-oxopropanoyl benzoate **50a** (yield: 77.0%). NaOMe impact on **50a** in methanol gave **1a** (yield: 86.0%). Similarly, the mixture of **46a** and DMAP in methanol was refluxed for 25-26 hr., followed by solvent evaporation, addition of TBME, overnight stand-off and filtration gave *trans*-isomer of 3-{[4-(4-chlorophenyl)cyclo-hexyl] acetyl}-3-(methyloxy)-2-benzofuran-1(3H)-one **51a** (yield: 14.7%) along with the by-product 3-(2-((1r,4r)-4-(4-chlorophenyl) cyclohex-yl)acetyl)-3- hydroxyisobenzofuran-1(3H)-one **52a** (**Scheme 13**). The disclosed process was simple and involved the use of cheap raw materials/reagents to prepare the product and key intermediates. The process avoids the silver mediated pathway and epimerization consequences to isolate **1**. The reported experiments were demonstrated on a substantial high scale including the Rosenmund method, disclosed by Iosub and others in 2018 [38] along with the details on impurity prevention and its elimination. With these consequences, the process fits well for large scale manufacturing of the drug.

In 2013, Dong et al. [39] reported the PTSA mediated condensation of 4-(4-chlorophenyl) cyclohexanol **53**(**a**, **b**) and naphtha-ene-1-ol **54** in the presence and absence of toluene to get **35**. The impact of H_2O_2 and HCl in acetonitrile on **35**(**a**, **b**), followed by chloroform extraction, water wash and solvent evaporation gave **36**(**a**, **b**). It was converted to 2,3-dibromo-2-[4-(4-chlorophenyl) cyclohexyl]-2,3-dihydronaphthalene-1,4-dione **55**(**a**, **b**), either by the use of Br_2 in AcOH or Br_2, 30.0% H_2O_2 and H_2SO_4 in carbon tetrachloride. Addition of DMSo to **55**(**a**, **b**) and heating to 60^{o}C for 2 hr., followed by water washing and precipitation gave 2-bromo-3-[4-(4-chlorophenyl)-cyclohexyl]-naphthalene-1,4 dione **56**(**a**, **b**). Similarly, NaOAc in AcOH impact on **55**(**a**, **b**) under reflux for one hour, followed by water addition, ethyl acetate extraction and solvent evaporation gave **56**(**a**, **b**). It was refluxed with NaOH in MeOH, followed by acidification to pH: 2-3, solvent evaporation, extraction to ethyl acetate and solvent evaporation given **1a**. Similarly, **56**(**a**, **b**) was refluxed with sodium carbonate (Na_2CO_3) in isopropyl alcohol, followed by filtration, distillation, ethyl acetate extraction and

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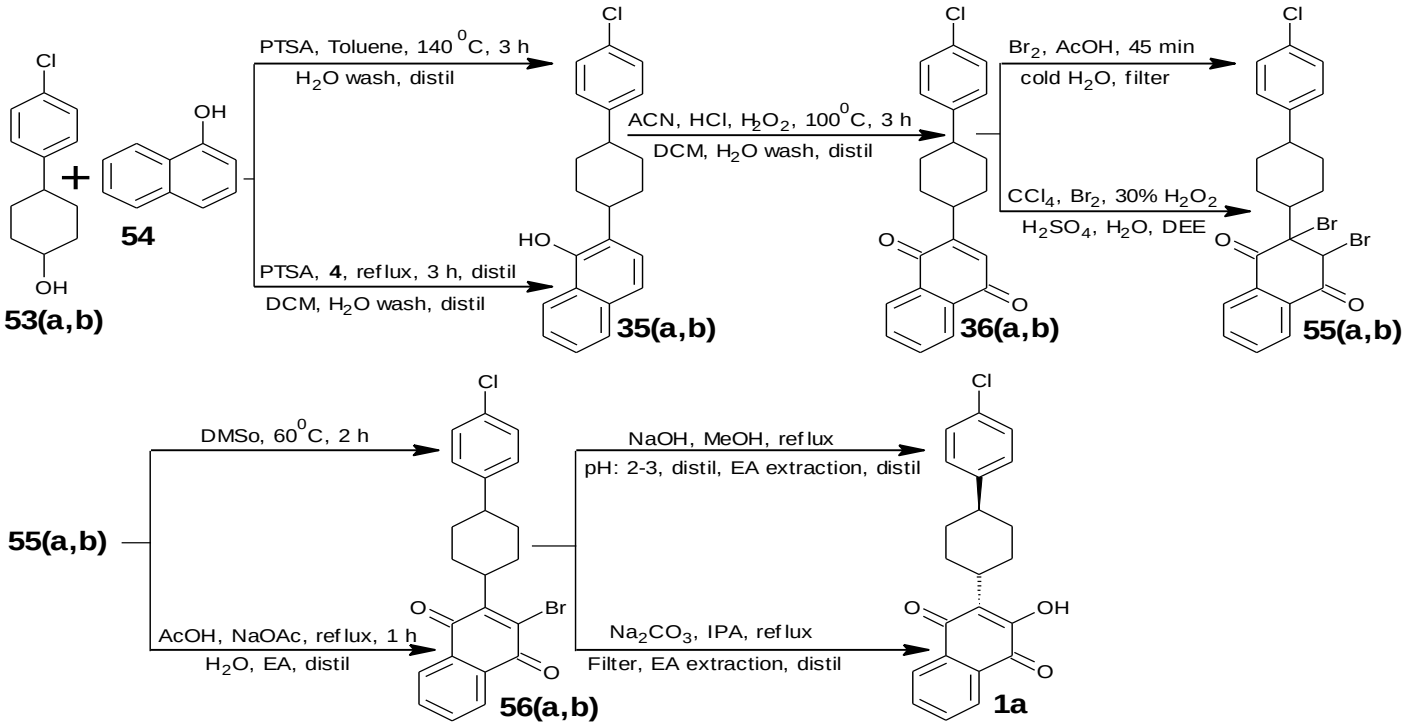
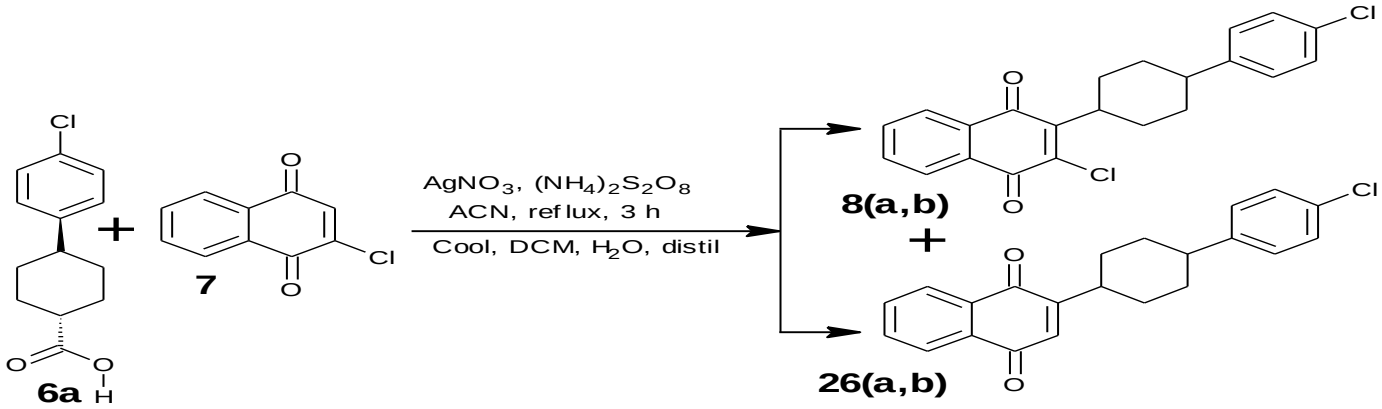
solvent evaporation gave **1a** (**Scheme 14**). The disclosed process uses commercially affordable and abundant key raw materials/reagents and also avoids the use of expensive silver to provide a good purity and (undisclosed) yield. Hence, the process suits well for scalability of the drug with minor modifications.



Scheme 14: Synthesis of **1a** from **53**(**a**, **b**) and **54**



Scheme 15a: Synthesis of **8**(**a**, **b**) from **6a** and **7**

In 2014, Dike et al. [41] had illustrated the silver catalyzed and persulfate driven condensation of **6a** and **7** in acetonitrile under reflux for 3 hr., followed by extraction to dichloromethane, water wash and solvent evaporation to get the surprising combined output of **8**(**a, b**) and **26**(**a, b**). It was evident by the results of HPLC and mass spectral analysis of the obtained yellowish-brown residue (**Scheme 15a**). A similar synthetic pathway was adopted for the condensation of **6a** and **23**, followed by dichloro-methane addition, water wash, distillation, aceto-nitrile slurry (twice) and filtration gave **26a** (yield: 20.8%) with a m.p. of 147-149°C. Glacial AcOH was added to **26a** and passed Cl_2 gas at 20°C, followed by filtration and bed wash to neutral pH giving **27**(**a**, **b**) (yield: 85.9%). It was suspended in glacial AcOH and anhydrous NaOAc was introduced and refluxed for 1 hr., followed by water addition, filtration and recrystallization in aceto-nitrile gave **8**(**a**, **b**) (yield: 89.0%) with a m.p. of 185-187°C. An alkali (KOH solution) driven hydrolysis of **8**(**a**, **b**) in methanol, followed by acidification, filtration and recrystallization in acetonitrile gave **1a** (yield: 85.0%) with a m.p. of 219-221°C.

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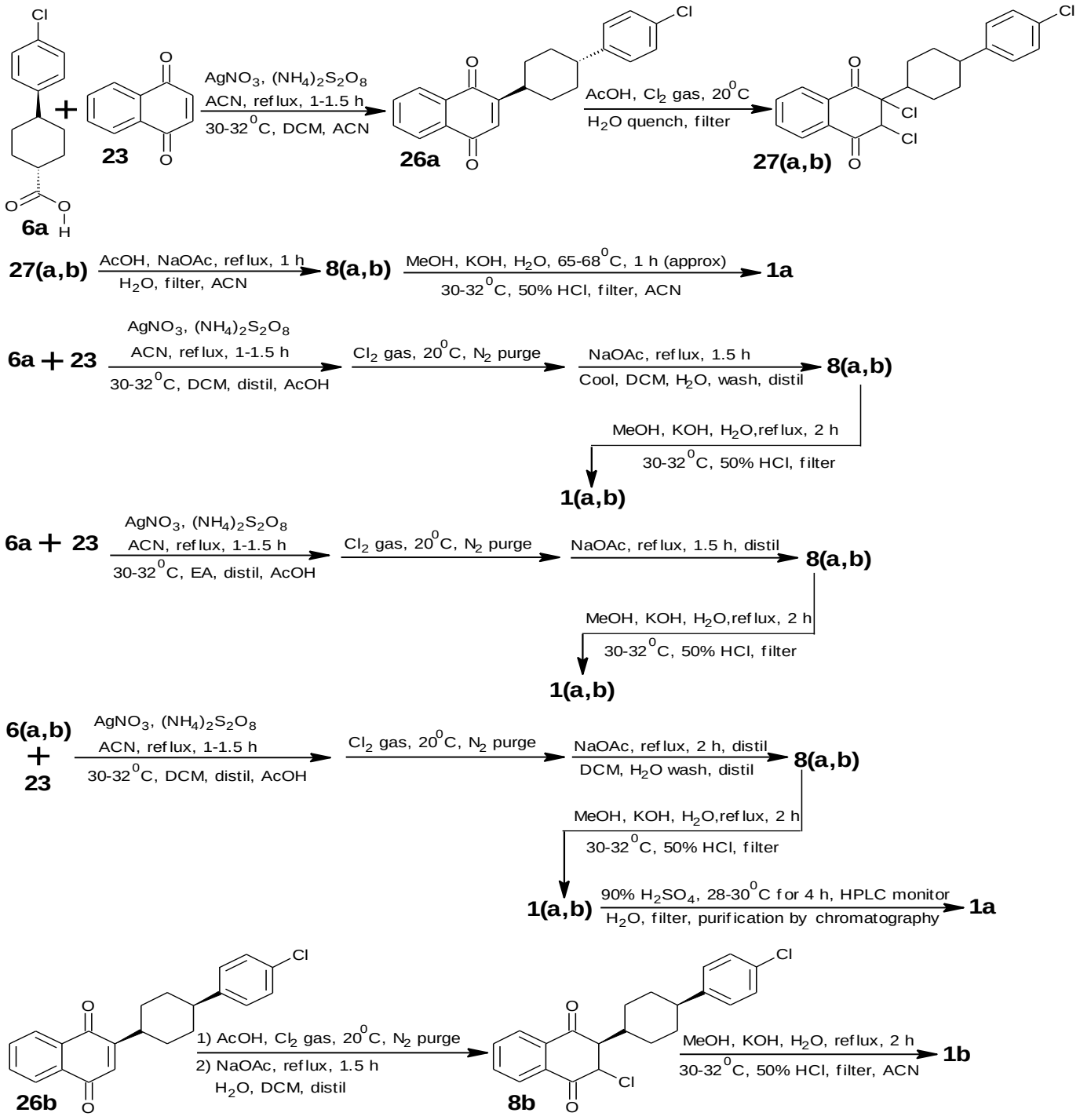
Two distinct experiments were done to isolate **1**(**a**, **b**) (yield: 81.3% and 84.6%) through a one pot process starting from **6a** and **23,** with minor changes in work-up the pathway. **1**(**a**, **b**) was successfully epimerized (in 2008, Zhu & others) [40] under the influence of 90% H_2SO_4 at 28-30^oC for 4 hr., followed by water quench and chromatographic purify-cation to get **1a** (yield: 42.0%). A similar synthetic strategy was employed to condense **6**(**a**, **b**) with **23** to isolate **1**(**a**, **b**), followed by epimerization and column chromatography to get **1a** (yield: 41.0%). An attempt to was made with success to convert **26b** to **8b** and then to **1b** (yield: 65.0%) by chlorination, hydrolysis, acidification and recrystallization in acetonitrile (**Scheme 15b**). The disclosed process was executed on reasonably large scale with good yield and purity. The multi-step process and the use of column chromatography to isolate **1a**, form a certain bottleneck for large-scale manufacturing of the drug.



Scheme 15b: Synthesis of **1a** and **1b** from **6a/6**(**a**, **b**) and **23**

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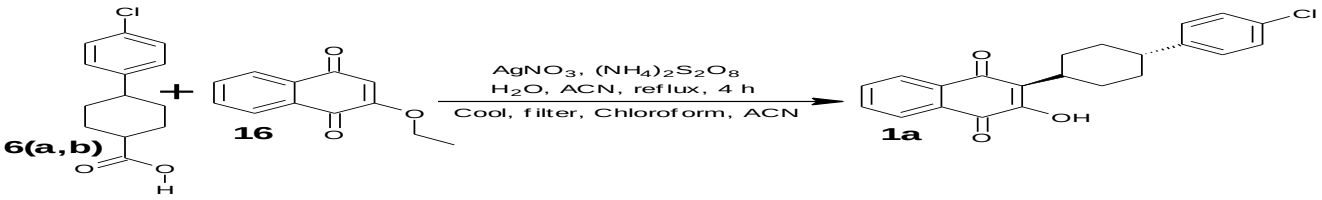
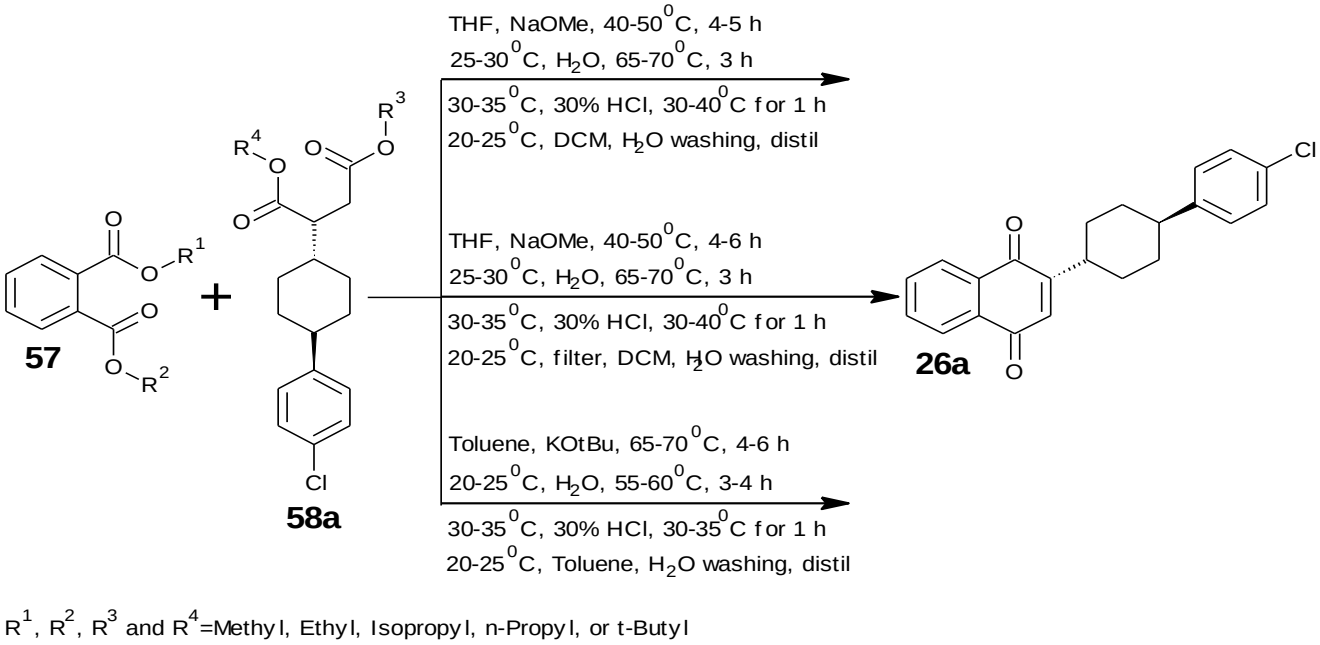
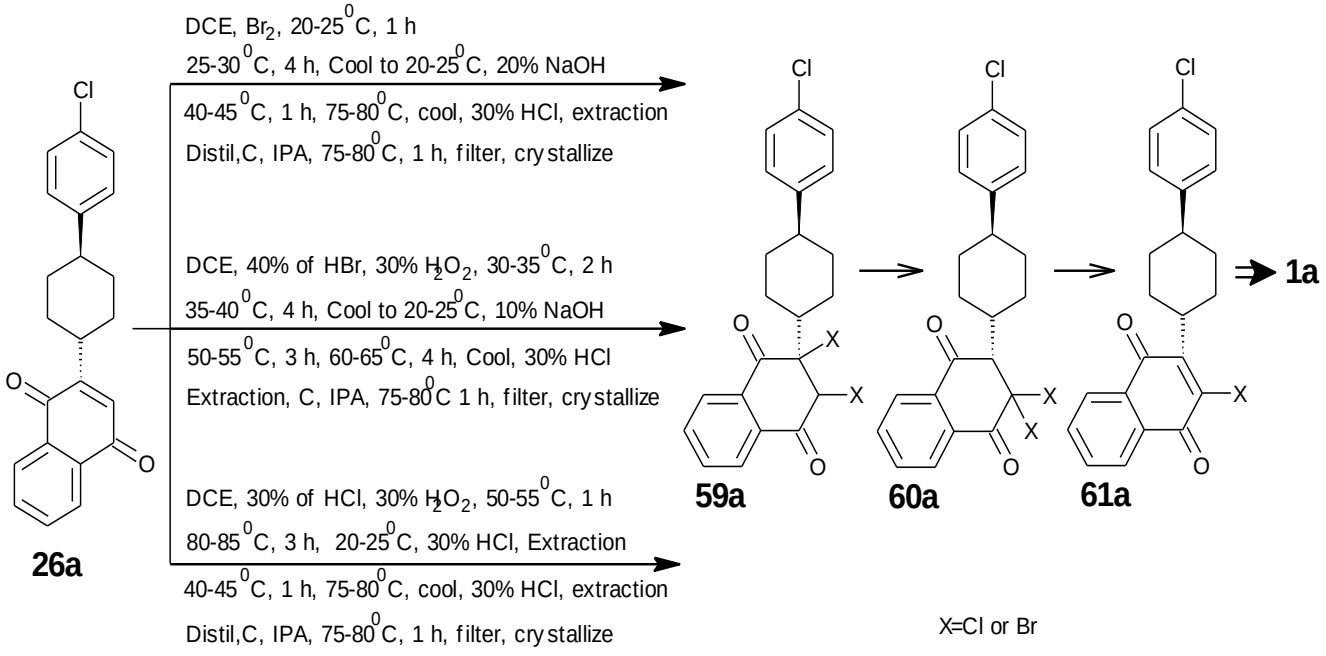


Scheme 16. Synthesis of **1a** from **6**(**a**, **b**) and **16**

In 2016, Zhang [42] demonstrated a simple one-step process for the synthesis of **1a** by the condensation of **6**(**a**, **b**) and **16** in acetonitrile and water under the mediation of silver and persulfate at reflux condition for 4 hr. After the reaction completion, it was cooled, filtered, solid was taken to chloroform, filtered to remove the insoluble and recrystallized in acetonitrile to get **1a** (**Scheme 16**). There is no mention of the process yield and recovery/reuse of silver salt. Based on the one-step pathway and the commercial viability of the key raw materials, the disclosed process would suit well for large-scale manufacturing of the drug.



Scheme 17a. Synthesis of **26a** from **57** and **58a**



Scheme 17b. Synthesis of **1a** from **26a**

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In 2018, Cui et al. [43] reported the NaOMe-mediated condensation of the phthalate derivative **57** and cyclohexyl succinate derivative **58a** in THF at 40-45^{o}C for 4-5 hr. It was followed by cooling, water addition, heating to 65-70^{o}C for 3 hr., cooling, acidification by HCl, dichloromethane addition, extraction, water wash and solvent evaporation gave **26a** (yield: 91.3%). A similar reaction pathway with minor changes gave **26a** (yield: 66.7%) and the use KOtBu in toluene to condense **57** with diethyl cyclohexyl succinate derivative **58a** gave **26a** (yield: 92.2%) (**Scheme 17a**). Further, it was subjected to halogenation, de-halogenation, hydrolysis, acidification and recrystallization in isopropyl alcohol to get **1a**. Meanwhile, the reaction would generate di-halo intermediates (**59a** and **60a**), and monohalo intermediate (**61a**) and they were not isolated. The halogenation was done by the use of either Br_2, HBr or HCl in dichloroethane (DCE) as solvent and hydrolysis by NaOH solution. An activated charcoal (C) driven de-colorization was done in isopropyl alcohol to get the crystals of **1a** (yield: 80%-90%, as per 4 distinct experiments) (**Scheme 17b**). The disclosed process has some advantages like the raw materials used are relatively cheap and abundant. Further, it avoids the use of expensive silver nitrate instead it propels by use of cheaper and commonly available reagents and solvents. The mild reaction conditions, high reaction selectivity, good yield and purity, would make this invention to suite for large-scale manufacturing of the drug.

A brief outline of the entire review work has been tabulated in **Table 2**, with the scheme number (S. N.), steps involved in the inventions and the key remarks on the process. Various raw materials, reagents and solvents were used for the synthesis of **1a** in one-step, two-step and multi-step process pathways. Among them, eleven disclosures had the mediation of silver salt for the synthesis of **1a**, remaining six disclosures were able to achieve the synthesis by the use of reagents other than silver salt. Stereo-specific intermediates and products along with their poor solubility in water and solvents, had allowed the possibility to go for the process development initiatives and contribute to the synthesis of drugs on a large scale. Minimum process steps, mild reaction conditions, use of readily available reagents/raw materials/solvents, high atom economy, least effluents etc. are the key aspects to be focused on for effective drug commercialization. These vital and critical aspects itself would form a bottleneck for the large-scale manufacturing of **1a** in most disclosed routes. In this regard, around twelve synthetic disclosures were peripherally found to suit scalability (with minor modifications), remaining 5 processes would require major modifications to go for scalability. Meantime, this review work will provide an opportunity for researchers to venture further to design a scalable process for **1a** in accordance with green chemistry principles. Recently a review work published by Khan and others [44] in 2023 comprehensively covered the details of the synthesis and applications of naphthoquinone-based drugs. More importantly, the work had wide view coverage of the synthesis of numerous drugs including **1a** in brief. Under a similar context, a review work by Spyroudis [15] in 2000 aimed broadly at the details of the synthesis and reactivity of hydroxyquinones. Our present venture is specific towards the synthetic aspects of drug **1a**, evolved by the thorough examination of the prior art disclosures with a progressive methodological flourish of **1a**.

Table 2: A brief outline of the review work for process steps involved and remarks on scalability.

S. N.	Process pathway	Silver salt mediation	Scalability
1	Multi-step	Y	N
2	Multi-step	Y	N
3	Two-step	Y	Y
4	One-step	Y	Y
5	Multi-step	Y	N
6	Multi-step	N	Y
7	Two-step	Y	Y
8	Two-step	Y	Y
9	Multi-step	Y	Y
10	Multi-step	N	N
11	Multi-step	N	Y
12	Two-step	Y	Y
13	Multi-step	N	Y
14	Multi-step	N	Y
15	Multi-step	Y	N
16	One-step	Y	Y
17	Multi-step	N	Y
Y = Yes, N = No			

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Conclusion: Silver-centric synthesis of **1a** has been the major process backbone, as per prior arts. Thus, avoiding the use of $AgNO_3$ would reduce the overall process cost to about 60.0%. Hence, a few inventions emerged by avoiding it for the synthesis of **1a**. Another ventured option in line with the context was the recovery of silver salt and its reuse for the reaction along with recovered solvents. A stiff process development studies were performed in a few works to achieve relatively better atom economy, purity and effluent reduction. In this review, we have considered the work of global researchers towards the synthesis of **1a** by covering all process details progressively disclosed by them to date. In line with it, around seventeen reaction schemes were drawn for the elaborate understanding of the pathway followed for the synthesis of **1a**. This study will provide a firm template to design a new synthetic route or re-work the existing routes to achieve the ideologies of green chemistry alongside the commercialization of **1a**.

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