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(54) Title: NOVEL METHOD FOR PREPARATION OF ATOVAQUONE

(57) Abstract: Provided is a process of preparation of 2-[trans-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone, i.e. Atovaquone [I] which is cost effective, green, and eco-friendly process, without separation of any diastereomers or geometric isomers of intermediates obtained during the reactions. Also provided is separation of 'cis' and 'trans' isomer of intermediates VI, VII and VIII through selective crystallization in an appropriate solvent. A method for converting 2-[cis-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone to 2-[trans-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone in presence of Lewis/Bronsted acid is also provided. A process for preparation of compound 2-(4-(4-chlorophenyl)-1-hydroxy cyclohexyl)-3,4-dihydronaphthalen-1 (2H)-one [IV] comprising condensation of (1,2-dihydronaphthalen-4-yloxy)trimethylsilane [II] with 4-(4-chlorophenyl)cyclohexanone [III] in presence of Lewis acid in organic solvent. The invention also encompasses a highly efficient and atomeconomic process for synthesis of compound [III] i.e. 4-(4-chlorophenyl)cyclohexanone as well as a process for synthesis of 2-[cis-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone. Further provided is a process for isomerization of cis-Atovaquone i.e. 2-[cis-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone to trans-Atovaquone i.e. 2-[trans-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone in presence of Lewis acid.

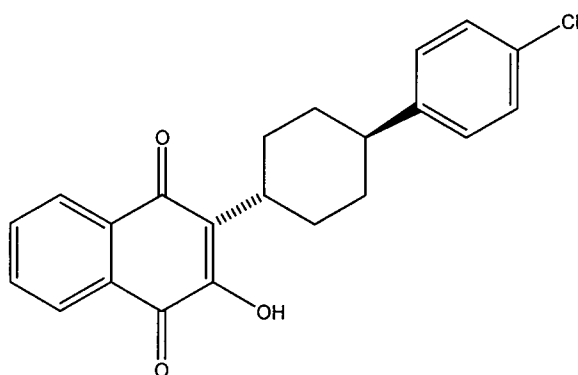


NOVEL METHOD FOR PREPARATION OF ATOVAQUONE**Field of the Invention:**

The invention relates to a novel process for preparation of 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone *i.e.* Atovaquone [I]. This invention also provides a novel process for preparation of 2-[*cis*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone and process for isomerization of 2-[*cis*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone to 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone in presence of a Lewis acid.

Background of the Invention:

2-[*Trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [CAS No. 95233-18-4], which is also called Atovaquone [I], has antipneumocystic activity and is used in the treatment of *Pneumocystis carinii* pneumonia, as disclosed in US patent number US 4981874. Further uses of Atovaquone as a therapeutic agent for malaria, toxoplasmosis and carcinoma or fibrosarcoma are disclosed in US patent number US 5206268, US 5856362 and US 5567738, respectively. The mechanism of action for Atovaquone involves the inhibition of mitochondrial electron transport in cytochrome *bc₁* complex of the parasite, which is linked to pyrimidine biosynthesis (Tetrahedron Lett, 1998, 39 7629).

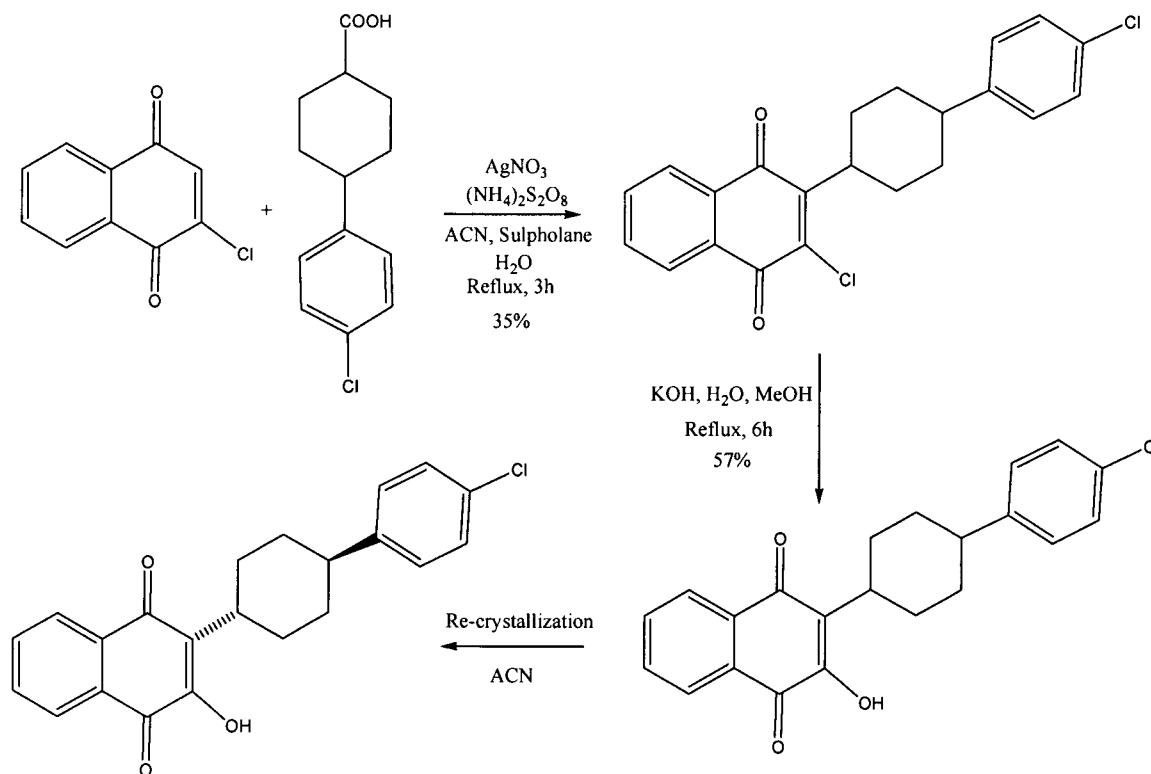


[I]

There are only few reports available for the synthesis of Atovaquone employing various synthetic alternatives essentially based on Hunsdiecker decarboxylative condensation, which proceeds through a radical mechanism. However, the overall yield of

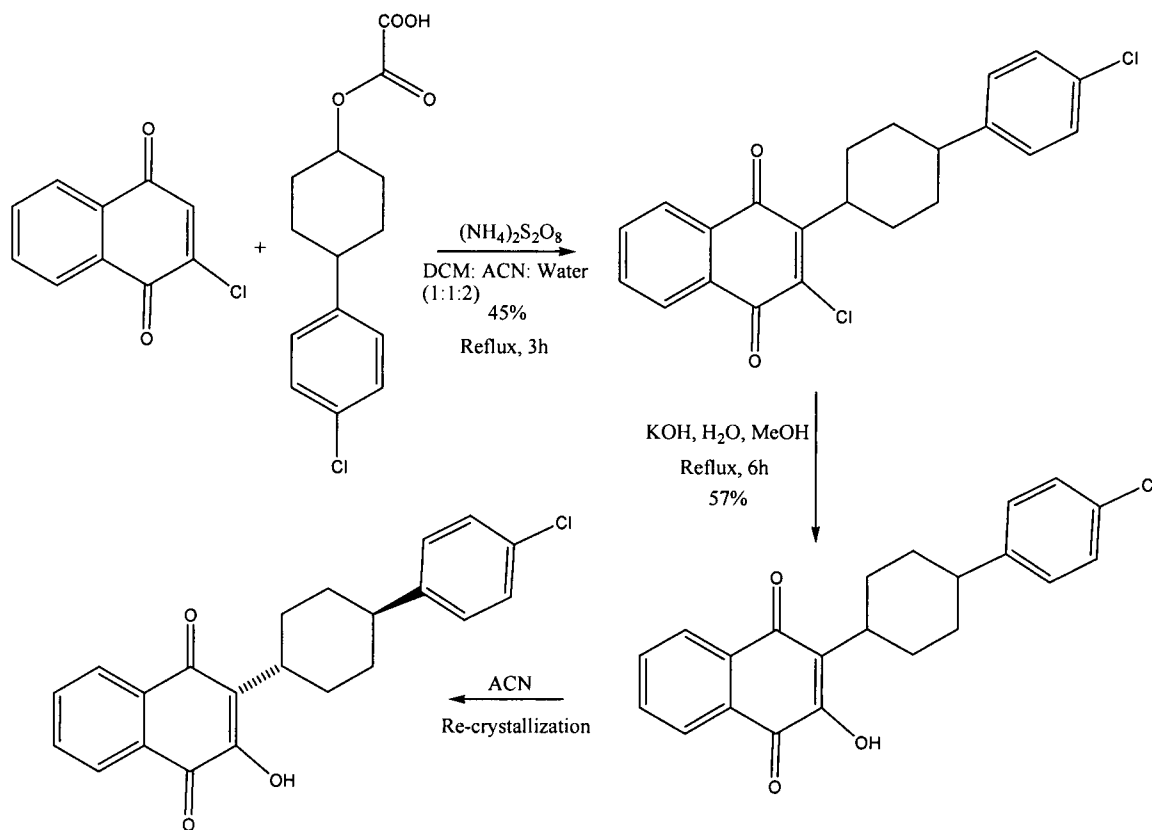
the desired product in almost all the reported processes is exceedingly poor *i.e.* economically far away from being attractive. Details of the reported syntheses are discussed hereinafter.

The method for synthesis of Atovaquone disclosed in US Patent No. 5,053,432 describes Hunsdiecker decarboxylative condensation between (4-(4-chlorophenyl)-cyclohexane 1-carboxylic acid and 2-chloro 1,4-naphthoquinone in presence of silver nitrate and ammonium persulfate to obtain 2-chloro-3-[4-(4-chloro-phenyl)-cyclohexyl]-[1,4]naphthoquinone, which was converted to (*cis/trans*)-2-hydroxy-3-[4-(4-chloro-phenyl)-cyclohexyl]-[1,4]naphthoquinone and on further re-crystallization through acetonitrile, the desired product *i.e.* *trans*-2-hydroxy-3-[4-(4-chloro-phenyl)-cyclohexyl]-[1,4]naphthoquinone was obtained (Scheme 1). The disadvantage with this process is that overall yield is very low (4-5 %) and it requires expensive catalyst such as silver nitrate. Moreover, it also requires a number of purification steps in different solvents to obtain the desired product, thereby, rendering this process economically not viable for manufacturing.



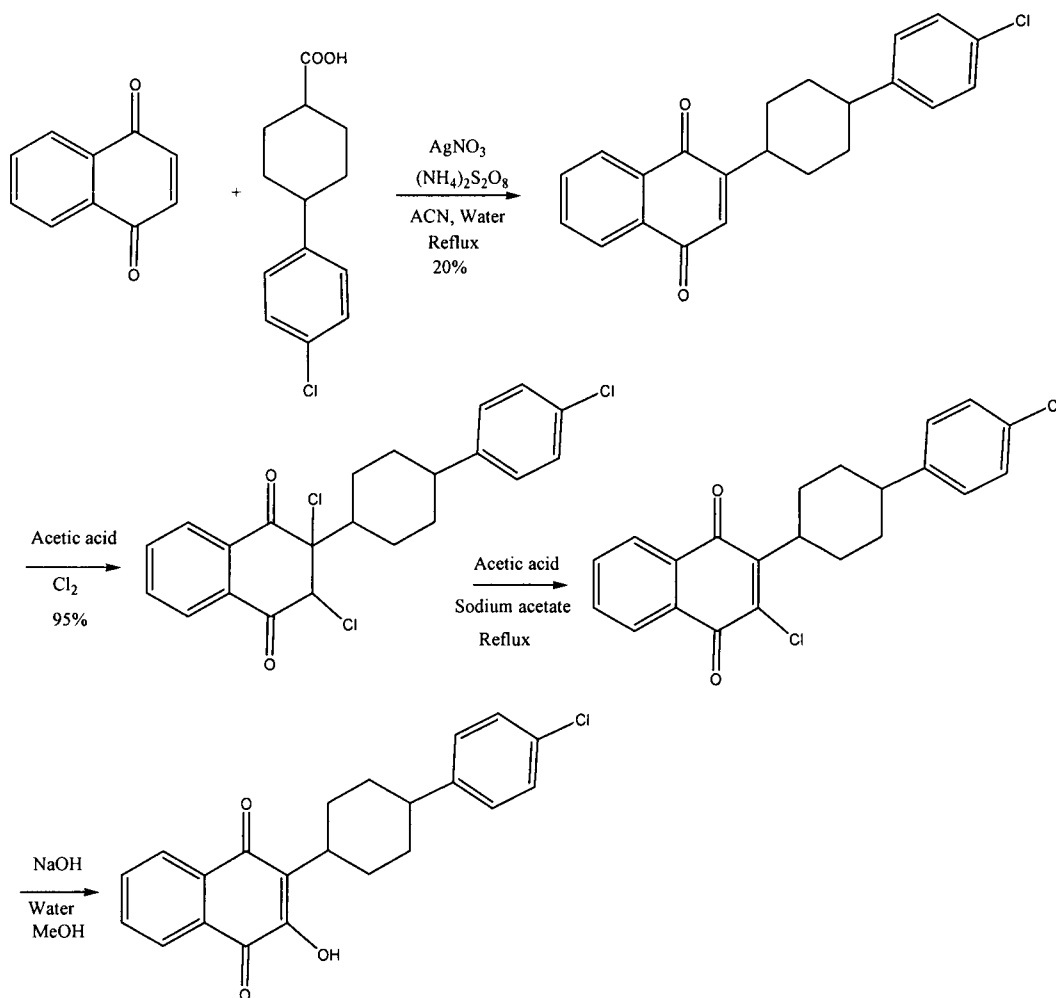
Scheme 1

The improved process for the Hunsdiecker decarboxylative condensation precursor *i.e.* oxalate mono acids in presence of ammonium persulfate, silver nitrate and phase transfer catalyst, Adogen® 464 to obtain 2-chloro-3-[4-(4-chloro-phenyl)-cyclohexyl]-[1,4]naphthoquinone has been reported by Williams and Clark [Tetrahedron Letters, 1998, 39, 7629-7632], which was subsequently converted to Atovaquone. This process reports 43% overall yield for 2-chloro-3-[4-(4-chloro-phenyl)-cyclohexyl]-[1,4]naphthoquinone. On further re-crystallization through acetonitrile, desired product *i.e.* *trans*-2-hydroxy-3-[4-(4-chloro-phenyl)-cyclohexyl]-[1,4]naphthoquinone was obtained (Scheme 2). Besides lower overall yield, this process also requires the expensive catalyst, silver nitrate hence rendering this process not attractive for large scale manufacturing.



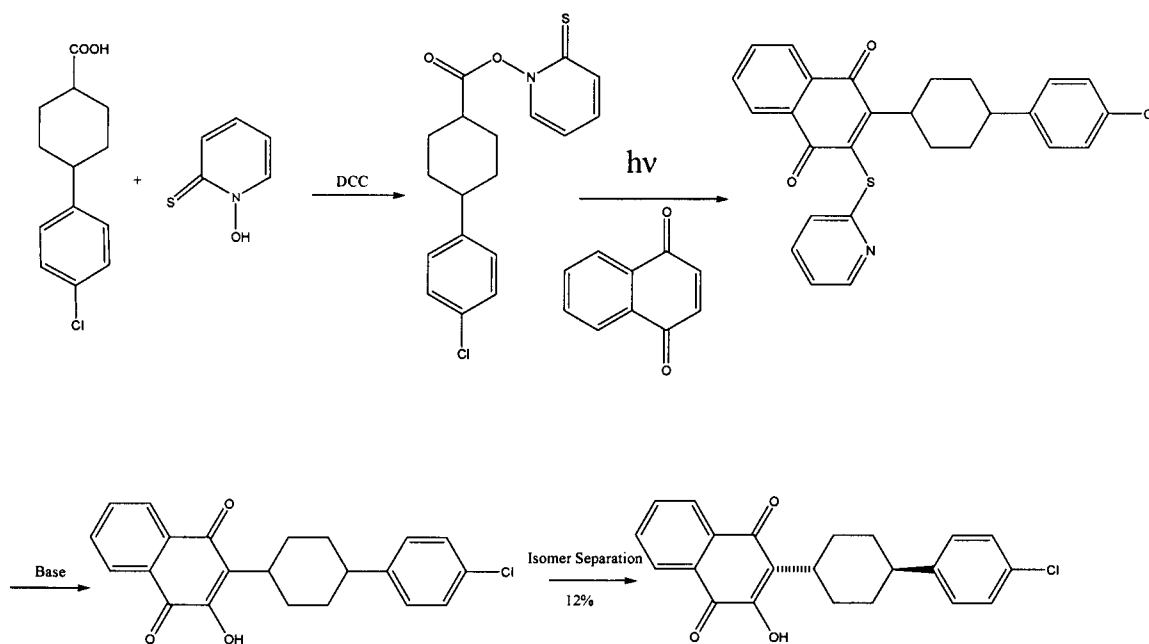
Scheme 2

WO 229/007991 A2 disclosed a method for synthesis of Atovaquone through formation of intermediates via Hunsdiecker decarboxylative condensation between 1,4-naphthoquinone and 4-(4-chlorophenyl) cyclohexane 1-carboxylic acid in presence of silver nitrate and ammonium persulfate to obtain 2-[4-(4-chloro-phenyl)cyclohexyl]-1,4-naphthoquinone, which was further converted to 2-[4-(4-chloro-phenyl)cyclohexyl]-2,3-dichloro-2,3-dihydro-1,4-naphthoquinone by using acetic acid and chlorine followed by conversion to 2-chloro-3-[4-(4-chloro-phenyl)-cyclohexyl]-[1,4]naphthoquinone, which was further converted to Atovaquone through base catalyzed hydrolysis (Scheme 3). Over all yield for the first step is very poor (20%) and moreover, chlorine gas was used in the second step. Hence, this process is not a practical process for commercial scale for obvious reasons.



Scheme 3

WO 2010/ 0001379A1 disclosed a method for synthesis of Atovaquone. In this process *trans*-4-(4-chlorophenyl)cyclohexane-1-carboxylic acid was reacted with N-hydroxy pyridine-2(1*H*)-thione in presence of DCC to obtain *trans*-2-thioxopyridin-1(2*H*)-yl-4-(4-chlorophenyl)-cyclohexane carboxylate, which was further reacted with 1,4-naphthoquinone under ultra violet irradiation with 400W halogen lamp to obtain 2-[4-(4-chlorophenyl)cyclohexyl]-3-(pyridine-2-ylthio) naphthalene-1,4 dione which was further hydrolyzed in presence of base followed by isomer separation to obtain Atovaquone (Scheme 4). However, besides higher material cost, the overall yield of the desired isomer is only 12% from the geometric isomer mixture *i.e.* from penultimate to ultimate.

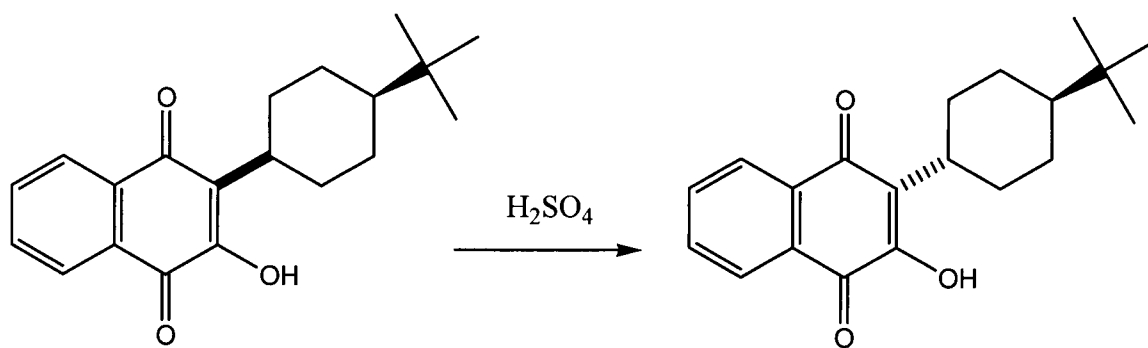


Scheme 4

Synthesis of similar type of compound *i.e.* 2-(4-*t*-butylcyclohexyl)-3-hydroxy-1,4-naphthoquinone by employing Hunsdiecker decarboxylative condensation between 2-chloro-1,4 naphthoquinone and 4-*t*-butylcyclohexane-1-carboxylic acid was reported in EP 0077551 B1 and by Hudson *et al* (Eur. J. Med. Chem. 1986, 21, 271-275).

Moreover, isomerization of *cis*-2-(4-*t*-butylcyclohexyl)-3-hydroxy-1, 4-naphthoquinone to *trans*-2-(4-*t*-butylcyclohexyl)-3-hydroxy-1, 4-naphthoquinone in presence

of concentrated sulphuric acid was also reported (Scheme 5). This established the fact that in the presence of a strong acid such as sulphuric acid, benzylic proton α to the naphthoquinon ring gets abstracted and leads to thermodynamically more stable geometric isomer.



Scheme 5

WO 2010/001378 A1 disclosed a method for conversion of *cis*-2-(4-(4-chlorophenyl)-3-hydroxy-1,4-naphthoquinone to *trans*-2-(4-(4-chlorophenyl)-3-hydroxy-1,4-naphthoquinone in the presence of strong acids such as sulphuric acid and methansulphonic acid.

Hence, it is evident from prior art that the processes reported in the literature for the industrial synthesis of Atovaquone are at present not industrially feasible processes with respect to cost and efficiencies, use of toxic chemicals and eco-hazardous operations. Hence, there is need for an eco-friendly, “green”, cost effective, easy-to-operate, industrial-scale synthesis of Atovaquone.

The present inventors have found a novel, cost effective, operation friendly, green process for preparation of the title compound. This invention also provides a novel process for preparation of ‘*cis*’ isomer of Atovaquone and process for converting ‘*cis*’ isomer of Atovaquone to pharmaceutically active form *i.e.* ‘*trans*’ isomer in presence of a Lewis acid.

Objects of the Invention:

Thus an object of this invention is to provide a novel cost effective and efficient process for the synthesis of Atovaquone [I].

Another object of the present invention is synthesis of the novel compound 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV] through Mukaiyama aldol condensation of (1,2-dihydronaphthalen-4-yloxy)trimethylsilane [II] with 4-(4-chlorophenyl)cyclohexanone [III] and further conversion of the Mukaiyama adduct to Atovaquone [I].

Yet another object of the present invention is synthesis of the novel compound 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one [V] from 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV] through dehydration and further conversion of it to Atovaquone [I].

Yet another object of the present invention is synthesis of the novel compound 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VI] from 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one [V] through hydrogenation in presence of noble metal catalysts and further conversion of it to Atovaquone [I].

Yet another object of the present invention is synthesis of the novel compound 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VII] from 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VI] through ketone bromination and further conversion of it to Atovaquone [I].

Yet another object of the present invention is synthesis of the novel compound 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII] from 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VII] through aromatization in presence of base and further conversion of it to Atovaquone [I].

Yet another object of the present invention is synthesis of the novel compound 2-(4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione [IX] from 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII] through oxidation and further conversion of it to Atovaquone [I].

Yet another object of the present invention is separation of '*cis*' isomer of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol from '*trans*' isomer of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol through an innovative crystallization process.

Yet another object of the present invention is synthesis of *cis*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione [XII] from *cis*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [XI] through oxidation.

Yet another object of the present invention is synthesis of *cis* isomer of Atovaquone from *cis*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione [XII].

Yet another object of the present invention is isomerization of “*cis*” isomer of Atovaquone to trans isomer of Atovaquone [I] in presence of a Lewis /Bronsted acid such as titanium tetrachloride, Sulfuric acid, triflic acid, methansulphonic acid.

Summary of Invention:

One aspect of the present invention is to provide 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone, *i.e.* Atovaquone [I] through a novel, cost effective, green, and eco-friendly process, without separation of any diastereomers or geometric isomers of intermediates obtained during the reactions

A process for preparation of 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone, *i.e.* Atovaquone [I] comprising the steps of-

- a) condensing (1,2-dihydronaphthalen-4-yloxy)trimethylsilane [II] with 4-(4-chlorophenyl)cyclohexanone [III] in presence of Lewis acid in organic solvent to obtain 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV]
- b) dehydration of 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV] in organic solvent and in presence of acid such as pTSA to obtain diastereomeric mixture of 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one[V]
- c) hydrogenation of 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one[V] with platinum oxide to obtain *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VI]
- d) optional selective crystallization of *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VI] to separate the ‘*cis*’

and 'trans' isomers of 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one [VI]

e) ketone bromination of *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one [VI] to obtain *cis/trans* mixture of 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one [VII]

f) in absence of step (d) optional selective crystallization of 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one [VII] to separate the 'cis' and 'trans' isomers of 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one [VII]

g) elimination of *cis/trans* mixture of 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one [VII] with a strong base to give *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII]

h) in absence of step (f) optionally crystallizing 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII] to separate the 'cis' and 'trans' isomers of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII]

i) oxidizing 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII] to obtain 2-(4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione [IX]

j) base catalyzed epoxidation of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione [IX] to 1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione [X] in presence of hydrogen peroxide

k) acid catalyzed hydrolysis of 1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione [X] to obtain 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [I]

Another aspect of the present invention is to provide separation of 'cis' and 'trans' isomer of intermediates VI, VII and VIII through selective crystallization in an appropriate solvent.

Another aspect of the present invention is to provide a method for converting 2-[*cis*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone to 2-[*trans*-4-(4'-

chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone in presence of Lewis/ Bronsted acid

Another aspect of the present invention is to provide process for preparation of compound 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV] comprising condensation of (1,2-dihydronaphthalen-4-yloxy)trimethylsilane [II] with 4-(4-chlorophenyl)cyclohexanone [III] in presence of Lewis acid in organic solvent.

Another aspect of the present invention is to provide, a highly efficient and atomeconomic process for synthesis of compound [III] *i.e.* 4-(4-chlorophenyl)cyclohexanone

The process for making compound of formula (III), as provided comprises the steps of-

a) Preparation of (4-chlorophenyl) magnesium bromide (Grignard reagent) by reacting 1-bromo-4-chlorobenzene (i) with magnesium turnings in presence of catalytic amount of iodine

b) reacting (4-chlorophenyl) magnesium bromide with 1,4-cyclohexanedione monoethylene ketal (ii) to obtain 8-(4-chlorophenyl)-1,4-dioxa-spiro[4.5]decan-8-ol (iii)

c) dehydration reaction of 8-(4-chlorophenyl)-1,4-dioxa-spiro[4.5]decan-8-ol (iii) in organic solvent and in presence of p-TSA and ethylene glycol to obtain 4-(4-chlorophenyl)-cyclohex-3-enone monoethylene ketal (iv)

d) hydrogenation of 4-(4-chlorophenyl)-cyclohex-3-enone monoethylene ketal (iv) in presence of noble metal catalyst such as palladium on carbon, platinum oxide, preferentially palladium on carbon to obtain compound 4-(4-chlorophenyl)-cyclohexanone monoethylene ketal (v)

e) deketalization of 4-(4-chlorophenyl)-cyclohexanone monoethylene ketal (v) in presence of *p*TSA in mixture of acetone: water to obtain 4-(4-chlorophenyl)cyclohexanone [III]

Another aspect of the present invention is to provide process for synthesis of 2-[*cis*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone comprising the steps of-

a) converting *Cis*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (XI), to *cis*-4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (XII) in presence of sulphuric acid /sodium nitrite or sodium bromate/acetic acid or acetic acid/hydrogen peroxide or ruthenium chloride/hydrogen peroxide/acetic acid

b) converting *cis*-4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (XII) to *cis*-1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (XIII) in presence of hydrogen peroxide and base.

c) converting *cis*-1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (XIII) to give *cis isomer of Atovaquone* in presence of sulfuric acid.

Another aspect is to provide a process for isomerization of *cis*-Atovaquone i.e. 2-[*cis*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone to *trans*-Atovaquone i.e. 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone in presence of Lewis acid

Further aspects of the invention are to provide the following compounds:

- a) 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV]
- b) 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one [V]
- c) 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VI]
- d) 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VII]
- e) 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII]
- f) 2-(4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione [IX]
- g) 1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione [X]

Brief description of accompanying Figures:

Figure I: Process for synthesis of Atovaquone [I] without separation of any diastereomers or geometric isomers of intermediates obtained during the reaction.

Figure II: Process for synthesis of '*cis*' isomer of Atovaquone [XIV] from *cis*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [XI]

Figure III: Process for isomerization of '*cis*' isomer of Atovaquone [XIV] to Atovaquone [I] *i.e.* desired '*trans*' isomer in presence of Lewis acid.

5 Figure IV: High yielding process for synthesis of key intermediate *i.e.* 4-(4-chlorophenyl)cyclohexanone [III].

Figure V: The ORTEP diagram of *trans*-2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV]

10 Figure VI: The ORTEP diagram of *cis*-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one

Figure VII: The ORTEP diagram of *trans*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol

Detailed Description of the Invention

15 The present invention relates to process for preparation of Atovaquone [I] as described in the scheme of reactions in Figure I.

(1,2-Dihydronaphthalen-4-yloxy)trimethylsilane (II) was condensed with 4-(4-chlorophenyl)cyclohexanone (III) in presence of titanium tetrachloride in an organic solvent such as dichloromethane to give *trans*-2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one (IV). Compound (IV) on dehydration in presence of *p*-TSA in an organic solvent such as toluene gave a mixture of diastereomers of 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one (V), which on further hydrogenation using platinum oxide in organic solvent such as ethyl acetate, acetone preferably acetone gave *cis/trans*-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one (VI). Compound (VI) was further reacted with bromine in presence of acetic acid
25 in an organic solvent such as diethyl ether to give *cis/trans*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one (VII). Compound (VII) was then treated with potassium *tert*-butoxide in organic solvent such as dimethoxyethane to get *cis/trans*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (VIII), which was further converted to *cis/trans*-4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (IX) in presence

of any of the following combination of reagents: sulphuric acid /sodium nitrite or sodium bromate/acetic acid or acetic acid/hydrogen peroxide or ruthenium chloride/hydrogen peroxide/acetic acid. This was subsequently converted to *cis/trans*-1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (X) in presence of hydrogen peroxide and base such as sodium carbonate. Compound (X) on hydrolysis with sulfuric acid gave Atovaquone (I).

The present invention also relates to separation of '*cis*' and '*trans*' isomer of intermediates VI, VII and VIII through selective crystallization in an appropriate solvent. The pure '*cis*' and '*trans*' isomers of intermediates VI, VII and VIII are respectively converted into pure '*cis*' and '*trans*' isomer of intermediate [X] by means of the chemistry described in scheme A. Furthermore, pure '*cis*' and '*trans*' isomer of intermediate [X] were respectively converted to 2-[*cis*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [XIV] (Figure II) and 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [I] *i.e.* Atovaquone [I] through acid catalyzed hydrolysis

Cis-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (XI), was converted to *cis*-4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (XII) in presence of any of the following combination of reagents: sulphuric acid /sodium nitrite or sodium bromate/acetic acid or acetic acid/hydrogen peroxide or ruthenium chloride/hydrogen peroxide/acetic acid, which was subsequently converted to *cis*-1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (XIII) in presence of hydrogen peroxide and base such as sodium carbonate. Compound (X) on hydrolysis with sulfuric acid gave *cis*-Atovaquone (XIV). (reaction Scheme of Figure II)

A method for converting 2-[*cis*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone to 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone in presence of Lewis/ Bronsted acid is also provided (reaction Scheme of Figure III)

Cis- Atovaquone or mixture of *cis/trans*-Atovaquone was converted to *trans*-Atovaquone in presence of Lewis acid such as titanium tetrachloride, in organic solvent such as dichloromethane.

Another aspect of the present invention is to provide , a highly efficient and atom economic process for synthesis of compound [III] *i.e.* 4-(4-chlorophenyl)cyclohexanone which is described below (reaction Scheme of Figure IV)

1-Bromo-4-chlorobenzene (i) was reacted with magnesium turnings in presence of catalytic amount of iodine in organic solvent such as tetrahydrofuran to obtain corresponding Grignard reagent, which was further reacted with 1,4-cyclohexanedione monoethylene ketal (ii) to obtain 8-(4-chlorophenyl)-1,4-dioxo-spiro[4.5]decan-8-ol (iii) in an average 90 % isolated yield. Compound (iii) was dehydrated in presence of *p*TSA and ethylene glycol in organic solvent such as toluene to obtain 4-(4-chlorophenyl)-cyclohex-3-enone monoethylene ketal (iv) in 93% isolated yield, which was further hydrogenated in presence of noble metal catalyst such as palladium on carbon, platinum oxide, preferentially palladium on carbon to obtain compound 4-(4-chlorophenyl)-cyclohexanone monoethylene ketal (v). Compound (v) was deketalized in presence of *p*TSA in mixture of acetone: water (50:50). After completion of deketalization, acetone was evaporated under reduced pressure to obtain aqueous slurry, which was added to dilute sodium bicarbonate solution and resulting mixture was cooled to 5 °C to obtain 4-(4-chlorophenyl) cyclohexanone [III] as light yellow solid in 88 % yield.

The addition of ethylene glycol played a crucial role in improving the yield of compound (iv). In the absence of ethylene glycol, not only the yields were found to be lower but also formation of innumerable number of impurities, rendering difficulty in crystallization of (iv).

The invention is described in further details below

A) Process for synthesis of Atovaquone [I]

Step 1 of Figure I

Mukaiyama aldol condensation is very well studied and widely used in organic synthesis. Mukaiyama aldol condensation is generally carried out in presence of Lewis acid or Lewis base in a polar aprotic solvent preferably halogenated solvent such as DCM at

temperature range of -70 to 0 °C. Lewis acids such as TiCl₄ (Mukaiyama, T. *et al.* Chem. Lett. 1973, 1011.; Mukaiyama, T. *et al.* J. Am. Chem. Soc. 1974, 96, 7503.; Mukaiyama, T. *et al.* Chem. Lett. 1975, 741); BF₃.Et₂O (Nakanura, E. *et al.* J. Am. Chem. Soc. 1977, 99, 961.; Sugimura, H. *et al.* Synlett. 1991, 153.); SnCl₄ (Mukaiyama, T. *et al.* Org. Synth. 1987, 65, 6) and Lewis bases such as CaCl₂ (Denmark, S. E. *et al.* Acc. Chem. Res 2000, 32, 432; Hosomi, A. *et al.* J. Am. Chem. Soc. 2002, 124, 536), Lithium amide (Mukaiyama, T. *et al.* Chem. Lett. 2002, 182) have been reported for Mukaiyama aldol condensation.

Mukaiyama aldol condensation of (1,2-dihydronaphthalen-4-yloxy)trimethylsilane of formula [II] with 4-(4-chlorophenyl)cyclohexanone [III] was carried out in presence of Lewis acid such as titanium tetrachloride in organic solvent such as dichloromethane at temperature -60 to -35 °C; preferably at -60 °C under inert atmosphere, (Step1 of Figure 1). After completion of reaction, titanium tetrachloride was quenched by adding chilled water at 0 °C. Organic layer was separated and washed with 5 % aqueous solution of sodium bicarbonate and brine. Evaporation of organic solvent afforded the crude *trans*-2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one, which was further re-crystallized from ethyl acetate to obtain pure *trans*-2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV] in 85 % isolated yield.

The structure of compound [IV] has been established from single crystal X-ray diffraction studies. The crystals are monoclinic (*a* = 9.9256 Å, *b* = 10.6118 Å, *c* = 16.9116 Å; $\alpha=90^\circ$, $\beta=98.4140^\circ$, $\gamma=90^\circ$) having a space group of P21/c, and *Z*=4.

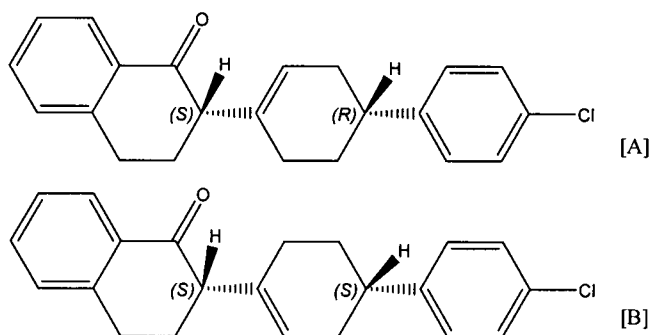
The ORTEP diagram of compound [IV] shows that the hydroxyl group has an axial conformation, whereas other bulky groups in 1, 4 position of the cyclohexane ring have equatorial conformation (Figure V). The hydrogen atoms of the hydroxyl group form a hydrogen bond with carbonyl oxygen of the ketone functionality of the 1- tetralone moiety.

Step 2 of Figure I

Mukaiyama aldol condensation product *i.e.* *trans*-2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV] was dehydrated in presence of acids such as sulfuric acid, *p*-toluene sulfonic acid, methane sulfonic acid and triflic acid

preferably p-toluene sulfonic acid in solvents such as dichloromethane, toluene, benzene; preferably toluene at temperature of about 25 to 110 °C, preferably 60 °C, which gave the diastereomeric mixture of 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one [V].

5 The corresponding tetra substituted α,β -unsaturated ketone, would apparently be thermodynamically most stable and expected as the desired product on dehydration, however, surprisingly compound [V] was obtained as the sole product presumably due to steric considerations. Compound [V] was characterized by NMR, IR and MS and further HPLC analysis showed that it is a mixture of two diastereomers [A] and [B].



At this stage no attempt was made to separate these stereoisomers and they were hydrogenated to obtain 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one (VI).

Step 3 of Figure I

Dehydrogenation of cyclic ketones to arenes or phenolic compounds is well known in literature. Springer *et al* has reported dehydrogenation of 1-tetralone or substituted 1-tetralone derivatives to corresponding naphthalene and corresponding 1-naphthol derivatives in presence of palladium on carbon (J.Org.Chem. 1971, 36(5) 686-689). Hence, hydrogenation of compound (V) was ruled out in presence of palladium on carbon, palladium hydroxide on carbon or Raney nickel and therefore hydrogenation was carried out in presence of 1 wt % loading of platinum oxide in mild hydrogen pressure (2-3 kg/cm²) to obtain 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one (VI).

2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one (VI) exists in *cis* and *trans* isomers, which was further confirmed by HPLC analysis and NMR spectroscopy.

Cis and *trans* isomers of 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one were separated through selective crystallization as it was observed that in cyclohexane, one isomer was more soluble than the other isomer and after recrystallizations in cyclohexane, one isomer was obtained in the pure form. Single crystal was obtained from the pure isomer and structure was assigned through a X-ray single crystal analysis and it was observed that obtained pure compound is *cis*-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one and it shows that the crystals are monoclinic ($a = 9.1928 \text{ \AA}$, $b = 10.9073 \text{ \AA}$, $c = 17.7399 \text{ \AA}$; $\alpha = 90^\circ$, $\beta = 97.1320^\circ$, $\gamma = 90^\circ$), having a space group of P21/c, and $Z = 4$.

The ORTEP diagram of *cis*-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one, where bulky groups in 1, 4 position of the cyclohexane ring have axial-equatorial conformation is shown in figure VI.

At this stage, geometric isomers of (4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one were not separated for further transformations and were carried forward as such as shown in Figure I.

Step 4 of Figure I

Cis/trans-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one (VI) was converted into *cis/trans*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one (VII) through ketone bromination method *i.e.* bromine and acetic acid.

Here also, if required, the geometric isomer of compound [VII] can be separated through selective crystallization from methanol to obtain pure *cis* and *trans* isomers of compound [VII] which could be further converted into respective *i.e.* *cis* and *trans* isomer of Atovaquone as per the process described in Figure I.

Step 5 of Figure I

β -bromo substituted 1-tetralone derivatives to corresponding substituted 1-naphthol derivative in presence of base such as triethylamine, piperidine, morpholine and

cyclohexylamine was reported (Tetrahedron Letter 2005, 46, 4187-92; JACS, 1957, 79, 230). When *cis/trans*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one (VII) was treated with of the above reported bases, desired product was not obtained. Therefore, *cis/trans*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one (VII) was treated with comparatively stronger base like alkoxides such as potassium *tert*-butoxide, sodium methoxide and sodium ethoxide to obtain corresponding 1-naphthol derivative i.e. *cis/trans*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (VIII).

Cis and trans isomers of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (VIII) were separated through selective crystallization as it was observed that in cyclohexane, one isomer was more soluble than the other isomer and after recrystallizations in cyclohexane, one isomer was obtained in the pure form. Single crystal was obtained from the pure isomer and structure was assigned through a X-ray single crystal analysis and it was observed that obtained pure compound is *trans*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol and it shows that the crystals are monoclinic ($a = 13.3526 \text{ \AA}$, $b = 7.9000 \text{ \AA}$, $c = 16.5550 \text{ \AA}$; $\alpha = 90^\circ$, $\beta = 96.95^\circ$, $\gamma = 90^\circ$), having space group of P21/c and Z value 4.

The ORTEP diagram of *trans*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol, where bulky groups in 1, 4 position of the cyclohexane ring have equatorial conformation conformation is shown in figure VII.

DSC melting point for *trans* 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol is 195.14°C

Step 6 of Figure I

Arnold and Larson have reported oxidation of naphthalene derivatives in presence of acetic acid and hydrogen peroxide to afford corresponding quinone derivatives (*Synthetic Communication*, 1940, 250-252). However, there is no report of oxidation of 1-naphthol derivatives to corresponding quinone derivatives under similar conditions.

When compound (VIII) was treated with hydrogen peroxide in acetic acid according to the reaction conditions reported in the abovementioned paper, it was observed that the reaction was sluggish and dark red coloured byproducts were also obtained. But, when bromide ion was added in the same reaction mixture, reaction was completed in 4 h, gave 50

% yield for compound (IX) and although the crude product was dark red coloured, number of byproducts was comparatively less. However, column flash chromatography was necessary for the separation of pure compound (IX) from crude product.

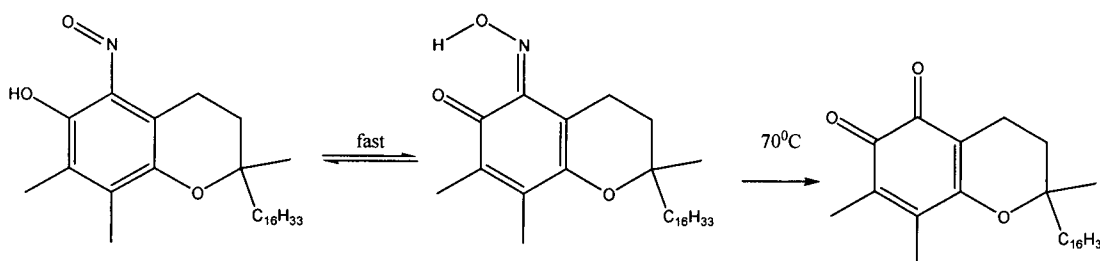
It was also observed that addition of bromide ion improves the rate of reaction presumably because of in situ oxidation of bromide ion by hydrogen peroxide to bromate and hence we thought of carrying out the reaction in presence of sodium bromate and acetic acid.

In spite of dearth of any literature procedure of such oxidation, compound (VIII) was oxidized in presence of sodium bromate/ acetic acid which yielded 66 % of compound (IX).

Alternatively, compound (VIII) was also converted into compound (IX) in presence of RuCl_3 / acetic acid and hydrogen peroxide (Tetrahedron Letter, 1983, 5249-5252).

Patel *et al* (Tetrahedron 2007, 63, 4067) has reported conversion of γ -tocopherol to corresponding ortho-quinone derivative via 5-nitroso- γ -tocopherol intermediate as shown in scheme 6.

Presumably this occurred by a concerted hydrogen transfer from phenolic hydroxyl functionality to nitroso group via a six member transition state *i.e.* intramolecular tautomerism



Scheme 6

The mechanistic implication of the above transformation was noted and compound (VIII) was converted to the corresponding nitroso derivative by treating with sodium nitrite and 50 % aqueous sulphuric acid in organic solvent such as 1,4-dioxane at temperature 25 to 75 °C; preferably at 70 °C which, to our satisfaction yielded compound (IX) in quantitative yield (step 6 of figure I). Interestingly, in the present case the tautomerism is intermolecular not intramolecular.

There was improvement in the yield as compared to earlier methods but to obtain pure compound (IX) column chromatography could not be avoided in all processes.

Step 6 and 7 of Figure I

Compound (IX) was converted to compound (X) in presence of hydrogen peroxide and base such as sodium carbonate (J. Org Chem, 1952, 74 3910-3915), which was further hydrolyzed in presence of a Bronsted acid such as sulfuric acid to obtain compound (I) (J. Org Chem, 1952, 74 3910-3915; US 5,053,432). Crude product was further re-crystallized from acetonitrile to obtain Atovaquone [I] in 99 % purity as shown by HPLC analytical method described in US monograph for relative substance and resolution of Atovaquone, wherein no *cis* isomer was observed.

B) Process for synthesis of *cis*-Atovaquone [XIV]

Geometric isomers of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII] *i.e.* *cis* and *trans* isomer were separated through selective crystallization in presence of cyclohexane, where *cis*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (XI) was soluble in cyclohexane and *trans*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol precipitated out.

cis-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (XI) was converted into 2-[*cis*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone (XIV) *i.e.* *cis* isomer of Atovaquone, as shown in Figure II through employing chemistry as described in steps 6 and 7 and further hydrolysis of compound [XIII] in presence of sulphuric acid.

C) Process for isomerization of *cis*- Atovaquone to *trans*-Atovaquone [I]

Isomerization of '*cis*' isomer of Atovaquone to '*trans*' isomer of Atovaquone was carried out in presence of a Lewis acid such as titanium tetrachloride.

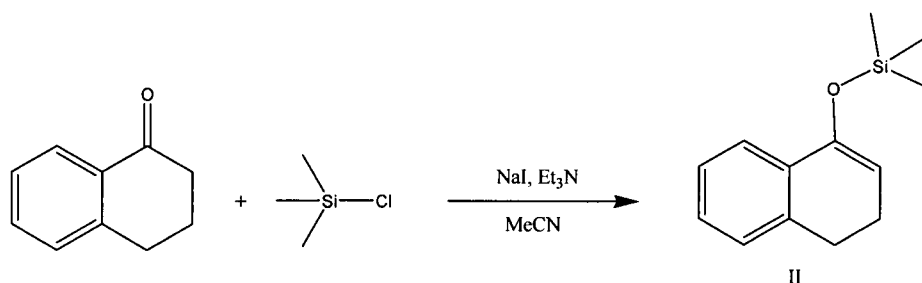
Nomenclatures used for the compounds mentioned herein are as understood from the CambridgeSoft® ChemOffice software *ChemDraw Ultra version 6.0.1*.

Analytical Methods:

The purity was determined by HPLC using a Shimadzu LC 2010 system equipped with a column (Purosphere star RP-18e (4.6 x 150mm), 5µm), column oven temperature 25 °C and UV visible detector (UV at 340nm). Mobile phase was buffer: acetonitrile (55:45) with flow rate 3.0 mL⁻¹, injection volume 20 µl. NMR spectra were obtained at 200 and 400

MHz Bruker instruments, with CDCl_3 as solvent unless otherwise stated. Chemical shifts (δ) are given in ppm relative to tetramethylsilane ($\delta = 0$ ppm). IR spectra were recorded on Perkin Elmer Spectrum (Model: Spectrum 100) and absorption bands are given in cm^{-1} . DSC was recorded on Perkin Elmer model Diamond DSC at the rate of $10^\circ\text{C}/\text{min}$, and endothermic peak was recorded in $^\circ\text{C}$ and ΔH is reported in J/g. Crystal structure of the single crystal was measured on Bruker Smart Apex CCD diffractometer having software SHELXTL-PLUS at temperature 293 (2) K and wavelength $0.71073 \text{ \AA}$ and θ range for data collection is 1.56 to 28.40° .

Example 1: Synthesis of (1, 2-dihydronaphthalen-4-yloxy)trimethylsilane (II)



To a reactor equipped with reflux condenser, nitrogen bubbler, dropping funnel and thermo-pocket, were charged α -tetralone (270.0 g, 1.85 mol) and triethylamine (514.0 g, 5.08 mol) at room temperature under nitrogen atmosphere. After stirring at room temperature for 15 min, trimethyl silyl chloride (541.0 g, 5.0 mol) was added drop wise over a period of 30-40 min while maintaining nitrogen atmosphere and stirred for around 1h at room temperature. Sodium iodide (369.0 g, 2.46 mol) was dissolved in acetonitrile (2.2 L) at RT and added to the reaction mass slowly while maintaining an internal temperature not more than 40°C . The resultant reaction mass was allowed to stir at room temperature for 2h. TLC was checked at this point for product formation and in case the reaction was found to be incomplete, an additional 1 mol equivalent of triethylamine was added to the reaction mass. On complete consumption of reactants, the reaction mass was poured into ice water (3 L) and extracted with *n*-pentane (2x 1 L). After separating, the organic layer was dried over

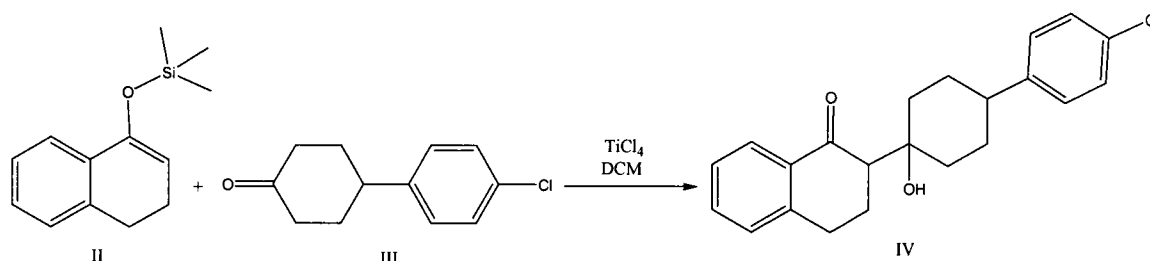
anhydrous potassium carbonate and solvent evaporated to give product as a brown oil (402.0 g, 96% yield). Generally yield of the product ranges from 90 to 97 %.

FTIR (neat): 3022, 3060, 2958, 2935, 2888, 2832, 1638, 1600, 1485, 1359, 1337, 1251, 1188, 1140, 1093, 919, 860, 845, 737 cm^{-1} .

^1H NMR (CDCl_3 , 200 MHz): δ 1.85 (s, 9H), 3.89-3.94 (m, 2H), 4.34-4.38 (t, 2H), 6.79 (s, 1H), 8.69-8.81 (m, 3H), 9.0-9.02 (d, 1H).

MS (EI): $\text{C}_{13}\text{H}_{18}\text{OSi}$: 218.1127; $[\text{M}+\text{H}]^+$: 219.10

Example 2: Synthesis of 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (IV)



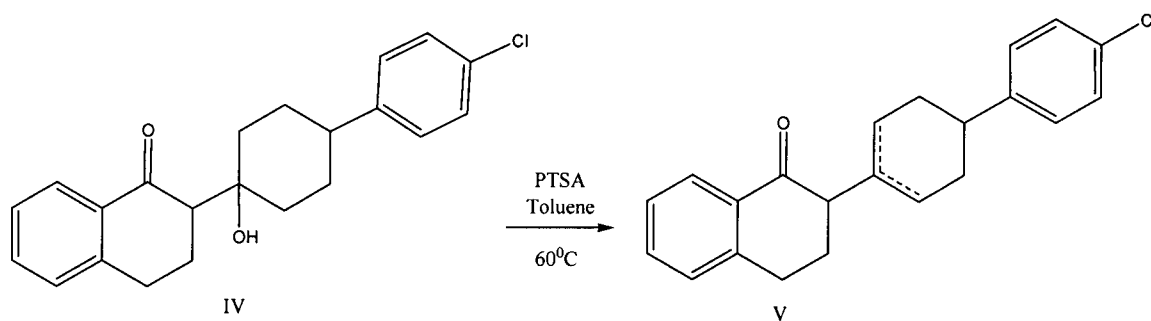
To a reactor equipped with, over head stirrer, reflux condenser, nitrogen bubbler, dropping funnel and thermo-pocket, was charged 4-(4-chlorophenyl)cyclohexanone (85.0 g, 0.41 mol) under a positive nitrogen pressure at 25 $^{\circ}\text{C}$. Freshly dried dichloromethane (850 mL) was added to dissolve the material and the reaction mass was cooled to -35 $^{\circ}\text{C}$. A 1 molar solution of titanium tetrachloride (85.4 g, 0.45 mol) in dry dichloromethane (550 mL) was added drop wise to the reaction mass. After complete addition of titanium tetrachloride reaction mixture was warmed to 0 $^{\circ}\text{C}$ and stirred for 1 h. Reaction mass was again cooled to -55 $^{\circ}\text{C}$ and at this temperature, a solution of (1,2-dihydronaphthalen-4-yloxy)trimethylsilane (111.3 g, 0.515 mol) in dichloromethane (1 L) was added and allowed to stir at -55 $^{\circ}\text{C}$ for 1h. After which, again reaction mixture was warmed to 0 $^{\circ}\text{C}$ and then quenched with ice water (2500 mL) under vigorous stirring and diluted with dichloromethane (3000 mL). Organic layer was separated and washed with saturated sodium bicarbonate solution (500 mL) and brine. After stripping off the DCM layer under reduced pressure, the residue was suspended

in ethyl acetate (300 mL) and resultant slurry was refluxed for 1h and cooled to RT. Resultant solid were filtered off to give the product as off-white solid. (122.3 g, 84.9 % yield). Generally yield of the product ranges from 78 to 85 %.

FTIR (neat): 3441, 2945, 2927, 2858, 1654, 1598, 1397, 1230, 1046, 962, 840, 751, 610 cm^{-1} .

- 5 **^1H NMR (CDCl_3 , 400 MHz):** δ 1.55(t, 1H), 1.68-1.79 (m, 4H), 1.91-2.02 (m, 2H), 2.04-2.11 (m, 2H), 2.32-2.36 (dd, 1H), 2.45 (t, 1H), 2.68 (dd, 1H), 3.05(d, 2H), 4.98 (s, 1H (OH)), 7.20-7.37 (m, 6H), 7.52 (t, 1H), 8.04 (d, 1H); **^{13}C NMR (CDCl_3 , 100 MHz):** δ 25.5, 28.6, 28.9, 29.5, 32.0, 35.7, 43.6, 57.1, 72.8, 126.8, 127.5, 128.3, 128.4, 128.5, 131.4, 133.1, 133.9, 144.2, 145.7, 202.8; **MS (EI):** $\text{C}_{22}\text{H}_{23}\text{ClO}_2$: 354.86; $[\text{M}]^+$: 355.85; **DSC peak at** 167.85 $^\circ\text{C}$ (10 $^\circ\text{C}/\text{min}$)
- 10 **PXRD [2θ] ($\text{Cu K}\alpha_1 = 1.54060 \text{ \AA}$, $\text{K}\alpha_2 = 1.54443 \text{ \AA}$, $\text{K}\beta = 1.39225 \text{ \AA}$; 40 mA, 45 kV):** 8.07, 8.81, 8.93, 9.76, 10.51, 15.60, 17.29, 17.44, 19.10, 19.32, 20.84, 22.96, 24.37, 27.96, 29.55,

Example 3: Synthesis of 2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2H)-one (V)



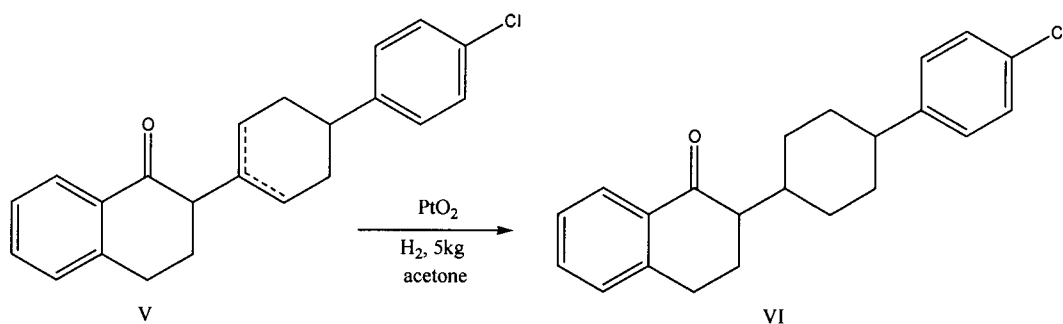
- 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (122.0 g, 0.0345mol) was charged in a reactor equipped with overhead stirrer, reflux condenser and thermo-pocket. Toluene (2 L) was added to suspended the material and *p*-toluene sulfonic acid (3.05 g, 2.5 mol%) was added to the reaction mass which was then heated to 60 $^\circ\text{C}$ and stirred for 2h. Progress of reaction was monitored on TLC. After completion of reaction, reaction mass was cooled to RT and solvent was evaporated under pressure to obtain residue. To the residue, was added ethyl acetate (1500 mL) and washed with sat. NaHCO_3 soln. and brine followed by evaporation of solvent to give crude product
- 20

which was further recrystallised from methanol to obtain white solid compound (V) (55.2 g, 50%). Generally yield of the product ranges from 45 to 56 %.

FTIR (neat): 3020, 3045, 2920, 2894, 2863, 2839, 1683, 1597, 1491, 1218, 1088, 818, 747 cm^{-1} .

5 **^1H NMR (CDCl_3 , 400 MHz):** δ 1.79-1.96 (m, 2H), 2.16-2.34 (m, 6H), 2.83-2.87 (m, 1H), 3.18 (s, 2H), 3.19-3.24 (m, 1H), 5.58 (d, 1H), 7.17-7.35 (m, 6H), 7.49 (t, 1H), 8.08 (d, 1H); **^{13}C NMR (CDCl_3 , 100 MHz):** δ 27.0 (27.2), 28.3 (28.5), 28.8, 29.8 (29.9), 33.4 (33.5), 39.3 (39.4), 55.7 (56.0), 124.1 (124.2), 126.7, 127.4 (127.5), 128.3 (128.31), 128.4 (128.5), 128.7, 131.5, 132.8 (132.9), 133.4, 136.0 (136.1), 144.0 (144.1), 145.4 (145.5), 198.8 (198.9); **MS (EI):**
10 $\text{C}_{22}\text{H}_{21}\text{ClO}$: 336.12; $[\text{M}+\text{H}]^+$: 337.10 DSC peak at 136.02. $^{\circ}\text{C}$ ($10^{\circ}\text{C}/\text{min}$)

Example 4: Synthesis of *cis/trans*-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (VI)



15

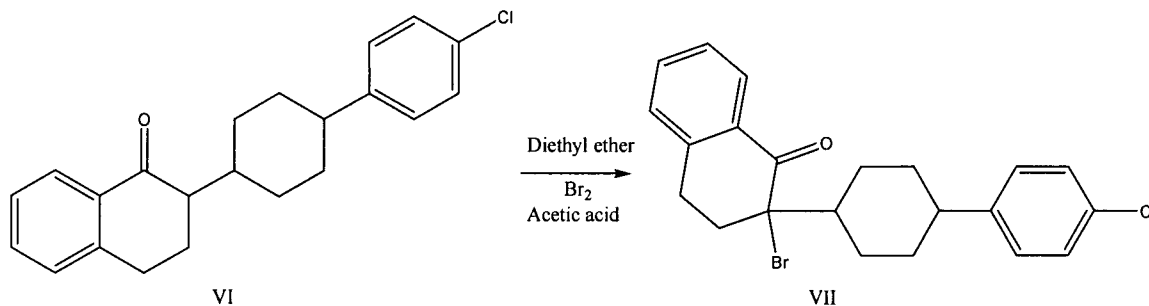
2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3, 4-dihydronaphthalen-1(2H)-one (51.0g, 0.151 mol) was dissolved in acetone (1.1 L) at RT and transferred to a Parr autoclave reactor. Platinum oxide (0.097 g, 3 mol %) was added to the reaction mass and flushed twice with
20 nitrogen and once with hydrogen. Subsequently, a hydrogen pressure of 5 kg/cm^2 was maintained for 4-5h at RT after which the platinum black was filtered off through a Celite bed. The mother liquor was evaporated under reduced pressure to give crude product which was re-crystallized from methanol to give product as white solid (43.29g, 90% yield). Generally yield of the product ranges from 85to 95 %.

Cis/trans-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (10 g) was suspended in cyclohexane (100 mL) and stirred for 1 h. *cis*-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one was soluble in cyclohexane and *trans*-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one remained insoluble (4.8 g). Single crystal was generated from cyclohexane layer which contain *cis*-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (Figure VI).

FTIR (neat): 2917, 2887, 2850, 1681, 1491, 1294, 1089, 1012, 749, 530 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): δ 1.24-1.28 (m, 1H), 1.44-1.59 (m, 3H), 1.74-1.85 (m, 3H), 1.90-1.96 (m, 3H), 2.02-2.09 (m, 2H), 2.19-2.27 (m, 1H), 2.99-3.09 (m, 2H), 7.14-7.24 (m, 2H), 7.25-7.35 (m, 5H), 7.47-7.5 (t, 1H), 8.05-8.07 (d, 1H); **MS (EI):** $\text{C}_{22}\text{H}_{23}\text{ClO}$: 338.15 $[\text{M}+\text{H}]^+$: 339.00; DSC peak at 82.95 $^{\circ}\text{C}$ (10 $^{\circ}\text{C}/\text{min}$)

Example 5: Synthesis of *cis/trans*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (VII) and method for separation of *cis* and *trans* isomers



Cis/trans-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (43.2 g, 0.127 mol) was charged into a reactor equipped with thermo-pocket and dropping funnel. Acetic acid (86.4 g) and diethyl ether (1.5 L) were added and the reaction mass was cooled to 0 $^{\circ}\text{C}$. Bromine (24.5 g, 0.153 mol) was dissolved in diethyl ether (100 mL) and added drop wise to the reaction mass at 0 $^{\circ}\text{C}$. The resultant orange solution was stirred at 0 $^{\circ}\text{C}$ for 1h and gradually the temperature was allowed to increase to 15-20 $^{\circ}\text{C}$ when the reaction mass started decolourizing, after which reaction temperature was allowed to increase upto 25 $^{\circ}\text{C}$. After

completion of reaction, dichloromethane (300 mL) was added to dissolve solid, if any, precipitated during the reaction. Organic layer was washed with water (2 x 500 mL) and then with aqueous solution of 5% sodium thiosulphate (500 mL). Solvent was removed from the reaction mass under reduced pressure to obtain product as white solid (53.1 g, 99 %).

5 Generally yield of the product ranges from 95 to 99 %.

Cis/trans-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (39 g) was suspended in methanol (100 mL) and stirred for 1 h. *cis*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one was soluble in methanol and *trans*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one

10 remained insoluble. Pure *trans*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one was obtained through filtration as white solid (19 g) and major *cis*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one was obtained after evaporation of solvent under reduced pressure as sticky semi-solid material (21 g).

15 ***Trans*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one**

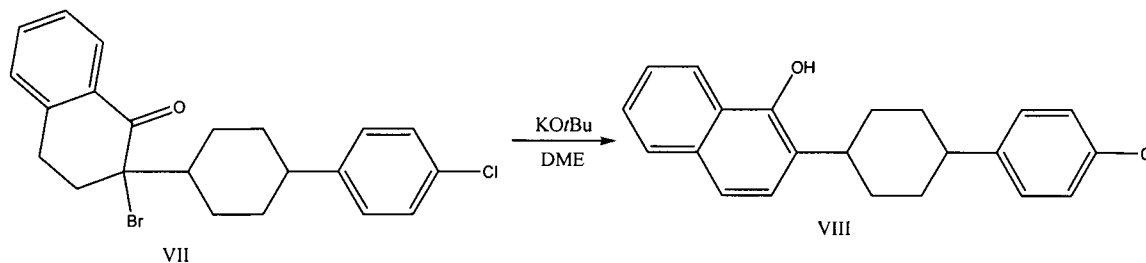
FTIR (neat): 2929, 2850, 1687, 1599, 1490, 1454, 1292, 1234, 1090, 1013, 916, 810, 747, 631 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 1.29-1.33 (m, 1H), 1.44-1.48 (m, 1H), 1.58-1.65 (m, 2H), 1.83-1.91 (m, 2H), 2.06-2.09 (d, 1H), 2.25-2.31 (m, 1H), 2.38-2.54 (m, 3H), 2.70-2.76 (t, 1H), 2.93-2.97 (d, 1H), 3.27-3.31 (m, 1H), 7.15-7.17 (d, 2H), 7.27-7.30 (m, 3H), 7.37-7.41 (t, 1H) 7.52-7.56 (t, 1H), 8.18-8.20 (d, 1H) ; **¹³C NMR (CDCl₃, 100 MHz):** δ 27.0, 28.3, 29.1, 31.5, 33.9, 34.2, 43.9, 44.2, 74.7, 127.1, 128.1, 128.3, 128.4, 128.6, 128.9, 129.1, 130.3, 131.6, 133.8, 142.5, 145.2, 190.3

DSC: peak at 182.95 °C

25

Example 6: Synthesis of *cis/trans*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (VIII) and method for separation of *cis* and *trans* isomers



Potassium *tert*-butoxide (31.2 g, 0.278 mol) was charged into a reactor containing dimethoxyethane (500 mL) at room temperature. Temperature of the reaction mass was increased to 40 °C and to this was added a solution of *cis/trans*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (53.0 g, 0.126 mol) in dimethoxyethane (500 mL). Temperature of the reaction mass was further increased to 80°C and was allowed to stir for 1.5 h at this temperature. Progress of reaction was monitored on TLC. After completion of reaction, reaction mass was cooled to RT and solvent was evaporated under reduced pressure and 10% aqueous solution of hydrochloric acid (180 mL) was added to the residue. The resultant mixture was extracted with DCM (150 mL) and evaporated to give crude product (47.0 g). Generally average yield of the product ranges from 70 to 80 %.

Mixture of *cis/trans*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (25 g) was suspended in cyclohexane and stirred for 1 h. *cis*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol was soluble in cyclohexane and *trans*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol remained insoluble. Pure *trans*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one was obtained through filtration as light orange solid (7.5 g) and major *cis*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one was obtained after evaporation of solvent under reduced pressure as sticky semi-solid material (11 g). Obtained major *cis*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol was further purified by column chromatography to obtain pure *cis*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol as sticky semi-solid brown colored material (7 g).

***Trans*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol**

FTIR (neat): 3563, 3016, 2928, 2853, 2400,, 1492, 1263,1216, 1094, 807, 768,755 cm^{-1} .

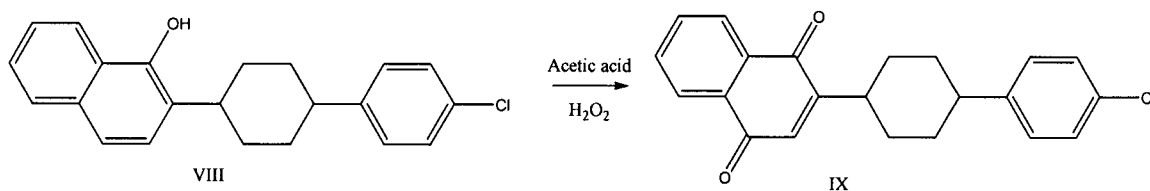
^1H NMR (CDCl_3 , 400 MHz): δ 1.63-1.85 (m, 4H), 2.06-2.09 (m, 4H), 2.68-2.70 (t, 1H), 3.03-3.08 (t, 1H), 7.15-7.17(d, 2H), 7.27-7.30 (m, 3H), 7.37-7.41 (t, 1H) 7.82-7.84 (d,1H), 8.12-8.14 (d,1H) ; **^{13}C NMR (CDCl_3 , 100 MHz):** δ 33.18, 34.58, 37.01, 43.51, 76.73, 127.1, 128.3, 129.0,

129.1, 130.3, 131.6, 133.8, 145.71, 147.24 **MS (EI):** $\text{C}_{22}\text{H}_{21}\text{ClO}$: 336.12; $[\text{M}-\text{H}]^-$: 335.20

DSC: peak at 195.14 $^{\circ}\text{C}$

PXRD [2 θ] (Cu $K_{\alpha 1}$ = 1.54060 Å, $K_{\alpha 2}$ = 1.54443 Å, K_{β} = 1.39225 Å; 40 mA, 45 kV): 10.76, 12.38, 13.00, 13.33, 13.76, 14.37, 15.51, 16.10, 17.41, 17.73, 18.71, 19.67, 20.05, 21.36, 22.39, 23.04, 23.40, 24.02, 24.56, 26.11, 27.72, 28.97, 30.01, 31.78

Example 7: Synthesis of *cis/trans*-4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (IX) in presence of acetic acid/ hydrogen peroxide



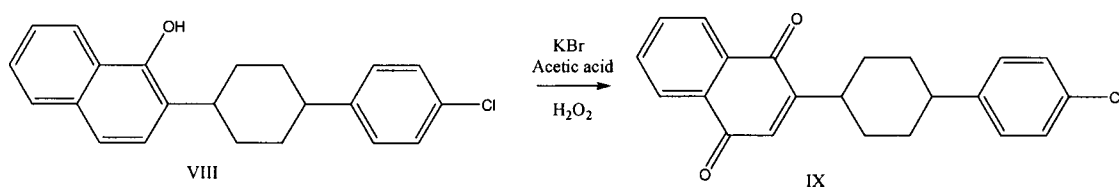
To 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (1.2 g, 3.5 mmol) taken in a RB flask, was added acetic acid (20 mL) and stirred for 15 min at RT. Temperature of the reaction mass was increased to 80 $^{\circ}\text{C}$ and a 30% solution of H_2O_2 (5 mL) was added to it drop wise over a period of 30 min at 80 $^{\circ}\text{C}$ and stirred for another 30 min. After cooling to RT, water (50 mL) was added to the reaction mass. The resultant mixture was extracted with DCM (3x 100 mL), dried over anhydrous Na_2SO_4 and evaporated to give crude product which was purified by column chromatography to give pure product as yellow solid. (0.4 g, 32% yield)

FTIR (neat): 3310, 2926, 2856, 1662, 1614, 1594, 1492, 1449, 1329, 1305, 1261, 1251, 1091, 1012, 937, 822, 779, cm^{-1} .

¹³C NMR (CDCl₃, 100 MHz): δ 26.92, 27.74, 29.81, 32.16, 33.93, 34.41, 36.21, 38.73, 43.39, 125.96, 126.00, 126.75, 126.46, 128.18, 128.46, 128.52, 128.62, 131.46, 131.68, 131.85, 131.9, 132.45, 132.53, 133.13, 133.67, 133.71, 134.11, 143.50, 145.28, 155.17, 155.64, 184.74, 184.90, 185.33, 185.50;

5

Example 8: Synthesis of 4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (IX) in presence of acetic acid/ hydrogen peroxide/potassium bromide

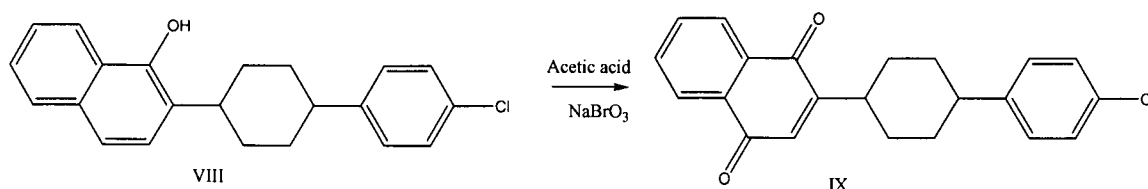


10

To 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (1.0 g, 2.9 mmol) taken in a RB flask, were added acetic acid (20 mL) and potassium bromide (1.0 g, 8.4 mmol) and stirred for 15 min at RT. Temperature of the reaction mass was increased to 80 °C and a 30% solution of H₂O₂ (5 mL) was added to it dropwise over a period of 30 min at 80 °C and stirred for another 30 min. After cooling to RT, water (50 mL) was added to the reaction mass. The resultant mixture was extracted with DCM (3x 100 mL), dried over anhydrous Na₂SO₄ and evaporated to give crude product which was purified by column chromatography to give pure product as yellow solid. (0.52 g, 50% yield)

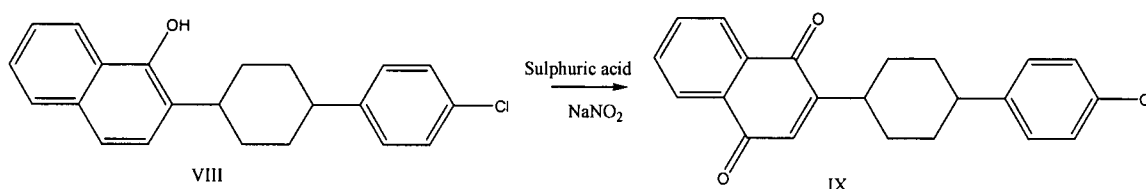
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20 **Example 8: Synthesis of 4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (IX) in presence of sodium bromate/ acetic acid**



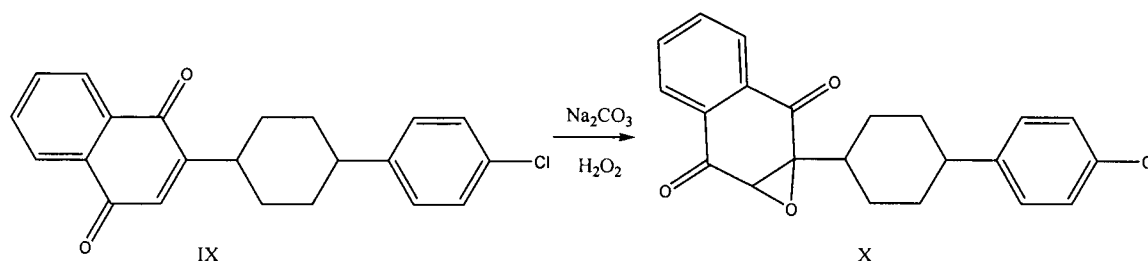
2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (5.1 g, 15.1 mmol) was added to acetic acid (70 mL) and resulting reaction mass was heated to 60 °C. Sodium bromate (1.5 g, 10 mmol) was added to the above reaction mixture and stirred for 1 h at 80 °C. Water (15 mL) was added to the reaction mixture and stirred for an additional 2 h at 80 °C. The reaction mixture was cooled to RT and water (200 mL) was added to it. The resultant mixture was extracted with dichloromethane (2 x 300 mL). Combined organic layer was dried over anhydrous Na₂SO₄ and evaporated to give crude product which was purified by column chromatography (stationary phase: Silica gel and mobile phase: 2% ethyl acetate in cyclohexane) to give pure product as yellow solid. (3.5 g, 66 % yield)

Example 9: Synthesis of 4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (IX) in presence of sodium nitrite/ 50% aqueous sulphuric acid.



To a stirred solution of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (42.3 g, 125.9 mmol) in 1,4-dioxane (850 mL) were added 50 % aqueous sulphuric acid (170 mL) and sodium nitrite (17.4 g, 251.7mmol) at 5 °C and temperature of the resultants reaction mixture was increased to 80 °C and stirred for another 2 h. After cooling to RT, water (50 mL) was added to the reaction mass and extracted with ethyl acetate (3x 500 mL), dried over anhydrous Na₂SO₄ and solvent was evaporated to crude product, which was further purified by column chromatography (stationary phase: Silica gel and mobile phase: 2% ethyl acetate in cyclohexane) to give pure product as yellow solid. (30.3 g, 70%)

Example 10: Synthesis of *cis/trans*-1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (X)



5

4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (13.5 g, 38.5 mmol) was charged into a reactor along with 1,4-dioxane (135 mL) at RT. To this were added sodium carbonate (4.5 g, 42.4 mmol) and a 30% soln. of H₂O₂ (5.23 g, 154.0 mmol) and the reaction mass was refluxed for 30 min. After cooling the reaction mass to RT, water (50 mL) was added and extracted with ethyl acetate (3*300 mL). Solvent was removed under reduced pressure to give product as off-white solid (13.7 g, 96% yield).

10

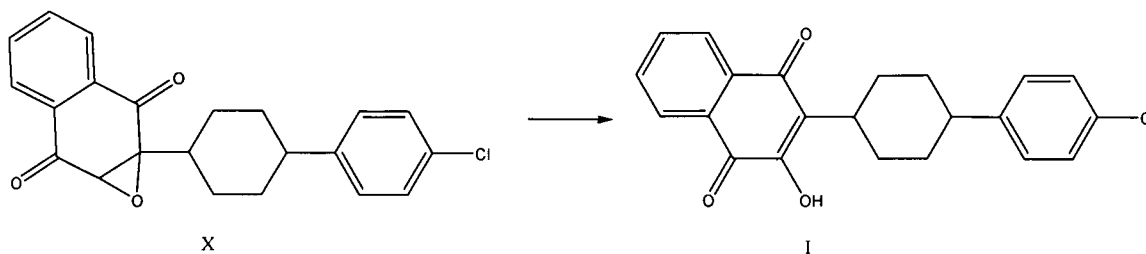
FTIR (KBr): 3370, 3078, 2944, 2928, 2900, 2859, 1695, 1594, 1490, 1451, 1306, 1287, 1157, 1089, 944, 886, 801, 725 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 1.28-1.41 (m, 2H), 1.56-1.62 (t, 2H), 1.9 (s, 4H), 3.96 (s, 1H) 7.16-7.18(d, 2H), 7.28-7.29 (d, 2H), 7.76-7.78 (t, 2H) 7.97-7.98 (d,2H), 8.03-8.05 (d,2H)

15

¹³C NMR (CDCl₃, 100 MHz): δ 26.6, 29.3, 33.3, 33.4, 34.3, 37.7, 43.3, 57.7, 58.2, 66.3, 66.9, 126.5, 126.6, 127.6, 128.4, 128.5, 131.5, 131.6, 132.8, 134.3, 134.6, 143.2, 145.2, 191.5, 192.1

20 Example 11: Synthesis of Atovaquone [I]



To 1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (13.5g, 1.6 mmol) taken in a reactor was added conc. H₂SO₄ (135 mL) and stirred for 5 h at RT. Water (2 L) was added to the reaction mass and extracted with DCM (3*200 mL). Solvent was evaporated under reduced pressure to give crude product which was further re-crystallized from acetonitrile to obtain pure compound as a yellow solid (10 g, 74% yield).

FTIR (KBr): 3375, 2958, 2924, 2853, 1659, 1646, 1625, 1594, 1490, 1369, 1344, 1277, 1248, 1216, 1089, 998, 822, 727, 656, 530 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 1.58 (q, 2H), 1.75 (d, 2H), 1.96 (d, 2H), 2.16-2.20 (m, 2H), 2.63 (t, 1H), 3.16 (t, 1H), 7.18 (d, 2H), 7.28 (d, 2H), 7.48 (s, 1H), 7.68 (t, 1H), 7.76 (t, 1H), 8.07 (d, 1H), 8.13 (d, 1H); **¹³C NMR (CDCl₃, 100 MHz):** δ 29.18, 34.34, 34.46, 34.64, 43.22, 126, 127, 127.25, 128.43, 129.19, 129.31, 131.45, 132.86, 133.12, 135.02, 146.05, 152.98, 181.80, 184.56; **MS (EI):** C₂₂H₁₉ClO₃: 366.1023; [M+Na]⁺: 388.95, [M-H]⁻: 365.30; DSC peak at 220.44 °C (10⁰C/min)

PXRD [2θ] (Cu K_{α1} = 1.54060 Å, K_{α2} = 1.54443 Å, K_β = 1.39225 Å; 40 mA, 45 kV): 7.30, 9.70, 10.79, 11.11, 11.83, 15.43, 16.16, 16.89, 17.39, 22.93, 24.62, 24.68, 25.35, 26.18, 26.84, 28.52, 28.70, 29.52, 30.68, 34.23, 36.84.

Example 12: Conversion of “cis” isomer of Atovaquone to “trans” isomer of Atovaquone in presence of Titanium tetrachloride.

Cis isomer of Atovaquone (0.5 g) was dissolved in dichloromethane (20 mL) and TiCl₄ (0.5 mL) was added to it at RT. Resulting reaction mixture was heated to 40 °C and stirred for 24 h. Reaction was monitored for conversion of *cis* isomer of Atovaquone to *trans*

isomer at different intervals. After 24 h, HPLC analysis showed the *cis* to *trans* ratio as 50:50.

HPLC Retention time for *cis* isomer: 19.33 min

HPLC Retention time for *trans* isomer: 22.66 min

5

Example 13: Conversion of “*cis*” isomer of Atovaquone to “*trans*” isomer of Atovaquone in presence of Sulphuric acid.

Cis/trans Atovaquone (0.5 g) was added in sulphuric acid (10 mL) at RT and stirred for 2 h, after which the reaction mixture was poured in ice water and product was extracted with dichloromethane, which was analyzed on HPLC as per resolution method given in US pharmacopoeia.

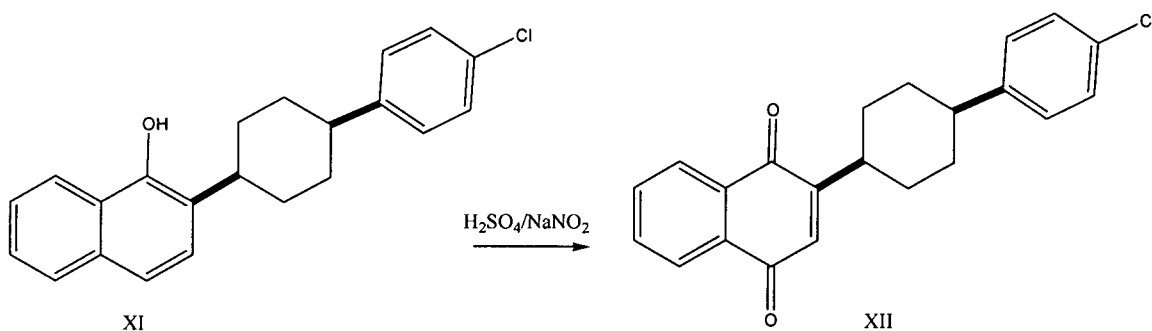
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HPLC Retention time for *cis* isomer: 19.33 min

HPLC Retention time for *trans* isomer: 22.66 min

15

Example 14: Synthesis of *cis*-4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (XII) in presence of Sodium Nitrite/ sulphuric acid



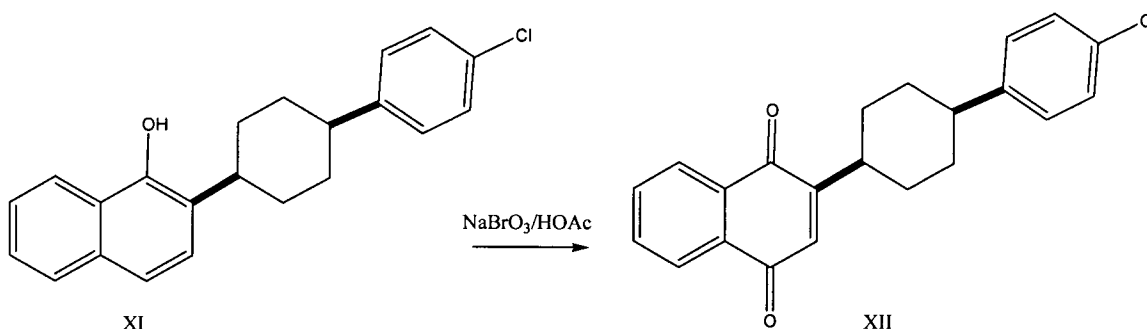
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To a stirred solution of *cis*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (0.5 g, 1.4 mmol) in 1,4 dioxane (20 mL) were added 50 % aqueous sulphuric acid (10 mL) and sodium nitrite (0.2 g, 2.9mmol) at 5 °C and temperature of the resultant reaction mixture was increased to 80 °C and stirred for 2 h. After cooling to RT, water (50 mL) was added to the reaction mass and extracted with DCM (3x 100 mL), dried over anhydrous Na₂SO₄ and

evaporated to give crude product which was purified by column chromatography (stationary phase: Silica gel and mobile phase: 2% ethyl acetate in cyclohexane) to give pure product as yellow solid. (0.34 g)

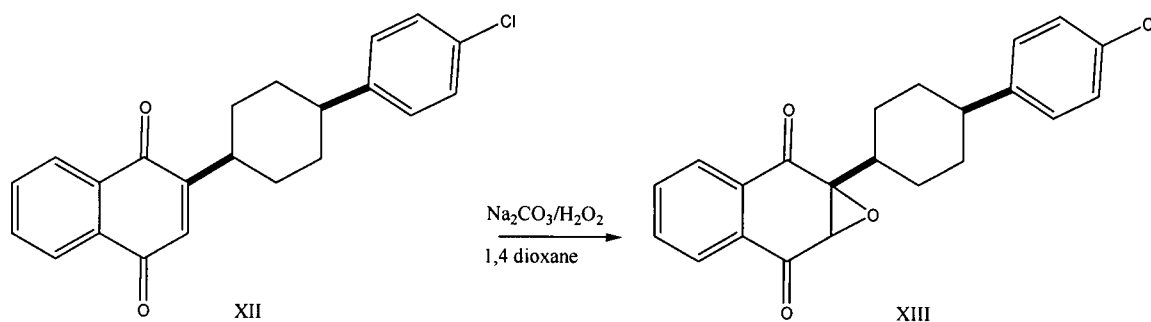
¹H NMR (CDCl₃, 400 MHz): δ 1.71-1.75 (m, 2H), 1.84-1.96 (m, 4H), 2.04-2.06 (m, 2H), 6.82 (s, 1H), 7.23-7.30 (dd, 4H), 7.73-7.75 (m, 2H), 8.06-8.12 (dd, 2H) ; **¹³C NMR (CDCl₃, 100 MHz):** δ 27.73, 27.84, 29.80, 34.41, 38.74, 127.1, 128.3, 129.0, 129.1, 130.3, 131.6, 133.8, 143.49, 155.18, 184.91, 185.34.

Example 15: Synthesis of 4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (XII) in presence of Sodium bromate/ acetic acid



To a stirred solution of *cis*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (5.0 g, 15 mmol) in acetic acid (75 mL) was added sodium bromate (1.48 g, 9.8 mmol) at 25 °C and resulting reaction mixture was stirred for another 30 min at 80 °C after which the reaction mixture was cooled to RT. Water (50 mL) was added to the reaction mass and extracted with DCM (3x 100 mL), dried over anhydrous Na₂SO₄ and solvent evaporated to give crude product which was purified by column chromatography (stationary phase: Silica gel and mobile phase: 2% ethyl acetate in cyclohexane) to give pure product as yellow solid. (3.0g, 58 % yield)

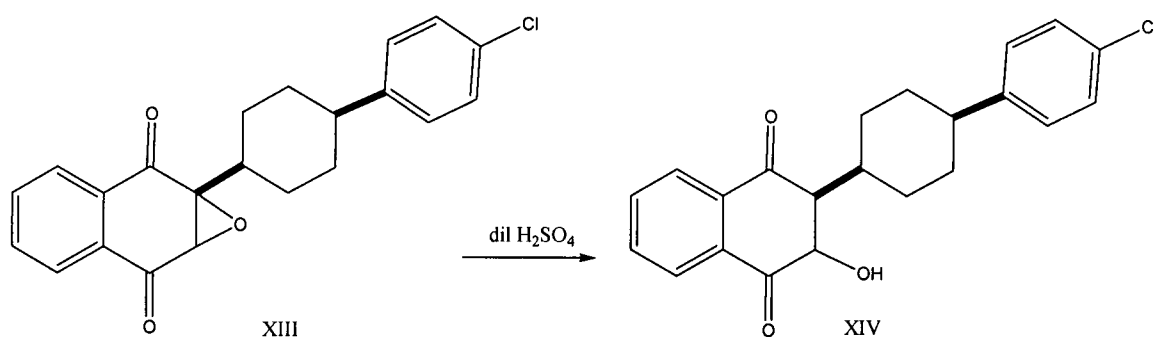
Example 16: Synthesis of 1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (XIII)



5 *Cis*-4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (1.85 g,) was charged into a reactor along with 1,4-dioxane (20 mL) at RT. Sodium carbonate (0.2 g, 2.0 mmol) was added to the above reaction mixture and a 30% soln. of H₂O₂ (1.5 ml, 20.0 mmol) was added drop wise and the reaction mass was heated to 80 °C and stirred at that temperature for 30 min. After cooling the reaction mass, water (50 mL) was added and extracted with ethyl acetate (100 mL). Solvent was removed under reduced pressure to give crude product as

 10 yellow solid (1.7 g, 90 % yield).

Example 17: Synthesis of *cis*-Atovaquone [XIV]

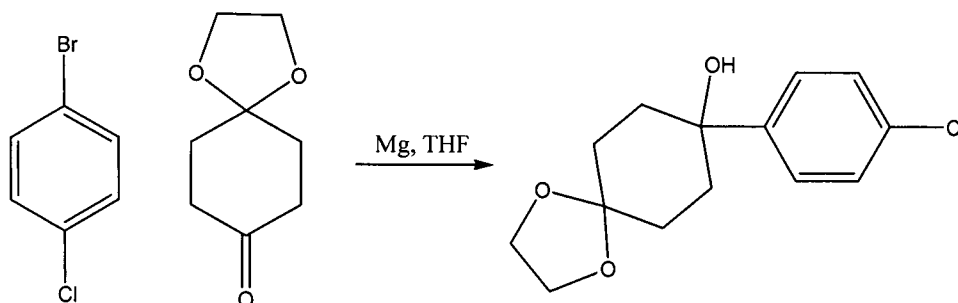


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Cis-1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (1.7 g, 4.7 mmol) was taken in a reactor and to it was added dilute H₂SO₄ (10 mL) and stirred for 20 min at RT. Water (100 mL) was added to the reaction mass and extracted with DCM (100 mL). HPLC analysis confirms *cis*-Atovaquone.

Retention time for *cis*-Atovaquone: 19.23 min

Example 18: Synthesis of 8-(4-chlorophenyl)-1,4-dioxa-spiro[4.5]decan-8-ol (iii)



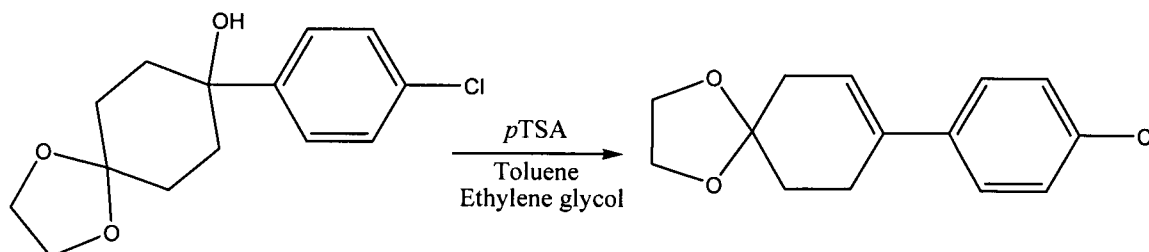
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Activated magnesium turnings (92.2g, 3.84 mol) were charged to a nitrogen dried reactor equipped with reflux condenser, nitrogen bubbler, thermo pocket and side arm addition funnel. Dry THF (2.0 L) and catalytic amount of iodine were added and reactor was gently heated. 1-Bromo 4-chlorobenzene (674.0 g, 3.52 mol) solution in THF (2 L) was added slowly into the above reaction mass at 50 °C to obtain corresponding Grignard reagent. To this Grignard reagent, solution of 1,4 cyclohexanedione mono-ethylene ketal (500.0 g, 3.20 mol) in THF (2 L) was added at 40-50 °C and resulting reaction mixture was heated at 50 °C for 1 h, after which the reaction mixture was quenched with aqueous solution of ammonium chloride and solvent was evaporated to obtain crude 8-(4-chlorophenyl)-1,4-dioxa-spiro[4.5]decan-8-ol (v), which was suspended in dilute hydrochloric acid (6 L) and stirred for 30 min and after filtration, white solid was obtained as product (764.0 g, 93% yield). Generally yield of the product ranges from 88 to 95 %.

¹H NMR (CDCl₃, 400 MHz): δ 1.49 -1.69 (d, 2H), 1.72-1.78 (d, 2H), 2.08-2.19 (m, 4H), 3.96-4.03 (m, 4H), 7.28-7.37 (m 2H), 7.41-7.48 (m, 2H). ¹³C NMR (CHCl₃, 100 MHz): δ 30.6, 36.5, 64.2, 64.3, 72.2, 108.2, 125.9, 128.6, 132.6, 147.0.

PXRD [2θ] (Cu K_{α1} = 1.54060 Å, K_{α2} = 1.54443 Å, K_β = 1.39225 Å; 40 mA, 45 kV): 8.09, 8.96, 12.30, 14.84, 16.43, 17.60, 17.93, 18.88, 20.92, 22.29, 24.70, 15.59, 30.02, 30.31

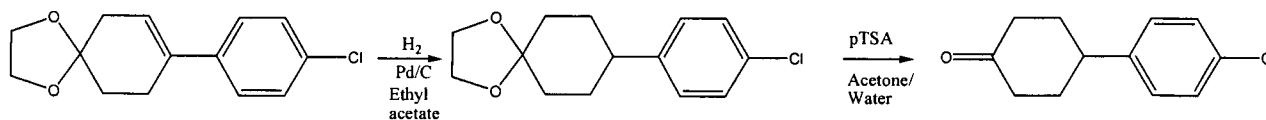
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Example 19: Synthesis of 4-(4-chlorophenyl)-cyclohex-3-enone monoethylene ketal (iv)

8-(4-chlorophenyl)-1,4-dioxaspiro[4.5]decan-8-ol (750.0 g, 2.8mol) was charged in a reactor equipped with Dean-Stark condenser and thermo-pocket. Toluene (15L) was added to suspended the material and *p*-toluene sulfonic acid (15.95 g, 3mol%) and ethylene glycol (250 mL, 2.8 mol) were added to the reaction mass which was then heated to 110 °C and stirred for 6h. Reaction was monitored by TLC and after complete consumption of starting material; reaction mass was cooled to room temperature. Solvent was evaporated under reduced pressure to obtain crude product, which was suspended in 1% aqueous sodium bicarbonate solution (1.5 L) and stirred for 1 h. Resulting suspension was filtered to obtain yellow solid (669.0 g, 93 % yield). Generally yield of the product ranges from 90 to 97 %.

FTIR (neat): 2877, 1644, 1495, 1243, 1123, 1024 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 1.91 -1.94 (t, 2H), 2.47 (s, 2H), 2.62-2.63 (t, 2H), 4.02 (s, 4H) 5.99 (s, 1H), 7.25- 7.33 (m, 4H); **¹³C NMR (CHCl₃, 100 MHz):** δ 27.8, 31.2, 36.1, 64.5, 107.5, 212.5, 122.1, 126.4, 128.2, 132.5, 135.2, 139.8.

Example 19: Synthesis of 4-(4-chlorophenyl)-cyclohexanone [III]

4-(4-Chlorophenyl)-cyclohex-3-enone monoethylene ketal (291.0 g, 1.15 mol) was dissolved in ethyl acetate (2.3 L) at RT and transferred to a Parr autoclave reactor. Palladium on carbon (9.0 g, 3 wt %) was added to the reaction mass and flushed twice with nitrogen and

once with hydrogen. Subsequently, a hydrogen pressure of 5-7 kg/cm² was maintained for 7h at RT. Reaction was monitored on TLC; after completion of reaction, palladium on carbon was filtered through a Celite bed. The mother liquor was evaporated under reduced pressure to give crude product as light yellow semi solid of 4-(4-Chlorophenyl)-cyclohexanone monoethylene ketal (v).

Crude 4-(4-Chlorophenyl)-cyclohexanone monoethylene ketal (v) was suspended in 50:50 acetone: water (1000 mL) at 25 °C and *p*-TSA (11.5 g, 5 mol %) was added to it. The reaction mass was heated to 70 °C and stirred for 3h after which it was cooled to RT. Acetone was evaporated under reduced pressure and resultant slurry was added to sodium bicarbonate solution and stirred for 30 min at 5 °C and filtered off to afford pure product as off-white solid (198.0 g, 88 % yield). Generally yield of the product ranges from 80 to 90 %.

FTIR (neat): 2939, 1712, 1490, 1164, 1091, 1013, 833 cm⁻¹.

¹H NMR (CDCl₃, 200 MHz): δ 1.85 -1.93 (m, 2H), 2.18-2.22 (m, 2H), 2.49-2.59 (m, 4H) 2.98-3.05 (m, 1H), 7.14-7.19 (m, 2H), 7.25-7.30 (m, 2H); **¹³C NMR (CHCl₃, 100 MHz):** δ 33.8, 41.3, 42.1, 128.0, 128.4, 132.2, 143.2, 210.7; **DSC** (10 °C/min): Peak at 63.39 °C

CLAIMS

- 5 1) A process to prepare 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinonnamely Atovaquone [I] comprising the steps of-
- i) condensing (1,2-dihydronaphthalen-4-yloxy)trimethylsilane [II] with 4-(4-chlorophenyl)cyclohexanone [III] in presence of Lewis acid in organic solvent to obtain 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-
10 one [IV]
- ii) dehydration of 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV] in organic solvent and in presence of acid such as pTSA to obtain diastereomeric mixture of 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one[V]
- 15 iii) hydrogenation of 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one[V] with PtO₂ to obtain *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VI]
- iv) optional selective crystallization of *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VI] to separate the '*cis*' and '*trans*' isomers of 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one
20
- v) ketone bromination of *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VI] to obtain *cis/trans* mixture of 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VII]
- 25 vi) in absence of step (d) optional selective crystallization of 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VII] to separate the '*cis*' and '*trans*' isomers of 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VII]

vii) elimination of *cis/trans* mixture of 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VII] with a strong base to give *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII]

viii) in absence of step (f) optionally crystallizing 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII] to separate the '*cis*' and '*trans*' isomers of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII]

ix) oxidizing *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII] to obtain *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione [IX]

x) base catalyzed epoxidation of *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione [IX] to *cis/trans* mixture of 1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-*b*]oxirene-2,7(1a*H*,7a*H*)-dione (X) in presence of hydrogen peroxide

xi) acid catalyzed hydrolysis of *cis/trans* mixture of 1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-*b*]oxirene-2,7(1a*H*,7a*H*)-dione (X) to obtain 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [I]

2) The process according to Claim 1 step i) wherein the Lewis acid used is titanium tetrachloride.

3) The process according to claim 1 step ii), wherein the dehydrating agent is selected from the group of Bronsted acids consisting of *p*-toluene sulfonic acid, methane sulfonic acid and triflic acid.

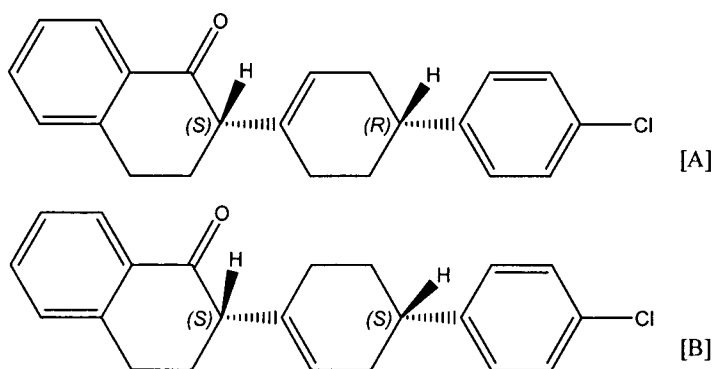
4) The process according to claim 1 step ii), wherein organic solvent is selected from the group consisting of dichloromethane, toluene and benzene.

5) The process according to claim 1 step iv) wherein the solvent used for selective crystallization is cyclohexane.

6) The process according to claim 1 step v), wherein the bromination is carried out with bromine in acetic acid in diethyl ether.

- 7) The process according to claim 1 step vi) wherein the solvent used for selective crystallization is methanol.
- 8) The process according to claim 1 step vii) wherein strong base used is selected from the group consisting of potassium *t*-butoxide, sodium methoxide and sodium ethoxide.
- 9) The process according to claim 1 step viii) wherein solvent used for selective crystallization is cyclohexane.
- 10) The process according to claim 1 step ix) wherein oxidation reaction is carried out by acetic acid/H₂O₂ or acetic acid/NaBrO₃ or sulfuric acid/NaNO₂ or RuCl₃/AcOH/H₂O₂.
- 11) The process according to claim 1 step x) wherein epoxidation reaction is carried out by sodium bicarbonate and hydrogen peroxide.
- 12) The process according to claim 1 step xi) wherein hydrolysis is carried out by sulfuric acid.
- 13) A compound 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV].
- 14) Compound 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV] adapted for use in preparation of 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [I].
- 15) A process to prepare compound 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV] comprising condensation of (1,2-dihydronaphthalen-4-yl)oxytrimethylsilane [II] with 4-(4-chlorophenyl)cyclohexanone [III] in presence of Lewis acid in organic solvent.
- 16) The process according to claim 15, wherein Lewis acid used is titanium tetrachloride.
- 17) The process according to claim 15, wherein the compound 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [IV] is obtained in *trans* configuration.

- 18) The compound according to claim 17, adapted for use in preparation of 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [I].
- 19) A compound 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one[V].
- 20) The process according to claim 1 step ii) wherein the compound (V) is obtained in a diastereomeric mixture of [A] and [B]



- 21) The compound according to claim 19, adapted for use in the preparation of 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [I].
- 22) A compound (1,2-dihydronaphthalen-4-yloxy)trimethylsilane [II]
- 23) A compound 4-(4-chlorophenyl)cyclohexanone [III]
- 24) A compound 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VI]
- 25) The compound according to claim 24, adapted for use in preparation of 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [I]
- 26) A compound 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2*H*)-one [VII]
- 27) The compound according to claim 26, adapted for use in preparation of 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [I]
- 28) A compound 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII]
- 29) The compound according to claim 28, adapted for use in preparation 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [I]

- 30) A compound 2-(4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione [IX]
- 31) The compound according to claim 30, adapted for use in preparation of 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [I]
- 32) A compound 1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (X)
- 33) The compound according to claim 32, adapted for use in preparation of 2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone [I]
- 34) A process for making a compound of formula (III), comprising the steps of-
- a) Preparation of (4-chlorophenyl)magnesium bromide (Grignard reagent) by reacting 1-bromo-4-chlorobenzene with magnesium turning in presence catalytic amount of iodine
- b) reacting (4-chlorophenyl)magnesium bromide with 1,4-cyclohexanedione monoethylene ketal to obtain 8-(4-chlorophenyl)-1,4-dioxo-spiro[4.5]decan-8-ol
- c) dehydration of 8-(4-chlorophenyl)-1,4-dioxo-spiro[4.5]decan-8-ol in toluene and in presence of *p*-TSA and ethylene glycol to obtain 4-(4-chlorophenyl)-cyclohex-3-enone monoethylene ketal
- d) hydrogenating 4-(4-chlorophenyl)-cyclohex-3-enone monoethylene ketal in presence of noble metal catalyst such as palladium on carbon, platinum oxide, to obtain compound 4-(4-chlorophenyl)-cyclohexanone monoethylene ketal
- e) deketalization of 4-(4-chlorophenyl)-cyclohexanone monoethylene ketal in presence of *p*TSA in mixture of acetone: water to obtain 4-(4-chlorophenyl)cyclohexanone [III]
- 35) A process for making a compound of formula (XIV), comprising the steps of-
- a) a process to convert *cis*-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (XI), to *cis*-4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (XII) in presence of sulphuric acid /sodium nitrite or sodium bromate/acetic acid or acetic acid/hydrogen peroxide or ruthenium chloride/hydrogen peroxide/acetic acid

b) a process to convert *cis*-4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (XII) to *cis*-1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (XIII) in presence of hydrogen peroxide and sodium bicarbonate.

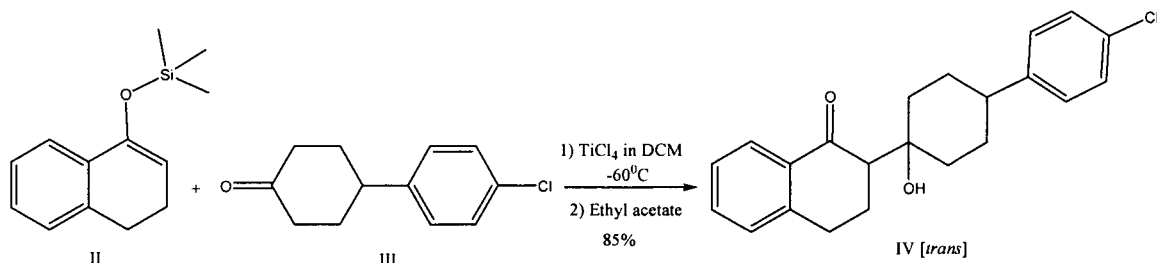
5 c) a process of converting *cis*-1a-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (XIII) to give *cis* isomer of Atovaquone in presence of sulfuric acid.

36) A process of isomerization of *cis* isomer of Atovaquone to trans-Atovaquone (2-[*trans*-4-(4'-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone) in presence of Lewis acid.

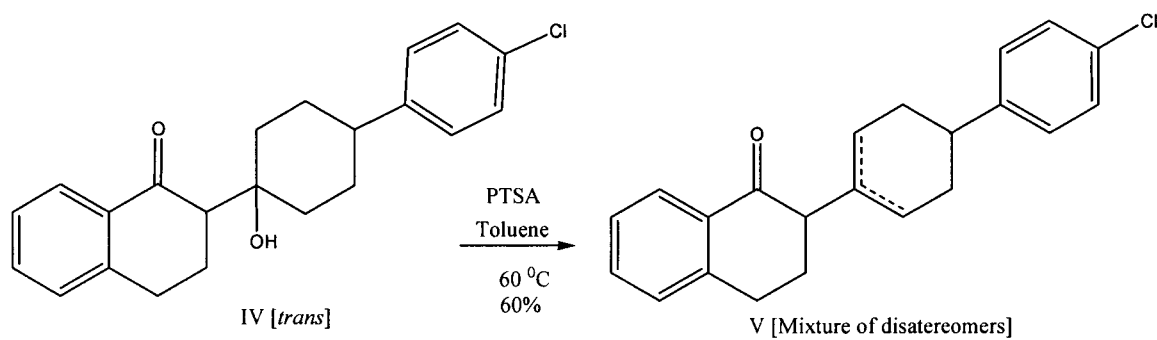
10 37) The process according to claim 36, wherein the Lewis acid used is titanium tetrachloride.

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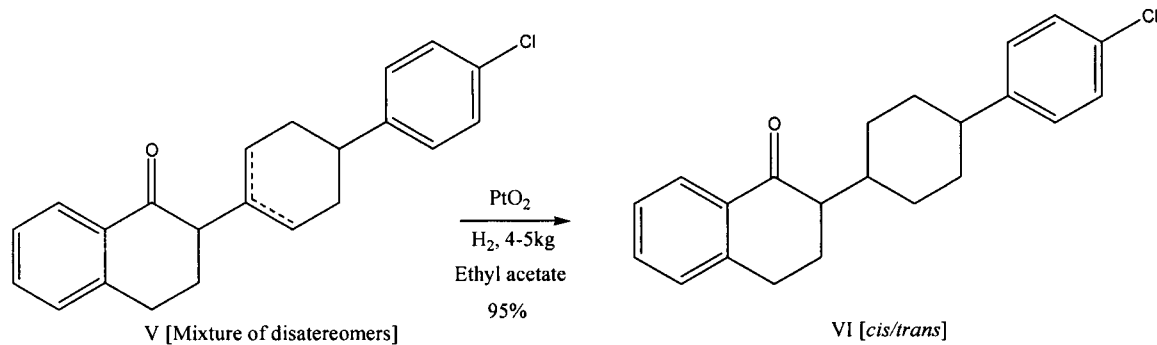
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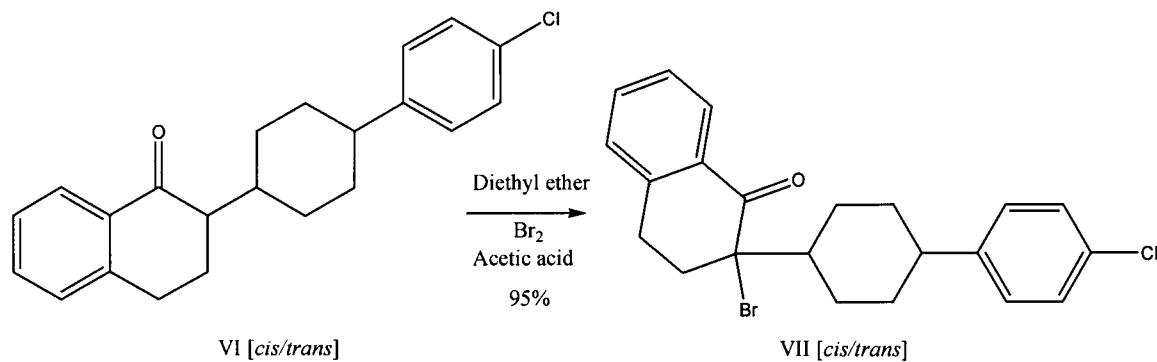
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STEP-3

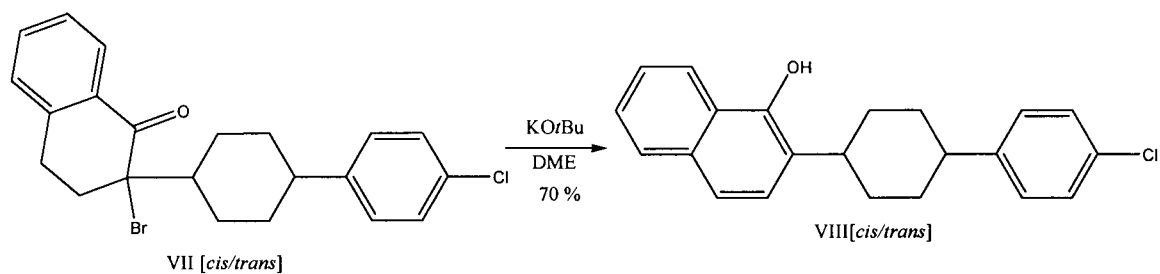


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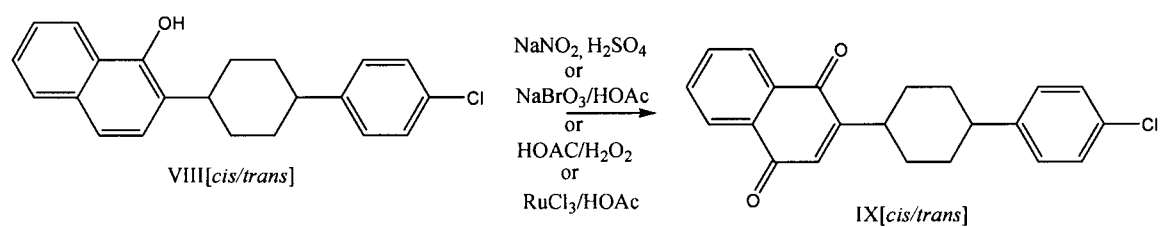


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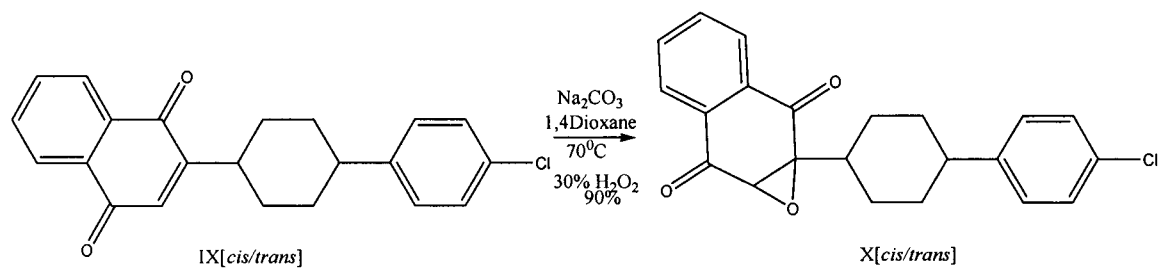
STEP-5



STEP-6



STEP-7



STEP-8

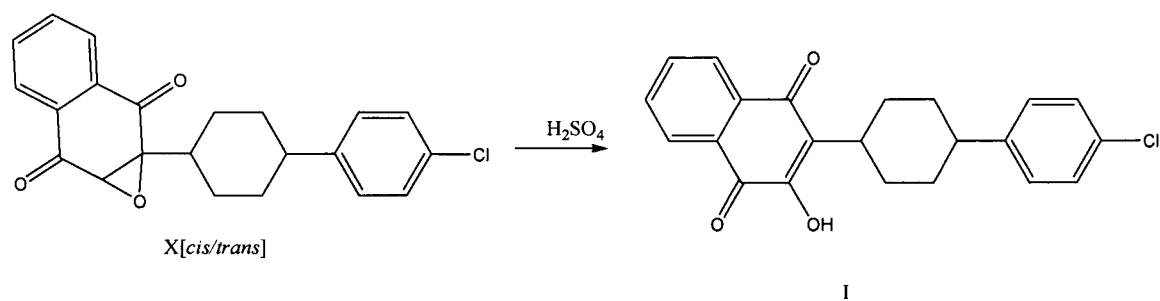
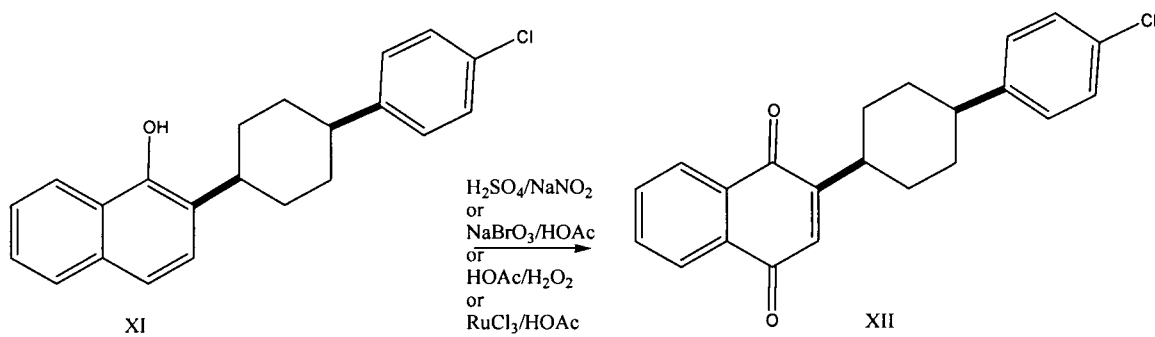
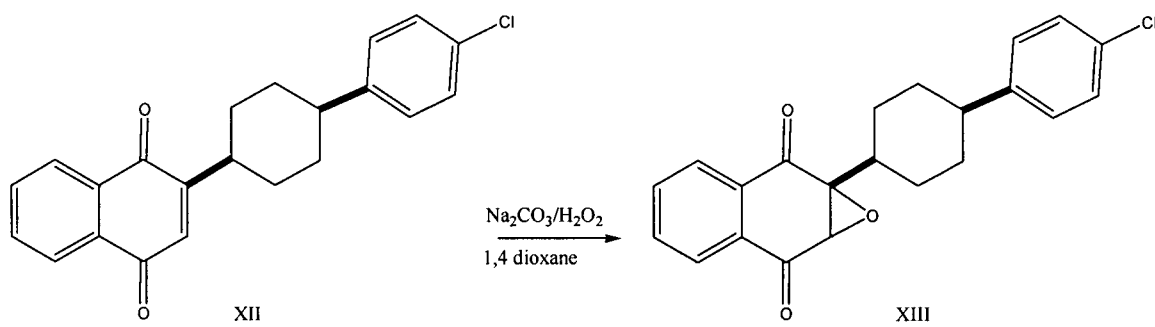
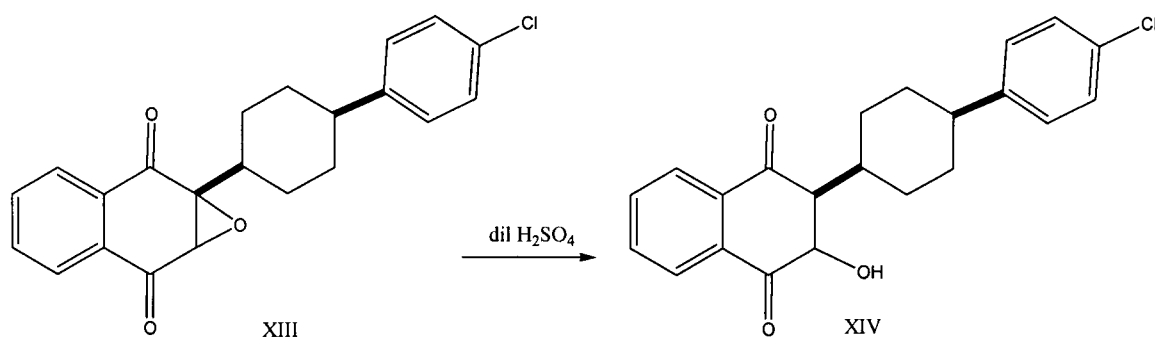


Figure I

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Step 1**Step 2****Step 3****Figure II**

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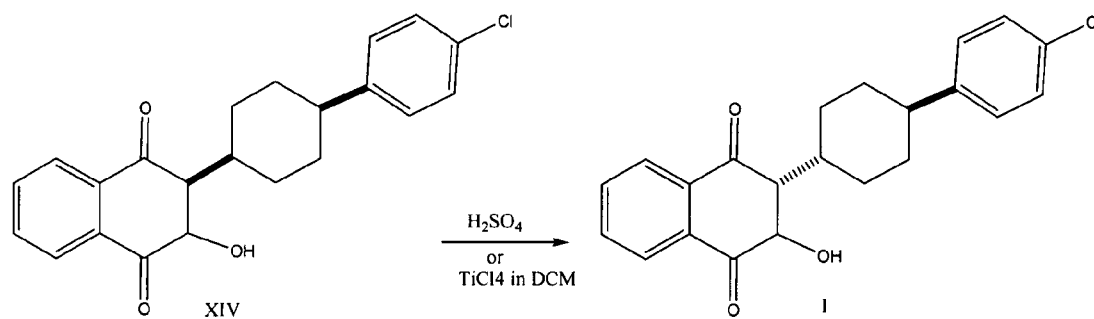


Figure III

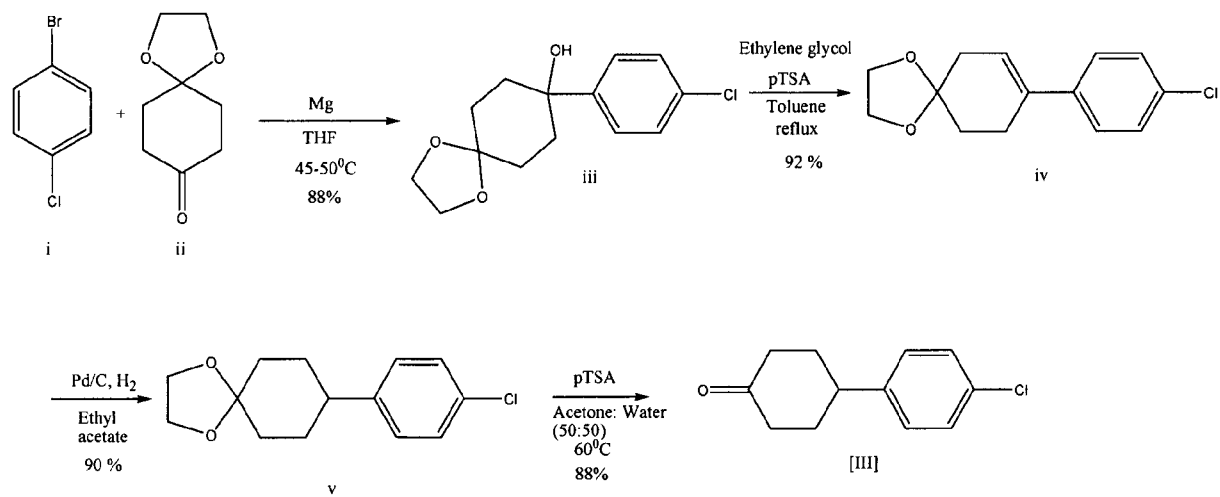


Figure IV

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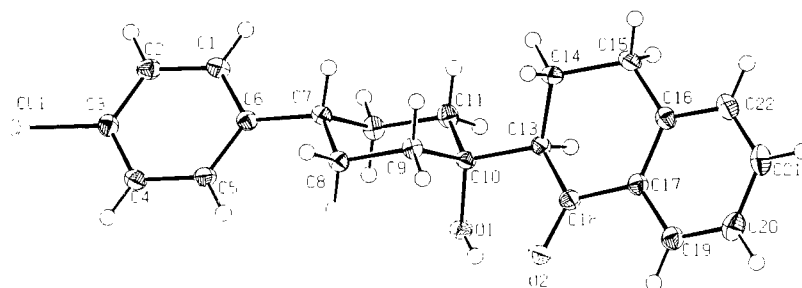


Figure V

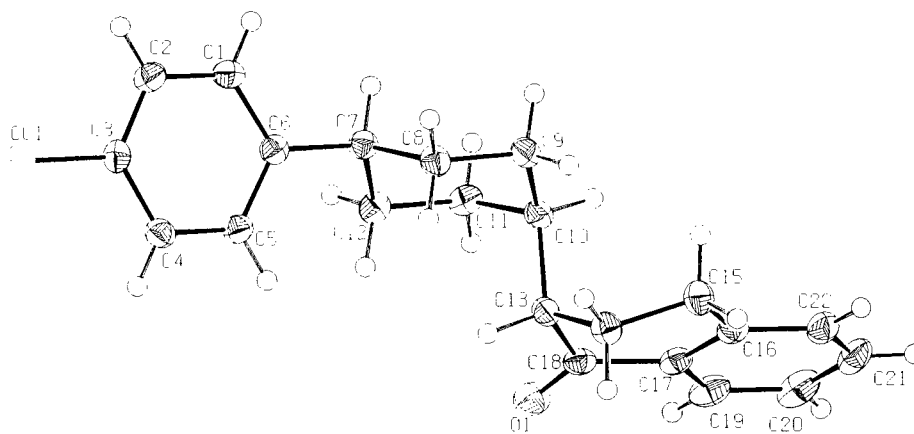


Figure VI

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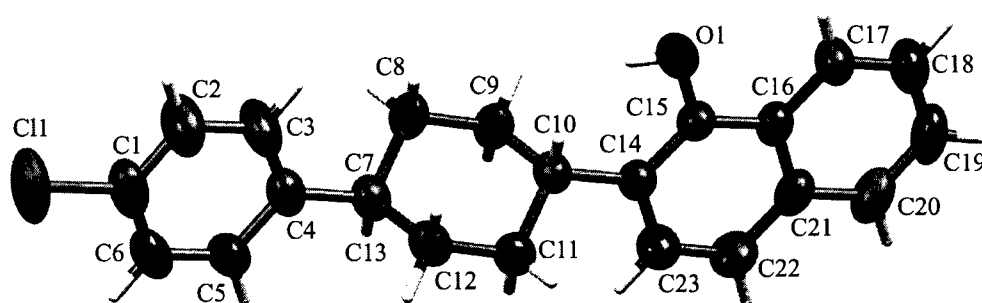


Figure VII

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2011/001507

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C46/00 C07C49/403 C07C49/427 C07C50/24 C07C50/26
C07C50/34

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WILLIAMS D R ET AL: "Synthesis of Atovaquone", TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 39, no. 42, 15 October 1998 (1998-10-15), pages 7629-7632, XP004134267, ISSN: 0040-4039, DOI: 10.1016/S0040-4039(98)01691-8 scheme 1;	23,34
X	----- WO 2009/007991 A2 (IPCA LAB LTD [IN]; KUMAR ASHOK [IN]; DIKE SUNEEL YESHWANT [IN]; MATHUR) 15 January 2009 (2009-01-15)	30,31
A	page 2, compound II; ----- -/--	1-29, 32-37



Further documents are listed in the continuation of Box C.



See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

5 June 2012

Date of mailing of the international search report

20/06/2012

Name and mailing address of the ISA/

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Authorized officer

Kleidernigg, Oliver

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/001507

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YASUYUKI KITA ET.AL.: "The chemistry of 0-silylated ketene acetals; a mild and facile preparation of trimethylsilyl enol ethers and of cyclic 0,0-, 0,S-, and S,S-acetals from enolizable carbonyl compounds", SYNTHESIS COMM., 1982, pages 1089-1091, XP002677214, Table 1, compound 3d; -----	22
X	EP 0 077 551 A2 (WELLCOME FOUND [GB]) 27 April 1983 (1983-04-27) example 5 -----	36,37

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2011/001507

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009007991 A2	15-01-2009	US 2010081847 A1 WO 2009007991 A2	01-04-2010 15-01-2009
EP 0077551 A2	27-04-1983	CA 1205083 A1 DE 3264133 D1 DK 459682 A EP 0077551 A2 GB 2107713 A IT 1200943 B JP 1793666 C JP 1935578 C JP 5001250 B JP 5097765 A JP 6072122 B JP 58079945 A US 4485117 A	27-05-1986 18-07-1985 17-04-1983 27-04-1983 05-05-1983 27-01-1989 14-10-1993 26-05-1995 07-01-1993 20-04-1993 14-09-1994 13-05-1983 27-11-1984