(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 January 2013 (31.01.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/014486 A1

(51) International Patent Classification:
C07C 45/65 (2006.01) *C07C 67/08* (2006.01)
C07C 49/477 (2006.01) *C07C 69/63* (2006.01)

(21) International Application Number:
PCT/IB2011/002134

(22) International Filing Date:
14 September 2011 (14.09.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1010/KOL/2011 28 July 2011 (28.07.2011) IN

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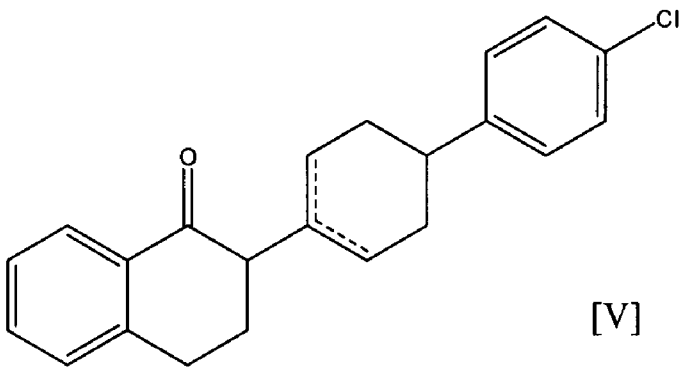
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: IMPROVED SYNTHESIS OF 2-(4-(4-CHLOROPHENYL) CYCLOHEX-1-ENYL) -3, 4-DIHYDRONAPHTHALEN-1 (2H)-ONE; AN INTERMEDIATE FOR ATOVAQUONE



[V]

(57) Abstract: A process for preparation of 2-(4-(4-chlorophenyl) cyclohex-l-enyl)-3,4-dihydronaphthalen- 1(2H)-one (V), key intermediate for synthesis of Atovaquone [I]. The process for preparation of compound(V) comprising of the steps of; i) Reaction of 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen- 1(2H)-one (IV) with trifluro acetic anhydride in presence of base in organic solvent to yield compound of formula (XIa) ii) Elimination of trifluoroacetyl functionality of compound (XIa) in organic solvent and in presence of organic base to give compound of formula (V). The invention also provides a Process for preparation of compound(XIa) comprising of the steps of; i) reaction of 2-(4-(4-chlorophenyl)-l-hydroxy cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (IV) with trifluro acetic anhydride in presence of organic base in organic solvent. A further process is provided for preparation of compound(V) from compound (XIa) comprising elimination reaction of trifluoroacetyl functionality compound (XIa) in organic solvent and in presence of organic base.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

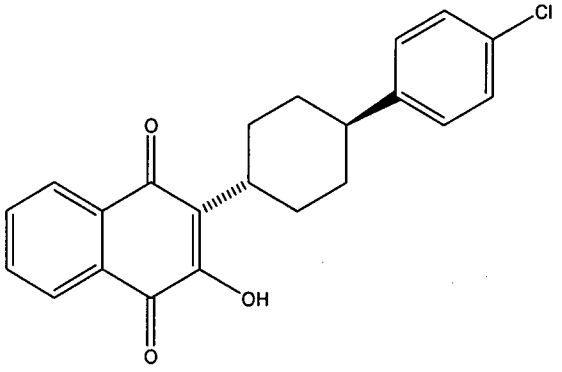
IMPROVED SYNTHESIS OF 2-(4-(4-CHLOROPHENYL) CYCLOHEX-1-ENYL)-3,4-DIHYDRONAPHTHALEN-1(2*H*)-ONE; AN INTERMEDIATE FOR ATOVAQUONE

FIELD OF THE INVENTION

The invention relates to a novel process for preparation of 2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one, key intermediate for synthesis of Atovaquone [I].

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 bc_1 complex of the parasite, which is linked to pyrimidine biosynthesis (Tetrahedron Lett, 1998, 39 7629).



[I]

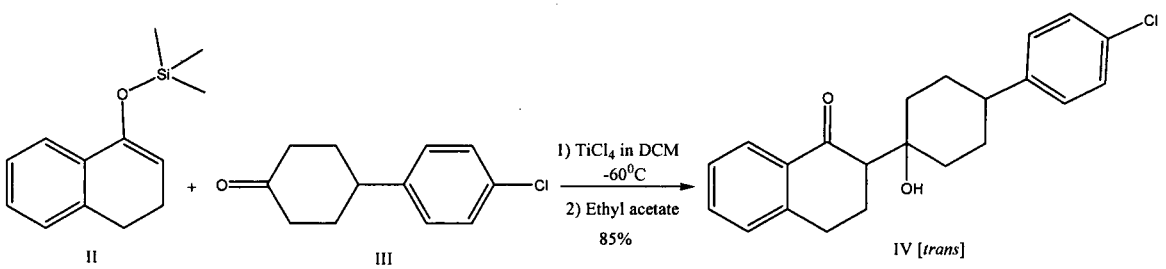
There are only few reports available for the synthesis of Atovaquone employing various synthetic alternatives essentially based on Hunsdiecker decarboxylative condensation, which proceeds through a radical mechanism. However, the overall yield of the desired product in almost all the reported processes is exceedingly poor *i.e.* economically far from being attractive.

Our previous co-pending PCT application numbered PCT/IB2011/001507 dated 28 June 2011 entitled "Novel method for synthesis of Atovaquone", describes a novel, cost effective, eco-friendly, industrial process for synthesis of Atovaquone without using any toxic, hazardous chemicals, disclosers of which, including prior art are incorporated herein by reference.

Stepwise schematic representation of chemistry employed in co-pending PCT application number PCT/IB2011/001507 entitled "Novel method for synthesis of Atovaquone" for synthesis of Atovaquone is shown below in Scheme I.

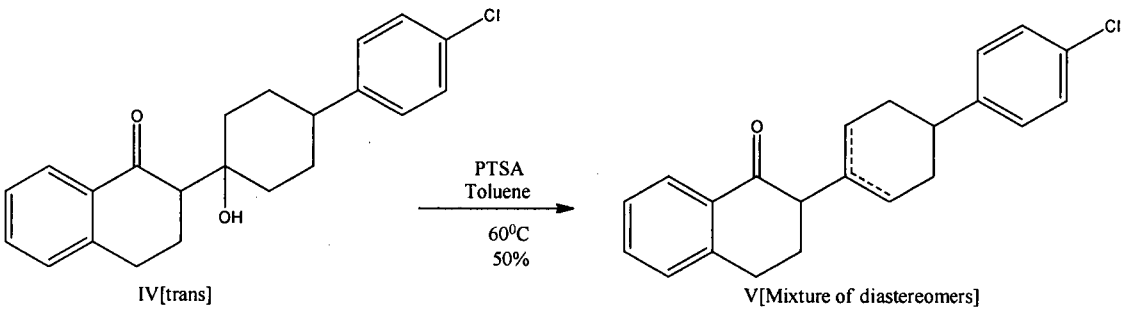
Scheme I

STEP-1



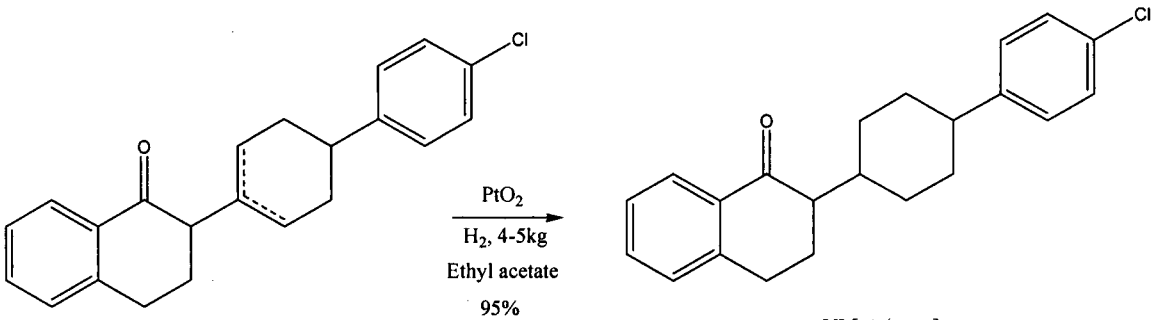
II III IV [*trans*]

STEP-2



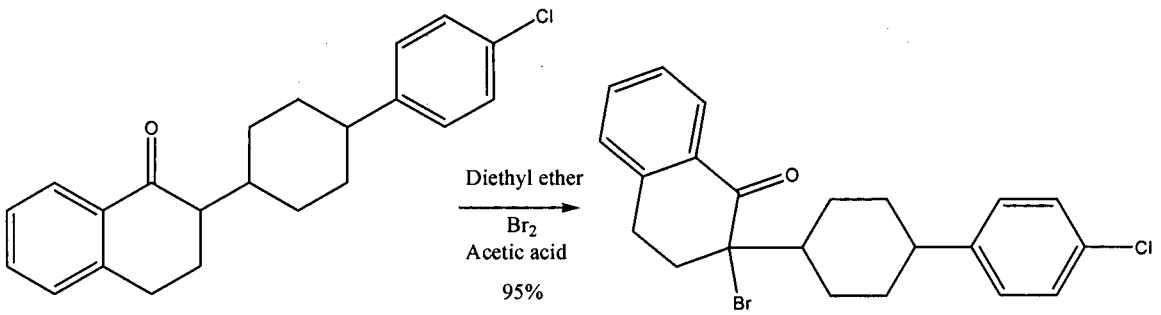
IV[trans] V[Mixture of diastereomers]

STEP-3



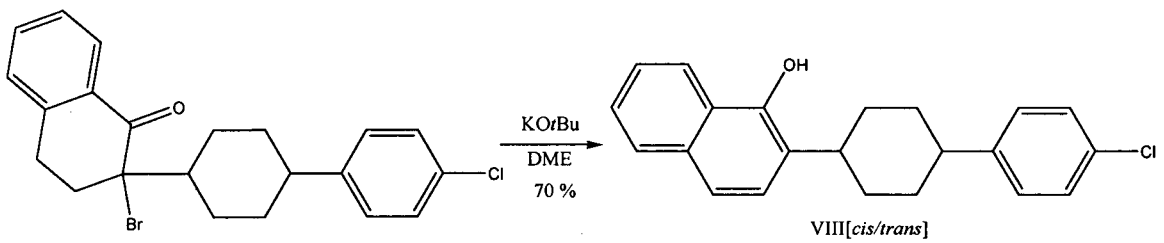
V [Mixture of disatereomers] VI [*cis/trans*]

STEP-4



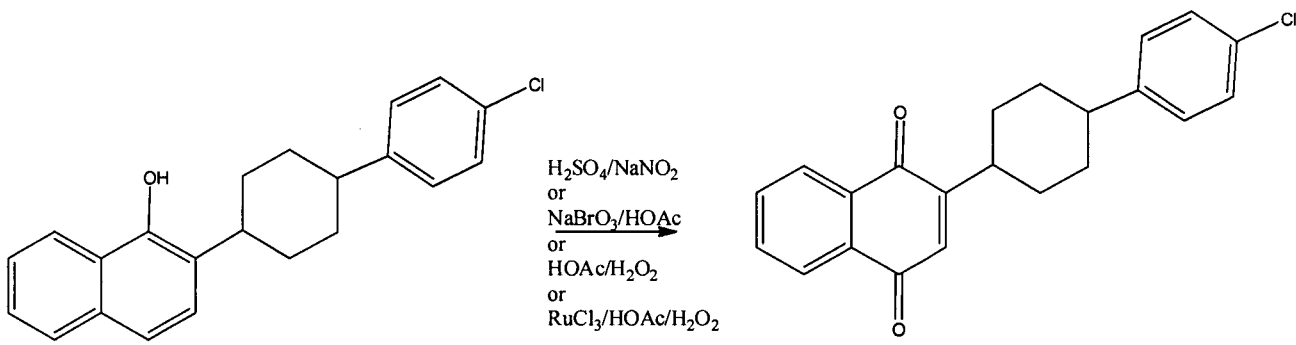
VI [*cis/trans*] VII [*cis/trans*]

STEP-5



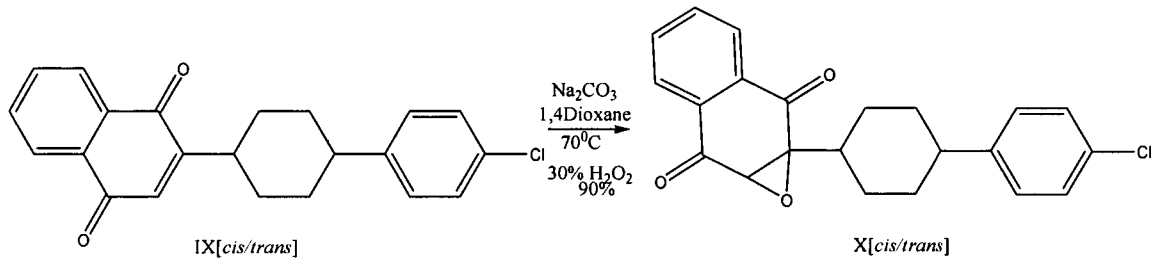
VII [*cis/trans*] VIII[*cis/trans*]

STEP-6



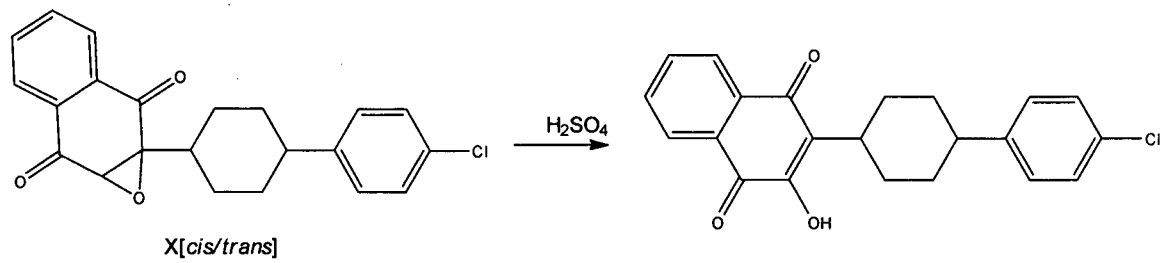
VIII (cis/trans) IX(cis/trans)

STEP-7



IX[*cis/trans*] X[*cis/trans*]

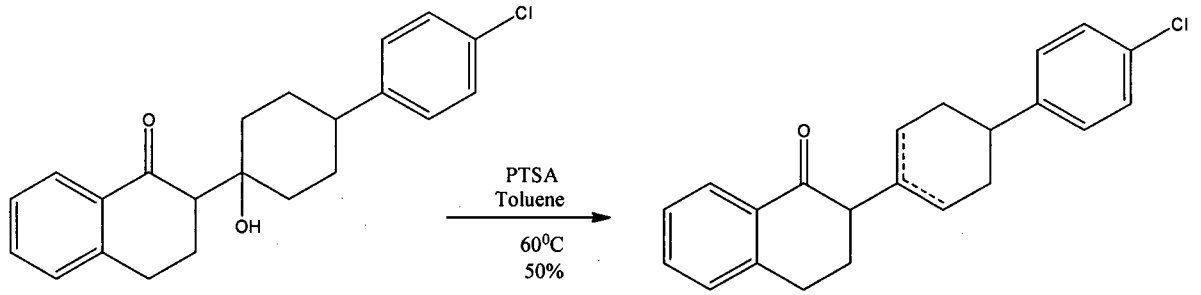
STEP-8



X[*cis/trans*] I [trans]

In the above scheme I, hydroxyl compound IV is dehydrated with a BrØnsted acid to yield compound V in around 50% isolated yield, schematically represented in Step 2, rendering process for the synthesis of Atovaquone poor in terms of atom economy and thus increasing the raw material cost for manufacture of Atovaquone.

Hence there is a need for invention of an efficient and more economic process for dehydration of compound (IV) to compound (V).



IV[trans] V[Mixture of diastereomers]

This invention describes a) Genesis of poor yield of compound (V) from compound (VI) and, b) An alternative chemistry which is efficient, easily operable, high yielding process for synthesis of compound (V) from compound (VI).

OBJECTS OF THE INVENTION

Thus an object of this invention is to provide a novel cost effective and efficient process for the synthesis of an intermediate of Atovaquone *i.e.* 2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one (V).

Another object of the present invention is synthesis of the novel compound 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl 2,2,2-trifluoroacetate (XIa) through esterifcation of 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(*2H*)-one (IV) with trifluro acetic anhydride.

Yet another object of the present invention is synthesis of the compound 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(*2H*)-one (V) from 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl 2,2,2-trifluoroacetate (XIa) through E2 elimination (elimination, bimolecular) of trifluro acetyl functionality.

SUMMARY OF INVENTION

An aspect of the present invention is to provide compound 2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one (V), a key intermediate for synthesis of Atovaquone through a novel, cost effective, green, and eco-friendly process.

A process for preparation of 2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one (V) comprising the steps of-

1) Esterification of 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(*2H*)-one (IV) with trifluro acetic anhydride in presence of base such as pyridine and catalytic amount of N-N-dimethyl amino pyridine (DMAP) in organic solvent such as dichloromethane to obtain 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl 2,2,2-trifluoroacetate (XIa) in quantitative yield.

2) Elimination of trifluoroacetyl functionality of 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl 2,2,2-trifluoroacetate (XIa) in organic solvent such as toluene or xylene and in presence of organic base such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or N,N-Diisopropylethylamine to obtain diastereomeric mixtures of 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(*2H*)-one [V] in excellent yields.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

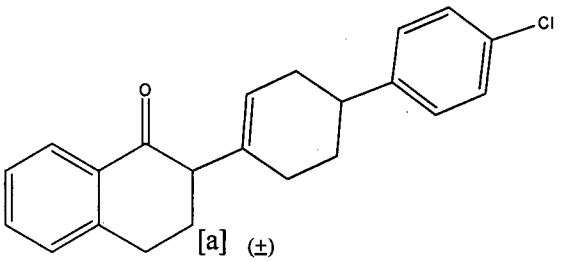
Fig 1: Scheme showing rate of protonation of compound (IV) for formation of compound (A) & (B) via path [A] and [B]

Fig 2: Scheme showing that in path A the A-I intermediate on a pericyclic "*ene*" reaction ((March's Advanced Organic Chemistry, 6th edition, Wiley Interscience, Chapter 17, page 1103-1105) gives diastereomeric mixture of compound (V)

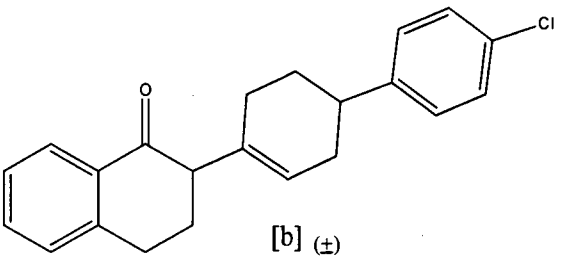
Fig 3: Scheme showing that in path B; oxygen of carbonyl functionality was protonated, which through "*retro-aldol*" reaction gives α-tetralone (XII) & 4-(4-chlorophenyl)cyclohexanone (III)

DETAILED DESCRIPTION OF THE INVENTION

On reaction of compound (IV) with catalytic amount of a BrØnsted acid to give compound (V), it has been observed that along with diastereiomeric mixture of compound (V) having the following structures [a] and [b],



[a] (±)



[b] (±)

two other product namely α-tetralone (XII) and 4-(4-chlorophenyl)cyclohexanone (III) are produced and the ratio of (V) and α-tetralone (XII) & 4-(4-chlorophenyl)cyclohexanone (III) taken together is found to be approximately 1:1.

Surprisingly, on reaction of compound (IV) with Lewis acid hardly any amount of compound (V) is formed, but it is observed that compound (IV) practically completely degraded to α-tetralone (XII) and 4-(4-chlorophenyl)cyclohexanone (III).

Hence, one could rationalized the rate of protonation of compound (IV) for formation of compound (A) & (B) via path [A] and [B] was comparable (figure 1) and subsequent reactions through path A and B are even faster which result in equal proportion of compound (V) and α-tetralone (XII) & 4-(4-chlorophenyl)cyclohexanone (III) taken together.

Once could further rationalized that in case of path A, where "OH" functionality was protonated and resulted into better leaving group which was readily eliminated via E1 elimination to yield tetra-substituted intermediate (A-I). This (A-I) intermediate on a pericyclic "*ene*" reaction ((March's Advanced Organic Chemistry, 6th edition, Wiley Interscience, Chapter 17, page 1103-1105) gives diastereomeric mixture of compound (V) (figure 2) as both the adjacent hydrogen are chemically equivalent.

In case of path B; oxygen of carbonyl functionality was protonated, which through "*retro-aldol*" reaction gives α-tetralone (XII) & 4-(4-chlorophenyl)cyclohexanone (III) as shown in figure 3.

In case of Lewis acid such as $TiCl_4$ or $ZrCl_4$ the reaction proceeds through only path B, hence only α-tetralone (XII) and 4-(4-chlorophenyl)cyclohexanone (III) are formed and no compound (V) is obtained.

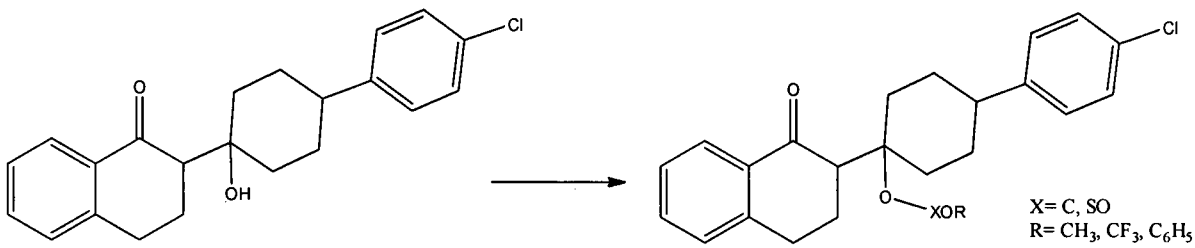
Since, olefin formation through E1 elimination mechanism did not give compound (V) in desirable yield from compound (IV), hence synthesis of compound (V) has been attempted through E2 elimination mechanism.

Surprisingly, it was also observed that compound (IV) is sensitive to bases giving rise to corresponding retro aldol products very fast in practically qutitative yields.

When "OH" functionality of compound (IV) was attempted to derivatise to its corresponding acetoxy derivative in presence of strong base such as sodium hydride, instead of obtaining the corresponding acetoxy product, complete reto-aldol reaction was observed to give α-tetralone (XII) and 4-(4-chlorophenyl)cyclohexanone (III).

Hence, selection of a base for carrying out esterification reaction was limited to only organic amine, which only polarizes hydroxyl function such as pyridine, *N,N*-di*iso*propylethylamine, *etc.*

Thus, "OH" functionality of compound (IV) was attempted to derivatise to its corresponding acetoxy or sulfonate derivative through reaction of compound (IV) with acetic anhydride/ pyridine, trifluroacetic anhydride/ pyridine, methane sulfonyl chloride/pyridine, trifilic anhydride/pyridine or toluene sulfonyl chloride/pyridine in presence of catalytic amount of N,N-dimethylamino pyridine (DMAP).



IV [trans] [XIa-d]

Surprisingly, only trifluroroacetate was obtained as a crystalline solid in excellent yield and in other cases no ester was formed.

The E2 elimination (March's Advanced Organic Chemistry, 6th edition, Wiley Interscience, Chapter 17, page 1477-1501) of compound (XI) on refluxing with DABCO in toluene for 5 h gave pure compound (V) in more than 90% isolated yield in 1:1 ratio of two diastereomers as theory demands, since two β-hydrogens are kinetically identical and proton abstraction is the rate determining step.

As per the present invention, the synthesis of compound (V) from compound (IV) comprised of the following two steps 1) synthesis of compound (XIa) from compound (IV) in 90% isolated yield (example 1) and 2) synthesis of compound (V) from compound (XIa) in 90% isolated yield (example 7). Hence overall isolated yield for compound (V) from compound (IV) comes to 81 %, which is 31% more than that obtained by the process reported in our co-pending PCT application PCT/IB2011/001507(Example 10; yield 50%).

It is worthwhile to mention that change in elimination mechanism from E1 elimination of compound (IV), to E2 elimination as mentioned hereinbefore resulted in significant improvement in atom economy of the process as no impurities were formed. This makes process efficient with respect to cost and operation friendliness.

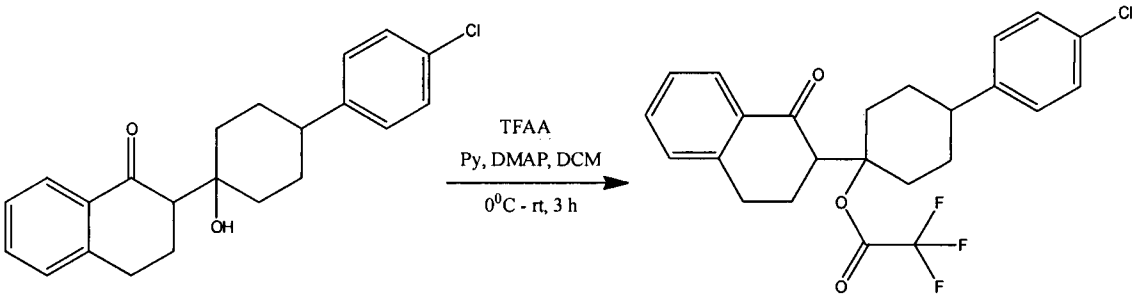
Indeed, improvement in the process for synthesis of compound (V) resulted in making the process for synthesis of Atovaquone described in our co-pending PCT application PCT/IB2011/001507, more competitive compared to all the reported literature processes.

Nomenclatures used for the compounds mentioned herein are as understood from the CambridgeSoft® ChemOffice software ChemDraw Ultra 12.

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 ^{0}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. Gas-Liquid chromatography analysis was carried out on Shimadzu GC 2010 using Column: DB-5 (30m x 0.53mm x 0.5mm) and having FID detector (Detector-300 ^{0}C, Injector- 280^{0}C; Nitrogen -4psi, 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 (δ = 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 ^{0}C/min, and endothermic peak was recorded in ^{0} C.

Example 1: Synthesis of 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl 2,2,2-trifluoroacetate (XIa)



To a reactor equipped with reflux condenser, dropping funnel and thermo-pocket, was charged 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1- (2*H*)-one

(15.0 g, 0.04 mol) and dissolved in dichloromethane (150 mL) at room temperature. To the above solution were added pyridine (8.4 g, 0.11 mol) and DMAP (0.3 g, 2.0 mmol). The reaction mass was cooled to 0 °C and trifluoroacetic anhydride (22.2 g, 0.11 mol) in dichloromethane (50 mL) was added into it in a dropwise manner over a period of 30 min. The resultant mixture was stirred at room temperature for 3 h after which DM water (300 mL) was added to it, followed by organic layer separation. The organic layer was washed with 1M HCl soln. (10 mL) and after separation and drying with anh. Na_2SO_4 solvent was evaporated to afford the desired product as an off-white solid (18.3 g, 96 % yield).

FTIR (neat): 3027, 2946, 2934, 2874, 1768, 1688, 1600, 1491, 1443, 1372, 1218, 1165, 1154, 1090 cm^{-1}.

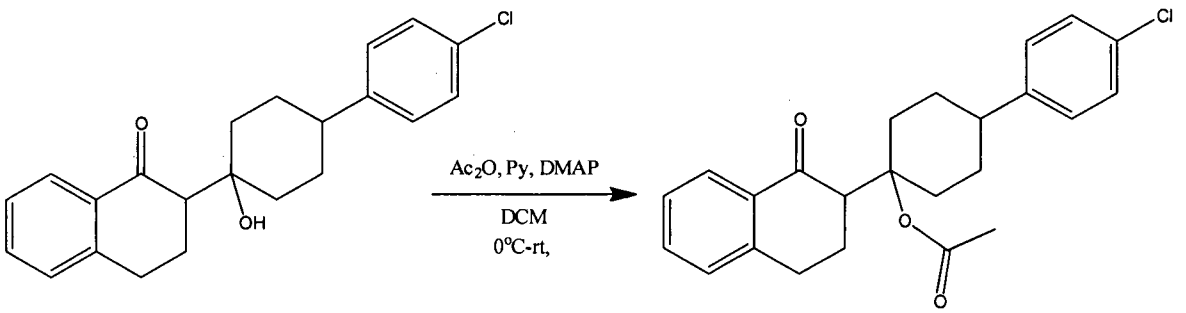
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.59-1.67 (m, 3H), 3.89-3.94 (m, 2H), 2.06-2.18 (m, 3H), 2.69-2.78 (m, 3H), 3.04-3.09 (m, 2H), 3.79-3.83 (m, 1H), 7.15 (d, 2H), 7.26-7.36 (m, 4H), 7.49-7.53 (m, 1H), 8.00 (d, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): 24.4, 28.4, 29.0, 29.3, 29.9, 31.4, 42.2, 52.4, 91.7, 126.8, 127.5, 128.0, 128.6, 131.8, 133.3, 133.6, 143.2, 144.7, 155.9, 156.3, 196.4.

MS (EI): $C_{24}H_{22}ClF_3O_3$: 450.12; $[M-(-OCOCF_3)]^+$: 337.10;

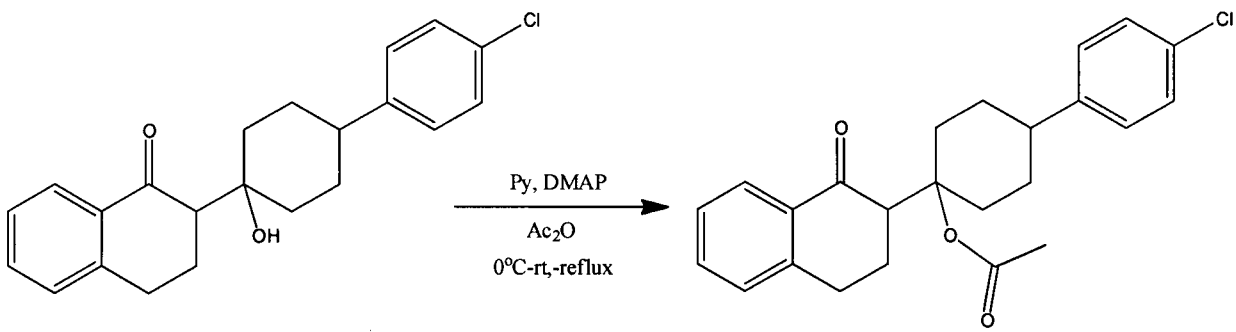
DSC peak at 148.56. °C (10°C/min)

Example 2: Synthesis of 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl acetate (XIb)



To a reactor equipped with reflux condenser, dropping funnel and thermo-pocket, was charged 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1-(2*H*)-one (10.0 g, 0.03 mol) and dissolved in dichloromethane (100 mL) at room temperature. To the above solution were added pyridine (3.4 g, 0.04 mol) and DMAP (0.2 g, 2.0 mmol). The reaction mass was cooled to 0 °C and acetic anhydride (4.5 g, 0.05 mol) in dichloromethane (20 mL) was added into it in a dropwise manner over a period of 20 min. The resultant mixture was stirred at room temperature for 24 h after which minor amount of the corresponding olefin product was identified by TLC analysis. However, majority of the starting material remained unchanged even after this time. The olefin product was not isolated due to very low yield.

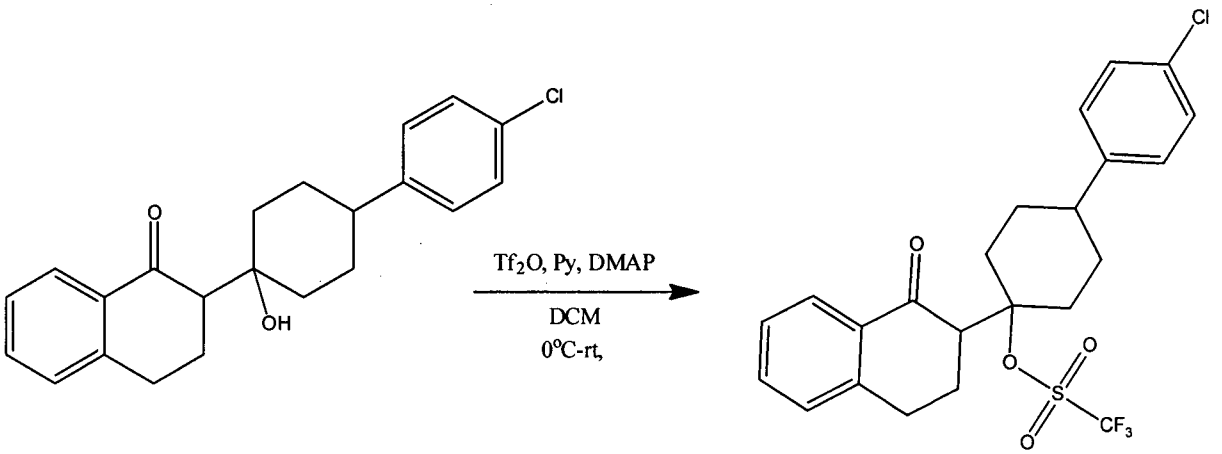
Example 3: Synthesis of 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl acetate (XIb) in acetic anhydride as the medium



To a reactor equipped with reflux condenser, dropping funnel and thermo-pocket, was charged 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1-(2*H*)-one (10.0 g, 0.03 mol) and dissolved in acetic anhydride (50 mL). To the above solution, cooled to 0 °C, were added pyridine (3.4 g, 0.04 mol) and DMAP (0.2 g, 2.0 mmol). The resultant mixture was stirred at room temperature for 2 h followed by stirring under reflux for 24 h

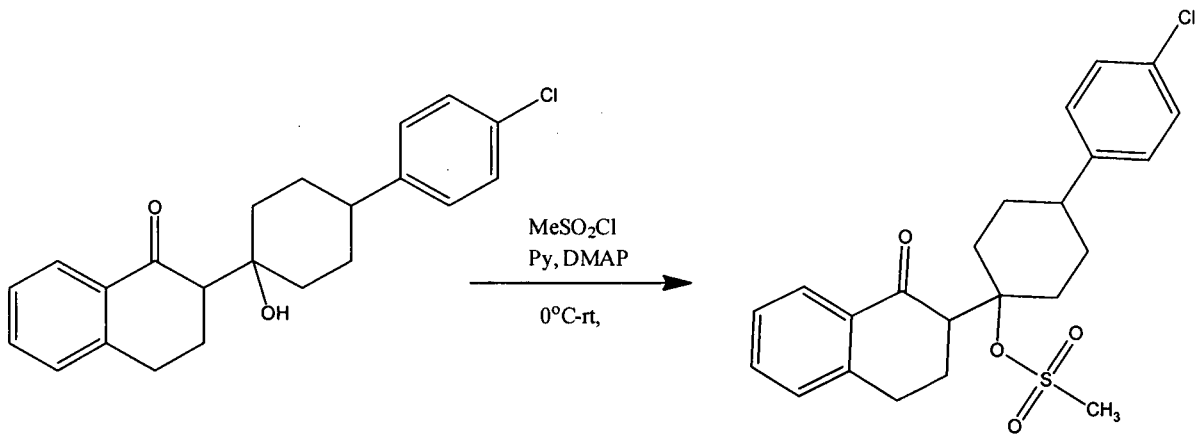
after which time the reaction mass turned black for which TLC analysis showed undesired spots concluding that reaction underwent undesired path.

Example 4: Synthesis of 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl trifluoromethanesulfonate (XIc)



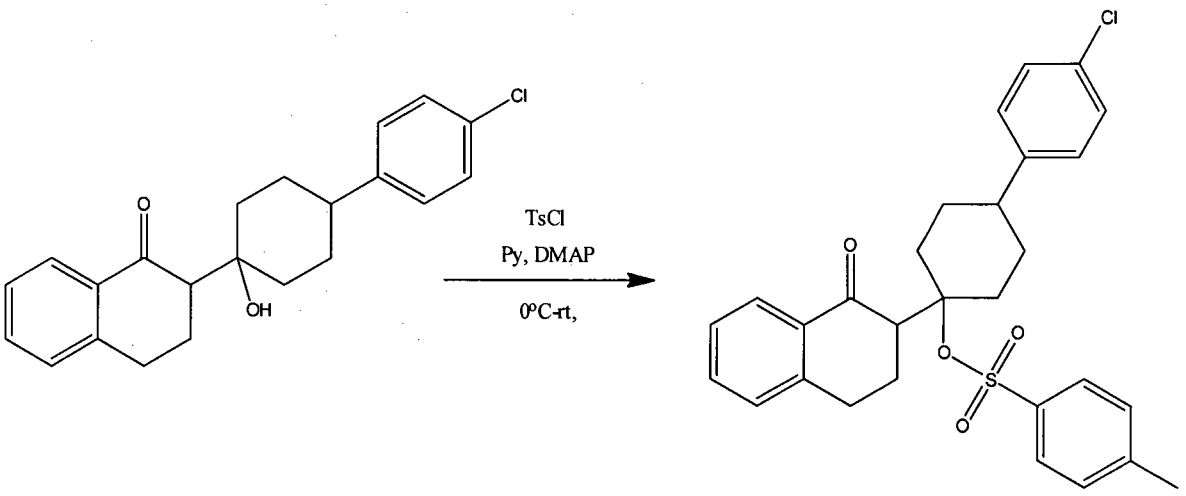
To a reactor equipped with reflux condenser, dropping funnel and thermo-pocket, was charged 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1-(2*H*)-one (5.0 g, 0.014 mol) and dissolved in dichloromethane (50 mL) at room temperature. To the above solution were added pyridine (2.8 g, 0.035 mol) and DMAP (0.2 g, 2.0 mmol). The reaction mass was cooled to 0 °C and triflic anhydride (10.0 g, 0.035 mol) in dichloromethane (30 mL) was added into it in a dropwise manner over a period of 20 min. The resultant mixture was stirred at room temperature for 24 h even after which time no conversion of the starting material could be observed due to which the reaction mass was disposed off carefully.

Example 5: Synthesis of 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl methanesulfonate (XIc)



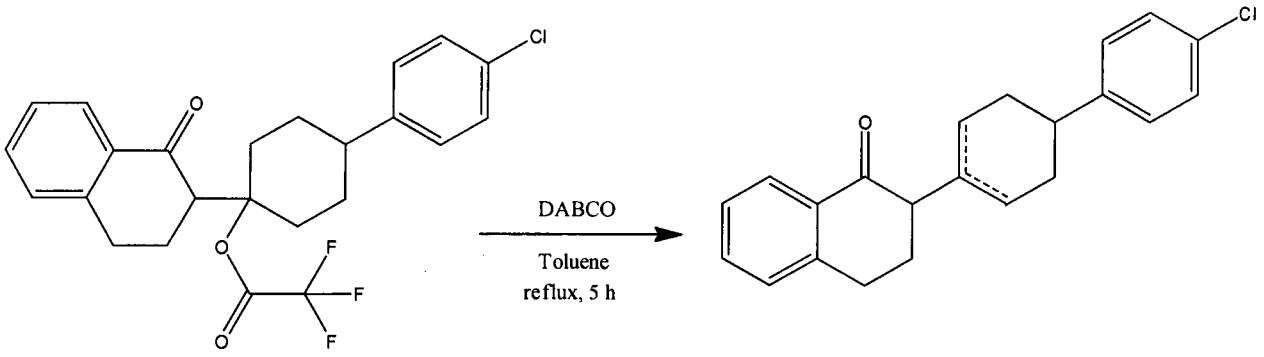
To a reactor equipped with reflux condenser, dropping funnel and thermo-pocket, was charged 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1-(2*H*)-one (5.0 g, 0.014 mol) and dissolved in pyridine (50 mL) at room temperature. To the above solution was added DMAP (0.2 g, 2.0 mmol). The reaction mass was cooled to 0 °C and methanesulfonyl chloride (2.5 g, 0.035 mol) in dichloromethane (30 mL) was added into it in a dropwise manner over a period of 20 min. The resultant mixture was stirred at room temperature for 24 h even after which time no conversion of the starting material could be observed due to which the reaction mass was disposed off carefully.

Example 6: Synthesis of 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl 4-methylbenzenesulfonate (XId)



To a reactor equipped with reflux condenser, dropping funnel and thermo-pocket, was charged 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1-(2*H*)-one (5.0 g, 0.014 mol) and dissolved in pyridine (50 mL) at room temperature. To the above solution was added DMAP (0.2 g, 2.0 mmol). The reaction mass was cooled to 0 °C and *p*-toluenesulfonyl chloride (4.0 g, 0.035 mol) in dichloromethane (30 mL) was added into it in a dropwise manner over a period of 20 min. The resultant mixture was stirred at room temperature for 24 h even after which time no conversion of the starting material could be observed due to which the reaction mass was disposed off carefully.

Example 7: Synthesis of 2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one (V) in presence of DABCO



To a reactor equipped with reflux condenser, dropping funnel and thermo-pocket, were charged 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl 2,2,2-trifluoroacetate (5.0 g, 0.01 mol) and DABCO (3.1 g, 0.027 mol) and dissolved in toluene (50 mL) at room temperature. The reaction mass was refluxed for 5 h after which it was cooled and toluene removed under reduced pressure. To the resultant residue was added 1 M HCl (20 mL) and extracted with dichloromethane (2x 50 mL). The organic layer was dried over anh. Na_2SO_4 and evaporated to obtain desired product which was recrystallized from methanol to give product as white solid (3.3 g, 90 % yield).

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

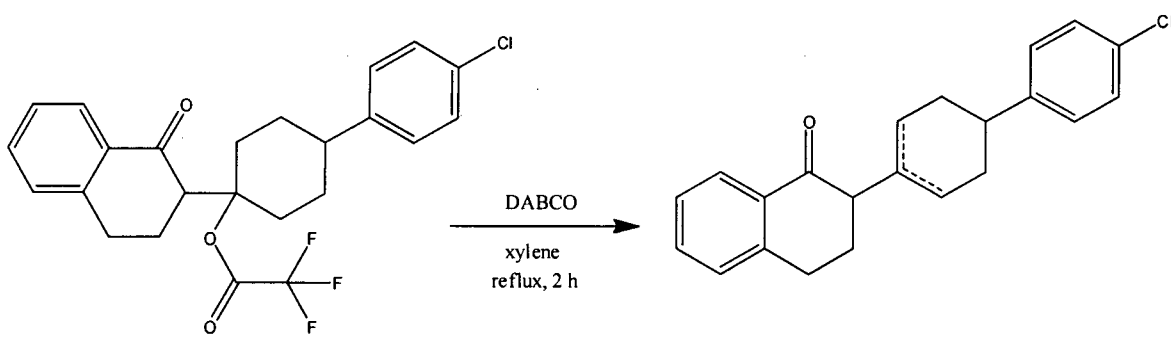
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.78-1.88 (m, 2H), 2.12-2.32 (m, 6H), 2.83-2.86 (m, 1H), 3.06 (s, 2H), 3.18-3.24 (m, 1H), 5.56 (d, 1H), 7.17-7.19 (m, 2H), 7.27-7.35 (m, 4H), 7.49 (t, 1H), 8.07 (d, 1H).

^{13}C NMR ($CDCl_3$, 50 MHz): 27.0, 27.2, 28.3, 28.4, 28.7, 29.8, 33.4, 39.4, 55.6, 56.0, 124.1, 124.2, 126.6, 127.4, 128.2, 128.4, 128.7, 131.8, 132.8, 136.0, 144.0, 145.4, 145.4, 198.8, 198.9.

MS (EI): $C_{22}H_{21}ClO$: 336.12; $[M+H]^+$: 337.10

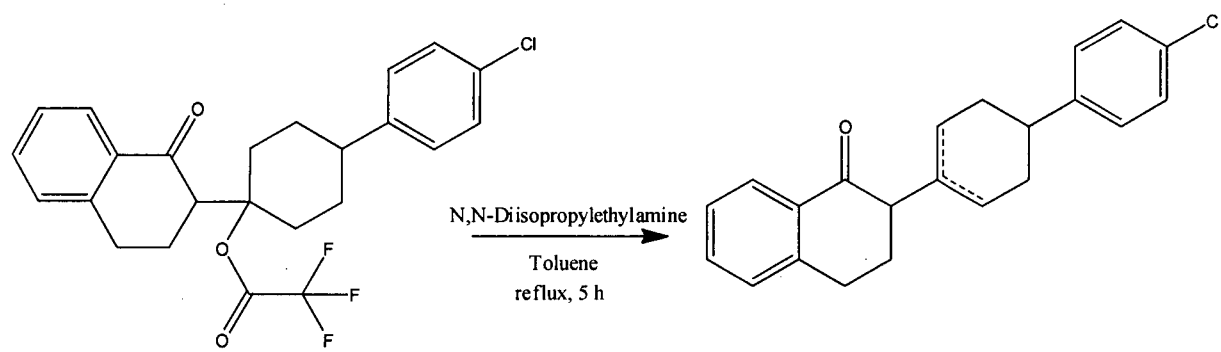
DSC peak at 136.02. ^{0}C (10^0C/min)

Example 8: Synthesis of 2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one (V) in presence of DABCO



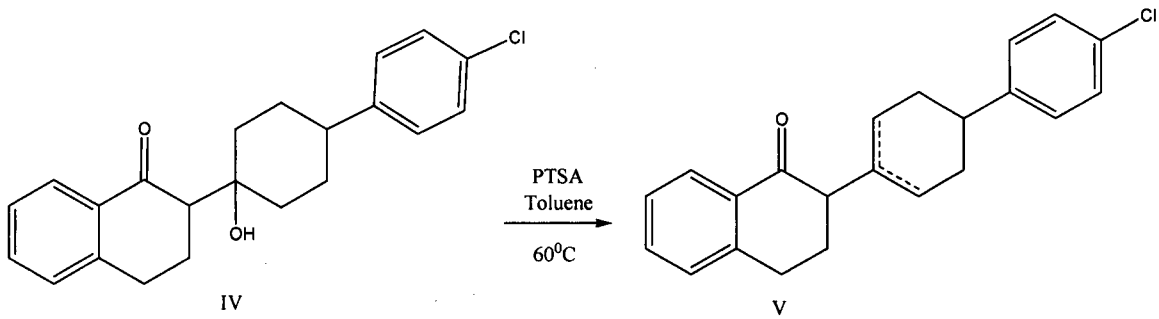
To a reactor equipped with reflux condenser, dropping funnel and thermo-pocket, were charged 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl 2,2,2-trifluoroacetate (5.0 g, 0.01 mol) and DABCO (3.1 g, 0.027 mol) and dissolved in xylene (50 mL) at room temperature. The reaction mass was refluxed for 2 h after which it was cooled and xylene removed under reduced pressure. To the resultant residue was added 1 M HCl (20 mL) and extracted with dichloromethane (2x 50 mL). The organic layer was dried over anh. Na_2SO_4 and evaporated to obtain desired product which was recrystallized from methanol to give product as white solid (3.31 g, 90 % yield).

Example 9: Synthesis of 2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one (V) in presence of N,N-Diisopropylethylamine



To a reactor equipped with reflux condenser, dropping funnel and thermo-pocket, were charged 4-(4-chlorophenyl)-1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)cyclohexyl 2,2,2-trifluoroacetate (5.0 g, 0.01 mol) and N,N-Diisopropylethylamine (3.6 g, 0.025 mol) and dissolved in toluene (50 mL) at room temperature. The reaction mass was refluxed for 5 h after which it was cooled and toluene removed under reduced pressure. To the resultant residue was added 1 M HCl (20 mL) and extracted with dichloromethane (2x 50 mL). The organic layer was dried over anh. Na_2SO_4 and evaporated to obtain desired product which was recrystallized from methanol to give product as white solid (3.0 g, 85 % yield).

Example 10: Synthesis of 2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2H)-one (V) (Co-pending PCT application PCT/IB2011/001507)



IV V

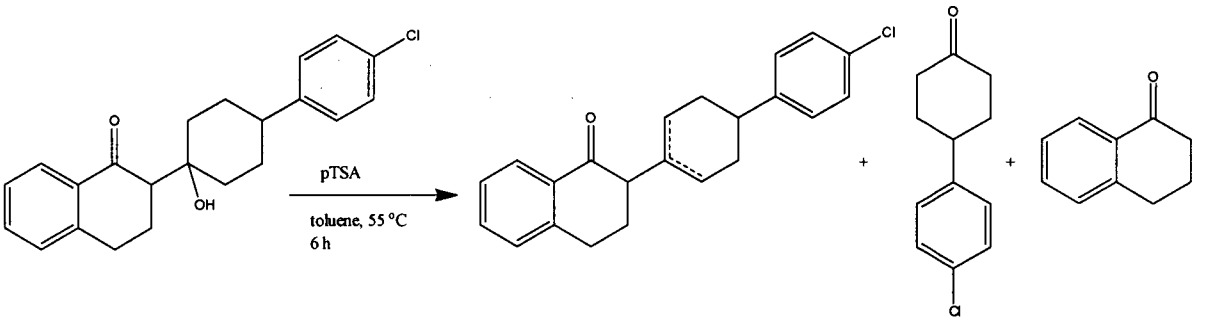
2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (122.0 g, 0.0.345mol) was charged in a reactor equipped with overhead stirrer, reflux condenser and thermo-pocket. Toluene (2 L) was added to suspend the material and *p*-toluene sulfonic acid (3.05 g, 2.5 mol %) was added to the reaction mass which was then heated to 60 °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 which was further re-crystallised from methanol to obtain white solid compound (V) (55.2 g, 50%).

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

^{1}H 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):** $C_{22}H_{21}ClO$: 336.12; $[M+H]^+$: 337.10 DSC peak at 136.02. ^0C (10^0C/min)

Example 11: Synthesis of 2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one in presence of *p*TSA



2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (12.0 g, 0.0.034 mol) was charged in a reactor equipped with overhead stirrer, reflux condenser and thermo-pocket. Toluene (200 mL) was added to suspend the material and *p*-toluene sulfonic acid (0.3 g, 2.5 mol %) was added to the reaction mass which was then heated to 60 °C and stirred for 6 h. 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 (150 mL) and washed with sat. $NaHCO_3$ soln. and brine followed by evaporation of solvent to give crude product which was further recrystallised from methanol to afford white solid compound (5.3 g, 50 % yield). The mother liquor obtained after re-crystallisation was subjected to GC analysis wherein both α-tetralone and 4-(4-chlorophenyl) cyclohexanone were identified to be present in approx. 1:1 ratio (by respective retention times and AUCs in the mother liquor) and in 50 % yield.

GC retention time:

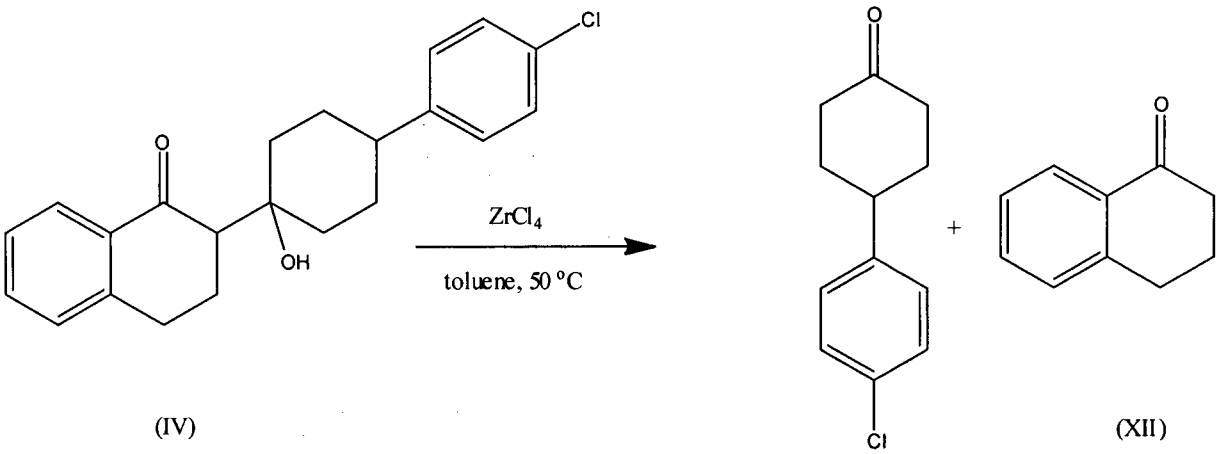
α-tetralone (XII): 17.21 min (Area % : 46)

4-(4-chlorophenyl) cyclohexanone (III): 24.31 min (Area % : 54)

Spectral data for 2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3,4-dihydronaphthalen-1(2*H*)-one:

FTIR (neat): 3020, 3045, 2920, 2894, 2863, 2839, 1683, 1597, 1491, 1218, 1088, 818, 747 cm^{-1}.**^{1}H 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):** $C_{22}H_{21}ClO$: 336.12; $[M+H]^+$: 337.10

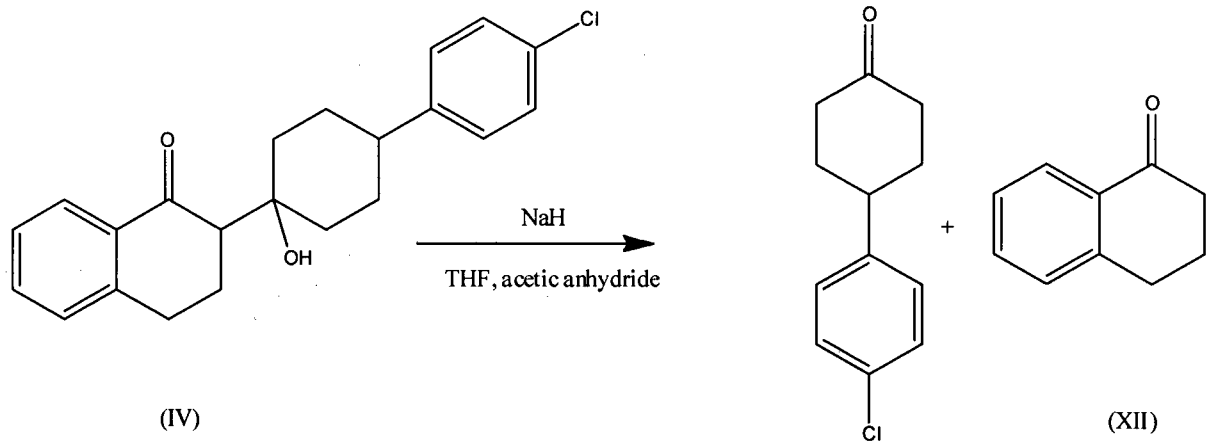
Example 12: Retro -Aldol reaction catalyzed by zirconium tetrachloride



(IV) (III) (XII)

To a reactor equipped with reflux condenser, dropping funnel and thermo-pocket, was charged 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1-(2*H*)-one (5.0 g, 0.04 mol) and dissolved in toluene (50 mL) at room temperature. To the above solution was added $ZrCl_4$ (0.33 g, 1.4 mmol) and the reaction mass was stirred at 50 °C for 2 h. The reaction mass showed complete conversion of starting material to α-tetralone and 4-(4-chlorophenyl) cyclohexanone in 1:1 ratio and no olefin product could be identified and isolated.

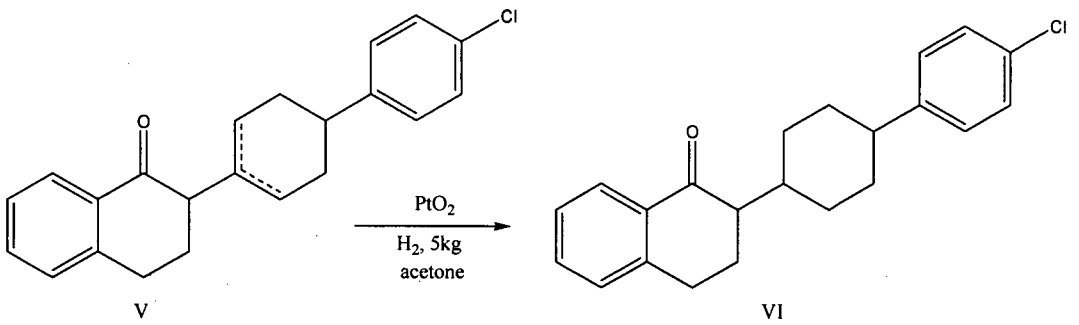
Example 13: Retro -Aldol reaction catalyzed by sodium hydride



(IV) (III) (XII)

To a reactor equipped with reflux condenser, dropping funnel and thermo-pocket, was charged with sodium hydride (0.36 g) and tetrahydrofurane (10 mL). To above reaction mixture solution of ((2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1-(2*H*)-one (1.0 g) and in tetrahydrofurane (10 mL) was added slowly at room temperature. The reaction mass was stirred at 25 °C for 0.5 h. Then acetic anhydride (0.31 g) was added and stirred further for 3 h at RT. The reaction mass showed complete conversion of starting material to α-tetralone and 4-(4-chlorophenyl) cyclohexanone in 1:1 ratio and no corresponding acylated product could be identified and isolated.

Example 14: Synthesis of *cis/trans*-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one (VI)



V VI

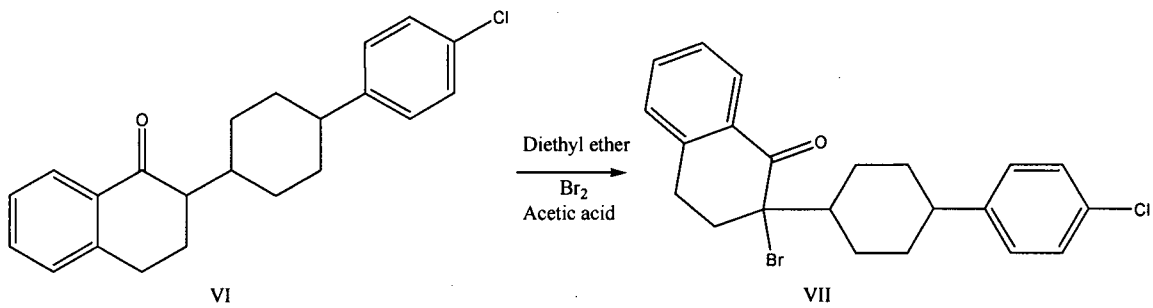
2-(4-(4-chlorophenyl) cyclohex-1-enyl)-3, 4-dihydronaphthalen-1(2H)-one (51.0g, 0.151 mol) was dissolved in acetone (1.1 L) at RT and transferred to a Parr autoclave reactor. Platinum oxide (0.097 g, 3 mol %) was added to the reaction mass and flushed twice with nitrogen and once with hydrogen. Subsequently, 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*-2-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one remained insoluble (4.8 g).

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

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24-1.28 (m, 1H), 1.44-1.59 (m, 3H), 1.74-1.85 (m, 3H), 1.90-196 (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):** $C_{22}H_{23}ClO$: 338.15 $[M+H]^+$: 339.00; DSC peak at 82.95 ^0C (10^0C/min)

Example 15: 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



VI VII

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 °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 °C. The resultant orange solution was stirred at 0 °C for 1h and gradually the temperature was allowed to increase to 15-20 °C when the reaction mass started decolourizing, after which reaction temperature was allowed to increase upto 25 ^{0}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 %). 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 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).

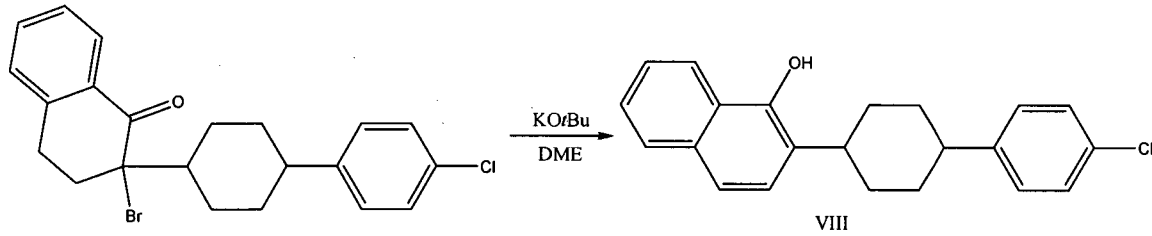
***Trans*-2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(2H)-one**

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

^{1}H NMR ($CDCl_3$, 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) ; **^{13}C NMR ($CDCl_3$, 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 ^{0}C

Example 16: Synthesis of cis/trans-2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol (VIII) and method for separation of *cis* and *trans* isomers



VII VIII

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}.

^{1}H 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):** $C_{22}H_{21}ClO$: 336.12; $[M-H]^-$: 335.20

DSC: peak at 195.14^{0}C

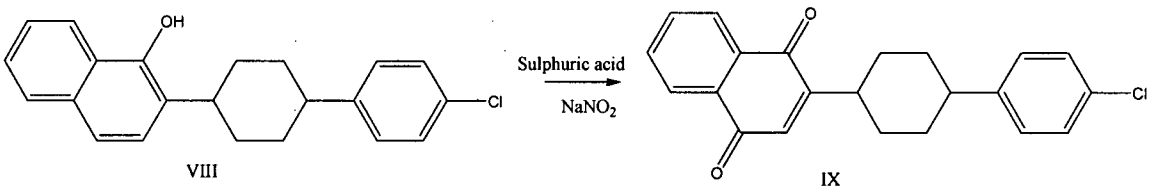
PXRD [2θ] (Cu $K_{\alpha 1}$ = 1.54060 Å, $K_{\alpha 2}$ = 1.54443 Å, K_{β} = 1.39225 Å; 40 mA, 45 kV): 10.76, 12.38, 13.00, 13.33, 13.76, 14.37, 15.51, 16.10, 17.41, 17.73, 18.71, 19.67, 20.05, 21.36, 22.39, 23.04, 23.40, 24.02, 24.56, 26.11, 27.72, 28.97, 30.01, 31.78

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

FTIR (neat): 3563, 3434, 2928, 2853, 1724, 1488, 1265, 1088, 806 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.29-1.33 (m, 1H), 1.44-1.48 (m, 1H), 1.55-1.67 (m, 3H), 1.82-1.88 (m, 2H), 2.06-2.09 (d, 1H), 2.24-2.31 (m, 1H), 2.37-2.54 (m, 2H), 2.70-2.76 (t, 1H), 2.93-2.97 (d, 1H), 3.26-3.34 (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), 8.17-8.19 (d,1H) ; **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 27.0, 28.3, 29.1, 31.5, 33.9, 34.1, 43.9, 44.2, 74.7, 127.1, 128.3, 129.0, 129.1, 130.3, 131.6, 133.8, 142.5, 145.2, 190.3 **MS (EI):** $C_{22}H_{21}ClO$: 336.12; $[M-H]^-$: 335.20

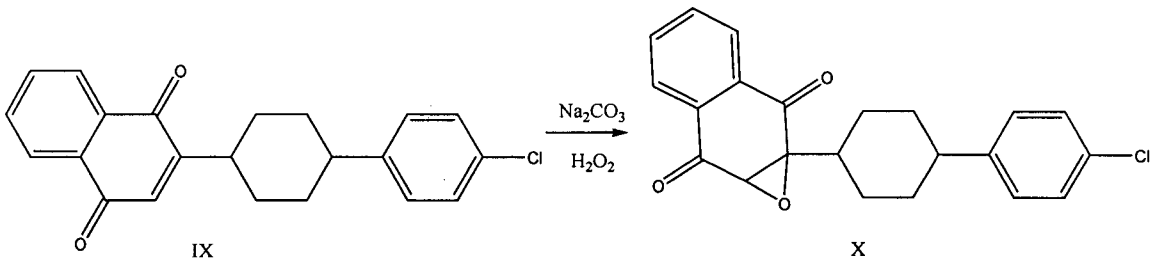
Example 17: Synthesis of 4-(4-chlorophenyl)cyclohexyl)naphthalene-1,4-dione (IX) in presence of sodium nitrite/ 50% aqueous sulphuric acid.



VIII IX

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 ^{0}C and temperature of the resultants reaction mixture was increased to 80 ^{0}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 Na_2SO_4 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 18: Synthesis of *cis/trans-1a*-(4-(4-chlorophenyl)cyclohexyl)naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (X)



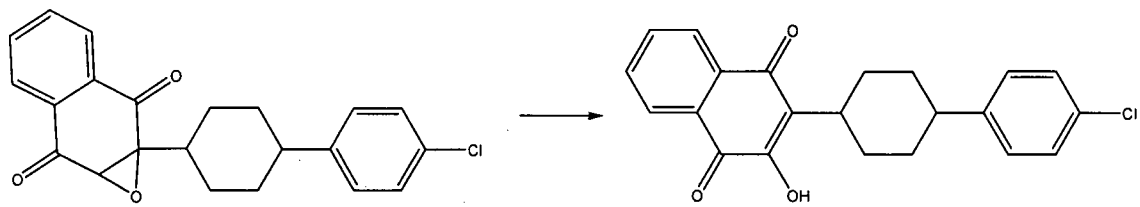
IX X

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 H_2O_2 (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).

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

^{1}H NMR ($CDCl_3$, 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) ;**^{13}C NMR ($CDCl_3$, 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

Example 19: Synthesis of Atovaquone [I]



X 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. H_2SO_4 (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}.

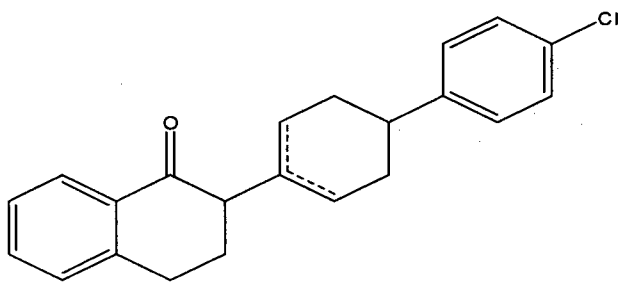
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.58 (q, 2H), 1.75 (d, 2H), 1.96 (d, 2H), 2.16-2.20 (m, 2H), 2.63 (t, 1H), 3.16 (t, 1H), 7.18 (d, 2H), 7.28 (d, 2H), 7.48 (s, 1H), 7.68 (t, 1H), 7.76 (t,1H), 8.07 (d, 1H), 8.13 (d, 1H); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 29.18, 34.34, 34.46, 34.64, 43.22, 126, 127, 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):** $C_{22}H_{19}ClO_3$: 366.1023; $[M+Na]^+$: 388.95, $[M-H]^-$: 365.30; DSC peak at 220.44 ^{0}C (10^0C/min)

DSC: peak at 221.2 ^{0}C

PXRD [2θ] (Cu $K_{\alpha1}$ = 1.54060 Å, $K_{\alpha2}$ = 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.

CLAIMS

1) A process for preparation of compound(V)



[V]

comprising of the steps of;

i) Reaction of 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(*2H*)-one (IV) with trifluro acetic anhydride in presence of base in organic solvent to yield compound of formula (XIa)

ii) Elimination of trifluoroacetyl functionality of compound (XIa) in organic solvent and in presence of organic base to give compound of formula (V)

2) The process according to Claim 1 step i) wherein base used is is pyridine/dimethyl amino pyridine (DMAP).

3) The process according to Claim 1 step i) wherein organic solvent used is dichlormethane.

4) The process according to Claim 1 step i) wherein reaction is carried out at 25-30^{0}C

5) The process according to Claim 1 step ii) wherein organic base used is 1,4-diazabicyclo[2.2.2]octane (DABCO) or N,N-Diisopropylethylamine.

6) The process according to Claim 1 step ii) wherein organic solvent used is toluene or xylene

7) The process according to Claim 1 step i) wherein reaction is carried out in tempreautre range 100-140^{0}C

8) A Process for preparation of compound(XIa) comprising of the steps of;

i) reaction of 2-(4-(4-chlorophenyl)-1-hydroxycyclohexyl)-3,4-dihydronaphthalen-1(*2H*)-one (IV) with trifluro acetic anhydride in presence of organic base in organic solvent.

9) The process according to Claim 8 step i) wherein base used is pyridine/dimethyl amino pyridine (DMAP).

10) The process according to Claim 8 step i) wherein organic solvent used is dichlormethane.

11) The process according to Claim 8 step i) wherein reaction is carried out at 25-30^{0}C

12) A Process for preparation of compound(V) from compound (XIa) comprising of the steps of;

i) Elimination reaction of trifluoroacetyl functionality compound (XIa) in organic solvent and in presence of organic base

13) The process according to Claim 12 step i) wherein organic base used is 1,4-diazabicyclo[2.2.2]octane (DABCO) or N,N-Diisopropylethylamine.

14) The process according to Claim 12 step i) wherein organic solvent used is toluene or xylene

15) The process according to Claim 12 step i) wherein reaction is carried out in tempreautre range 100-140^{0}C

16) A Process of conversion of compound (V) into Atovaquone (I) comprising the steps of;

i) hydrogenation of 2-(4-(4-chlorophenyl)cyclohex-1-enyl)-3,4-dihydronaphthalen-1(*2H*)-one[V] with PtO_2 to obtain *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(*2H*)-one [VI]

ii) 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]

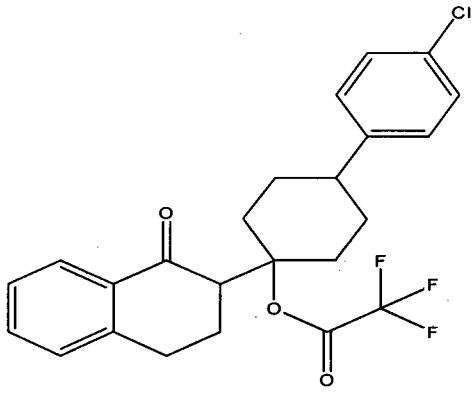
iii) elimination of *cis/trans* mixture of 2-bromo-2-(4-(4-chlorophenyl)cyclohexyl)-3,4-dihydronaphthalen-1(*2H*)-one [VII] with a strong base to give *cis/trans* mixture of 2-(4-(4-chlorophenyl)cyclohexyl)naphthalen-1-ol [VIII]

iv) 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]

v) 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(1aH,7aH)-dione (X) in presence of hydrogen peroxide

vi) acid catalyzed hydrolysis of *cis/trans* mixture 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]

17) Compound of formula (XIa)



(XIa)

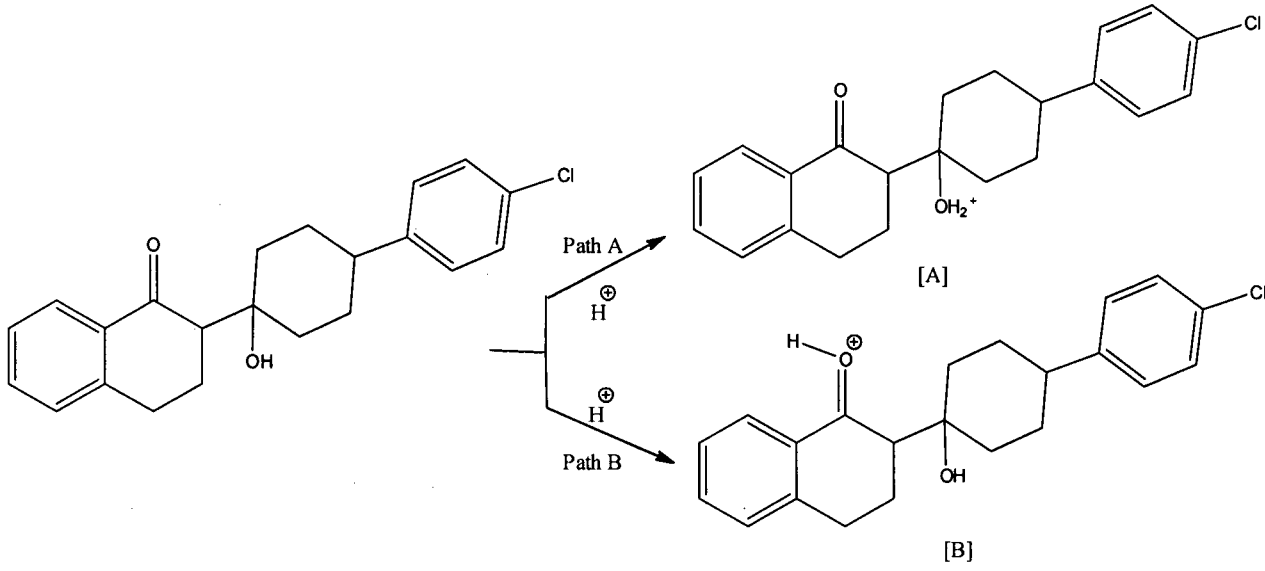


Figure 1

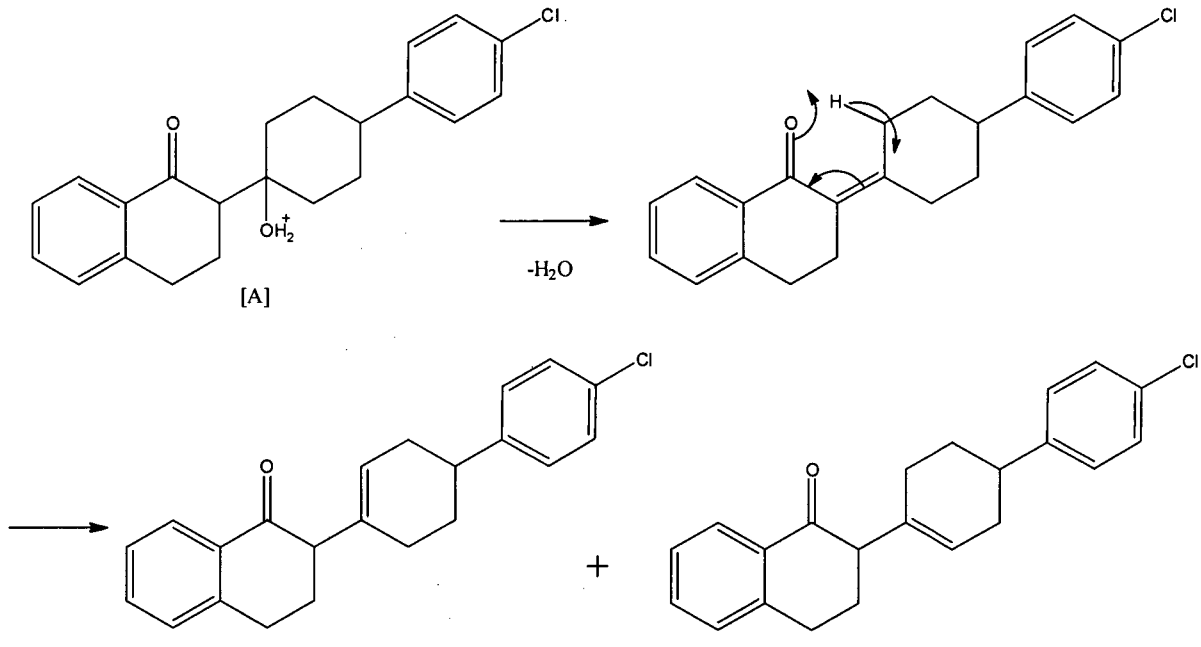


Figure 2

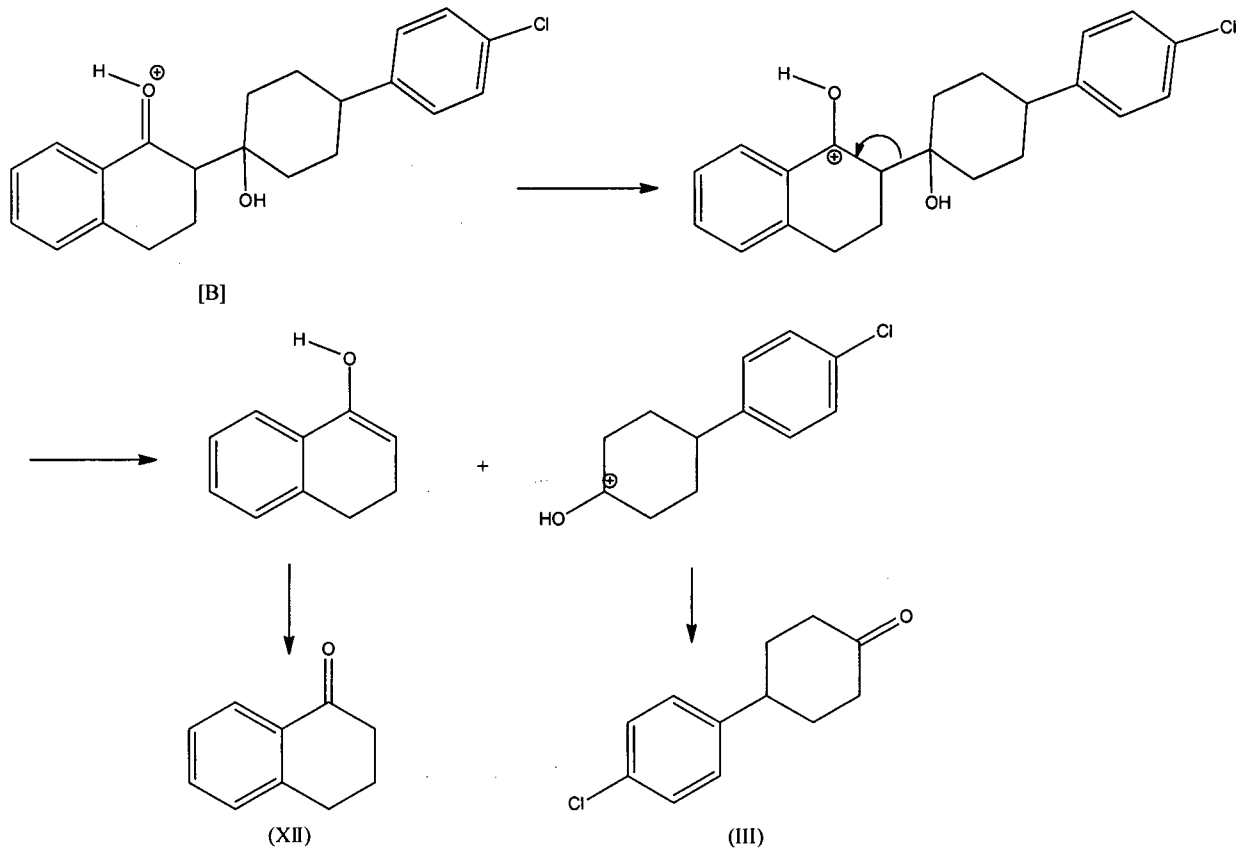


Figure 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/002134

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C45/65 C07C49/477 C07C67/08 C07C69/63
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)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	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 the whole document	1-17
A	WO 2008/122988 A1 (CADILA HEALTHCARE LIMITED [IN]; VERMA SHYAM SUNDER [IN]; PATEL DHIMANT) 16 October 2008 (2008-10-16) claim 8	1-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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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	Date of mailing of the international search report
4 June 2012	14/06/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	O'Sullivan, Paul

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/002134

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008122988 A1	16-10-2008	NONE	