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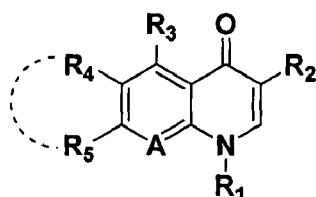
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(54) **Title:** A PROCESS FOR THE PREPARATION OF THE CORE STRUCTURE IN QUINOLONE AND NAPHTHYRIDONE CLASS OF ANTIBIOTICS



(VII)

(57) **Abstract:** This invention relates to quinolone- and naphthyridone derivatives represented by the general formula VII, and a process for their preparation using Baylis-Hillman adducts from substituted aromatic or hetero-aromatic aldehydes and amines of interest as the starting materials. After the tandem Aza-Michael addition and SNAr cyclization, the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline or 4-hydroxy-1, 2,3,4- tetrahydro-1,8-naphthyridine derivative was subjected to oxidation to get the quinolone or naphthyridone skeleton in one step in good to excellent yields.

Title: A PROCESS FOR THE PREPARATION OF THE CORE STRUCTURE IN QUINOLONE AND NAPHTHYRIDONE CLASS OF ANTIBIOTICS

Applicant's Name: INDIAN INSTITUTE OF TECHNOLOGY MADRAS

Priority application no.: 1542/CHE/2012 dated 18/04/2012

FIELD OF THE INVENTION

The invention relates to a process for preparing therapeutically important quinolone and naphthyridone derivatives.

BACKGROUND OF THE INVENTION

The quinolone and naphthyridone skeletons are integral part of the structure of antibiotics such as Ciprofloxacin (I), Levofloxacin (II) and Gemifloxacin (III) shown in Figure 1. They are active against both gram-positive and gram-negative bacteria and are currently in clinical use to treat different types of infections. The fact that Ciprofloxacin and Levofloxacin together generate ~3 billion US dollars per year in US alone show the high demand of this class of antibiotics. Compounds from this class have recently been shown to possess promising anti-HIV-1 integrase, anti-cancer, anti-tuberculosis and anti-malarial activities. This has resulted in a renewed interest in the synthesis and biological activities of quinolones and naphthyridones.

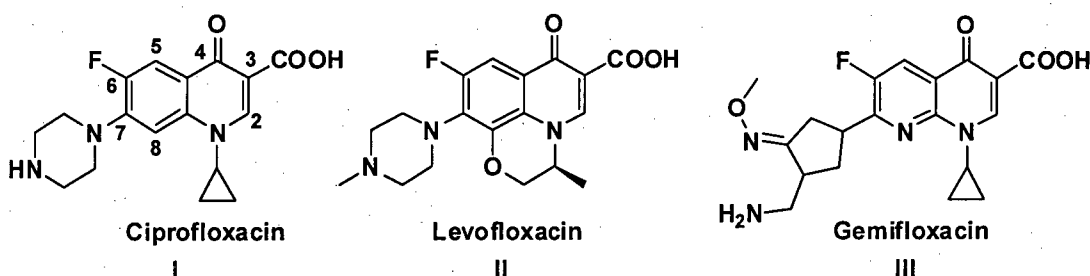


Figure 1. Examples of quinolone and naphthyridone based antibiotics

Quinolones with nitro- or amino functionalities at the 6th position have recently emerged as a second line of chemotherapeutic agents from this class. A number of 6-nitroquinolones studied, for example, were active against *E. coli*, and had potencies in the same order as that of fluoroquinolones. Most importantly, these

compounds possessed activity against *Mycobacterium tuberculosis* with MIC₅₀ value of 0.2 μ M (eg. Compound IV, Figure 2) and were found to be more active than Ciprofloxacin and Ofloxacin. Cecchetti et al. have studied the activity of 6-amino quinolones against various gram-positive and gram-negative bacteria and have found them more active against staphylococci as well as those strains which are methicillin- and ciprofloxacin-resistant (eg. Compound V, Figure 2). In a related study, Stevens et al. have found that 6-amino quinolones show activity against cytomegalovirus (CMV) as well which shows the potential of this class of compounds to act as broad spectrum anti-infective agents. Derivatization of C-7 and N-1 positions of these scaffolds with suitable groups and their structure-activity relationship studies have led to the identification of new compounds (eg. Compound VI, Figure 2) with activity against HIV-1 and HIV-2 in both acutely and chronically infected cells. Existing anti-HIV drugs such as Maraviroc, Ritonavir, Tenofovir target viral proteins such as Reverse Transcriptase, protease, and integrase (De Clercq, E. "New developments in anti-HIV chemotherapy" *Biochim. Biophys. Acta, Mol. Basis Dis.* 2002, 1587, 258-275; De Clercq, E. "Antiviral therapy for human immunodeficiency virus infections" *Clin Microbiol Rev.* 1995, 8, 200-39; Opar, A. "New HIV drug classes on the horizon" *Nat. Rev. Drug Discovery* 2007, 6, 258-259). The 6-aminoquinolones on the other hand are believed to interfere with the trans-activation step of transcription which represents a new therapeutic strategy against HIV.

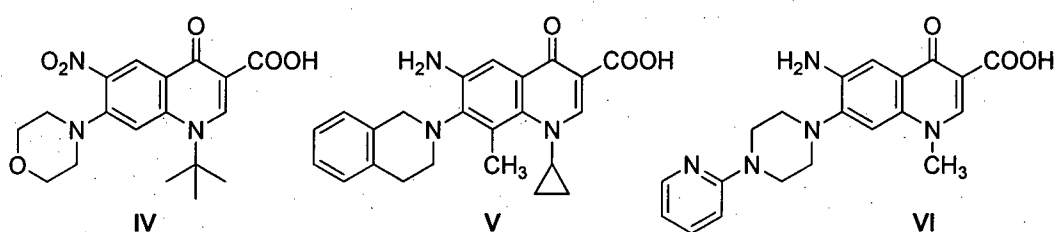


Figure 2. Examples of known nitro- and amino- quinolone based antibiotics

The amino-quinolones studied thus far were accessed from the corresponding nitro quinolones through catalytic reduction using Raney nickel or palladium on carbon (Cecchetti, V. et al., "Studies on 6-aminoquinolones: Synthesis and antibacterial evaluation of 6-amino-8-methylquinolones" *J. Med. Chem.* 1996, 39, 436-45). New and efficient synthetic approaches towards these precursors are still in great demand considering their therapeutic importance.

Synthesis and various biological activities of 4-quinolones, naphthyridones or related heterocycles have been reported in the literature and are described in the following references:

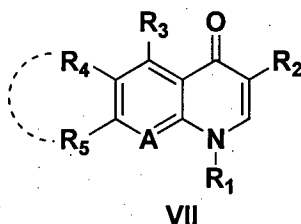
Emmerson, A. M et al., "The quinolones: Decades of development and use" J. Antimicrob. Chemother. 2003, 51, 13-20; Mitscher, L. A. "Bacterial Topoisomerase Inhibitors: Quinolone and Pyridone Antibacterial Agents" Chem. Rev. 2005, 105, 559-592; Anderson, V. R. et al., "Levofloxacin: a review of its use as a high-dose, short-course treatment for bacterial infection" Drugs 2008, 68, 535-565; Boteva, A. A.; et al., "The methods of synthesis, modification, and biological activity of 4-quinolones" Chem. Heterocycl. Compd. 2009, 45, 757-785; Bouzard, D. et al., "Fluoronaphthyridines and quinolones as antibacterial agents. 1. Synthesis and structure-activity relationship of new 1-substituted derivatives" J. Med. Chem. 1989, 32, 537-542; Wolfson, J. S. et al., "Norfloxacin: a new targeted fluoroquinolone antimicrobial agent" Ann. Intern. Med. 1988, 108, 238-251; Raja, A et al., "Fresh from the pipeline: Telithromycin" Nat. Rev. Drug Discovery 2004, 3, 733-734; Sato, M. et al., "Quinolone Carboxylic Acids as a Novel Monoketo Acid Class of Human Immunodeficiency Virus Type 1 Integrase Inhibitors" J. Med. Chem. 2009, 52, 4869-4882; Sissi, C. et al., "The quinolone family: From antibacterial to anticancer agents" Curr. Med. Chem.: Anti-Cancer Agents 2003, 3, 439-450; Hadjeri, M. et al., "Antimitotic Activity of 5-Hydroxy-7-methoxy-2-phenyl-4-quinolones" J. Med. Chem. 2004, 47, 4964-4970. Mahmoudi, N. et al., "In vitro activities of 25 quinolones and fluoroquinolones against liver and blood stage Plasmodium spp" Antimicrob. Agents Chemother. 2003, 47, 2636-2639. Shul'gina, M. V. et al., "Mechanisms of the antibacterial activity of fluoroquinolones and nitroquinolones with respect to Escherichia coli K12" Pharm. Chem. J. 1999, 33, 343-347; Artico, M. et al., "Nitroquinolones with broad-spectrum antimycobacterial activity in vitro" Bioorg. Med. Chem. Lett. 1999, 9, 1651-1656; Sbardella, G. et al., "New 6-nitroquinolones: synthesis and antimicrobial activities" Farmaco 2004, 59, 463-471; Cecchetti, V. et al., "6-Aminoquinolones: A New Class of Quinolone Antibacterials" J. Med. Chem. 1995, 38, 973-82; Cecchetti, V. et al., "Studies on 6-aminoquinolones: Synthesis and antibacterial evaluation of 6-amino-8-methylquinolones" J. Med. Chem. 1996, 39, 436-45; Loregian, A. et al.,

"The 6-aminoquinolone WC5 inhibits human cytomegalovirus replication at an early stage by interfering with the transactivating activity of viral immediate-early 2 protein" *Antimicrob. Agents Chemother.* 2010, 54, 1930-1940; Cecchetti, V. et al., "6-Aminoquinolones as New Potential Anti-HIV Agents" *J. Med. Chem.* 2000, 43, 3799-3802; Stevens, M. et al., "Cell-dependent interference of a series of new 6-aminoquinolone derivatives with viral (HIV/CMV) transactivation" *J. Antimicrob. Chemother.* 2005, 56, 847-855; Tabarrini, O. et al., "Structure Modifications of 6-Aminoquinolones with Potent Anti-HIV Activity" *J. Med. Chem.* 2004, 47, 5567-5578; Richter, S. N. "Antiviral 6-amino-quinolones: Molecular basis for potency and selectivity" *Bioorg. Med. Chem. Lett.* 2005, 15, 4247-4251; Viola, G. et al., V. "6-Aminoquinolones: photostability, cellular distribution and phototoxicity" *Toxicol. in Vitro* 2004, 18, 581-592.

In this disclosure, we report a quick and highly efficient method to access the quinolones and naphthyridone derivatives from readily available Baylis-Hillman adducts. The strategy involves only two reaction steps and doesn't employ any toxic reagents. High yields, absence of side reactions and adaptability for scale-up are some of the attractive features of this strategy.

SUMMARY OF THE INVENTION:

This invention relates to a novel process for the synthesis of quinolone and naphthyridone derivatives of the general formula VII through an intermediate of the general formula X.



In which,

R₁ represents alkyl, arylalkyl, aryl, alkenyl, alkynyl, cycloalkyl, phenyl, heteroaryl groups etc.

R_2 represents ester, cyano, amide, aldehyde, keto, phosphonate, sulfoxide, sulphone groups etc.

R_3 represents hydrogen, F, Cl, Br, I, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, cyano, amino or - NHR_1 , $-N(R_1)_2$ groups etc.

R_4 represents $-NO_2$, $-CN$, $-COR_1$, Phenyl, $-F$, $-NH_2$, $-NHR_1$, $-N(R_1)_2$ etc.

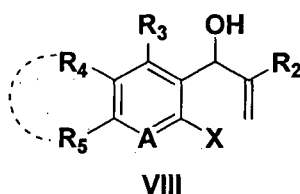
R_5 represents halogen, hydrogen, cyclic secondary amines, $-NH_2$, $-NHR_1$, $-N(R_1)_2$ etc.

R_4 and R_5 can also be part of a mono- or polycyclic ring systems.

A represents N, CH, CF, CCl, $COCH_3$, CCN etc.

The process includes the following steps,

a) Reacting Baylis-Hillman adduct of formula (VIII)



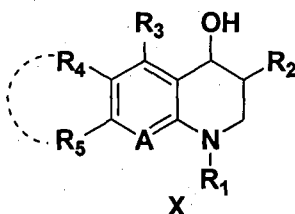
in which R_2 , R_3 , R_5 and A each are as defined under the formula (VII) and X represents I, Br, Cl, F, OTs, OTf; R_4 can be H or R_1 if A represents a hetero-atom such as N. If A is CH, R_4 need to be an electron withdrawing substituent such as NO_2 , CN, COR_1 etc.

with an amine of the general formula IX

R_1-NH_2 (IX),

in which R_1 is as defined under the formula (VII)

in the presence of a base to produce 4-hydroxy-1,2,3,4-tetrahydroquinoline or 4-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridine derivative of the general formula X

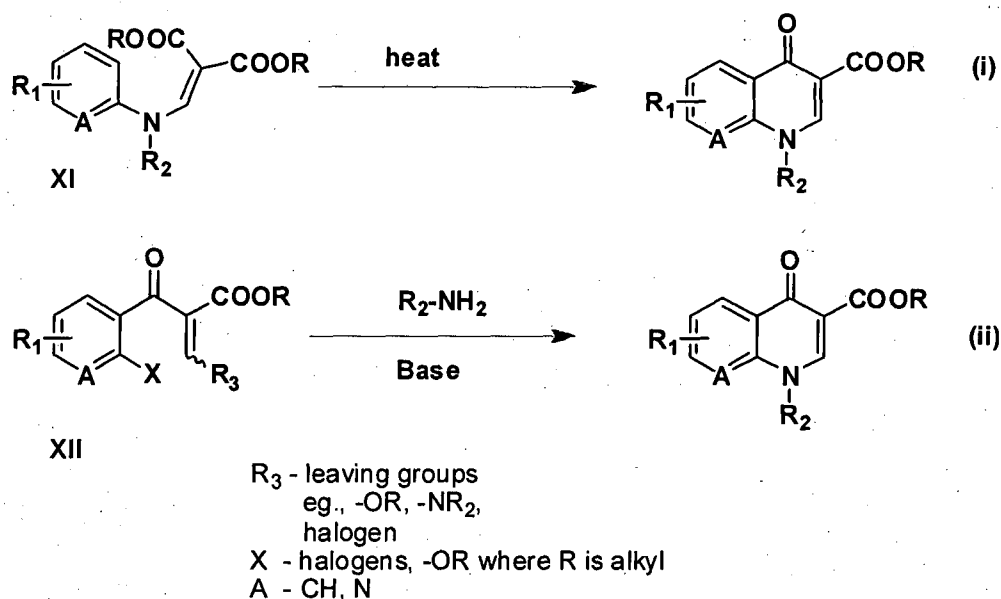


in which R_1 , R_2 , R_3 , R_4 , R_5 and A each are as defined under the formula (VII)

b) Subjecting 4-hydroxy-1,2,3,4-tetrahydroquinoline or 4-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridine derivative of the general formula X to oxidation with an oxidant to produce the quinolone or naphthyridone derivative of the formula VII in one step.

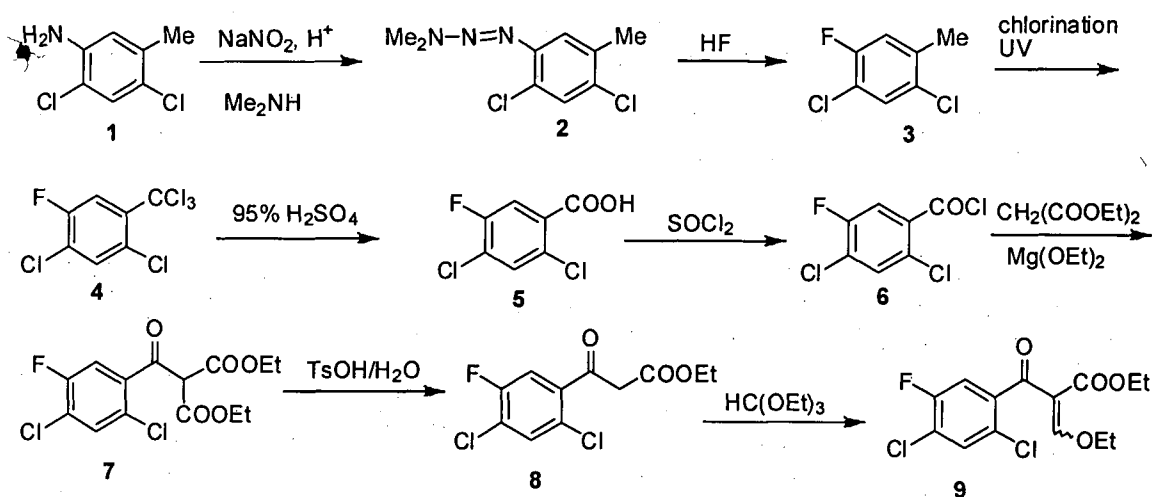
PRIOR ART

Although there are a number of patents and journal publications on the synthesis of quinolones, naphthyridones and related heterocycles, they mainly follow one of the two general strategies (i or ii, Scheme 1) and involve either skeleton XI or XII as intermediates (Boteva, A. A. et al., Chem. Heterocycl. Compd. 2009, 45, 757-785; Mitscher, L. A. Chem. Rev. 2005, 105, 559-592). They mainly differ in the nature of these intermediates and the synthetic strategies adopted to prepare them. The transformation of these intermediates to the target quinolones or naphthyridones more or less follows a similar route.



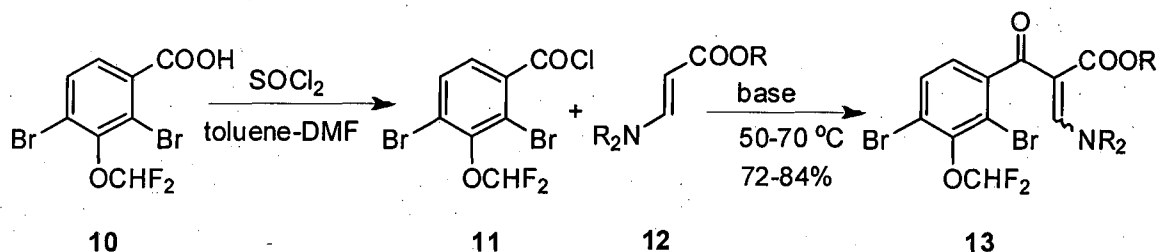
Scheme 1. General approaches towards quinolones and naphthyridone derivatives
 Specific examples for the synthesis of quinolones and naphthyridones following the above mentioned general strategies are given below:

1) The invention by Grohe et al. presented in Canadian Patent No. 1,218,067 discloses the synthesis of the intermediate 9 from readily available dihalo-metatoluidine derivative 1 and its transformation to quinolone skeleton by reaction with amines as shown below (Scheme 2).



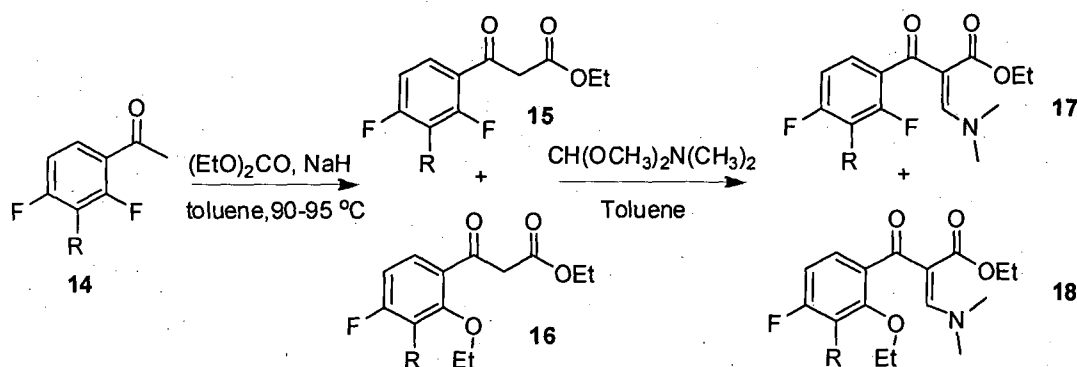
Scheme 2.

2) Prosenjit Bose et al. (U.S. Pat. No. US 2004/0267019 A1) has reported the synthesis of intermediate 13 starting from benzoic acid derivative 10 as shown below which was later reacted with various amines to get the quinolone skeleton (Scheme 3).



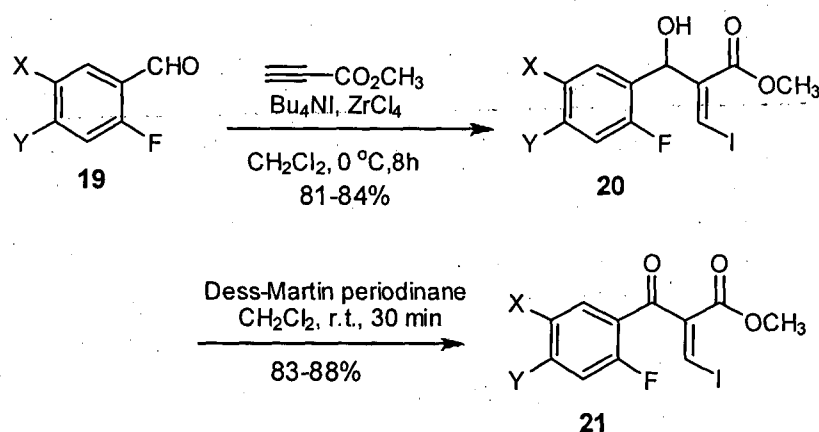
Scheme 3.

3) Jared Lynn Randall (U.S. Pat. No. 6,803,469 B2) accessed the intermediates 17 & 18 starting from substituted acetophenone 14 as shown below. Compound 14 was first reacted with diethyl carbonate to get a mixture of products 15 and 16 which was reacted with an amine capable of undergoing Knoevenagel reaction to get the intermediates 17 and 18 (Scheme 4). After amine addition, elimination and cyclization steps, they gave the corresponding quinolone in an overall yield of 82%.



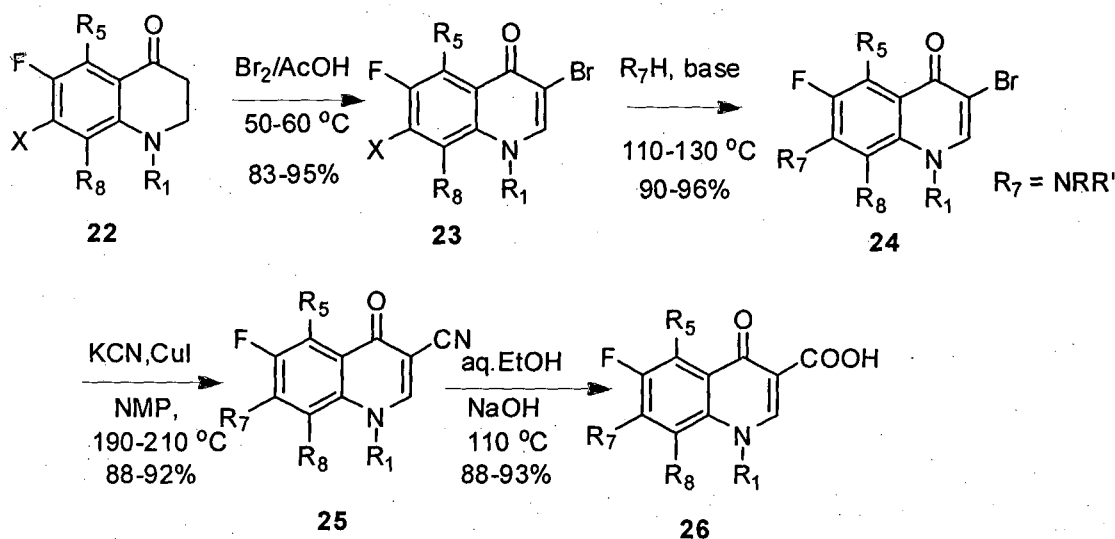
Scheme 4.

4) Wan Pyo Hong and Lee developed a synthetic route towards the intermediate 21 from suitably substituted aromatic aldehyde 19 and methyl propiolate in presence of tetra butyl ammonium iodide and ZrCl₄ as shown below (Synthesis 2006, 6, 963-68). The product 20 on oxidation with Dess-Martin periodinane gave the intermediate 21 in 83-88% yields (Scheme 5).



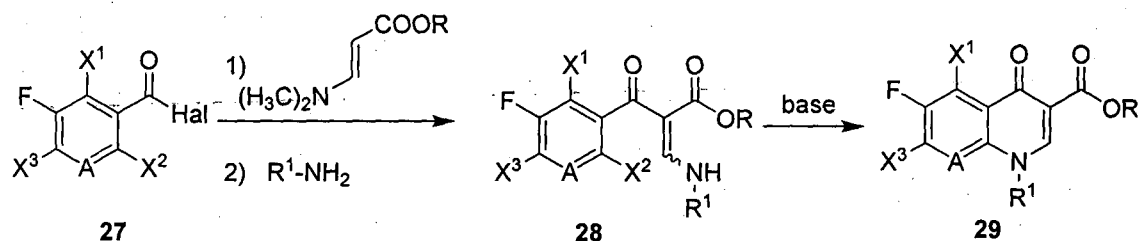
Scheme 5.

5) Egle et al. (U.S. Patent No. 5,914,401) developed a new process to make quinolones starting from the compound 22. The strategy involves bromination, amine substitution, cyanation and hydrolysis as the key steps (Scheme 6).



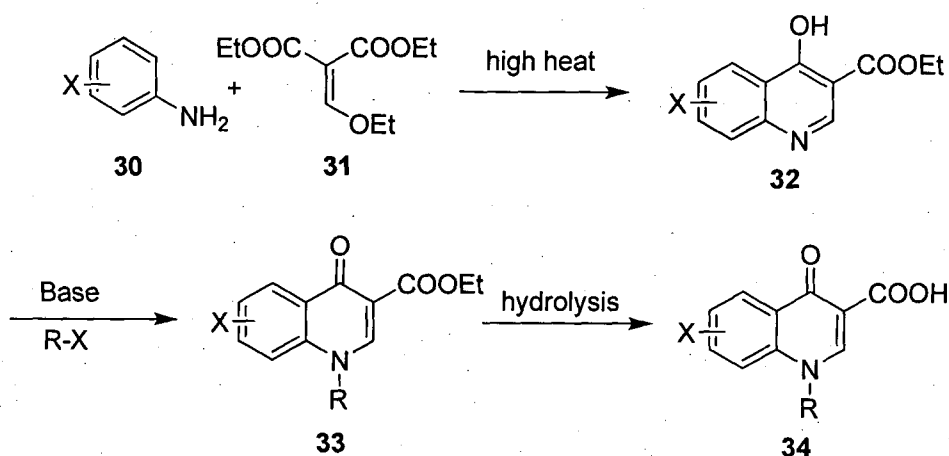
Scheme 6.

6) Zerbes et al. (U.S. Pat. No. 5,639,886) has developed a one-pot method towards substituted quinolones in an overall yield of 83-87% as shown in Scheme 7.



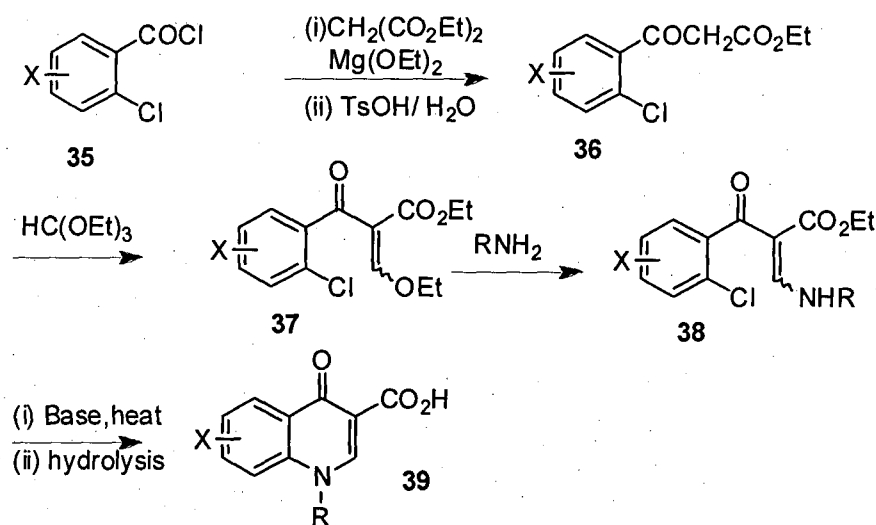
Scheme 7.

7) In the method developed by Gould et al. (J. Am. Chem. Soc. 1939, 61, 2890-2895), a substituted aniline **30** on reaction with diethyl 2-(ethoxymethylene)malonate **31** at high temperature undergoes addition-elimination and cycloacylation steps to give 4-hydroxyquinoline-3-carboxylate derivative **32**. N-alkylation of this intermediate using appropriate alkyl halide gave substituted quinolones (Scheme 8). A limitation of this approach is the generality of the N-functionalization step.



Scheme 8.

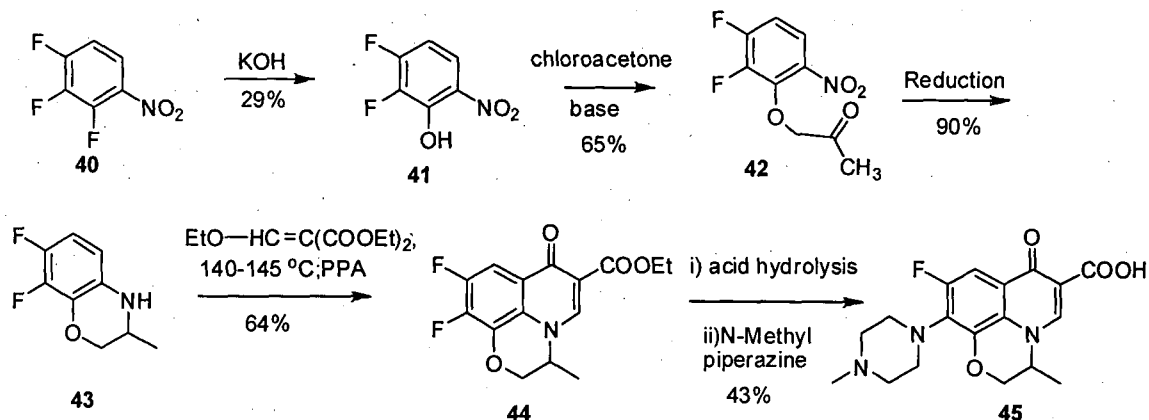
8) Grohe-heitzer approach (Mitscher, L. A. Chem. Rev. 2005, 105, 559-592; Silva, D. et al. Curr. Med. Chem. 2003, 10, 21-39) shown below offers some advantages over the method discussed above (Gould et al.) especially in accessing a wider variety of N-alkylated quinolone derivatives. In this, an orthohalo aroylhalide **35** is initially converted to an aroylmalonate ester **36** through an acylation reaction. Condensation of **36** with an orthoester generates the key intermediate **37**, which can be reacted with an amine to form the quinolone through addition-elimination-cyclization sequence (Scheme 9).



Scheme 9.

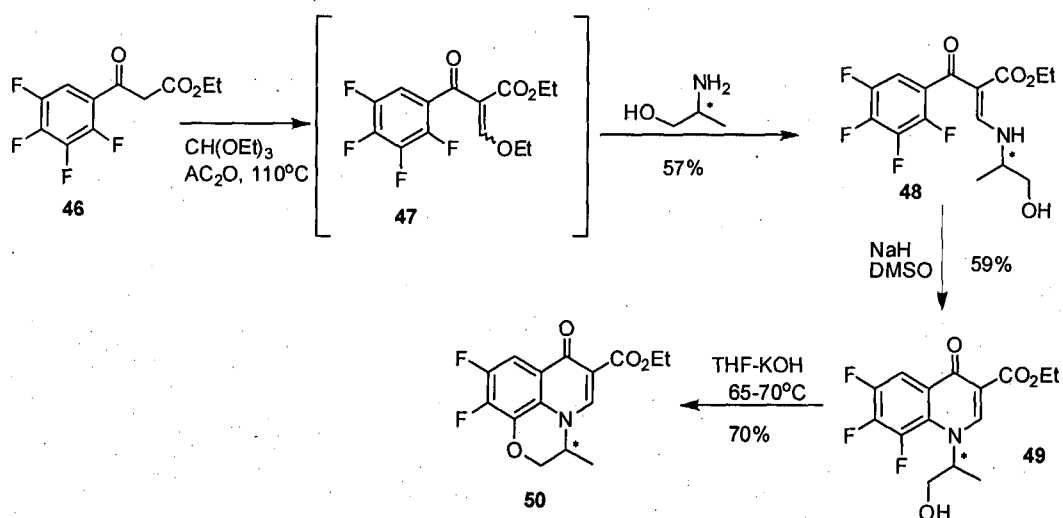
9) Gerster and Hayakawa developed an approach that can give N1-C8-bridged tricyclic quinolones of the type **45** (J. Med. Chem. 1987, 30, 839-843; Canadian Patent 1,167,840) starting from 2,3,4-trifluoronitrobenzene **40** as shown below. The transformation involves Gould-Jacobs cyclisation of benzoxacin derivative **43**, which

was prepared by reductive cyclization of 42. The racemic nature of 43 is the major bottleneck that decreases the optical purity of 45 (Scheme 10).



Scheme 10.

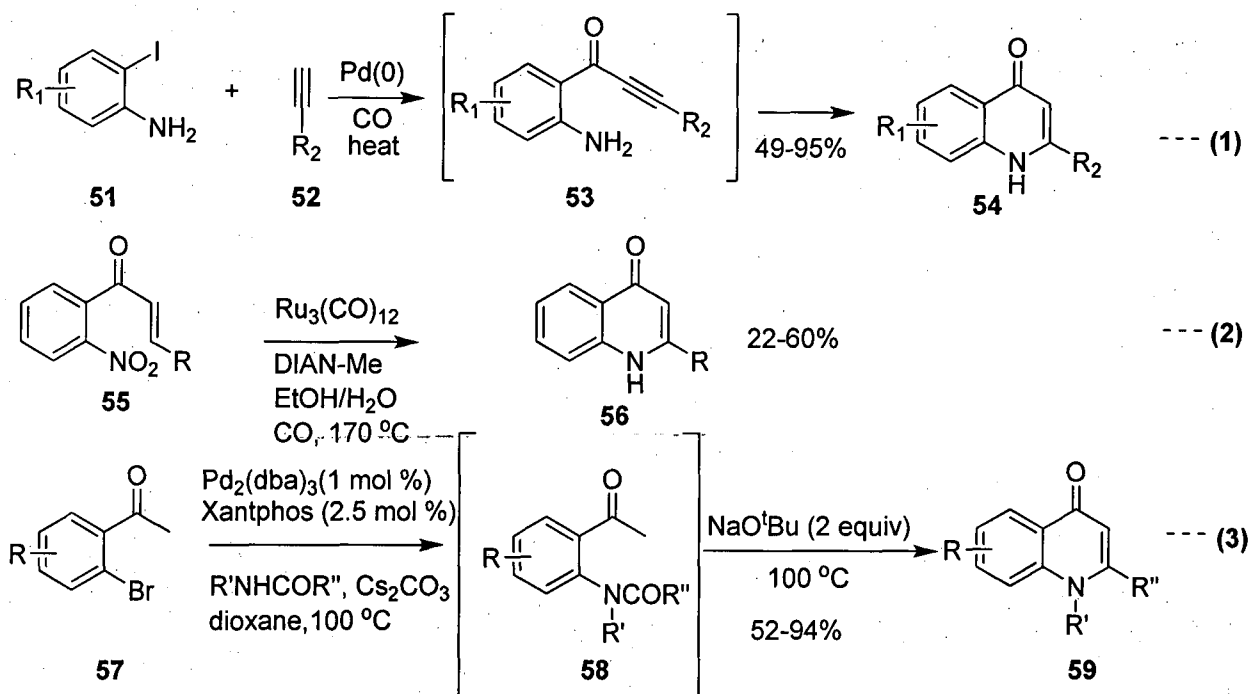
10) Mitscher and Chu (J. Med. Chem. 1987, 30, 2283-2286) has reported the synthesis of optically pure (both + and – isomers) Ofloxacin (49) through Grohe-Heitzer cyclisation using the intermediate 47 and R- or S- alaninol as shown below (Scheme 11).



Scheme 11.

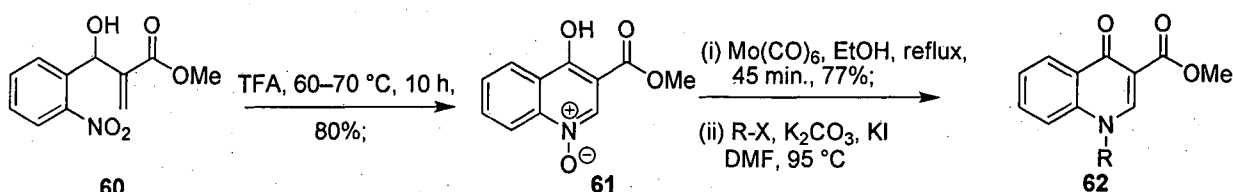
11) 4-Quinolones can also be constructed from precursors such as 51, 55 and 57 under organometallic catalysis as shown below (Scheme 12). Kalinin et al., (Tetrahedron Lett, 1992, 33, 373-376) and Sigeru Torii et al., (Tetrahedron 1993, 49, 6773) synthesized 2-substituted 4-quinolone 54 using palladium catalysed carbonylative coupling of o-iodoanilines with terminal arylacetylenes as shown in Scheme 12-(1). Tollari et al., (J. Chem. Soc., Chem. Commun. 1994, 1741-42) used

Ruthenium-catalysed reductive cyclisation of 55 to synthesize 2-aryl quinolones as shown in Scheme 12-(2). Camps cyclisation (Camps, R. Chem. Ber. 1899, 32, 3228) involves synthesis of 4-quinolones through base-promoted cyclisation of N-(keto-aryl)amides 58. Along similar lines, Jinkun Huang et al., (Org. Lett., 2008, 10, 2609-12) have synthesized 4-quinolones in one pot via palladium catalysed amidation of 2-acetylbromoarenes 57 and the subsequent base promoted cyclisation as shown in Scheme 12-(3).



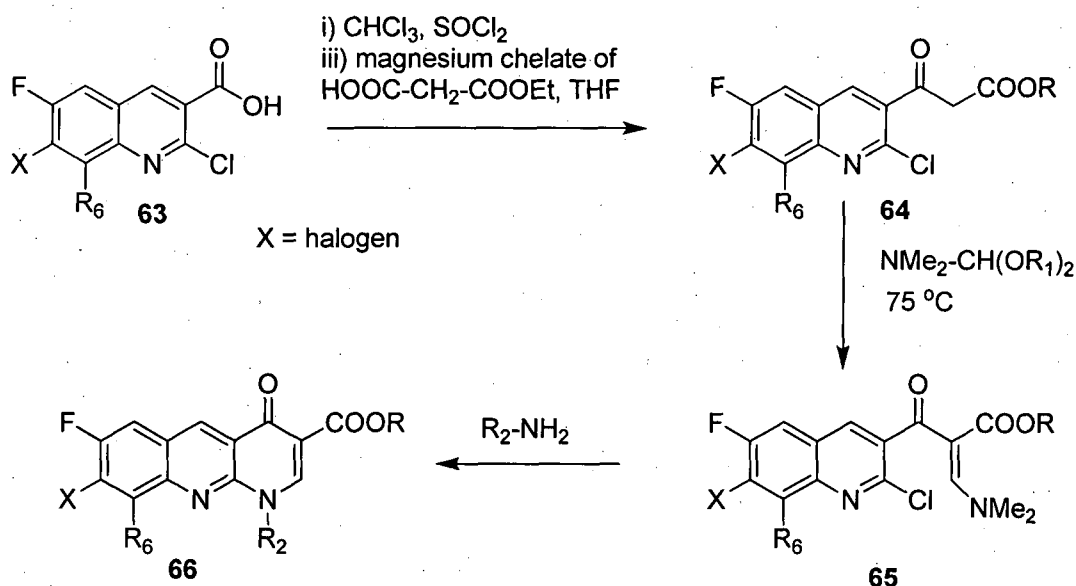
Scheme 12.

12) Amarante et al. (Tetrahedron 2010, 66, 4370-4376) has reported the synthesis of quinolone 62 through reduction of the intermediate 61 using molybdenum hexacarbonyl in ethanol and subsequent N-alkylation as shown below (Scheme 13). The N-oxides of 4-hydroxyquinoline (61) were prepared through TFA-mediated cyclization of the corresponding Baylis-Hillman adduct 60.



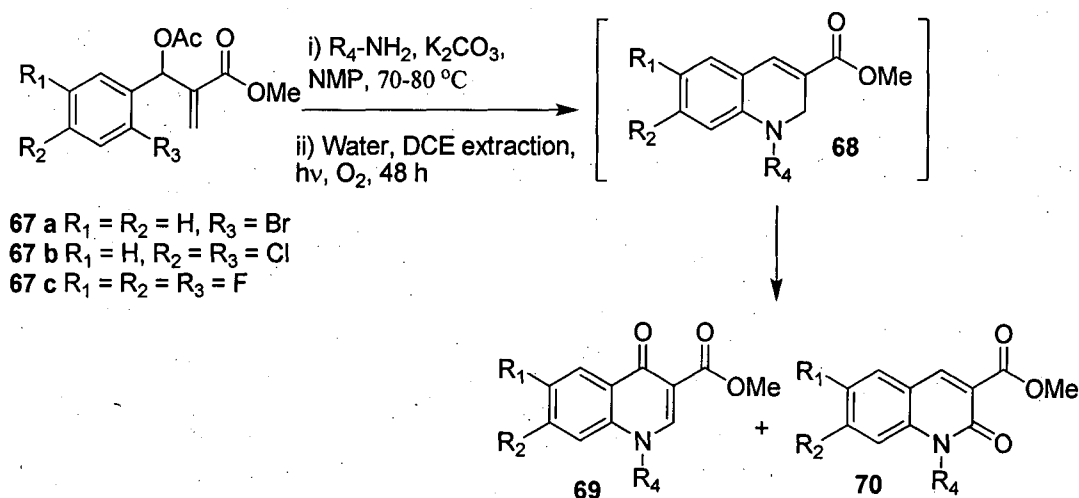
Scheme 13.

13) The patent application by Antoine et al. (U.S. Pat. No. 5,004,745) discloses the synthesis of benzonaphthyridones (66) from the intermediate 65 as shown in scheme 14.



Scheme 14.

14) Recently, we have developed a synthetic route towards 4- and 2-quinolones using Baylis-Hillman acetates and amines as the starting materials (John, N. and Muraleedharan, K. M. Synthesis 2011, 20, 3379-3388). This involves the initial formation of 1,2-dihydroquinolines (68) from Baylis-Hillman acetates and amines through $\text{S}_{\text{N}}2'$ - $\text{S}_{\text{N}}\text{Ar}$ cyclization steps. These intermediates (68) when exposed to light and oxygen gave both 4- and 2-quinolones through sensitized oxidation or a ($\Delta^{3,4}$ - $\Delta^{2,3}$ shift) $\rightarrow$ oxidation sequence (Scheme 15).

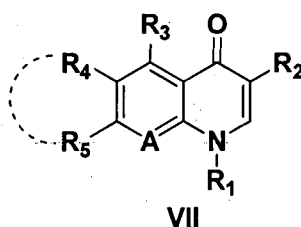


Scheme 15.

Multiple reaction steps, harsh reaction conditions, high temperature, toxic reagents, low yields or involvement of sensitive intermediates are some of the drawbacks of the above-mentioned methods, which need to be addressed. The synthetic strategy discussed in this invention is an entirely new approach and utilize Baylis-Hillman adducts and amines as the starting materials. The transformation involves a tandem Michael addition- S_NAr cyclization followed by oxidation, and is amenable for scale up.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a process for the synthesis of compounds of the general formula VII



Where, the substituent R_1 can be H, C_1 - C_{20} alkyl, C_1 - C_{20} aryl alkyl, C_3 - C_6 cycloalkyl, C_4 - C_6 heterocycloalkyl, C_1 - C_{20} alkoxy, $-NH_2$, $-NHR_1$, $-N(R_1)_2$, C_2 - C_{10} alkenyl, C_3 - C_{10} alkynyl, phenyl, 5 to 6-membered heteroaryl, bicyclic aromatic or heteroaromatic rings, biaryls or heteroatom substituted biaryls, optionally substituted with one or more of, including, but not limited to, the substituents, such as I, Br, Cl, F, lower alkyl groups such as C_1 - C_5 , alkoxy, cyano, nitro, amino. The term 'alkyl' denotes branched or straight-chain hydrocarbons, or hydrocarbon chains with saturated/unsaturated rings in-between or at the terminus.

R_2 represents an electron withdrawing group such as $-COOR_1$, $-CN$, $-NO_2$, $-CONH_2$, $-CONHR_1$, $-CON(R_1)_2$, $-CHO$, $-COR_1$, $-COSEt$, $-PO(OEt)_2$, $-PO(OMe)_2$, $-SO_2Ph$, $-SO_3Ph$ and $SOPh$ wherein R_1 is same as defined above.

R_3 represents all the substituents included under R_1 and others such as F, Cl, Br, I, C_1 - C_4 alkoxy, $-COR_1$, CN, NO_2 , NH_2 , $-NHR_1$, $-N(R_1)_2$.

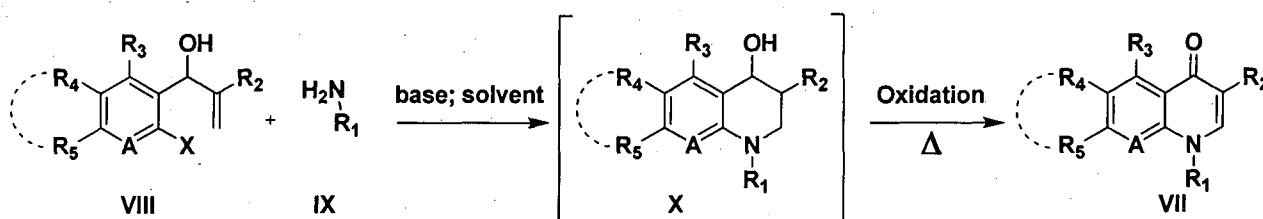
R₄ represents all the substituents included under R₁. This also includes -NO₂, -CN, -COR₁, aryl, heteroaryl, F, Cl, Br, I, -NH₂, -NHR₁, -N(R₁)₂.

R₅ represents all the substituents included under R₁. This also includes I, Br, Cl, F, C₁-C₁₀ alkoxy, cyano, NH₂, -NHR₁, -N(R₁)₂, or a compound with open chain, mono-, bi- or tricyclic saturated or unsaturated system with at least one ring with a nucleophilic atom such as nitrogen.

R₄ and R₅ can also be part of a mono- or polycyclic ring systems which are part of non-aromatic, aromatic and heteroaromatic compounds which is optionally substituted at one or more of the ring atoms with substituents mentioned under R₁ and others such as F, Cl, Br, I, C₁-C₄ alkoxy, -COR₁, CN, NO₂, NH₂, -NHR₁, -N(R₁)₂.

A can be CH, CF, CCl, CBr, Cl, CCN, C-R₁, N, COCH₃, C-NO₂, C-NH₂, C-NHR₁, C-N(R₁)₂.

The process for the preparation of VII involves reaction of Baylis-Hillman adducts (VIII) with various amines (IX) to effect aza-Michael addition and S_NAr cyclization and subsequent oxidation of the intermediate X to get the target skeleton VII (Scheme 16).



Scheme 16.

Baylis-Hillman adducts (VIII) were prepared in very good yields using the reported procedure which involves the reaction of substituted aromatic or heteroaromatic aldehydes with various Michael acceptors in presence of a base such as DABCO (Baylis and Hillman, German Patent 2,155,113 (1972)). These adducts were then

converted to the quinolones or naphthyridones in two steps (steps a and step b) as discussed below.

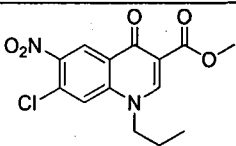
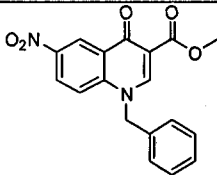
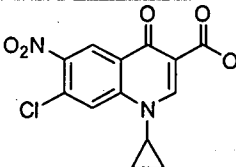
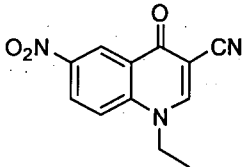
Step a) This involves heating a solution containing a mixture of the Baylis-Hillman adduct (VIII) and the desired amine (IX) in a polar solvent (eg. NMP) in presence of a base (eg. Et₃N) to get the 4-hydroxy-1,2,3,4-tetrahydroquinoline or 4-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridine derivative (X, scheme 16). Two equivalents each of the primary amine and the base were used in all the reactions and the reaction temperature and reaction time respectively ranged from room temperature to 70-80 °C and 1-12 h depending on the nature of the reactants.

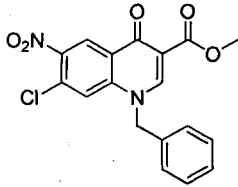
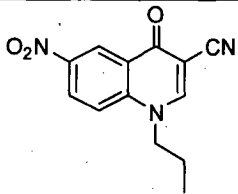
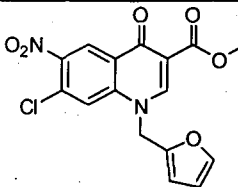
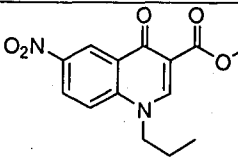
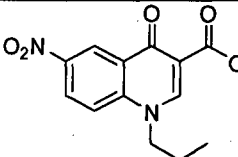
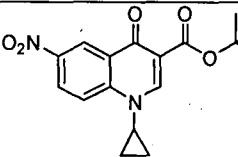
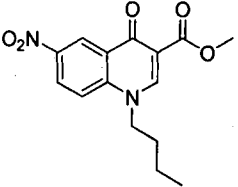
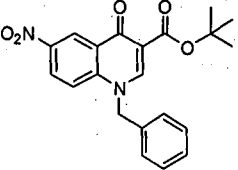
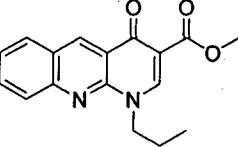
The solvent used in step a) include but not limited to, N-methylpyrrolidinone (NMP), N,N-dimethylformamide (DMF), N,N-dimethyl acetamide, nitromethane, acetonitrile, methanol, tertiary butanol, dimethylsulfoxide (DMSO), methyl tert-butyl ether, dimethoxyethane (DME), tetrahydrofuran (THF), dioxane, acetone, hexafluorobenzene, benzene, toluene, xylene, dichloromethane, dichloroethane, chloroform and ethyl acetate, butylacetate, their homologues, or a mixture of one or more of the above-mentioned solvents. Herein, NMP is the solvent of choice considering the efficiency and rate of Michael addition and S_NAr cyclisation steps. The bases used in this reaction includes, but not limited to amines such as triethyl amine, Diisopropyl ethyl amine (DIPEA), N-alkylpyrrolidines, N-alkyl morpholines, N-alkylpiperidines, 1,8-Diazabicycloundec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), pyridine, DMAP (N,N-dimethylaminopyridine), pyrimidine, N-alkylpyrrole, N-alkylindole, and N-alkylimidazole. Other bases include potassium carbonate, sodium carbonate, cesium carbonate, sodium tert-butoxide and potassium tert-butoxide.

Dilution of the reaction mixture with ethyl acetate followed by water wash and evaporation of the solvent gives a residue which can be directly taken forward for oxidation without purification. For extraction, chloroform or dichloromethane also can be used. The unreacted amine and the excess base present can be removed either during evaporation or by water work-up.

Step b) This step involves the oxidation of the intermediate X to the target skeleton VII. The solvent used in step b includes but not limited to the solvents mentioned under step (a). Other possible solvents are water, and ionic liquids such as [bmim]BF₄ and [bmim]PF₆. Alcoholic solvents such as methanol should be avoided due to their sensitivity to oxidation; acetonitrile was found superior to others in terms of the yields of products shown here. The preferred temperature of the reaction for the examples presented here ranged between 70-80 °C. The oxidising reagent can be selected from the group comprising of, but not limited to 2-iodoxybenzoic acid (IBX), Oxone and 2-iodoxybenzoic acid (IBX), Oxone and 2-iodo benzoic acid, Oxone and iodosobenzoic acid (IBA), N-methylmorpholine-N-oxide (NMO) and 2-iodoxybenzoic acid (IBX), 4-methoxypyridine-N-oxide (MPO) and 2-iodoxybenzoic acid (IBX), 2-iodoxybenzenesulfonic acid (IBS), 2-iodobenzenesulfonic acid and Oxone, sodium or potassium 2-iodobenzenesulfonate and Oxone; Dess-Martin periodinane or IBX substituted on the aromatic ring with one or more C1-C6 alkoxy chains, F, R₁, NO₂, COOH - N(R₁)₃ and mixtures thereof, wherein R₁ is defined as above (ref. Nicolaou, K. C. et al., Iodine(V) Reagents in Organic Synthesis. Part 4. o-Iodoxybenzoic Acid as a Chemospecific Tool for Single Electron Transfer-Based Oxidation Processes. J. Am. Chem. Soc. 2002, 124, 2245-2258); for the examples presented in table 1, IBX was found most appropriate. For the best results, 2-2.2 equivalents of IBX was necessary and the time taken for the complete oxidation varied from 5-24 h depending upon the substrates.

Table 1: List of quinolones and benzonaphthyridones synthesised

ry	Compound No.	Structures	Overall Yield ^a (%)	Entr y	Compound No.	Structures	Overall Yield ^a (%)
	VII-A		80	7	VII-G		70
	VII-B		74	8	VII-H		73

VII-C		77		9	VII-I		70
VII-D		87		10	VII-J		90
VII-E		86		11	VII-K		87
VII-F		83		12	VII-L		81
				13	VII-M		90

^a The overall yield starting from Baylis-Hillman adduct is presented here.

GENERAL EXPERIMENTAL PROCEDURE

The appropriate amine IX (2 mmol) was added to a stirred solution containing a mixture of Baylis-Hillman adduct VIII (1 mmol) and triethylamine (2 mmol) in N-methyl-2-pyrrolidinone (NMP; 3 mL). The mixture was heated at 70-75 °C until the starting materials were consumed, then cooled to room temperature, diluted with ethyl acetate (30 mL), and washed with water (3 x 20 mL). The organic layer was dried using sodium sulphate, filtered and evaporated under reduced pressure to

get a residue. This residue was dissolved in acetonitrile (20 mL), 2-iodoxybenzoic acid (IBX) (2.2 mmol) was added to it, and the mixture heated at 70-75 °C for 5-24 h. Once the starting materials were consumed, the byproduct was removed by filtration. The filtrate was diluted with ethyl acetate (20 mL) and washed with 10 % aq. NaHCO₃ solution (20 mL). The organic layer was dried using sodium sulphate, filtered and evaporated under reduced pressure and the residue was chromatographed on silica gel using ethyl acetate-hexanes mixture in a gradient mode to get the product. When the experiment was repeated in large scales (eg. Compound VIII-A), the column chromatographic purification was not necessary and the product was obtained in pure form by simple crystallization.

EXAMPLES

EXAMPLE 1

Methyl 7-chloro-6-nitro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (VII-A)

Methyl 2-((2,4-dichloro-5-nitrophenyl)(hydroxy)methyl)acrylate (1 g, 3.28 mmol) was reacted with propylamine (0.39 g, 0.54 mL, 6.56 mmol) in presence of triethylamine (0.9 mL, 6.56 mmol) in NMP (10 mL) at 75 °C for 1 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (2 g, 7.14 mmol) by heating the mixture for 12 h according to the general procedure discussed above to get VII-A (850 mg, 80% yield) as a pale yellow crystalline solid. HRMS (ESI) exact mass calcd. for C₁₄H₁₄N₂O₅Cl [M+H]⁺ 325.0591, found [M+ H]⁺ 325.0588.

EXAMPLE 2

Methyl 7-chloro-1-cyclopropyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (VII-B)

methyl 2-((2,4-dichloro-5-nitrophenyl)(hydroxy)methyl)acrylate (0.2 g, 0.66 mmol) was reacted with cyclopropylamine (0.075 g, 0.091 mL, 1.32 mmol) in presence of triethylamine (0.2 mL, 1.47 mmol) in NMP (2 mL) at 70 °C for 7 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (407 mg, 1.45 mmol) by heating the mixture for 20 h according to the general procedure discussed above to get VII-B (78 mg, 74% yield) as a pale yellow crystalline solid. HRMS (ESI) exact mass calcd. for C₁₄H₁₄N₂O₅Cl [M+H]⁺ 325.0591, found [M+H]⁺ 325.0580.

EXAMPLE 3

Methyl 1-benzyl-7-chloro-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (VII-C)

Methyl 2-((2,4-dichloro-5-nitrophenyl)(hydroxy)methyl)acrylate (0.2 g, 0.66 mmol) was reacted with benzylamine (0.141 g, 0.144 mL, 1.32 mmol) in presence of triethylamine (0.2 mL, 1.47 mmol) in NMP (2 mL) at 75 °C for 4 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (407 mg, 1.45 mmol) by heating the mixture for 24 h according to the general procedure discussed above to get VII-C (188 mg, 77% yield) as a pale yellow crystalline solid. HRMS (ESI) exact mass calcd. for $C_{18}H_{14}N_2O_5Cl$ $[M+H]^+$ 373.0591, found $[M+H]^+$ 373.0575.

EXAMPLE 4

Methyl 7-chloro-1-(furan-2-ylmethyl)-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (VII-D)

Methyl 2-((2,4-dichloro-5-nitrophenyl)(hydroxy)methyl)acrylate (0.2 g, 0.66 mmol) was reacted with furfurylamine (0.128 g, 0.117 mL, 1.32 mmol) in presence of triethylamine (0.2 mL, 1.47 mmol) in NMP (2 mL) at 75 °C for 4 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (407 mg, 1.45 mmol) by heating the mixture for 10 h according to the general procedure discussed above to get VII-D (206 mg, 87% yield) as a pale yellow crystalline solid. HRMS (ESI) exact mass calcd. for $C_{16}H_{12}N_2O_6Cl$ $[M+H]^+$ 363.0384, found $[M+H]^+$ 363.0366.

EXAMPLE 5

Methyl 6-nitro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (VII-E)

Methyl 2-((2-chloro-5-nitrophenyl)(hydroxy)methyl)acrylate (0.2 g, 0.74 mmol) was reacted with propylamine (0.087 g, 0.12 mL, 1.48 mmol) in presence of triethylamine (0.2 mL, 1.47 mmol) in NMP (2 mL) at 75 °C for 12 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (456 mg, 1.63 mmol) by heating the mixture for 12 h according to the general procedure discussed above to get VII-E (184 mg, 86% yield) as a pale yellow crystalline solid. HRMS (ESI) exact mass calcd. for $C_{14}H_{15}N_2O_5$ $[M+H]^+$ 291.0981, found $[M+H]^+$ 291.0969.

EXAMPLE 6

Methyl 1-butyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (VII-F)

Methyl 2-((2-chloro-5-nitrophenyl)(hydroxy)methyl)acrylate (0.2 g, 0.74 mmol) was reacted with butylamine (0.108 g, 0.146 mL, 1.48 mmol) in presence of triethylamine (0.2 mL, 1.47 mmol) in NMP (2 mL) at 75 °C for 3 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (456 mg, 1.63 mmol) by heating the mixture for 12 h according to the general procedure discussed above to get VII-F (186 mg, 83% yield) as a pale yellow crystalline solid.

R_f (20% EtOAc/hexanes) = 0.67; mp 142-144 °C; ^1H NMR (400 MHz, CDCl_3) δ 9.17 (s, 1H, $-\text{C}_2\text{H}$), 8.46 (s, 1H, ArH), 8.40 (dd, 1H, ArH, $J = 9.3, 2.6$ Hz), 7.58 (d, 1H, ArH, $J = 9.3$ Hz), 4.24 (t, 2H, $\text{N}-\text{CH}_2-\text{CH}_2$, $J = 7.2$ Hz), 3.88 (s, 3H, $-\text{OCH}_3$), 1.88 (pentet, 2H, $\text{CH}_2-\text{CH}_2-\text{CH}_2$, $J = 7.2$ Hz), 1.60-1.40 (m, 2H, $\text{CH}_2-\text{CH}_2-\text{CH}_3$), 0.99 (t, 3H, CH_2-CH_3 , $J = 7.2$ Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 173.0, 165.2, 150.2, 144.3, 142.6, 129.0, 126.9, 124.2, 117.5, 112.1, 54.5, 52.3, 30.9, 20.0, -13.6 ppm; IR (KBr) cm^{-1} : 2962, 1690, 1648, 1613, 1556, 1515, 1485, 1334, 1231, 1200, 1157, 1125, 1065, 837; HRMS (ESI) exact mass calcd. for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 305.1137, found $[\text{M}+\text{H}]^+$ 305.1133.

EXAMPLE 7

Methyl 1-benzyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (VII-G)

Methyl 2-((2-chloro-5-nitrophenyl)(hydroxy)methyl)acrylate (0.2 g, 0.74 mmol) was reacted with benzylamine (0.159 g, 0.162 mL, 1.48 mmol) in presence of triethylamine (0.2 mL, 1.47 mmol) in NMP (2 mL) at 75 °C for 5 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (456 mg, 1.63 mmol) by heating the mixture for 20 h according to the general procedure discussed above to get VII-G (174 mg, 70% yield) as a pale yellow crystalline solid. HRMS (ESI) exact mass calcd. for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 339.0981, found $[\text{M}+\text{H}]^+$ 339.0992.

EXAMPLE 8

1-ethyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carbonitrile (VII-H)

2-((2-chloro-5-nitrophenyl)(hydroxy)methyl)acrylonitrile (0.2 g, 0.84 mmol) was

reacted with ethylamine (0.108 g, 0.09 mL, 1.68 mmol) in presence of triethylamine (0.24 mL, 1.68 mmol) in NMP (2 mL) at 75 °C for 2 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (518 mg, 1.85 mmol) by heating the mixture for 24 h according to the general procedure discussed above to get VII-H (148 mg, 73% yield) as a pale yellow crystalline solid. HRMS (ESI) exact mass calcd. for $C_{12}H_9N_3O_3K$ $[M+K]^+$ 282.0281, found $[M+K]^+$ 282.0293.

EXAMPLE 9

6-nitro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carbonitrile (VII-I)

2-((2-chloro-5-nitrophenyl)(hydroxy)methyl)acrylonitrile (0.2 g, 0.84 mmol) was reacted with propylamine (0.099 g, 0.138 mL, 1.68 mmol) in presence of triethylamine (0.24 mL, 1.68 mmol) in NMP (2 mL) at 75 °C for 10 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (518 mg, 1.85 mmol) by heating the mixture for 12 h according to the general procedure discussed above to get VII-I (151 mg, 70% yield) as a pale yellow crystalline solid. HRMS (ESI) exact mass calcd. for $C_{13}H_{11}N_3O_3K$ $[M+K]^+$ 296.0437, found $[M+K]^+$ 296.0437.

EXAMPLE 10

tert-butyl 6-nitro-4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylate (VII-J)

tert-butyl 2-((2-chloro-5-nitrophenyl)(hydroxy)methyl)acrylate (0.2 g, 0.64 mmol) was reacted with propylamine (0.076 g, 0.105 mL, 1.28 mmol) in presence of triethylamine (0.2 mL, 1.47 mmol) in NMP (2 mL) at 75 °C for 4 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (393 mg, 1.41 mmol) by heating the mixture for 10 h according to the general procedure discussed above to get VII-J (191 mg, 90% yield) as a pale yellow crystalline solid. HRMS (ESI) exact mass calcd. for $C_{17}H_{21}N_2O_5$ $[M+H]^+$ 333.1450, found $[M+H]^+$ 333.1467.

EXAMPLE 11

tert-butyl 1-cyclopropyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (VII-K)

tert-butyl 2-((2-chloro-5-nitrophenyl)(hydroxy)methyl)acrylate (0.2 g, 0.64 mmol) was reacted with cyclopropylamine (0.073 g, 0.089 mL, 1.28 mmol) in presence of triethylamine (0.2 mL, 1.47 mmol) in NMP (2 mL) at 75 °C for 12 h and the resulting

4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (393 mg, 1.41 mmol) by heating the mixture for 12 h according to the general procedure discussed above to get VII-K (183 mg, 87% yield) as a pale yellow crystalline solid. HRMS (ESI) exact mass calcd. for $C_{17}H_{19}N_2O_5$ $[M+H]^+$ 331.1294, found $[M+H]^+$ 331.1285.

EXAMPLE 12

tert-butyl 1-benzyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (VII-L)

tert-butyl 2-((2-chloro-5-nitrophenyl)(hydroxy)methyl)acrylate (0.2 g, 0.64 mmol) was reacted with benzylamine (0.137 g, 0.140 mL, 1.27 mmol) in presence of triethylamine (0.2 mL, 1.47 mmol) in NMP (2 mL) at 75 °C for 8 h and the resulting 4-hydroxy-1,2,3,4-tetrahydroquinoline derivative was oxidized using IBX (393 mg, 1.41 mmol) by heating the mixture for 24 h according to the general procedure discussed above to get VII-L (196 mg, 81% yield) as a pale yellow crystalline solid. HRMS (ESI) exact mass calcd. for $C_{21}H_{21}N_2O_5$ $[M+H]^+$ 381.1450, found $[M+H]^+$ 381.1455.

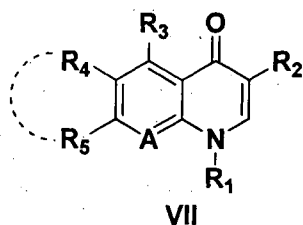
EXAMPLE 13

methyl 4-oxo-1-propyl-1,4-dihydrobenzo[b][1,8]naphthyridine-3-carboxylate (VII-M)

Methyl 2-((2-chloroquinolin-3-yl)(hydroxy)methyl)acrylate (0.1 g, 0.36 mmol) was reacted with propylamine (0.042 g, 0.060 mL, 0.72 mmol) in presence of triethylamine (0.1 mL, 0.7 mmol) in NMP (1 mL) at 75 °C for 5 h and the resulting 4-hydroxytetrahydro naphthyridine derivative was oxidized using IBX (222 mg, 0.79 mmol) by heating the mixture for 8 h according to the general procedure discussed above to get VII-M (96 mg, 90% yield) as a colourless crystalline solid. HRMS (ESI) exact mass calcd. for $C_{17}H_{17}N_2O_3$ $[M+H]^+$ 297.1239, found $[M+H]^+$ 297.1224.

CLAIMS:

1. Quinolones and naphthyridones of the general formula VII



in which,

the substituent R_1 can be H, C_1 - C_{20} alkyl, C_1 - C_{20} aryl alkyl, C_3 - C_6 cycloalkyl, C_4 - C_6 heterocycloalkyl, C_1 - C_{20} alkoxy, $-NH_2$, $-NHR_1$, $-N(R_1)_2$, C_2 - C_{10} alkenyl, C_3 - C_{10} alkynyl, phenyl, 5 to 6-membered heteroaryl, bicyclic aromatic or heteroaromatic rings, biaryls or heteroatom substituted biaryls, optionally substituted with one or more of, substituents such as I, Br, Cl, F, lower alkyl groups such as C_1 - C_5 , alkoxy, cyano, nitro, amino.

R_2 represents an electron withdrawing group such as $-COOR_1$, $-CN$, $-NO_2$, $-CONH_2$, $-CONHR_1$, $-CON(R_1)_2$, $-CHO$, $-COR_1$, $-COSEt$, $-PO(OEt)_2$, $-PO(OMe)_2$, $-SO_2Ph$, $-SO_3Ph$ and $SOPh$ wherein R_1 is same as defined above.

R_3 represents all the substituents included under R_1 and others such as F, Cl, Br, I, C_1 - C_4 alkoxy, $-COR_1$, CN , NO_2 , NH_2 , $-NHR_1$, $-N(R_1)_2$.

R_4 represents all the substituents included under R_1 , further including NO_2 , CN , $-COR_1$, aryl, heteroaryl, F, Cl, Br, I, $-NH_2$, $-NHR_1$, $-N(R_1)_2$.

R_5 represents all the substituents included under R_1 , further including I, Br, Cl, F, C_1 - C_{10} alkoxy, cyano, NH_2 , $-NHR_1$, $-N(R_1)_2$, or a compound with open chain, mono-, bi- or tricyclic saturated or unsaturated system with at least one ring with a nucleophilic atom such as nitrogen.

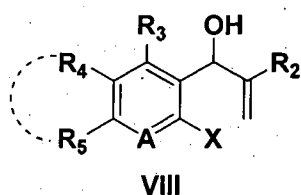
R_4 and R_5 may be part of a mono- or polycyclic ring system which are part of non-aromatic, aromatic and heteroaromatic compounds which is optionally substituted at one or more of the ring atoms with substituents mentioned under R_1 and others such as F, Cl, Br, I, C_1 - C_4 alkoxy, $-COR_1$, CN , NO_2 , NH_2 , $-NHR_1$, $-N(R_1)_2$.

A can be CH, CF, CCl, CBr, Cl, CCN, C- R_1 , N, $COCH_3$, C- NO_2 , C- NH_2 , C- NHR_1 , C- $N(R_1)_2$.

2. The quinolones and naphthyridones of the general formula VII as claimed in claim 1, wherein 'alkyl' denotes branched or straight-chain hydrocarbons with or without heteroatoms in-between, or hydrocarbon chains with saturated/unsaturated rings in-between or at the terminus, and wherein the term 'alkoxy' refers to the group $-OR_1$ where R_1 represents all the groups defined under the formula (VII)

3. A process for preparing quinolones and naphthyridones of the general formula VII comprising the steps:

a) Reacting Baylis-Hillman adduct of formula (VIII)

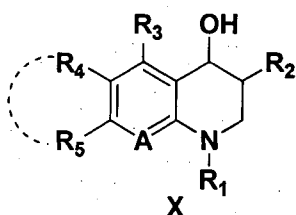


in which R_2 , R_3 , R_4 , R_5 and A each are as defined under the formula (VII) and X represents I, Br, Cl, F, OTs, OTf. R_4 can be H or R_1 if A represents a hetero-atom such as N. If A is CH, R_4 need to be an electron withdrawing substituent such as NO_2 , CN, COR_1 etc.

with an amine of formula IX

R_1-NH_2 ----- (IX), in which R_1 is as defined under formula (VII)

in the presence of a base to produce 4-hydroxy-1,2,3,4-tetrahydroquinoline or 4-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridine derivative of the general formula X



in which R_1 , R_2 , R_3 , R_4 , R_5 and A are each as defined under formulas (VII) & (VIII), and

b) Subjecting 4-hydroxy-1,2,3,4- tetrahydroquinoline or 4-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridine derivative of the formula X to oxidation with an oxidizing agent to produce the quinolone or naphthyridone derivative of formula VII

4. The process as claimed in claim 3, wherein the intermediate of the general

formula X obtained after step a) was taken to the next step without chromatographic purification.

5. The process as claimed in claim 3, wherein the solvent used in step a) is selected from a group comprising of N-methylpyrrolidinone (NMP), N,N-dimethylformamide (DMF), N,N-dimethyl acetamide, nitromethane, acetonitrile, methanol, tertiary butanol, dimethylsulfoxide (DMSO), methyl tert-butyl ether, dimethoxyethane (DME), tetrahydrofuran (THF), dioxane, acetone, hexafluorobenzene, benzene, toluene, xylene, dichloromethane, dichloroethane, chloroform and ethyl acetate, butylacetate, their homologues, or a mixture of one or more of the above-mentioned solvents.

6. The process as claimed in claim 3, wherein the solvent used in step b) is selected from a group of solvents comprising of N-methylpyrrolidinone (NMP), N,N-dimethylformamide (DMF), N,N-dimethyl acetamide, nitromethane, acetonitrile, tertiary butanol, dimethylsulfoxide (DMSO), methyl tert-butyl ether, dimethoxyethane (DME), tetrahydrofuran (THF), dioxane, acetone, hexafluorobenzene, water, ionic liquids such as [bmim]BF₄, [bmim]PF₆, benzene, toluene, xylene, dichloromethane, dichloroethane, chloroform and ethyl acetate, butylacetate, their homologues, or a mixture of one or more of the above-mentioned solvents.

7. The process as claimed in claim 3 wherein the step a) is carried out at a temperature ranging from 25 °C to 80 °C, and the step b) is carried out at a temperature ranging from 25 °C to 80 °C.

8. The process as claimed in claim 3, wherein the reaction time for step a) range from 1-12 h and that of step b) range from 5-24 h.

9. The process as claimed in claim 3, wherein the base used includes amines such as triethylamine, Diisopropylethylamine (DIPEA), N-alkylpyrrolidines, N-alkyl morpholines, N-alkylpiperidines, 1,8-Diazabicycloundec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), pyridine, DMAP (N, N-dimethylamino pyridine), pyrimidine, N-alkylpyrrole, N-alkylindole, and N-alkylimidazole. Other bases include potassium carbonate, sodium

carbonate, cesium carbonate, sodium tert-butoxide and potassium tert-butoxide.

10. The process as claimed in claim 3, the oxidising agent used in step b) can be selected from the group comprising of, but not limited to 2-iodoxybenzoic acid (IBX), Oxone and 2-iodoxybenzoic acid (IBX), Oxone and 2-iodobenzoic acid, Oxone and iodosobenzoic acid (IBA), N-methylmorpholine-N-oxide (NMO) and 2-iodoxybenzoic acid (IBX), 4-methoxypyridine-N-oxide (MPO) and 2-iodoxybenzoic acid (IBX), 2-iodoxybenzenesulfonic acid (IBS), 2-iodobenzenesulfonic acid and Oxone, sodium or potassium 2-iodobenzenesulfonate and Oxone; Dess-Martin periodinane or IBX substituted on the aromatic ring with one or more C₁-C₆ alkoxy chains, F, NO₂, COOH, R₁, -N(R₁)₃ and mixtures thereof wherein R₁ is defined as above.

11. The process as claimed in claim 3, the amines of the general formula R₁-NH₂ used in step a) possess the same R₁ groups as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2013/000199A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/233 C07D471/04
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)
C07D

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, WPI Data, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOHN NAPOLEON ET AL: "Direct Transformation of Baylis-Hillman Acetates into N-Substituted Quinolones through an SN2' -> SNAr -> ([Delta]3,4-[Delta]2,3 Shift) -> Oxidation Sequence", SYNTHESIS, vol. 2011, no. 20, 1 October 2011 (2011-10-01), pages 3379-3388, XP055073288, ISSN: 0039-7881, DOI: 10.1055/s-0030-1260189 table 2 ----- -/--	1-11



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

"E" earlier application or patent but published on or after the international filing date

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2013/000199

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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X	ORIANA TABARRINI ET AL: "Structure Modifications of 6-Aminoquinolones with Potent Anti-HIV Activity 1", JOURNAL OF MEDICINAL CHEMISTRY, vol. 47, no. 22, 1 October 2004 (2004-10-01), pages 5567-5578, XP055073348, ISSN: 0022-2623, DOI: 10.1021/jm049721p table 1 -----	1,2
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Information on patent family members

International application No

PCT/IN2013/000199

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