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DEVELOPMENTS IN QUINOLINE SYNTHESIS: A REVIEW

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ABSTRACT
Quinoline ring structure is obtained by *o*-condensation of benzene ring with pyridine. It is also called l-azanaphthalene or benzo[b]pyridine. Since first synthesis quinoline, number of methods has been discovered to enhance reaction yield, decrease reaction time as well as reduce hazardous reagents and reaction conditions. Compound with quinoline core are widely used for industrial purposes and also exhibit a broad range of biological activities. An overview of synthetic methodologies used for the construction of quinoline ring is also described.

Keywords: Quinoline, pharmacological activity, synthetic methodology, micelles.

Introduction

Heterocyclic form the largest of the classical divisions of organic chemistry. Besides, they are of immense importance not only both biologically and industrially but to the functioning of any developed human society as well. The most of pharmaceutical products that mimic natural products with biological activity are heterocycles. Many of the important advances against disease have been made by designing and testing new structures, which are frequently heterocyclic derivatives. Now, it is well accepted fact that the physiological or biological property of a compound depends upon three factors. The first and perhaps most important is the heterocyclic moiety present in the particular compound. The second factor is the nature of the substituents and the third factor is the position of the substituents. Many heterocycles and their derivatives of different oxidation level are well known. Naturally occurring nitrogen, oxygen and sulfur-containing heterocyclic compounds perform important biological functions in nature.
Quinoline is a hygroscopic, unpleasant-smelling, colorless, oily liquid. It found in coal tar and bone oil, and is synthesized from phenyl amine and nitrobenzene. Quinoline is a basic compound and so forms salts with mineral acids also it forms quaternary ammonium compounds with haloalkanes. Quinine, a member of the cinchona alkaloid family, is one of the oldest antimalarial agents and was first extracted from cinchona tree bark in the late 1600s. The cinchona species is native to the Andean region of South America, but when its

therapeutic potential was realized, Dutch and British colonialists quickly established plantations in their south-east Asian colonies. It was first isolated by Runge in 1834, from coal tar bases and subsequently Gerhardt in 1842 obtained it from the alkaline pyrolysis of cinchonine which is an alkaloid related to quinoline hence the name quinoline is derived. The word quinine is derived from *quina* a Spanish version of a local South American name for the bark of quinine-containing Cinchona species. It is used for synthesis of medicines and dyes. Quinolines and their derivatives are receiving increasing importance due to their wide range of biological and pharmacological activities. Quinoline ring structure is obtained by *o*-condensation of benzene ring with pyridine. It is also called l-azanaphthalene or benzo[b]pyridine. In quinoline, the nitrogen atom is one atom away from the position at which the rings are fused. In an isomer, isoquinoline, the nitrogen atom is positioned two atoms away from the fused ring. The numbering in quinoline starts from the nitrogen atom which is assigned first position.

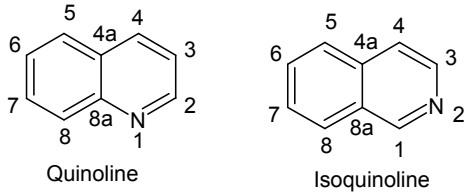


Figure-1: Quinoline and Isoquinoline

Molecular structure and general properties of Quinoline

Quinoline and isoquinoline are related to pyridine exactly as benzene related to naphthalene i.e. both the molecules contain 10 π electrons. The presence of electron donating groups at 2- and 4-positions of quinoline ring increases its basicity. The pyridine ring of quinoline is electron deficient. Hence, 2- and 4 positions are favorable for nucleophilic attack. The π-electron densities have been calculated for quinoline by the molecular orbital method and show that these two positions are electron deficiency. The electrophilic attack preferentially takes place at 5 and 8-positions of Quinoline because for pyridine the lone pair of electrons on the nitrogen atom is not involved in resonance. Quinoline is an aromatic compound having 47.3 kcal/mol resonance energy. The valence bond description of quinoline shows two of the neutral contributors, (1) and (3), to the resonance hybrid as quinonoid in character, whereas in (Fig-2) the heterocycle must exist in the form of a 1,3-diene. The presence of the pyridine nucleus is reflected by the inclusion of doubly charged canonical forms.

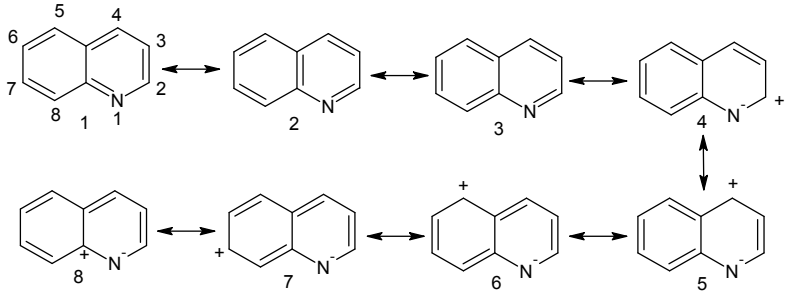
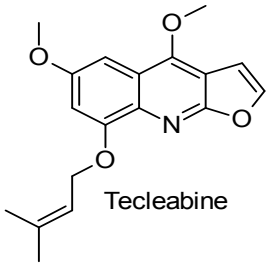


Figure-2: Resonance in Quinoline

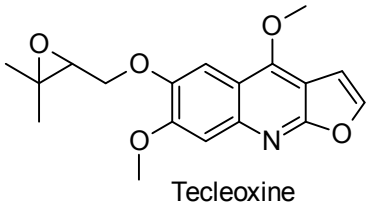
However, the representations (6) to (8) involve disruption of both monocyclic π systems simultaneously, it follows that these resonance structures are of higher energy contribute very much less to the overall description of the molecule than do the alternatives (4) and (5) that affect only the pyridine system. The bond lengths of quinolines, which are irregular which support the resonance description thus the 1-2, 5-6 and 7-8 bonds are little shorter than that of the carbon-carbon bond in benzene means quinoline show more double bond character. Dipole moment of Quinoline is 2.9 D which is directed towards the nitrogen atom.

Quinoline-based Natural and Synthetic Products

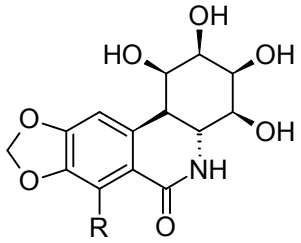
Research in the synthesis of newer and novel heterocycles is an ever aspiring area, as they are widely prevalent in nature and plays a pivotal role in the pharmaceutical and drug industry. Because of their ability to mimic the structure of peptides and binding to proteins, functionalized heterocycles are interesting scaffolds for the preparation of diversity-oriented compound libraries for medicinal and pharmaceutical applications. Among heterocycles quinoline derivatives are one of the most important structural moiety, being widespread in nature and present as a key structural component in a large number of families of biologically active compounds. Several quinoline derivatives isolated from natural resources or prepared synthetically are significant with respect to medicinal chemistry and biomedical use. Quinoline and quinolinone ring systems are present in a diverse array of natural products such as tecleabine, tecleoxime, pancratistatin, plakinidine and quinine.



Tecleabine

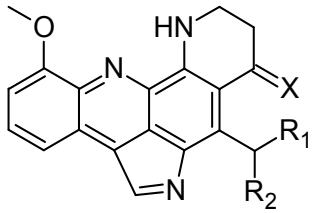


Tecleoxine



R = OH, Pancratistatin

R = H, 7-Deoxypancratistatin

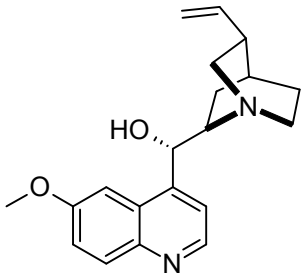


R_1 = H, R_2 = Me, X = O, Plakinidine A

R_1 = Me, R_2 = Me, X = O, Plakinidine B

R_1 = H, R_2 = Me, X = O, (9,10-Didehydro)Plakinidine C

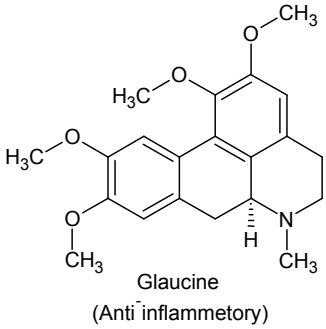
R_1 = H, R_2 = H, X = O, Plakinidine D



Quinine

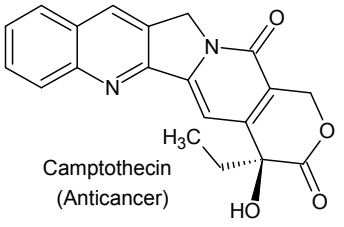
Figure-3: Naturally occurring Quinoline containing natural products

Quinoline and its derivatives are used for the preparation of many nano- and mesostructures having enhanced biological as well as photophysical properties.[I] Quinolines and their derivatives are very important compounds because of their wide occurrence in natural products and biologically active compounds.[II]



Glaucine

(Anti inflammetory)



Camptothecin

(Anticancer)

Figure-4: Quinoline alkaloids having pharmacological activity

The quinoline nucleus can also be frequently recognized in the structure of numerous naturally occurring alkaloids having interesting pharmacological activity. A large variety of quinolines have displayed interesting physiological activities and found important applications as pharmaceuticals and agrochemicals, as well as in general synthetic building blocks. Often the type and degree of substitution of the quinoline ring has a profound effect on the biological activity. In 1934 Chloroquine was first synthesized and became the most widely used antimalarial drug by the 1940s.[III] The success of this class has been based on better clinical efficacy, minimum host toxicity and cost-effective synthesis.[IV] However, the value of quinoline-based antimalarials has been seriously eroded in recent years, mainly because of the development and spread of parasitic resistance.[V]

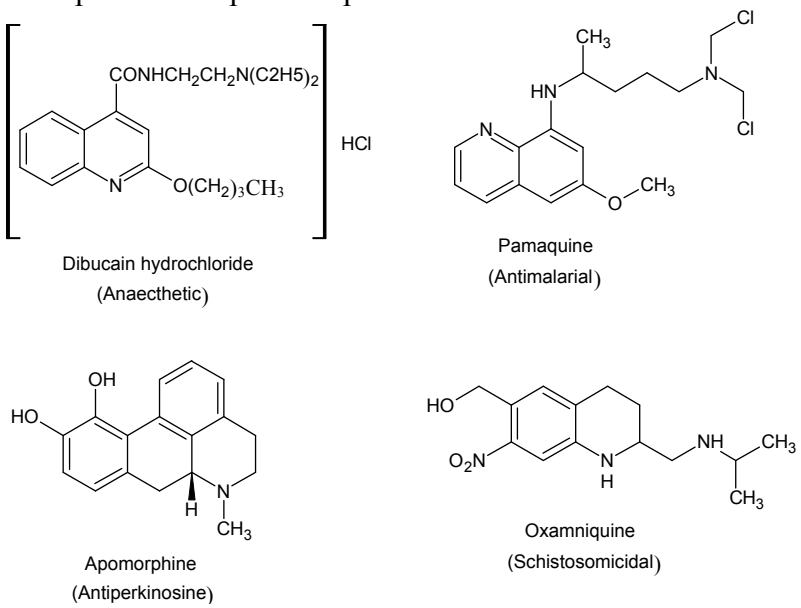


Figure-5: Clinically used synthetic quinolines

Although much of the current research effort is directed to the identification of novel chemotherapeutic targets, it is not fully understood the mode of action and the complete mechanism of resistance to the quinoline compounds, this knowledge would help to the design of novel, potent and inexpensive alternative quinoline antimalarials. Some pharmacologically useful quinoline derivatives such as Dibucaine hydrochloride is an anaesthetic, Apomorphine **is** antiperkinosine, Pamaquine is an antimalarial agent and Oxamniquine is schistosomicidal.

Major quinoline research has been focused on pharmaceuticals. Some of the important targets have included treatment of parasitic infections such as Malaria and Leishmaniasis as well as Antitumor agents such as Sterionigrin , Dynemicin A, Luotonin and Camptothecin**.**[IV-IX] Isolation of natural product and biological activity assays continue to identify new potentially important Quinoline alkaloids from both plants as well as marine animals**.**[X-XX]

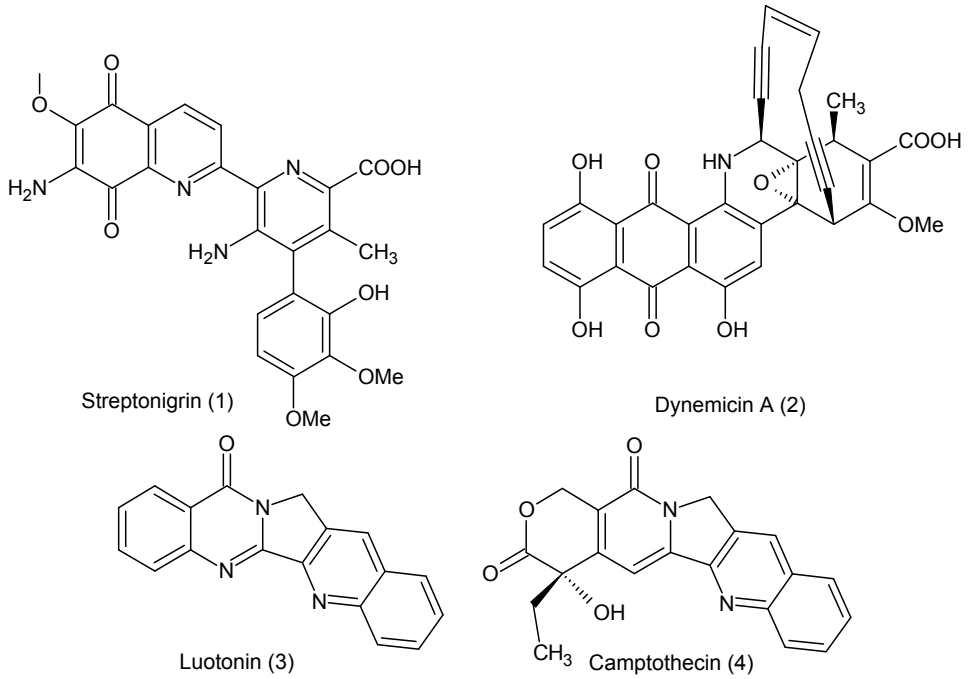


Figure-6: Quinoline-based Natural Product

General Methods of Preparation

The early work was concentrated on fight against Malaria a fight yet this going on. Even with centuries of work on quinine[XXI] its asymmetric synthesis was only recently achieved by Strok.[XXII] New techniques have been generated quinoline's heterocyclic ring synthesis. In order to categorize each of the new quinoline synthesis techniques, it is necessary to compare them to the classical methods. To date, there are six named reactions used to generate the quinoline ring system. Those named reactions can be broken down into two classes based on the substitution pattern of the starting materials. [XXIII] Those begin with unsubstituted anilines include the Skraup, Doebner-von Miller, Conrad-Limpach-Knorr, and Combes synthesis. Those synthesis begin with ortho-substituted anilines include the Friedlander, Pfitzinger, Niemantowski and Borsche synthesis. Although each technique has its own set of advantages and limitations, the Skraup and Friedlander work set the baseline for all other variations.

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1. SKRAUP AND SKRAUP-LIKE TECHNIQUES

The Skraup, Doebner-von Miller, Conrad-Limpach-Knorr and Combes synthesis each start with Aniline as the nucleophilic nitrogen component, and vary in the additional electrophilic 3-carbon piece added (Scheme 1). In the Skraup synthesis [XXIV] Aniline was heated with Glycerin, Sulfuric acid and an oxidizing agent, such as Nitrobenzene, to form quinoline. Doebner and von Miller [XXV] substituted 1,2-Glycols or α,β-unsaturated aldehydes for the Glycerine, to condense with the aniline to form the same pyridinoid ring. The Conrad-Limpach-Knorr reaction used acetoacetic esters [XXVI-XXVII] and the Combes method [XXVIII] involved heating Aniline with Acetylacetone.

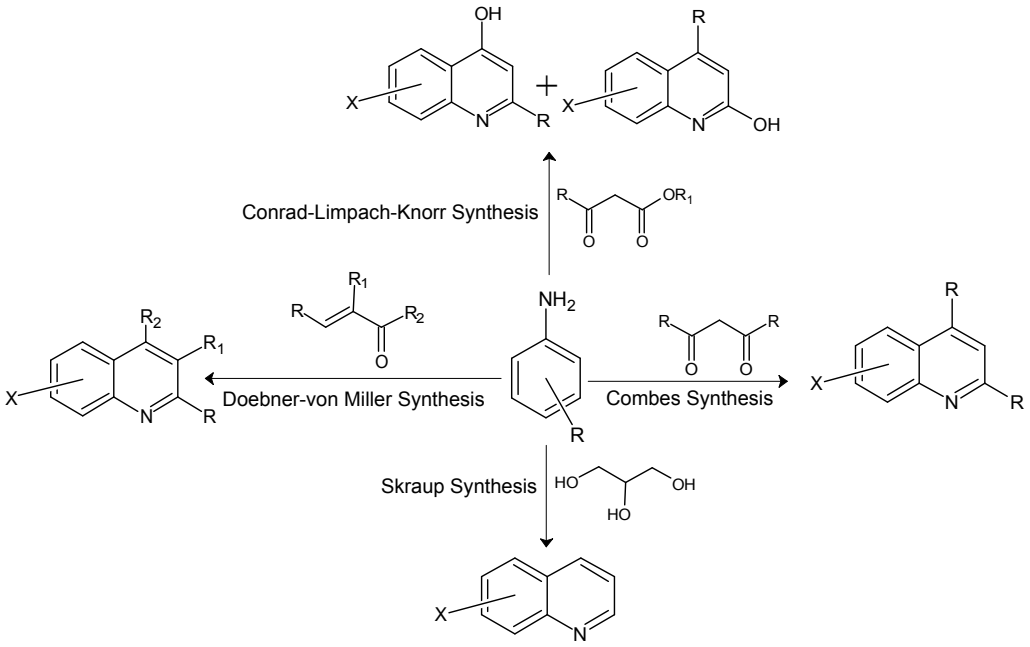

Figure 7: **More Quinoline-based Product Targets**

2. Wrobel quinoline synthesis

The harsh conditions required for these reactions—high temperatures and highly acidic medium have prompted considerable work in modifying the procedure to find milder, yet regiospecific conditions. In 2002, Theoclitou and coworkers used microwaves to shorten the times of Skraup reactions from 60 hours down to 1 hour with similar yields. Since this improvement was not sufficient for their goal of developing a combinatorial Skraup synthesis, they also developed a route using Scandium triflate catalysis. This improved the yield significantly, and along with the microwave assistance, produced the desired Skraup reaction products at room temperature, in an expedient manner. [XXIX]

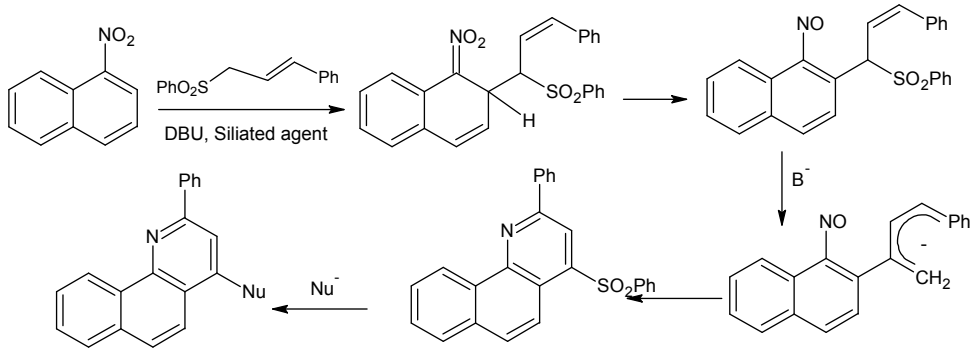

Figure-8: Synthesis of 2-Arylquinolines

In 1998, Wrobel developed a quinoline synthesis analogous to the Skraup synthesis, switching the polarity of the two components. He used nitroarenes as an electrophilic nitrogen source and cinnamyl phenyl sulfone, which under mildly basic conditions formed a nucleophilic three-carbon unit. This procedure formed 2-phenyl, -4-phenylsulfonyl quinolines which could be treated with various nucleophiles to undergo SNAr reactions with the phenyl sulfone to generate 2-arylquinolines with a variety of substituents at 4th position. [XXX]

3. Modified Skraup synthesis

Ila and co-workers developed a modified Skraup synthesis using 3-bis(methylthio)acrolein as a "surrogate" acrolein, which was synthesized from vinyl acetate.[XXXI] This mild method was an improvement over their previous work which used a similar oxoketene-N,S-anilinoacetal

in a regioselective synthesis of functionalized quinolines through Vilsmeier cyclization (Scheme 11, lower equation). Both cyclizations were facile with N,S-acetals of aniline bearing strongly activating groups. The resulting 2-methylthio-quinolines could be further manipulated, by dethiomethylation with Raney nickel, or replaced by various 15 nucleophiles to generate 2-alkyl, aryl or amino quinolines [XXXII-XXXIII] Wang also reported using remarkably similar aroylketene dithioacetals with o-aminobenzoic acids to generate 2-methylthio-3-aroylquinolones.[XXXIV]

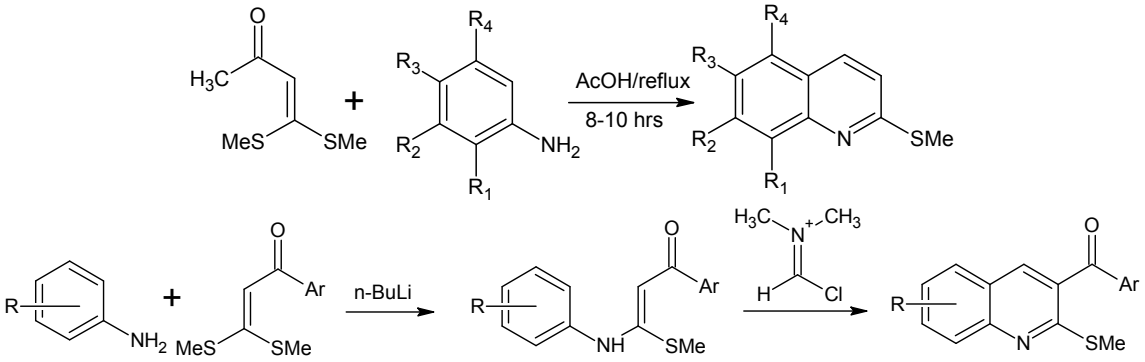

Figure-9: Synthesis of 2-methylthio-3-aroylquinolones

4. Improved Vilsmeier-type cyclization

Katritzky improved Vilsmeier-type cyclization by using benzotriazole iminium salts and N-arylimines. Then resultant vinamidium salts were readily transformed into 2- and 3-alkyl quinolines through a tandem cyclization elimination process in refluxing THF.[XXXV]

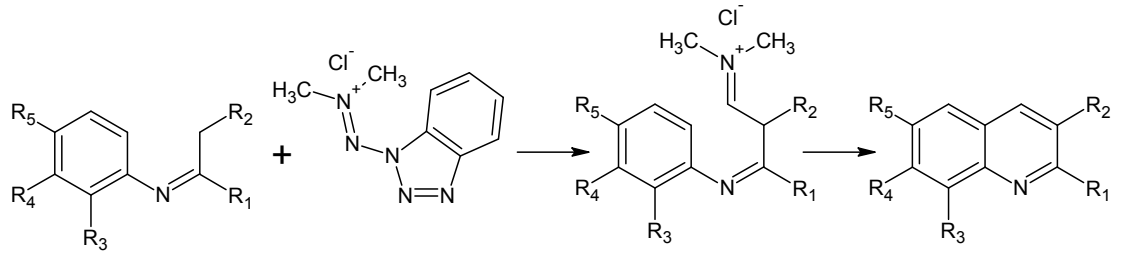

Figure-10: Katritzky improved Vilsmeier-type cyclization

5. Improvements to the Skraup/Doebnervon Miller processes

Focusing research and development on the reaction conditions, improvements to the Skraup/Doebnervon Miller processes have been recently achieved using solid-phase, two-phase, and vapour-phase procedures. In 2003, Ranu et al. described a solvent-free microwave-indused Doebner-von Miller synthesis of 4-alkylquinolines. His conditions utilized the aniline and alkyl vinyl ketone adsorbed onto silica gel impregnated with indium chloride. Within short time microwave irradiation gives excellent yields of 4- alkylquinolines by using a variety of alkyl, alkoxyl, halide and hydroxyl substituted anilines. This technique was also demonstrated to be effective at making alkyldihydroquinolines, using disubstituted alkyl vinyl ketones. [XXXVI-XXXVII] a solid-phase microwave-assisted synthesis of 2,4-alkylquinolines also reported by Kidwai. Vinylous amide condensed from chlorofluoroaniline and α,β-unsaturated methyl ketone undergo cyclisation on acidic alumina under solvent-free conditions. This results in clean quinoline product without the use of mineral acids or toxic and flammable organic solvents. [XXXVIII] A two-phase reaction rout for the Doebner-von Miller synthesis was introduced by Matsugi and co-workers. Their production of 2-alkyl quinolines was optimized using a toluene/6M HCl two-phase reaction medium. The α,β-unsaturated aldehyde from toluene phase get protonated at the phase interface and enter into aqueous phase. The protonated anilines remained in the aqueous phase. This setup prevented the polymerization of the aldehydes which makes the Doebner-von Miller reaction efficient

both in yield, and in product isolation. [XXXIX] Li also reported a two-phase Doebner-von Miller reaction using similar conditions involved 12N HCl, toluene and a phase-transfer catalyst. In their work 5 mol % of triethylbenzylammonium chloride produced optimal yields of the desired 2-methyl-8-quinoline carboxylic acid. [XL] Vapour phase rout of reaction have also been reported as an improvement to the Skraup synthesis of alkylquinoline. Campanati have desined simple process by using acid-treated K10 Montmorillonite clay, 2-ethylaniline and gasous ethylene glycol. Efficient synthesis of 2-methyl-8-ethylquinoline has been achieved by using heterogeneous catalysis and also it was verified that the intermediate crotonaldehyde proposed by Doebner-von Miller. Moderate yields were reported based on the amount of ethylene glycol used. [XLI] The applications of a process initially reported by Corey was elaborated by Carrigan [XLII] using dimethyl oxoglutaconate. By using this procedure twenty-six quinoline-2,4-dicarboxylic acids were produced subsequently screened as glutamate vesicular transport protein inhibitor.[XLIII] Zhang also used the Corey modification, using dimethyl oxoglutaconate and a 3-methoxyaniline. Instead of the quinoline formation, Zhang observed addition at the position para to the amino group. This product could not cyclize in a Doebner-von Miller manner, and was reported as a possible alternative mechanism for the reaction, proposing that the benzenoid addition may occur first followed by cyclization. However this proposal was specifically caveated by the uniqueness of the substrate used, both due to electronics of the electron-rich arene and the sterics of their 5,6-indole ring. [XLIV]

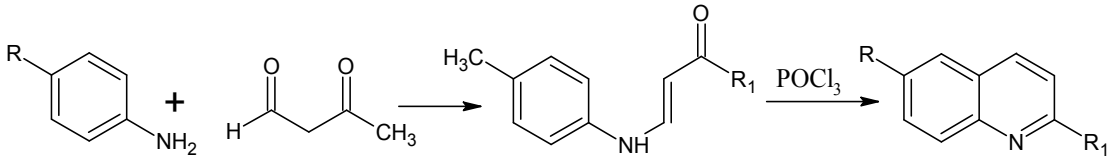

Figure-11: Modified Doebnervon Miller processes

6. Modified Conrad-Limpach-Knorr and Combes reactions

Recent applications of modified Conrad-Limpach-Knorr and Combes reactions are rarer than that of Skraup and Doebner-von Miller. In 2003, Schlosser's group, along with the aforementioned mechanistic study, reported on the preparation of a range of trifluoromethyl-substituted quinolines, using ethyl trifluoroacetoacetate. After subsequent transformations, this Conrad-Limpach-Knorr type, acid-catalyzed condensation with anilines produced high yields of the desired trifluoromethyl quinoline carboxylic acids. [XLV] Conrad-Limpach-Knorr reaction was used by Nicolaou and coworkers (1996) in their partial synthesis of the CDE ring of dynemicin A (**2**). In this reaction, desired 2-carboethoxy-4-hydroxyquinoline was obtained by reacting p-anisidine with diethyl oxalacetate under acidic conditions and then intermediate is thermally cyclized with 75% yield.

7. Friedlander and Similar Reactions

The second major classes of quinoline synthesis starts with 2-substituted anilines, and are designed by creating variations in the Friedländer synthesis, including the Pfitzinger, Niemantowski and Borsche syntheses. Since its initial discovery in 1882, the Friedlander synthesis is by far the most widely applied, and modified, Quinoline synthesis to date. [XLVI]

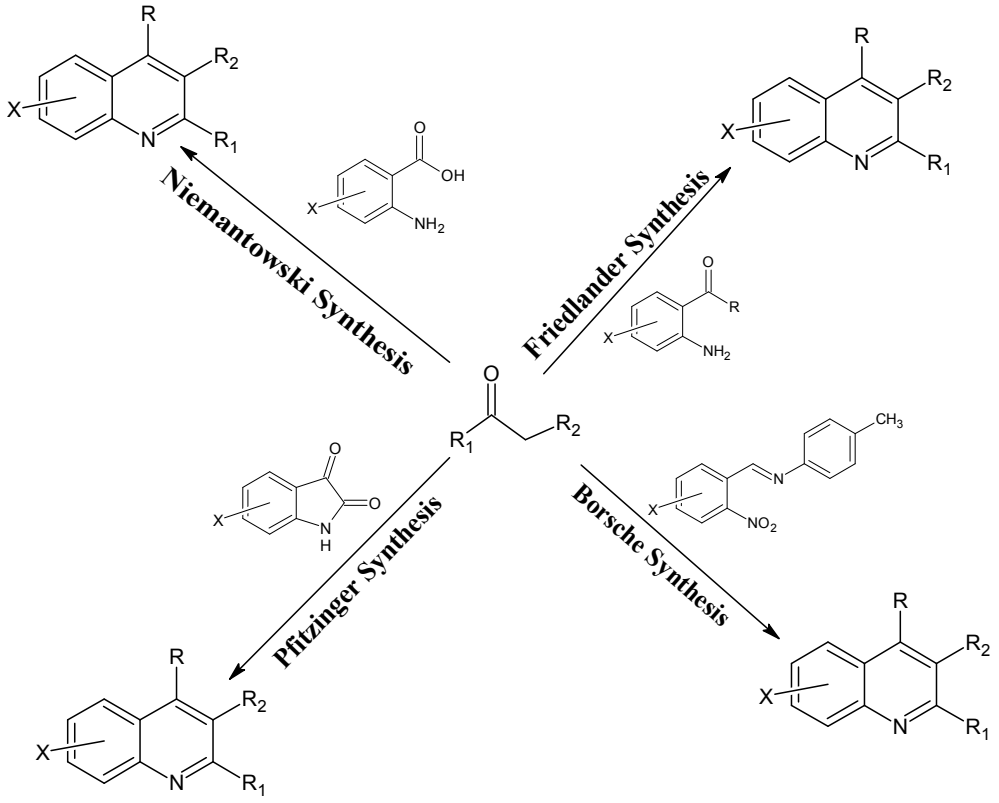

Figure-12: Conversion of α-methylene carbonyl into quinoline.

The basic Friedlander reaction involves the condensation of ortho-aminobenzaldehyde or o-amino benzyl ketone with the two carbons derived from an α-methylene carbonyl unit. The major variants of the Friedlander vary not in the methylene carbonyl, but in the starting aniline derivative. The Borsche reaction [XLVII] starts with arylimines, the Pfitzinger reaction [XLVIII] starts with isatin, and the Niemantowski reactions starts with o-aminobenzyl carboxylic acids.

8. Bracke Synthesis.

Examples of the use of the Friedlander reaction can be found throughout the literature. Bracke reported synthesis of thermally stable anthrazoline polymers in 1969 by polycondensation of 4,6-diaminoisophthalaldehyde with 2,6-diacetylpyridine, bis(p-acetyl-phenyl), and p-diacetylbenzene**.** [XLIX] Parfitt introduced the synthesis of benzo[a]phenanthrolines prepared by a double Friedländer condensation of 2,2'-diaminobenzophenone with diketones.[L] Weinreb and Kende used Friedlander reactions to assemble the quinoline ring in their synthesis of streptonigrin.[LI] More recently, the synthesis of an inhibitor of HMG-CoA (the rate-limiting enzyme in sterol biosynthesis in animals and plants) was conducted by Suzuki, using a Friedlander synthesis of the 2-cyclopropyl-4-(p-fluorophenyl)-3-quinoline carboxylic ester intermediate. [LII] This p-toluenesulfonic acid catalyzed condensation produced the desired product in 90% yield, and was suitable for the proposed industrial scale up of this synthesis. In 2000, Camps targeted the synthesis of an acetyl-cholinesterase inhibitor, dubbed huprine X as a potential treatment for Alzheimer's disease.

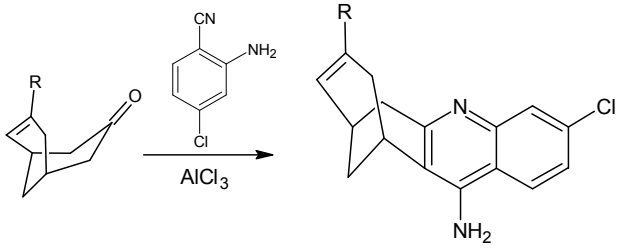

Figure-13: Synthesis of bicycloquinoline

This reaction involved a Friedlander condensation of 4-chloro-2-aminobenzonitrile with their previously developed bicyclononenone to give the desired bicycloquinoline with 41% yield.[LIII]

9. Solvent-free, clay-catalyzed Friedlander reactions

As was seen in the Skraup/Doebner-von Miller syntheses, the Friedländer approach has been limited only by the availability of the starting materials, and the harshness of the reaction conditions. Many recent works have focused on improving those reaction conditions, including various solvent and solvent-free systems, newer catalyst applications, and more robust and versatile starting materials than the relatively unstable o-aminobenzaldehydes. In 1997, solvent-free, clay-catalyzed Friedländer reactions were been developed by Yadav group at the Indian Institute of Chemical Technology. These heterogeneous reactions produced yields equivalent to those reported in the literature for similar transformations in solvent, with significantly shorter reaction times, and cleaner product isolations. [LIV] In 2005, Yadav outlined the use of sulfamic acid as a heterogeneous catalyst in Friedlander condensations by using solvent-free procedure. Cyclic and acyclic alkyl ketones were condensed with o-aminobenzophenones to produce a variety of 2,3-alkyl-4-phenylquinolines in excellent yield.[LV] Yadav's group also developed the use of silver phosphotungstate as a heteropolyacid catalyst for the Friedlander condensation of 2-aminobenzophenone with acetyl acetone. This reaction produced an exceptional 89% yield, in 4.5 hours. [LVI] Yadav's group also reported the use of 5 mol % Bismuth (III) triflate as a catalyst for the same Friedlander reaction, reporting virtually the same improvements: 91% yield in 4 hrs at room temperature in Ethanol. This is a dramatic improvement over traditional acid-catalyzed reactions that require longer reaction times as well as refluxing conditions.[LVII]

10. Vilsmeier Approach.

In 1995, Otto Meth-Cohn reviewed his longstanding "Vilsmeier Approach" and described a newer "Reverse Vilsmeier Approach" to quinolines. The "Vilsmeier Approach" converted acylanilides to α-chloroenamines with $POCl_3$, then used N,N-dimethylformamide to electrocyclise and finaly formylate the enamines. This reaction produces 2-chloro-3-formyl-quinolines in good yields.

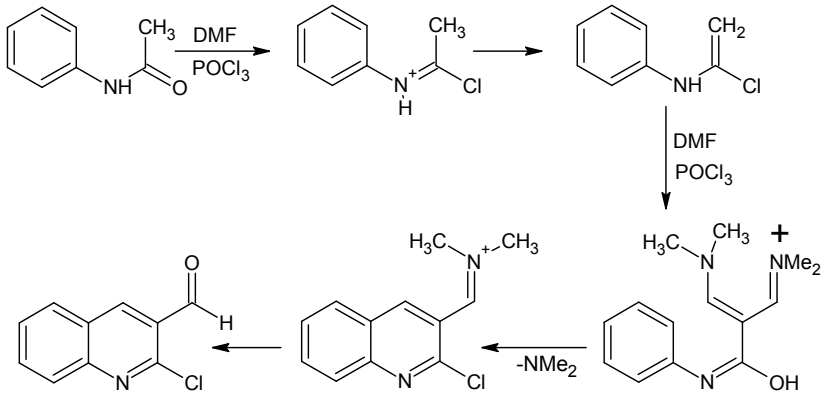

Figure-14: Vilsmeier Approach

11. Reverse Vilsmeier Approach

In Meth-Cohn's "Reverse Vilsmeier Approach" Vilsmeier reagent was prepared by using N-methylformanilide and reacted with electron-rich alkenes. After reaction with a second equivalent of Vilsmeier reagent, cyclization occurred to form N-methylquinolinium salts.[LVIII]

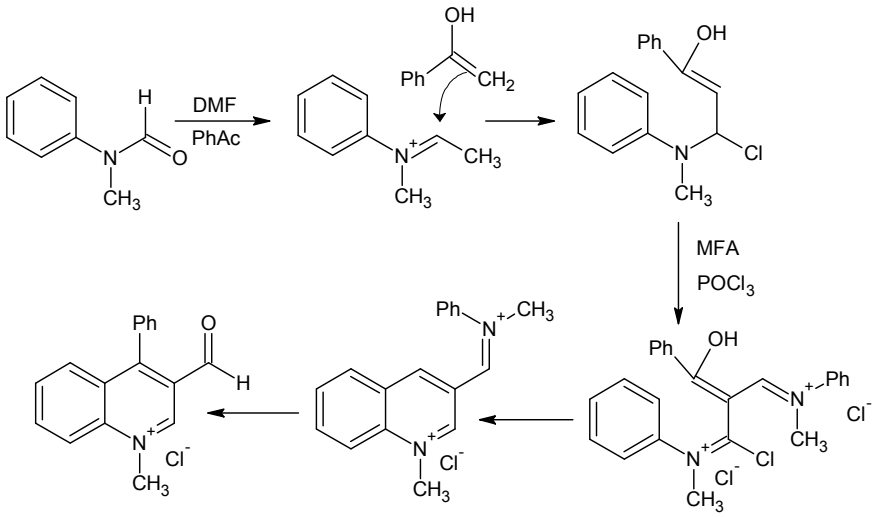

Figure-15: Reverse Vilsmeier Approach

12. Synthesis of 2-chloro-3-formylquinolines in presence of micelles.

The 2-chloro-3-formylquinolines are versatile precursors. The precursors were prepared from according to literature procedure which involves double formylation (using Vielsmeier-Hack formylation method) of acetanilide at the β-position. The reaction sequence is as follows.

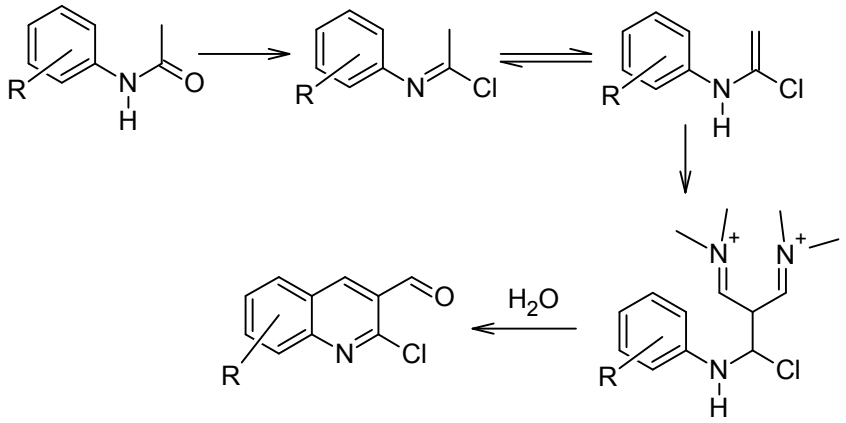

Figure-16: Synthesis of substituted 2-chloro-3-formylquinolines

The mole ratio of acetanilide, DMF and $POCl_3$ is 1:2.5:7 respectively and the temperature of 96 °C were standardized as the optimum condition to get the maximum yield of the precursor. Yields are generally good and particularly with anilides carrying electron donating groups. In contrast to above observations, acetanilide carrying electron withdrawing groups (NO_2, Cl) afforded poor yield or no reaction. To increase the yield many developments were made which included microwave assisted Vilsmeier reaction and formylation in the miceller media. The micelles act as a tiny reactor and are produced by using either Triton- X-100, cetyltrimethyl ammonium bromide (CTAB) or sodium n-dodecyl sulphate (SDS) in acetonitrile under Vilsmeier condition. In this methodology the yields were increased even acetanilides bearing electron withdrawing group. [LIX]

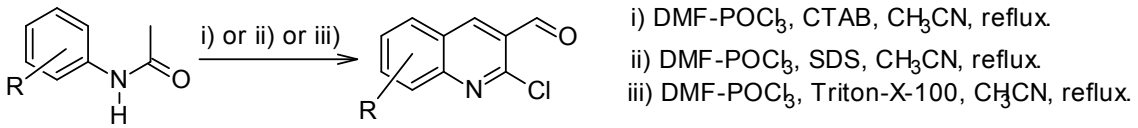

Figure-16: Synthesis of substituted 2-chloro-3-formylquinolines in presence of micelles

Conclusion:

Quinoline compounds have been widely explored for industrial applications. However, the biological activity of this class of compounds deserves further investigation. Although the research on this subject is incipient, a number of reports disclosing the effects of the quinoline compounds on the pathogens of clinical interest have recently been increasing. Compounds containing quinoline core have been shown to be promising leads for the design of more efficient antimicrobial agents. Advances in this field will require analyses of the structure–activity relationships of the quinoline based compounds as well as the mechanism of action of these compounds.

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References

I. (a) Zhang X, Shetty A S, Jenekhe S A, *Macromolecules*, 32, 7422, **1999**; (b) Jenekhe S A, Lu L, Alam M M, *Macromolecules*, 34, 7315, **2001**.

II. (a) Markees D G, Dewey V C, Kidder G W, *J. Med. Chem.*, 13, 324, **1970**; (b) Campbell S F, Hardstone J D, Palmer M J, *J. Med. Chem.*, 31, 1031, **1988**; (c) Maguire M P, Sheets K R, McVety K, Spada A P, Zilberstein A, *J. Med. Chem.*, 37, 2129, **1994**; (d) Kalluraya B, Sreenivasa S, *Farmaco,* 53, 399, **1998;** (e) Roma G, Braccio M D, Grossi G, Mattioli F, Ghia M, *Eur. J. Med. Chem.*, 35, 1021, **2000**; (f) Chen Y L, Fang K C, Sheu J Y, Hsu S L, Tzeng C C, *J. Med. Chem.*, 44, 2374, **2001**.

III. Loeb LF, Clarke WM, Coatney GR, Coggeshall LT, Dieuaide FR, Dochez AR (1946) Activity of a new antimalarial agent, Chloroquine (SN 7618). JAMA 130:1069–1070

IV. Wells TN, Poll EM Discov Med., (2010) 9:389–398

V. Winstanley PA, Ward SA, Snow RW (2002) Clinical status and implications of antimalarial drug resistance. Microb Infect 4:157–164

VI. Bringmann, G.; Reichert, Y.; Kane, V. V. Tetrahedron **2004**, 60, 3539-3574.

VII. Hibino, S.; Weinreb, S. M. J. Org. Chem. **1977**, 42, 232-6.

VIII. Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. J. Am. Chem. Soc. **1997**, 119, 6072-6094.

IX. Nicolaou, K. C.; Gross, J. L.; Kerr, M. A. J. Heterocycl. Chem. **1996**, 33,735-746.

X. Michael, J. P. Nat. Prod. Rep. **2003**, 20, 476-493.

XI. Michael, J. P. Nat. Prod. Rep. **1995**, 12, 465-475.

XII. Michael, J. P. Nat. Prod. Rep. **1994**, 11, 163-172.

XIII. Michael, J. P. Nat. Prod. Rep. **1993**, 10, 99-108.

XIV. Michael, J. P. Nat. Prod. Rep. **1991**, 8, 53-68.

XV. Fournet, A.; Barrios, A. A.; Munoz, V.; Hocquemiller, R.; Cave, A.; Bruneton, J. Antimicrob. Agents Chemother. **1993**, 37, 859-63.

XVI. Fournet, A.; Hocquemiller, R.; Roblot, F.; Cave, A.; Richomme, P.; Bruneton, J. J. Nat. Prod. **1993**, 56, 1547-52.

XVII. Fournet, A.; Vagneur, B.; Richomme, P.; Bruneton, J. Can. J. Chem. **1989**, 67, 2116-18.

XVIII. Caron, S.; Desfosses, S.; Dionne, R.; Theberge, N.; Burnell, R. H. J. Nat. Prod. **1993**, 56, 138-9.

XIX. Fokialakis, N.; Magiatis, P.; Terzis, A.; Tillequin, F.; Skaltsounis, A. L. Tetrahedron Lett. **2001**, 42, 5323-5325.

XX. Boyd, D. R.; Sharma, N. D.; Barr, S. A.; Carroll, J. G.; Mackerracher, D.; Malone, J. F. Perkin Trans. 1 **2000**, 3397-3405.

XXI. Hibino, S.; Weinreb, S. M. J. Org. Chem. **1977**, 42, 232-6.

XXII. Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. J. Am. Chem. Soc. **2001**, 123, 3239-3242.

XXIII. Kouznetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. Curr. Org. Chem. **2005**, 9, 141 161.

XXIV. Skraup, Z. H. Ber. Dtsch. Chem. Ges. **1880**, 13, 2086. as reviewed by Kouznetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M., Curr. Org. Chem., **2005**, 9, 141-161.

XXV. Doebner; von Miller, W. Ber. Dtsch., Chem. Ges., **1881**, 14, 2812. As reviewed by Kouznetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. Curr. Org. Chem. **2005**, 9, 141-161.

XXVI. Misani, F.; Bogert, M. T. J. Org. Chem. **1945**, 10, 347-65.

XXVII. Steck, E. A.; Hallock, L. L.; Holland, A. J.; Fletcher, L. T. J. Am. Chem. Soc. **1948**, 70, 1012-15.

XXVIII. Born, J. L. J. Org. Chem. **1972**, 37, 3952-3.

XXIX. Theoclitou, M.-E.; Robinson, L. A. Tetrahedron Lett. **2002**, 43, 3907-3910.

XXX. Wrobel, Z. Tetrahedron **1998**, 54, 2607-2618.

XXXI. Bischler, A. Ber. Dtsch. Chem. Ges. **1892**, 25, 2864. as reviewed by Eisch, J. J.; Dluzniewski, T. J. Org. Chem. **1989**, 54, 1269-1274.

XXXII. Mahata, P. K.; Venkatesh, C.; Kumar, U. K. S.; Ila, H.; Junjappa, H. J. Org. Chem. **2003**, 68, 3966-3975. 172

XXXIII. Panda, K.; Siddiqui, I.; Mahata, P. K.; Ila, H.; Junjappa, H. Synlett **2004**, 449-452.

XXXIV. Wang, M. X.; Liu, Y.; Huang, Z. T. Tetrahedron Lett. **2001**, 42, 2553-2555.

XXXV. Katritzky, A. R.; Arend, M. J. Org. Chem. **1998**, 63, 9989-9991.

XXXVI. Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. Tetrahedron **2003**, 59, 813-819.

XXXVII. Ranu, B. C.; Hajra, A.; Jana, U. Tetrahedron Lett. **2000**, 41, 531-533.

XXXVIII. Kidwai, M.; Bhushan, K. R.; Sapra, P.; Saxena, R. K.; Gupta, R. Biorg. Med. Chem. **2000**, 8, 69-72.

XXXIX. Matsugi, M.; Tabusa, F.; Minamikawa, J. Tetrahedron Lett. **2000**, 41, 8523- 8525.

XL. Li, X. G.; Cheng, X.; Zhou, Q. L. Synth. Commun. **2002**, 32, 2477-2481.

XLI. Campanati, M.; Savini, P.; Taglianai, A.; Vaccari, A.; Piccolo, O. Catal. Lett. **1997**, 47, 247-250.

XLII. Corey, E. J.; Tramontano, A. J. Am. Chem. Soc. **1981**, 103, 5599-5600.

XLIII. Carrigan, C. N.; Esslinger, C. S.; Bartlett, R. D.; Bridges, R. J.; Thompson, C. M. Bioorg. Med. Chem. Lett. **1999**, 9, 2607-2612.

XLIV. Zhang, Z. P.; Tillekeratne, L. M. V.; Hudson, R. A. Tetrahedron Lett. **1998**, 39, 5133-5134.

XLV. Cottet, F.; Marull, M.; Lefebvre, O.; Schlosser, M. Eur. J. Org. Chem. **2003**, 1559-1568.

XLVI. Cheng, C. C.; Yan, S. J. Organic Reactions **1982**, 28, 37-201.

XLVII. Borsche, W.; Ried, W. Ann. **1943**, 554, 269-90.
XLVIII. Henze, H. R.; Carroll, D. W. J. Am. Chem. Soc. **1954**, 76, 4580-4584.
XLIX. Bracke, W. Macromolecules **1969**, 2, 286-289.
L. Parfitt, R. T. New Compounds **1966**, 161-162.
LI. Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T.-T. J. Am. Chem. Soc. **1981**, 104, 536-544.
LII. Suzuki, M.; Tanikawa, K.; Sakoda, R. Heterocycles **1999**, 50, 479-483.
LIII. Camps, P.; Cusack, B.; Mallender, W. D.; El Achab, R.; Morral, J.; Munoz- Torrero, D.; Rosenberry, T. L. Mol. Pharmacol. **2000**, 57, 409-417.
LIV. Sabitha, G.; Babu, R. S.; Reddy, B. V. S.; Yadav, J. S. Synth. Commun. **1999**, 29, 4403-4408.
LV. Yadav, J. S.; Rao, P. P.; Sreenu, D.; Rao, R. S.; Kumar, V. N.; Nagaiah, K.; Prasad, A. R. Tetrahedron Lett. **2005**, 46, 7249-7253.
LVI. Yadav, J. S.; Reddy, B. V. S.; Sreedhar, P.; Rao, R. S.; Nagaiah, K. Synthesis **2004**, 2381-2385.
LVII. Yadav, J. S.; Reddy, B. V. S.; Premalatha, K. Synlett **2004**, 963-966.
LVIII. Meth-Cohn, O.; Taylor, D. L. Tetrahedron **1995**, 51, 12869-82.
LIX. M. M. Ali, Tasneem, K. C., Rajanna, P. K., Sai Prakash, *Synlett,* **2001(2),** 251–253.

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