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Polyhydroquinoline : Different Methods of Synthesis and its Various Biological Activities

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ABSTRACT

Substituted polyhydroquinoline derivatives are an important class of heterocyclic compounds. In recent years, heterocyclic analogues and its derivatives have attracted strong interest due to their immense importance in the design and discovery of new compounds for pharmaceutical applications. Polyhydroquinoline derivatives are a class of chemical compounds that exhibit a wide range of biological and pharmacological activities such as anticancer, antitubercular, nuerotrophic and effective cardiovascular agents. The current review focuses on various approaches for synthesizing substituted polyhydroquinoline with potential activities.

Keywords: Substituted polyhydroquinoline derivatives, anticancer, antitubercular, neurotrophic agent

I. INTRODUCTION

Heterocyclic compound plays an important role in the design and discovery of new compounds for pharmaceutical applications. Among various biologically active heterocyclic scaffolds, polyhydroquinoline are an important class of biologically active heterocycles. In recent years, much attention has been focused on the synthesis of 1, 4-dihydropyridine [1, 4-DHPs] compounds due to their significant biological and pharmacological activities[1]. In particular, dihydropyridine drugs such as clinidipine, nifedipine, nicardipine and others are effective cardiovascular agent for the treatment of hypertension[2] (Figure 1).

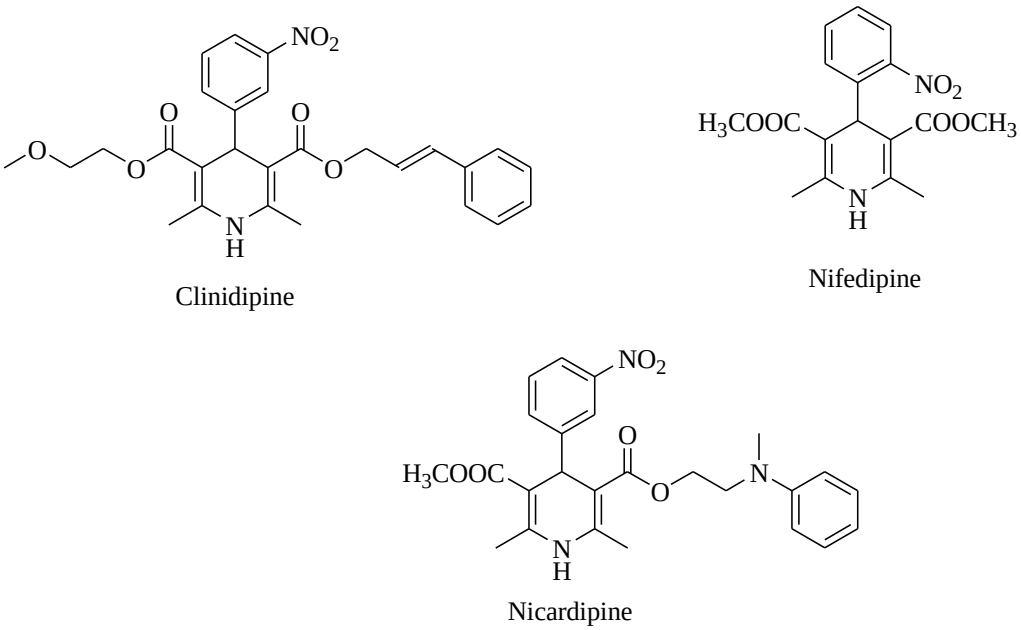
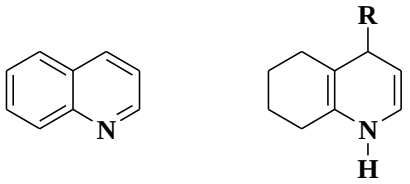


Figure 1: Dihydropyridine drugs

Some of them have anti tubercular properties[3], anticancer[4], neurotropic[5], neuropeptide YY1 receptor antagonists[6], neuroprotective[7], platelet ant aggregation[8], bronchodilating[9] and antidibetic activities[10], in addition cerebral antiischemic activity in the treatment of Alzheimer's disease[11] and as chemo sensitizer in tumor therapy[12]. 1, 4-dihydropyridine is analogues of NADH coenzymes which have been explored for their calcium channel activity. These examples show the extraordinary potential of new DHP derivatives as a source of promising therapeutic candidates.

Polyhydroquinoline are fused member rings containing quinoline bearing heterocycles. The fundamental structure of quinoline and many other pharmacologically and biologically active compounds is nitrogen.



1 **2**

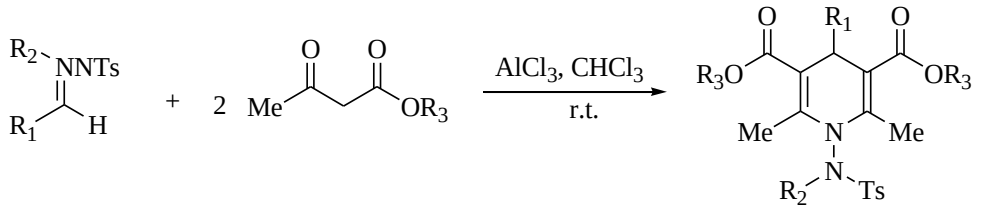
Quinoline (1) is structurally related to isoquinoline. Both are benzopyridines, which are composed of a benzene ring fused to pyridine ring.

A) Synthesis

In the literature, many approaches had been reported. This study included a list of methodologies.

1) Scheme I

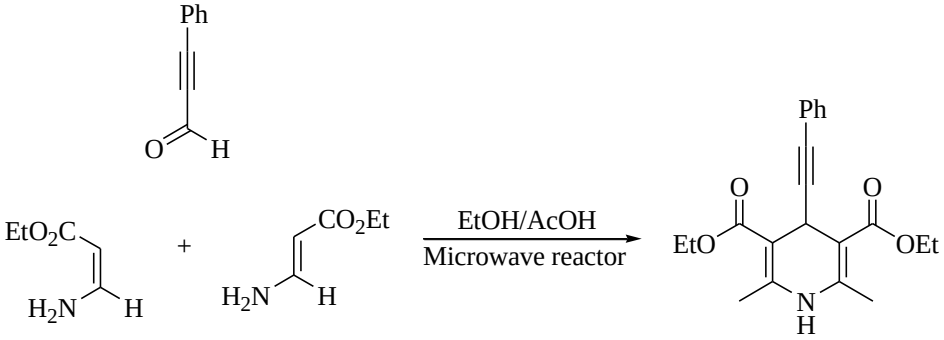
H. Wang et al[13] have reported the synthesis of [1, 4] dihydropyridine derivatives by the reaction of N-tosylhydrazones with ethyl acetoacetate in presence of various Bronsted acids and Lewis acids in $CHCl_3$ at room temperature.



Scheme-I

2) Scheme II

Bagley M. C. et al[14] have studied the synthesis of dihydropyridine by using the reaction of ethyl β-aminocrotonate and phenyl propynal under continuous flow in microwave reactor processing in presence of ethyl alcohol and acetic acid as solvent.

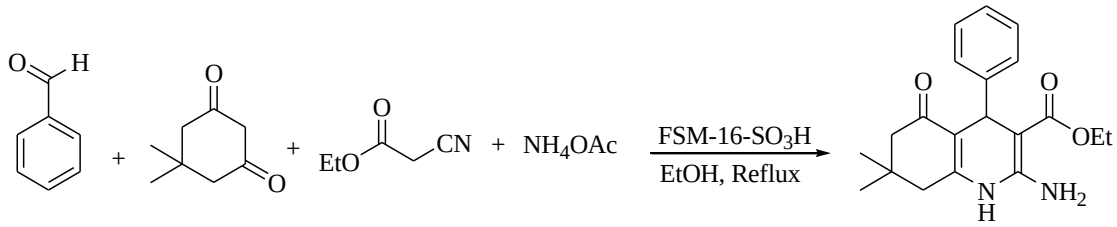


II-10

Scheme-II

3) Scheme III

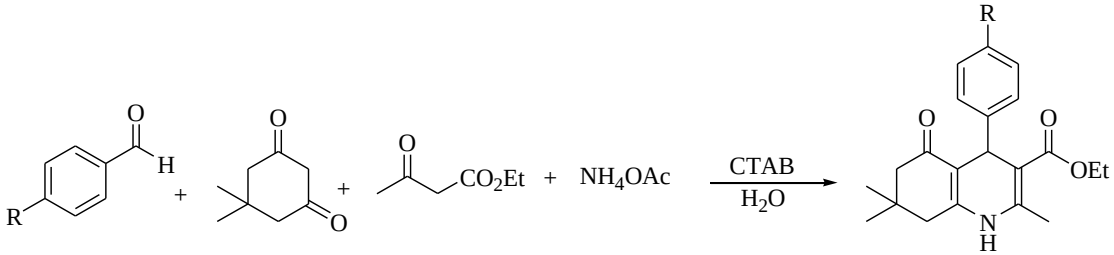
Alibeik M. A. et al[15] have developed novel synthesis of polyhydroquinoline from dimedone, aryl aldehyde, ammonium acetate and ethyl cyanoacetate through Knoevenagel condensation followed by Michael addition reaction in the presence of FSM-16-SO_3H as heterogeneous solid acid catalyst.



Scheme- III

4) Scheme IV

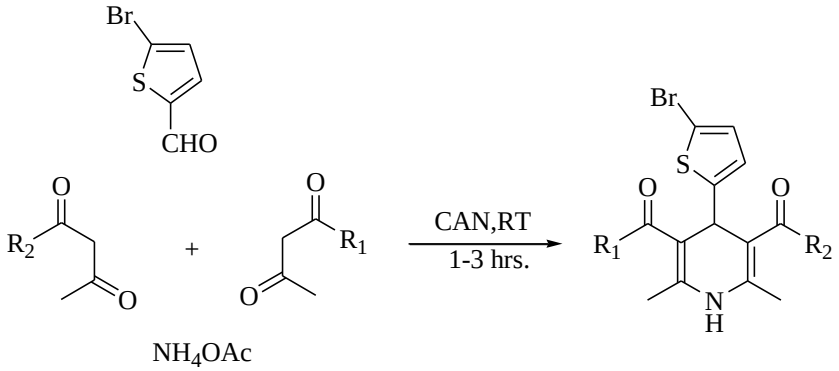
Xia J. J. et al[16] have reported the synthesis of polyhydroquinoline derivatives by the one pot Hantzsch condensation of aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexanedione, ethylacetoacetate and ammonium acetate refluxing in water in presence of Cetyltrimethylammoniumbromide (CTAB).



Scheme-IV

5) Scheme V

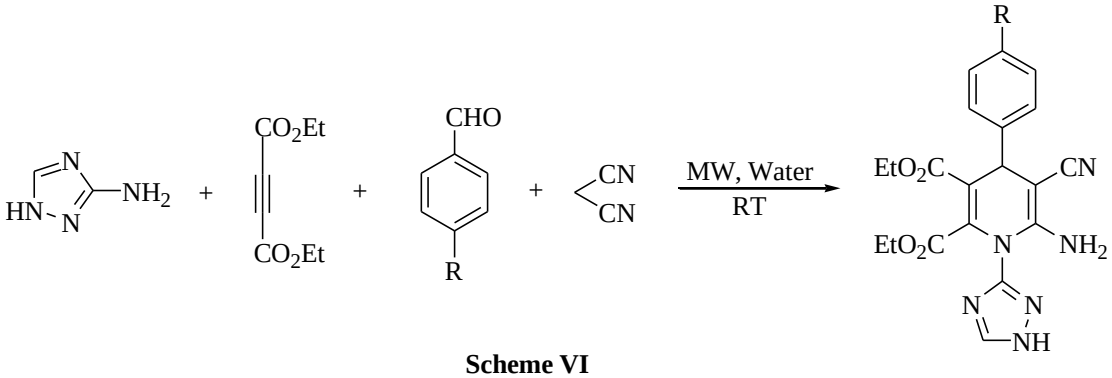
Sharma M. G. et al[17] have carried out a novel green and efficient one pot multicomponent synthesis of polyhydroquinoline by the reaction of 1,3-diones, 5-bromothiophene-2-carboxaldehyde and ammonium acetate in presence of Ceric Ammonium Nitrate (CAN) at room temperature under solvent free condition.



Scheme V

6) Scheme VI

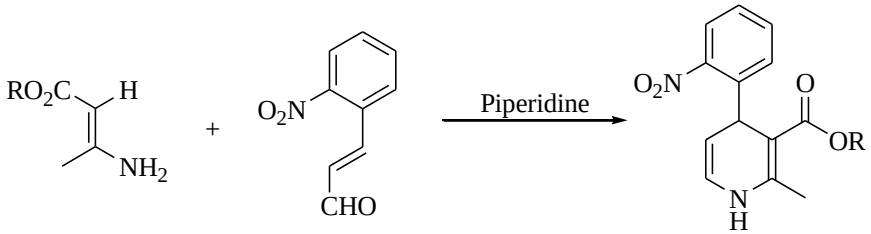
Kenu N. et al[18] have reported a highly efficient green protocol for developing a novel [1,4] dihydropyridine analogs through the one pot condensation of 1H-1,2,4-triazol-3amine with aromatic aldehyde, diethyl acetylenedicarboxylate and malononitrile in water under microwave irradiation and solvent free condition.



Scheme VI

7) Scheme VII

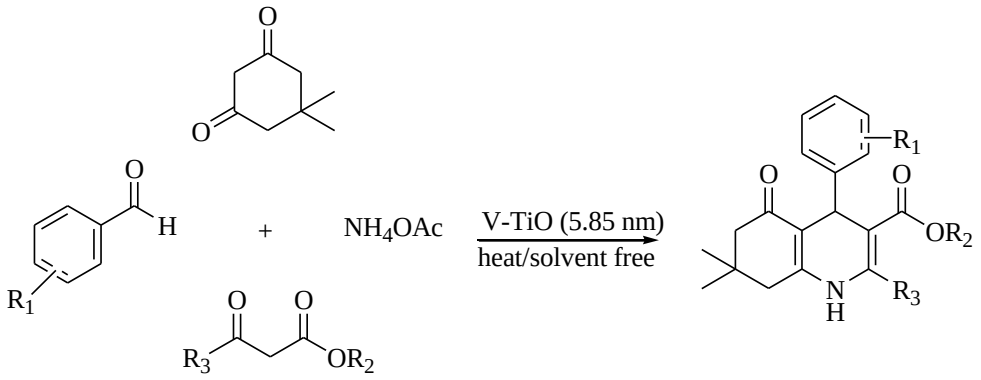
Mojarrad J. S. et al[19] showed piperidine catalyzed condensation of an alkyl 3-aminocrotonate with 2-nitrocinnamaldehyde afforded alkyl 2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridinr-3-carboxylate.



Scheme-VII

8) Scheme VIII

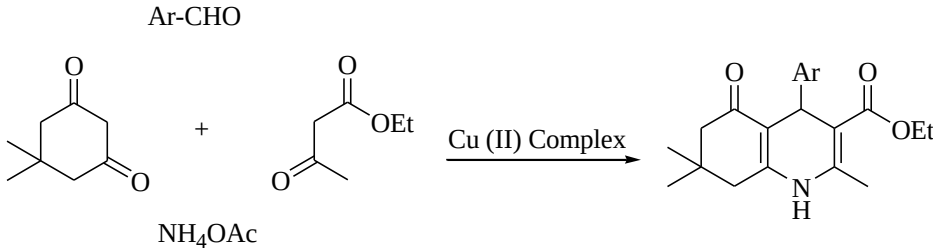
Dharma Rao G. B. et al[20] reported the solvent free synthesis of polyhydroquinoline derivatives using mesoporous Vanadium ion doped titania nanoparticles as a robust heterogenous catalyst via Hantzsch reaction.



Scheme-VIII

9) Scheme IX

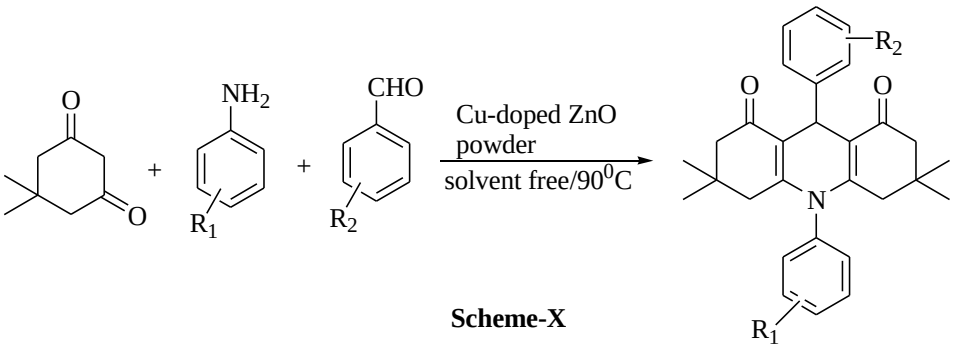
Allameh S. et al[21] reported an efficient and facile synthesis of polyhydroquinolines through Hantzsch reaction catalyzed by novel and reusable Cu (II) complex.



Scheme-IX

10) Scheme X

Alinezhad H. et al[22] studied a simple and convenient one step method for synthesis of acridines and their derivatives by condensation of aromatic aldehydes, cyclic diketones and aryl amines using Cu-doped ZnO nano crystalline powder as a catalyst.



Scheme-X

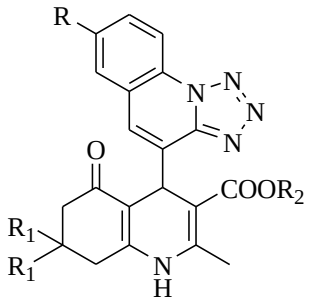
B) Biological activity

1) Antimicrobial activity

Despite enormous advancements in medicinal chemistry, infectious diseases produced by bacteria, fungi, viruses and parasites remain a severe hazard to public health. These microbes are responsible for a variety of diseases including pneumonia, amoebiasis, typhoid, malaria, common cough and cold infections as well as more serious diseases such as tuberculosis, influenza, syphilis and AIDS. From the discovery of the molecule to the current day, several methodologies have been used to investigate the role of the polyhydroquinoline moiety as an antibacterial agent.

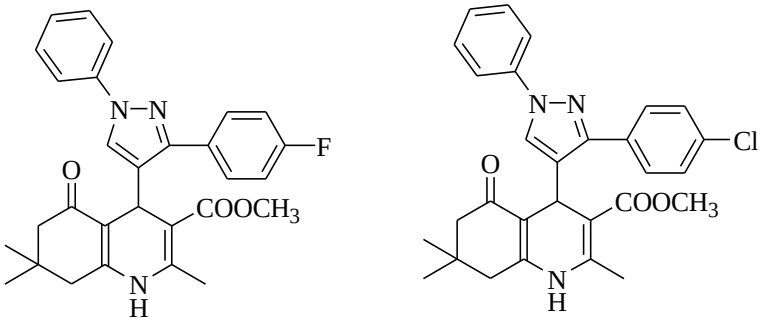
Ladani N. K., et al[23] synthesized tetrazolo[1,5-a]quinoline based 1,4-dihydropyridines, acridine-1,8-diones and polyhydroquinolines by four component coupling component reaction of tetrazolo[1,5-a]quinoline-4-carbaldehyde,dimedone/cyclohexane-1,3-dione,ethyl/methyl acetoacetate and ammonium acetate and screened

for their antimicrobial activity against Escherichia coli, Bacillus subtilis, Streptococcus aureus, Rhizopus oryzae, Aspergillus niger and ampicillin (10 µg/mL) and griseofulvin (10 µg/mL) were used as standard drug for antibacterial and antifungal activity respectively.



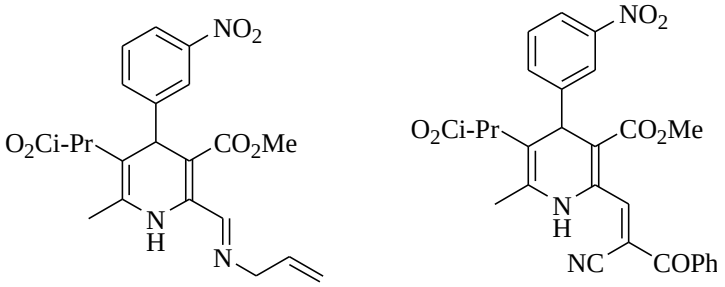
R= OCH_3, R_1=CH_3, R_2=C_2H_5

Jamale, D. K., et al[24] synthesized a series of 4-(1H-pyrazol-4-yl)-polyhydroquinolines through one pot four component Hantzsch condensation of 1,3-diphenyl-1H-pyrazole, 4-carbaldehydes, ammonium acetate dimedone and alkyl acetoacetate in glycerol. The synthesized compounds were screened for their antimicrobial activity against Mycobacterium tuberculosis using microplate Alamar blue assay at minimum inhibitory concentration of 1.6 µg/mL. Pyrazinamide, streptomycin and ciprofloxacin were used as standard drug.



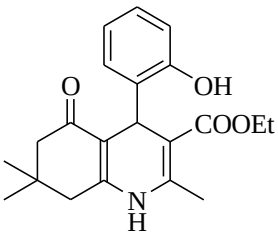
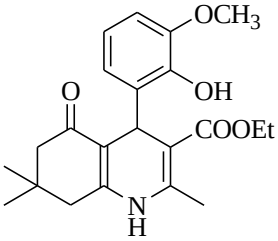
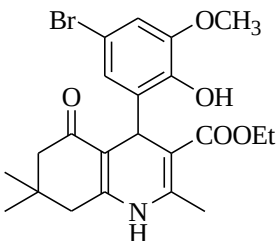
I **II**

Olejnikova, P., et al[25] synthesized 3-methyl-5-isopropyl (or ethyl) 6-methyl-4-nitro-phenyl-1,4-dihydropyridine -3,5-dicarboxylate derivatives. The compounds were screened for antibacterial activity against Mycobacterium smegmatis (MIC_{33}=9 µg.mL^{-1}), Staphylococcus aureus (MIC_{33}=25 µg.mL^{-1}), Escherichia coli (MIC_{33}=100 µg.mL^{-1}) minimum inhibitory concentration. In addition, the synthesized compound also shows its antibacterial power on the acid fast bacterial species M. smegmatis and on Gram positive S. aueus.

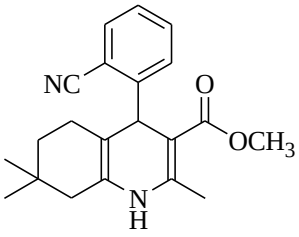
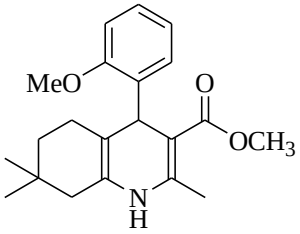
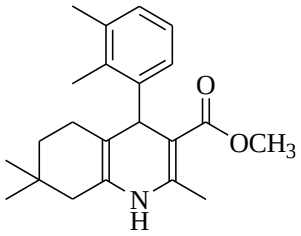


2) Anticancer Activity

Jadhvar, S. C. et al[26] have reported an effective synthesis of bioactive polyhydroquinoline derivatives via condensation of substituted salicyaldehyde, dimedone, ethyl acetoacetate and ammonium acetate catalyzed by 3-methyl-1-sulphonic acid immidazolium chloride ([Msim]Cl). The synthesized derivatives show significantly satisfactory inhibition activities against human breast cancer cells (MCF7) at different minimum inhibitory concentration of 10, 20, 40 and 50 µg/mL. Adriamycin or doxorubicin was used as standard drug.

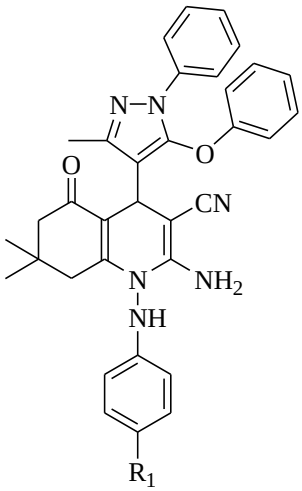




Fan, X.-X., et al[27] reported a synthesis of series polyhydroquinoline derivatives by condensation of methyl-3-amino-crotonate, aromatic aldehyde and 1,1-dimethyl-3,5-cyclohexanedione (dimedone) in ethanol. The synthesized compounds exhibit higher anticancer activity against four cancer cells (Saos-2, MG-63, 143B and U2-OS) at 100μg/mL of inhibitory concentration with penicillin and streptomycin as standard drug.

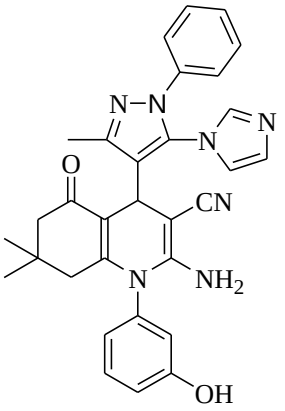




3) Antimalarial Activity

Karad, S. C. et al[28] synthesized a novel series of polyhydroquinoline compounds by one pot three component cyclocondensation reaction of 3-methyl-5-substtuted aryloxy-1-phenyl-1H-pyrazole-4-carbaldehydes with malononitrile and various enhydrazinoketones in presence of piperidine as basic catalyst. The synthesized compounds were screened for antimalarial activity against Plasmodium falciparum and exhibited excellent antimalarial potency against quinine and chloroquine as standard drug.



Kalaria, P. N. et al[29] reported one pot three component cyclocondensation reaction of 5-(1H-imidazol-1-yl)-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde with various enaminones and different active methylene compounds in absolute ethanol. The synthesized compounds A and B were screened for their in vitro antimalerial activity against Plasmodium falciparum, in vitro antibacterial activity against a panel of pathogenic strains of bacteria and fungi, and also for antitubercular activity against Mycobacterium tuberculosis H37Rv strain at 250 μg/mL and 100 μg/mL.



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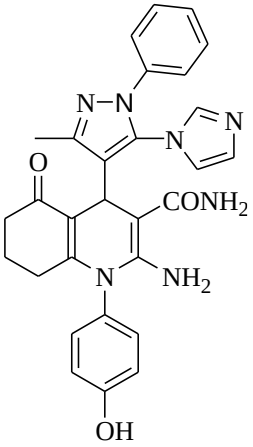

B

Conclusion

The reviewed substituted polyhydroquinoline had shown wide spectrum of biological activities to that of standard medication tested. In comparison to other compounds the biological profile of these polyhydroquinoline is vastly improved.

Acknowledgement

The authors are thankful to the Principal, Sant Dnyaneshwar Mahavidyalaya, Soegoan, Dist-Aurangabad, M. S. for constant encouragement and motivation.

Declaration of Interest

The authors report no conflict of interest.

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