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Comprehensive Study of Substituted Quinoline Derivatives and evaluated for their biological activities

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Abstract
In the present investigation different catagories of amidoalkylated products have been synthesized using mineral acid catalysts, Lewis acid catalysts and under thermal conditions with the object of studying their biological effects, on experimental animals. Different catagories of the compounds have been synthesized and evaluated for their biological activities.
Keywords: *amidoalkylated, biological activities, ligand*

I. Introduction

Quinoline is an aromatic, heterocyclic, nitrogen containing compound which is having a benzene ring fused with a pyridine ring at two adjacent carbon atoms. The quinoline nucleus exhibit diverse biological activities such as anticancer, antimalarial, antitubercular, antibacterial, antiprotozoal, antiproliferative, anti-inflammatory, antihypertensive, and anti-HIV activity. One of the potent quinoline derivatives is 8-hydroxy quinoline. It is obtained from plants as well as by synthesis. It is basically a small, planar and lipophilic molecule having an array of biological activities and also good metal chelating properties.

It was discovered that 8-hydroxy quinoline (oxine) had antimicrobial activity and also was a good chelating agent. Originally it was thought that the antimicrobial activity was due to the chelation of oxine with heavy metals, i.e. oxine prevented the utilization of essential trace metals required by the bacteria and fungi. However, it was shown that in the absence of metals, oxine was ineffective as an antimicrobial agent and thus it was the chelate which was responsible for bioactivity. In addition, quaternary ammonium derivatives are found 100% ionized and often have marked antibacterial properties. This effect is brought about by lysis (rupture) of the bacterial cell wall. One of the problems with this group of antibacterial agents is that the NR atom forms electrovalent bonds with negatively charged group on serum proteins. In order to circumvent this problem, bulky groups are placed on the quaternary nitrogen atom e.g. benzyl group which impedes the NR atom serum protein interaction. Further, a chelate is formed between a ligand and a metal to form a ring structure. While many metals form chelates the atom on the ligand which reacts with the metal is almost invariably oxygen, sulphur or nitrogen. The bonds which are formed between the liquid and the metal are either; (i) co-ordinate covalent bond, where by the liquid provides both of the electrons in the bond and is usually represented as X -> M (X=ligand atom and M=metal) or (ii) covalent bond; where by both the ligand atom and metal provide an electron in the bond (X-M bond).

Some examples of Type-I : Substituted Quinoline Derivatives are

(a)1-Aryl-8-aralkylamido/imido-7-hydroxy-4-methyl-2-oxoquinolines.

(b)7-Arylamino-1-(a-ethyl-3-naphthyl)-4-methyl-2-oxoquinolines.

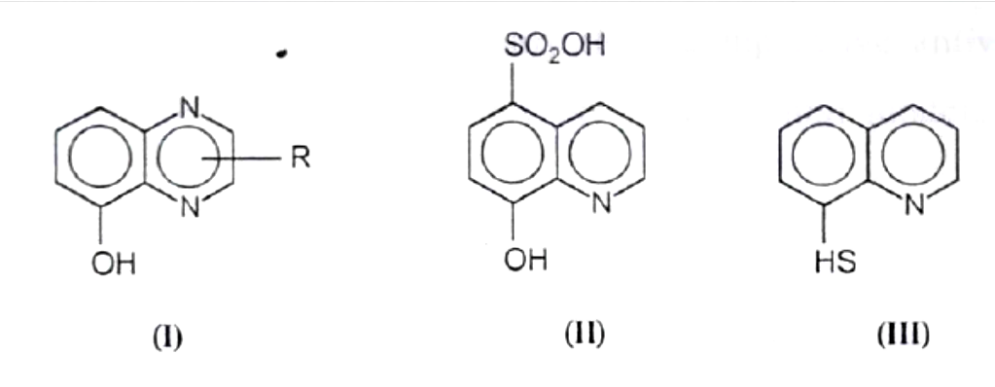
(c)7-Arylamino-4-methyl-1-(3'-carboxyl phenyl ethyl)-2oxo-quinolines.

The antimalarial activity of quinoline derivatives is known since long. Most of the drugs belong to this catagory still today, however, these quinoline drugs are found to be active against the erythrocytic forms of most of malarial parasites ultimately affecting a clinical cure. They do not cause prevention of the disease, and they are inactive against the liver-infecting forms. The development of quinoline derivatives was made after the acute shortage of Cinchona bark during the second world war. The mode of action of most quinoline derivatives are not fully known. However, it is thought that the quinoline have the rapid blood schizonticidal effects, form complexes with DNA by intercalation by interaction with purine bases (adenine and guanine). In this way they inhibit nucleic acid synthesis and therefore, protein synthesis in the rapidly dividing blood schizont and in the gametocytes. Mafloquine does not bind to DNA though it is rapidly acting blood schizonticide. The 8-aminoquinolines are thought to act through a metabolite and do bind to DNA from in vitro studies. They many have mitrocondrial site of action?. Quinoline derivatives were evaluated for their antiviral activity at a latter stage. 8-Hydroxy-glyoxyhemiacetats and 5-phenylglyoxylidene amino-8-hydroxy quinoline have been demonstrated to possess therapeutic significance against virsus APR-8 in eggs". Several 1-substituted dihydro isoquinolines related to acetamide were claimed to be inhibitors of viral neuraminidase and thus of possible use against influenza virus which carried neuramine dase as a surface enzyme. This compound inactivated

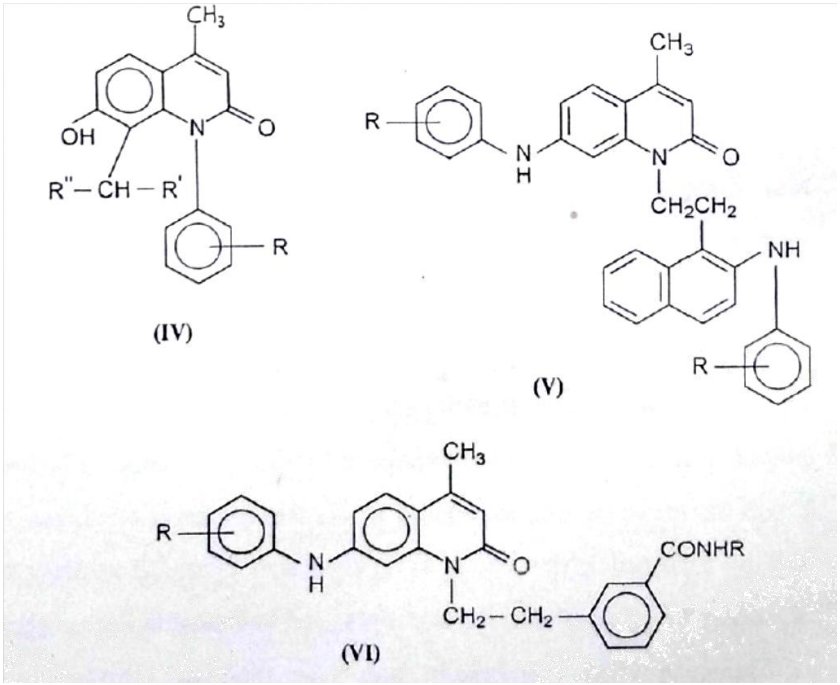
myxoviruses when incubated together. It was active in vivo but not in vitro against influenza, Echo I, Columbia SK and herpes viruses. It was of low toxicity to animals and a single dose of 4.0 g to human volunteers had no adverse effects. It was screened in a double blind clinical trial not against influenza but rhinovirus strain24. Oral doses for seven days did not produce any adverse effects but neither was the course of infection altered, 9/10 drug treated volenteers being infected compared with 10/11 placebo treated. The treated patients all had less severe symptoms and shed less virus than the controls.

Physicochemical studies have been made extensively for quinoline derivatives with regard to their antimicrobial activity. Thus, in a series of 4-aza-8-hydroxy-quinoline (I), the incorporation of alkyl groups on to the heterocyclic ring revealed that as the partition coefficient (liquid/water) increased, so antimicrobial properties increased. This result was interpreted as the assisting via the cell walls. When highly charged or ionizable groups (II) where placed on the quinoline ring antimicrobial activity decreased and this was attributed to the difficulty the compounds had to penetrate cell walls. In ascending a homologous series, the following increases in physical properties occurs. For example, boiling point, viscosity, surface activity, and partition coefficient (oil/water), whereas aqueous solubility decreases.

It is often observed that activity increases upto a point after which bioactivity falls. The point at which maximum activity is found is called the 'cut off point'. The maximum activity was found with six carbon atom in the alkyl chain, with these compounds the cut off point is when n=5. These results may be explained as follows. As the number of carbon atom in the side chain increases, the antimicrobial activity increases due to the increase in partition coefficient and hence the penetration of the cell wall is enhanced. At the end of point the maximum activity is reached and when n=6, the activity falls due to the water solubility of the compound being too low to be sufficiently high content in the aqueous phase. This view was strengthened by the observation of Ferguson who showed that the cut off point was reached when the log of the aqueous solubility decreased at a higher rate than the log of the concentration of the compounds to exert antimicrobial effects. It is the next higher homolog, e.g. seven carbon atoms for evaluation against microorganism, there is a lack of aqueous solubility in the medium and insufficient amount of compound is available to exert a more lethal effect than in the previous compound six carbon in the side chain. These experiments reveal the significance of the relative hydrophobicity and hydrophilicity in various series of molecules and now-a-days this concept has been incorporated into the Hansh a values, which are important parameters in explaining and predicting bioactivity Isosteric replacement of the oxygen atom of oxine by sulphur gave a chelating agent (III) with antimicrobial properties.



The author, therefore thought it worthwhile to extend the scope and validity of these observations to the synthesis of some new quinoline derivatives of the general structure types (IV), (V) and (VI) with the main object of evaluating antiviral and antibacterial activities8,9,10.



These target molecules (III to VI) having the same nucleus, the quinoline one with different polar substituents have been synthesized in order to study their comparative antiviral and antibacterial activities in suitable experimental models.

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