Journal of Advances in Science and Technology

Vol. IV, Issue No. VII, November-2012, ISSN 2230-9659

AN ANALYSIS UPON VARIOUS VERSATILE HETEROCYCLIC QUINOLINE DERIVATIVES: BIOLOGICAL AND ANTIMICROBIAL ACTIVITY

AN INTERNATIONALLY INDEXED PEER REVIEWED & REFEREED JOURNAL

www.ignited.in

Journal of Advances in Science and Technology
Vol. IV, Issue No. VII, November-2012, ISSN 2230-9659

An Analysis upon Various Versatile Heterocyclic Quinoline Derivatives: Biological and Antimicrobial Activity

Jaydeep S. Rathod

Research Scholar, CMJ University, Shillong, Meghalaya

Abstract – Quinoline and its fused heterocyclic derivatives tested with diverse pharmacological activity constitute an important class of compounds for new drug development. Therefore, many researchers have synthesized these compounds as target structures and evaluated their biological activities. The present review provides an in depth view of work done so far on quinoline and its biological activities covering anticancer, ant mycobacterial, antimicrobial, anticonvulsant, anti-inflammatory and cardiovascular activities.

New heterocyclic compounds containing quinoline fragment were synthesized. They were characterized by elemental analyses as well as IR and PMR spectroscopic analyses. These compounds were treated with metal (Mn(II), Ni(II) and Cu(II) salts to produce complexes. The complexes were identified and characterized by elemental analyses, IR and electronic spectral studies and magnetic moment studies. The magnetic behaviour and spectroscopic investigation of complexes indicate mononuclear octahedral structure of all the complexes. All heterocyclic compounds and metal complexes were screened for antimicrobial activity against Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis, Escherichia coli and Klebsiella pneumonia using DMF as a solvent.

Microbial infections are one of the leading diseases which are responsible for millions of deaths every year because of lack of effective antimicrobial therapy and this situation becomes more complicated because of microbial resistance towards conventional antibiotics. Quinoline derivatives have proved their medicinal importance by having broad spectrum of pharmacological activities like antimicrobial, anticancer, antiviral and anti-inflammatory activities etc.

----------♦----------

INTRODUCTION

Heterocyclic compounds are of particular interest in medicinal chemistry, and this has catalysed the discovery and development of much new heterocyclic chemistry and methods. The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implication for the diversity of its synthetic procedure and for the physiological and industrial significance. Synthetic heterocyclic chemistry has influenced almost every place of human life and the synthesized compounds have found their application in diverse field as medicine, agriculture and various industries. Synthetic heterocyclic drugs are used as hypnotics, anticonvulsants, antiseptics, antineoplastic, antiviral, antihistaminic, anti-tumor etc.

Quinolines are versatile nitrogen containing heterocyclic compounds, possessing various biological and pharmacological activities such as antibacterial, antidepressant, antitrichomonal, herbicidal, antifungal and antimalarial. The fused quinoline system, tetrazolo[1,5-*a*]quinoline a promising anti-inflammatory and antimicrobial agent has been reported by only few researchers. Considering the above facts it was thought worth to synthesize some new tetrazolo[1,5-*a*]quinoline derivatives where active heterocyclic moieties such as octahydroquinazolinone, 1,4-dihydropyridine, acridine-1,8-dione, polyhydroquinoline, imidazole and chromene moiety have been introduced in the heterocyclic system.

Heterocyclic compounds are comprehensively explored for their antimicrobial activity. Quinolines are also heterocyclic compounds. They contain nitrogen as hetero atom. They are known for their antimicrobial activities (Abdel-Moty et al.,2005; Eswaran et al., 2009; Jumade et al., 2009). Formation of quinoline containing complexes is also reported by chemists. Complexes of quinolines and

their various derivatives are also assessed for their antimicrobial activities (Alazawi et al., 2007).

Considering the medicinal significance of quinoline containing compounds, such novel heterocyclic compounds were synthesized to develop potent bioactive molecules. These compounds were treated with metal salts of Mn(II), Ni(II) and Cu(II) to synthesize complexes. Structures of heterocyclic compounds and metal complexes were confirmed with elemental analyses and spectroscopic studies. All compounds and complexes were screened for antibacterial activity.

Quinoline and its derivatives have always attracted both synthetic and biological chemist because of its diverse chemical and pharmacological properties. Apart from classical method for the synthesis of quinoline ring available like Skraup, Doebner-von Miller, Friedländer, Pfitzinger, Conrad-Limpach, Combes syntheses. Various new methods have been developed which employed metallic or organometellic reagents such as CuCN, LiCl. Ruthenium (III) chloride $RuCl_3.nH_2O/3PPh_3$ Ytterbium (III) triflate $Yb(OTf)_3$, Tungsten vinylidene complex $W(CO)_5(THF)$, Boron trifluoride etherate $BF_3.OEt_2$, Benzotriazoleiminium salts etc. for the synthesis of quinoline derivatives.

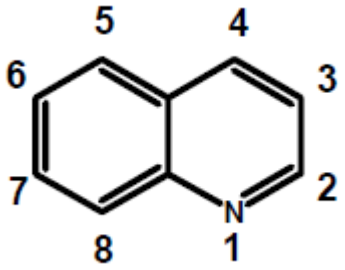
Moreover, the quinoline ring system occurs in various natural products, especially in alkaloids and is often used for the design of many synthetic compounds with diverse pharmacological properties. There are number of natural products of quinoline skeleton used as a medicine or employed as lead molecule for the development newer and potent molecules.

Microorganisms like bacteria and fungi are becoming resistant to conventional antimicrobial therapy because of acquired resistance which is encoded by resistance genes in the DNA of the microbe. Resistance genes can arise through spontaneous mutations in the microbial DNA and these genes can also transfer from drug-resistant microbes to drug-sensitive ones. Therefore, antibiotic resistance problem demand continuous discovery and development of new antibacterial agents by modification of existing classes including fluoroquinolones, tetracyclines, aminoglycosides, p-lactams and identification of inhibitors against previously unexploited antibacterial targets by different mode of action.

Various heterocyclic compounds have shown antimicrobial potential and quinoline is one of the most promising heterocyclic nuclei having prominent antibacterial and antifungal activity. Quinoline is characterized by a double ring structure composed of benzene and pyridine ring fused at two adjacent carbon atoms. Die benzene ring contains six carbon atoms, while the pyridine ring contains five carbon atoms and a nitrogen atom having molecular formula of C_9H_7N[4].

SYNTHESIS AND CHARACTERIZATION

Nitrogen containing heterocyclic compounds like quinoline has received considerable attention in recent years due to their biological and pharmaceutical activities. Quinoline contains a phenyl ring fused to a pyridine ring. Quinoline is also known as benzpyridine. The numbering system for the quinoline is as follows:



Different methods used for the synthesis of quinoline and its derivatives have been reported in literature. Bangdiwala et al. reported synthesis of 4-hydroxyquinoline. Raychaudhuri et al. studied side products in the preparation of ethyl 7-chloro-4-hydroxyquinoline-3-carboxylate as a intermediate for chloroquine. Synthesis of quinolines with several substituents in the pyridine ring have also been reported by Moszew and co-workers. A direct synthesis of quinoline derivatives from nitro compounds was done by Lachowicz et al. Synthesis of substituted 7-chloroquinoline derivatives and seleno-substituted quinolines have also been reported.

Further, physicochemical study of various new complexes of hexachloroosmate anions with quinoline derivatives was documented by Craciunescu et al. Cesaire et al. studied ultraviolet absorption spectra of 4-amino-7-chloroquinoline derivatives as a function of pH. The structure-activity relationships in some new quinoline derivatives was studied by Leclerc et al.

These quinoline derivatives are known to have wide spectrum of therapeutic activities such as: antiulcer, anti-HIV, antihypertensive, antimalarial, antihistamine, diuretic, herbicidal, anticancer cardiovascular etc. Carissimi et al. reported antibacterial and antifungal activities of 8-hydroxyquinolines. The antimycoplasmal, antimalarial and antidepressant properties of some of these derivatives have also been reported. The antimicrobial activities of a variety of these quinolines have been studied by various workers. Cai et al. reported hypocholesterolemic activity of some thiophenyl quinolines.

Synthesis of 1,5-Benzodiazepines –

1,5-benzodiazepine consists of a phenyl ring fused with seven membered heterocyclic ring having two nitrogen atoms at one and five positions.

Different methods have been reported for the synthesis of benzodiazepines and its derivatives. Barltrop et al. studied the chemistry of benzodiazepine and derivatives of benzotropone. Bell et al. has reported the new synthesis of substituted benzodiazepin -2-one 4-oxide. Synthesis of some other substituted benzodiazepines has also been reported by Kaegi, Pastor et al and Tsuchiya. The solid phase and combinatorial synthesis of benzodiazepines on a solid support was done by Ellman. Aromatic derivatives of 2,3-dihydro-1H-1,5-benzodiazepine have also been synthesized by Orlov et al. Huang and Wang documented a new route for synthesis of 1,5-benzodiazepines. Recently, synthesis of benzodiazepine derivatives has been reported by various other methods.

Further, these benzodiazepine derivatives are known to have wide spectrum of biological activities such as anticonvulsant, CNS active agent, neuroleptic, antihypertensive, antiproliferative, anti-inflammatory, cardiovascular, antiamnesic, antimicrobial, anthelmintic etc. Hester reported sedative and antispasmodic effect of some triazolebenzodiazepines.

Psychotropic activity of some 4-amino-1,5-benzodiazepines have also been studied by Bauer et al.. Golik has also worked on 2,4-benzodiazepine as a potent CNS agent. The structure-activity relationship studies of some benzodiazepines as oxytocin antagonist and antitumor antibiotics have been documented. The antimicrobial, antifungal and anthelmintic activities of 3H-1,5-benzodiazepine derivatives have been studied by Kumar et al.. Recently, many workers have been reported some other biologically active benzodiazepines.

ANTIMICROBIAL ACTIVITY

Heterocyclic compounds and complexes were screened for their antimicrobial activity using agar diffusion technique against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Escherichia coli* and *Klebsiella pneumonia* using DMF as a solvent (Jones et al., 1984; Barry, 1986; Xia et al.,2001, Kurtoglu et al., 2007; Rollas et al., 2007). The culture strains of bacteria were kept on agar slant at 37oC for 24 hrs. Nutrient agar plates were seeded with 0.1ml of bacterial strain prepared in sterile saline (0.85 %) of 105 CFU/ml dilution.

For every bacterial strain, the wells (diameter 6 mm) were filled with 0.1 ml solution at fixed concentration of 25 µg/ml. All the plates were incubated at 37oC for 24 hrs. The inhibition zone was measured in mm. The activity was compared with known antibiotics like Penicillin, Ampicillin, Tetracycline, Chloramphenicol and Norfloxacin.

BIOLOGICAL ACTIVITY

Antimalarial -

Most important use of the quinoline ring is its antimalarial potential. Bisquinolines developed by Raynes et al. (1996) are found to possess a good degree of antimalarial activity against both chloroquine-resistant and chloroquinesensitive parasites. Analogues of ferrochloroquine were also found to have antimalarial activity by Chibale et al. (2000). In these analogues carbon chain of chloroquine is replaced by hydrophobic ferrocenyl group. Certain 7-chloroquinolinyl thioureas are potential antimalarial agents.

Certain 4-aminoquinoline triazines also have antimalarial activity screened against chloroquinine (CQ) sensitive strain 3D7 of P. falciparum in an in vitro model. Shiraki et al. (2011) developed certain 5-aryl-8-aminoquinolines [34] with promising antimalarial activity which had lesser haemolytic activity compared to tafenoquine.

Analgesic activity -

4-Substituted-7-trifluoromethylquinolines have been found to have a good analgesic activity. The activity is attributed to their nitric oxide releasing properties. Gomtsyan et al. (2005) developed a quinoline [41] based analgesic agent whose activity was attributed to its antagonism at Vanilloid receptors.

Anti-inflammatory activity -

2-(Furan-2-yl)-4-phenoxy-quinoline [43, 44] derivatives developed by Chen et al. (2006) are found to be inhibitors of lysozyme and b-glucuronidase release. Baba et al. (1996) developed a quinoline derivative [45] with potent anti-inflammatory effect in adjuvant arthritis rat model. Certain quinoline derivatives [46, 47] have been developed for treating osteoarthritis. These are amino-acetamide inhibitors of Aggrecanase-2.

Antineoplastic-

Some of the amido-anilinoquinolines act as anti-tumour agents by inhibiting CSF-1R kinase. Novel 4-hydroxyquinolines [49] are histone acetyltransferase (HAT) inhibitors. Miller et al. (2009) developed a few 3-cyanoquinolines [50] as inhibitors of insulin like growth factor receptors (IGF-1R) for the treatment of cancer.

Antifungal -

Gholap et al. (2007) developed certain tetrahydroquinolines [62] which are found to have a good degree of activity against fungi Candida

albicans, Fusarium oxysporum and Mucor sp. Kharkar et al. (2009) developed a series of quinoline derivatives [63] using terbenafine as lead as antifungal agents. The developed compounds contained different bulky aromatic rings in the side chain. The compounds were designed using LeapFrog drug design program.

Antiviral-

Anilidoquinoline [65] derivatives synthesized by Ghosh et al. (2008) are found to have a good degree of in vitro activity against Japanese encephalitis virus. Certain quinoline derivatives act by behaving as HIV-1 Tat–TAR interaction inhibitors.

CONCLUSION

Many researchers have synthesized quinoline and its fused heterocyclic derivatives. These observations have been guiding for the development of new quinoline derivatives that possess varied biological activities i.e. anticancer, antimycobacterial, antimicrobial, anticonvulsant, antiinflamatory and cardiovascular activities. A lot of work have been done and more to go. Development of newer quinolines have immense possibilities and scope for drug development scientist. We have presented a concise compilation of this work to aid in present knowledge and to help researchers to explore an interesting quinoline class.

Quinoline nucleus has occupied a pivotal position in the modem medicinal chemistry as per literature. This manuscript has compiled updated information about the antimicrobial potential of various quinoline derivatives. This valuable information may be utilized further by the researchers for drug design and development of better
antimicrobial agents for future to save the valuable life of patients.

REFERENCES

- Abdel-Moty, Samia G., Abdel-Rahman, Mostafa H., Elsherief, Hosney A., and Kafafy, Abdel-Hamid, N. (2005) Synthesis of some quinoline thiosemicarbazone derivatives of potential antimicrobial activity. *Bulletin of Pharmaceutical Sciences* 28(1): 79-93.
- Alazawi S. A. S. and Alhamadani A. A. S. (2007) Synthesis and characterization of mixed ligand complexes of 8- hydroxyquinoline and schiff base with some metal ions. *Um-Salama Science Journal* 4(1): 102-109.
- B. M. Kiran, B. P. Nandeshwarappa, G. K. Prakash, V. P. Vaidya, K. M. Mahadevan;
- Baba, A., Kawamura, N., Makino, H., Ohta, Y., Taketomi, S., Sohda, T., 1996. Studies on disease modifying antirheumatic drugs: synthesis of novel quinoline and quinazoline derivatives and their anti-inflammatory effect. J. Med. Chem. 39, 5176–5182.
- Chen, Y., Zhao, Y., Lu, C., Tzeng, C., Wang, J.P., 2006. Synthesis, cytotoxicity, and antiinflammatory evaluation of 2-(furan-2-yl)-4-(phenoxy)quinoline derivatives. Part 4. Bioorg. Med. Chem. 14, 4373–4378.
- Chibale, K., Moss, J.R., Blackie, M., Schalkwyk, D., Smith, P.J., 2000. New amine and urea analogs of ferrochloroquine: synthesis, antimalarial activity in vitro and electrochemical studies. Tetrahedron Lett. 41, 6231–6235.
- Crousse, B.; Bégué, J.-P.; Bonnet-Delpon, D. Synthesis of 2-CF3- tetrahydroquinoline and quinoline derivatives from CF3-*N* Arylaldimine. *J. Org. Chem*., 2000, *65*, 5009-5013.
- Dunning, S. Jaroch, M. Kochanny, W. Lee, X. Lian, M. Liang, S. Lu, J. Onuffer, G. Phillips, G. Wei, B. Ye, Bin; Preparation of substituted quinolines useful as CCR5 receptor antagonists, PCT Int. Appl. 241 pp. (2004).
- Eswaran, S., Adhikari, A. V., and Shetty, N. S. (2009) Synthesis and antimicrobial activities of novel quinoline derivatives carrying 1,2,4-triazole moiety. *European Journal of Medicinal Chemistry* 44(11): 4637-4647.
- Gholap, A.R., Toti, K.S., Shirazi, F., Kumari, R., Bhat, M.K., Deshpande, M.V., Srinivasan, K.V., 2007. Synthesis and evaluation of antifungal properties of a series of the novel 2-amino-5-oxo-4- phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile and its analogues. Bioorg. Med. Chem. 15, 6705–6715.
- Ghosh J, Swarup V, Saxena A, Das S, Hazra A, Paira P, Banerjee S, Mondal NB, Basu A., 2008. Therapeutic effect of a novel anilidoquinoline derivative, 2-(2-methyl-quinoline-4ylamino)-N-(2- chlorophenyl)-acetamide, in Japanese encephalitis: correlation with in vitro neuroprotection. Int. J. Antimicrob. Agents 32, 349–354.
- Gomtsyan, A., Bayburt, E.K., Schmidt, R.G., Zheng, G.Z., Perner, P.J., Didomenico, S., Koenig, J.R., Turner, S., Jinkerson, T., Drizin, I., Hannick, S.M., Macri, B.S., McDonald, H.A., Honore, P., Wismer, C.T., Marsh, K.C., Wetter, J., Stewart, K.D., Oie, T., Jarvis, M.F., Surowy, C.S., Faltynek, C.R., Lee, C.H., 2005. Novel transient receptor potential

vanilloid 1 receptor antagonists for the treatment of pain: structure–activity relationships for ureas with quinoline, isoquinoline, quinazoline, phthalazine, quinoxaline, and cinnoline moieties. J. Med. Chem. 48, 744–752.

- Jumade, P. P., Wadher, S. J., Chourasia, A. J., Kharabe, U. V., Mude, D., and Yeole, P. G. (2009) Synthesis of newer mannich bases of quinoline derivative for antimicrobial activity. *International Journal of Chemical Sciences* 7(3): 1518-1530.
- Kharb R, Sharma PC, Shaharyar M. Pharmacological Significance of
- M. A. Dave, N. S. Desai, A. V. Naidu; Synthesis and biological activities of substituted 7-chloroquinoline derivatives, part I, *Asian J. Chem*., 13, 459-64 (2001).
- Raynes, K., Foley, M., Tilley, L., Deady, L.W., 1996. Novel bisquinoline antimalarials: synthesis, antimalarial activity and inhibition of haem polymerisation. Biochem. Pharmacol. 52, 551– 559.
- S. Delarue-Cochin, P. Grellier, L. Maes, E. Mouray, C. Sergheraert, P. Melnyk; Synthesis and antimalarial activity of carbamate and amide derivatives of 4- anilinoquinoline, *Euro. J. Med. Chem*., 43, 2045-55 (2008).
- Sangu, K.; Fuchibe, K.; Akiyama, T. A Novel approach to 2- arylated quinolines: electrocyclization of alkynyl imines via vinylidene complexes. *Org. Lett*., 2004, *6*, 353-355.
- Shiraki, H., Kozar, M.P., Melendez, V., Hudson, T.H., Ohrt, C., Magill, A.J., Lin, A.J., 2011. Antimalarial activity of novel 5-aryl- 8-aminoquinoline derivatives. J. Med. Chem. 54, 131–142.
- Swenson, R.E.; Sowin, T.J.; Zhang, H.Q. Synthesis of substituted quinolines using the dianion addition of *N*-Boc-anilines and □-tolylsulfonyl-α,β-unsaturated ketones. *J. Org. Chem.,* 2002, *67*, 9182-9185.
- Synthesis of new seleno-substituted quinolines, *Phos. Sul. Sil. Rel. Ele*., 182, 993-1002 (2007).
- Triazole Scaffold. J Enzyme Inlhb Med Chem 2011; 26(1): 1-21.