International Journal of ChemTech Research
CODEN (USA): IJCRGG ISSN: 0974-4290
Vol.9, No.03 pp 629-634, 2016

An Overview: The biologically important quninoline derivatives

V. Vijayakumar*

Centre for Organic and Medicinal Chemistry, SAS, VIT University, Vellore-632014, India

Abstract: Heterocyclic compounds are widely prevalent in animal kingdom as well as in plant kingdom and they play various roles in metabolic processes. A large number of heterocyclic compounds are in clinical practice as a drug, while many of them find industrial utility and hence the syntheses of heterocyclic compounds and understanding of the biological importance of specific heterocyclic class will be an interesting field of synthetic organic chemists.

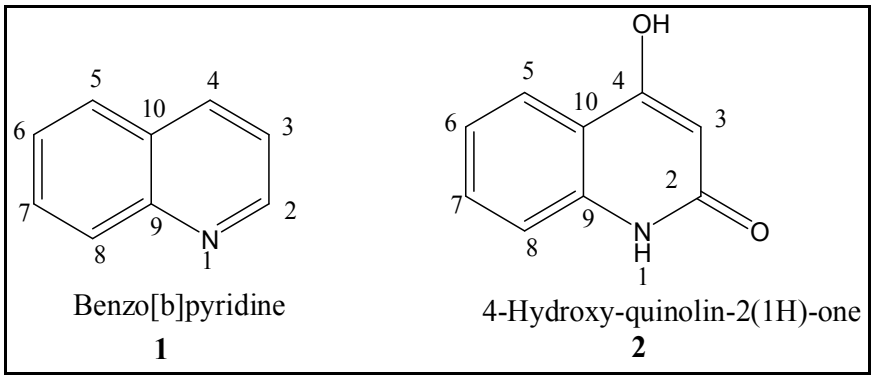
Introduction:

In recent years, there has been a growing interest pertaining to the synthesis of bioactive compounds in the field of organic chemistry. A cyclic organic compound containing at least one atom other than carbon is designated as *heterocycles*. Nitrogen, oxygen and sulphur are the most common hetero atoms but heterocyclic rings with other hetero atoms also widely known. A large number of heterocyclic compounds are essential to life. Various compounds such as alkaloids, antibiotic, essential amino acids, vitamins, haemoglobin, hormones and a large number of drugs and dyes contain heterocyclic ring systems.

Living organisms, particularly mankind were highly depending on bio-active molecules to treat various diseases. Presently, tremendous research is in progress to develop the drug molecules; usually these molecules were derived or isolated either from natural (biological) sources or through the synthesis. Due the extraordinary context of disease reducing properties of heterocycles, they were prescribed for various types of treatment[1,2]. The significance of the heterocycles in the drug industry was also revealed by the recent survey in US which showed that more than 90 % of drugs sold recently in the US market were reported to have at least one heterocycle in it. The presence of oxygen, sulfur and nitrogen as hetero atoms increasing the hydrogen bond forming ability of heterocycle with the protein targets was the uniqueness of the heterocycle. Heterocycles also have greater chelating property, so that they bind to the metal ions and block certain process like metal poisoning (toxicity) or enzyme action[3-5].

Quinoline derivatives:

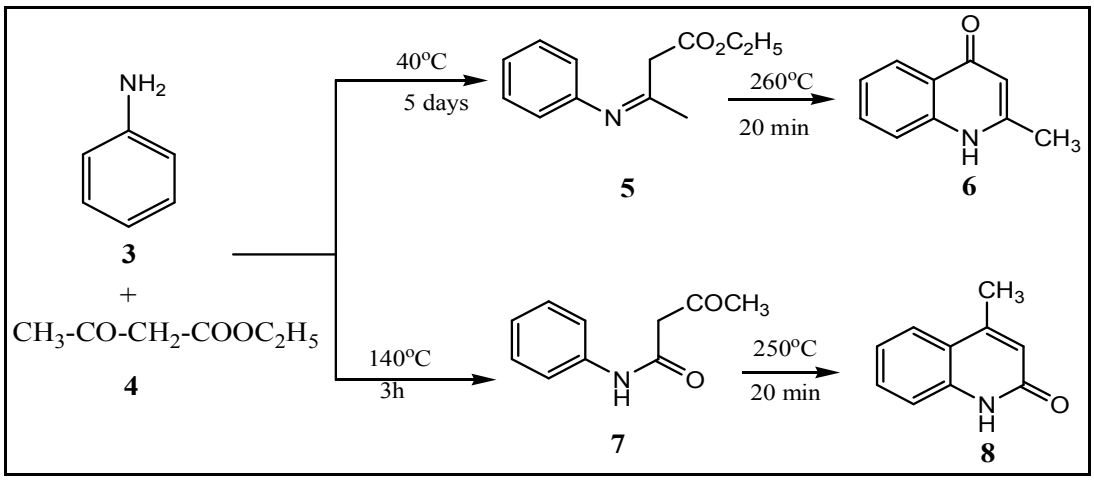
One of the important classes of heterocyclic chemistry is quinolone chemistry. The heterocyclic compound quinoline is Benzo[b]pyridine. Generally quinoline derivatives are synthesized by Skraup's, Doebener-Miller's and Friedlander's synthesis. Quinolines are weakly basic (pKa = 4.94) and placed in between aniline (pKa = 4.58) and pyridine (pKa = 5.17). The pyridine ring in quinoline is electron deficient therefore nucleophilic attack takes place at second and fourth positions and the electrophilic attack takes place at fifth and eighth positions.



The 2- and 4-hydroxyquinolines are usually prepared by Conrad-Limpach or Knorr synthesis[6]. These quinolinols behave as typical phenols and respond positive to neutral ferric chloride test[7].

1.1. Synthesis and Importance of Quinolines

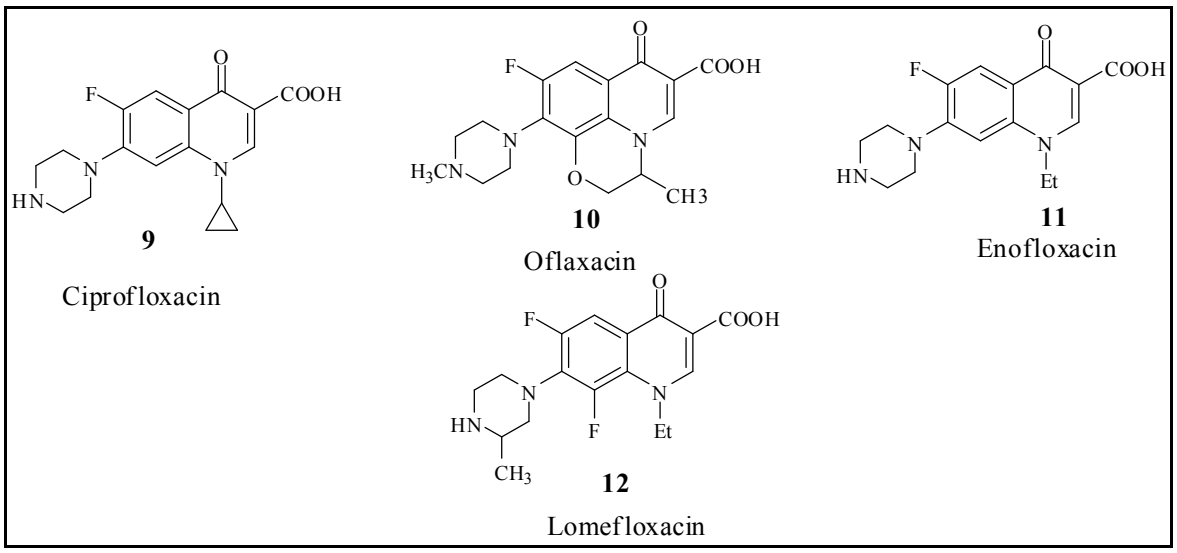
In Conrad-Limpach synthesis aryl amines (**3**) condense with the keto group of □-ketoesters (**4**) to yield kinetically controlled anil (**5**) at low temperature, which cyclizes to 2-methyl-4-quinolone (**6**) on heating. On the other hand, the anilide (**7**) is obtained as thermodynamically controlled product at high temperature, which cyclizes to 4-methyl-2-quinolone (**8**) either upon heating or in presence of acid.



Quinolones are known for their therapeutic applications such as genitourinary infections, prostatitis, respiratory diseases, sexually transmitted diseases, gastroenteritis, skin and soft tissue infections[8]. Apart from that, quinolones have extensive biological activities such as antimicrobial[9], antimalarial [10], anticancer[11], anti-HIV[12] (Sucheta, 2005), and antiangiogenic[13] activities.

The 4-aryl-3-hydroxy-2-quinolones are found to be produced by some species of mold fungi of the genus *Penicillium*[14]. Since then the rarely encountered and less studied 3-substituted quinolones have become a subject of great interest of the synthetic organic chemists. However the discovery of nalidixic acid as antibacterial agent gave impetus to the synthesis of various 3-carboxysubstituted quinolin-4(1*H*)-ones, of which some are drug molecules in the clinical practice.

The structural modifications on quinolone moiety resulted in first, second, third and fourth-generation quinolones. First-generation agents *viz.,* nalidixic acid and cinoxacin have moderate *Gram negative* activity and minimal systemic distribution. Second-generation quinolones have expanded *Gram negative* activity and atypical pathogen coverage but limited *Gram positive* activity. These agents are most active against aerobic *Gram negative Bacilli*. One of the second generation agents, ciprofloxacin (**9**) remains the most active quinolone against *Pseudomonas aeruginosa*[15].



Marginal susceptibility and acquired resistance limit the usefulness of second-generation quinolones in the treatment of staphylococcal, streptococcal and enterococcal infections. Third-generation quinolones ofloxacin (**10)**, sparfloxacin, gatifloxacin retain expanded *Gram negative* and atypical intracellular activity but have improved *Gram positive* coverage. Finally, fourth-generation agents such as moxifloxacin, trovafloxacin have emerged to improve *Gram positive* coverage, maintain *Gram negative* coverage and gain anaerobic coverage.[16]

Many of quinolin-2(1*H*)-one derivative has been identified as non steroidal compounds and as compositions that are high affinity, high specificity agonists, partial agonists (i.e., partial activators and/or tissue-specific activators) and antagonists for androgen receptor (AR) and progesterone receptor (PR). Regulation of a gene by such factors requires both Intracellular receptor (IR) and corresponding ligands, which have the ability to selectively bind the IR in a way that affects gene transcription. The natural hormones for steroid receptors have been known for a long time, such as testosterone for androgen receptor (AR) and progesterone for progesterone receptor (PR). Androgen and progesterone receptor modulators are known to play an important role in health of both men and women. For example, AR antagonists, such as cyproterone acetate, flutamide and casodex are useful in the treatment of prostatic hyperplasia and cancer of the prostate. AR agonists, such as fluoxymesterone are used in the treatment of hypogonadism. PR agonists, such as medroxyprogesterone acetate are used in birth control formulations in combination with estrogen or as a synthetic estrogen analogue. Further, antagonists of PR are potentially useful for contraception and in the treatment of chronic disorders, such as certain hormone dependent cancers of the breast, ovary and uterus. Due to increased life expectancies development of tissue selective, safer, orally active AR and PR modulators are desirable to improve the quality of life. A group of hydroquinoline derivatives was recently described as AR and PR modulators[17]. Analogues of quinolone, oxindole, benzooxazinone derivatives have been described as cardiotonic agents.[18,19] 2-Quinolone derivatives are reported to exhibit farnesyl transferase inhibiting activity. Some of the patents describe[20] a class of novel 1, 2-annelated quinoline compounds bearing a nitrogen- or carbon-linked imidazole showing farnesyl protein transferase and geranyl transferase inhibiting activity. The other reported quinolone derivatives are useful for the treatment and prevention of cerebral disorders such as ischemic attack, a cardiac or respiratory arrest, a cerebral thrombosis or embolism or a cerebral trauma, cerebral senility, dementia following multiple infarcts, Alzheimer's disease or Pick's disease and for the treatment of olivopontocerebellar and other neurodegenerative ailments such as Huntington's chorea for the treatment of tinnitus and also found to have an antipsychotic activity, which makes them suitable, for the treatment of schizophrenia [21].

Marcus Vinícius Nora De Souza (2005) reported [22] various functionalities which are responsible for binding and drug action of quinolone pharmacophore.

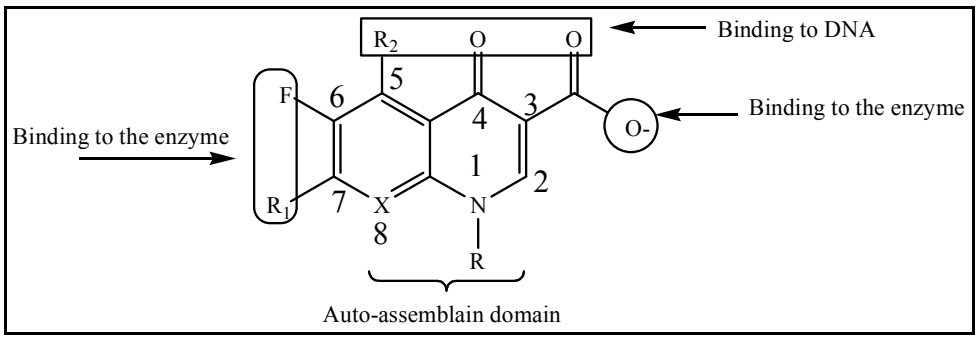
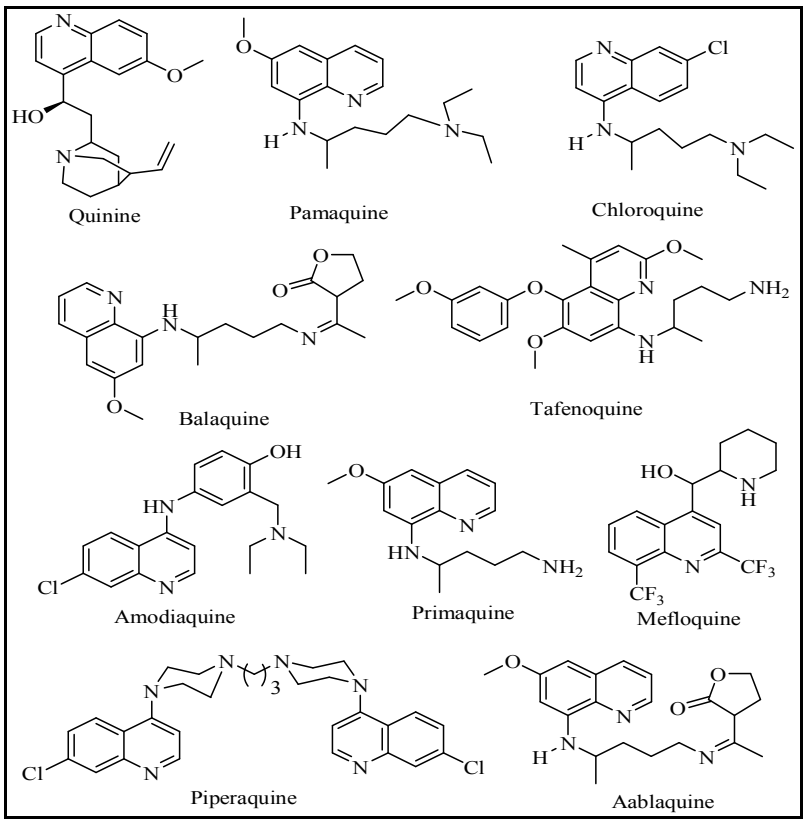


Fig 1.1 Structure of 4-quinolone pharmacophore

The 4-hydroxyquinolines, 4-hydroxycoumarines, 4-hydroxypyridones and 4-hydroxy-2-pyrones with aliphatic acyl groups at position three were found to be of much interest because of their biological activities. The Structure Activity Relationship (SAR) studies clearly revealed the role of various parts of 3-functionalized-2(1*H*)-quinolones.[23] reported that the presence of β-carbonyls is responsible for brain penetrating ability. The literature survey supports the clinical and structural importance of 3-functionalized-2(1*H*)-quinolones.

Among the 3-functionalised quinolones, the 3-acetyl-4-hydroxy-quinolin-2(1*H*)-one which is of our interest, itself is a drug molecule with antimalarial, antiviral, anti microbial and antiallergic activities[24, 25, 26]. Various research groups have reported the pharmacological activities such as N-methyl-D-aspartate (NMDA) receptor antagonist, serotonin receptor antagonist for compounds with 4-hydroxy quinolin-2(1*H*)-one pharmacophore [27-29]. Since 1800's extensive research were carryout on quinolone derivatives to develop new molecules which are acting as drugs, agrochemicals, dyestuffs and materials. Quinine was a first antimalarial drug used up to 1930 since from its isolation (it is isolated from Cinchona tree by Pelletier and Caventou in 1850). Chloroquine was discovered by Hans Andersag in 1934, which forms 'Ferriphotoporphyrin-Chlorquine' complex with free heam that generated during trophozoite feeding, which is highly toxic to the parasite. Some modified quinolone compounds were shown as anti-tumor agents to treat breast cancer, , human purine protein binding agents, anti-parasitic. Most of the quinoline ring systems are well being used as precursor and active biomolecules for the treatment of malarial disease few of them are given below.



We have reported a rapid microwave assisted synthesis of 1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3-(aryl)prop-2-en-1-ones and their anti bacterial and anti fungal evaluation.in that work few 1-(6-chloro-2-methyl-4-phenylquinolin-3-yl)-3-(aryl)prop-2-en-1-ones were synthesized by microwave assisted synthesis, the antimicrobial activities of synthesized compounds were screened against Gram negative organisms such as *Escherichia coli* (ATCC 25922), *Bacillus subtilis* (ATCC 117788), *Salmonella typhi* (ATCC 25264), *Gram positive Staphylococcus aureus* (ATCC 700699) and fungal organisms such as *Aspergillus flavus*, *Aspergillus fumigatus* and *Candida utilius*. Apart from that, some reports on theoretical aspects like stability and reactivity also been explored through single crystal studies[30-33] and DFT studies.

Conclusion:

There are many reports on quinoline derivatives and about their medicinal applications. Still structural modifications to get better properties are being continued, we have explored the synthesis of some quinoline derivatives and their unambiguous structural determination through single crystal X-ray diffraction method. This review reported some of the medicinally important quinoline derivatives with their applications.

References

1. Joule, J. A. and K. Mills (2012).Heterocycles in Medicine. In *Heterocyclic Chemistry at a Glance*, John Wiley & Sons, Ltd, pp. 167-179.
2. Lednicer, D (2008). Drugs Based on Five-Membered Heterocycles, *Strategies for Organic Drug Synthesis and Design, Second Edition*, pp. 239-318.
3. Baumann, M. and I. R. Baxendale (2013). An overview of the synthetic routes to the best selling drugs containing 6-membered heterocycles, *Beilstein J. Org. Chem.*, Vol. 9, No. 1, pp. 2265-2319.
4. Broughton, H. B. and I. A. Watson (2004). Selection of heterocycles for drug design, *J. Mol. Graph.Model.* Vol. 23, No. 1, pp. 51-58.
5. Dua, R., S. Shrivastava, S. Sonwane and S. Srivastava (2011). Pharmacological ignificance of synthetic heterocycles scaffold: a review, *Adv. Biol. Res. (Rennes),* Vol. 5, No. 3, pp. 120-144.
6. Banzal, R.K. (2001). Heterocyclic Chemistry. 3rd Ed. New Age International Ltd, pp. 332-333.
7. Vaughan, W.R. (1946). 2, 4-Dihydroxy-3-quinolyl methyl ketones, J. Am. Chem. Soc., Vol. 68, No. 2, pp. 324-325.
8. Siporin, C., C.L. Heifetz and J.M. Domagala (1990). The New Generation of Quinolones, Marcel Dekker, INC, Newyork, pp. 2-42.
9. Lange, J.H.M., C.P. Verveer, J.M. Osanabrug and G.M. Visser (2001). Rapid microwave enhanced synthesis of 4-hydroxyquinolinones under solvent-free conditions. Tetrahedron Lett, Vol. 42, No. 7, pp. 1367-1369.
10. Hennequin, L.F., A.P. Thomas, C. Johnstone, E. S. E. Stokes, P. A. Ple, J.J.M. Lohmann, D.J. Ogilvie, M. Dukes, S.R. Wedge, J.O. Curwen, J. Kendrew and C.L.V. Brempt (1999). Design and Structure−Activity Relationship of a New Class of Potent VEGF Receptor Tyrosine Kinase Inhibitors, J. Med. Chem., Vol. 42, No. 26, pp. 5369-5389.
11. Carmeliet, P. and R.K. Jain (2000). Review article angiogenesis in cancer and other diseases, Nature, Vol. 407, No 11. pp. 249-257.
12. Sucheta, K. and B.V. Rao (2005). Microwave induced solvent-free synthesis of substituted 1,5-benzodiazepine derivatives, Indian J. Chem., Vol. 44B, No. 10, pp. 2152- 2154.
13. Ullrich, A. and J. Schlessinger (1990). Signal transduction by receptors with tyrosine kinase activity, Cell, Vol. 61, No.2, pp. 203-212.
14. Luckner, M. (1980). Alkaloid Biosynthesis in Penicillium cyclopium--Does It Reflect General Features of Secondary Metabolism, J. Nat. Prod., Vol. 43, No. 1, pp 21–40.
15. Hooper, D.C. (2000). New uses for new and old quinolones and the challenge of resistance. Clin. Infect. Dis., Vol. 30, No.2, pp. 243-254.
16. Ambrose, P.G, R.C.J. Owens, R. Quintiliani and C.H. Nightingale (1997). New generations of quinolones: with particular attention to levofloxacin, Conn. Med., Vol. 61,No.5, pp. 269-72.
17. Jones, T. K., D.T. Winn, L. Zhi, G.L. Hamann, C.M. Tegley and C.L.F. Pooley (1997). Steroid receptor modulator compounds and methods, US Patent 5,688,808.

18. Combs, D.W. (1992). 6-benzoxazinyl- and 6-benzothiazinyl 2,3,4,5-tetrahydropyridazin- 3-ones, US Patent 5081242.
19. Campbell, S.F., D.S. Morris and D.A.Roberts (1990). Imidazo[4,5-b]pyridyl quinolone cardiac stimulants, US Patent 4898872.
20. Palmer, P.A. and I.D. Horak (2001). Farnesyl Protein Transferase Inhibitor Combintions ith Anti-tumor Nucleoside Derivatives, WO/2001/064195.
21. Frost, W.F., R. Jonathan, Lardenois, Patrick, Bertin, Jean, Saarmets, A. Rousselle and Corinne (1991). Derivatives of (1-hydroxy-2-piperidylalkyl-indol-2-ones, 2-quinolinones, 2-benzo(B)azapinones, benzimidazol-2-ones, and quinazolin-2-ones, their preparation and their application in therapeutics, United States Patent 5,034,401.
22. Marcus Vinicius Nora De Souza (2005). New Fluoroquinolones: A Class of Potent Antibiotics, Mini-Reviews in Medicinal Chemistry, Vol.5, No.11, pp.1009-1017.
23. Detsi, A., V. Bardakos, J. Markpoulos and O.I. Markopoulou (1996). Reactions of 2- methyl-3,1-benzoxazin-4-one with active methylene compounds: a new route to 3- substituted 4-hydroxyquinolin-2(1H)-ones, J. Chem. Soc. Perkin I, pp. 2909-2913.
24. Mornika.Y., K. Takahashi. S. Hata and S. Yamada (1981). 1. Antiallergic agents. I. Pyranoquinoline derivatives, Eur. J Med. Chem., Vol. 16, No. 3, 251-256.
25. Ukrainets, I.V., N.L. Bereznyakova1 and I.A. Turaibei (2008). Synthesis, structure and antiviral activity of N-R-amides of 2-hydroxy-4-oxo-4H-pyrido[1,2- a]pyrimidine-3- carboxylic acids, Chem. Heterocycl. Comp, Vol. 44, No. 1, pp. 50-63.
26. Jayashree, B.S., T. Seeja and Yogendra Nayak (2010). Design and synthesis of 2- quinolones as antioxidants and antimicrobials: a rational approach, Med. Chem.Res., 19 (2), 193-209.
27. Chapman, A.G., N. Durmuller, B.L. Harrison, B.M. Baron, N. Parvez and B.S. Meldrum (1997). Anticonvulsant activity of a novel NMDA/glycine site antagonist, MDL 104,653, against kindled and sound-induced seizures, Eur.J. Pharmacol, Vol. 274, No.1-3, pp. 83- 88.
28. Rowley, M., J.J. Kulagowski, A.P. Watt, D. Rathbone, G.I. Stevenson, R.W. Carling, R. Baker, G.R. Marshall, J.A. Kemp, A.C. Foster, S. Grimwood, R. Hargreaves, C. Hurley, K.L. Saywell, M.D. Tricklebank and P.D. Leeson (1997). Effect of Plasma Protein Binding on in Vivo Activity and Brain Penetration of Glycine/NMDA Receptor Antagonists, J. Med. Chem., Vol. 40, No. 25, pp. 4053–4068.
29. Hayashi, H.,Y. Miwa, S. Ichikawa, N. Yoda, I. Miki, A. Ishii, M. Kono, T. Yasuzawa and F. Suzuki (1993). 5-HT3 Receptor antagonists. 4-Hydroxy-4-quinolinecarboxylic acid derivatives, J. Med. Chem, Vol. 36, No.5, pp. 617–626.
30. S. Sarveswari, V. Vijayakumar 2011. Synthesis and characterization of new 3-(4,5-dihydro-5-aryl)isoxazol-3-yl)-4-hydroxyquinolin-2(1*H*)-ones and 3-(4-styryl)isoxazolo[4,5-*c*]quinolin-4(5*H*)-one. *Arabian Journal of Chemistry*, (*In Press, Corrected Proof)*, *Available online 19 September 2011*
31. S. Sarveswari, R. Prasath, P.S. Mathew, Deepak Chopra, T. Narasimhamurthy, V. Vijayakumar, 2012. Synthesis and an Evaluation of Molecular Conformation and Crystal Packing in Two Substituted 4-Phenylquinolines J. Chem. Crystallogr. 2012, 42 (6) 583-587
32. S. Sarveswari and V. Vijayakumar, 2012**.** An efficient microwave assisted eco-friendly synthesis of 6-chloro-3-(3-arylacryl oyl)-2-methyl-4-phenylquinolines and their conversion to 6-chloro-3-(1-phenyl-5-aryl-4,5-dihydro-1H-pyrazol-3-yl)-2-methyl-4-phenylquinolines. J. Chin. Chem. Soc., 59, (1), 66-71.
33. S. Sarveswari, A. Srikanth, N. Arul Murugan, V. Vijayakumar, Jerry P. Jasinski, Hanna C. Beauchesne, Ethan E. Jarvis. 2015. Synthesis, characterization of (3*E*)-1-(6-chloro-2-methyl-4-phenyl quinolin-3-Yl)-3-aryl prop-2-en-1-ones through IR, NMR, single crystal X-ray diffraction and insights into their electronic structure using DFT calculations *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *Volume 136, Part B*, *1010-1017.*

*****