CHAPTER 8

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The research work embodied in this thesis entitled, “Synthesis and Biological Applications of Novel Quinoline Derivatives” is the synthesis of many derivatives of the medicinally important heterocyclic compound quinoline which are very likely to be bioactive and therefore establish their efficacy as possible lead compounds in developing useful drugs.

New substituted quinoline derivatives namely (3-(2-chloroquinolin-3-yl)oxiran-2-yl)(phenyl)methanones (1-11) with epoxy functional group and (E)-1-((2-aryloxyquinolin-3-yl)methylene)thiosemicarbazides (12-21) with thiosemicarbazide and phenoxy groups as substituents were successfully synthesized and characterized by various spectroscopic and other analytical methods. Their pharmacological properties were investigated by in vitro procedures and computational in silico studies.

Studies on (3-(2-chloroquinolin-3-yl)oxiran-2-yl)(phenyl)methanones (1-11)

From the experiments described in Chapters 2-7 we conclude that we have developed an elegant synthesis of (3-(2-chloroquinolin-3-yl)oxiran-2-yl)(phenyl)methanones (1-11) by the modification of the Darzen’s condensation procedure. The oxiranes were obtained as a mixture of cis and trans isomers in excellent yields. Among them the compounds 1, 2, 4-7, 10 and 11 were mainly trans isomers and we could obtain them in pure form by column chromatography. On the other hand compounds 3, 8 and 9 had significant amounts of cis isomers, which proved difficult to be separated by column chromatography. However, repeated recrystallization by slow solvent evaporation of ethyl acetate solutions of small amounts of 3 and 8 produced some good crystals of pure cis isomers, which were used to carry out single crystal X-ray analysis. The trans isomers of 1 and 9 were also subjected to X-ray analysis. The structures of all the eleven derivatives were supported by their IR, $^1$H and $^{13}$C NMR spectral and HRMS data. Among the eleven compounds we are reporting here only 1 and 2 are known in the literature, though their preparation is a bit different from our procedure. The remaining nine compounds are novel and have not been reported so far according to sci-finder and reaxys search results.
Computational *in silico* studies show that all the eleven quinolyl oxirane derivatives comply with Lipinski’s rule of five and are bioactive. Based on the computational QSAR studies of toxicity the compounds 1 and 9 are predicted to be the least toxic. A highly reliable QSAR model T.E.S.T was applied for this study. Experiments were carried out for estimating *in vitro* toxicity of the oxiranes using brine shrimp nauplii and antimicrobial evaluations were conducted by established methods. From these studies we conclude that compounds 4 and 5 are the most efficient antimicrobials with least toxicity against brine shrimps while all the other compounds show moderate activity as antibacterial and antifungal agents. In addition, *in silico* molecular docking against GlcN-6-P synthase studies were conducted. It was found that the results from both the sources were reasonably comparable. This observation of agreement between the experimental and computational results leads us to conclude that the compounds have the potential to be lead compounds for developing antimicrobial agents or any other similar medicinal compounds.

Radical scavenging efficiency of these compounds has been studied by their reaction with two free radicals, namely ABTS and DPPH. An important outcome of this study is that the compound 11 is a better free radical scavenger than the standard, i.e., ascorbic acid, and that the compound 9 is as good as the standard in its effectiveness towards ABTS radical scavenging property. From DPPH method we conclude that compound 7 is the most efficient radical scavenger. The negative results of DNA cleavage studies indicate that these compounds do not exert adverse effect on the biological processes in the human body.

All these studies strongly indicate that the quinolinyl oxiranes 1-11 are promising molecules for further *in vivo* investigation as antifungal and anticancer agents. From the literature survey and review on epoxides, we could infer that very little biological evaluation of epoxides has been carried out so far. In view of this, the synthesis of quinoline containing epoxides (1-11) and study of their biological properties is a significant step in filling this gap. The difficulty of separating the compounds 3, 8 and 9 as single isomers is not an insurmountable problem, and suitable methods can be developed for this purpose. However, for the present study it was not indispensable and hence we did not invest much time on that. Further QSAR studies on these quinoline epoxy compounds can be carried out to obtain lead compounds for drug development processes.
Studies on \((E)-1-(2\text{-aryloxyquinolin}-3\text{-yl})\text{methylene} \text{thiosemicarbazides} \((12-21)\)

Novel \((E)-1-(2\text{-aryloxyquinolin}-3\text{-yl})\text{methylene} \text{thiosemicarbazides} \((12-21)\) were synthesized by reacting 2-chloroquinoline-3-carbaldehyde and its substituted derivatives first with phenols and then condensing the phenoxy products obtained with thiosemicarbazide. All the products were obtained in high purity and excellent yield. The identity of the compounds was established by their IR, \(^1\)H and \(^{13}\)C NMR spectra and HRMS data. The novelty of these compounds has been checked using sci-finder and reaxys search engines. They were evaluated for their biological activities by various \textit{in vitro} and \textit{in silico} procedures.

From the computational \textit{in silico} studies we conclude that all of them comply with the Lipinski’s rule of five and are bioactive. The \textit{in silico} toxicity estimation using QSAR model, T.E.S.T., indicates that compound 21 can be a lead compound with the least toxicity. The present \textit{in silico} findings serve as a base to further investigate the properties of these new compounds.

The \textit{in vitro} antimicrobial evaluation studies lead us to conclude that a few of them are reasonably good antibacterial and antifungal agents with activities close to standard antibiotics. The scavenging efficiency of these compounds by DPPH and ABTS methods proves that they are effective free radical scavengers. Most of these compounds show a better efficiency in scavenging DPPH free radicals than ABTS free radicals.

From the MTT assay we conclude that compound 18 exhibits good antiproliferative activity. To our delight, the same compound was found to be the most efficient ligand to bind to the receptor protein EGFR tyrosine kinase with 3 hydrogen bonds and lowest docking energy. The agreement between the experimental and the computational results strongly indicate the good potential of compound 18, and may be even the other compounds, hold for further \textit{in vivo} studies that can be carried out in the direction of developing them into anticancer agents.

The synthesized quinoline containing thiosemicarbazides are proved to exhibit various biological properties. Further studies may be undertaken to prepare metal complexes as they are likely to have much better biological properties than the parent thiosemicarbazides. QSAR modeling on structural modification studies can be carried out to find lead compounds with better biological activities.
The *in silico* and *in vitro* studies of quinoline derivatives that we synthesized exhibit good biological activities and from this we conclude that they have the potential of taking them to next stage of drug discovery i.e. they may be further considered to *in vivo* studies.