CHAPTER - 5

CONCLUSION

Science is a way of thinking much more than it is a body of knowledge - Carl Sagan
5.1. CONCLUSIONS

Currently, high-throughput screening is a common strategy in the pharmaceutical industry in order to find hits against a new target. The objective of screening these large compound collections is to provide medicinal chemists with starting points for synthetic optimization of drug candidates. The disadvantage, however, from this approach is that more and more research groups use the same commercially available compound collections. As a result, the same (or at least structurally very similar hits) are obtained by different research groups. Therefore, pharmaceutical industry no longer uses these hits, as most of the scaffolds are covered by patents and cannot be used to generate new intellectual property.

The heterocycle nucleus is one of the most important and well known heterocycles which is a common and integral feature of a variety of natural products and medicinal agents. Heterocycle nucleus is present as a core structural component in an array of drug categories such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, antihypertensive, and antimicrobial agents etc., Many reviews reflect the contribution of heterocycle to the development of society from a biological point of view as well as to the understanding of life processes and to the efforts to improve the quality of life. Heterocycles play an important role in biochemical processes because the side groups of the most typical and essential constituents of living cells, DNA and RNA, are based on aromatic heterocycles. The presence of heterocycles in all kinds of organic compounds of interest in biology, pharmacology, optics, electronics, and material sciences and so on is very well known. Between them, sulfur and oxygen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis. The grounds of this interest were their biological activities and unique structures that led to several applications in different
areas of pharmaceutical and agrochemical research or, more recently, in material sciences. The present paper is an attempt to review the pharmacological activities reported for heterocyles in the current literature with an update of recent research findings on these nuclei.

The chemistry of nitrogen and oxygen containing heterocycle is a rapidly changing subject whose almost frenetic activity is attested by the countless research papers appearing in established journals and by the proliferation of monography and reviews on varied subjects like photochemistry, pharmacology, industrial to mention a few. This expansion of knowledge and application poses pedagogical problems; it is difficult for only an organic chemist to be cognizant of development over the whole field in all the important areas of its application. Yet the field of nitrogen and oxygen containing heterocycle provides an opportunity for an organic chemist to synthesize new molecules whose structural activity relationship may present areas of application in the field of medical sciences and alike. Based on these extensive applications of nitrogen and oxygen containing heterocycle especially as anticancer and antioxidant agents and also due to broad applications of oxadiazole and pyrimidone analogues. The present work deals with the integration of benzophenone and pyrimidone moiety with oxadiazole ring which has been accomplished. The application of newly synthesized compounds was confirmed by biological assays.

The synthesis of a series of potentially biologically active 2,5-di(4-benzoyl)phenoxy methyl-1,3,4-oxadiazoles (9a-j) were achieved via a multistep synthesis sequence and their application as anticancer agents was confirmed. Newly synthesized 1,3,4-oxadiazole analogues 9a-j were assessed for cytotoxicity against human leukemia cell lines CEM (T-cell leukemia) and K562 (Chronic myelogenous leukemia). The effective concentrations of compounds 9a-j required to inhibit CEM and K562 cell
growth and survival were determined first by carrying out dose response experiments using trypan blue dye exclusion assay. The cell viability was further assessed by MTT assay, Lactate dehydrogenase assay and fluorescence activated cell sorting analysis. Also DNA fragmentation assay was performed to assess the potential of compounds to damage DNA. Compounds 9b and 9i with chloro group play a dominant role in inhibiting the leukemic cell proliferation.

When the pyrimidone ring was incorporated into aryl acetohydrazide moiety resulted in N-[2-(6-oxo-6H-pyrimidin-1-yl)-acetyl]-hydrazides (5a-j). These analogues displayed potential antioxidant activity based on a series of assays namely DPPH radical scavenging, lipid peroxidation, reducing power, hydroxyl radical scavenging and metal chelating ability. Nevertheless, compounds 5g and 5j with trifluoro methyl and N,N-dimethyl amino group, respectively exhibited good antioxidant activity.

Moreover these analogues were exhibited XO inhibitory activity. The inhibitory activity of the compounds 5a-j against XO was compared with standard drug allopurinol and interestingly compounds 5c, 5d and 5f with iodo, methyl and methoxy groups respectively shown good activity. This was further confirmed by molecular docking studies.

Based on the importance of pyrimidone appended oxadiazole analogues, the synthesis of 3-(5-phenyl-[1,3,4]oxadiazol-2-ylmethyl)-3H-2-pyrimidone (6a-j) were achieved in moderate yield. However these analogues exhibited significant antimicrobial activity with a degree of variation against Gram-positive and Gram-negative bacteria and also against fungal strains.

5.2. SCOPE FOR FUTURE WORK

The field of oxadiazole and pyrimidones is intimately involves synthesis of its analogues and thereby the production of new systems for newer applications. The interesting property of acetohydrazide group present in the intermediates during the
synthesis of oxadiazole and pyrimidones is due to the ease of extension of the side chain by the involvement of CONHNH$_2$ group. Utilization of this side chain results in the formation of heterocyclic rings. The biological activity of benzophenone integrated with a heterocyclic ring paves the way for a plethora of theoretically available organic molecules. As the field expands, the compounds that interest crystallographers, pharmacologists, industrialists become more varied. Such compounds run the gamut of man’s fancy from imitating naturally occurring molecules to bizarre arrangement of atoms designed to test the ever evolving tenets of structural theory. Thus at the heart of chemistry of oxadiazole and pyrimidone analogues is the ability to integrate heterocyclic rings containing biological activity as is manifested in the field of neutraceuticals.

The author, wish to emphasize that a synthetic programme of oxadiazole and pyrimidone analogues of any magnitude is a comprehensive experience which involves the application of the knowledge and techniques of varied fields.

There is an ample scope for further research and development in this area. For instance, benzophenone and acetohydrazide moiety, can be incorporated with other heterocyclic rings viz., isooxazoline, thazine, pyridine, pyridazine, pyrimidine, pyrazine and triazine, thiazolidinone and coumarin which is a best anticancer agent and biological assays of these analogues can be performed.