PREFACE

The recent advances in the field of pharmaceutical technology and ever expanding worldwide research in medicinal chemistry have resulted in the continual influx of novel drugs in therapeutics. There are various pharmaceutical compounds available which may be anticancer, antibiotic, antineoplastic, analgesic, antifungal, antihypertensive, antiviral, anxiolytic, antiallergic, sedative, antipsychotic, antidepressant, etc. During the past few decades, there has been a dramatic increase in the number of organic compounds that could be used to alleviate the sufferings from several diseases. This has been possible due to novel approaches adapted by the synthetic organic chemists all over the world. The scope and utility of these organic compounds is enormous, and ranges from treating diseases to the maintenance of human health.

The work embodied in this thesis entitled “SYNTHESIS AND BIOLOGICAL SCREENING OF NEW PYRIMIDINE, OXADIAZOLE AND TRIAZOLE DERIVATIVES” comprises of eight chapters.

Chapter I contains the general introduction to heterocyclic compounds and biological activity. The scope of the present work is also highlighted, and finally references were listed.

Chapter II describes the synthesis and antiproliferative activity of some new fluorinated Schiff bases derived from 1,2,4-triazoles. A series fluorinated Schiff bases derived from 1,2,4-triazoles were synthesized and the formation of new products was confirmed by recording their elemental analyses, FT-IR, $^1$H NMR, $^{13}$C NMR, LC-MS and elemental analysis.New compounds were evaluated for their antiproliferative effect using the MTT assay method against four human cancer cell lines (K562, COLO-205, MDA-MB231 and IMR-32) for the time period of 24 h.

Fluorine or trifluoromethyl-containing compounds are well known to play an important role in biochemistry. A series of new Schiff bases 4(a-j)were synthesized and their antiproliferative activity has been evaluated. Antiproliferative assay results indicated that these derivatives have high antiproliferative activity againstColo-205,IMR-32 and MDA-MB 231. Compound 4g containing o-trifluoromethyl...
group appeared to be the most active against the Colo-205, IMR-32 and MDA-MB 231 cell lines. From the experimental results, it could be concluded that the introduction of the 1,2,4-triazole moiety and electron withdrawing group has significant potential to obtain new antiproliferative compounds. From this work, a few active molecules (4f, 4g and 4h) were identified which are capable of inhibiting the growth of human cancer cell lines in vitro.

**Chapter III** describes the synthesis of new 5-chloro-8-bromo-3-aryl-1,2,4-triazolo[4,3-c]pyrimidines and their antimicrobial activity. A series of new 5-chloro-8-bromo-3-aryl-1,2,4-triazolo[4,3-c]pyrimidine derivatives (8a–j) were synthesized and characterized by different spectral studies. Ten new compounds 8(a–j) were tested in vitro for their antimicrobial activity against clinically isolated strains. Variable and modest activities were observed against the investigated strains of bacteria and fungi.

The formation of products was confirmed by recording their elemental analyses, FT-IR, $^1$H NMR, $^{13}$C NMR and LC-MS. Compounds 8(a–j) were tested in vitro for their antibacterial activity against two Gram-positive and two Gram-negative bacterial strains. Commercial antibiotics such as bacteriomyein and gentamycin were used as standard drugs. Compound 8f was found to be more potent against Gram-positive and -negative bacterial strains with the zone of inhibition, respectively, 27–29 mm. Compounds 8i and 8j exhibited good antibacterial activity against all the bacterial strains. Compounds 8b–8e were showed moderate antibacterial activity and compound 8b was found to be slightly active than 8c–8e. Compounds 8g and 8h were found to be moderate antibacterial activity and compound 8a was weakly active against tested bacterial strains. The in vitro antifungal activity of the new pyrimidine derivatives (8a–j) was studied against the fungal strain. Compounds 8f, 8i, and 8j showed good inhibition against F. oxysporum. Compounds 8b, 8c, 8d, and 8e exhibited moderate antifungal activity against tested fungal strain. Compounds 8g and 8h exhibited moderate antifungal activity against F. oxysporum. On the other hand, the lowest antifungal effect was detected for compound 8a against tested fungal strain. Among the compounds 8(a–j) the antimicrobial inhibitory activity follows the order 8f>8i>8j>8b>8e>8d>8c>8h>8g>8a against tested microbial strains. Therefore,
this work presents a new class of potent, wide-spectrum antimicrobial activity of the compounds.

Chapter IV describes the synthesis antimicrobial evaluation of some new 1,3,4-oxadiazoles bearing 5-chloro-2-methoxyphenyl moiety. A series of new 1,3,4-oxadiazole derivatives 12(a–h), containing 5-chloro-2-methoxy benzohydrazide moiety were synthesized by the reaction of 5-chloro-2 methoxybenzoate with different aromatic carboxylic acids. These newly synthesized compounds were characterized by FT-IR, $^1$H NMR, LC-MS, and also by elemental analysis. All the newly synthesized compounds were screened for their antibacterial and antifungal activities. Antimicrobial studies revealed that compounds 12c, 12f, and 12g showed significant activity against tested strains.

The antibacterial activity of compounds 12(a–h) was evaluated and compared with bacteriomyein and gentamycin as standard drug. All the tested compounds showed antibacterial activity against four pathogenic bacterial strains. Among the series 12(a–h), compound 12c exhibited an elevated antibacterial activity against tested bacterial strains. Compounds 12f and 12g showed good antibacterial activity against all the tested organisms. Compounds 12h, 12b, 12a, 12d, and 12e showed moderate inhibitory activity. The in vitro antifungal activity of the synthesized compounds 12(a–h) was studied against Fusarium oxysporum. The compounds 12c, 12f, and 12g showed good antifungal activity and compounds 12h, 12b, 12a, 12d, and 4e were found to be moderately active against tested fungal strain.

In this study, different electron withdrawing and electron donating groups attached to oxadiazone ring as substituents were link to benzene ring. The close survey of antimicrobial efficacy indicated that the inhibition values of all the compounds exhibited a varied range of antibacterial and antifungal activities against all the tested microbial strains. The electron donating methoxy group in 12c showed good antimicrobial activity against tested microbial strains. The methoxy group and electron withdrawing fluorine atom in 12f and 12g produce enhanced antimicrobial activity. Compounds 12a, 12b, 12d, 12e and 12h exhibited moderate activity when compared 12c, 12f and 12g. The above studies reveal that the nature of the linkage (substituent on aromatic ring) influences the antimicrobial activity. Among the
compounds, $12(a-h)$ showed antimicrobial activity in the order of $12c > 12f > 12g > 12h > 12b > 12a > 12d > 12e$ against tested bacterial and fungal strains.

Chapter V describes the Synthesis and biological activity of some pyrimidine derivatives. A series of new pyrimidine derivatives were synthesized and structurally characterized by $^1$H NMR, LC-MS, FT-IR and elemental analyses. Anticonvulsant study was done by MES seizure model and rotorod method was employed to determine the neurotoxicity. Antioxidant activity was done by DPPH method.

In the present study, the anticonvulsant activity of the synthesized compounds was evaluated by MES model at the dose of 100 mg/kg. Compounds $16c$ and $17c$ were shown good protective effect on MES induced seizure, and the effect was nearer to that of standard (phenytoin). Similarly, compounds $13$, $14$, $15$, $16a$, $16b$, $16d$, $17a$, $17b$ and $17d$ showed moderate protective effects and a significant difference in protectiveness were observed when compared to standard group. All the compounds were examined for their neurotoxicity using rotorod method given in the dose of 100 mg/kg. Except compounds $13$, $14$ and $15$, none of the compounds showed neurotoxicity. These compounds showed 25 % toxicity compared to standard at 2h of oral administration. Among the synthesized compounds $13$, $14$, $15$, $16(a-d)$ and $17(a-d)$, all the compounds showed activity in the range of 27.11-72.57 % in comparison to phenytoin which completely inhibited the convulsions produced by electroconvulsometer, but compound $17c$ having electron withdrawing groups showed excellent anticonvulsant activity.

The in vitro scavenging assay of DPPH radicals was performed spectrophotometrically with ascorbic acid as positive control. The percentage scavenging effects of the compound $16b$ at 100, 150, 200 µg/ml is 32.2, 43.4, 54.8. The percentage inhibition of the compound $17b$ at 100, 150, 200 µg/ml are 51.1, 60.8, 68.1, respectively. Ascorbic acid presented a scavenging effect of 98.2 % at the concentration of 200µg/ml. The good inhibition of $17c$ showed 52.0 %, 61.7 % and 69.2 % at 200 µg/ml. All the compounds except $16b$, $17b$ and $17c$ exhibited lower inhibition. Electron donating methoxy group in $16b$, $17b$ and $17c$ showed more antioxidant activity when compared to other compounds in the series.
Chapter VI describes the synthesis of \( N-\{5\text{-aryl}\text{-}1,3,4\text{-oxadiazole-2-yl}\text{methyl}\}\text{-4-methoxyaniline derivatives and their anticonvulsant activity.} \) A series of some new 2,5-disubstituted-1,3,4-oxadiazoles (21a–i) have been conveniently synthesized by intramolecular oxidative cyclization of (E)-2-(arylbenzylidene)-2-[(4-methoxyphenyl)amino]acetohydrazides promoted by iodobenzene diacetate as an oxidant. The structures of the synthesized compounds have been confirmed by \(^1\text{H}\) NMR, \(^{13}\text{C}\) NMR, FT-IR, LC-MS, and elemental analysis. All the newly synthesized compounds were screened for their anticonvulsant activity against maximal electroshock (MES) seizure method.

The anticonvulsant activity of the nine newly synthesized 2,5-disubstituted-1,3,4-oxadiazoles (21a–i) was evaluated by MES induced seizure in rats at the dose of 100mg/kg. Compounds 21g, 21d, and 21a demonstrated significant protective effect on MES induced seizure. Similarly, compounds 21e, 21i, and 21h that showed moderate protective effect and a significant difference in protectiveness were observed when compared to standard group. Compounds 21f, 21c, and 21b have relatively lower anticonvulsant potencies. All the compounds were examined for their neurotoxicity on mice using rotarod method given in the dose of 100mg/kg. Except for compounds 21f, 21c, and 21b, none of the compounds showed neurotoxicity. These compounds showed 25% toxicity compared to standard once at 2 h of oral administration. The structure activity relationship study of these compounds indicates that the introduction of a benzene ring at position 5 of 1,3,4-oxadiazole ring; trifluoromethyl substituent at the para position showed the best anticonvulsant activity in 21g. Compounds 21d and 21a possessing a chloro group had good anticonvulsant activity in the MES model. Both compounds did not exhibit neurotoxicity at the highest administered dose. The fluoro and methoxy groups in 21e resulted in increased anticonvulsant activity. The presence of bromo group in 21i and nitro group in 21h shows moderate anticonvulsant activity. Anticonvulsant activity has increased considerably when methyl group in 21b was replaced with tolyl variation 21c. The presence of electron releasing methoxy group in benzene ring.

Chapter VII describes the synthesis and antiproliferative activity of 2,5-disubstituted-1,3,4-oxadiazoles containing trifluoromethylbenzenesulfonamide moiety. A series of some new 2,5-disubstituted-1,3,4-oxadiazoles 27(a–j) have been...
conveniently synthesized by intermolecular oxidative cyclization of (E)-2-(arylbenzylidene)-2-[(4-methoxyphenyl)amino]acetohydrazides promoted by iodobenzene diacetate as an oxidant. The synthesized compounds were characterized by elemental analyses, FT-IR, LC-MS, $^1$H NMR and $^{13}$C NMR spectral studies. All the compounds were evaluated for their in vitro antiproliferative effect using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay method against four human cancer cell lines (K562, Colo-205, MDA-MB 231, IMR-32) for the time period of 24 h.

The antiproliferative action of the synthesized compounds 27(a−j) was tested against four different cell lines. The activity was evaluated by measuring the levels of surviving cells after incubation for 24 h with the test samples using the MTT colorimetric assay based on the ability of metabolically active cells to convert the pale yellow MTT to a blue formazan product which is quantifiable spectrophotometrically. The results were expressed as percentage of cell proliferation compared with cells in control (cells treated with vehicle, 0.1% DMSO). Structure activity relationship can be drawn for the derivatives 27(d−i) containing electronegative atoms, which reveals that, compound 27h has more electronegative fluorine atom compared to 27(d−g) and 27i having other halogen atoms. In the same aspect, compound 27i has disubstituted chlorine atom exhibits relatively good inhibition compared to 27(d−g) which are having mono substituted halogen atom. Introducing electron donating methoxy groups to 27(a−c) and 27j of the phenyl ring of the substituent at ortho, meta and para positions resulted in the loss of activity. However, the presence of electron withdrawing groups in the phenyl ring increased the antiproliferative efficacy.

Chapter VIII describes the synthesis and in vitro Antiproliferative activity of New S-alkylated Bis-1,2,4-Triazole Derivatives. A series of new S-alkylated bis- 1,2,4-triazole derivatives were synthesized by the reaction of 5,5′-Methylenebis(4-(4-fluorophenyl)-4H-1,2,4-triazole-3-thiol) with different benzyl bromides. All the synthesized compounds were characterized using $^1$H NMR, LC-MS and elemental analyses. New compounds were evaluated for their antiproliferative effect using the MTT assay method against four human cancer cell lines (K562, COLO-205, MDA-MB231 and IMR-32) for the time period of 24 h.
The results of the biological screening experiments revealed that within the library of compounds 31(a–n), three compounds 31j and 31n showed good activity and the remaining compounds showed moderate activity. These compounds contain trifluoromethyl substituent on the benzene ring at different position. Among the compounds, compound 31j exhibited 74 %, 78 % and 71 % (at 10µM) inhibitory activity against Colo-205, MDA-MB 231 and IMR-32 cell lines, respectively, whereas compound 31n showed less inhibitory activity against K562. The good inhibition by these compounds could be attributed to the presence of electron withdrawing trifluoromethyl group. Similarly, compound 31m showed 70 %, 69 % and 66 % antiproliferation against Colo-205, MDA-MB 231 and IMR-32 cell lines, respectively. Compounds 31e and 31f are more potent than difluorinated 1,2,4-triazole compounds. Similarly, other compounds in the series showed moderate activity. However, the presence of electron withdrawing groups in the phenyl ring increased the antiproliferative efficacy. Based on their growth inhibitory activity data on cancer cells, monofluorine and trifluoromethyl-containing 1,2,4-triazole compounds were found to effectively inhibit the growth of cancer cells. The role of 1,2,4-triazole and electron withdrawing groups on the benzene ring are important for antiproliferative activity, and it is common in all derivatives.