The chemistry of heterocyclic compounds is as logical as the chemistry of aliphatic and olefinic compounds. Out of the more than twenty million chemical compounds currently registered, about one half contains heterocyclic system. Some of the significant organic compounds like alkaloids, antibiotics, essential amino acids, vitamins, hemoglobin, hormones, chlorophyll and dye stuffs contain heterocyclic ring. Heterocycles are important because of their natural abundance and these are also significant due to their chemical, biological and technological applications. The heterocyclic substrates have great applicability in pharmaceutics and most of the drugs in clinical uses are based on heterocyclic constitution as they have specific chemical reactivity. The majority of synthetic heterocyclics have found widespread use, for example as anticancer agents, antitubercular, analgesics, hypnotics, pesticides, insecticides and weed killers. These compounds are the integral part of the synthetic organic chemistry and most of these substrates are of the immense importance to the biological and industrial purposes. The majority of pharmaceuticals and biologically active agrochemicals are the heterocyclic products while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are the heterocyclic substrates in nature.

The **Chapter-I** presents many examples from the literature in the area of general heterocyclic chemistry. Majority of heterocyclic systems described here are significant due to their biological activities. Major emphasis has been laid down upon the various applications of the variety of the five membered heterocyclic derivatives containing the two nitrogen atoms at the 1,2 and 1,3-positions and compounds particularly pyrazoline, thiadiazolines and related derivatives are very significant from the synthetic and biological significance point of view. It was evident from the literature studies that chalcones and thiosemicarbazones are found to be very important synthones and with proper designing these intermediates can be subjected to the synthesis of the variety of heterocyclic compounds. Hence the chapters (**IIa, IIb, III, IVa & IVb**) of the thesis have been devoted upon the chemical transformations of chalcones, bischalcones and thiosemicarbazones for the generation of novel heterocyclic compounds.

The **Chapter-II** has been divided into two parts **IIa & IIb**. In part **IIa**, synthesis of alkoxy substituted furyl/thienyl-pyrazolines have been described. These compounds were obtained starting from O-hydroxy-acetophenone which was reacted with furfural
and thiophene-2-carboxaldehyde in the presence of NaOH/EtOH at 0°C to provide chalcone 2a & 2b respectively which were O-alkylated with suitable alkylation agents (allyl bromide, benzyl chloride, bromo ethylacetate & 1-chloromethyl-napthalene) to furnish alkoxy-chalcones 3a-3d & 4a-4d. The later further underwent cyclization reactions with phenyl hydrazine in the presence of EtOH/AcOH under refluxing conditions to yield pyrazolines 5a-5d and 6a-6d in good yields (Scheme-1).

![Scheme-1]

In the Chapter-IIb, the investigations have been carried out upon the synthesis of alkoxy N-thiocarbamoyl-pyrazolines. These significant heterocyclics have been prepared from the cyclocondensation reactions of chalcones 3a-3d and 4a-4d with thiosemicarbazide under the EtOH/NaOH conditions to furnish 7a-7d and 8a-8d as the final pyrazoline derivatives (Scheme-2).
Scheme-2

The \textit{trans} geometry around C-2 & C-3 double bond in alkoxy-chalcones was confirmed from the coupling value of $J_{2,3}=15.8$ Hz. The IR spectra of these compounds exhibited strong absorption at 1660-1650 cm$^{-1}$ due to the presence of conjugated carbonyl group.

The sterochemical disposition of the hydrogens H-X, H-M & H-A belonging to the pyrazoline ring (alkoxy-pyrazolines) have been ascertained from the study of coupling constant ($J$). The vicinal coupling between H-X & H-M was found to be 12.1 Hz which describes that these hydrogens are \textit{cis} to each other while \textit{trans} relationship between H-X & H-A was evident from the coupling constant of $J_{XA}=6.5$ Hz. The coupling value of 17.5 Hz between H-M & H-A evidently indicates their geminal placement at C-4. The phenyl rings at N-1 and C-5 are certainly \textit{trans} oriented to avoid any intramolecular repulsion. The C=N moiety of the pyrazoline ring became evident from the strong absorption in the IR spectra at 1602-1594 cm$^{-1}$.

This study represents a general method for the synthesis of alkoxy N-phenyl/thiocarbamoyl- pyrazolines under the ordinary conditions.

The \textbf{Chapter-III} includes the cyclization reactions of the alkoxy-thiosemicarbazones which lead to the formation of new thiadiazolines and quinoxaline based thiazoles.

The reaction of p-hydroxybenzaldehyde 9 with suitable alkylating agent (allyl bromide, benzyl chloride, bromo ethyl acetate, 1-chloromethyl-naphthalene, ethyl iodide and propyl iodide) provided 4-alkoxy-bezaldehyde 10a-10f which were easily condensed with thiosemicarbazide by refluxing in EtOH/HCl medium to give thiosemicarbazones 11a-11f. The later were refluxed under Ac$_2$O medium to yield new thiadiazolines 12a-12f (Scheme-3).
Scheme-3
To investigate the cyclization behavior of 11a-11f, these intermediates were also reacted with 2,3-dichloroquinoxaline in alcoholic medium to furnish thiazoles 13a-13f as the final products (Scheme-4).

Scheme-4
The final products (12a-12f & 13a-13f) of the above reactions (Scheme-3 & Scheme-4) have been obtained in very good yield by using simple protocols. Bischalcones are the molecules which are formed by joining two chalcone moieties together through the carbon chains of varying lengths and structures. The easy cyclization reactions of chalcones have prompted us to investigate the chemical transformations of the bischalcones in order to obtained novel bis(hetero)cyclic compounds. The results of chemical transformations of the bischalcones are presented in Chapter-IV that has been further sub divided into two parts IVa and IVb.

In Chapter-IVa synthesis of the furyl-bischalcones 14a-14e built around the aliphatic chains of varying lengths have been described. The cyclocondensation reactions of 14a-14e with phenyl hydrazine under the usual alcoholic and AcOH medium resulted in the formation of novel bipyrazolines 16a-16e (Scheme-5).
To generalize above syntheses, the researches have also been focused upon the thienyl-bischalcones 15a-15e which were also converted to bispyrazolines 17a-17e by reacting with phenyl hydrazine (Scheme-5).

The bischalcones 14a-14e & 15a-15e required for above study were obtained in good yields from the O-alkylation of furyl/thienyl-chalcone 2a & 2b respectively with suitable 1,ω-dibromoalkanes in the presence of anhydrous K$_2$CO$_3$/dry acetone and
Bu$_4$N$^+$T as the phase transfer catalyst. The use of PTC in these syntheses not only reduced the reaction times drastically but also improved the yield of bischalcones.

The Chapter-IVb concerns with the extensive reactions of bischalcones (14a-14e & 15a-15e) with thiosemicarbazide in the presence of NaOH/EtOH under refluxing conditions and these reactions could furnish new N-thiocarbamoyl-bispyrazolines 18a-18e & 19a-19e in good yields (Scheme-6). The main purpose of this study was to investigate the utility of thiosemicarbazide as the cyclizing agent in place of phenyl hydrazine and also to investigate the effect of thiocarbamoyl group upon the antibacterial behavior of the resulting bispyrazolines.

Scheme-6

The values of coupling constant ($J_{vic}$ & $J_{gem}$) were used to ascertain the stereochemical features of the bischalcones 14a-14e & 15a-15e (H-2 & H-3; $J_{trans}$=15.7 Hz) and bispyrazolines 16a-16e, 17a-17e, 18a-18e & 19a-19e (H-X, H-M & H-A; $J_{A,X}$=6.5 Hz, $J_{M,X}$=12.2 Hz & $J_{M,A}$=17.7 Hz).
To investigate the biological significance of the final products, the compounds 5a-5d, 6a-6d, 7a-7d, 8a-8d, 12a-12d, 13a-13d, 16a-16e, 17a-17e, 18a-18e and 19a-19e were also subjected to their antibacterial analysis against the four bacteria strains namely A. hydrophila, Y. enterocolitica, L. monocytogenes & S. aureus.

*In vitro* antibacterial activities of above heterocyclics were carried out using the culture by the disc diffusion method using nutrient broth medium [contained (mcg/ml): beef extract 1 g; peptone 5 g; pH 7.0]. In the disc-diffusion method, sterile paper discs (5 mm) impregnated with compound dissolved in dimethylsulfoxide (DMSO) at the concentration of 100 µg/ml were used. Gentamicin and Tetracycline were used as the standard drugs, whereas DMSO poured disc was used as negative control. Then, the paper discs impregnated with the solution of the compounds were placed on the surface of the media inoculated with the microorganisms (A. hydrophila, Y. enterocolitica, L. monocytogenes & S. aureus). The susceptibility of the bacteria to the test compounds were determined by the formation of an inhibitory zone after 24 hrs of incubation at 37°C. After incubation, the diameters of the inhibition zones (mm) were measured. The MIC (µg/ml) of these compounds were also determined by using Serial tube dilution method at the concentration of 50, 40, 30, 20 & 10 µg/ml.

Most of the studied compounds exhibited good to excellent activity against the tested microorganisms which was evident from their zone of inhibitions (mm) and MIC (µg/ml) results. The distinct differences in the antibacterial property of these compounds further justify the purpose of this study. The importance of such work lies in the possibility that the new compounds might be more efficacious drugs against bacteria for which a thorough investigation regarding the structure–activity relationship, toxicity and their biological effects could be helpful in designing more potent antibacterial agents for therapeutic use.

Thus, in these studies variety of the alkoxy substituted pyrazolines, bispyrazolines, thiadiazolines and thiazoles have been prepared in good yields under the ordinary conditions which are also associated to the good antibacterial activities.
The chalcones and bischalcones used in these studies have been synthesized through a sequence of several steps. The N-phenyl-pyrazolines, N-thiocarbamoyl-pyrazolines, N-phenyl-bispyrazolines, N-thiocarbamoyl-bispyrazolines, thiadiazolines and thiazoles obtained in this study were thoroughly purified by crystallizations in appropriate solvents. The structures of the newly synthesized intermediates and final heterocyclic/bisheterocyclic compounds have been confirmed from the rigorous analysis of their IR, $^1$H-NMR (400 MHz, CDCl$_3$/DMSO-$d_6$) and $^{13}$C-NMR (100 MHz, CDCl$_3$/DMSO-$d_6$) spectral parameters. The mass spectral fragmentation data have also been utilized to confirm the structures of the prepared compounds.
LIST OF PUBLICATIONS

1. **Synthesis, studies and in vitro-antibacterial activity 4 of N-substituted 5-(furan-2-yl)-phenyl-pyrazolines**
   Mamta Rani, Mohamad Yusuf, Salman Ahamad Khan, P.P. Sahota and G. andove

2. **Synthesis and in-vitro-antibacterial activity of [5-(furan-2-yl) - phenyl]-4, 5-carbothioamide-pyrazolines**
   Mamta Rani, Mohamad Yusuf and Salman Ahamad Khan

3. **Synthesis and biological evalutions of thia Diazoline derivatives**
   Mamta Rani and Mohamad Yusuf
   *Heterocyclic communication* (Communicated Manuscript-ID: HC.2011.0059)

4. **Synthesis, studies and in vitro antibacterial activity of some 5-(thiophene-2-yl)-phenyl-pyrazoline derivatives**
   Mamta Rani and Mohamad Yusuf

5. **Synthesis and in-vitro antibacterial activity of some alkoxy based N-substituted –5-(furan-2-yl)-phenyl-bispyrazolines**
   Mamta Rani and Mohamad Yusuf

6. **Synthesis and in-vitro antibacterial activity of some bis-5-(thiophen-2-yl)-carbothioamide-pyrazoline derivatives**
   Mamta Rani and Mohamad Yusuf
   *European Journal of Chemistry* **2012** (Accepted Manuscript, MS No. 476-3462-2-CE-1).