Introduction:

Infectious diseases are liable for a significant proportion of deaths worldwide and according to the World Health Organization (WHO), antimicrobial agents are deliberated to be "miracle drugs" that are the leading weapons in the cure of infectious diseases. Unfortunately, a number of the recent clinically valuable antimicrobial agents are becoming less effective because of the growth of microbial resistance. So, there is a crucial need for the discovery or optimization of newer antimicrobial agents that are active against resistant microorganisms.

Organic cyclic compounds having one atom other than carbon in their ring formation are designated as "heterocyclic compounds". Now a day various heterocyclic compounds containing nitrogen, sulphur, oxygen and other hetero atoms are known. The chemistry of heterocyclic compounds is as logical as that of aliphatic or aromatic compounds in character, depending on their electronic constitution. The curiosity of study of heterocyclic compounds was important in both theoretical as well as practical point of view. They are extensively distributed in nature and are necessary for life in different ways. The organic compound has heterocycle nucleus in central position performs biological activity in several agrochemical and pharmaceutical areas. Literature survey revealed that most of the heterocyclic compounds are beneficial in biosynthesis as well as in drug metabolism. In last decades much attention has been dedicated on the synthesis of heterocycles containing nitrogen and sulphur hetero atoms because of their biological and medicinal significance.

Nowadays an important aim in the synthetic organic chemistry is the improvement of new reagents and catalysts which are more active and selective, nontoxic, easily available and non-hazardous than the traditional ones. In the context of this doctoral dissertation, the thesis entitled "**Synthesis and studies of biologically active N and S heterocycles"** clearly reflects the objective, which is to develop the new biologically active different quinazolinone derivatives by condensing triazole, Schiff base and indole nucleus. Several biologically active cyclopropyl oxime derivatives were also synthesized. In present form the thesis consists of Fives chapters.

Chapter 1: Study of developments of biologically active Quinazolinones derivatives: A review

Chapter 2: Synthesis, characterization and antimicrobial evaluation of N-(4-oxo-2phenyl/thiophenylquinazolin-3(*4H*)-yl)-1H-indole-2 or 3-carboxamide derivatives.

Chapter 3: Design synthesis, characterization and antimicrobial evaluation of 1H-1,2,3-triazole and (substituted-phenyl)quinazolin-4(3H)-one derivatives.

Chapter 4: Synthesis, characterization and bio evaluation of N-(substituted)-2-[4-oxo-2-phenylquinazolin-3*(4H)*-yl] acetohydrazide derivatives.

Chapter 5: Synthesis characterization and bio evaluation of 4-alkoxy/aryloxyphenyl cyclopropyl methane oxime derivatives.

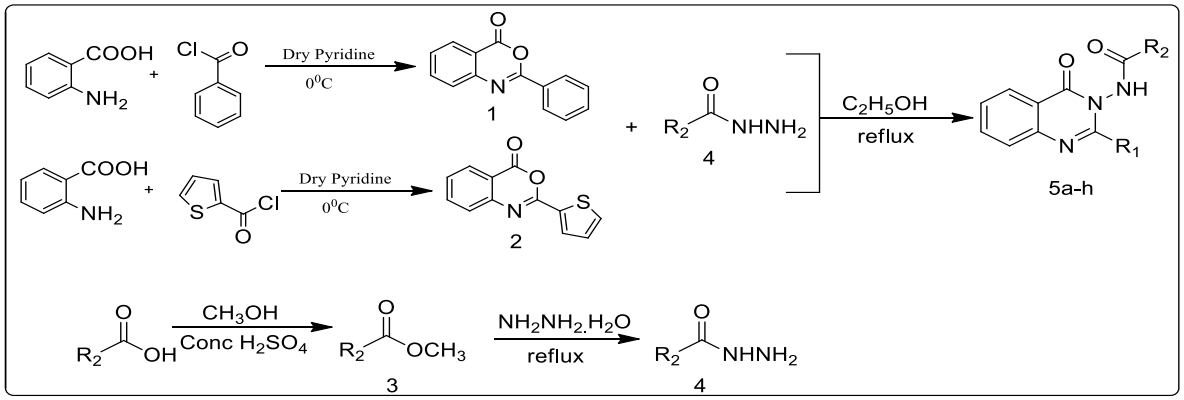
Chapter 1: Study of developments of biologically active Quinazolinones derivatives: A review

Quinazolinone-4(3H)-one skeleton has been constantly rewarded as a promising versatile lead molecule with a crucial importance in modern medicinal chemistry. Quinazolinone-4(3H)-one scaffolds produced by reaction of anthranilic acid and benzoyl chloride in pyridine at 0ºC. Several types of structurally different Quinazolinone-4(3H)-one have been designed, synthesized and evaluated for antibacterial, antifungal, anti-inflammatory, anticancer, anticonvulsant, anti-tubercular, anti-diabetic, antimalarial, antihypertensive activities since last decade. In this section, we were also discussed several quinazolinone based under clinical trial and marketed drugs.

Chapter 2: Synthesis, characterization and antimicrobial evaluation of N-(4-oxo-2phenyl/thiophenylquinazolin-3(*4H*)-yl)-1H-indole-2 or 3-carboxamide derivatives.

Looking to the medicinal importance of 4(3H)-quinazolinone and indole ring, we report in this chapter the synthesis of new class of heterocyclic molecules in which all of these moieties are present and try to develop potential bioactive molecules. A series of 5-subsituted Indole-2 or 3-carbohydrazide condensed with Quinazolinone-4(3H)-one nucleus has been synthesized and their structure characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and Mass spectrophotometry.

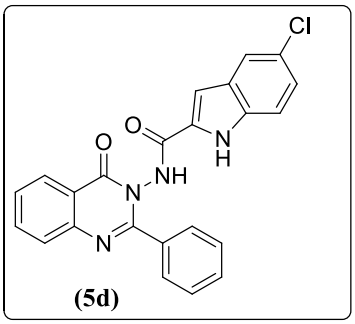
The devised synthetic route for the preparation of the final compounds **5(a-h)** is delineated in **scheme-1**.

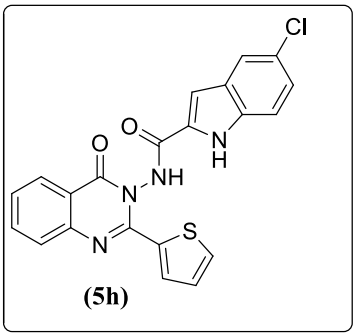


All the newly synthesized quinazolinone derivatives were screened for their *in vitro* antimicrobial activity against various strains of microorganism to determine the "zone of inhibition" by Mueller - Hinton agar dilution methods (disc diffusion method).

Results of antimicrobial evaluation demonstrated that among all tested compounds **5(a-h)**, the compounds (**5d**) and (**5h**) were exhibited most potent antibacterial and antifungal activity against used reference drug. The compounds **5d & 5h** were possess active inhibition against all the tested strains and this may be attributed to the presence of chlorine in the compound. Hence, the replacement of 5- chloroindole nucleus by simple indole ring shows decrease in antimicrobial activity. Rest of the synthesized compounds exhibited moderate to good antimicrobial activity against all organisms.

In this chapter also discussed 'Lipinski rule' of five and it was found that majority of the synthesized compound followed aforesaid. The structure of compounds (**5d**) and (**5h**) are shown below.

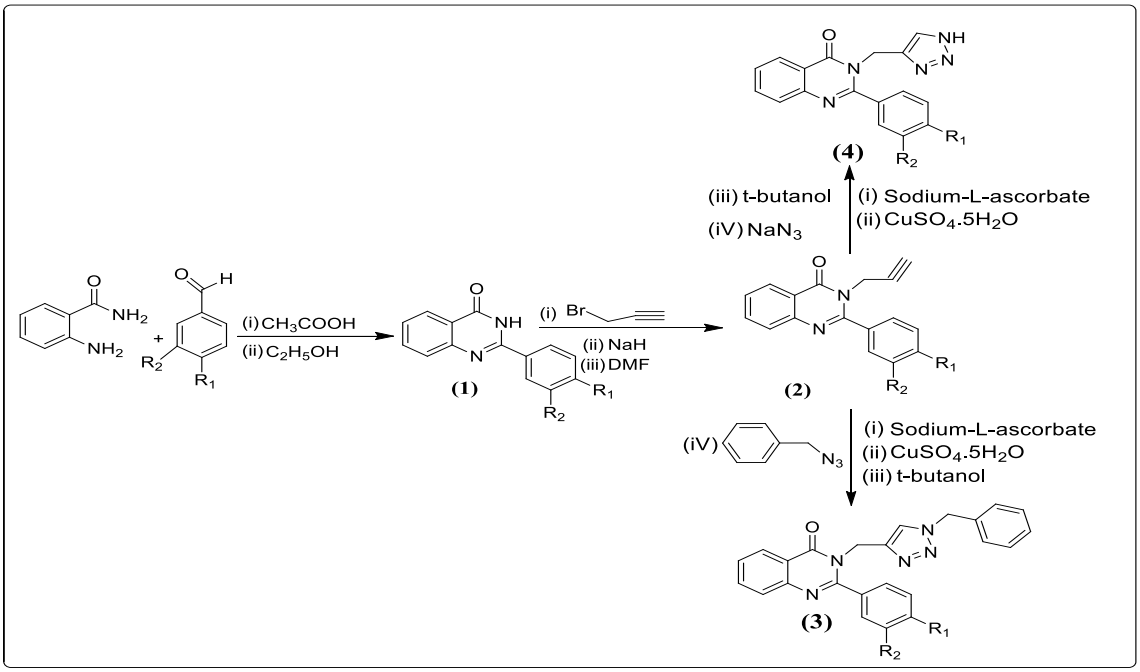




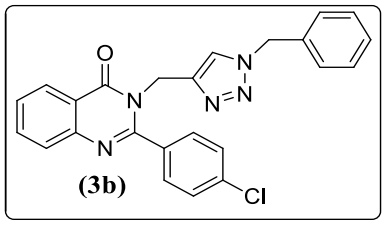
Chapter 3: Design synthesis, characterization and antimicrobial evaluation of 1H-1,2,3-triazole and (substituted-phenyl)quinazolin-4(3H)-one derivatives.

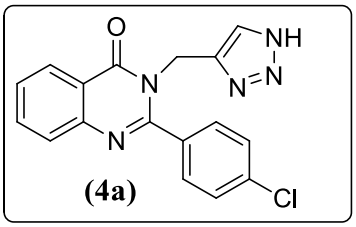
Literature study is evident that more effectual biologically compounds can be design and synthesized by linking two or more pharmaceutically active heterocyclic compounds

together in a single molecular framework. Against this background and as a part of our general program in the continued research for newer antimicrobial agent, it has been designed to combine active 1,2,3-triazole and benzaoxinone moiety to developed bi heterocyclic system. The entire strategy for synthesis of novel 1*H*-1,2,3-triazole and (substituted-phenyl)quinazolin-4(3*H*)-one derivatives are depicted in **scheme-1**.



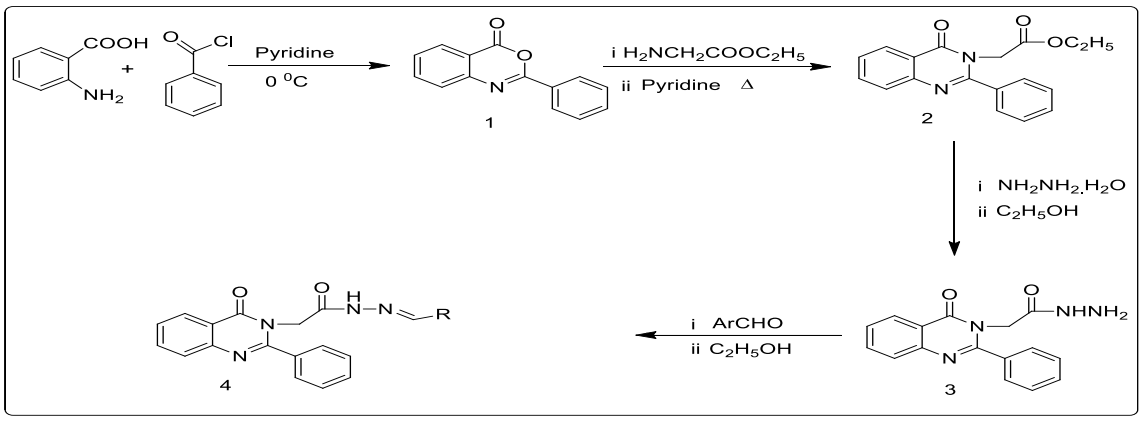
The synthesized compounds **3(a-d) and 4(a-d)** were evaluated *in vitro* for antimicrobial activity against *S. aureus, E. coli, S. typhi* and *C. albicans*. Streptomycin and fluconazole used as reference drugs. The discovery of the antimicrobial efficacy results exposed that most of the screened compounds demonstrated variable inhibitory effects on the growth of the tested gram-positive or gram-negative bacterial strains and *C. albicans*. After antibacterial evaluation, the results revealed that compounds **3b & 4b** displayed better antibacterial potency compared to streptomycin inhibiting the growth of *S. aureus*, *E. coli* and *S. typhi* with zone of inhibition 20, 21, 16 and 19, 18, 17 mm respectively and antifungal potency compared to and fluconazole inhibiting the growth of C. albicans with zone of inhibition 18 and 16. The rest of the newly synthesized compounds displayed moderate to good antibacterial activity. The structure of compound compounds **3b & 4b** are shown below.





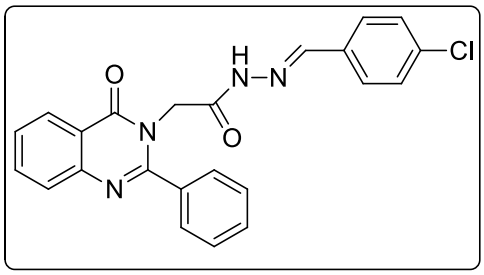
Chapter 4: Synthesis, characterization and bio evaluation of N-(substituted)-2-[4-oxo-2-phenylquinazolin-3*(4H)*-yl] acetohydrazide derivatives.

Based on the importance of quinazolinone and Schiff base in medicinal chemistry, our attention was attracted towards synthesis of novel hybrid quinazolinone derivatives in order to find more potent molecules for various types of diseases. If both quinazolinone and Schiff base scaffolds are condensed as single molecule and developed newer hybrid N-(substituted)-2-[4-Oxo-2-phenylquinazolin-3*(4H)*-yl] acetohydrazide derivatives, it will be afford as excellent bioactive compound. Here, we envisioned a short, modular synthetic route for construction of N-(substituted)-2-[4-oxo-2-phenylquinazolin-3*(4H)*-yl] acetohydrazide derivatives, starting from simple, commercially available and relatively cheap starting materials as outlined in **Scheme-1.**



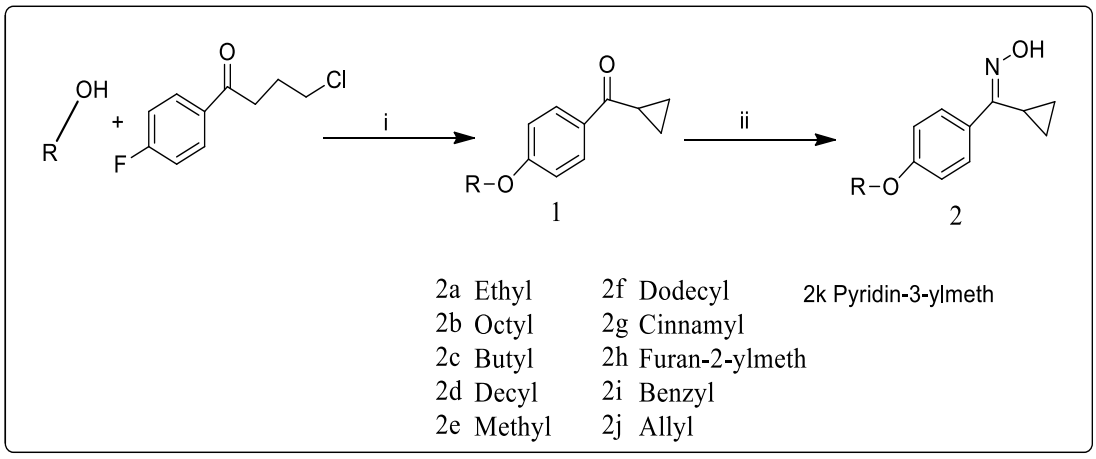
All the synthesized compounds **4(a-g**) were screened for their *in vitro* antibacterial and antifungal activities against various microorganisms to determine minimum inhibitory concentrations (MICs) in µg/mL by micro dilution method. Ciprofloxacin and fluconazole were used as standard drugs for parent moieties. Among all *in vitro* antimicrobial screened compounds, the compound **(4d)** showed excellent antibacterial and antifungal activities because it has chlorine group at para position of phenyl ring. The electron with drawing nature of chlorine group was responsible for increasing lipophilicity of molecule, which corresponds to increasing the antibacterial and

antifungal activities of newly synthesized compounds. The minimum inhibitory concentration of compound **(4d)** was (10.5 µg/mL) against S. aureus and S. typhi during antibacterial evaluation. However, It has (5.25µg/mL) against *C. albicans* during antifungal screening. The structure of compound **(4d)** is shown below**.**



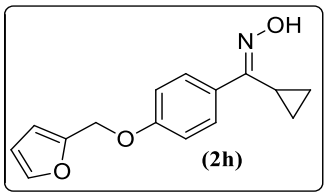
Chapter 5: Synthesis characterization and bio evaluation of 4-alkoxy/aryloxyphenyl cyclopropyl methane oxime derivatives.

Based on pharmaceutical significance of cyclopropyl methane, oximes and oximes ether we clubbed both moiety in same molecule and developed new hybrid 4-alkoxy/aryloxyphenyl cyclopropyl methane oxime derivatives. It may enhance the drug activities of compounds to some extent or they might possess some of the mentioned biological activities in **chapter 5**. The Synthesis of 4-alkoxy/aryloxyphenyl cyclopropyl methane oxime from **2(a-k)** followed the general pathway outlined in **scheme-1.** The structures of all the synthesized molecules shown in **chapter 5** were characterized on the basis of their spectroscopic data.

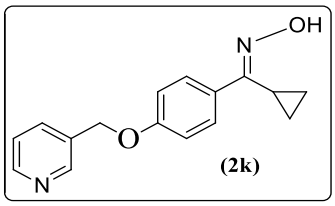


Reagents and conditions (i) NaH, TBAB, THF, 0^0C-RT (ii) $NH_2OH.HCl$, Py:EtOH (1:1), 80^0C

In present chapter all newly synthesized compounds **2(a-k**) were screened for their *in-vitro* antibacterial activity against *Staphylococcus aureus* (Gram-positive bacterial strains), Escherichia coli and *Salmonella typhi* (Gram-negative bacterial strains) via the conventional agar-dilution method. Streptomycin was used as the reference standard. The results of the *in-vitro* antibacterial activity screening of the novel series of substituted cyclopropyl methane oxime derivatives exhibited in Table 1. Among all tested compounds, three compounds (**2h**) and (**2k**) was exhibited excellent antibacterial activity against both Gram-positive and Gram-negative bacterial strains. However, all other compounds in the series were found to have moderate to good antibacterial activity against both Gram-positive and Gram-negative bacteria as compared to the standard reference compounds. The structures of all antibacterial active compounds are shown below.



(2h)



(2k)

Conclusion:

The main purpose of this thesis is to provide diverse pharmacological activities of quinazolinone moiety. Literature survey revealed that quinazolinone motif and its analogs are affective for various pathological conditions, which are discussed in brief in this thesis. The possible new useful drugs were synthesized by slight modifications in the substituents on the basic quinazolinone nucleus. In recent years different types of quinazolinone based drugs were designed and synthesized by biologists as well as chemists. This drugs exhibit better activity against pathogen and less toxicity. In general, simple and diverse nature of synthetic methods for the development of quinazolinone-based heterocyclic compounds with potential biological applications will be, advantageous in future for development of medicinal chemistry research.