THESIS ABSTRACT

Heterocyclic chemistry is a vast, ever growing and expanding area of research in the field of organic chemistry. The synthetic and pharmaceutical chemists have keen interest in the study of heterocycles due to their biological significance as well as industrial applications. Majority of the drugs having at least one heterocyclic nucleus in their skeleton. Among various kinds of heterocycles nitrogen containing nucleus constitute an easily accessible one and found in many biologically active compounds. Further, the literature unveiled that the combination of different pharmacophores enhances the biological activity. Therefore, by considering the above observations, the present investigation was undertaken with the aim of design and synthesize new biologically significant heterocyclic hybrids possessing different pharmacophores.

The current research work was carried out for the thesis entitled “Synthesis Characterization and Biological Studies of New Isoxazoline, Thiazole and Pyrazole Derivatives” has been presented in five chapters.

First chapter deals with the general introduction and rest of the chapters contain a general introduction briefs about the literature related to the current research work and their biological importance, followed by brief explanation on the synthetic schemes along with assignment of spectral data of representative compounds of the series and their biological evaluation. Experimental section includes materials, methods, general protocol for synthesis and biological assay followed by analytical characterization data of synthesized compounds. The results and discussions are summarized in the conclusion part. An exhaustive bibliography followed by appendices are included at the end of each chapter.
CHAPTER 1: An Introduction to Heterocycles and Their Biological Significance

The chapter briefs about the introduction to heterocycles and their applications. An exhaustive literature review was explored on biologically significant molecules possessing isoxazoline, thiazole and pyrazole nucleus followed by a concise introduction to scope and objectives of the present work. A complete bibliography was cited at the end of the chapter.

CHAPTER 2: Synthesis, Characterization and Biological Evaluation of Coumarin Tethered Isoxazolines

The chapter 2 deals with the synthesis of coumarin tethered isoxazolines and their biological evaluation. Coumarin derivatives have attracted considerable interest of bioorganic medicinal chemists due to their diversified biological properties and pharmaceutical applications as antimicrobials, anticancer agents, monoamine oxidase inhibitor, etc. Further, isoxazoline nucleus is also reported as a fruitful motif of biologically important molecules possessing a wide spectrum of therapeutic properties, such as antimicrobial, anticancer, anti-inflammatory, antioxidant, etc.

In view of the above observations, a new series of coumarin tethered isoxazoline derivatives (16a-I) bearing various groups at the C-3 position of isoxazoline ring and coumarin moiety linked through linker at the C-5 position was synthesized according to the Scheme 1 by following earlier reported protocol. Synthesized titled compounds were completely characterized by IR, NMR and mass spectroscopic techniques.
Scheme 1. Synthesis of Coumarin Tethered Isoxazolines

All synthesized coumarin tethered isoxazolines (16a-l) were evaluated for antimicrobial activity against a panel of pathogenic bacteria and fungi, antibiofilm activity against *P. aeruginosa* and anticancer activity through standard procedures.

About 50% of the coumarins *i.e.*, 16c, 16d, 16g, 16f, 16j and 16l were found to be active against all the bacteria and fungi tested. *B. subtilis* was found highly susceptible to the coumarin tethered isoxazolines with zone of inhibition ranging between 30 mm and 36 mm and the compounds were moderately active (zone of inhibition 11 mm to 30 mm) against the remaining bacteria tested. Against fungi, 16j was highly potential with a zone of inhibition 28 mm and least potentiality was exhibited by 16h (17 mm) against *C. albicans*. The zone of inhibition of the active compounds was between 15 mm to 30 mm against *M. canis* and *M. gypseum*. The MIC of the tested compound was between 9.76 μg/mL and 78.12 μg/mL against all the bacteria and fungi tested. Further, the results of antibiofilm activity revealed that
compounds 16c, 16f, 16j and 16k recorded a better inhibition of biofilm formation by P. aeruginosa, of which compound 16c was found to be a potent antibiofilm agent.

The cytotoxicity and anticancer studies demonstrated that compound 16c was cytotoxic selectively against UACC 903 cancer cell lines. Further, 16c was selected to estimate the antitumor and antiangiogenic activity. In order to inhibit the proliferation of endothelial cells, EAT bearing mice treated with compound 16c showed reduction in the body weight, ascites volume, cell number and increased in the survivability. The studies also showed that 16c has an antiangiogenic effect displayed by decrease in the blood vessel formation in peritoneum lining of treated mice and formation of avascular zone in the CAM. The above data suggest that the compound 16c can be considered as a good antitumor and antiangiogenic agent which could be useful for drug development to combat various types of cancer.

**CHAPTER 3: A New Efficient Method for the Synthesis of 4,5-Disubstituted Thiazole and Antimicrobial Studies**

This chapter contains a general introduction of thiazole nucleus and their diversified biological importance followed by a detailed literature review on different classical and non-classical methods for the synthesis of thiazoles from various substrates. According to the literature survey, synthesis of thiazoles from classical and conventional methods are associated with several disadvantages, such as the need of harsh reaction conditions like high temperature, toxic metals as catalysts, less stable precursors and difficulties with syntheses of pre-functionalized intermediates/starting materials.

Hence, developed a new efficient click strategy for the synthesis of 4,5-disubstituted thiazoles 3-6 from various dithiocarboxylates 1(a-i) and different isocyanides 2(a-d) via base (sodium hydride) induced cyclization with an excellent
yield under mild condition (Scheme 3). The noteworthy advantages of this method are short reaction time, broad functional group tolerance, ease workup and isolation.

Scheme 2. Synthesis of 4,5-Disubstituted Thiazoles

Further, some synthesized thiazoles were checked for the antimicrobial potency through agar well diffusion method. Results unveiled that the tested thiazoles exhibited a broad spectrum antibacterial activity except (3a and 5g). The thiazoles exhibited a maximum zone of inhibition (24 to 34 mm) against B. subtilis and least (11 to 19 mm) against E. coli except for 6c. MIC of the compounds against the bacterial pathogens was in the range of 9.76 μg/mL and 78.12 μg/mL. MIC of 39.06 μg/mL and 19.53 μg/mL were common, exhibited by majority of tested compounds. The compound 3f and 6c was observed as potent antifungal agents against C. albicans and M. canis with a MIC of 19.53 μg/mL. The common MIC observed against M. canis and M. gypseum was 78.12 μg/mL and 156.2 μg/mL. Analysis of the results of the MIC also showed that C. albicans was more susceptible pathogen to the synthesized thiazoles derivatives (recorded by least MIC) compared with M. canis and M. gypseum.

Among all tested compounds, compounds 6c showed significant and broad spectrum antimicrobial activity as compared with the standard.
CHAPTER 4: Synthesis of New Series of Benzofuran-Pyrazole Hybrids and Their Antioxidant, Antimicrobial and Antibiofilm Activities

The chapter presents a brief introduction of benzofuran derivatives and their biological significance. Recent research studies reported that benzofuran derivatives exhibited diversified pharmacological properties such as antibacterial, antifungal, antibiofilm, antioxidant, etc. In addition, pyrazole derivatives were also reported to possess various biological activities such as antioxidant, antimicrobial, anticancer, etc. The potential usefulness of benzofuran and pyrazole in pharmaceuticals, synthesized a series of novel benzofuran-pyrazole hybrids (5a-l) according to the Scheme 3 by following reported procedure with slight modifications and all titled compounds were characterized by IR, $^1$H and $^{13}$C NMR and mass spectroscopy. Further, the structure of compound 5h was confirmed by single crystal X-ray diffraction studies.

Scheme 3. Synthesis of Benzofuran-Pyrazole Hybrids

All synthesized benzofuran pyrazole-hybrids (5a-l) were checked for antioxidant, antimicrobial and antibiofilm activity.
Results of the biological activities revealed that few of the molecules exhibited potent antioxidant, antimicrobial and antibiofilm activities. Among a series of benzofuran-pyrazole hybrids, compound 5a, 5b and 5c showed moderate activity in both assays. The IC$_{50}$ of the active compounds were 101-125 μM and 98-109 μM in DPPH and ABTS assays respectively. Among the compounds tested for antimicrobial potential, the compounds 5c and 5j exhibited significant antibacterial and antifungal activity against the spectrum of pathogens tested except Lactobacillus. The results of antibiofilm activity revealed that compounds 5b, 5c and 5d recorded a better inhibition of biofilm formation by P. aeruginosa, of which compound 5b was most active with an MIC of 20 μM. Further, inhibition of biofilm formation by compound 5b was confirmed by fluorescence staining assay.

Activities of the tested compounds are comparable to the respective standards evaluated and hence the experimental results suggested that benzofuran-pyrazole hybrids could be the promising lead candidate for the design and development of new class of antioxidant, antimicrobial and antibiofilm agents.

**CHAPTER 5: Synthesis of New Series of Tetrahydrocurcumin Conjugated Pyrazole Derivatives and Their Antioxidant and Antidiabetic Studies**

The present chapter includes a general introduction to curcumin and its analogues along with their biological importance. The literature study described that curcuminoids and pyrazole derivatives are efficient bioactive molecules. Hence, a series of new THC conjugated pyrazoles (8a-k) were synthesized according to the Scheme 4 following the previously reported protocols with slight modifications and were characterized using IR, NMR (1H and 13C) and mass spectroscopic techniques.
Later, the antioxidant potential of THC conjugated pyrazoles (8a-k) were checked via DPPH and ABTS radical scavenging assay. Result unveiled that most of them possess moderate to good antioxidant activity, of which, compounds 8i and 8j showed an excellent inhibition of DPPH radicals. However, the compounds 8b, 8e and 8f showed least antioxidant activity and rest of the compounds were found to be inactive. Further, the compounds quenched the ABTS radicals in a similar manner of DPPH method. The potent compound 8i exhibited a similar activity demonstrated by standard ascorbic acid in both assays and hence concluded as the potent antioxidant.

Further, the titled compounds were evaluated for antidiabetic activity via inhibition of sucrase and α-amylase enzymes. The results indicated that some of the tested compounds inhibited sucrase and α-amylase to a certain extent. Compound 8i exhibited a prominent inhibitory activity, followed by compound 8j, whereas remaining compounds showed minimum or no activity. Therefore, compound 8i bearing electron releasing group such as methoxy emerged as promising antidiabetic agent, which may be exploited for future studies.