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An Analysis upon Some Novel Heterocyclic Compounds with Antimicrobial Activity

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Abstract – 2-Chloro–N-{4-(4-chlorophenyl)-6-[4-{dimethylamino) phenyl] pyrimidin-2-yl} acetamide were allowed to react separately with different secondary amines in presence of alkaline medium to yield the corresponding secondary amine derivatives substituted heterocycls. The compounds obtained were identified by spectral data and screened for antimicrobial activity. The result shows that all samples are more or less active agents against various microorganisms.

Among heterocyclic compounds five-membered heterocycles constitute a wide and differentiated group with broad spectrum of biological activity. The systems with different kind and number of heteroatoms are described. Among each subgroup structure-activity relationships and pharmacophore models are discussed as well as interactions with the molecular target.

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INTRODUCTION

The history of heterocyclic chemistry began in the 1800's, in step with the development of organic chemistry. Heterocyclic compounds have great applicability in pharmaceutics because they have specific chemical reactivity. The majority of synthetic heterocyclic compounds have found widespread use, for example as anticancer agents, antitubercular, analeptics, analgesic, hypnotics and as pesticides, insecticides and weed killers. Various synthetic procedures have been developed and considerable diversity in the ring is achieved. Heterocyclic compounds are enormous, their chemistry is complex and synthesizing them requires great skill. Important drugs, poisons and medicines (both natural and synthetic) such as sulphathiazole, pyrenthrin , rotenmone , alpidem , zolpidem , fluconazole , strychnine, reserpine , certain of the antihistamines, the ergot alkaloids caffeine, cocaine, barbiturates, etc. are heterocyclic compounds.

Heterocyclic compounds played a vital role in biological processes and are wide spread as natural products. They are widely found in nature particularly in nucleic acids, plant alkaloids, anthocyanins and flavones as well as in haemin and chlorophyll. Additionally some vitamins, proteins,hormones contain aromatic heterocyclic system. Synthetically produced heterocycles designed by organic chemists are used for instance as agrochemicals and pharmaceuticals and play an important role in human life. Heterocycles have enormous potential as the most promising molecules as lead structures for the design of new drugs.

Heterocyclic compounds are occupying a prime place in heterocyclic chemistry owing to their valuable properties as therapeutic agents, drugs, dyestuffs etc. These compounds are reported to process antimicrobial, anti-inflammatory, ant diabetic, hem regulatory, blood platelet aggregation inhibiting property and also the pesticidal properties .It is also reported in various journals that these compounds are showing very good antibiotic activities. Some of the compounds belonging to this group were screened for anti HIV activity and found to have very good activity.

Looking to these interesting biological activities associated with these compounds it prompted as to synthesis of some novel heterocyclic compounds belonging to Pyrazolines, Imidazolones, Iso-oxazolines, Pyrimidiens and heterocyclic diazo compounds. From the earlier days of development of organic Chemistry to present .heterocyclic compounds have held center stage in the development of molecules to enhance quality of human life. For example, more than seventy percent of drugs used today are heterocyclic compounds .They arc widely distributed in nature and are-key intermediates in many biological processes.

Generally, heterocyclic compounds isolated from natural sources act as lead compounds for the development of new molecules of biological interest.

Today, most of the heterocyclic drugs are not extracted from natural sources but are synthesized from readily available fine chemicals. In this aspect synthesis and characterization of new molecular entities incorporating heterocyclic structures is of high importance. There are multiple benefits exploring this type of organic chemistry. Firstly, this research helps to unravel intrinsic chemical behavior of small molecules which still remain mysterious. Secondly, this research may generate development of new methods for synthesis .Thirdly characterization of a set of compounds by spectral means would create bench marks for characterization of similar molecules. Finally, biological evaluation of the prepared compounds may expose lead compounds for further structural fine tuning.

Among organic compounds, those incorporating one or more sulfur atoms are interesting because of unique properties imparted by this element. Owing to polarization characteristics and to the presence of an adjacent and vacant d orbital, sulfur stabilizes negative charge next to it and positive charge on one after. Sulfur in addition to this a well-known disease malaria accounts three million deaths annually and every 30s an African child killed by malaria, reported by WHO. In recent years, pyrazoline unit attached with flourenecarbazole–based polymers provided the properties such as better thermal stability, higher photoluminescence quantum efficiency and film forming property hence could be used as light emitting material. Although heterocyclic compounds may be inorganic, most contain within the ring structure at least one atom of carbon, and one or more elements such as sulfur oxygen, or nitrogen. Since non-carbons are usually considered to have replaced carbon atoms, they are called hetero atoms. The structures may consist of either aromatic or nonaromatic rings .Heterocyclic chemistry is the branch of chemistry dealing with the synthesis, properties and applications of heterocycles.

Every year number of reports is published on preparation of these compounds and their application in chemical reactions. The usage of most of the antimicrobial agents is limited, not only by the rapidly developing drug resistance, but also by the unsatisfactory status of present treatments of bacterial and fungal infections and drug side effects. This has spewed the scientists to develop the new antibacterial agents having broad antimicrobial spectrum.

Medicine is the most valuable assets to fight against the various disease of human health. With respect to a variety of biological activities, heterocyclic compounds occupy nearly first place among the other classes of organic compounds1-2. The core structure is widely used in clinically very important antibiotics like Penicillin, Thienamycin and Quinoline-based compound. Among them fluoroquinolones are known to display anti-TB activity, Mefloquine is known for its antibacterial and anti-tubercular activity.

Although heterocyclic compounds may be inorganic, most contain within the ring structure at least one atom of carbon, and one or more elements such as sulfur, oxygen, or nitrogen. Since non-carbons are usually considered to have replaced carbon atoms, they are called heteroatoms. The structures may consist of either aromatic or non-aromatic rings.

Heterocyclic chemistry is the branch of chemistry dealing with the synthesis, properties, and applications of heterocycles.

Heterocyclic derivatives, seen as a group, can be divided into two broad areas: aromatic and non-aromatic. In Figure 1, five-membered rings are shown in the first row, and the derivative 1 corresponds to the aromatic derivative, furan, while tetrahydrofuran, dihydrofuran-2-one, and dihydrofuran-2,5-dione are not aromatic, and their reactivity would be not unlike that expected of an ether, an ester, or a carboxylic anhydride, respectively.

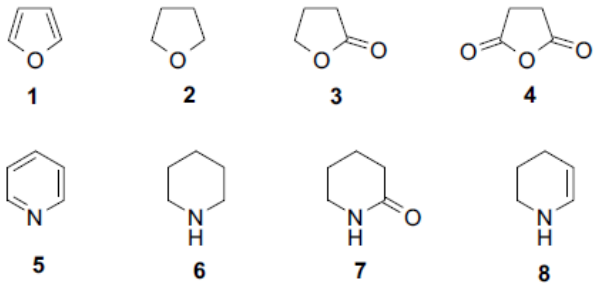

Figure 1 Examples of heterocyclic compounds.

The second row shows six-membered rings, initially in an aromatic form as Pyridine, while Piperidine, Piperidin-2-one, and 1,2,3,4-tetrahydropyridine are not aromatic; their reactivity would not be very different from that expected of an amine, amide, or enamine, respectively. In general, the reactivity of aromatic heterocycles, which is a combination of that expected from an aromatic system combined with the influence of the heteroatoms involved, is usually more complex, while the reactivity of the non-aromatic systems is not too different from the usual non-cyclic derivatives.

NEW FIVE-MEMBERED RING HETEROCYCLIC COMPOUNDS

Bacterial and fungal infections have been for many centuries a major cause of death in humans. In the 19th century the main reasons of morbidity among children and adults were pneumonia, tuberculosis, diarrhea and diphtheria. It was found in late 19th century that many common diseases are caused by microscopic pathogens which led to introduction of antiseptic procedures in order to diminish mortality related to postsurgical infections. Furthermore, sanitation and hygiene also contributed to reduction of the mortality caused by bacterial infections. Finally, the discovery of the first compounds with

antimicrobial activity made it possible to conquer multiple infectious diseases, including the first compound with antimicrobial activity elaborated against syphilis in 1911 by Erlich. The discovery of Penicillin and later streptomycin revolutionized treatment of many diseases, including pneumonia and tuberculosis. The next breakthrough was the development of Cephalosporin with broad activity against gram-positive and also some gram-negative bacteria.

Despite the relevance of infectious disease as main causes of human morbidity and mortality, the development of new antibacterial is not among the highest priorities for pharmaceutical companies. New antibacterial compounds are necessary to replace those that have become less effective as a result of the emergence of a high level of resistance amongst target bacteria. One of most serious problems of contemporary medicine is drug-resistant tuberculosis, occurring not only in developing countries (where it often accompanies AIDS) but also in some well-developed countries. Most drugs present nowadays at the market are diverse heterocyclic compounds, i.e. compounds which possess a ring structure with one or more atoms different than carbon atom inside the ring. Among heterocyclic compounds five-membered heterocycles constitute a wide and differentiated group with broad spectrum of biological activity. Compounds from this class are present in nature as constituents of nucleic acids, some important amino acids, alkaloids and hormones. The members of this group such as Pyrazole, Imidazole, Oxazole, Triazole, Thiadiazole, Oxadiazole, Thiazole are particularly important antibacterial and antifungal agents including Tazobactam, Cefatrizine, Rufinamide, Fluconazole, Itraconazole, Voriconazole, Posaconazole and Ketoconazole. The presented chapter focuses on the medicinal chemistry of novel five-membered ring heterocyclic compounds with antibacterial and antifungal activity. The literature from the years 2007-2013 is covered. The systems with different kind and number of heteroatoms are described. Among each subgroup structure-activity relationships and pharmacophore models are discussed as well as interactions with the molecular target (if known).

Pyrazole derivatives - Pyrazoles, the well-known five-membered heterocycles having two adjacent nitrogen atoms within the ring, have received considerable interests in the fields of medicinal chemistry. These derivatives are the subject of many research studies due to their widespread potential antimicrobial activities. Changes in their structure have offered a high degree of diversity that has been proven useful for the development of new therapeutic agents having improved potency and lesser toxicity.

Imidazole derivatives - Imidazole is a planar five-member heterocyclic ring with two nitrogen atoms in ring at the 1st and 3rd positions. The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents.

Thiazole derivatives - Thiazole is five-member heterocyclic compound having two heterocyclic atoms nitrogen and Sulphur in the position 1 and 3. Thiazole derivatives are one of the most important classes of heterocycles in medicinal chemistry due to its wide range of biological activities. These derivatives showed antibacterial, antifungal, anti-HIV, anti-inflammatory, anticonvulsant and antitumor activities. Furthermore, there are some important drugs containing Thiazole moiety too, e.g. Sulfathiazole - antimicrobial drug, Ritonavir – anti-HIV drug, Abafungin and Ravuconazole – antifungal drugs and antibiotics (penicillin, cephalosporin and micrococcin).

Oxazolidone derivatives - Oxazolidinones are a new class of antibacterial agents with activity against a large number of Gram-positive organisms.

Drug Linezolid is the first and only member of the oxazolidinone series. Eperezolid and AZD2563 are still potential drug candidates and they have been used as the structural precursors for modification. In Eperezolid, Linezolid's morpholine moiety was replaced by piperazine ring with $COCH_2OH$ substituent attached to N-4 piperazine position. The first modification of Eperezolid include derivatives having substituted urea group on the piperazine ring at the 4-position. These compounds exhibited antibacterial activity equivalent to Linezolid. Compounds having aryl substituted urea group which contain such substituents as fluorine, methoxy and chlorine in aryl ring (3-FC_6H_4NH, 2-$CH_3OC_6H_4NH$, 2, 4-ClC_6H_3NH) exhibited antibacterial activity against *S. aureus*.

NOVEL HETEROCYCLIC COMPOUNDS FROM HYDROXYBENZOPHENONES

Over the past several years the emergence of organisms resistant to nearly all the class of antimicrobial agents has become a serious public health concern. In general, bacteria have the genetic ability to transmit and acquire resistance to drugs, which are utilized as therapeutic agents.

Since past two decades there has been significant increase in the frequency of systematic fungal infection in man. The first orally active antifungal agent that was effective against a broad array of systematic and superficial fungal infections was ketoconazole. Further a number of azole antifungal

agent's viz., itraconazole, Fluconazole, Voriconazole, Ravuconazole etc., and glucan synthesis inhibitor Caspofungin have been introduced to the clinic. Antibiotics are one of our most important weapons in fighting bacterial infections and have greatly benefited the health-related quality of human life since their introduction. However, over the past few decades these health benefits are under threat as many commonly used antibiotics have become less and less effective against certain illnesses not only because many of them produce toxic reactions but also due to emergence of drug resistant bacteria. It is essential to investigate newer drugs with lesser resistance.

During the past years extensive evidences have been accumulated to establish the efficiency of benzophenone analogues as antimicrobial agent. Benzophenone analogue (garcinol) has been isolated from the stem bark of *Garcinia huillensis* grown in Zaire and used in central-African traditional medicine and this has been shown to exhibit chemotherapeutical activity against gram-positive and gram-negative *cocci*, mycobacteria and fungi. Recently Selvi et al have shown antifungal activity of benzophenone analogues, at its lower concentration. Besides Chloro substituted benzophenones have exhibited more antifungal activity. Moreover, a large number of Oxadiazoles, Triazoles and Triazolothiadiazine have been shown to exhibit significant antimicrobial activity against *S. Aureus, C. Albicans, C. Krusei, C. Parapsilosis, T. Paradoxa, E. Coli, B. Subtilis* and *P. Aeruginosa*. These initial reports, thereafter stimulated us to integrate 1,3,4-oxadiazole-2-(3H)thione and triazolothiadiazine moieties in benzophenone framework, since these systems possess well documented antimicrobial activity.

The synthesis of the hitherto unreported title compounds in 70% yield. Hydroxybenzophenones 1a–e on reaction with ethyl chloroacetate affords ethyl (2-aroylaryloxy) acetates 2a–e in excellent yield, which on treatment with hydrazine hydrate yields corresponding

2-(2-aroylaryloxy) acetohydrazides 3a–e. Intramolecular cyclization of 3a–e with carbon disulfide resulted 5-(2-aroylaryloxy)methyl-1,3,4-oxadiazole-2-(3H) thiones 4a–e. Compounds 4a–e were further treated with hydrazine hydrate to obtain compounds 4-amino-5-(2-aroylaryloxy) methyl-1,2,4-triazole-3-(2H) thiones 5a–e. The preparations of novel 3-(2-aroylaryloxy)methyl-6-phenyl-1,2,4-triazolo [3,4-b] [1,3,4] thiadiazine 6a–e were achieved from 5a–e with phenacyl bromide .

STRUCTURE AND REACTIVITY OF AROMATIC FIVE-MEMBERED SYSTEMS

As is indicated in most handbooks of heterocyclic chemistry, a pictorial valence bond resonance description is used in most chapters, as a simple way to rationalize the reactivity of the most important aromatic heterocycles. Two examples are described in detail as representative of most of the aromatic rings considered: pyrrole as a model of the p-excessive rings, and pyridine as a model of the p-deficient ones.

Pyrrole has a structure that is isoelectronic with the cyclopentadienyl anion, but is electrically neutral, having a nitrogen atom with a pair of electrons, which is part of the aromatic sextet, and its resonance hybrid can be represented as a combination of main forms I–V (Figure 2), one without charge, and the others with charge separation. As expected, not all forms contribute equally to the structure of the pyrrole, with the order of importance being I > III, IV > II, V, that is, the major contribution is produced by the non-charged form, and, of the charged ones, those in which the nitrogen is using its lone pair of electrons. As a combination of all forms, structure 9 indicates how the heteroatom bears a partial positive charge, while the carbon positions show an increase in electronic density, compared with the typical aromatic system, benzene. Thus, a p-excessive system such as pyrrole would be easily attacked by electrophiles and not by nucleophiles.

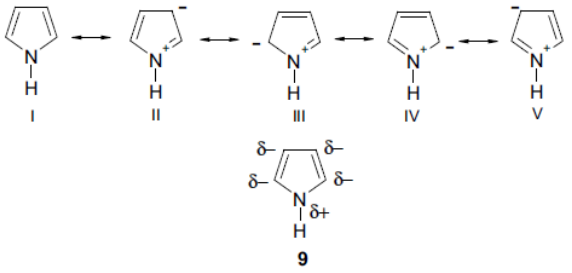

Figure 2 Resonance hybrids of pyrrole.

Figure 3 indicates how the attack of an electrophile usually proceeds. The major isomer 13 is formed through intermediates 10–11–12, of which the intermediate 10 contributes most to the stabilization of the intermediate. Alternatively, a minor isomer 16 is produced through the less stable intermediates 14 and 15.

Alternatively, Figure 4 shows the attack of a nucleophile on pyrrole. Intermediate 17 is not stabilized, and the lone pair of electrons on the heteroatom does not contribute to the progress of the process. The only process that usually can be detected is deprotonation of the N–H bond to generate the pyrrolate (18), which can be used to make a bond with a suitable electrophile (i.e., an alkyl halide) to produce the N-substituted pyrrole 19.

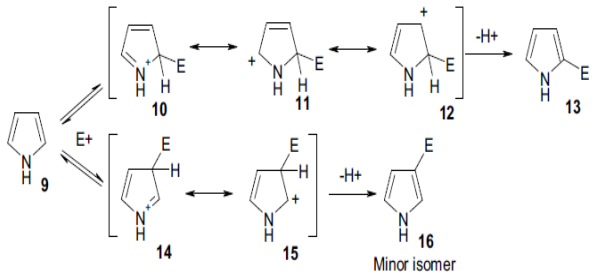

Figure 3 Electrophilic attack on pyrrole.

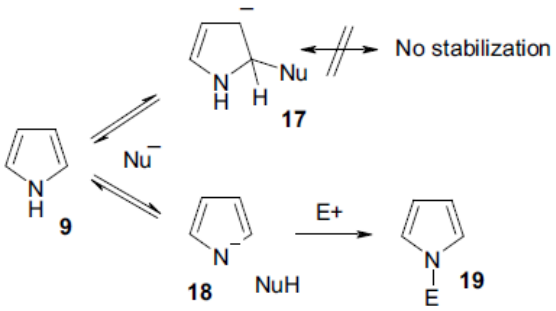

Figure 4 Attack on pyrrole by nucleophiles.

This behavior can be extended with small differences to other p-excessive heterocycles, with the limit due to the existence or not of a N–H bond at position 1. In the case of rings like thiazole or isoxazole, the lack of the acidic bond makes the process 9–18–19 impossible.

ANTIBACTERIAL ACTIVITY

The antibacterial activity of all the synthesized compounds (1-10) were examined against different Gram-positive (*Bacillus cerus* and *Staphylococcus aureus)* and Gram-negative (*Escherichia coli*) organisms & anti-fungal activity against (*Candida albicans*) by measuring zone of inhibition. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water were done as per the standard procedure. Discs measuring 6.25mm in diameter were punched from Whatman No.1 filter paper. Stock solutions of synthesized compounds diluted in DMF. The antibacterial activity was performed by agar diffusion method at the concentration level of 50mcg/ml. Streptomycin was used as standard drug at a concentration of 50 mcg/ml. The results of the antibacterial activity are shown in Table 1.

Compd. No.	R	ANTIBACTERIAL ACTIVITY INHIBITION (50mcg/ml) % Inhibition in E.coli	% Inhibition in B.cerus	% Inhibition in S.aureus	% Inhibition in Candida al.
1	$-N(CH_3)_2$	-	-	-	-
2	$-N(C_2H_5)_2$	-	-	Moderately sensitive	-
3	$-N(C_6H_5)_2$	-	-	16	15
4	$-N(C_3H_3N)$	-	Moderately sensitive	-	-
5	$-N(C_8H_6)$	-	-	-	-
6	$-N(C_7H_8)$	-	17	19	16
7	$-N(C_8H_{10})$	-	18	18	15
8	$-N(C_4H_8)$	-	16	18	15
9	$-N(C_4H_8O)$	-	-	-	-
10	$-N(C_4H_6O)$	-	Moderately sensitive	Moderately sensitive	-

Table 1: Antimicrobial data of synthesized compounds.

CONCLUSION

The Main focus of this research work was to synthesize, characterize and evaluate antimicrobial, antibacterial activity against anti-histaminic, anti-inflammatory activities of the synthesized Heterocyclic Derivative. Structure of synthesized compounds were confirmed & characterized with the help of analytical data's. It has pharmaceutical and industrial applications there is always a strong need for new and efficient processes in synthesizing of new Heterocycles. Developing environmental friendly and effective technologies coupled with green chemistry is a major challenge facing the chemical community. In Heterocyclic compound having chlorophenyl type linkage has shown good activity against the bacterial strains.

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