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REVIEW ARTICLE

An Overview on Some Benzimidazole and Sulfonamide Derivatives with Anti-Microbial Activity

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ABSTRACT

Benzimidazoles and sulfonamides play an important role in medical field with so many pharmacological activities such as antimicrobial, antiviral, antidiabetic and anticancer activity. The potency of these clinically useful drugs in treatment of microbial infections and other activities encouraged the development of some more potent and significant compounds. Benzimidazoles are remarkably effective compounds, extensive biochemical and pharmacological studies have confirmed that these molecules are effective against various strains of microorganisms. This review is summarized to know about the chemistry of different derivatives of substituted sulfonamides and benzimidazoles along with their anti-microbial activities.

Key words: Substituted Sulfonamides, Benzimidazoles, Chemistry, Anti-microbial activities.

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INTRODUCTION

Antimicrobial agents are the drugs, chemicals, or other substances that kill or slow the growth of microbes. They include antibacterial drugs, antiviral agents, antifungal agents, antiparasitic drug [1]. For the past 60 years, antimicrobial chemotherapy has been the mainstay of medical intervention against infectious diseases caused by various pathogens. Since then, numerous classes of antimicrobial agents have been discovered, and literally hundreds of drugs are available for use today. Antimicrobials are among the most commonly used of all drugs [2]. Since the introduction of penicillin in the 1940s, antimicrobials have a history of success in controlling morbidity due to infectious diseases [3]. The regular use of antimicrobial agents causes various problems such as toxicity, hypersensitivity reactions, drug resistance, superinfection (suprainfection), nutritional deficiencies and masking of an infection [4]. The incidence of invasive microbial infections caused by opportunistic pathogens, often characterized by high mortality rates, has been increasing past two decades. Patients who become severely immunocompromised because of underlying diseases such as leukemia or recently acquired immunodeficiency syndrome or patients who undergo cancer chemotherapy or organ transplantation are particularly susceptible to opportunistic microbial infection. Almost all major classes of antibiotics have encountered resistance in clinical applications. The emergence of bacterial resistance to β-lactam antibiotics, macrolides, quinolones and vancomycin is becoming a major worldwide health problem.

A matter of concern in the treatment of microbial infections is the limited number of efficacious antimicrobial drugs. Many of the currently available drugs are toxic, enable recurrence because they are bacteriostatic/fungistatic and not bactericidal/fungicidal or lead to the development of resistance due in part to the prolonged periods of administration. There is a real perceived need for the discovery of new compounds that are endowed with antimicrobial activities, possibly acting through mechanisms of action, which are distinct from those of well known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant. It is therefore critical to realize that antimicrobial drug effectiveness, widely accepted as a common good, its increasing resistance cannot be taken for granted. Thus, an urgent need for new potent classes of antibiotics with novel modes of action persists [5].

Importance of heterocyclic compounds as antimicrobial agents

The biological activity of the compounds is mainly dependent on their molecular structures [6]. Heterocyclic compounds are acquiring more importance in recent years as these can be found in a large number of compounds which display biological activity [7]. Heterocyclic compounds particularly five and six member heterocycles have attracted the attention of pharmaceutical community over the years due to their therapeutic value [8].

Polyfunctionalized heterocyclic compounds containing Nitrogen, sulphur, oxygen as heteroatoms play important roles in the drug discovery process [9]. Analysis of drugs in late development stages or in the market shows that 68% of them are heterocycles [10]. Therefore, it is not surprising that during past decades, compounds bearing heterocyclic nuclei have

received much attention due to their chemotherapeutic value in the development of novel antimicrobials and antihelmintics [11]. A few classes of chemotherapeutic agents [4] on the basis of heterocyclic rings are mentioned below.

1. Sulfonamides and related compounds *e.g.* [Sulfadiazine]
2. Diaminopyridines *e.g.* [Trimethoprim]
3. Quinolines *e.g.* [Ciprofloxacin]
4. Beta lactam *e.g*. [Pencillins]
5. Tetracyclines *e.g.* [Doxycycline]
6. Nitrobenzene derivatives *e.g.* [Chloramphenicol]
7. Aminoglycosides *e.g.* [Streptomycin]
8. Macrolide *e.g.* [Erythromycin]
9. Lincosamide *e.g.* [Clindamycin]
10. Glycopeptide *e.g.* [Clindamycin]
11. Oxazolidinone *e.g.* [Linezolid]
12. Polypeptide *e.g.* [Colistin]
13. Nitrofuran derivatives *e.g.* [Nitrofurantoin]
14. Nitromidazoles *e.g.* [Metronidazole]
15. Nicotinic acid derivatives *e.g.* [Isoniazid]
16. Polyene *e.g.* [Nystatin]
17. Azole derivatives *e.g.* [Miconazole]

Therefore, these heterocyclic compounds are being synthesized in terms of operational simplicity, non-toxicity, reusability, environment and economical acceptability.

Literature Review

Despite of the availability of a number of antimicrobial agents the main matter of concern in the treatment of microbial infections is the limited number of efficacious antimicrobial drugs [11]. Infectious microbial diseases remain pressing problems world-wide, because resistance to a number of antimicrobial agents among variety of clinically significant species of microorganisms has become an important global health problem. One way to battle with this challenge is the conscious usage of the currently marketed antibiotics; the other is the development of novel antimicrobial agents. Hence, there will always be a vital need to discover new chemotherapeutic agents to avert the emergence of resistance and ideally shorten the duration of therapy [12].

The outcome of numerous attempts to new structural prototype in the search for effective antimicrobials indicates that the benimidazoles still remain as one of the most versatile class of compounds against microbes [13].

Compounds bearing benzimidazoles moiety are reported to possess a number of interesting biological activities such as antitubercular, anticancer, anthelmintic, antiallergic, antioxidant, antihistaminic and antimicrobial [14]. In recent years benzimidazoles have been

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reported to act as topoisomerase-I inhibitors, selective neuropeptide YYI receptor antagonists, angitensin-II inhibitors, 5-HT_3 antagonist in isolated guinea-pig ileum, in the treatment of interstitial cystitis and as a factor Xa inhibitors [15].

2.1 Benzimidazole: The benzimidazoles contain a phenyl ring fused to an imidazole ring as indicated below (fig 2.1).

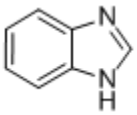

Figure 2.1: 1*H*-benzimidazole

This important group of substances has found practical applications in a number of fields. Historically, the first benzimidazole was prepared in 1872 by Hoebrecker, who obtained 2,5(or 2,6)-dimethylbenzimidazole (fig 2.2) by the reduction of 2-nitro-4-methylacetanilide [16].

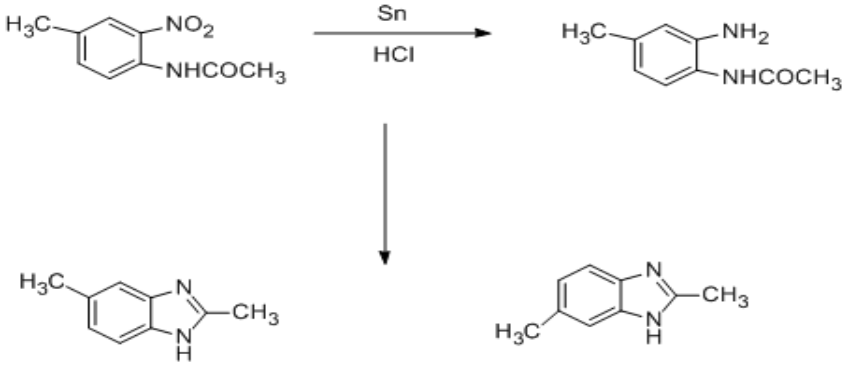

Figure 2.2: Synthesis of 2,5 (or 2,6)-dimethylbenzimidazole

Brown and coworkers in 1961 discovered that thiabendazole possessed potent activity against gastrointestinal nematodes sparked development of the benzimidazoles as broad-spectrum anthelmintic agents. The hundreds of derivatives tested, those therapeutically useful have modifications at the 2 and/or 5 positions of the benzimidazole ring [17].

2.1.1 Spectral properties of benzimidazoles

1) *Infra red* (IR) *spectroscopy:* The absorption spectra of benzimidazole near the 2850Å indicates the presence of the aryl ring , absorption near the 3107Å indicates the presence of N-H stretch and 1690Å indicates the presence of C-N stretch.

2) *Nuclear magnetic resonance* (NMR) *spectroscopy:* An important feature of this work is that the protonation parameters derived from simple five and six membered heterocycles can be used to predict chemical shift changes resulting from nitrogen protonation and deprotonation in more complex molecules.δ7-9 values shows multiplet indicates the presence of benzimidazole aryl ring.

3) *^{13}Carbon NMR:* The spectra shows different carbon peaks at range of δ0-200 compared to TMS. For benzimidazoles the range starts from δ115-144.Overlapping is easily confirmed by triplet, doublet peaks obtained. Low intensity peaks show the presence of proton less carbons. So carbonyl group at which position is recognized.

4) *Mass spectroscopy:* The fragmentation pathways of simple benzimidazoles are similar to those of imidazoles. The spectrum of benzimidazole indicates a sequential loss of two molecules of hydrogen cyanide from the molecular ion, the first of which is nonspecific as evidenced by deuterium labeling procedures. A characteristic feature in the fragmentation of 2-n-propylbenzimidazole is the elimination of ethylene from the molecular ion, 2-acylthiophenes, 2-acyl and 2- benzoylbenzimidazoles are characterized by loss of carbon monoxide from the molecular ion [18].

2.1.2 Physical properties of benzimidazoles

The melting point of number of the benzimidazoles indicated that the introduction of a substituent into 1-position in general lowers the melting point. Benzimidazoles with the imide nitrogen are usually soluble in polar solvents and less soluble in organic solvents.

With introduction of other non-polar substituents in various positions of the benzimidazole ring, the solubility in nonpolar solvents is increased. Benzimidazole distills unchanged above 300 °C. Benzimidazoles are weakly basic, being somewhat less basic than the imidazoles and are in general soluble in dilute acids. Benzimidazoles are also sufficiently acidic to be generally soluble in aqueous alkali and form N-metallic compounds. The acidic properties of the benzimidazoles, like those of the imidazoles, seem to be due to stabilization of ion by resonance. The more acidic benzimidazoles may be soluble in less basic solution, such as potassium carbonate solution.

Hunter and Marriot determined the molecular weight of a number of benzimidazoles from freezing point data in naphthalene solution over a range of concentrations. Evidence was obtained indicating molecular association through N-H-N bonds in those compounds possessing an unsubstituted NH grouping. The strength of this bond is evidently enhanced by resonance of the benzimidazole nucleus. The dipole moment of benzimidazole has been determined, the values that have been obtaine being 3.93-4.08 D (in dioxane).

2.1.3 Chemical properties of benzimidazoles

(A) Reactions of the benzimidazole ring: The benzimidazole ring possesses a high degree of stability. Benzimidazole is not affected by concentrated sulfuric acid, hot hydrochloric acid as well as alkalis. Oxidation cleaves the benzene ring of benzimidazole only under vigorous conditions. The benzimidazole ring is also quite resistant to reduction but under certain conditions the tetrahydro and hexahydrobenzimidazoles may be prepared by catalytic reduction.

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(1) *Reactions involving 1 and 3-positions:* Benzimidazoles form salts e.g. with acids readily forms monohydrochloride, mononitrate, monopicrate, monoacetate.

Alkylations: Benzimidazoles, undergoes alkylation with alkyl halides, yielding 1-alkylbenzimidazoles and under more vigorous conditions, 1,3-dialkylbenzimidazolium halides (fig 2.3).

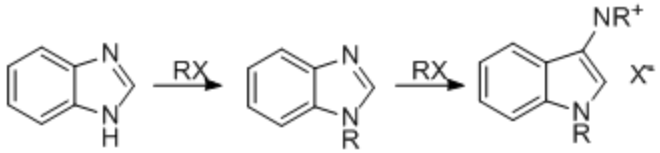

Figure 2.3: Alkylation of benzimidazole

Benzimidazoles also react with acylating, Grignard reagents and metal. The benzimidazole also forms mannich bases by reacting formaldehyde and piperidne.

(2) *Hydrogenation and dehydrogenation reactions:* Until very recently it was thought that benzimidazole ring was stable to reduction. Catalytic reduction of benzimidazole even under high pressure with nickel as the catalyst is reported to give negative results. 2-Phenylbenzimidazole gives only 2-cyclohexylbenzimidazole. Hydrogenation of 2-(*p*-dimethylaminostyryl) benzimidazole with nickel at atmospheric pressure saturates only the olefinic linkage in the 2-positions (fig 2.4).

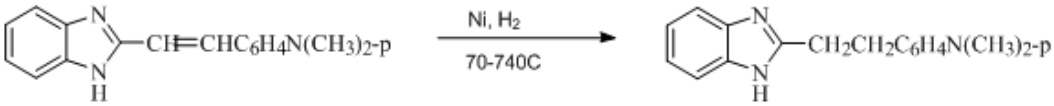

Figure 2.4: Hydrogenation of benzimidazole

A number of hydrogenated benzimidazoles have been prepared also by chemical methods. Hexahydro-2(3*H*)-benzimidazolone may be obtained by the reaction between hexahydro-*o*-phenylenediamine and phosgene in sodium hydroxide solution. Attempted dehydrogenation of tetrahydrobenzimidazoles with palladium sponge does not give the corresponding benzimidazole but instead a compound of high molecular weight.

(3) *Cleavage of the imidazole ring:* The imidazole ring of benzimidazoles may be cleaved by one of the several methods by reacting with pseudobases, acid anhydrides and halide.

(4) *Halogenation:* When 2,5(or 2,6)-dimethylbenzimidazole is an aqueous acid solution on treatment with saturated solution of bleaching powder at 0-5 °C. 1-chloro-2,5(or 2,6)-dimethylbenzimidazole is obtained (fig 2.5).

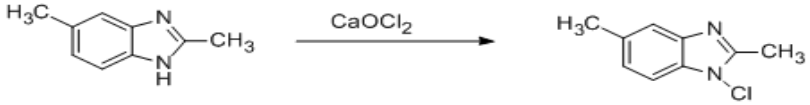

Figure 2.5: Halogenation of benzimidazoles

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Reactions involving the 2-methyl or methylene group: The methyl group of 2-methylbenzimidazoles is comparable in its activity to the methyl group of α-picoline, quinaldine, or methyl ketones and shows most of the same reactions of these compounds. The benzimidazoles ring, like the pyridine and quinoline ring, because of its electron attracting nature imparts a positive character to the carbon atom of the 2-methyl group. 2-Methylbenzimidazoles, for example, react with aromatic aldehydes in aldol type condensations in a manner analogous to α-picoline quinaldine.

(5) *Nitration:* The nitration of benzimidazoles proceeds readily. In most cases nitration appears to take place preferentially at the 5 or 6 position. However, the nitro group may also enter the 4 or 7 position, especially if the 5 or 6 poition is blocked.

(B) Reactions involving substituent groups: The various useful transformations can be successfully carried out various substituents in benzimidazoles. Some of the conversions are discussed below (fig 2.6).

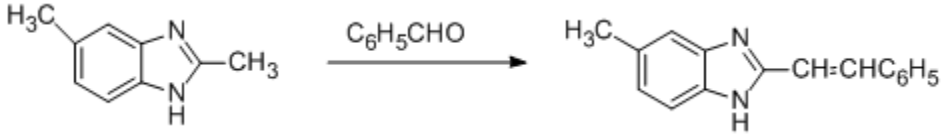

Figure 2.6: Reaction involving the 2-methyl or methylene group

(1) *Reactions of 2-benzimidazolecaboxylic acids:* Benzimidazoles containing a carboxyl group in the 2-positions readily undergo decarboxylation on heating. 2-benzimidazolecarboxylic acid on heating above its melting point, for example, yields benzimidazoles (fig 2.7).

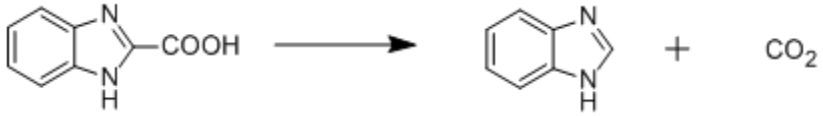

Figure 2.7: Reaction of 2-benzimidazolecarboxlic acids

(2) *Reactions of 2-(α-haloalkyl)benzimidazoles:* 2-(α-Chloroisopropyl) benzimidazole when refluxed in dry alcoholic solution in the presence of pyridine gives a good yield of 2-(α-ethoxyisopropyl)benzimidazoles and hence reacts in a manner analogous to tritylchloride (triphenylmethyl chloride) (fig 2.8).

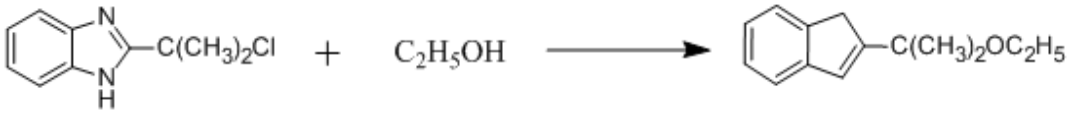

Figure 2.8: Reaction of 2-(α-haloalkyl) benzimidazoles

(3) *Reactions of 2-(3H)-Benzimidazolones:* 2(3*H*)-Benzimidazolones (or 2-hydroxybenzimidazoles) are extremely stable treatment of substances.2 (3*H*)-benzimidazolone is not split by treatment with benzoyl chloride in alkaline solution. 2(3*H*)-benzimidazolones show many of the reactions of 2-hydroxypyridines and 2-hydroxyquinolines; for example, 2(3*H*)-benzimidazolone with phosphorous oxychloride or phosphorous pentachloride yields the 2-chloro derivative (fig 2.9).

ISSN: 0975-8585

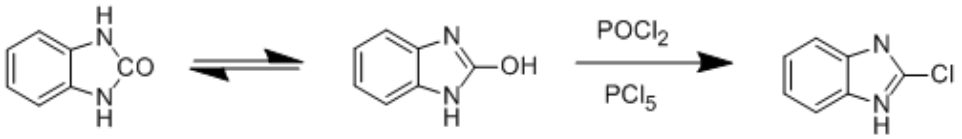

Figure 2.9: Reaction of 2-(3*H*)-benzimidazolones

(4) *2(3H)-Benzimidazolethiones:* 2(3*H*)-Benzimidazolethiones or 2-mercaptobenzimidazoles) are generally stable substances and are soluble in dilute alkali. Alkylation occurs readily with replacement of the mercapto hydrogen to yield S-alkylated derivatives, and a number of these derivatives have been prepared (fig 2.10).

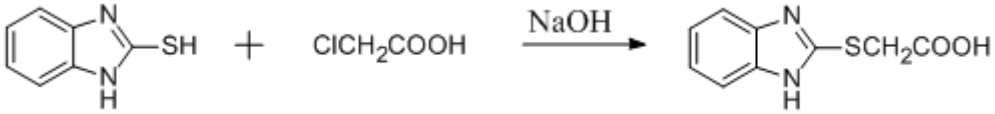

Figure 2.10: Reaction of 2(3*H*)-benzimidazolethione

(5) *2-Aminobenzimidazoles:* 2-Aminobenzimidazole with acetic anhydride gives 2-acetyl aminobenzimidazole (fig 2.11).

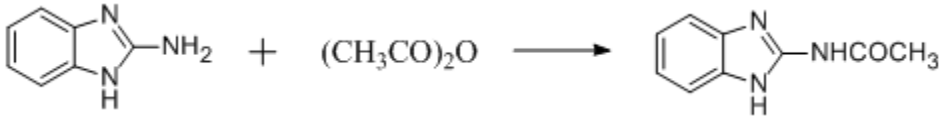

Figure 2.11: Reaction of 2-Aminobenzimidazoles

(6) *Oxidation:* Benzimidazoles are stable to oxidation. By vigorous conditions of oxidation (potassium permanganate in hot alkaline solution) it is partially possible to oxidize benzimidazoles to obtain a small amount of imidazoledicarboxylic acid (fig 2.12).

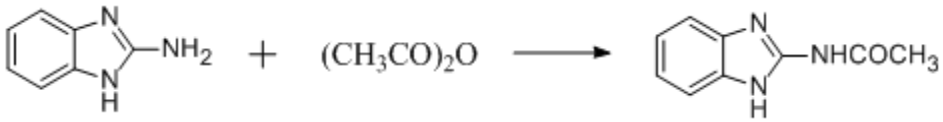

Figure 2.12: Reaction of Oxidation of benzimidazole

Because of the stability of the benzimidazoles ring to oxidation it is possible to oxidize substituent group without affecting the ring. By the oxidation of the substituent groups a variety of benzimidazolecarboxylic acids have been prepare.

2.2 Methods for synthesis of benzimidazoles:

Practically all synthesis of benzimidazoles starts with benzene derivatives possessing nitrogen-containing functional group at position ortho. So, the starting material for benzimidazole synthesis possesses the function designated by formula (fig 2.13):

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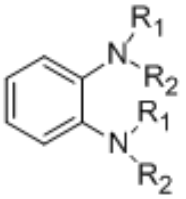

Figure 2.13: Starting material for benzimidazoles synthesis

The various strategies for the synthesis of benzimidazoles are discussed below.

2.2.1 From *o*-phenylenediamines

(a) ***By reaction of carboxylic acid and carboxylic acid derivatives:*** *o*-phenylenediamines react readily with most carboxylic acids to give 2-substituted benzimidazoles in very good yield. Also, *o*-phenylenediamines and their dihydrochlorides also react with various carboxylic acid derivatives like anhydrides, ester, amides and acid chlorides to yield the corresponding benzimidazoles (fig 2.14).

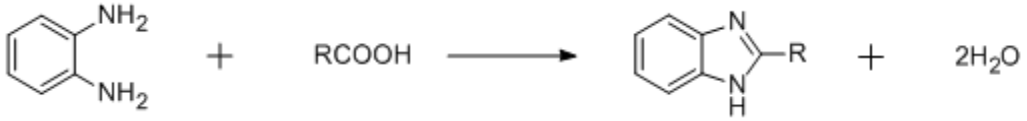

Figure 2.14: Reaction with carboxylic acids and carboxylic acid derivatives

(b) ***By reaction with lactones:*** Valerolactone when refluxed with *o*-phenylenediamines gives only a small yield of 1, 2-(1-methyltrimethylene) benzimidazoles (fig 2.15).

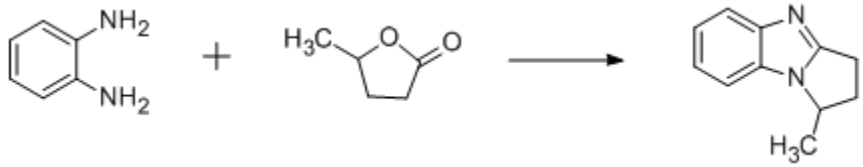

Figure 2.15: Reaction with lactones

(c) ***By reaction with nitriles:*** Cyanogen bromide reacts with *o*-phenylenediamines to give 2-aminobenzimidazoles in good yield. The reaction is carried out by mixing equimolecular amounts of the reactants in aqueous suspensions (fig 2.16).

Figure 2.16: Reactions with nitriles

(d) ***By reaction with aldehydes:*** Under the correct conditions aldehydes may reacted with *o*-phenylenediamines to yield 2-substituted benzimidazoles. Due improvement of oxidation reaction was best carried out under oxidative conditions (fig 2.17).

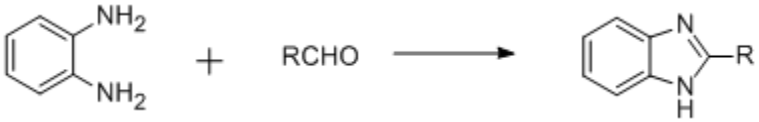

Figure 2.17: Reaction with aldehydes

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(e) ***By reaction with ketones:*** The author had investigated the reaction with a number of ketones. The direct elimination of the alkyl group and of hydrogen (as R-H) may be assumed to be due to the gain in resonance stabilization on conversion to the benzimidazoles.

(f) ***By reaction with imino-ethers and imino-thioethers:*** The synthesis of benzimidazoles from imino ethers or imino thioethers and *o*-phenylenediamines had been investigated by King and Acheson. This reaction was illustrated by the preparation of 2-phenylbenzimidazole from *o*-phenylenediamine and benzimino methyl ether (fig 2.18).

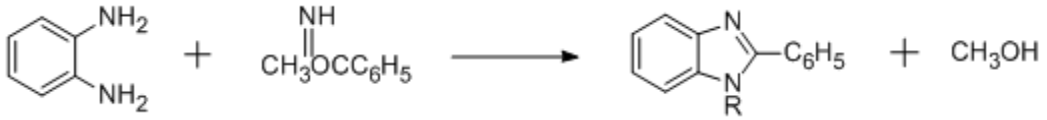

Figure 2.18: Reaction with imino-ethers and imino-thioether

(g) ***By reaction with amidines and guanidines:*** Diphenylformamidine gives an 85.5 per cent yield of benzimidazoles when heated at about 125°C with *o*-phenylenediamine (fig 2.19).

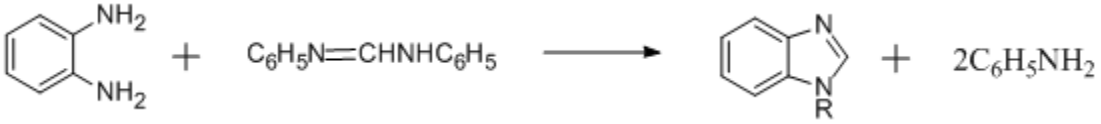

Figure 2.19: Reaction with aminidines and guanidines

(h) ***By reaction with urea:*** *o*-phenylenediamine dihidrochloride when heated with urea at 130°C gives 2(3*H*)-benzimidazolone (fig 2.20).

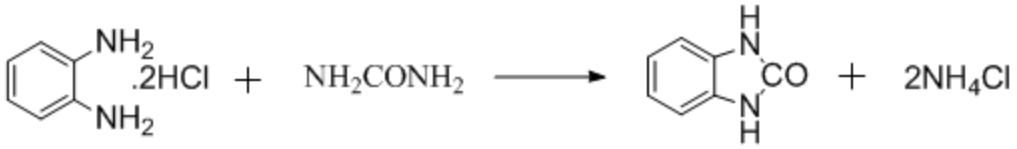

Figure 2.20: Reaction with urea

(i) ***By reaction with carbon disulfide:*** The reaction was carried out usually by heating the reactants in alcoholic solutions withor without the addition of alkali to the reaction mix and led to the synthesis of 2(3*H*)- Benzimizalethidone (fig 2.21).

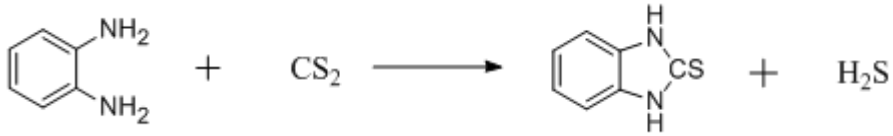

Figure 2.21: Reaction with carbon disulfide

(j) ***By reaction with thiophosgene:*** Billter and Steiner obtained 2(3*H*)-benzimidazolthione and 5-methyl-2(3*H*)-benzimidazolthione by the reaction of thiophosgene on *o*-phenylenediamine and 3,4-diaminotoulene, respectively. 3,4-Diaminobenzenearsonic acid thiophosgene gave 78% yield of 2(3*H*)-benzimidazolethione-5-arsonic acid (fig 2.22).

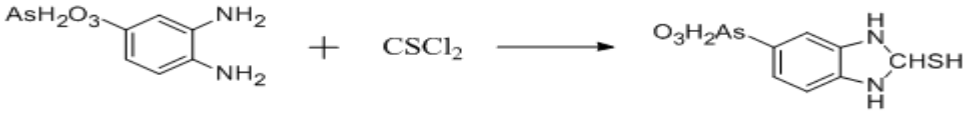

Figure 2.22: Reaction with thiophosgene

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(m) ***By reaction of 2-aminobenzimidazoles:*** 2-Arylaminobenzimidazoles were prepared by the action of diarylcarbodimides on *o*-phenylenediamines (fig 2.23).

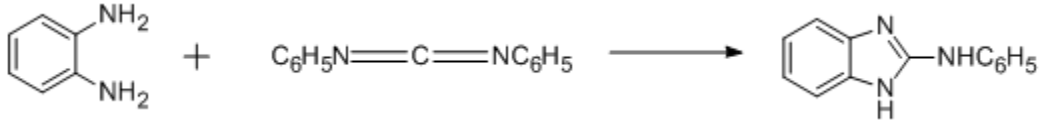

Figure 2.23: Reaction with 2-aminobenzinidazoles

2.2.2 From monoacyl- and diacyl-*o*-phenylenediamines:

Triacetylaminobenzene on ring closure gave 2-methyl -4(or 7)-acetyl-aminobenzimidazole (fig 2.24).

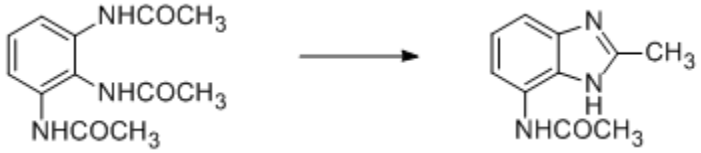

Figure 2.24: Reaction with 2-methyl-4(or 7)-acetyl-aminobenzimidazole

2.2.3 By reduction of acetylated *o*-nitroanilines:

N-substituted acylated *o*-nitroanilines lead to 1-substituted benzimidazoles. For example, N-methyl-2-nitro-4-methylacetanilide on reduction yields 1,2,5-trimethylbenzimidazole (fig 2.25).

Figure 2.25: Reduction of acetylated *o*-nitroanilines

2.2.4 From *o*-aminoazo compounds: *o*-aminoazo compounds react with aldehydes to form schiffs bases in the normal manner. The resulting schiffs bases were found to undergo isomerization (boiling acetic acid) with the shifting of a hydrogen atom to form N-arylaminobenzimidazoles (fig 2.26).

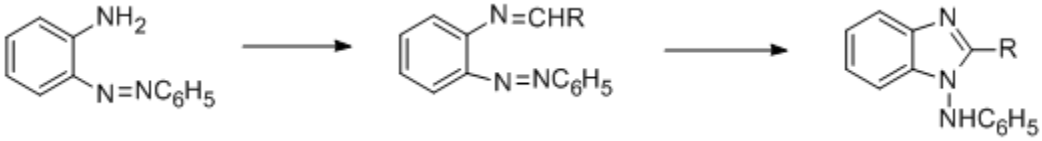

Figure 2.26: Reaction to form N-arylaminobenzomidazoles

2.2.5 From phenylurethans: 2(3*H*)-Benzimidazolone was prepared by Rudolph by heating *o*-aminophenylurethan above its melting point [16] (fig 2.27).

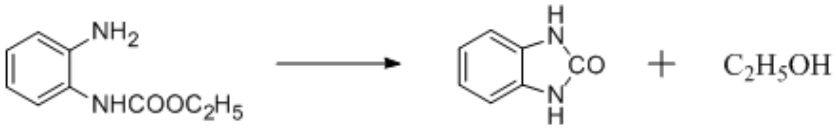

Figure 2.27: Formation of 2(3*H*)-Benzimidazolone

2.2.6 Advanced methods of synthesis of benzimidazoles

1. The protocol for the synthesis of variety benzimidazoles using a catalytic amount of $TiCl_4$ and silica sulfuric acid under exteremly mild solvent free conditions given by Shinde *et al.* In 2007 and Baltork *et al.* in 2008 respectively [19,20].
2. Synthesis of 1-alkyl/aralkyl-2-(1-arylsulphonylalkyl) benzimidazoles under PTC conditions given by Dubey *et al.* in 2007 [21].
3. Synthesis of 2-substituted benzimidazoles by microwave in the presence of alumina-methanesulfonic acid given by Niknam *et al.* in 2007 [22].

2.3 Chemistry of Sulfonamides

In chemistry, the sulfonamide (fig 2.28) functional group (also spelt sulphonamid) is -S $(=O)_2$-NH_2, a sulfonyl group connected to an amine group. The general formula is RSO_2NH_2, where R is some organic group. Individual members differ in the nature of N^1 (sulfonamide N) substitution, which governs solubility, potency and pharmacokinetic property. A free amino group in the *p*- position (N^4) is required for antibacterial activity. The sulfonamide family includes sulfadiazine, sulfamethizole (brand name: Thiosulfil Forte), sulfamethoxazole (Gantanol), sulfasilazine (Azulfidine), sulfisoxazole (Gantrisin), and various high-strength combinations of three sulfonamides. Sulfa drugs kill bacteria and fungi by interfering with cell metabolism. They were the wonder drugs before penicillin and are still used today. Because sulfa drugs concentrate in the urine before being excreted, treating urinary tract infections is one of their most common uses. Sulfa drugs can have a number of potentially dangerous interactions with prescription and over-the-counter drugs (including PABA sunscreens), and are not appropriate for patients with some health conditions. Be sure your doctor knows about any other medications you take and your full health history before taking sulfonamides [23].

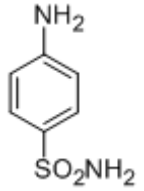

Figure 2.28: Structure of sulfonamide

Sulfonamides were the first effective chemotherapeutic agents employed systematically for the prevention and the cure of bacterial infections in humans and other animal systems. After the introduction of the penicillin and other antibiotics the popularity of sulfonamides decreased. However they are still used as sulfa drugs in certain therapeutic fields especially in the case of ophthalmic infections and for urinary and gastrointestinal infections. Multidrug resistance (MDR) remains as a significant problem for microbial infection treatments. Additionally the threat of bioterrorism using agents such as weaponized Bacillus anthracis and Yersinia pestis highlight the need for continuing research in infectious diseases and the search for new therapeutic agents.

ISSN: 0975-8585

2.4 Benzimidazoles as Antimicrobials

1. A series of 1-methyl-N-[(substituted-phenylmethylidine)-*H*-benzimidazole-2-amines showing antibacterial and cytotoxic properties for Gram positive bacteria (*S.aureus*, *B. pumillus*) and Gram negative bacteria (*E.coli*) were synthesized by Noolvi *et al.* 2011 [24].

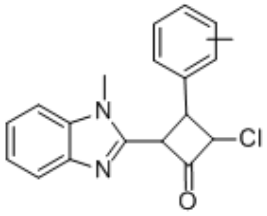

Figure2.29:1-methyl-N-[(substituted-phenylmethylidine)-*H*-benzimidazole-2-amines

2. Some novel Thieno[2,3-d]pyrimidin-4(3*H*)-ones containing benzimidazol-2-yl-thioethyl and benzimidazol-2-yl-methanethioethyl moiety in second position of pyrimidine ring were synthesized determining their antitrichinellosis and antiprotozoal effects by Mavrova *et al*. 2010 [25].

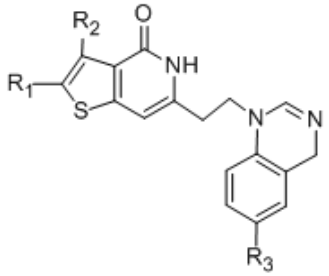

Figure 2.30: Thieno-[2, 3-d]pyrimidin-4(3*H*)-ones

3. Synthesis and in vitro antibacterial evaluation against Gram positive bacteria (*B.thurningiensis*) and Gram negative bacteria (*E.coli*) of various series including 2-substituted-3a,4,9a-tetrahydro-4,9-benzeno-benz(f)isoindole-1,3-diones: benzimidazoles(4) acetybenzimidazole (5) were done by Goude *et al.* 2010 [26].

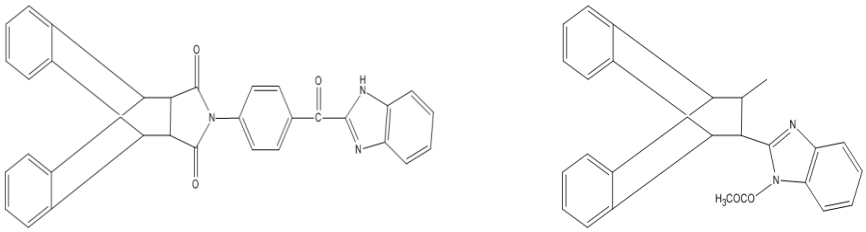

Figure 2.31: 2-substituted-3a,4, 9a-tetrahydro-4,9-benzeno-benz(f)isoindole-1,3-diones:benzimidazoles(4) acetylbenzimidazole (5)

4. A novel amine derived bis-benzimidazole showed antibacterial efficiency against *C.albicans*, *B.proteus*, which were designed by the systematical structural modification of Fluconazole by Zhore *et al.* 2010 [27].

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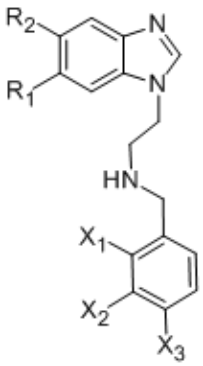

Figure 2.32: Fluconazole and amine derived bis-benzimidazole

5. A series of novel 2-substituted benzimidazoles analogues having potent activity against Gram positive bacteria (*B.subtilis*), Gram negative bacteria (*E.coli*) and antifungal activity for *T.virdae* were synthesized by Rauf *et al.* 2009 [28].

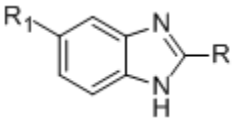

Figure 2.33: 2-substituted-1*H*-benzimidazole

6. A series of novel 5-(nitro/bromo)-styryl-2-benzimidazoles are synthesized showing antitubercular activity against Bacterium tuberculosis, anti-bacterial activity against *S.aureus* done by Hosmani *et al.* 2009 [29].

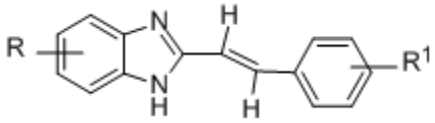

Figure 2.34: 5-(nitro/bromo)-styryl-2-benzimidazoles

7. Synthesis of 2-azetidinones derivatives of 2-methyl-1*H*-benzimidazoles showing antibacterial activity against *B.subtilis* (Gram positive) and *E.coli* (Gram negative) was done by Lal *et al.* 2009. 3-chloro-1-{5-[(2-methyl-1H-benzimidazol-1-yl)methyl]-1,3,4-thiadiazol-2-yl}-4-(substituted)phenylazetidine-2-one [30].

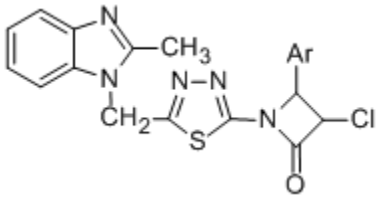

Figure 2.35: 3-chloro-1-{5-[(2-methyl-1*H*-benzimidazole-1-yl)methyl]-1,3,4-thiadiazol-2-yl}- 4-(substituted)phenylazetidin-2-one

8. Some 1-{[5-(alkyl/aryl)-1,3,4-oxadiazol-2-yl]methyl}-2alkyl-1*H*-benzimidazoles showing potent activity against Gram positive bacteria (*S.aureus* ATCC29123), (*J.mutans* MTCC 890) with Gram negative (*E.coli*) and antifungal activity (*A. niger)* were synthesized by Lal *et al.* 2009 [31].

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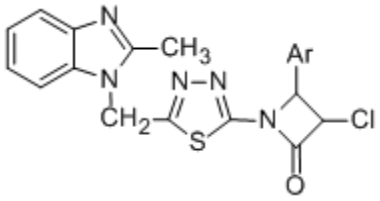

Figure 2.36: 1-{[5-(alkyl/aryl)-1,3,4-oxadiazol-2-yl]methyl}-2alkyl-1*H*- benzimidazoles

9. 2-(Amino-/isopropylamino-/chloro-/bromo-)benzimidazoles analogues having potent activity against methicillin-resistant staphylococcus were synthesized by Tuncbilek *et al.* 2009 [32].

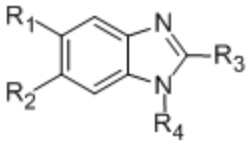

Figure 2.37: 2-(Amino-/isopropylamino-/chloro-/bromo-)benzimidazoles analogues

10. Synthesis of 2-alkenesubstituted benzimidazoles, tetrahydrobenzimidazoles was done by Sharma *et al.* 2009 [11].

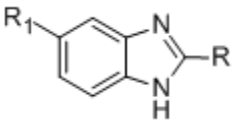

Figure 2.38: 2-alkenesubstituted benzimidazoles, tetrahydrobenzimidazoles

11. A series 2-(substituted phenyl)-1*H*-benzimidazoles were synthesized by Sharma *et al.* 2009 [33].

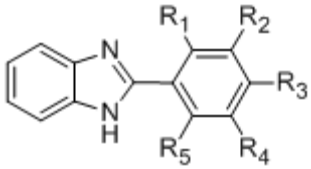

Figure 2.39: 2-(substituted phenyl)-1*H*-benzimidazoles

12. Baviskar *et al*. synthesized 1-(4-(1*H*-benzo[d]imidazol-1-yl)phenyl)-3-chloro-4-phenyl aztidin-2-one in 2009 [34].

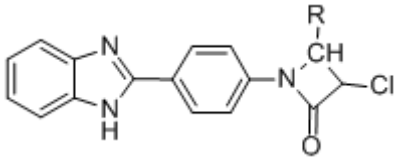

Figure 2.40: 1-(4-(1*H*-benzo[d]imidazol-1-yl)phenyl)-3-chloro-4-phenyl aztidin-2-one

13. A series of novel phenyl and benzimidazoles substituted benzyl ethers evaluated forantibacterial (*S.aureus, E.coli*) and antifungal activities (*C.albicans, C.krusei*) was reported by Guven *et al*. (2007) [35].

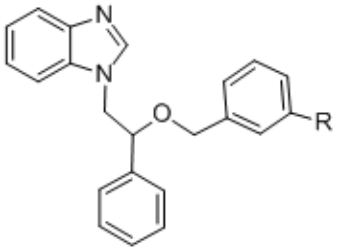

Figure 2.41: Structure of Phenyl substituted benzyl ether

14. Substituted 5-[2-(2-methylbenzimidazole-1-yl)ethyl]-3-diethylaminoethyl were tested against one strain of Gram +ve bacteria (Bacillus cereus), Gram –ve bacteria (Eschericia coli) by El-masry *et al*. (2005) [36].

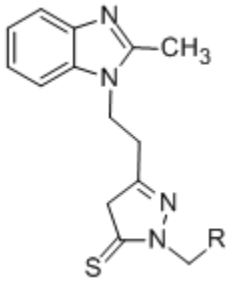

Figure2.42: Structureof 5-[2-(2-methylbenzimidazole-1-yl)ethyl]-3-diethylaminoethyl

15. A novel series of Schiff bases of 4-(4-aminophenyl)-morphine were screened for antibacterial (*S.aureus, S.epidermis*) and antifungal (*C.albicans, A.niger*) by Panneerselvam *et al.* (2005) [37]

Figure 2.43: Structure of 4-(4-aminophenyl)-morphine

16. Various N-alkyl and N-acyl derivatives of 2-(4-thiazolyl)-1*H*-benzimidazole were screened for their antifungal and antibacterial activity by Pawar *et al.* (2004) [38].

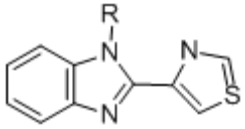

Figure 2.44: Structure of 2-(4-thiazolyl)-1*H*-benzimidazole

17. Some new 2-substituted-phenyl-1*H*-benzimidazoles-5-carbonitril with their potent activity against *Candida* species was reported by Goker *et al*. (2002) [39].

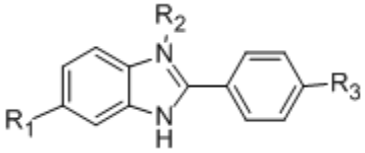

Figure 2.45: Structure of 2-substituted-phenyl-1*H*-benzimidazoles-5-carbonitril

18. Synthesis and antiparasitic activity of 1*H*-benzimidazole derivatives were tested against protozoa *Giardia lambia*, *Entamoeba hystolytica* by Valdez *et al*. (2002) [40].

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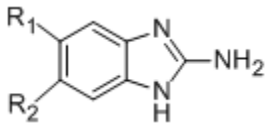

Figure 2.46: Structure of 2-amino-1-*H*-benzmidazole

2.5 Sulfonamides as antimicrobials:

1. New aryldisulfonamides were synthesized showing antibacterial activities against Gram positive bacteria (*S.aureus* ATCC 25953), (*B.aureus* ATCC 6633) and Gram negative bacteria *(E.coli* ATCC 11230) were done by Alyar *et al.* 2011 [41].

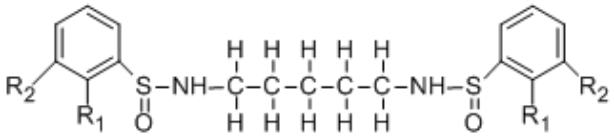

Figure 2.47: Structure of aryldisulfonamides

2. Symmetrically substituted metal-free phthalocyamine and its transitional metal were prepared which showed anti microbial (antibacterial and antifungal) activities such as *B. catarrhalis* and *C. albicans* by Kantikin *et al.* 2011 [42].

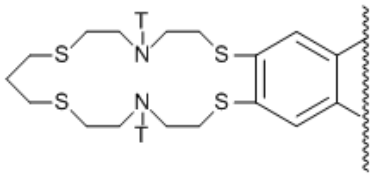

Figure 2.48: Structure of substituted metal-free phthalocyamine

3. 1,3-diaryl-4-formylpyrazoles synthesized and evaluated for their antibacterial activity against *S.aureus, B.subtilis* (Gram positive), *E.coli, P.aeruginosa* (Gram negative) and antifungal activity for *A.niger* and *A.flavus* by Sharma *et al.* 2011 [43].

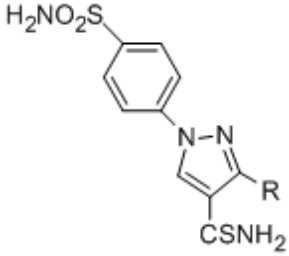

Figure 2.49: Structure of 1,3-diaryl-4-formylpyrazoles

4. A series of new and novel coumarin-6-sulfonamides have been synthesized as antimicrobials such as antibacterial and antifungal activity by Kulkarni *et al.* 2009 [44].

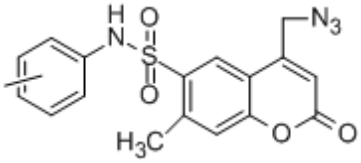

Figure 2.50: Structure of coumarin-6-sulfonamides

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5. A new series of sulfonamide derived Schiff bases were synthesized showing antibacterial, antifungal and cytotoxic properties by Hadda *et al.* 2010 [45].

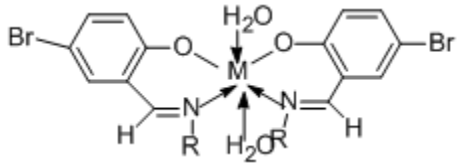

Figure 2.51: Structure of derived schiff base

6. Substituted sulfonamides were reacted with different aromatic aldehydes to form schiff's bases to determine potent antimicrobial activity against *K.pneumonia* (Gram positive) and *S.epidermidis* (Gram negative) by Singh *et al.* 2010 [46].

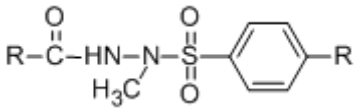

Figure 2.52: {[(E)-phenylmethylidene]amino}benzenesulfonamide

7. Substituted sulfonamides with aromatic aldehydes in formation of schiff's base showed good antibacterial and antifungal activity by Kadadevar *et al.* 2010 [47].

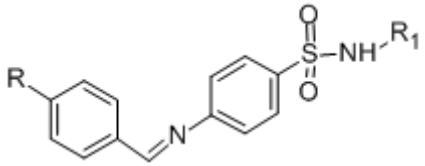

Figure 2.53: N-(2-substituted benzylidine)-4-sulfonamide benzenamine.

8. Some novel derivatives such as 5-substituted-2-mercapto-1,3,4 oxadiazoles then corresponding 5-esters,amides and benzenediasulfonamides have been prepared which showed antimicrobial activity on Gram positive and Gram negative bacteria by Zareef *et al.* 2008 [48].

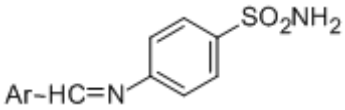

Figure 2.54: Structure of 5-substituted-2-mercapto-1,3,4 oxadiazoles

9. [N-(2-hydroxy-4-nitro-phenyl)-4-methyl-benzenesulfonamid] showed increased antimicrobial activity against Gram positive bacteria (Nocardia) which was synthesized by Isik *et al.* 2006 [49].

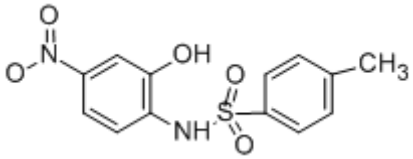

Figure 2.55: Structure of [N-(2-hydroxy-4-nitro-phenyl)-4-methyl-benzenesulfonamid]

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