

The Importance of 2-AminoThiazole Schiff Bases as Antimicrobial and Anticancer Agents

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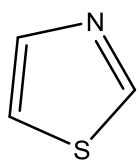
ABSTRACT

The pharmacophore 2-aminothiazole has an interesting role in pharmaceutical chemistry as this led to the synthesis of many types of compounds with diverse biological activity. Schiff base derivatives at the same time contribute to drug evolution importantly. In this review, the Schiff base derivatives of 2-aminothiazole formed and some of their metal complexes are being focused on, and the antimicrobial and anticancer activity of them is being illustrated.

KEYWORDS: Pharmacophore 2-aminothiazole; Schiff bases; Metal complexes.

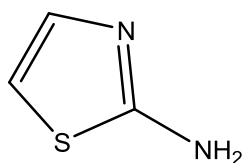
INTRODUCTION

Cyclic organic compounds having the hetero nitrogen and sulfur atoms are called Thiazoles (1). The pharmacophore 2-aminothiazole (2) is an interesting building block in pharmaceutical chemistry used as a starting point for the synthesis of many heterocyclic compounds with a broad range of biological activity [1-3] such as anti-bacterial [4,5], antifungal [6,7], anti-HIV [8,9], anti-cancer [10,11], anti-inflammatory [6,12], also their effect in degenerative brain diseases (Alzheimer's, and Parkinson's diseases) [13,14], allergies [15], hypertension [16], and as hypnotics [17], analgesics [18], and with Antithrombotics as antagonist of fibrinogen receptor [19].



Thiazole

(1)



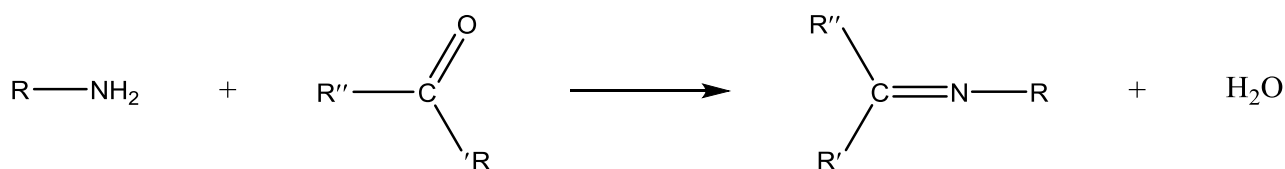
2-Aminothiazole

(2)

Famotidine is an example of drugs sold in market for treatment of peptic ulcer and gastro-esophageal reflux that has the 2-aminothiazole nucleus [20, 21]. Other examples are: Abafungin, a drug used for dermatomycoses [22], a third generation Cephalosporin, Cefdinir which is broad spectrum semi-synthetic antibiotic [23], and meloxicam a NSAID [24].

Thiazole derivatives are known of having very important antitumor or cytotoxic effect and many of these derivatives were designed for targeting specific pathways. An example of these Thiazole-containing compounds that have been introduced into clinical trials and cancer therapy are Dabrafenib and Dasatinib which are with tyrosine kinase inhibitory activity [25, 26].

Imine was firstly prepared by Hugo Schiff in the 19-century [27-29]. Schiff base is synthesized by combining of an aldehyde or a ketone with a primary amine; this is done by replacing of carbonyl group of the aldehyde or ketone with an imine group, Scheme 1 [28-30].



Scheme 1. General synthesis reaction of Schiff base.

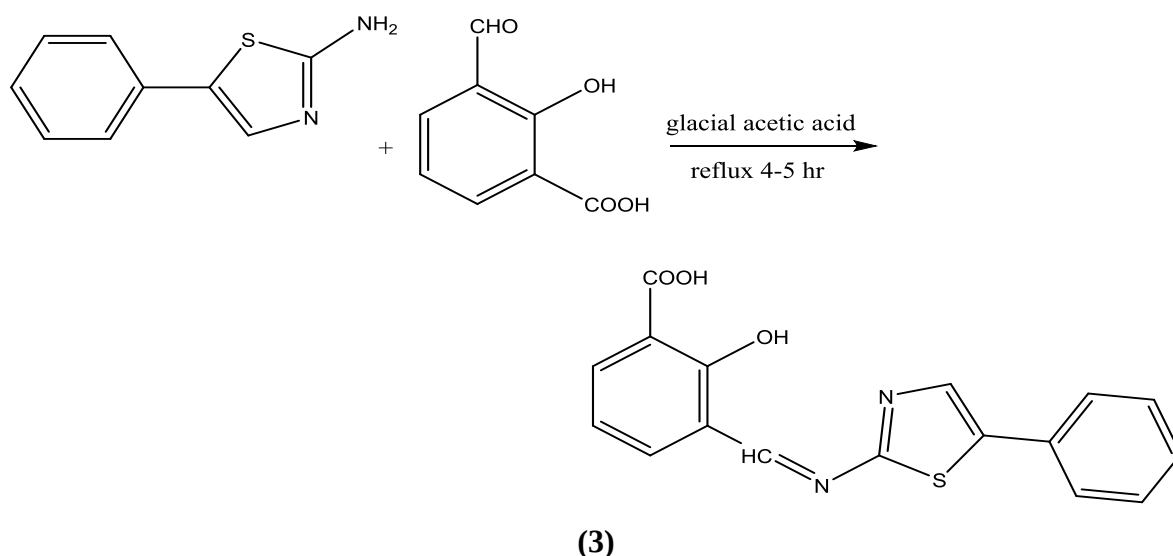
The azomethine C=N bond in compounds is of great importance for effect because of the remarkable antibacterial, antifungal, and anticancer activities found in them [31]. As a consequence, Schiff bases are of an important application in pharmaceutical industry [32].

Schiff bases also represent important ligands for metals through coordination to the nitrogen atom in imine and to other donating groups [33]. This is because Schiff bases can bind to metals at different sites to form complexes for example: zinc (II), nickel (II), cobalt (II), or copper (II) [34-36]. The coordination of metal ion to nitrogen of imine and other molecule's donor centers. The obtained metal complexes of these Schiff bases attracted special attention in medicinal and pharmaceutical field since they affect the biological activity of ligand as a result to the shape, size, distribution, redox potential, and charge density differences [37,38].

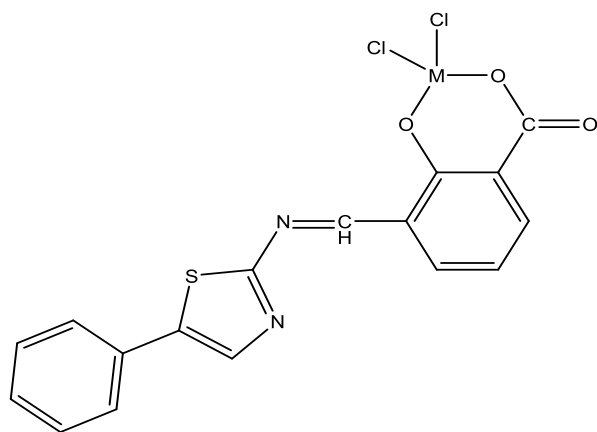
As a result, many studies were done by synthesizing of aminothiazole containing Schiff base complexes and screening their antibacterial [39] and antifungal activities [40].

The complexes of transition metals also had an important binding ability with the DNA molecule [41], by cleaving or interacting with certain parts of DNA molecule and this give these compounds an important role in treatment of cancer [42]. Some of these coordination compounds can bind and damage the cancer cell's DNA and inhibit their growth [43].

The reaction of metal chloride with Schiff base ligand 3-((4-phenylthiazol-2-ylimino) methyl)-2-hydroxybenzoic acid (**3**) to form 1:1 ratio metal complex (**4**), (**5**), (**6**), (**7**), and (**8**) are shown in Scheme 2 and Figure 1. Then studying the cleavage of DNA, the antibacterial, the antifungal and the cytotoxic effects of the compounds synthesized were done [44].



Scheme 2. Synthesis of 3-((4-phenylthiazol-2-ylimino) methyl)-2-hydroxybenzoic acid ligand Schiff base.



M=Cu, Co, Cd, Zn and Ni
(4), (5), (6), (7), and (8)

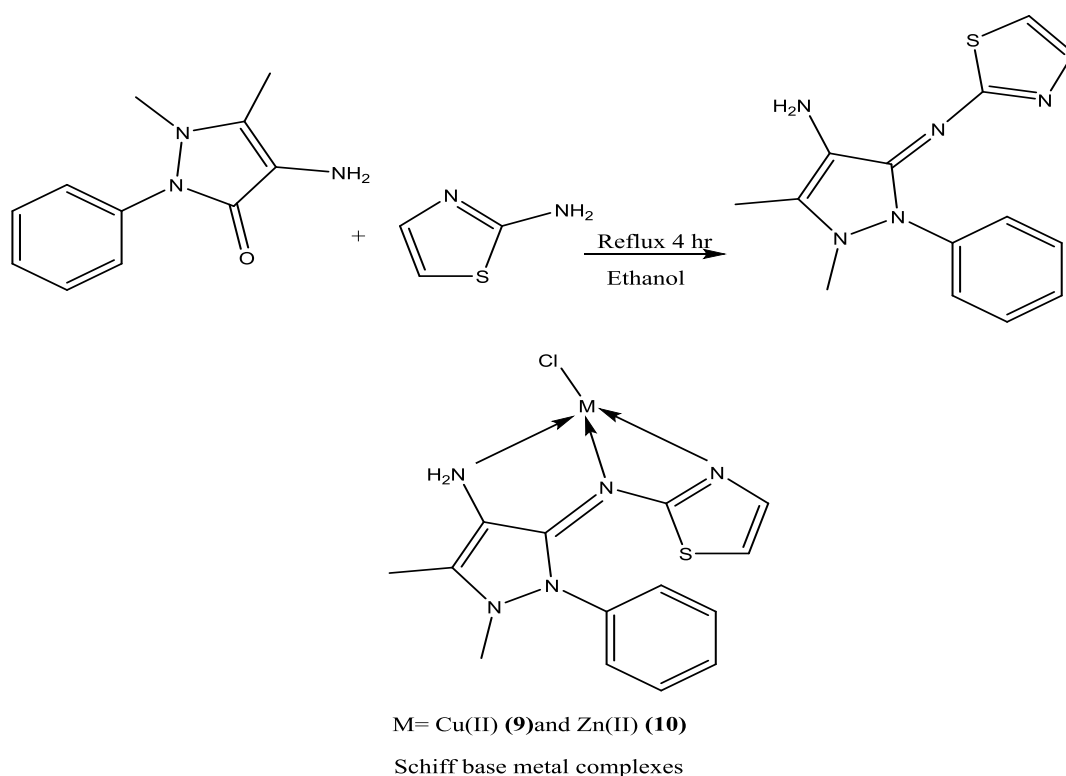
Figure 1. Structure of complex as proposed.

The antimicrobial study shows that the ligand has antimicrobial activity which could be due to the imine C=N bond, but by comparing the antimicrobial effect of the ligand with the metal complexes, the complexes had greater activity, which means that the coordination with metals increased activity. This is consistent with the theory of chelation [45, 46].

The delocalization of the π -electrons in the whole chelate enhances the lipophilicity of it and as a result the permeability through the bacteria lipid membranes [47]. The cytotoxicity of (4) and (8) complexes is high therefore they are important for anticancer clinical trials [44].

Copper and zinc complexes (9) and (10) of the 2-aminothiazole Schiff base of 4-aminoantipyrine are found in Scheme 3. They show important biological activity.

The ligand Schiff base and their metal complexes antibacterial activities were tested toward the following bacteria: *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* using tetracycline as a standard [48]. The metal complexes have a great activity when compared to the free ligand because of the metal complexes higher lipophilicity, this result in better permeation through cell membrane therefore greater antibacterial activity, or could be the ligand and metal combined activity [49, 50].



Scheme 3. Copper and zinc complexes with the 2-aminothiazole Schiff base of 4-aminoantipyrine.

As revealed, all complexes interacted with DNA in the *in silico* DNA-metal complex combination. These complexes antimicrobial

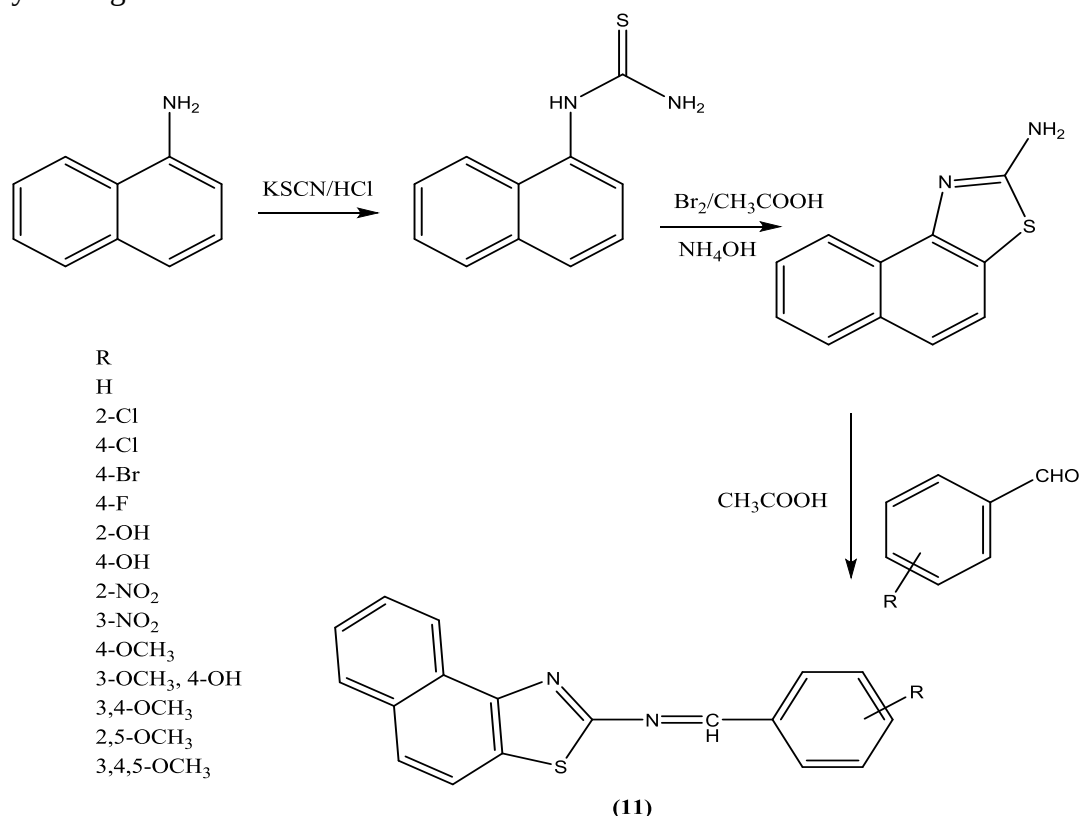
study were evaluated against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, and

Pseudomonas aeruginosa, and showed more cidal activity compared to the ligand [48].

Combination of Thiazole with naphthalene ring by forming azomethine bond to form new Schiff bases is seen in Scheme 4.

The lipophilicity of naphthalene increased the permeability through bacterial membrane. The

Ni (II), Co (II) and Cu (II) complexes (**12**), (**13**), and (**14**) respectively with 2-(2'-hydroxy) benzylideneaminonaphthothiazole (**11**) are shown in Figure 2, and their antibacterial activities were done.



Scheme 4. Synthesis reaction of thiazole ring Schiff bases combined with naphthalene.

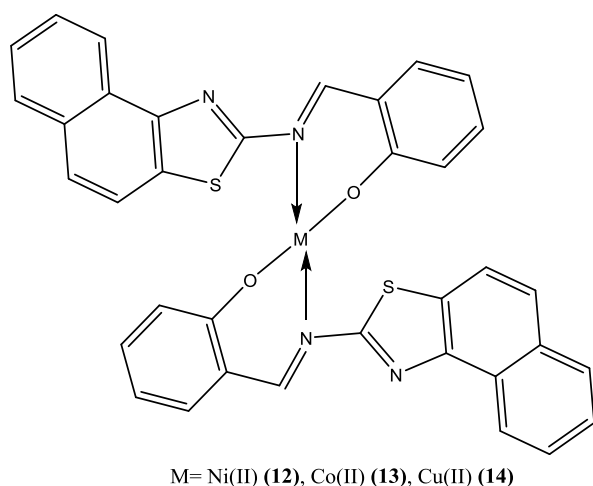


Figure 2. Co (II), Ni (II), Cu (II) Complexes with compound (11)

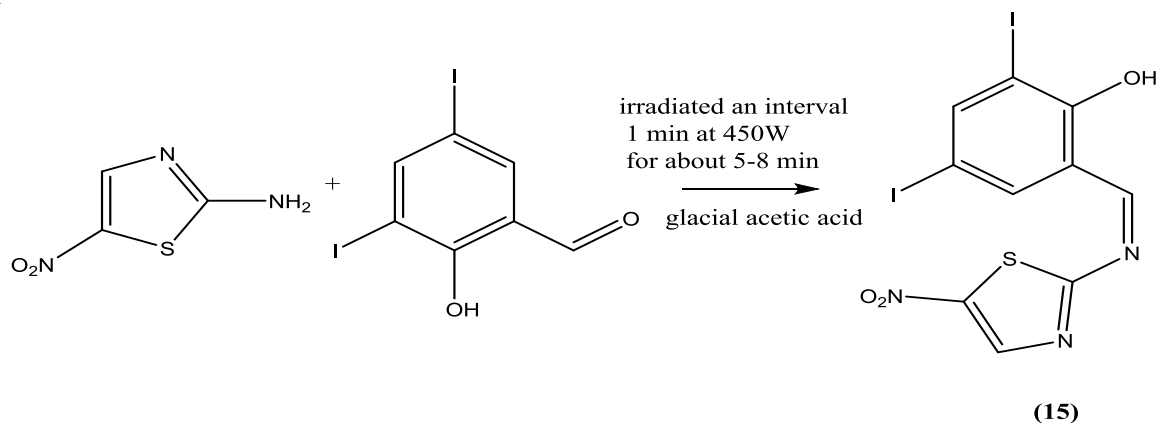
All compounds showed moderate inhibition of Gram-positive and Gram-negative bacterial growth but the 2-(2'-hydroxy) benzylideneaminonaphthothiazole Schiff base show higher

inhibition when compared to other Schiff bases, on the other hand the complex of Cu (II) metal has the highest effect. It was concluded that the methoxy group at different positions in the aromatic ring, had less effect on the growth of microorganism, while the halogens, hydroxyl, and nitro functional groups had good inhibitory effect [51].

Reaction of 2-amino-5-nitrothiazole and substituted salicylaldehyde by microwave to synthesize new Schiff base (**15**) is found in Scheme 5, then formation of its copper complex. Antimicrobial study was done on two G⁺ and two G⁻ bacteria and fungi using disk diffusion method.

The study revealed that compound (**15**) Schiff base was in active against bacteria on the other hand Cu (II) complex had moderate action

against *E. coli*, and *S. aureus* and show high inhibitory effect toward *Bacillus subtilis* and no action on *Pseudomonas putida*. The complex of metal had a great inhibitory effect toward fungi as compared to free Schiff base.



Scheme 5. Schiff base synthesis reaction using microwave.

The differences in the lipophilicity of the Schiff base and Cu (II) complex result in differences in their activity toward microorganisms, because the high lipid solubility of compound increases its permeability through microorganism cell [52-54]. Also, the decrease in polarity due to metal coordination [55] led by sharing of the positive charge of ion partially with donor groups of chelate [56]. This makes the metal chelate more lipophilic and can highly permeate the lipid membrane of microorganism [57], and destroy those [58].

Schiff base of substituted 4-acetyl-1-phenyl-3-methyl-2-pyrazolin-5-one and 2-amino-4-phenylthiazole and their metal Mn (II), Fe(II), Co(II), Ni(II) and Cu(II) complexes found in Figure 3.

The antimicrobial activity studied for the ligand Schiff base and for the metal complexes revealed that the metal complexes have higher inhibition action on bacteria such as: *Escherichia coli*, *Bacillus subtilis*, *S. aureus*, *A. niger* and *S. cerevisiae* than Schiff base ligand. Showing order of biological activity as follows: Co (II) =Ni (II) > Mn (II), Fe (III), Cu (II) [59,60].

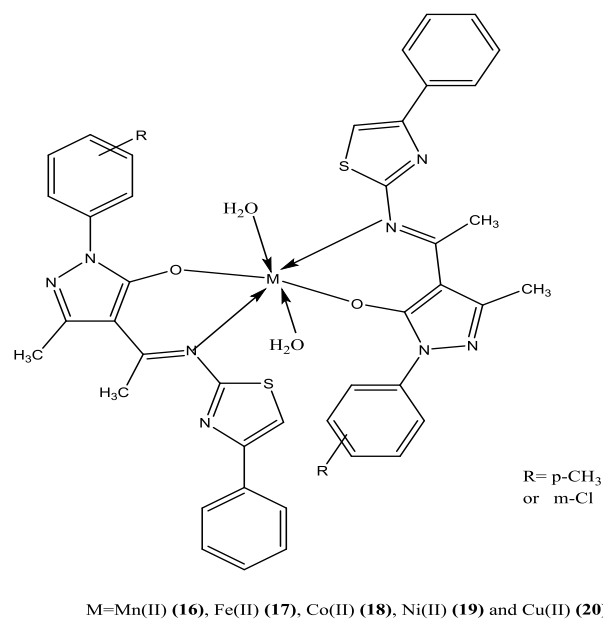
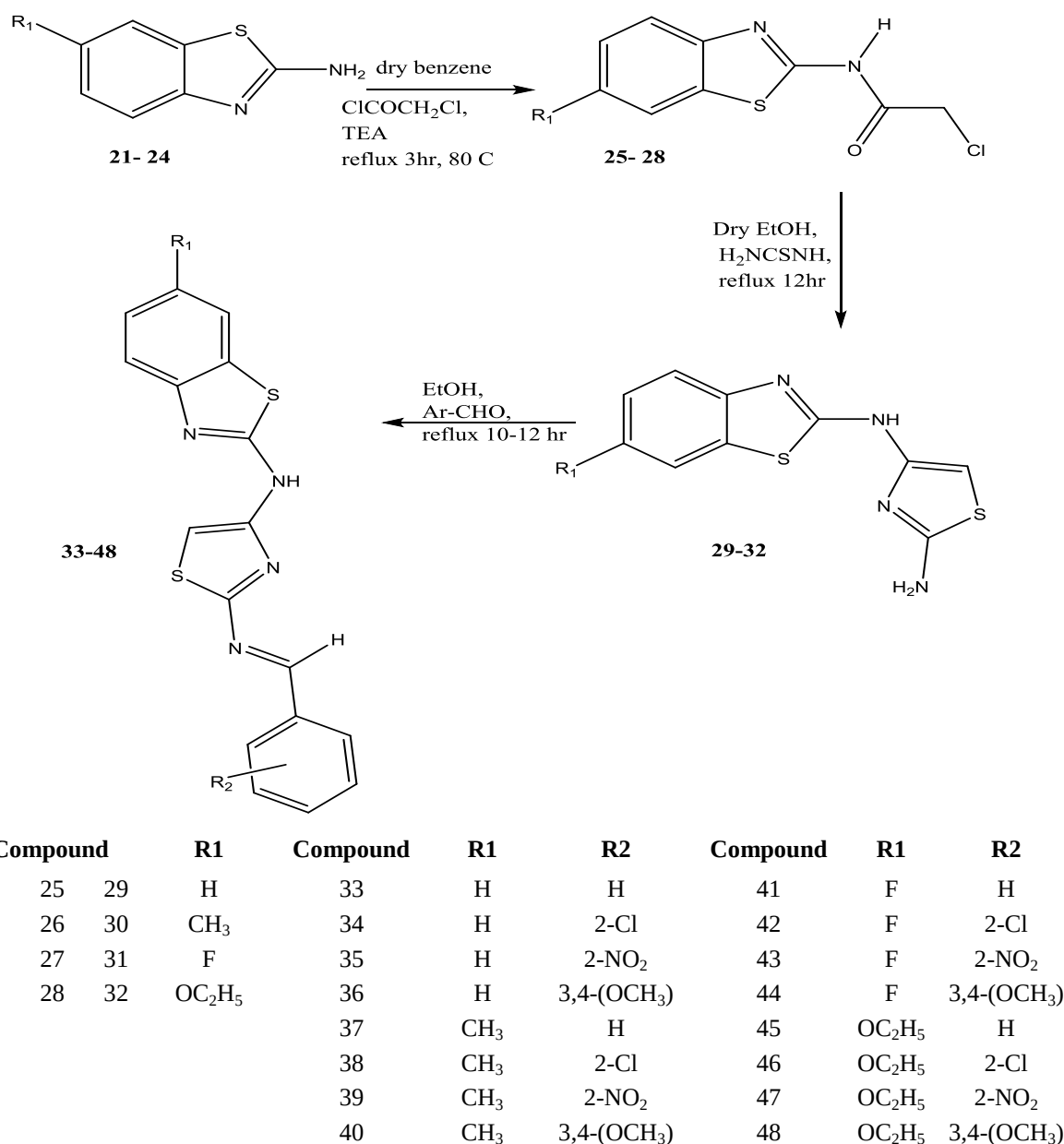


Figure 3. Schiff base of substituted 4-acetyl-1-phenyl-3-methyl-2-pyrazolin-5-one and 2-amino-4-phenylthiazole and Mn(II), Fe(II), Co(II), Ni(II) and Cu(II) complexes.

New compounds having 2-aminobenzothiazole ring were synthesized found in Scheme 6.



Scheme 6. The general synthesis reaction of compounds (29-48).

Compound (44) bearing the methoxy group which is an electron releasing group had an increased activity against *B. subtilis* and *S. aureus* G⁺ bacteria. Substitution at position 6 of the benzothiazole ring with fluoro group which is an electron withdrawing group gave an inhibitory activity against G⁺ and G⁻ bacteria, as revealed by the structure activity relationship. On the other hand, compounds (33)-(36) having no substitution showed moderate inhibitory effect against bacteria. An excellent antifungal activity is shown by compound (42) when compared to all other compounds. It is agreed that the 2-chloro electron attracting group on the phenyl ring and 6-fluoro on benzothiazole ring increased the effect toward fungi. Compound (46) shows a high anthelmintic activity as compared to mebendazole. The ethoxy

group which is an electron releasing group on the benzothiazole ring 6-position in compounds (45)-(48) showed a high anthelmintic effect. Compounds (34), (38), (42) and (46) with chloro group which is an electron attracting group on phenyl ring have a great anthelmintic activity on the contrary with the electron releasing 3, 4-dimethoxy group that gave least activity [61].

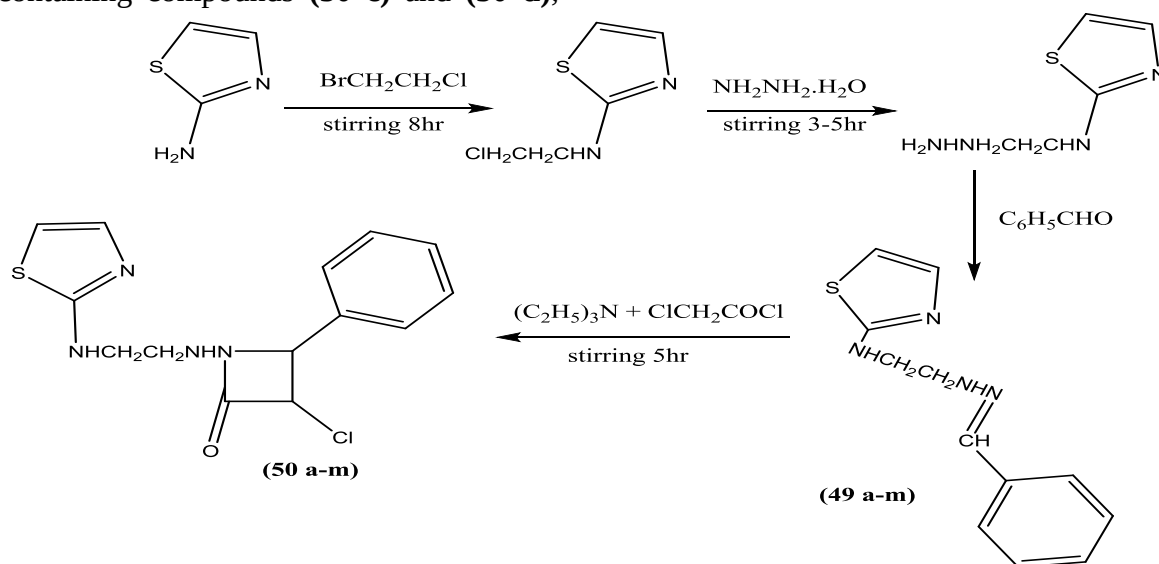
Many classes of antibiotic have an important unit which is the azetidinone and the chemistry of this unit is of importance inside the body effect. The combination of 2-aminothiazole moiety and azetidinone unit resulted in synthesis of compounds N-[2-(2-aminothiazolyl)ethyl]-4-(substituted phenyl)-3-chloro-2-oxo-1-iminoazetidines found in Scheme 7. The

antibacterial, antifungal and anti-inflammatory studies for these compounds were done.

Different and important activity is shown by all compounds (**50a–m**) against microorganisms, depending on the substitution.

The nitro group containing compounds (**50 h**), (**50 i**) and (**50 j**) have higher activity than the chloro group containing compounds (**50 c**) and (**50 d**),

and the bromo group containing compounds (**50 e**) and (**50 f**), on the other hand chloro and bromo compounds have higher activity than the other derivatives.



Compound	Ar	Compound	Ar
49 a and 50 a	C ₆ H ₅	49 h and 50 h	4-NO ₂ C ₆ H ₄
49 b and 50 b	4-Cl C ₆ H ₄	49 i and 50 i	3-NO ₂ C ₆ H ₄
49 c and 50 c	3-Cl C ₆ H ₄	49 j and 50 j	2-NO ₂ C ₆ H ₄
49 d and 50 d	2-Cl C ₆ H ₄	49 k and 50 k	4-CH ₃ O C ₆ H ₄
49 e and 50 e	4-Br C ₆ H ₄	49 l and 50 l	4-CH ₃ C ₆ H ₄
49 f and 50 f	3-Br C ₆ H ₄	49 m and 50 m	4-HO C ₆ H ₄
49 g and 50 g	2-BrC ₆ H ₄		

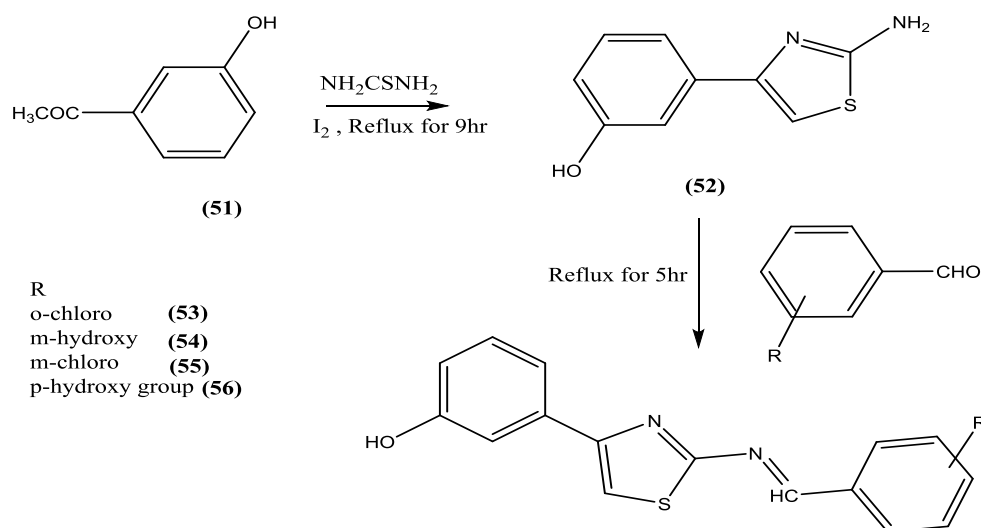
Scheme 7. Synthesis of compounds (50 a-m).

Based on SAR it is concluded that the activity of compounds depends on the substituent electron attracting effect. As a result, the order of activity can be arranged from increased to decreased electron attracting effect as follows: NO₂ > Cl > Br > OH > > OCH₃ > CH₃ [62].

Compounds with 2-aminothiazole nucleus are found in Scheme 8, and their antimicrobial activity was studied against the following microbes: *P. aeruginosa*, *S. aureus*, *E. coli* and *A.*

flavus, *C. albicans*, *A. fumigatus*) by disk diffusion method.

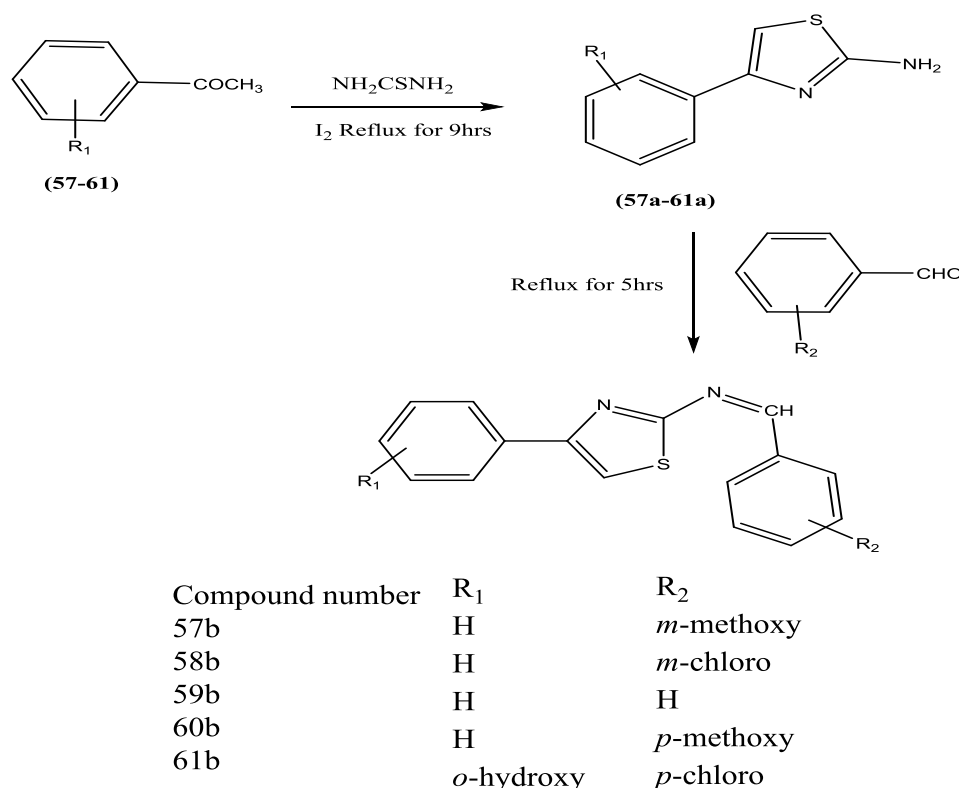
Compound (**55**) gave higher inhibitory effect against *Escherichia coli*, *Staphylococcus aureus*, *Asperigillus flavus* and *Asperigillus fumigates*. On the other hand, compound (**53**) gave higher inhibitory effect against *Pseudomonas aeruginosa*. In addition, compounds (**53**) and compound (**55**) gave equal high inhibitory effect against *Candida albicans* [63].



Scheme 8. Synthesis of 2- aminothiazole Schiff bases.

Another study shows the synthesis of N-(substituted benzylidene)-4-(substituted phenyl) thiazole-2-amine in Scheme 9, and the antimicrobial study for these compounds were done using disk diffusion method. Result shows compound (61b) having the maximum inhibitory

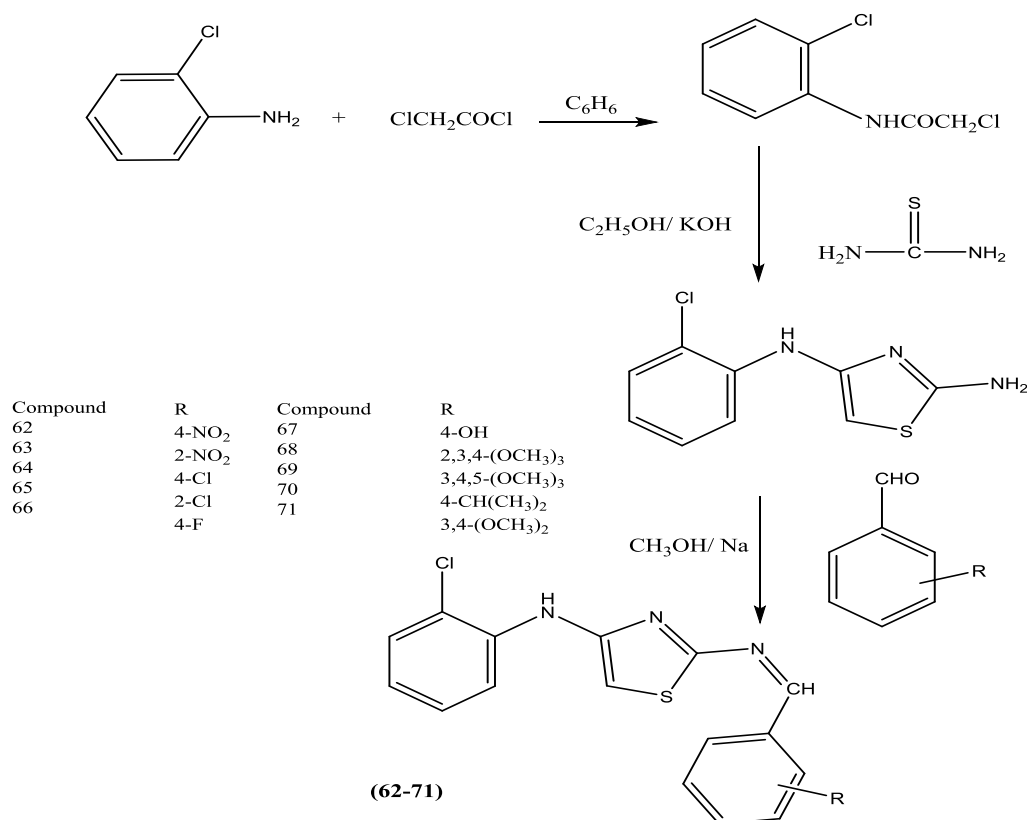
effect against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, *Asperigillus fumigatus* and *Asperigillus flavus*. The explanation for this could be due to both para-chloro group and ortho-hydroxy [64].



Scheme 9. 2- aminothiazole Schiff bases derivatives.

Novel Schiff bases were synthesized by the reaction of various aromatic aldehydes with 2-amino-4-(2-chloroanilino)-1, 3-thiazole this is found in Scheme 10. Then the antimicrobial study was done and these compounds show high

inhibitory effect toward some bacteria and fungi selected.



Scheme 10. Reaction for synthesis of Schiff bases of different aromatic aldehydes with 2-amino-4-(2-chloroanilino)-1, 3-thiazole.

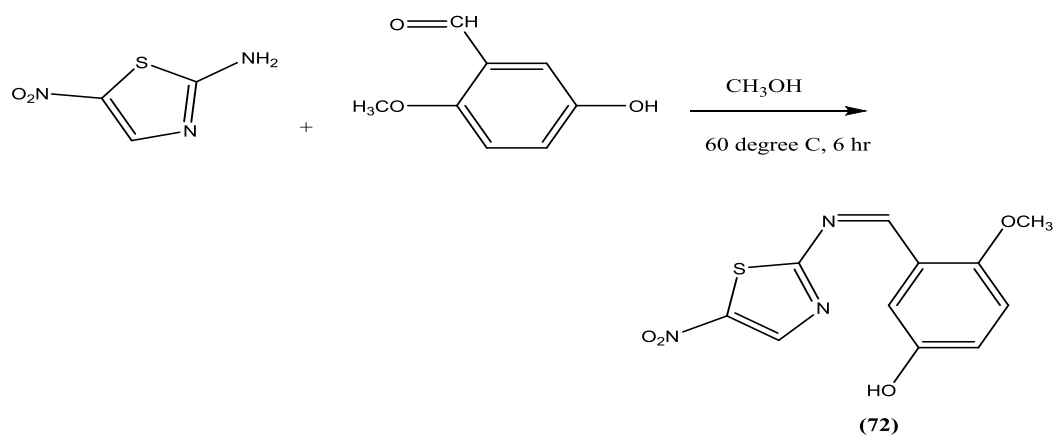
The 2-aminothiazole derivatives gave a good inhibitory effect against G⁺ and G⁻ bacteria. The para position halogen group resulted in a derivative with better activity. Meaning that electron withdrawing groups show increased inhibitory effect compared to electron donating groups. No compound, whilst, gave any important inhibitory effect against fungi compared with Amphotericin B that is used as antifungal standard [65].

The antimicrobial activity of 3-(5-nitrothiazol-2-ylimino) methyl-4-methoxyphenol, shown in Scheme 11, is done on some bacteria (*E. coli* and *R. solanacearum*) and some fungi (*F. oxysporum* and *A. niger*) and found to be active against these microbes. It was found that the nitro group which is an electron attracting group could cause the potent effect as it can change the tertiary structure

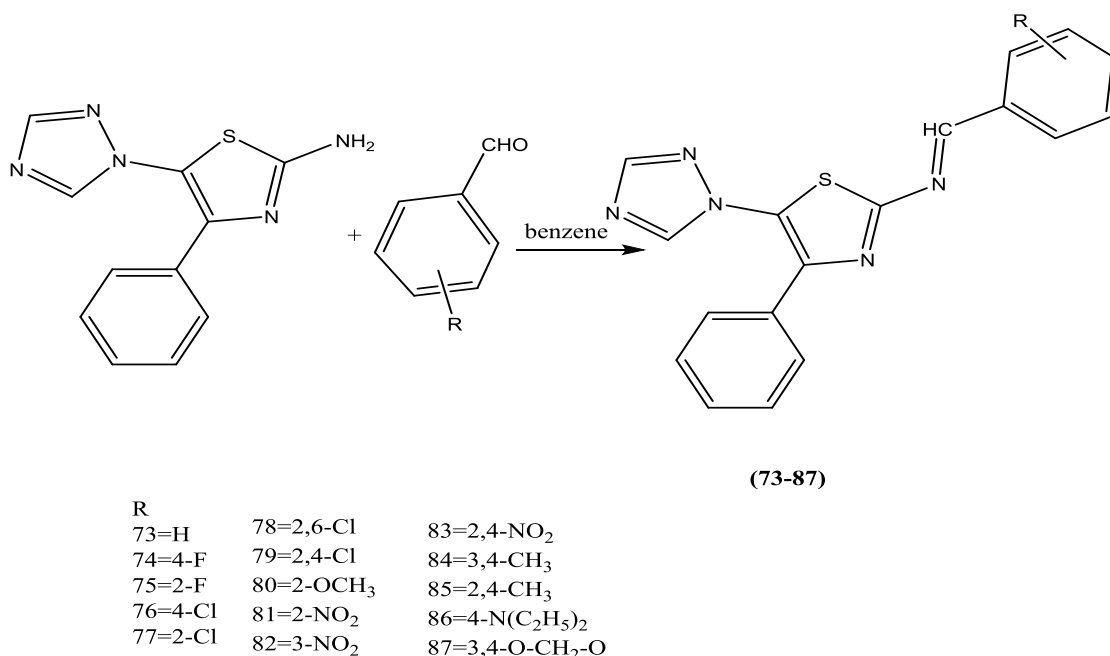
of proteins of membrane and as a consequence change the growth [66].

Synthesis of a number of Schiff bases of new 2-aminothiazole derivatives with an arylidene nucleus bearing different substituents is seen in Scheme 12. And the study of their in vitro action toward three human cancer cell lines was done.

The MTT method, which is a colorimetric assay used in testing cytotoxicity of chemicals and for screening of drugs, is used to test the synthesized compounds for their in vitro antitumor effect using a concentration of 10 µmol/l against the following: BGC-823 (stomach cancer) and Hep-2 (larynx cancer) and HL-60 (leukemia). It was seen that the phenyl ring bearing 2, 4-dinitro groups and 2, 4-dichloro, 3-nitro, found in compounds **79**, **82**, and **83**, had a good effect toward HL-60, BGC-823, and Hep-2 tumor cell lines.



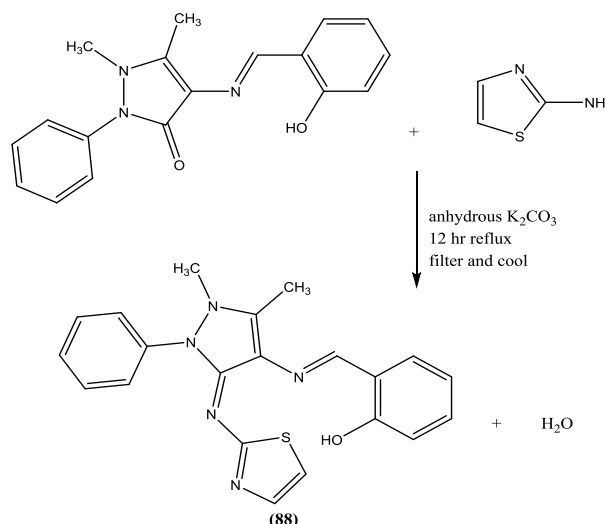
Scheme 11. Synthesis reaction of 3-(5-nitrothiazol-2-ylimino) methyl-4-methoxyphenol.



Scheme 12. A series of Schiff bases were synthesized by combination of different aldehydes and arylidene moiety with 2-aminothiazole.

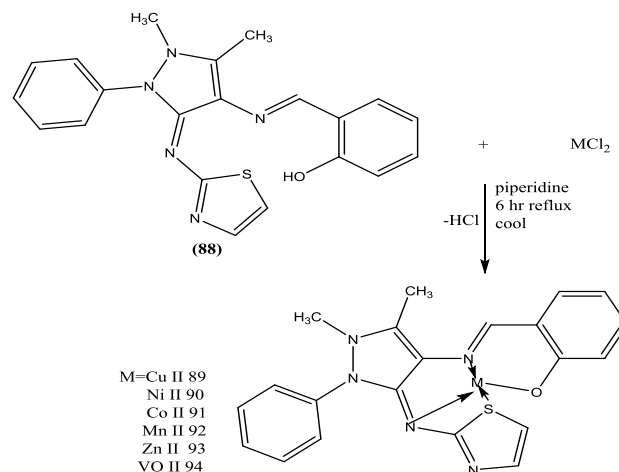
An inhibition ratio of 91.97%, 98.49%, and 91.16% on HL60, BGC-823, and Hep-2, respectively were shown by compound **83**. These results encourage scientists to do more in vitro studies on other human cell lines regarding compounds **79**, **82**, and **83** to find the most active one to be used for in vivo preclinical studies [67].

A new Schiff base of salicylaldehyde-4-iminoantipyrine and 2-aminothiazole was synthesized, found in Scheme 13, followed by preparation of their transition metal complexes, Scheme 14. The synthesized compounds complete structural properties and then the antimicrobial study were determined on some bacteria and fungi also studies of DNA interaction were done.

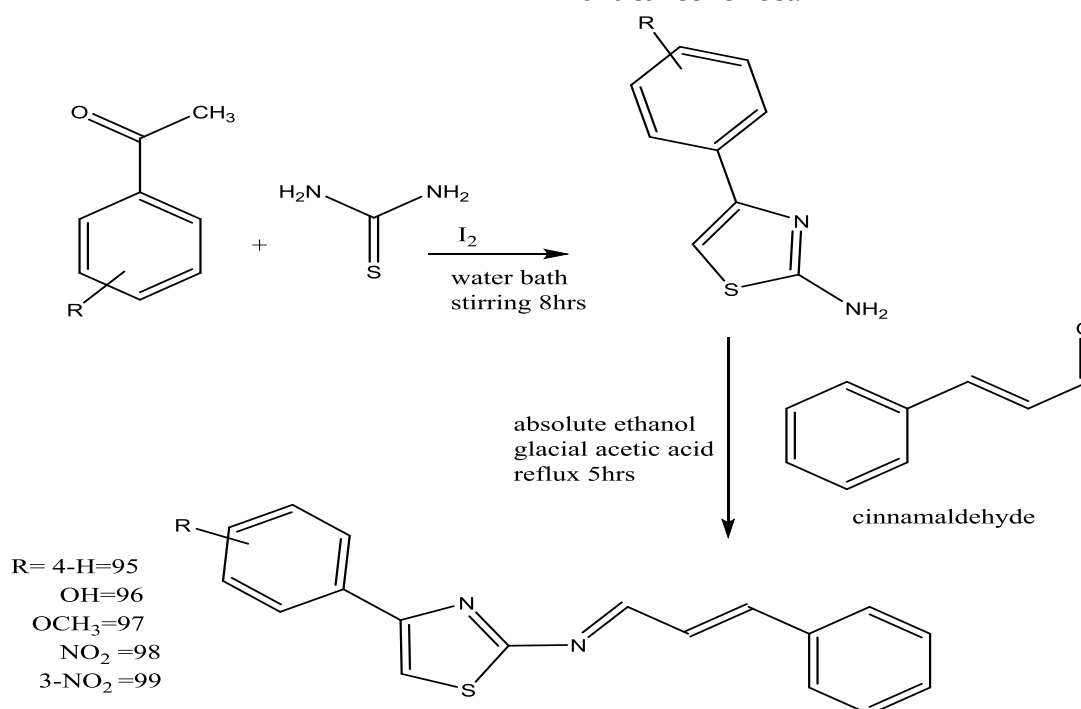


Scheme13. Schiff base of salicylaldehyde-4-iminoantipyrine and 2-aminothiazole.

In addition, the Schiff base and their metal complexes antimicrobial study were done on G- (*E. coli*, *Klebsiella pneumoniae*, and *Salmonella typhi*), G+ (*Staphylococcus aureus*, and *Bacillus subtilis*) and fungi species using well diffusion method. From results seen, it is concluded that the Cu-ligand and VO-ligand complexes have more inhibitory effect than the Schiff base because of increased lipid solubility. The compounds mode of action is forming a hydrogen bond between the azomethine atom and cell constituents active center leading to interfere with normal cell growth [68].



It was found that 2-aminothiazole derivatives possess antitumor activity by inhibition of kinases [69] in addition to the fact that cinnamaldehyde can inhibit the proliferation of tumor cell [70], this gave an idea of combination of cinnamaldehyde with 2-amino-4-phenyl thiazole forming a Schiff base, Scheme 15, and then studying in vitro anticancer effect.



The in vitro cytotoxicity study using MTT assay shows that compound (**97**) has high cytotoxicity effect (IC₅₀ equal to 29.44µg/ml) on cervical carcinoma cell lines. This result is in consequence with the great interaction between compound and receptor in molecular docking analysis. The reason for this high effect may be because of the

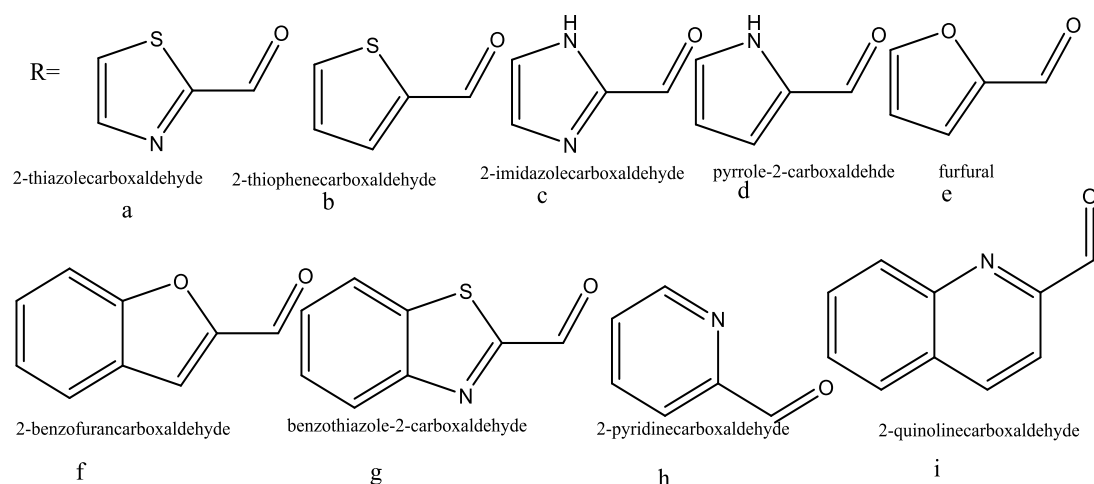
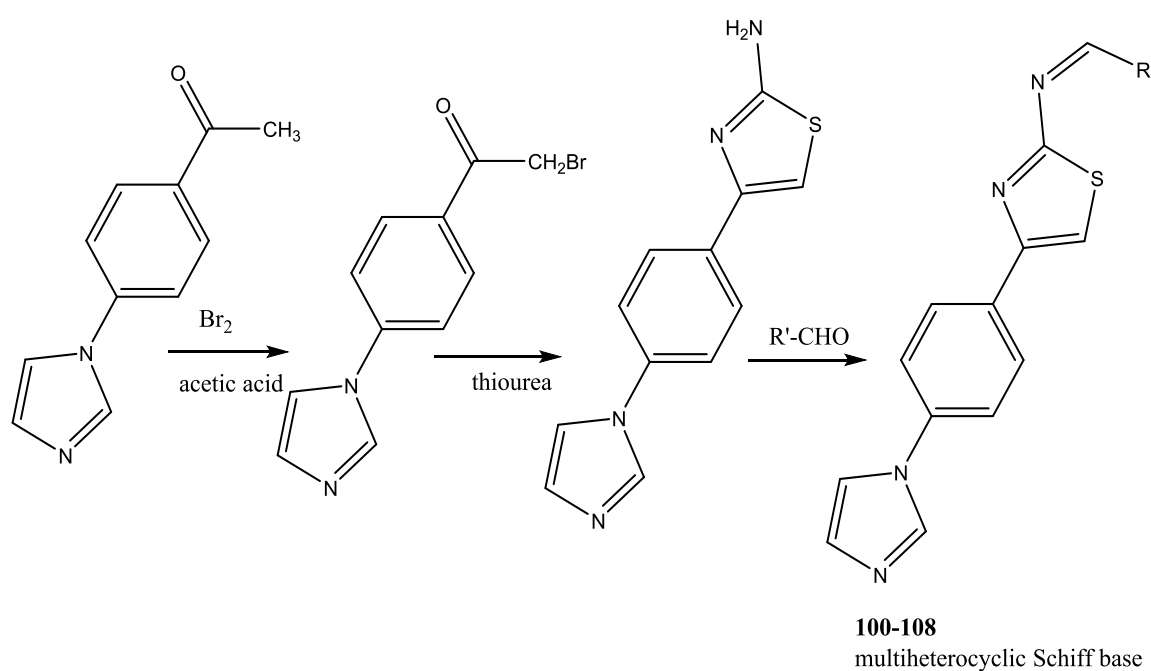
electron releasing, *p*-methoxy group, due to great ability for hydrogen bonding than others. Compound (**98**) with an IC₅₀ of 31.74 μg/ml and compound (**96**) with a 45.69 μg/ml IC₅₀ show an important effect. From this we can conclude that presence of para-electron releasing groups show

high cytotoxicity effect when compared to others [71].

A number of Schiff base compounds were synthesized using different heterocyclic rings this is seen in Scheme 14. All of the target compounds (**100-108**) have thiazole and imidazole nuclei but the Schiff base is attached to different heterocyclic rings. Three human cancer cell lines were used to study the *in vitro* cytotoxic effect of these compounds, these are: human breast cancer (MCF7), human colon cancer (HCT116), and human prostate cancer (DU145), also a healthy skin fibroblast (SF) to investigate the cytotoxicity them against normal cells.

It was concluded that the heterocyclic and benzene rings together have a great effect toward DU145 and MCF7. The sulfur heteroatom showed the most significant effect toward HCT116, in addition to the nitrogen heteroatom. Compounds (**100**), (**106**), and (**108**) showed a significant effect toward the three cancer cell lines.

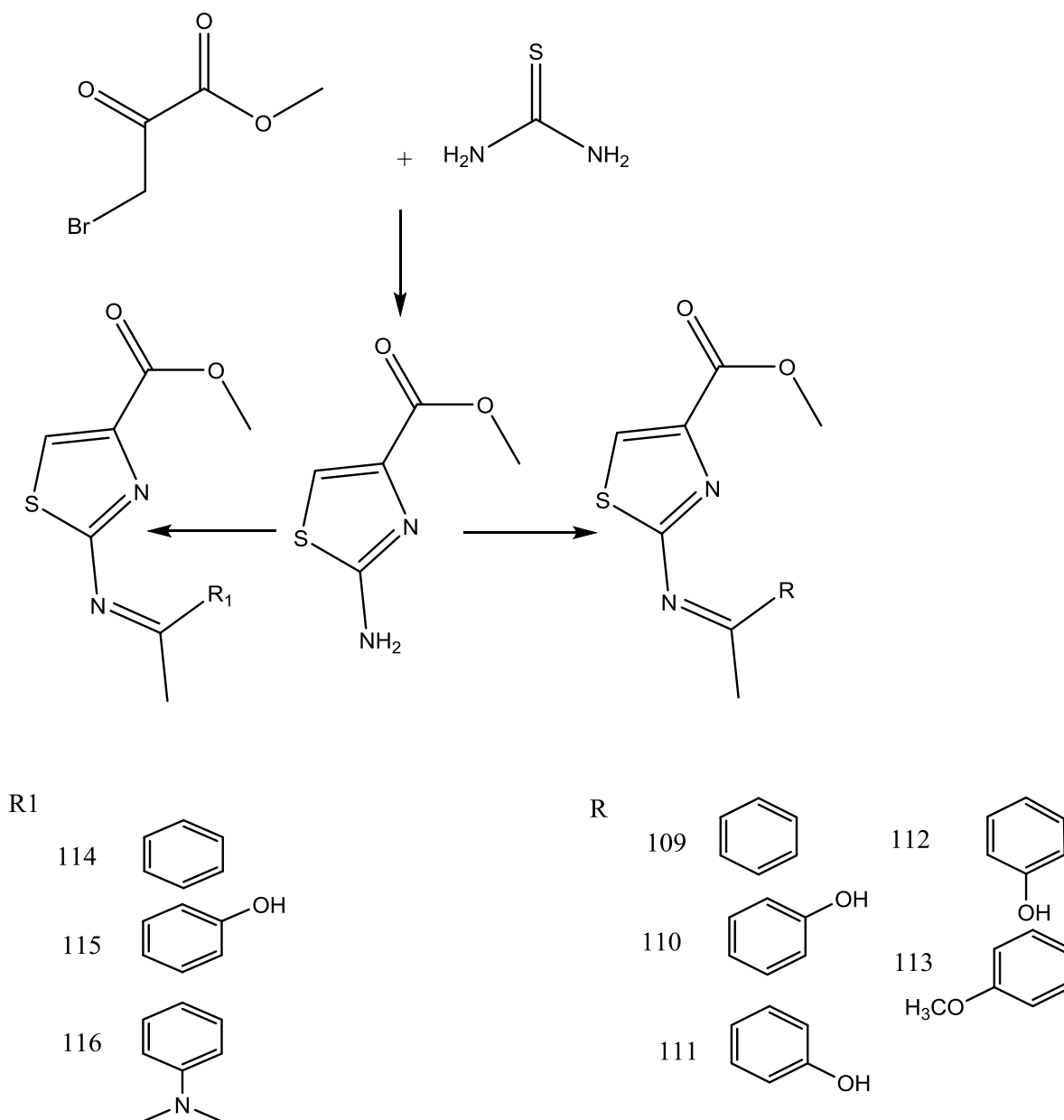
The effect toward normal skin fibroblast cells was the same for all the target compounds showing IC₅₀s of >50 $\mu\text{mol/L}$ this indicates that these molecules are tolerable by the normal cells. On the other hands, compounds with oxygen heteroatom gave no activity [72].



Scheme 16. Reaction of synthesis of imidazolylphenyl-heterocyclic-2-ylmethylene-thiazole-2-amines.

Derivatives of ethyl-2-aminothiazole-4-carboxylate Schiff base were designed and synthesized. Docking studies of the designed compounds, and binding affinities were done using antimicrobial target uridine diphosphate-N-acetylmuramate/l-alanine ligase enzyme.

This enzyme found in bacteria catalyzes the synthesis of peptidoglycan which is an important element for cell wall of bacteria. Targeting the enzyme will lead to destroying bacterial cell integrity and causing bacterial cell death.



Scheme 17. Synthesis of ethyl 2-aminothiazolecarboxylate and the derivatives.

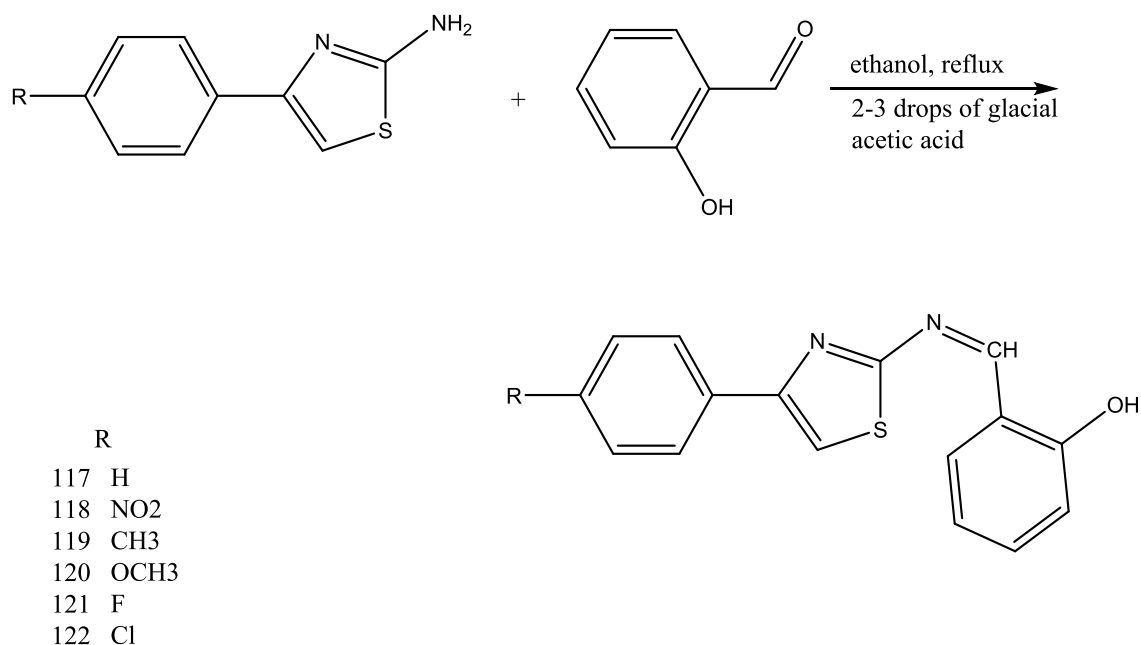
The synthesized compounds show good activity against the selected G⁺ bacteria *Staphylococcus epidermidis* and *Staphylococcus aureus* and the G⁻ bacteria *Escherichia coli* and *Pseudomonas aeruginosa*. Compounds (109), (110) gave inhibitory effect against *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*, while compounds (112), (115) gave inhibitory effect

against *Staphylococcus aureus* and *Escherichia coli*. Compounds (109), (110), and (112) gave maximum activity against *Candida glabrata* and *Candida albicans* which in addition show sensitivity toward compound (114), and (115).

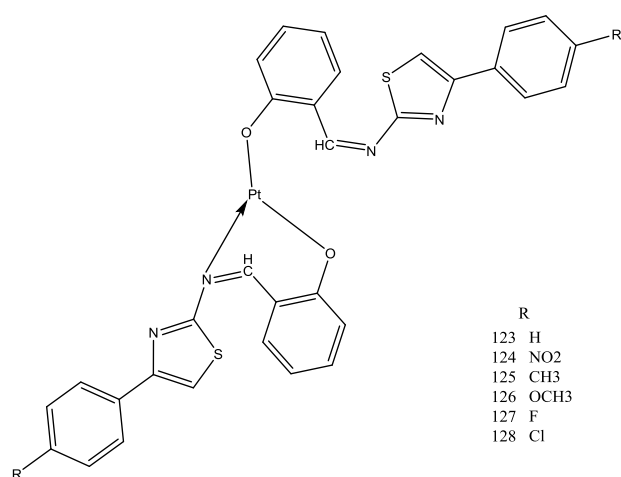
Docking studies show hydroxyl group on benzene ring bearing compounds had great affinity of binding in comparison to other derivatives. The

derivatives designed represent the best lead compounds to act on target UDP-N-acetylmuramate/l-alanine ligase microbial enzyme [73].

Synthesis of 2-hydroxybenzylidene-4-(4-substitutedphenyl)-2-amino-thiazole Schiff base seen in Scheme 18 and their platinum complexes Scheme 19 in which platinum ion bonded to both imine group Schiff bases and hydroxyl group of aromatic ring in a square planar complex followed by studying their biological activities.



Scheme 18. Synthesis of 2-Hydroxybenzylidene-4-(4-SubstitutedPhenyl)-2-amino-thiazole Schiff base.



Scheme 19. Synthesis of platinum Schiff base complex.

The antioxidant study of the Schiff bases in comparison to their complexes shows that the platinum complexes are more active. This is because of the increase in the stability of radicals electronically by platinum metal since as it is known that anti-oxidation process involves proton or electron transfer from the antioxidant compound to the free radical producing a stable neutral compound that ends the free radical chain reaction.

Cytotoxicity measurement on human breast cancer cell line (MCF-7) by Schiff bases (**120**), (**121**) and their platinum complexes (**126**), (**127**) showed that the Schiff bases IC₅₀ is higher (higher inhibitory effect) than their corresponding Pt (II) complexes [74].

CONCLUSIONS

Since nucleus has occupied an essential position in the modern organic synthesis and medicinal chemistry, this motivate the chemists to design a new thiazole scaffolds containing Schiff bases and using them as powerful ligands in coordination chemistry to prepare an active complexes which exhibited a broad spectrum of pharmacological activities. In this review we focused on recent synthesis of Schiff bases of 2-amino thiazole and investigating their antimicrobial and anticancer activity as Schiff bases or as their metal complexes. This review will help to design new thiazole Schiff-based molecules and chelating as ligands with transition metals to prepare novel complexes for different biological targets.

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