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

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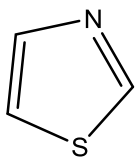
ABSTRACT

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.

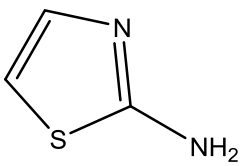
INTRODUCTION

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)



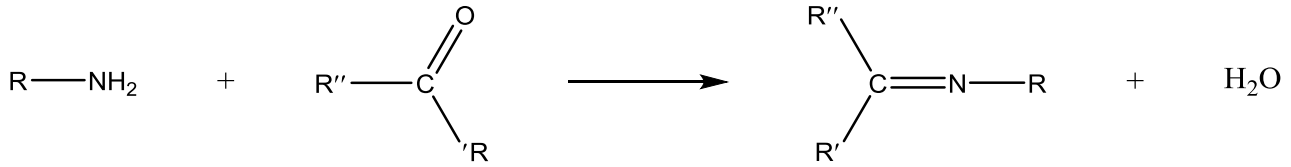
2-Aminothiazole

(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**.**

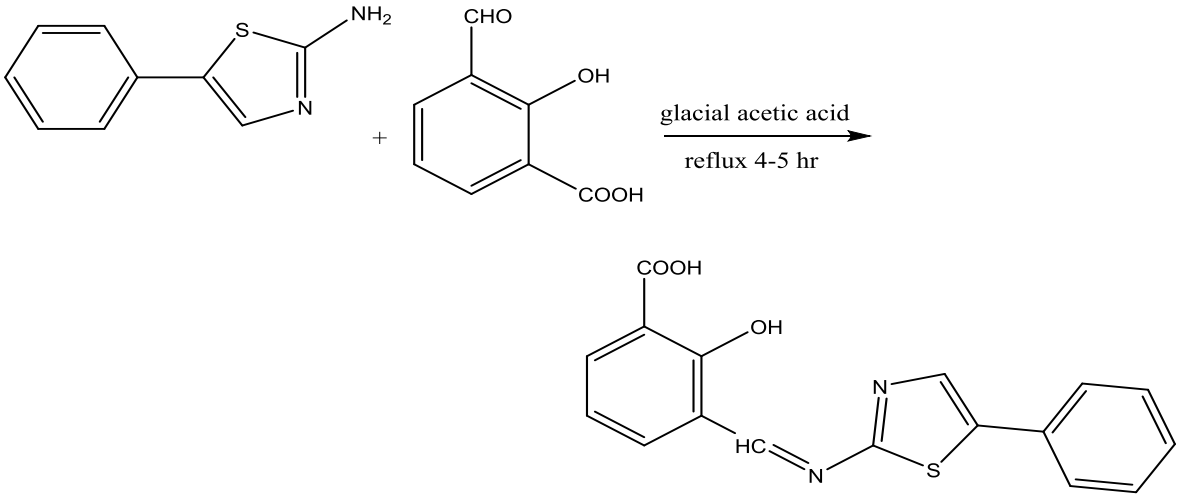
The azomethine C=N bond in compounds is of great importance for effect because of the remarkable antibacterial, antifungal, and anticancer activities found in them [31]. As a consequence, Schiff bases are of an important application in pharmaceutical industry [32].

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].



(3)

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

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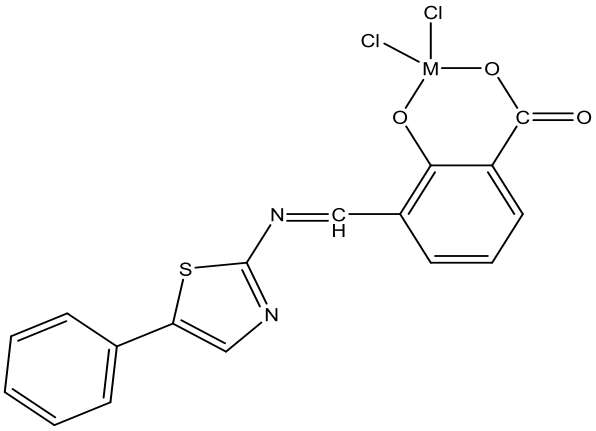


M=Cu, Co, Cd, Zn and Ni
(4) ,(5), (6), (7), and (8)

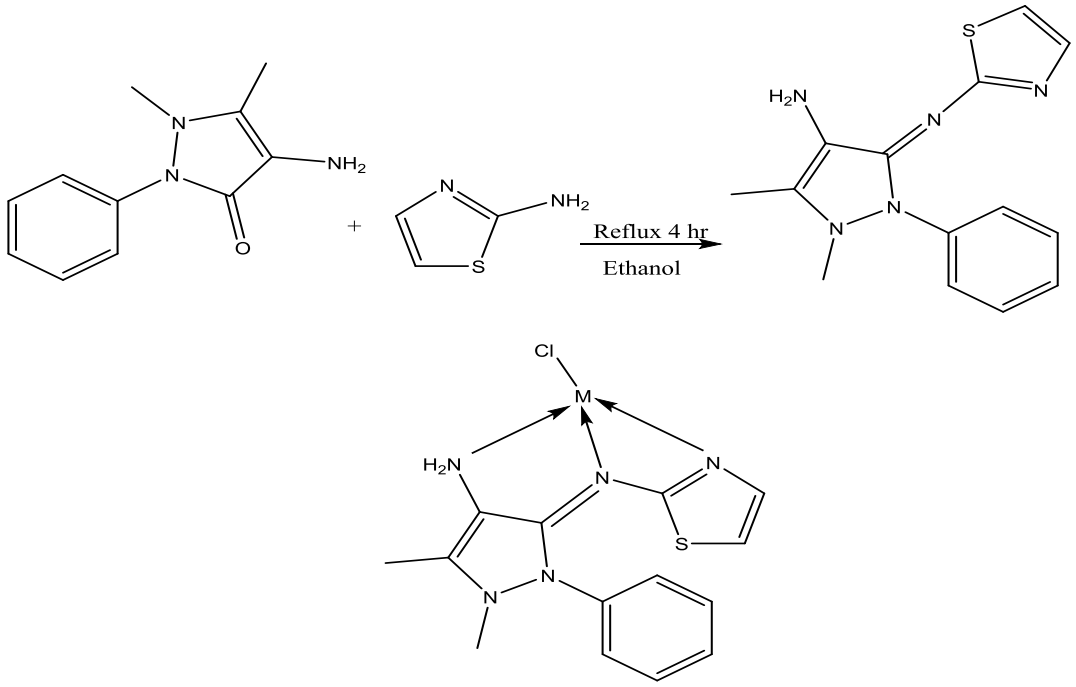
Figure 1. Structure of complex as proposed.

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].



M= Cu(II) **(9)**and Zn(II) **(10)**

Schiff base metal complexes

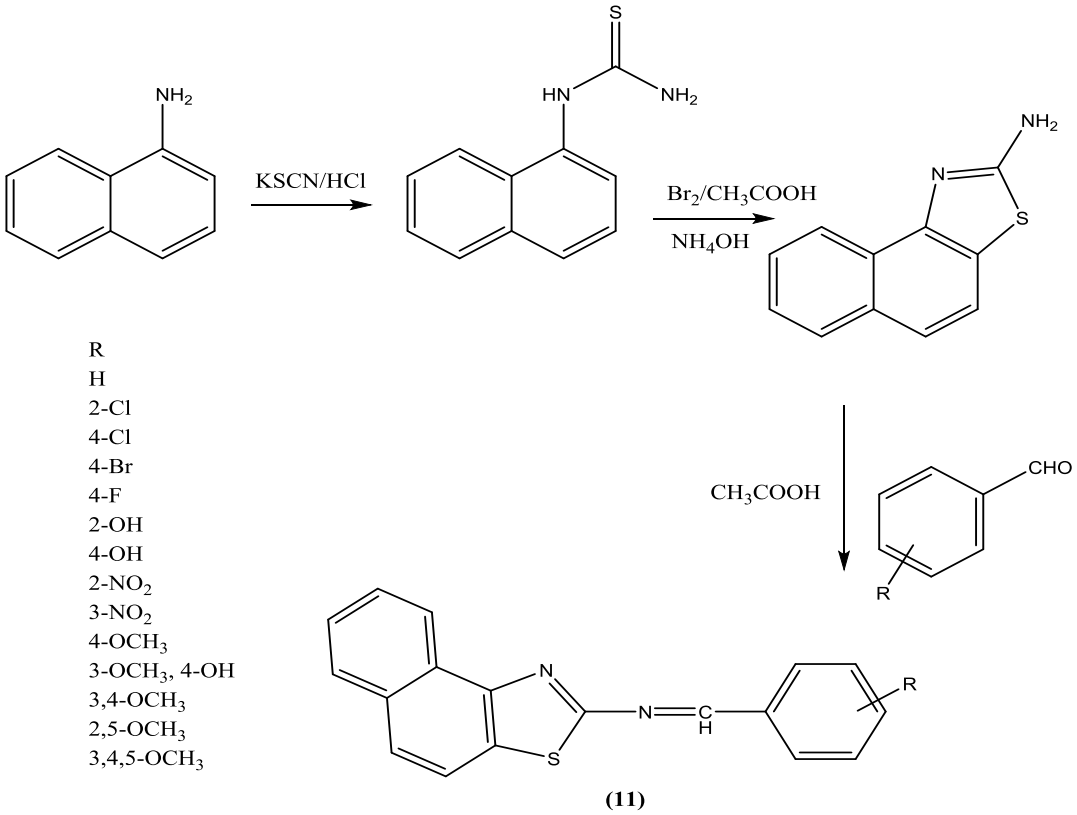
Scheme 3. Copper and zinc complexes with the 2-aminothiazole Schiff base of 4-aminoantipyrine.

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].

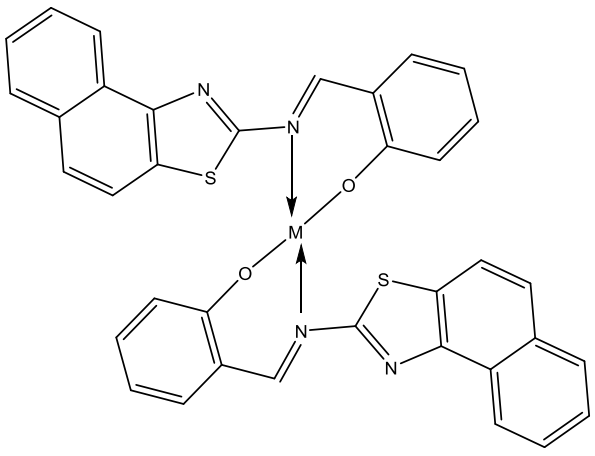
Combination of Thiazole with naphthalene ring by forming azomethine bond to form new Schiff bases is seen in Scheme 4.

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.



(11)

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



M= Ni(II) **(12)**, Co(II) **(13)**, Cu(II) **(14)**

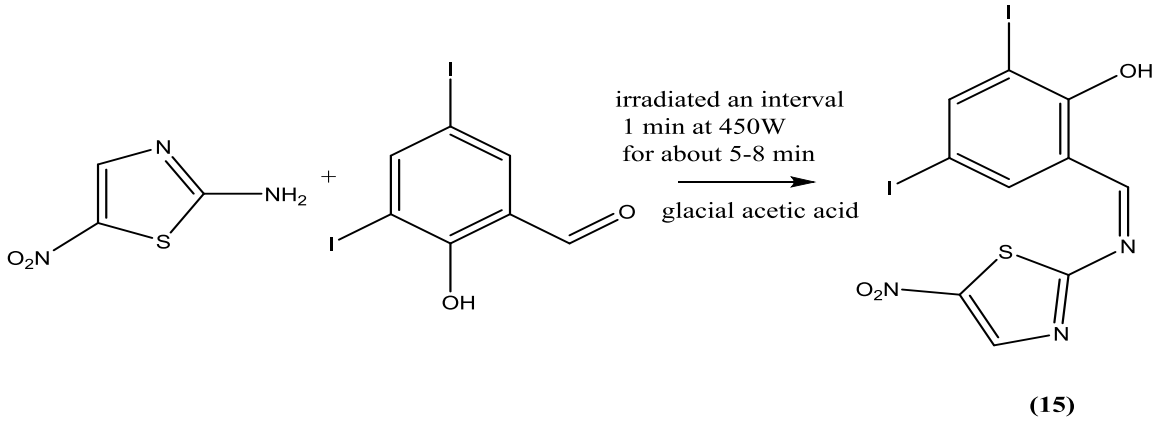
Figure 2. Co (II), Ni (II), Cu (II) Complexes with compound (11)

All compounds showed moderate inhibition of Gram-positive and Gram-negative bacterial growth but the 2-(2'-hydroxy) benzylidene-aminonaphthothiazole 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-amino5-nitrothiazole and substituted salicyldehyde 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.

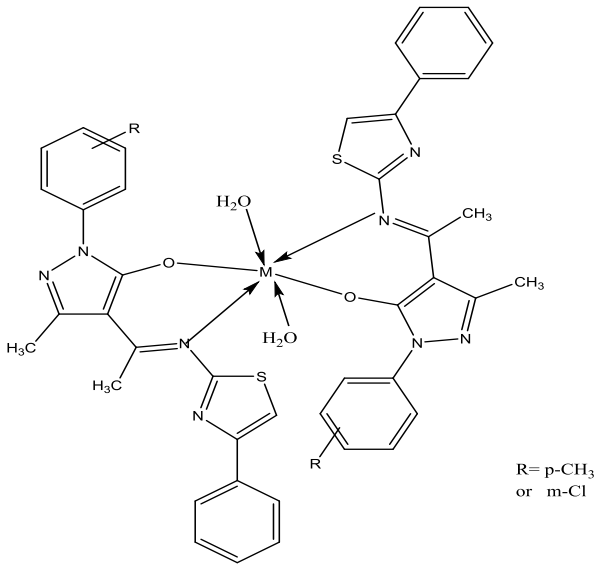


Scheme 5. Schiff base synthesis reaction using microwave.

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.

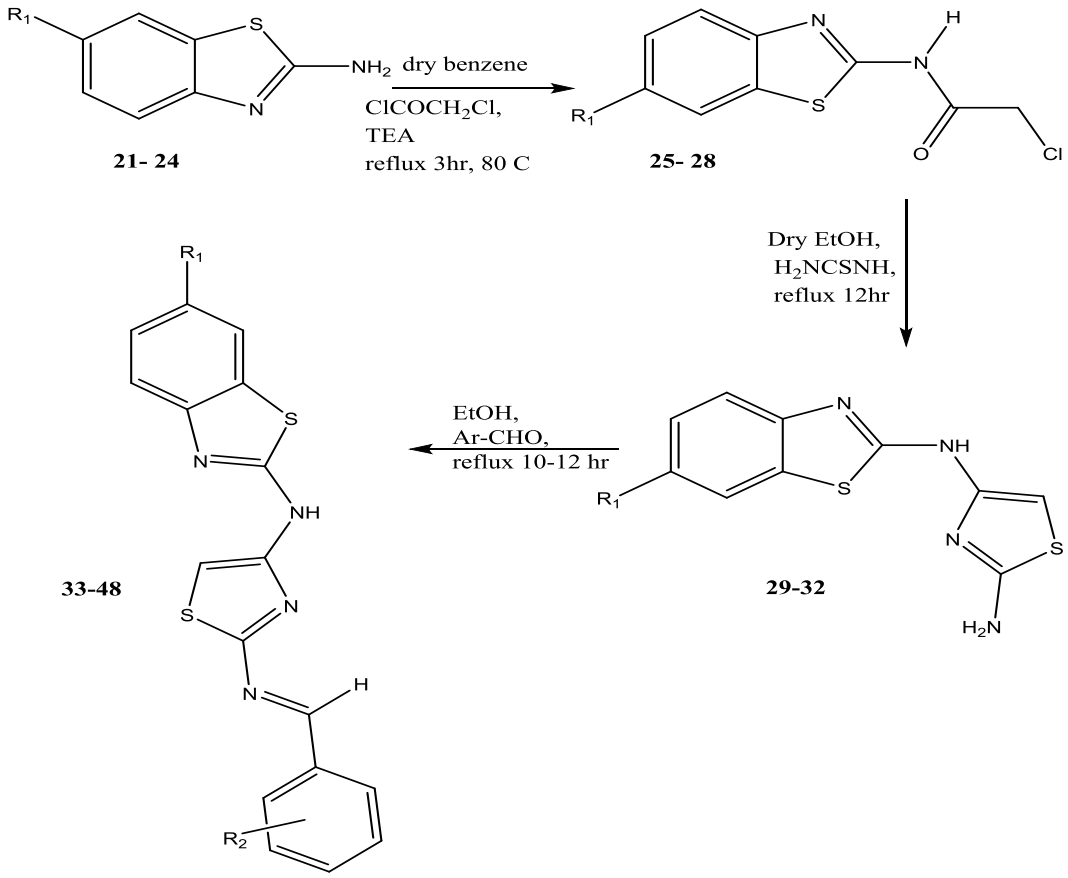
The antimicrobial activity studied for the ligand Schiff base and for the metal complexes revealed that the metal complexes have higher inhibition action on bacteria such as: *Escherichia coli*, *Bacillus subtilis*, *S. aureus*, *A. niger* and *S. cerevisiae* than Schiff base ligand. Showing order of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



M=Mn(II) **(16)**, Fe(II) **(17)**, Co(II) **(18)**, Ni(II) **(19)** and Cu(II) **(20)**

Figure 3. Schiff base of substituted 4-acetyl-1-phenyl-3-methyl-2-pyrazolin-5-one and 2-amino-4-phenylthiazole and 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.



Compound			R1	Compound	R1	R2	Compound	R1	R2
21	25	29	H	33	H	H	41	F	H
22	26	30	CH_3	34	H	2-Cl	42	F	2-Cl
23	27	31	F	35	H	2-NO_2	43	F	2-NO_2
24	28	32	OC_2H_5	36	H	3,4-(OCH_3)	44	F	3,4-(OCH_3)
				37	CH_3	H	45	OC_2H_5	H
				38	CH_3	2-Cl	46	OC_2H_5	2-Cl
				39	CH_3	2-NO_2	47	OC_2H_5	2-NO_2
				40	CH_3	3,4-(OCH_3)	48	OC_2H_5	3,4-(OCH_3)

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

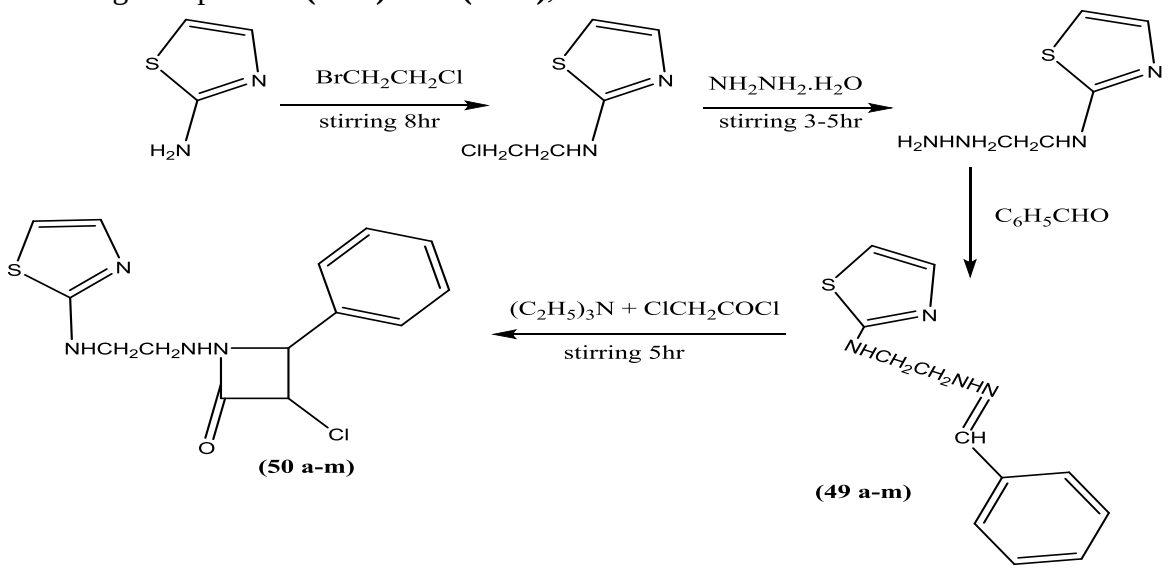
Compound **(44)** bearing the methoxy group which is an electron releasing group had an increased activity against *B. subtilis* and *S. aureus* G+ bacteria. Substitution at position 6 of the benzothiazole ring with fluoro group which is an electron withdrawing group gave an inhibitory activity against 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.



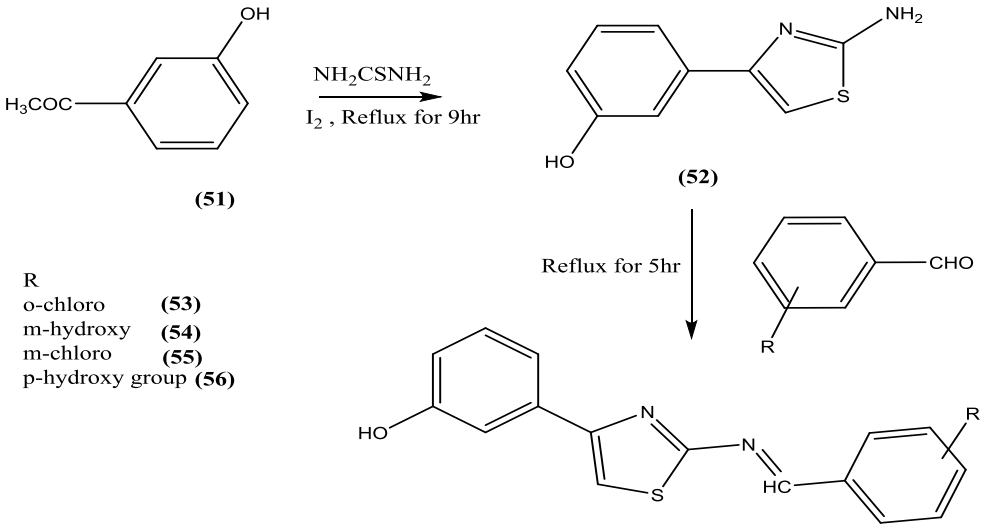
Compound	Ar	Compound	Ar
49 a and 50 a	C_6H_5	49 h and 50 h	4-NO_2 C_6H_4
49 b and 50 b	4-Cl C_6H_4	49 i and 50 i	3-NO_2 C_6H_4
49 c and 50 c	3-Cl C_6H_4	49 j and 50 j	2-NO_2 C_6H_4
49 d and 50 d	2-Cl C_6H_4	49 k and 50 k	4-CH_3O C_6H_4
49 e and 50 e	4-Br C_6H_4	49 l and 50 l	4-CH_3 C_6H_4
49 f and 50 f	3-Br C_6H_4	49 m and 50m	4-HO C_6H_4
49 g and 50 g	2-BrC_6H_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: NO_2 > Cl > Br > OH > > OCH_3 > CH_3 [62].

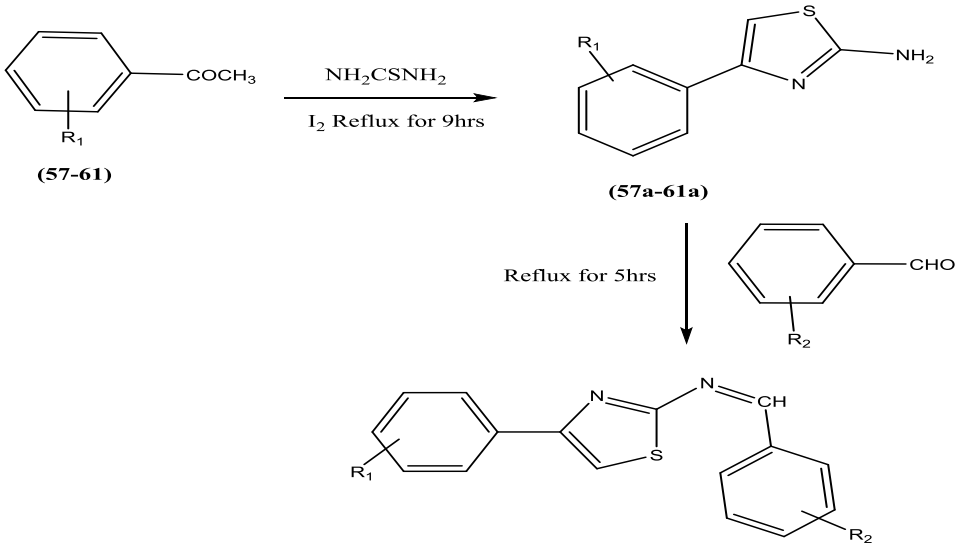
Compounds with 2-aminothiazole nucleus are found in Scheme 8, and their antimicrobial activity was studied against the following microbes: *P. aeruginosa*, *S. aureus*, *E. coli* and *A. flavus*, *C. albicans*, *A. fumigatus*) by disk diffusion method.

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].



Compound number	R_1	R_2
57b	H	*m*-methoxy
58b	H	*m*-chloro
59b	H	H
60b	H	*p*-methoxy
61b	*o*-hydroxy	*p*-chloro

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.

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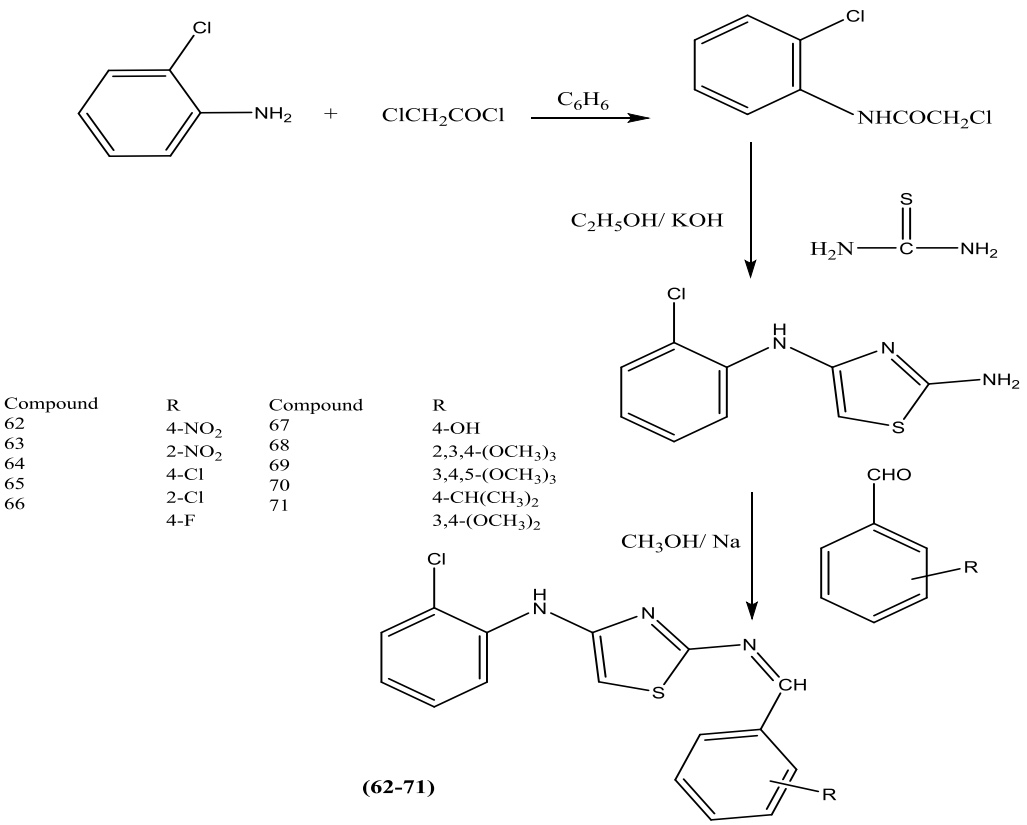


Compound	R	Compound	R
62	4-NO_2	67	4-OH
63	2-NO_2	68	2,3,4-$(OCH_3)_3$
64	4-Cl	69	3,4,5-$(OCH_3)_3$
65	2-Cl	70	4-$CH(CH_3)_2$
66	4-F	71	3,4-$(OCH_3)_2$

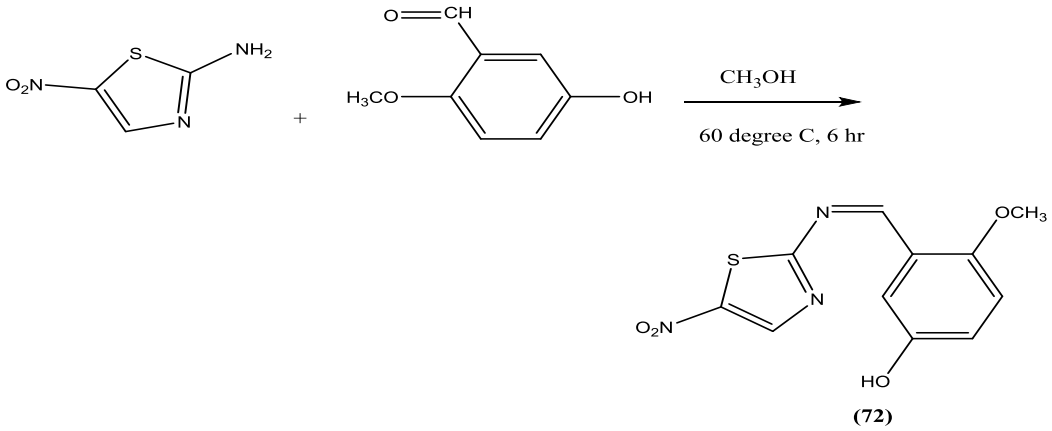
Scheme 10. Reaction for synthesis of Schiff bases of different aromatic aldehydes with 2-amino-4-(2-chloroanilino)-1, 3-thiazole.

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].

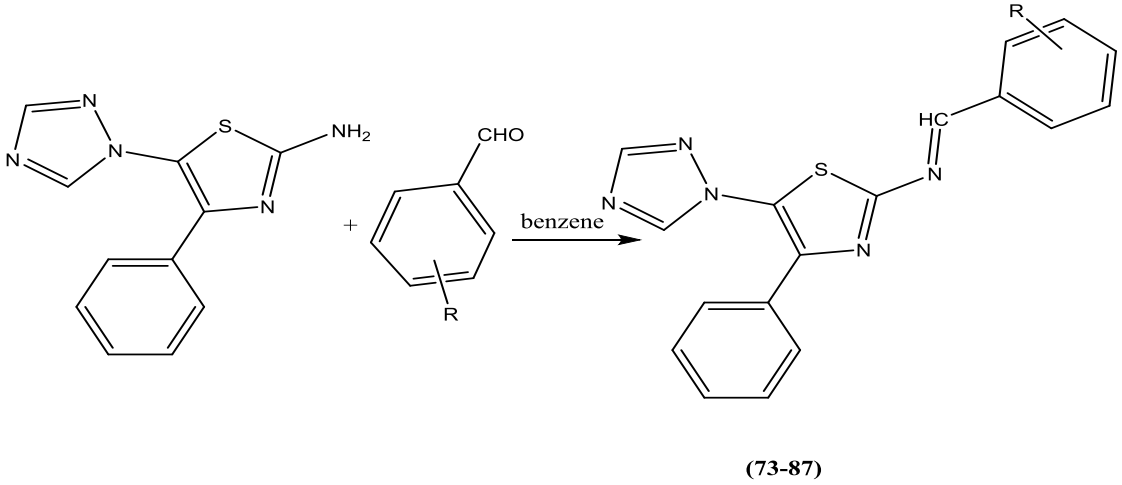
The antimicrobial activity of 3-(5-nitrothiazol-2-ylimino) methyl)-4-methoxyphenol, shown in Scheme 11, is done on some bacteria (*E. coli and R. solanacearum*) and some fungi (*F. oxysporum and A. niger*) and found to be active against these microbes. It was found that the nitro group which is an electron 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 µ mol/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.

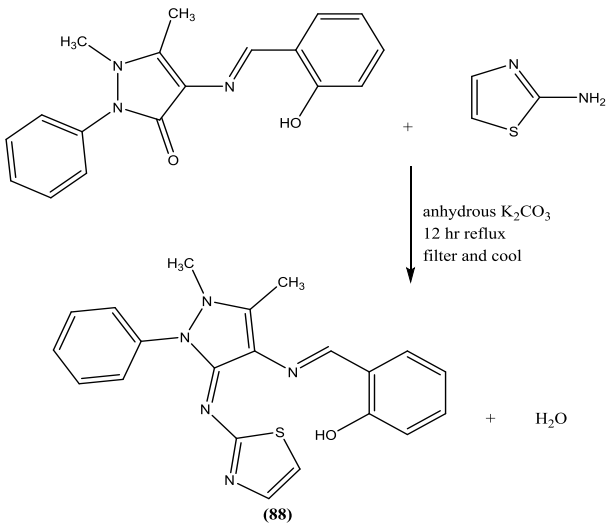


R		
73=H	78=2,6-Cl	83=2,4-NO_2
74=4-F	79=2,4-Cl	84=3,4-CH_3
75=2-F	80=2-OCH_3	85=2,4-CH_3
76=4-Cl	81=2-NO_2	86=4-$N(C_2H_5)_2$
77=2-Cl	82=3-NO_2	87=3,4-O-CH_2-O

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 salicylalidene-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 salicylalidene-4-iminoantipyrine and 2-aminothiazole.

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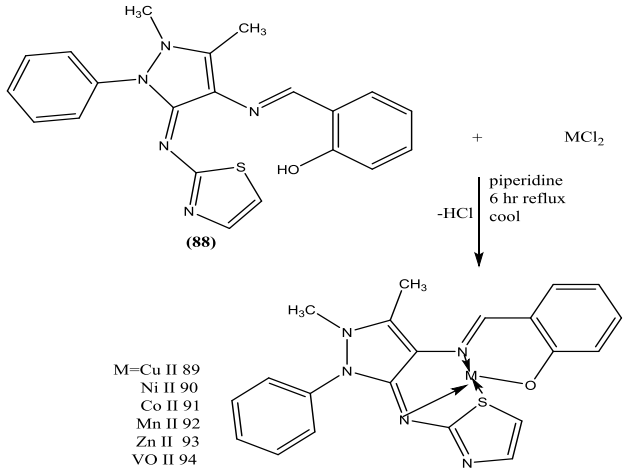
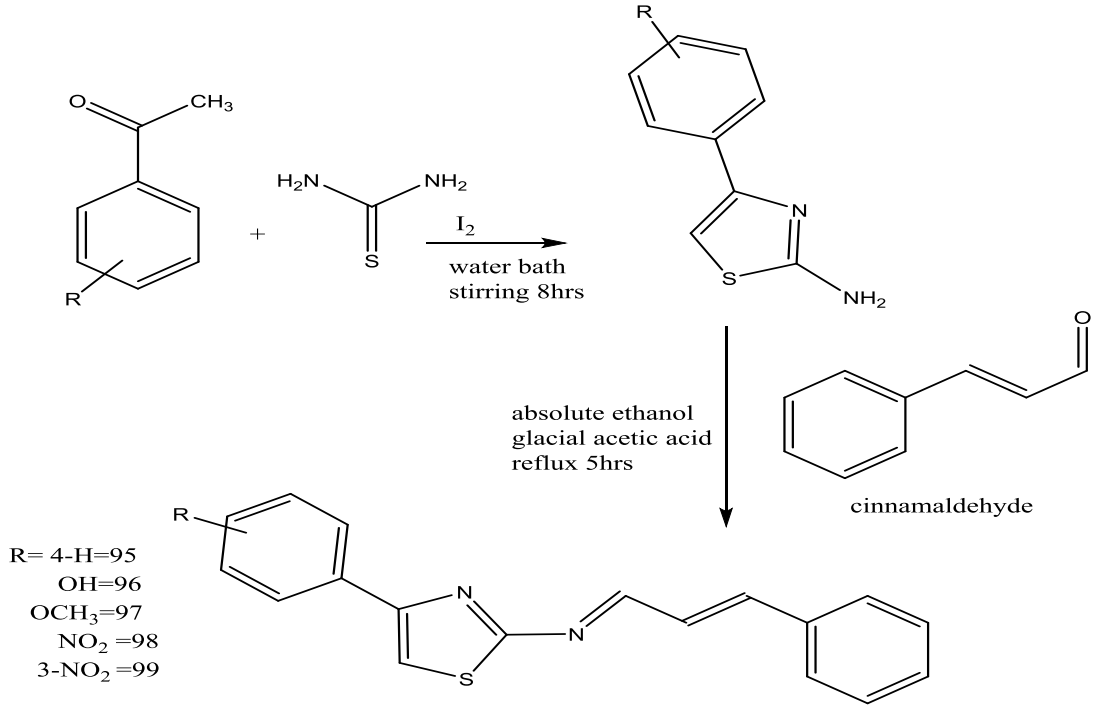
It was found from the interaction studies of the copper-compound complex with DNA that intercalation happen between complex and DNA binding. Studies of anticancer effect of the Schiff base and their metal complexes were done on breast cancer cell line and resulted in high inhibition of growth for the chelates.

In addition, the Schiff base and their metal complexes antimicrobial study were done on G- (*E coli, Klebsiella pneumoniea,* and *Salmonella typhi*), G+ (*Staphylococcus aureus*, and *Bacillus subtillis*) 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].



Scheme 14. Schiff base transition metal complexes.

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.



Scheme 15. Different derivatives of cinnamaldehyde thiazole Schiff base.

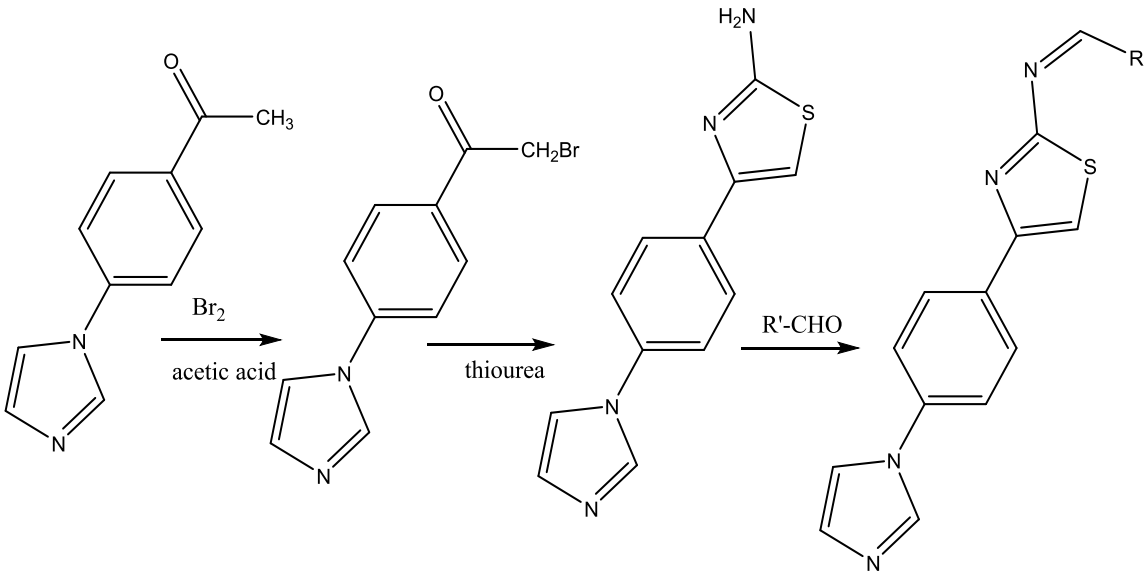
The in vitro cytotoxicity study using MTT assay shows that compound **(97)** has high cytotoxicity effect (IC50 equal to 29.44µg/ml) on cervical carcinoma cell lines. This result is in consequence with the great interaction between compound and receptor in molecular docking analysis. The reason for this 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 31.74µg/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

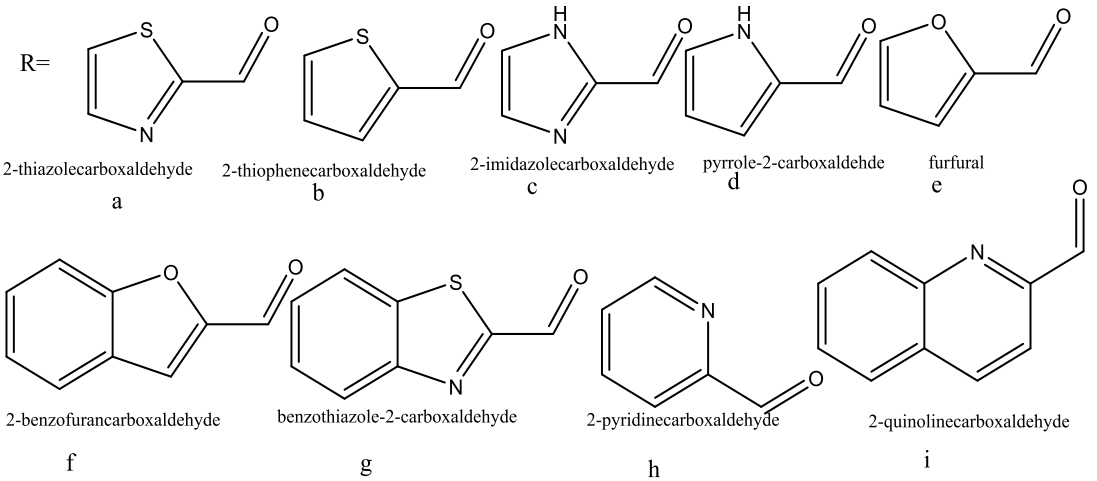
high cytotoxicity effect when compared to others [71].

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.

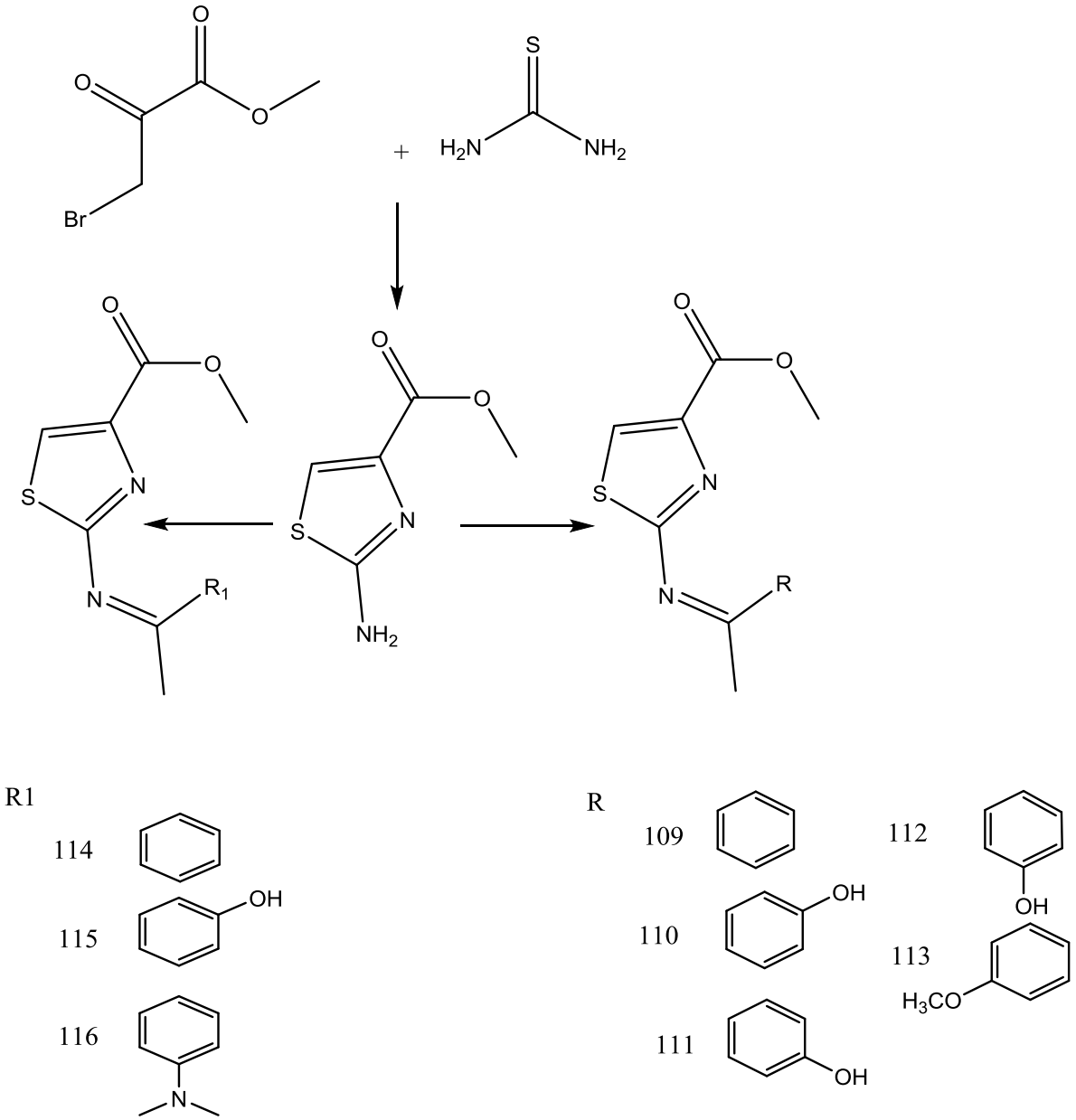
The effect toward normal skin fibroblast cells was the same for all the target compounds showing IC50s of >50 μmol/L this indicates that these molecules are tolerable by the normal cells. On the other hands, compounds with oxygen heteroatom gave no activity [72].





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 diphosphateN-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.



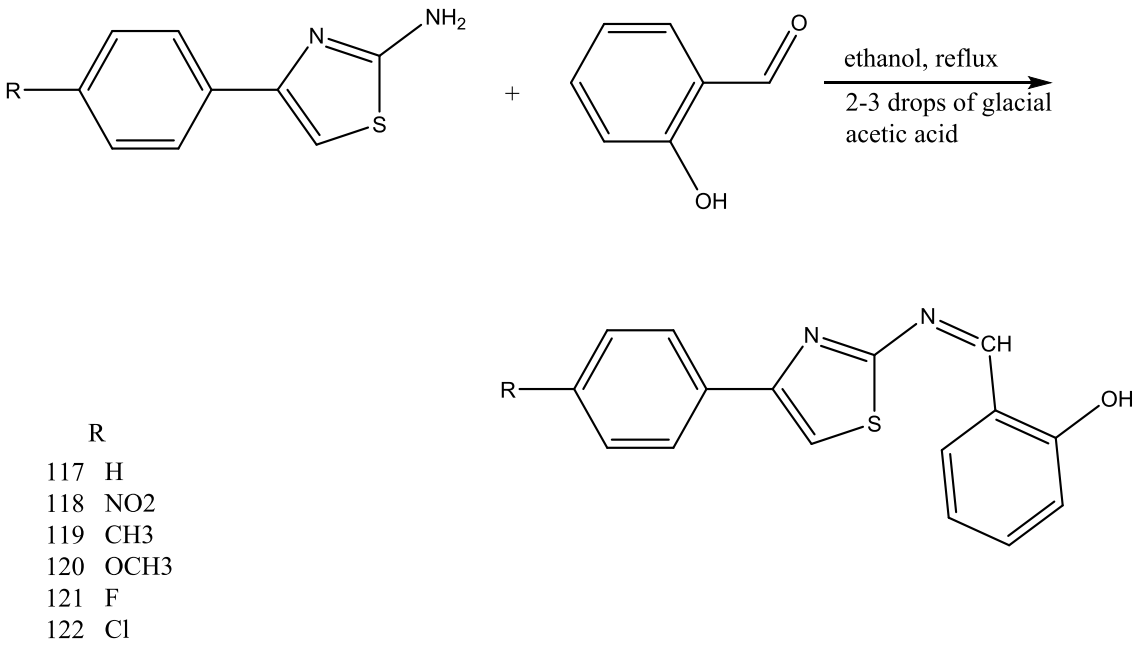
Scheme 17. Synthesis of ethyl 2-aminothiazolecarboxylate and the derivatives.

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

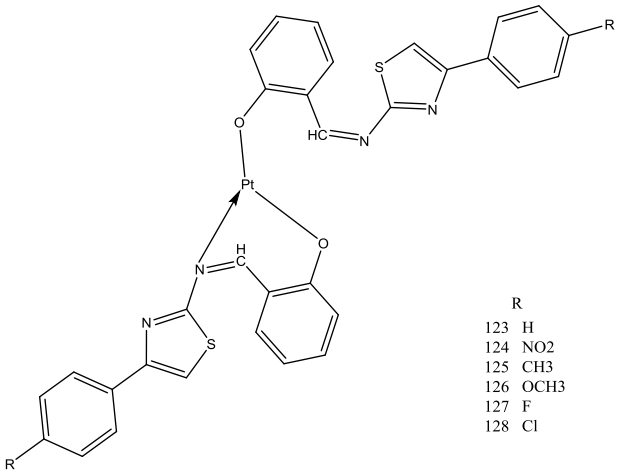
derivatives designed represent the best lead compounds to act on target UDP-N-acetylmuramate/l-alanine ligase microbial enzyme [73].

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.



R	
117	H
118	NO2
119	CH3
120	OCH3
121	F
122	Cl

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



R	
123	H
124	NO2
125	CH3
126	OCH3
127	F
128	Cl

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.

REFERENCES

[1] Narendra S., Uma S. Sharma, Niranjan S., Sushil K. and Umesh K. Sharma, Synthesis and antimicrobial activity of some novel 2-amino thiazole derivatives, *J. Chem. Pharm. Res*.; 2010, 2(3):691-698.

[2] Entesar O. Al-Tamimi and Hussein F. Abdul Mahdi, Synthesis and Characterization of New Compounds containing 2-amino Thiazole Ring from Amino Benzoic Acid, *Int. J. Curr. Microbiol. App. Sci*; 2016, 5(8): 1-13.

[3] Ankit Kr. Jain, Rajeev k Singla, Birendra Shrivastava, Thiazole: A Remarkable Antimicrobial And Antioxidant Agents, *Newsletter*; 2011, 2:1072-1084.

[4] Tsuji, K.; Ishikawa, H., Synthesis and anti-pseudomonal activity of new 2-isocephems with a dihydroxypyridone moiety at C-7, *Bioorg. Med. Chem. Lett*.; 1994, 4: 1601-06.

[5] Nedaa A. A. Rahim and Ammar A Mahmood Kubba, Synthesis, Characterization and Antimicrobial Evaluation with DFT Study of New Two-Amino-4-(4-Chlorophenyl) Thiazole Derivatives, *Iraqi J Pharm Sci*; 2018, 27(1): 79-88.

[6] Karabasanagouda T., Adhikari A V., Dhanwad R., and Parameshwarappa G., Synthesis of Some New 2-(4Alkylthiophenoxy)-4-Substituted-1, 3Thiazoles As Possible AntiInflammatory And Antimicrobial Agents, *Indian J. Chem*.; 2008, 47b: 144-152.

[7] Khan KM., Ambreen N., Karim A., Saied S., Amyn A., Ahmed A., and Perveen S., Schiff Bases Of Thiazole As Antibacterial And Antifungal Agents, *J. Pharmacy Res*.; 2012, 5: 651-656.

[8] Frank, W. B., Amanda, S. C., Marita, H.S., Richard, J., Nils, G.J., Et.Al, Phenethylthiazolethiourea (Pett) Compounds, A New Class Of Hiv-1 Reverse Transcriptase Inhibitors. 1. Synthesis and Basic Structure-Activity Relationship Studies Of Pett Analogs, *J. Med. Chem*.; 1995, 38: 4929-36.

[9] P. Bhattacharya, j. T. leonard, K. Roy, Bioorg., Exploring QSAR of thiazole and thiadiazole derivatives as potent and selective human adenosine A3 receptor antagonists using FA and GFA techniques, *Med. Chem*.; 2005,13(4): 1159-1165.

[10] Kumar Y., Green R., Wise DS. , Wotring LL., and Townsend LB., Synthesis Of 2,4-Disubstituted Thiazoles And Selenazoles As Potential Antifilarial And Antitumor Agents. 2. 2-Arylamido And 2-Alkylamido Derivatives Of 2-Amino4-(Isothiocyanatomethyl)Thiazole And 2-Amino-4-(Isothiocyanatomethyl) Selenazole, *J. Med. Chem*.; 1993, 36: 3849-3852.

[11] Zhi-Hua Zhang, Hong-Mei Wu, Sai-Nan Deng, Xiao-Yu Cai, Yu Yao, Muriira Cyrus Mwenda, et.al., Design, Synthesis, and Anticancer Activities of Novel 2-Amino-4-phenylthiazole Scaffold Containing Amide Moieties, *Hindawi Journal of Chemistry*; 2018:1-8.

[12] Fortuna, H.; James, D.R.; Robert, W.D.; Francis, A.K.; Roland, L.W; Steven P.S.; James, H.H.; Patrick, R.Y.; George W.C. 3-[1-(2-Benzoxazolyl) hydrazino] propanenitrile derivatives: inhibitors of immune complex induced inflammation, *J. Med. Chem*.; 1988, 31: 1719-28.

[13] Gindher, T.; Reddy, R. B.; Prasanna, B.; Chandra Mouli, G. V. P.; Synthesis and pharmacological evaluation of thiazoles, *Ind. J. Chem*.; 2001, 40B: 1279.

[14] Chandra B. Mishra, Shikha Kumari, Manisha Tiwari, Thiazole: A promising heterocycle for the development of potent CNS active agents, *European Journal of Medicinal Chemistry*; 2015, 92: 1-34.

[15] K. D. Hargrave, F. K. Hess, J. T. Oliver, N-(4-Substituted-Thiazolyl) Oxamic Acid Derivatives, A New Series of Potent, Orally Active Antiallergy Agents, *J. Med. Chem*.; 1983, 26 (8): 1158-63.

[16] W. C. Patt, H. W. Hamilton, M. D. Taylor, et al., Structure-activity relationships of a series of 2-amino-4-thiazole-containing renin inhibitors, *J. Med. Chem*.; 1992, 35(14): 2562-72.

[17] N. G. ergenc, N. S. capan, S. Gunay, m. Ozkirimli Gungor, S. Ozbey, e. Kendi, Synthesis and hypnotic activity of new 4-

thiazolidinone and 2-thioxo-4,5-imidazolidinedione derivatives, *Arch. Pharm. Pharm. Med. Chem*.; 1999, 332: 343-347.

[18] Cartner J.S., Kramer S., Talley J.J., Penning T and Collins P., Synthesis and activity of sulfonamide-substituted 4, 5-diaryl thiazoles as selective cyclo oxygenase-2 inhibitors, *Bioorg. Med.Chem. Lett*.; 1999: 1171-1174

[19] Badore A., Bordes M.F., de Cointet P., Savi P. and Bernat A. et. al., New orally active non-peptide fibrinogen receptor (GpIIb-IIIa) antagonists: Idenfictionofethy l3-(N-(4-(-Amino (ethoxycarbonyl)imino)methyl)phenyl)-1,3 thiazole-2-yl)-N-(1-ethoxycarbonyl) methyl)piperid-4-yl amino) propionate (SR121787) as potent and long acting antithrombotic agent, *Journal of Med. Chemistry*; 1997, 40: 3393-3401.

[20] Laine, L.; Kivitz, A.J.; Bello, A.E.; Grahn, A.Y.; Schiff, M.H.; Taha, A.S. Double-blind randomized trials of single-Tablet ibuprofen/high-dose famotidine vs. ibuprofen alone for reduction of gastric and duodenal ulcers, *Am. J. Gastroenterol*; 2012, 107: 379–386.

[21] Das D, Sikdar P, Bairagi M. Recent developments of 2-aminothiazoles in medicinal chemistry, *European Journal of Medicinal Chemistry*; 2016, 109:89-98.

[22] Borelli, C.; Schaller, M.; Niewerth, M.; Nocker, K.; Baasner, B.; Berg, D.; Tiemann, R.; Tietjen, K.; Fugmann, B.; Lang-Fugmann, S.; et al. Modes of action of the new arylguanidine abafungin beyond interference with ergosterol biosynthesis and in vitro activity against medically important fungi, *Chemotherapy*; 2008, 54: 245-259.

[23] Guay, D.R.P. Cefdinir: An advanced-generation, broad-spectrum oral cephalosporin, *Clin. Ther*; 2002, 24: 473-489.

[24] Luger P, Daneck K, Engel W, Trummlitz G, Wagner K. Structure and physicochemical properties of meloxicam, a new NSAID, *EurJPharmSci*.; 1996, 4(3):175-87.

[25] Adileh Ayati, Saeed Emami, Setareh Moghimi, Alireza Foroumadi, Thiazole in the targeted anticancer drug discovery, *FutureMed.Chem*. 2019, 11(15): 1929–1952.

[26] Bang-Chi C., Rulin Z., Bei Wang, Roberto D., Jean L., Pierre S., Masaki E., Balu B., and Joel C. Barrisha , A new and efficient preparation of 2-aminothiazole-5-carbamides: applications to the synthesis of the anti-cancer drug dasatinib , *ARKIVOC;* 2010, 6: 32-38.

[27] Katarzyna B., Elżbieta L.Chruscinska, Schiff bases –interesting range of applications in various fields of science, *CHEMIK*; 2014, 68, (2): 129-134.

[28] Anant P., Devjani A., Application of Schiff bases and their metal complexes-A Review, *IJCRGG*; 2011, 3, (4): 1891-1896.

[29] Wenling Q., Sha L., Mauro P. and Stefano B., Schiff Bases: A Short Survey on an Evergreen Chemistry Tool, *Molecule*s; 2013, 18(10): 12264-12289.

[30] Mithun R. and Biplab D., Chemistry & Biological importance of Heterocyclic Schiff Bases, *International Research Journal of Pure & Applied Chemistry*; 2013, 3(3): 232-249.

[31] Anita Rani, Manoj Kumar, Rajshree Khare and Hardeep Singh Tuli, Schiff bases as an antimicrobial agent: A review, *Journal of Biological and Chemical Sciences*; 2015, 2(1): 62-91.

[32] Anand P, Patil VM, Sharma VK, Khosa RL, Masand N. Schiff bases: A Review on Biological Insights, *Int J Drug Design Dis*; 2012, 3: 851.

[33] Muthal B.N., Raut B.N., Tekale A.S., Synthesis, characterization, stability constant and microbial activity of schiff bases and their CoII, NiII, CuII & ZnII Metal Chelates, *International Journal of Chemical Studies*; 2015, 3(2): 12-16.

[34] Kashyap SJ, Garg VK, Sharma PK, Kumar N, Dudhe R, Gupta JK. Thiazoles: having diverse biological activities, *Med Chem Res*; 2012, 21: 2132.

[35] More PG, Karale NN, Lawanda AS, Rajmane SV, Pawar SV, Patil RH. A 4-(o-methoxyphenyl)-2-aminothiazole: an anti-quorum sensing compound, *Med Chem Res*; 2013, 22: 4183.

[36] More PG, Karale NN, Lawanda AS, Narang N, Patil RH. Synthesis and anti-biofilm activity of thiazole Schiff bases, *Med Chem Res*; 2014, 23: 790.

[37] Patel RN. Structural, magnetic and spectroscopic characterization of two unusual end-on bis(μ-acetato/μ-nitrato) bridged copper(II) complexes with N′-[phenyl(pyridin-2-yl)methylidene]furan-2carbohydrazide and (2E,4Z)-N,2-dimethylhepta-2,4,6-trienamide-1-phenyl -1-pyridin-2-ylmethanimine (1:1) as capping ligands. Inorg Chim Acta; 2010, 363: 3838.

[38] Wu H, Kou F, Jia F, Liu B, Yuan J, Bai YJ. Synthesis, Crystal Structure, and Spectra Properties of the Cadmium (II) Complex with Bis (N-allylbenzimidazol-2-ylmethyl) benzylamine, *Photochem Photobiol B: Biolog*; 2011, 105: 190.

[39] Gulrez N., Riyaz S., Antimicrobial, electrochemical and thermodynamic studies of Schiff base complexes and their potential as anticarcinogenic and antitumor agents: A review, IOSR *Journal of Applied Chemistry*; 2017, 10, (10): 40-51.

[40] Buchheidt D, Skladny H, Baust C, Hehlmann R. Systemic infections with Candida sp. and Aspergillus sp. in immunocompromised patients with hematological malignancies: current serological and molecular diagnostic methods, *Chemotherapy;* 2000, 46: 219.

[41] Li Y, Zheng YY, Ming FW. Synthesis, characterization, DNA binding properties and antioxidant activity of Ln (III) complexes with hesperetin-4-one-(benzoyl) hydrazine, *Eur J Med Chem*; 2009, 44(11):4585-95.

[42] Nicola M, Cristin M, Valentina G, Domenico O, Mauro R, Elisabetta G, et al. Revisiting [Pt Cl2(cis-1,4-DACH)]: An Underestimated Antitumor Drug with Potential Application to the Treatment of Oxaliplatin-Refractory Colorectal Cancer, *J Med Chem* ; 2012, 55(16):7182-92.

[43] Olga N, Jana K, Vendula B, Ctirad H, Marie V, Haimei C, et al. Conformation of DNA modified by monofunctional Ru (II) arene complexes: Recognition by DNA binding proteins and repair. Relationship to cytotoxicity, *Chem Biol*; 2005, 12(1):121-9.

[44] Shambuling K., Parvati A., Irfan N. Shaikh, Basavaraj M. Kalshetty, Synthesis, Characterization and Antimicrobial Activity of some Metal Complexes Derived from Thiazole Schiff Bases with In-vitro Cytotoxicity and DNA Cleavage Studies, *Indian Journal of Pharmaceutical Education and Research*; 2017, 51 (3): 490-501.

[45] Amith KS, Sulekh C. Complexation of Nitrogen and Sulphur donor Schiff's Base Ligand to Cr (III) and Ni (II) metal ions: Synthesis, Spectroscopic and Antipathogenic Studies, *Spectrochimica Acta* A; 2011, 78(1):337-42.

[46] Zahid. HC, Arif M, Muhammad AA, Claudiu TS. Metal Based antibacterial and antifungal agents: Synthesis, Characterization, and In vitro Biological evaluation of Co(II), Cu (II), Ni (II), and Zn (II) complexes with Amino acidderived Compounds, *Bioinorganic Chemistry and Applications*; 2006: 1- 13.

[47] Abd El-Wahab ZH, Mahmoud MM, Salman AA, El-Shetary BA, Faheim AA. Co (II), Ce (III) and UO2 (VI) Bis-Salicylatothiosemicarbazide Complexes: Binary and Ternary complexes, thermal studies and antimicrobial activity, *Spectrochimica Acta A*; 2004, 60(12):2861-73.

[48] J Senthil Kumaran, S Priya, J Gowsika, N Jayachandramani S and Mahalakshmi, Synthesis, Spectroscopic Characterization, In Silico DNA Studies and Antibacterial Activites of Copper(Ii) and Zinc(Ii) Complexes derived from Thiazole based Pyrazolone Derivatives, Research Journal of Pharmaceutical, *Biological and Chemical Sciences*; 2013, 4 (2): 279.

[49] Belaid S, Landreau A, Djebbar S, Benali-Baitich O, Bouet G, Bouchara J P,Synthesis, characterization and antifungal activity of a series of manganese(II) and copper(II) complexes with ligands derived from reduced N,N'-O-phenylenebis(salicylideneimine), *J Inorg Biochem* ; 2008, 102 (1):63-69.

[50] Dharamaraj N, Viswanathamurthi P, Natarajan K, Ruthenium(Ii) Complexes Containing Bidentate Schiff Bases and Their Antifungal Activity, *Trans Met Chem*; 2001, 26 (1-2): 105-109.

[51] Azam F., Singh S., Khokhra S. Lal, Prakash O., Synthesis of Schiff bases of naphtha[1,2-d]thiazol-2-amine and metal complexes of 2-(2'-hydroxy) benzylideneaminonaphthothiazole as potential antimicrobial agents, *J Zhejiang Univ Sci B*; 2007 8(6):446-452.

[52] S. K. Sengupta, O. P. Pandey, B. K. Srivastava, V. K. Sharma, Synthesis, structural and biochemical aspects of titanocene and zirconocene chelates of acetylferrocenyl thiosemicarbazones; *Transition Met. Chem*; 1998, 23(4): 349-353.

[53] J. Parekh, P. Inamdhar, R. Nair, S. Baluja, S. Chandra, Synthesis and antibacterial activity of some Schiff bases derived from 4-aminobenzoic acid; *J. Serb. Chem. Soc*; 2005, 70(10):1155–116.

[54] Y. Vaghasia, R. Nair, M. Soni, S. Baluja, S. Chandra, Synthesis, structural determination and antibacterial activity of compounds derived from vanillin and 4-aminoantipyrine; *J. Serb. Chem. Soc*.; 2004, 69 (12): 991-998.

[55] B.C.J. Bayer; An introduction to ligand field. McGraw Hill, New York, 1962.

[56] A.B.P. Lever; Inorganic electronic spectroscopy Elsevier, Amsterdam, 1984.

[57] Hassan UM, Chohan ZH, Supuran CT, Antibacterial Zn(II) compounds of Schiff base derived from some benzothiazoles; *Main Group Met Chem*; 2002, 25(5): 291-296.

[58] Shrivastava G, Shrivastava M, Shrivastava G; Antimicrobial activity of Schiff Base of 2-Amino 5Nitrothiazole and its Copper complex; *PharmaTutor;* 2018, 6(9): 1-5.

[59] A. S. Thakar, K. S. Pandya, K. T. Joshi, A. M. Pancholi, Synthesis, Characterization and Antibacterial Activity of Novel Schiff Bases Derived from 4-Phenyl-2-aminothiazole and their Mn(II), Fe(II), Co(II), Ni(II) and Cu(II) Metal complexes, *E-Journal of Chemistry*; 2011, 8(4): 1556-1565.

[60] Ambit T., Krishenakant J., Kishor P. and ARVIND P., Coordination Modes of a Schiff Base Derived from Substituted 2-Aminothiazole with Chromium(III), Manganese(II), Iron(II), Cobalt(II), Nickel(II) and Copper(II) Metal Ions: Synthesis, Spectroscopic and Antimicrobial Studies, *E-Journal of Chemistry;* 2011, 8(4): 1750-1764.

[61] Nikhil D. Amnerkar, Bhoomendra A. Bhongade, Kishore P. Bhusari, Synthesis and biological evaluation of some 4-(6-substituted-1,3-benzothiazol-2-yl) amino-1,3-thiazole-2-amines and their Schiff bases, *Arabian Journal of Chemistry*; 2015, 8: 545-552.

[62] Pushkal S., Ritu S., Santosh K. Srivastava and Savitri D. Srivastava, Synthesis of 2-oxoazetidine derivatives of 2-aminothiazole and their biological activity, *J. Serb. Chem. Soc*.; 2012, 77 (5): 599–605.

[63] Rajul G., Neeraj K. Fuloria, Shivkanya F., Synthesis and Antimicrobial Profile of Some Newer 2-Aminothiazole Derivatives, *Turk J Pharm Sci*; 2013, 10 (3): 425-434.

[64] Rajul G., Neeraj K. Fuloria, Shivkanya F., Synthesis and Antimicrobial Activity Evaluation of some Schiff Bases Derived From 2-Aminothiazole Derivatives, *Indonesian J. Pharm*.; 2013, 24 (1): 35 - 39.

[65] R. Karki, G.K. Rao, A. Gupta, G. Mariappan, S.Adhikari, Synthesis, Characterization and Antimicrobial Activities of Schiff bases of 2-amino-4-(O-chloroanilino)-1, 3-thiazole, *Journal of Applied Pharmaceutical Science*; 2013, 3 (07): 093-096.

[66] Vinusha HM, Shiva Prasad K, Chandan S and Muneera Begum, Imino-4-Methoxyphenol Thiazole Derived Schiff Base Ligands: Synthesis, Spectral Characterization and Antimicrobial Activity, *Chem Sci J*; 2015, 6(3):1-4.

[67] Xin Z., Ling S., Zhong J., Jian-Bing L., Hong D., and Jian-Xin F., Synthesis and Antitumor Activity Evaluation of Some Schiff Bases Derived from 2-Aminothiazole Derivatives, *Heteroatom Chemistry*; 2007, 18 (1): 55-59.

[68] A. Palanimurugan, A. Kulandaisamy, DNA, in vitro antimicrobial/anticancer activities and biocidal based statistical analysis of Schiff base metal complexes derived from salicylalidene-4-4imino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and 2-aminothiazole, *Journal of organometallic chemistry*; 2018, 861: 263-274.

[69] Minghua L, Seung WK, Yoojin S. Discovery of 2-aminothiazole derivatives as anticancer agents. *Bulletin of Korean society*; 2010, 31(6):1463-1464.

[70] Jeong TC, Koh WS, Kwon BM, Yoon SY. Cinnamaldehyde inhibits lymphocyte proliferation and modulates T-cell differentiation. *International Journal of Immunopharmacology;* 1998, 20 (11):643-660.

[71] Shruthy V. S, ShaKkkeela Y., In Silico Design, Doking, Synthesis And Evaluation Of Thiazole Schiff Bases, *International Journal of Pharmacy and Pharmaceutical Sciences*; 2014, 6 (3): 271-275.

[72] Nikhil M. Parekh, Bhupendra M. Mistry, Muthuraman P., Surendra K. Shinde, Rahul V Patel, Investigation of Anticancer Potencies of Newly Generated Schiff Base Imidazolylphenylheterocyclic-2-Ylmethylenethiazole-2-Amines, *Chinese Chemical Letters*; 2017, 28:602-606.

[73] Saima Ejaz1, Humaira Nadeem, Rehan Zafar Paracha, Sadia Sarwar and Sadaf Ejaz, Designing, Synthesis and Characterization of 2-Aminothiazole-4-Carboxylate Schiff Bases; Antimicrobial Evaluation Against Multidrug Resistant Strains and Molecular Docking, *Bmc Chemistry*; 2019, 115: 1-13.

[74] Zahra Aldelfy, Zeki Al-Shamkani, Mohammed Al-Assadi, 2-Hydroxybenzylidene-4-(4-Substitutedphenyl)-2-Amino Thiazole and Their Pt (Ii) Complexes: Synthesis, Characterization and Biological Study, *Egypt.J.Chem.* 2019, 62(10): 1851 – 1867.