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Review Article

Importance of the Applicability of *O*-Vanillin Schiff Base Complexes: Review

Ali Mostafa Hassan[1], Ahmed Osman Said[2]*

[1] *Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City 11884, Egypt*
[2] *Senior Researcher Chemist, Greater Cairo Water Company, Cairo, Egypt*

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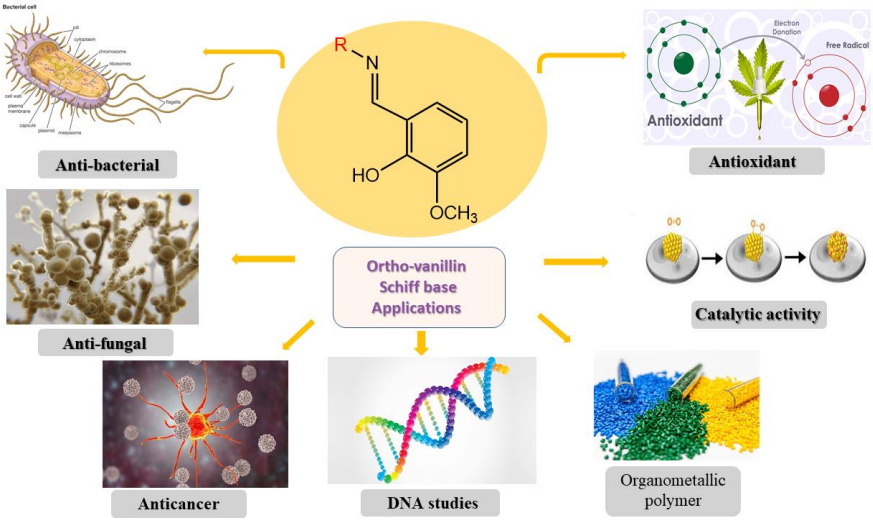
Antimicrobial
Cytotoxic
Antioxidant

ABSTRACT

Ortho-vanillin Schiff base are multipurpose ligands which are synthesized from the condensation of 2-Hydroxy-3-methoxybenzaldehyde with amines compounds to designing an infinite number of potential compounds. Ortho-vanillin Schiff base grow into very common in coordination chemistry for the reason that it can form compounds that have high stability with most metals, and this is due to nitrogen (N) of azomethine group beside two oxygen (O) atoms of hydroxyl and methoxy groups. Ortho-vanillin Schiff base and its metal complexes are very important as antibacterial, antifungal, antioxidant and anticancer, Also, many available pharmaceutical researches predict how these compounds can interaction with DNA. Many efforts are made in the possibility of using Ortho-vanillin Schiff base as catalyst, polymers, dyes, Analogues and pharmaceutical fields. This review will try to shed light on the most used applications by researchers of Ortho-vanillin Schiff base compounds to stimulate more and more efforts to achieve maximum benefit from potential infinite number of compounds.

GRAPHICAL ABSTRACT



* Corresponding author: Ahmed Osman Said
✉ E-mail: chem2you@gmail.com
☎ Tel number: +201551278690
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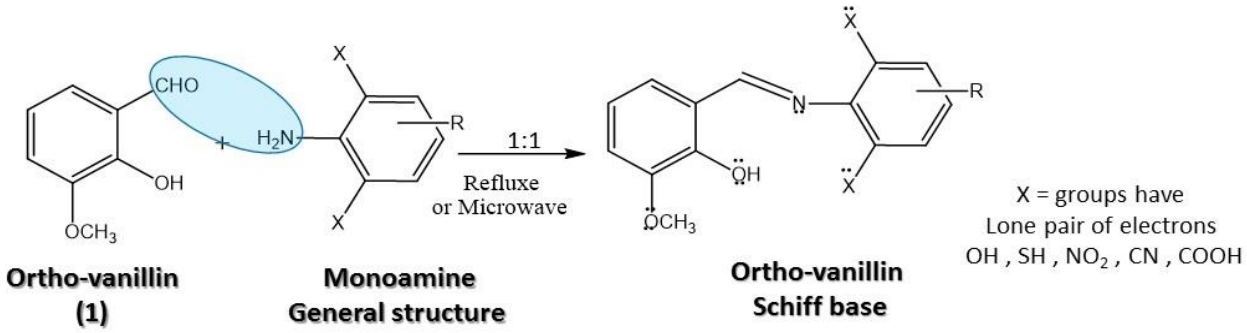
Introduction

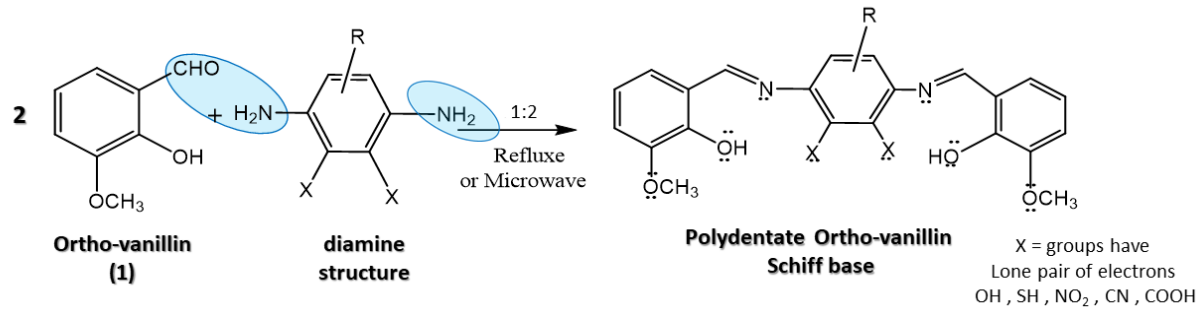
One of the most substantial part of coordination chemistry is designing a new ligand such as Schiff bases with bidentate or multi-dentate behavior from several amines and aldehydes, and their chelating with various metals ion to form infinite number of potential compounds. Ortho-vanillin Schiff base are similar to salicylaldehyde Schiff base, known as bidentate or polydentate ligands due to the presence of hydroxyl group at ortho position near azomethine group. Salicylaldehyde Schiff base have been studied extensively [1-3]. We expect that salicylaldehyde will be replaced with ortho-vanillin in the recent research due to the scarcity of research on ortho vanillin compared to salicylaldehyde. In addition to the availability and low cost of ortho-vanillin, the key difference between the o-vanillin Schiff base and salicylaldehyde Schiff base is resulted from the presence of the -OCH_3 group that confers the behavior of these ligands: the -OCH_3 groups offer extra coordinating sites [4-6]. In this review we will summarize most of the applied aspects of ortho-vanillin Schiff base and clarify what are compounds already preparing, what are the metals that interacted with ligands, what are the best results. Additionally, what are types of bacteria, fungi or cancer cells are tested in detail to facilitate the process of completing and developing research or avoiding deficiencies in subsequent research.

Importance of Ortho-Vanillin Schiff Bases

2-Hydroxy-3-methoxybenzaldehyde (Ortho-vanillin) **1** is an organic yellow crystalline solid existing from plant extracts and essential oils, ortho-Vanillin is one of isomers of 4-Hydroxy-3-methoxybenzaldehyde (vanillin) that used as a flavor and extracted from vanilla plant, ortho-Vanillin include ether, aldehyde and phenol functional group in the one benzene ring. The multiplicity of its functional groups makes it an ideal compound for entering into many organic reactions as Schiff base reaction. Ortho-vanillin is distinguished from Vanillin by the presence of the hydroxyl group in the ortho position in the middle between aldehyde and methoxy groups, this makes the complexes of Ortho-vanillin Schiff base more stable, easier and faster to chelating with most metal ions. Bidentate or higher ligands can be designed by condensation reaction of ortho-vanillin with monoamine compounds Scheme 1 [5-10]. Also, A tetradentate or polydentate ligands can be synthesized by condensation reaction of ortho-vanillin with diamine compounds Scheme 2 in 2:1 molar ration [11].



Scheme 1. General scheme for synthesis of Ortho-vanillin Schiff base in 1:1 molar ration



Scheme 2. General scheme for synthesis of Ortho-vanillin Schiff base in 2:1 molar ration

Various applications used to search for potential efficacy of ortho-vanillin Schiff base ligands and its complexes are including the anti-bacterial, antifungal, anticancer and Cytotoxicity evaluation, DNA infarction and cleavage, molecular docking, anti-oxidant studies, catalytic activity, formation of novel polymer and removing of metals from water, as well as many other potential applications (Figure 1).

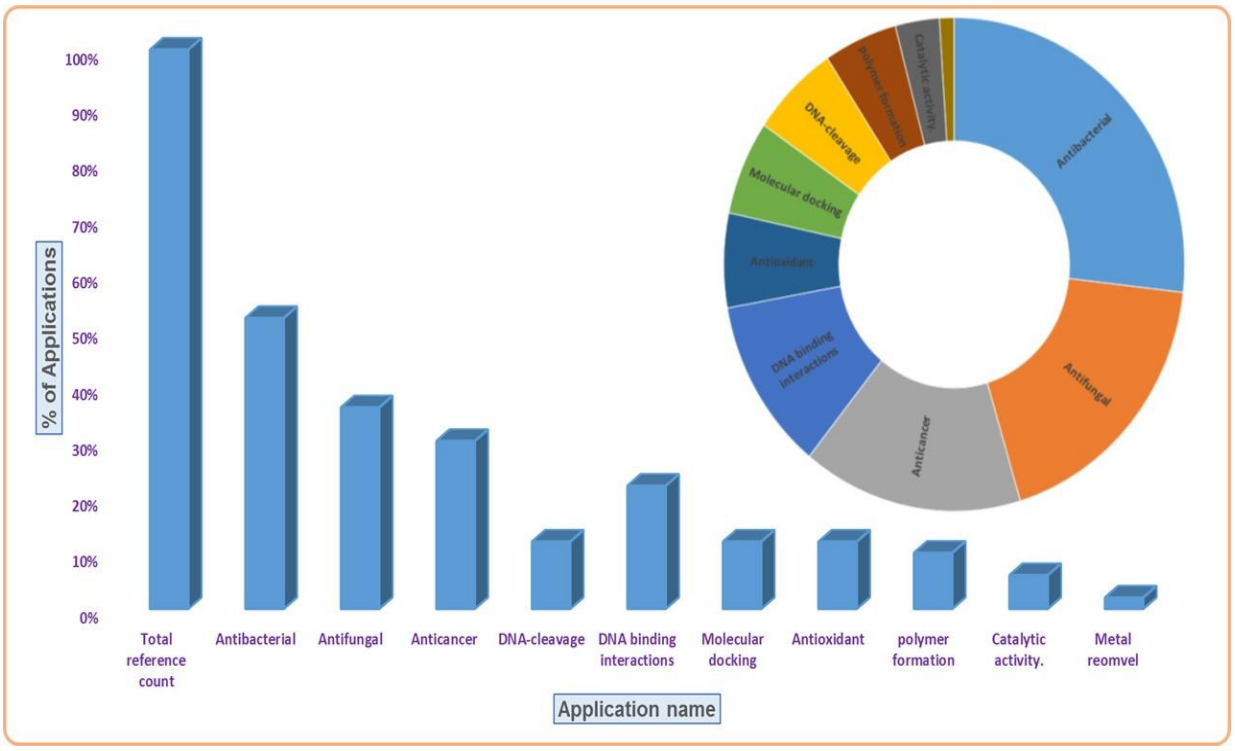


Figure 1. Ortho-vanillin Schiff bases and its complexes Application

Ortho-Vanillin Schiff Bases as Anti-Bacterial

Scanning for antibacterial activity is the most application that researchers will be interested in after obtaining novel Schiff bases and its complexes, this is due to several factors, including ease and availability of antibacterial testing, availability of different bacterial cultures, time taken to experiment is not long. Generally, one of the most important reasons that scientific importance of finding new drugs and compounds to kill different types of bacteria and those that might gain resistance against commercial antibiotics. Synthesis of ortho-vanillin Schiff

bases and their metal complexes is an attractive approach to discovering new drugs to bridge the resulting deficit from bacterial resistance to traditional drugs. The bactericidal activity of metal complexes is typically higher than free Schiff bases compounds, which is basically due to entering of metal ion on the normal cell process. A possible mode for increase in antibacterial activity may be considered in the light of Overton's concept [12] and the Tweedy's chelation theory [13].

Researchers use several bacteria species to study the effectiveness of free Schiff bases and its complexes such as *E*. coli, Pseudomonas aeruginosa, Salmonella, Bacillus cereus, Staphylococcus aureus, Enterobacter aerogenes, Klebsiella Pneumoniae, Streptococcus pyogenes, *H*. pylori, *B*. stearothermophilus, *M*. tuberculosis H37Ra, *M*. tuberculosis H37Rv, Shigellafl exneri, *P*. vulgaris and Methicillin-resistant Staphylococcus aureus (MRSA). often the bacteria used are divided into Gram-positive and Gram-negative bacteria, *E*. coli bacteria were the most Gram-negative species used for the study of activity, while Staphylococcus aureus was the most used as an example of a gram positive (Figure 2). The disc diffusion method [14] is often utilized to evaluate the sensitivity of drugs and determination of Zone of Inhibition, Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC), frequently compounds are studied compared to standardized positive control such as Cephalothin, Gentamicin, Ampicillin and Tetracycline.

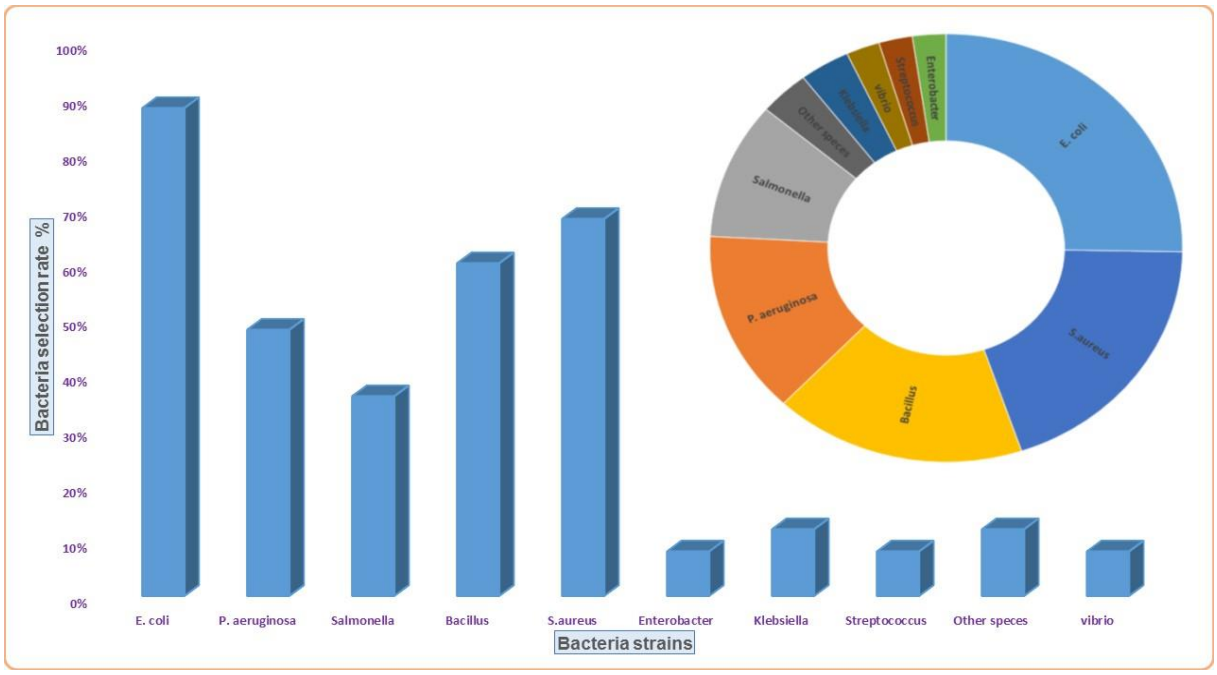
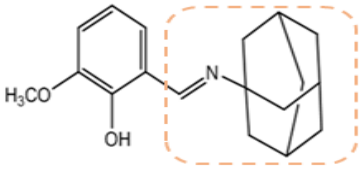


Figure 2. Bacterial strains used for anti-bacterial activity screening by ortho-vanillin Schiff bases and its complexes

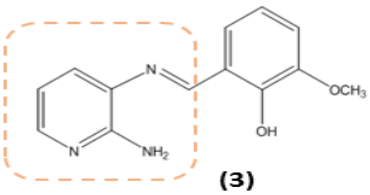
Zhao *et al.* [15] prepared and characterized a new metal com plexes of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) with ortho-vanillin Schiff base derived from Adamantaneamine **2,** and he has studied the activity of Schiff base and their complexes against *E*-coli at different concentrations, the results showed that metals complexes are more active than ligand. Schiff base derived from ortho-vanillin and chitosan showed antibacterial activity against *B*. subtilis,

E. coli and pseudomonas. The results compared with Ampicillin [16]. Two Schiff base prepared by reaction of ortho-vanillin and 2, 3-diaminopyridine at room temperature in molar ratio 1:1 **3** and 2:1 **4** and their metals complexes revealed antibacterial activity against salmonella, *P*. aeruginosa, the results showed that both ligands are more active than its metals complexes [17]. Neelakantan *et al*. prepared and characterized a two Schiff base derived from ortho-vanillin and 2-amino benzothiazole **5**, 2-Amino-N-(2-pyridyl)-benzene sulfonamide **6** and their complexes of Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) in the present of 1, 10-phenanthroline as mixed ligand with *O*-vanillidene-2-aminobenzothiazole **5**, [18]. The free ortho-vanillin Schiff base and its complexes have been screened for antibacterial activity against salmonella, *P*. aeruginosa, *E*. coli, Vibrio parahaemolyticus at different incubation period, the result showed that metals complexes are more active than corresponding ligand, these results were in accordance with the basis of Tweedy's chelation theory [13].



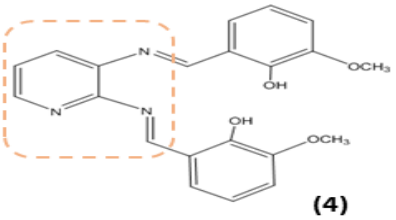
(2)

M= Mn, Co, Ni, Cu, Zn



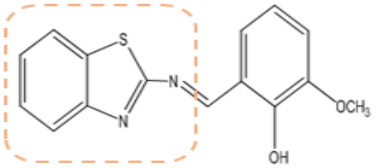
(3)

M= Fe, Ni, Cu, Zn



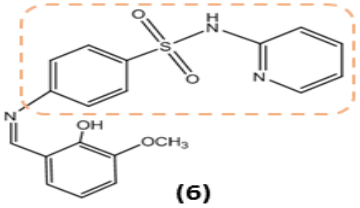
(4)

M= Fe, Ni, Cu, Zn



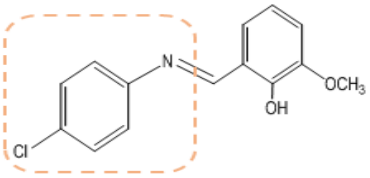
(5)

M= Mn, Co, Ni, Cu, Zn



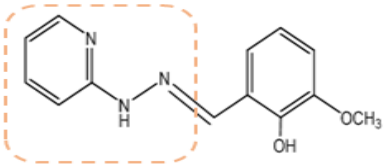
(6)

M= Mn, Co, Ni, Cu, Zn



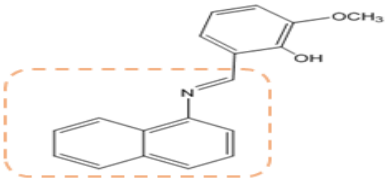
(7)

M= Cr, Co, Ni, Cu



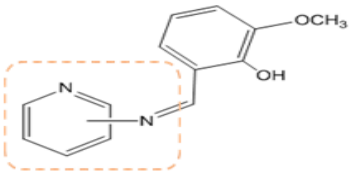
(8)

M= Sn salts



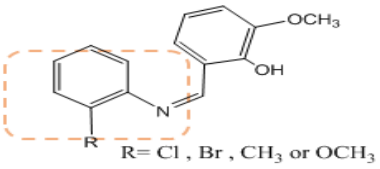
(9)

M= Cu



(10)

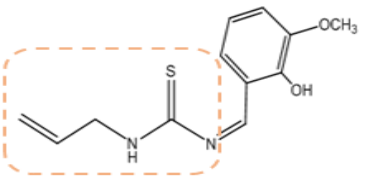
M= Cu



R= Cl , Br , CH_3 or OCH_3

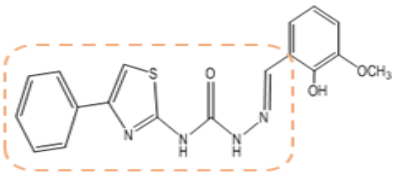
(11)

M= Cu



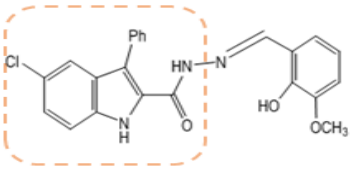
(12)

M= Ni, Cu ,Zn



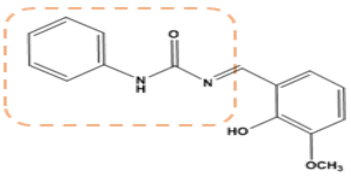
(13)

M= Co ,Ni, Cu ,Zn



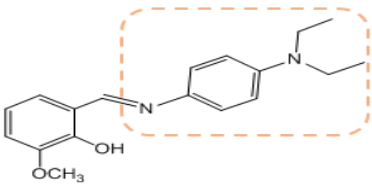
(14)

M= Co ,Ni, Cu ,Zn



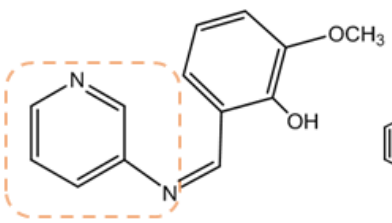
(15)

M= Mn ,Co ,Ni, Cu ,Zn , Zr



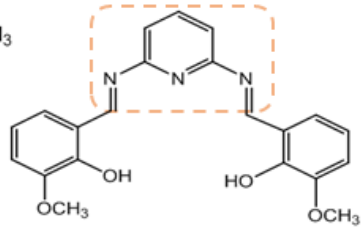
(16)

M= Mn ,Co ,Ni, Cu ,Zn , Zr



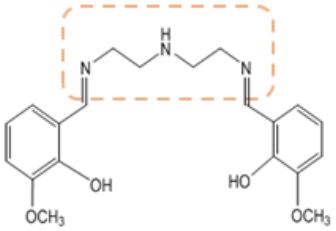
(17)

M= Tellurium (IV) salts



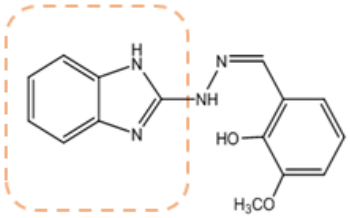
(18)

M= Bi



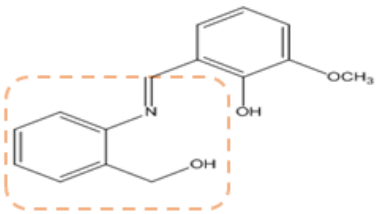
(19)

M= Cu



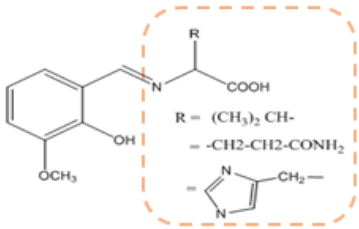
(20)

M= Co ,Ni, Cu ,Zn



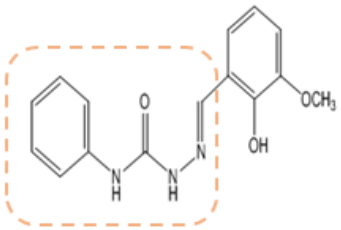
(21)

M= Cr, Co, Ni, Cu



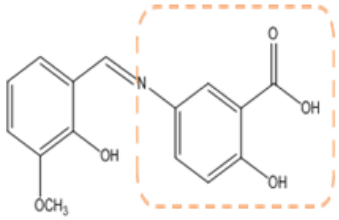
(22)

M= Co ,Ni, Cu ,Zn



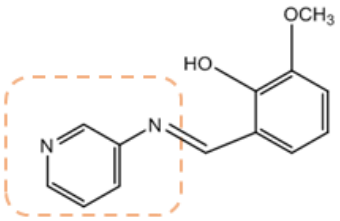
(23)

M= Ru



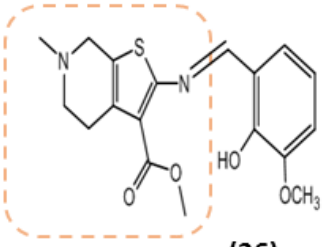
(24)

M= Mn ,Co , Cu ,Zn



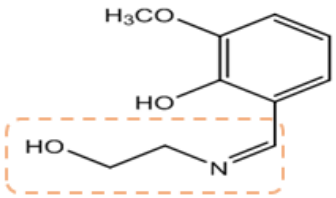
(25)

M= Co



(26)

M= Ru, Co ,Ni



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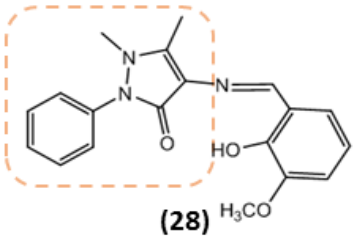
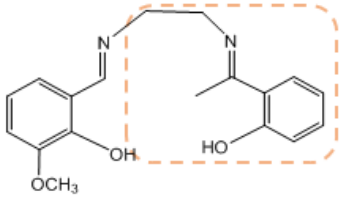


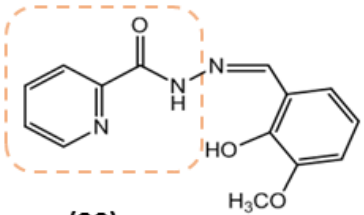
(28)

M= V, Fe, Co, Ni, Zn



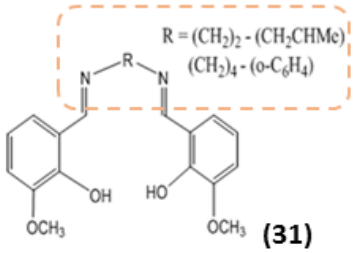
(29)

M= Cr ,Fe , Co, Ni, Cu , Zn



(30)

M= Cr, Mn, Cu



(31)

M= Ru

Schiff base derived from ortho-vanillin and p-chloroaniline **7** and their complexes of Cr (III), Co(II), Ni(II) and Cu(II) have been synthesized by reflux and microwave technique [19], Schiff base

and its complexes showed antibacterial activity against *E*. coli, *S*. aureus at different concentrations. The results compared with Streptomycin, the results showed moderate to high activity against *E*. coli and *S*. aureus. Norrihan Sam *et al*. used a set of organotin(IV) chloride with ortho-om vanillin-2-hydrazinopyridine hydrazone **8** Schiff base ligand to formation of novel five complexes. Four of the five organotin complexes prepared by Norrihan [20] were given a moderate activity with Bacillus cereus, *S*. aureus, Enterobacter aerogenes and *E*. coli compared with doxycycline drug. Sobola Abdullahi *et al*. prepared a new Cu(II) complexes of five Schiff bases derived from ortho-vanillin and 1-aminonaphthalene **9**, 2-aminopyridine and 3-aminopyridine **10**, ortho-substituted Aniline **11**, he studied antibacterial activity against Bacillus subtilis, Staphylococcus aureus, *E*. coli by disc diffusion method and minimum inhibitory concentration technique, the results showed moderate to low activity in most cases [21-22].

Rizwana and Santha used N-allyl thiourea to formation a new ortho-vanillin Schiff base **12** and their metal complexes of Ni(II), Cu(II) and Zn (II) in the present of sodium perchlorate, free Schiff base and perchlorate ion of ortho-vanillin Schiff base complexes showed moderate to high antibacterial activity against Klebsiella Pneumoniae, Bacillus Cereus, Pseudomonas compared with Ciprofloxacin [23]. G.Y. Nagesh *et al*. prepared novel two ortho-vanillin Schiff bases with N-(4-phenylthiazol-2-yl) hydrazine carboxamide **13** and 5-chloro-3-phenyl-1H-indole-2-carboxy-hydrazide **14** and their metal complexes of Co (II), Ni(II), Cu (II) and Zn (II), and he has studied the activity of Schiff base and their complexes against *S*. aureus, *B*. Subtilis *E*. coli and salmonella by minimum inhibitory concentration technique, the results showed moderate activity compared with Gentamicin, this result confirm that all metals complexes are more active than corresponding free ligand [24-25].

Ali M. Hassan *et al.* [26-27]. Utilized phenyl urea **15** and N, N-Diethyl-p-phenylenediamine **16** to formation a two novel ortho-vanillin Schiff base and their metal complexes of Mn (II), Co (II), Ni(II), Cu (II), Zn (II) and Zr (IV) by Conventional and Microwave techniques. All ligands and their metal complexes were screened for the antimicrobial activity against *S*. aureus, B. Subtilis, *E*. coli and Salmonella. typhi, the results showed moderate to high activity, copper complex of N, N-Diethyl-p-phenylenediamine ortho-vanillin Schiff base achieved a highest inhibition zone diameter against E. coli compared with Cephalothin. Organyltellurium (IV) complexes of ortho-vanillin Schiff base with 3-aminopyridine **17** have been synthesized by Malik A [28]. Free Schiff base and Tellurium(IV) complexes were screened for the antimicrobial activity against *S*. aureus, *S*. pyogenes, *P*. aeruginosa and *E*. coli by minimum inhibitory concentration method compared with Ampicillin and Chloramphenicol as positive control. Xu Li *et al*. prepared a bismuth(III) metal complex of ortho-vanillin Schiff base with 2,6-pyridinediamine in 2:1 molar ratio **18**. Xu Li studied the bioactivity against H. pylori and S. Pombo cell lines by using half inhibition concentration (IC_{50}) parameter, the results showed that the (IC_{50}) increases with the increase in concentration of the Schiff base but decreases with bismuth complex against H. pylori [29].

Copper complex of ortho-vanillin Schiff base **19** with diethylenetriamine in molar ratio 2:1 have been synthesized and studied for anti-mycobacterial activity by Kuheli Das *et al*. [30], Minimum inhibition concentrations and minimum bactericidal concentrations techniques used to study activity against M. tuberculosis $H_{37}Ra$ and M. tuberculosis $H_{37}Rv$ strains, the results showed moderate activity comparing with Streptomycin and Ethambutol. ortho-

vanillin Schiff base with 2-hydrazinobenzimidazole **20** and their metal complexes of Co (II), Ni (II), Cu (II)and Zn (II) have been synthesized by Ranjan K [31]. the results showed moderate activity for Schiff base and relative high for complexes against *B*. subtilis, *B*. stearothermophilus, *E*. coli, Salmonella. typhi. B. Kavitha *et al*. used 2-Aminobenzyl alcohol to formation a novel ortho-vanillin Schiff base **21** and its complexes of Cr (III), Co (II), Cu (II) and Zn (II) [32]. the results showed that complexes are more active than ligand compared with Streptomycin. Some of new ortho-vanillin Schiff bases with amino acids L-valine, L-glutamine and L-histidine **22** and their metals complexes of Co (II), Ni (II), Cu (II) and Zn (II) have been developed by Sivasankaran *et al.* [33], Copper complex of ortho-vanillin Schiff base with amino acid achieved very high activity compared with Ampicillin. Ruthenium (II) carbonyl with ortho-vanillin Schiff base and N (4)-phenylsemicarbazide **23** have been prepared by Jayabalakrishnan *et al*. [34]. the results showed moderate activity comparing with Streptomycin against Bacillus and pseudomonas. ortho-vanillin Schiff base with 5-Aminosalicylic acid and its metal complexes of Mn (II), Co (II), Cu (II) and Zn (II) **24** have been synthesized by Shaheen *et al.* [35]. Ligand and their complexes exhibit high activity against aureus *E*. Coli, *P*. aersginosa, Shigellafl exneri, *P*. vulgaris and Bacillus. Cobalt complexes of ortho-vanillin Schiff base with 3-Aminopyridine **25** have been synthesized by Shaibu *et al.* [36], the result showed that metals complexes are more active than Schiff base ligand.

Nevin Turan *et al.* prepared a novel ortho-vanillin Schiff base with (*E*)-methyl 2-amino-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*] pyridine-3-carboxylate **26** and its complexes of Ru(II), Co(II) and Ni(II) [37], Schiff base and all metal complexes have been screened for antibacterial activity against seven type of organism at different concentrations ranged from 10 -80 µL and compered with five type of Antibiotic. ortho-vanillin Schiff base with ethanolamine **27** have been synthesized by Zubair *et al.* [38]. The result showed that Schiff base more active than standard drug, Cefixime against Staphylococci, *E*. Coli, MRSA, *K*. Pneumoniae and *S*. Aureus. Ortho-vanillin Schiff base with 4-Aminoantipyrine **28** and its metal complexes of V (IV), Fe(III), Co(II), Ni(II) and Zn (II) have been prepared by B. Anupama *et al.* [39]. The result showed that Schiff base antibacterial inactive at different concentrations but its complexes showed moderate to high activity *E*. coli and *S*. aureus. Subin and Aravindakshan prepared a new Schiff base derived from *O*-vanillin, O-hydroxyacetophenone with 1,2-ethylenediamine **29** and its transition metal complexes [40]. The results showed moderate to high activity comparing with different standard drug. Cr(III), Mn(II) and Cu (II) complexes of ortho-vanillin Schiff base with picolinohydrazide **30** have been synthesized by Gamil Al-Hazmi *et al.* [41]. The result showed that Schiff base and its complexes inactive against *S*. aureus and showed low activity against *E*. coli compared with Ampicillin as standard drug.

Ortho-Vanillin Schiff Bases As Antifungal

Scanning for antifungal activity is the second most common application after antibacterial, researchers often use the same methods used to search for anti-bacterial activity, therefore, we find that most of the researches conduct anti-bacterial and anti-fungal results in one table under the name of antimicrobial activity [21-23] or biological evaluation [24, 29], Researchers use several fungi species to study the effectiveness of free Schiff bases and its complexes such as Candida albicans, Candida kefyr, Aspergillus niger, Aspergillus clavatus, Aspergillus fumigatus, Aspergillus Flavus, Rhizobus, Pencillum, Trichoderma virida, Saccharomyces cerevisiae, Fusarium oxysporum, Cladosporiumoxysporum ,

S. pombe, Sclerotium rolfsii, Macrophamina phaseolina, Y. lipolytica, S. cereviciae, C. Tropicalis (Figure 3). The disc diffusion method [14] is often used to study of sensitivity of drugs and determination of Zone of Inhibition compared with standardized positive control such as Flucanazole, Ketoconazole, cycloheximide and Nystatin.

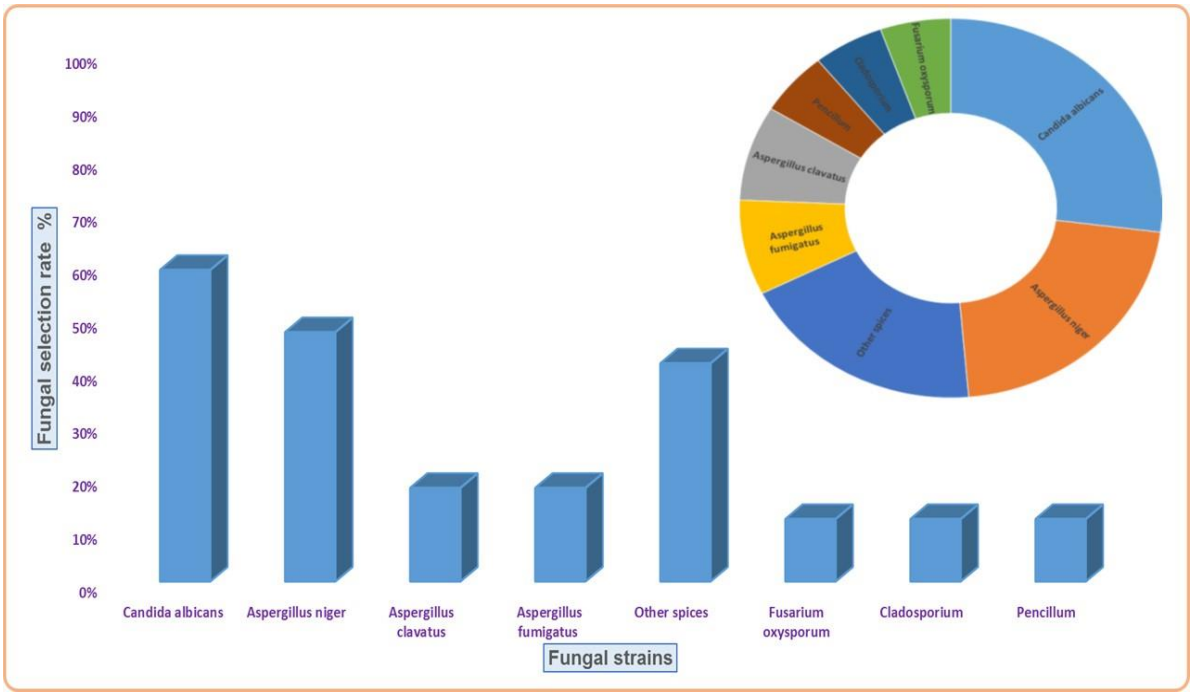


Figure 3. Fungal strains used for anti-fungal activity screening by ortho-vanillin Schiff bases and its complexes

Neelakantan *et al.* prepared a two ortho-vanillin Schiff base **5**, **6** and its transition metal complexes [18], ligand and their complexes showed moderate to low activity against Aspergillus niger, Pencillum, Trichoderma virida, Saccharomyces cerevisiae. Complexes of ortho-vanillin Schiff base with p-chloroaniline **7** showed moderate activity against Aspergillus nigre, Fusarium oxysporum at different concentrations compared with Flucanazole drug [19]. Ortho-vanillin Schiff base with 2-methoxyaniline **11** achieved a great inhibition zone diameter against Candida albicans compared with Ketoconazole (44 mm for Schiff base, 20 mm for Ketoconazole) [22]. Ni (II), Cu (II) and Zn (II) complexes of ortho-vanillin Schiff base with N-allyl thiourea in the present of sodium perchlorate **12** achieved a very high inhibition zone diameter against Aspergillus niger, Candida albicans, Candida kefyr compared with Ketoconazole [23]. A novel two ortho-vanillin Schiff bases **13**, **14** and their metal complexes of Co (II), Ni(II), Cu (II) and Zn (II) showed moderate antifungal activity against C. albicans, C. oxysporum, A. niger compared with Fluconazole [24-25]. Copper complex of ortho-vanillin Schiff bases with phenyl urea **15** showed high antifungal activity against C. albicans compared with cycloheximide [26]. ortho-vanillin Schiff bases with N, N-Diethyl-p-phenylenediamine **16** is more antifungal active than its complexes against A. fumigatus, C. albicans [27]. Organyltellurium (IV) complexes of ortho-vanillin Schiff base with 3-aminopyridine **17** showed moderate activity against *A*. niger, *C*. albicans and *A*. clavatus [28]. Ortho-vanillin Schiff bases with 2-Aminobenzyl alcohol **21** and its complexes showed moderate activity against

Sclerotium rolfsii and Macrophamina phaseolina compared with Streptomycin, the result showed that all metals complexes are more antifungal active than free ligand [32]. Cobalt complex of ortho-vanillin Schiff base **26** showed a high activity at different concentrations ranged from 10 -80 µL against *Y*. lipolytica, *C*. albicans, *S*. cereviciae [37]. Ortho-vanillin Schiff base with ethanolamine **27** showed moderate activity *A*. niger, *A*. fumigates, *A*. flavus and *M*. species compared with Terbinafine [38]. Ruthenium (II) complexes of ortho-vanillin Schiff base with some aliphatic diamine **31** showed low antifungal active at different concentrations against Fusarium *sp*. [41].

Anticancer and Cytotoxicity Evaluation

When a researcher obtains new compounds resulting from the Schiff reaction, the search for cytotoxicity assessment against different cancer cell line is very important and more attractive than other uses. One of the biggest obstacles facing researchers is the unavailability of cancer cells easily compared to bacteria and fungi, as well as the relatively high cost of anticancer tests. Although the search for new safe anti-cancer drugs is of utmost importance due to the spread of cancer all over the world, Organometallic compounds are the most likely compounds to produce anti-cancer drugs, because they combine toxicity of metals and toxicity in organic compounds, as is the case in Cisplatin drug. Researchers often use the MTT assay to evaluation of cytotoxicity in different cancer cell line such as breast cancer cell line (MCF-7), human colon cancer cell line (HCT-116, HT-29), human liver cancer cell line (HepG2), HeLa cells, human pancreatic cancer cell line (MIA PaCa-2), murine melanoma cell line (B16-F10), MDA-MB-231 cell line, mouse lung fibroblast cell line (L929), human immortalized myelogenous leukemia cell line (k-562), human leukemia cell line (HL-60), adenocarcinomic human alveolar basal epithelial cells (A-549), ovarian cancer cell line (SK-OV-3, A2780), human prostate cancer (LNCaP, DU145), human bladder cancer (EJ-28, RT-11), and glioblastoma cancer (U87, SJ-G2). (Figure 4) However, in some other cases, researchers used Brine shrimp lethality bioassay [20, 36] method to evaluation of cytotoxicity. Half maximal inhibitory concentration IC_{50} is commonly used as a measure of drug activity against different cancer cell line, it is known that a higher IC_{50} value means lower cytotoxicity activity.

Vanillin and its isomer ortho-vanillin **1** molecules showed high cytotoxicity against human melanoma cell line A-375 [42]. Ortho-vanillin Schiff base with phenyl urea **15** showed low cytotoxicity against MCF-7, HCT-116 cell line compared with Cisplatin, but its complexes showed moderate activity against the same cell lines, these results confirm that the organometallic compounds have a higher cytotoxicity than the organic compounds [26]. Ortho-vanillin Schiff base **16** and their complexes showed moderate to high cytotoxicity against HepG2, HCT-116 cell line compared with Cisplatin [27]. Complexes of ortho-vanillin Schiff base with 2-Aminobenzyl alcohol **21** showed low cytotoxicity against HeLa, MiaPaca2, B16F10 cell lines [32]. Copper complex of ortho-vanillin Schiff base **29** exhibited highest cytotoxicity against DLA cell line compared with its free Schiff base and other related complexes [40]. María R. Rodríguez *et al*. prepared a novel ortho-vanillin Schiff base with 2-thiophenemethylamine **32** and its complexes of Cu (II), Zn (II) [43], oxidovanadium (IV) [44]. Copper complex of ortho-vanillin Schiff base **32** exhibited very high activity against MCF-7, MDA-MB-231 cell line compared with Cisplatin (MCF-7, IC_{50} (µM), 13.9 for Copper complex, 19.2 for Cisplatin). Zinc complex of ortho-vanillin Schiff base with (R)-(+)-2-amino-3-phenyl-1-propanol **33** showed high cytotoxicity against K-562, HL-60, A-549 and Hela cell line compared with Cisplatin, ortho-

vanillin Schiff base with 2-amino-2-ethyl-1,3-propanediol **34** and its zinc complex showed low cytotoxicity against the same cell lines [45]. dinuclear of Ni (II) complex of ortho-vanillin Schiff base with ortho-phenylenediamine in 2:1 molar ratio **35** achieved very high cytotoxicity against HCT-116 cell line (IC_{50} 0.81 ± 0.22 µM) [46].

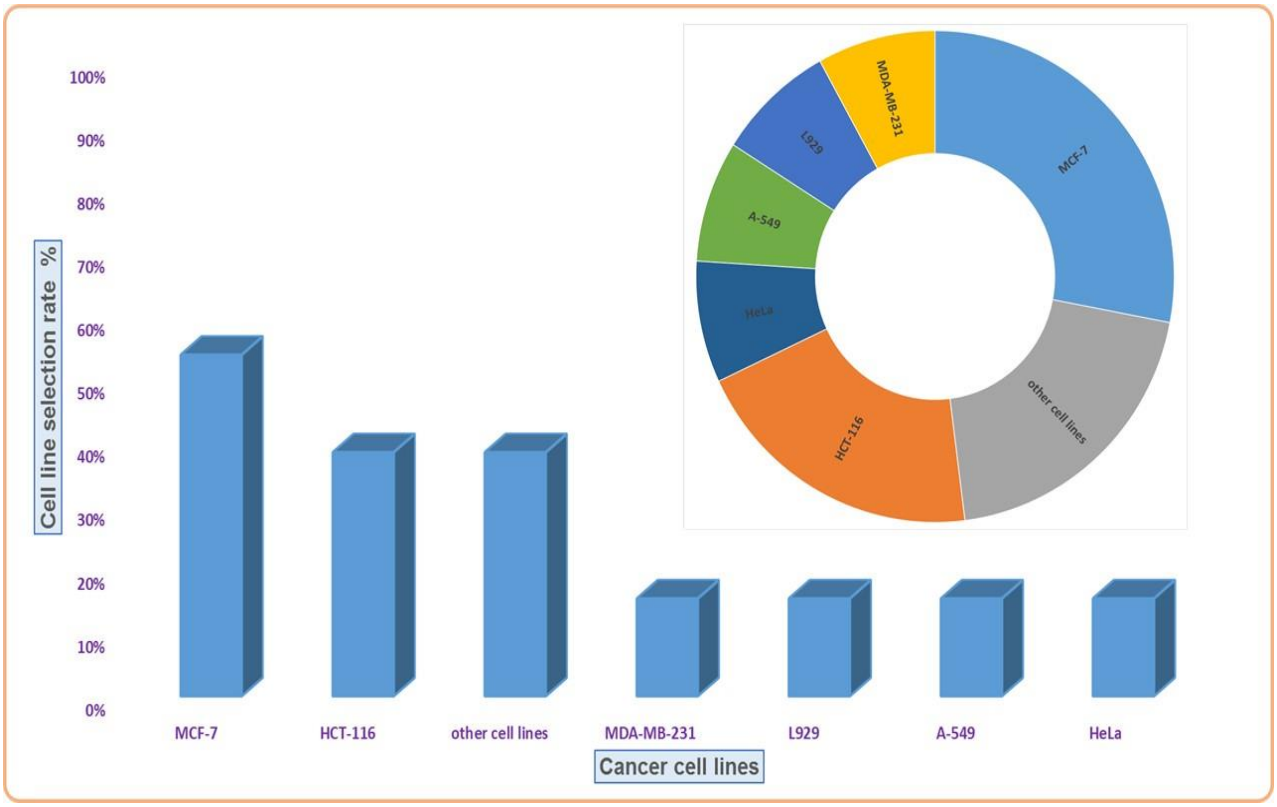
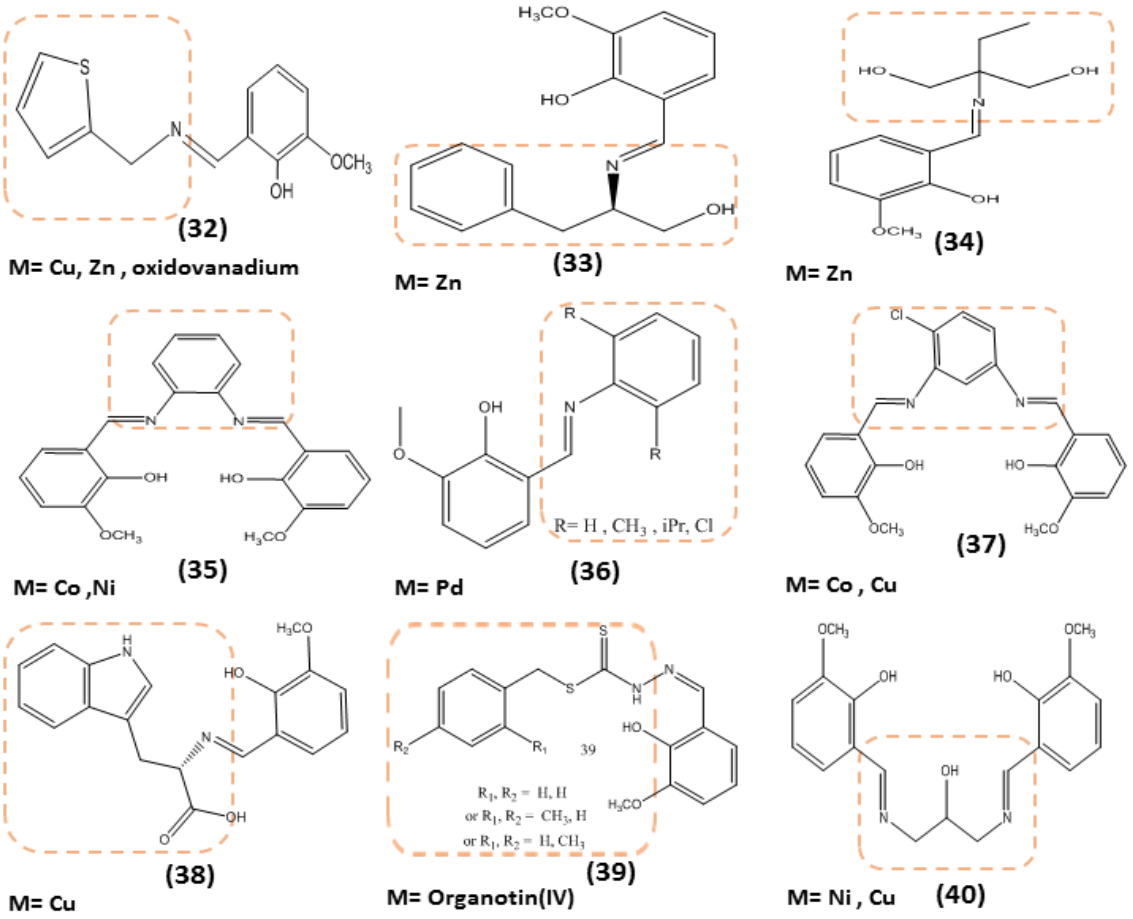


Figure 4. Cancer cell lines used for cytotoxicity evaluation by ortho-vanillin Schiff bases and its complexes

Zeinab Faghih *et al.* prepared a set of ortho-vanillin Schiff base with ortho-substituted Aniline **36** and its Pd (II) complexes, palladium complex of ortho-vanillin Schiff base with Aniline achieved highest cytotoxicity against MCF-7, A549, SKOV3 cell line compared with Cisplatin (MCF-7, IC_{50} (µM), 7.21 for palladium complex, 61.56 for Cisplatin) [47]. Copper complex of ortho-vanillin Schiff base with 4-chloro-m-phenylenediamine **37** in molar ratio 2:1 achieved very high cytotoxicity against HCT-116 cell line compared with 5FU (IC_{50} (µM), 4.2 for Copper complex, 4.6 for 5FU) [48]. Ortho-vanillin Schiff base with L-tryptophan **38** and its copper complexes in the present of pyridine and imidazole showed moderate activity against MCF-7 cell line [49]. Organotin (IV) complexes of a set of novel ortho-vanillin Schiff base with S-R-dithiocarbazate **39** have been synthesized by Enis Nadia *et al.*, free Schiff bases and its organotin complexes have been screened cytotoxicity for activity against thirteen cell line, many of complexes achieved very high cytotoxicity compared with Cisplatin [50]. Copper complex of ortho-vanillin Schiff base 1,3-diamino-2-propanol in molar ratio 2:1 **40** in the present of pyrazole showed moderate cytotoxicity against LNCaP, MCF-7 cell line [51].



DNA Studies and Molecular Docking

To study the effect of new drugs on DNA, researchers depend on several techniques such as DNA Cleavage Activity, DNA Binding Studies, and molecular docking, often this study are in place in addition to other antimicrobial or Cytotoxicity studies. the main purpose of the DNA studies is to find out the activity of drugs on different types of DNA such as pBR322 plasmid, DNA [24, 37], Calf-thymus DNA [25, 32, 39] , Salmon sperm DNA [38], EB–DNA adduct [45, 49], pET28a plasmid [47] , plasmid pUC19 DNA [49] , HS-DNA and bovine serum albumin BSA [51]. determination of DNA Cleavage Activity based on Agarose gel electrophoresis method [51], while DNA Binding Studies depend on UV-visible and Fluorescence Spectroscopy measurements and viscometery measurements [24]. Molecular docking is used to predict how closely the compounds will bond with the DNA of different proteins such as structure of E. coli (PDB ID: 1C14- chain A) [41], (PDB ID: 1BNA) [50]. Molecular docking is used by computer and software such as AutoDock Vina to study the potential for application of new compounds to a target protein.

Ortho-vanillin Schiff base with 2, 2-dimethyl-1, 3-propanediamine in molar ratio 2:1 **41** and its zinc complex have been synthesized and studied by docking of zinc complex with two type of protein (M. tuberculosis and B. megaterium) [52]. Anindita De *et al.* prepared an ortho-vanillin Schiff base with glycine **42** and their complexes of Mn (II), Fe (II), Co (III), Ni (II), Cu (II) and Zn (II), copper complex showed best binding affinity with Tyrosine Kinase (1t46) protein, while iron and copper complexes showed maximum

cleavage of DNA against E. Coli genome [53]. Ortho-vanillin Schiff base with L-valine **43** in the present of 1,10-phenanthroline and its oxovanadium have been synthesized and studied by interaction with two different type of DNA (CT-DNA, EB–DNA adduct) [54]. Xiao-Ju *et al.* study of DNA interaction of ortho-vanillin Schiff base with p-Toluidine **44** and its La (III) complex with EB-DNA [55]. Interaction of bovine serum albumin BSA with ortho-vanillin Schiff base with trimethoprim **45** have been studied by Xu Li *et al.* [56].

Antioxidant Activity of Ortho-Vanillin Schiff Bases

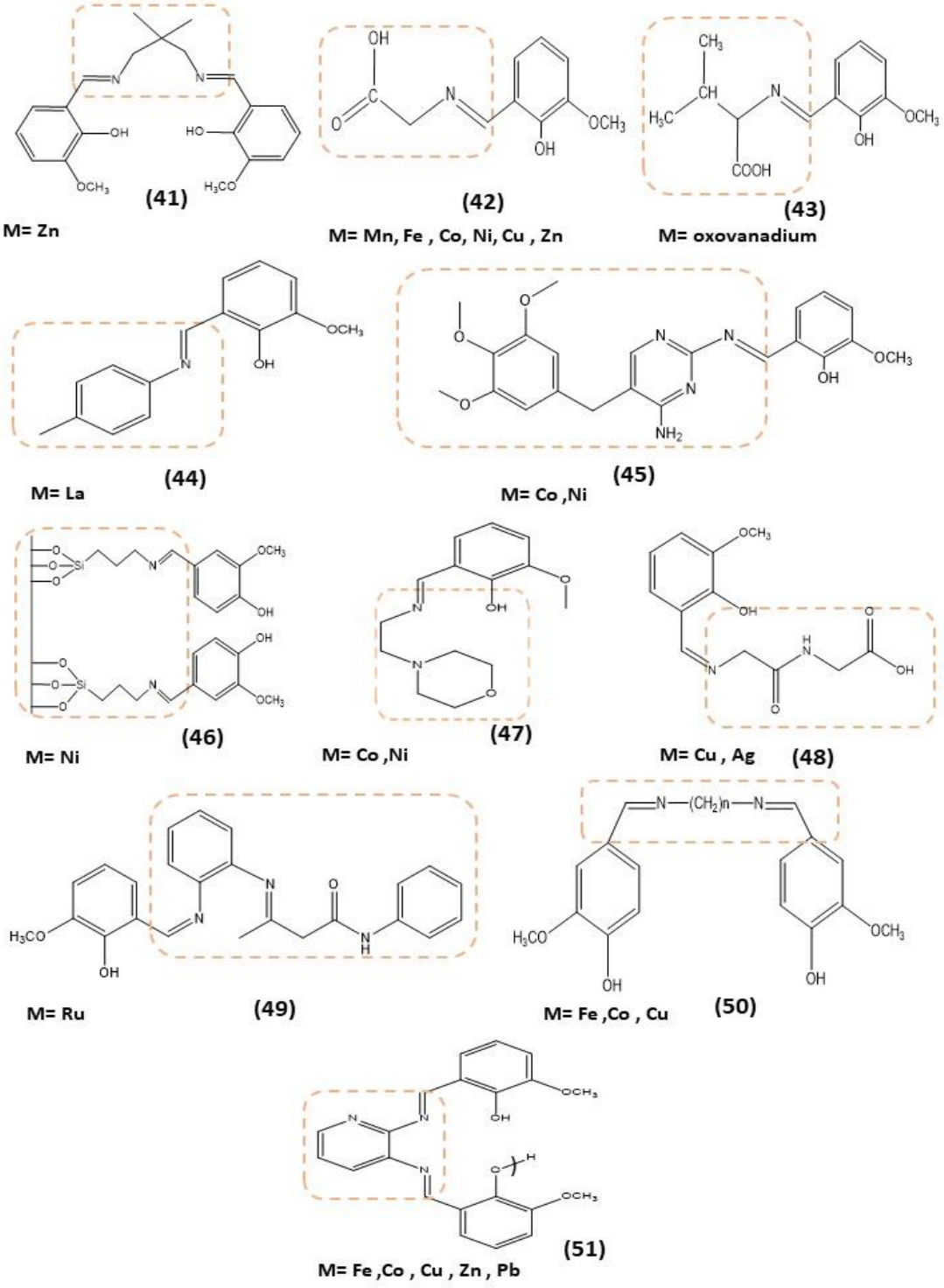
The discovery of a new compound capable of acting as an antioxidant is extremely important in many industries such as cosmetics and nutritional supplements, several methods of measurement are used to determine how well a drug works as an antioxidant such as free radical scavenging activity (DPPH) method [38, 57] , total antioxidant activity by thiocyanate method [58], total reduction capability by method of Oyaizu [59], measurement of reactive oxygen species (ROS) [50], hydroxy radical scavenging activity , superoxide dismutase (SOD) [41]. ortho-vanillin Schiff base and its complexes should be compared with standard compounds such as butylated hydroxy anisole (BHA) and ascorbic acid.

Ortho-vanillin Schiff bases with and 5-chloro-3-phenyl-1H-indole-2-carboxy-hydrazide **14** and their metal complexes of Co (II) and Cu (II) exhibited moderate scavenging activity compared with vitamin C [25]. Ortho-vanillin Schiff base **26** and its complexes have been studied by three methods, (DPPH) method , thiocyanate method , Oyaizu method , the result showed that ligand and all complexes were close to or higher than the butylated hydroxyanisole standard drug [37]. Ortho-vanillin Schiff base with picolinohydrazide **30** and its complexes have been studied by (DPPH) method and superoxide dismutase method, free ligand, and its Mn (II) complex showed the highest scavenging activity [41]. Reactive oxygen species (ROS) for two complexes of ortho-vanillin Schiff base **39** with organotin have been used to evaluate of antioxidant activity with hydrogen peroxide as positive control [50]. Hydroxy radical scavenging activity for ortho-vanillin Schiff base **35** and its zinc complex have been studied by Wen Wu *et al.* [60].

Miscellaneous Applications

In this part we discuss the catalytic activity, formation of polymer based on ortho-vanillin Schiff base, Sorption of metal ions from liquid effluents by using ortho-vanillin Schiff base with chitosan [61] , modification of Lignin by vanillin to formation Schiff base can act as self-healing adhesives with anti-fungal activity [62]. Mohsen Nikoorazm *et al*. prepared a novel low cost and safe catalyst by using complex of Ni (II) vanillin Schiff base with MCM-41 composite **46,** this catalyst can be easily removed from the solution with filtration and can be used again easily [63]. Nickel complex of ortho-vanillin Schiff base with 4-(2-aminoethyl) morpholine **47** have been studied as catalyst for epoxidation reaction of olefins [64]. Yang Zou *et al*. design a new organometallic polymer using copper and silver complexes of ortho-vanillin Schiff base with glycylglycine **48** [65]. Padma Priya *et al*. prepared a novel ruthenium (III) complexes of ortho-vanillin Schiff base with o-phenylenediamine in the present of acetoacetanilide **49** and study its catalytic activity toward oxidation of alcohols and aryl – aryl coupling reactions [66]. Sashikala1 and Syed prepared and characterized a polymer of chitosan with ortho-vanillin [67]. divanillin Schiff base polymer **50** and its complexes of Cu (II), Fe (II), and Co (II) have been synthesized and studied by Ananda and Ashfaqur [68]. ismet Kaya

synthesized and studied organometallic polymer using ortho-vanillin Schiff base with 51 2, 3-diaminopyridine and its transition metal complexes [69].



Conclusion

Ortho vanillin Schiff bases and their derivatives can be a great chelating ligand when they condensed with amines in 1:1 and 2:1 molar ratio to produce multidentate Schiff base ligands suitable to generate complexes with several metal ions. We expect that salicylaldehyde will be

replaced with ortho-vanillin in the recent research due to the scarcity of research on ortho vanillin compared to salicylaldehyde. Ortho-vanillin Schiff base ligands and their complexes showed many applications as anti-bacterial activity, antifungal activity, anticancer and Cytotoxicity activity, DNA infarction and cleavage, molecular docking. Also, we can use it as an antioxidant, catalytic active material, the formation of novel polymer and removing of metals from water, as well as many other potential applications.

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Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Ali M. Hassan : 0000-0001-9509-9266
Ahmed O. Said : 0000-0002-2473-9315

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