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Transition Metal Complexes of 4-Aminoantipyrine Derivatives and Their Antimicrobial Applications

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Abstract—Transition metal complexes of 4-aminoantipyrine derivatives have been gaining great interest due to their rich coordination chemistry and potential applications in the field of pharmaceutical science. The presence of a free amine and a cyclic ketone functionality makes 4-aminoantipyrine an attractive amphoteric substrate for Schiff base formation. Varieties of aldehydes/ketones or amines of versatile steric, electronic and functional nature could be condensed with the 4-aminoantipyrine motif to obtain the ligand systems of multidenticity and diverse coordination behaviour. The transition metal complexes obtained from these ligand systems exhibit unique structural and functional properties. This review compiles the important transition metal complexes developed from the Schiff base derivatives of 4-aminoantipyrine, and their utility as antibacterial and antifungal agents. Rationale of the strategies involved in the development of highly potential antimicrobial agents is discussed.

Keywords: 4-aminoantipyrine, Schiff base, transition metal complexes, coordination chemistry, antibacterial activity, antifungal activity

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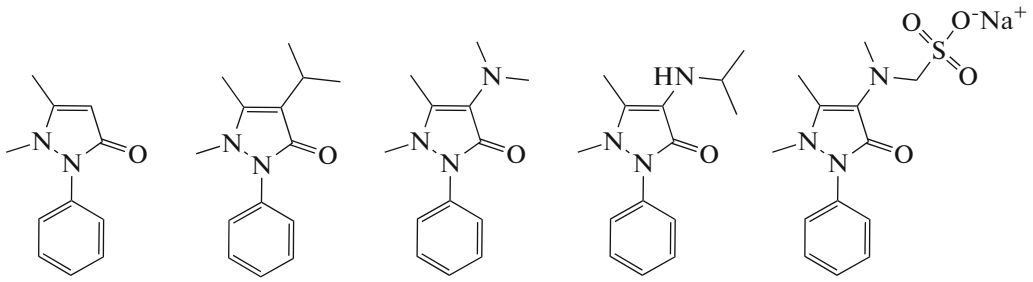
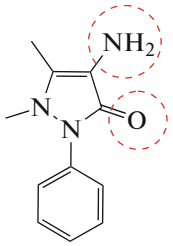
INTRODUCTION

Antipyrine (1,5-dimethyl-2-phenylpyrazole-3-one) L^1 is a compound that contains a pyrazolone moiety, a five membered heterocyclic ring containing two adjacent nitrogen and a ketone group in the same molecule. The term antipyrine was first given by Ludwig Knorr in the late 18th century, which was the first synthetic analgesic medicine and most widely used drug until the synthesis of aspirin in the early 20th century [1, 2]. Many of the antipyrine based compounds have been developed by the strategic derivatization, viz. isopropyl antipyrine L^2, aminopyrine L^3, Ramifenazone L^4 and Dipyrone L^5 etc. and are extensively being used as anti-inflammatory and analgesic drugs worldwide [3, 4].



L^1 L^2 L^3 L^4 L^5

4-Aminoantipyrine (Ampyrone) is an antipyrine derivative with an amino group in its C-4 position, which possess large range of biological activities [5]. Exploiting the reactive nature of amino group, various derivatives of this system have been developed, especially by reacting with aldehyde/keto compounds to form Schiff bases or by condensing with acyl or alkyl halides. On the other hand, reactivity of the cyclic ketonic group have also been utilized to couple with various amine derivatives to obtain the compounds of interesting ligational behaviour. Further these derivatives have been used as ligands to develop versatile transition metal complexes possessing potential biological applications, such as, anti-inflammatory [6], anticonvulsant [7], cytotoxic [8], superoxide dismutase (SOD) [9], antidiabetic [10] activities, etc.

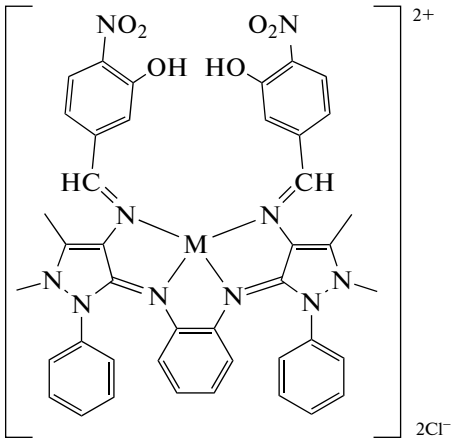


L^6

In recent years, there is a burgeoning growth in the development of various transition metal complexes using the ligands derived from 4-aminoantipyrine, especially due to their potential antimicrobial applications. This review compiles the important transition metal complexes derived from 4-aminoantipyrine that are exploited for their antimicrobial efficacies. Furter the details of the synthetic strategies used for the development of the complexes, coordination chemistry and insights of the structure activity relationships established are also provided. Considering the growing interest and need of development of highly potential antimicrobial agents, especially, in this post-pandemic (COVID 19) period, where the antimicrobial infections (considered as secondary infections) caused severe clinical problems and casualties [11–15], we believe that this review will be useful to understand the progress of 4-aminoantipyrine based metallo-antimicrobial agents and hence can promote further developments.

TRANSITION METAL COMPLEXES OF 4-AMINOANTIPYRINE DERIVATIVES AS ANTIMICROBIAL AGENTS

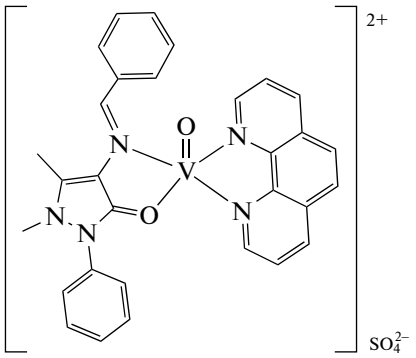
In the literature, we found that, transition metal complexes obtained from the Schiff base derivative of 4-aminoantipyrine motif developed by Raman et al. [16] were the first set of compounds investigated for antimicrobial activity. In this work, the Schiff base derivative was synthesized by reacting 4-aminoantipyrine with 3-hydroxy-4-nitrobenzaldehyde and *o*-phenylenediamine in a 2 : 2 : 1 stoichiometric ratio. This ligand was reacted with various transition metal precursors to obtain a series of eight complexes **1**–**8**, which were fully characterized using various spectral and analytical tools. All the complexes were found to have square–planar geometry except the vanadyl(II) complex **1**, which exhibited a square-pyramidal geometry. All the compounds were investigated for their antimicrobial activity against bacteria (*S. typhi*, *S. aureus*, *E. coli* and *B. subtilis* as well as fungi, *A. niger*, *A. flavus* and *R. bataicola*). All the compounds exhibited better activity against bacterial strains over fungi, and the metal complexes were found to be more active as compared to the ligand, with the copper(II) complex **5** as a lead compound. Although no detailed studies were carried out to understand the mode of action, the chelation effect is expected to help in the penetration of the complexes into lipid membranes of the microorganisms and disturb the respiration process by blocking the metal binding sites of key enzymes. Among all the complexes, the cobalt(II) complex **3**, nickel(II) complex **4** and copper(II) complex **5**, exhibited remarkable DNA cleavage activity (Calf Thymus DNA, CT-DNA) in the presence of hydrogen peroxide, which was attributed to their profound redox properties.



1 M = VO(II)
2 M = Mn(II)
3 M = Co(II)
4 M = Ni(II)
5 M = Cu(II)
6 M = Zn(II)
7 M = Cd(II)
8 M = Hg(II)

Raman group [17] further developed a series of three mixed ligand vanadyl(II) complexes **9**–**11** using three different 4-aminoantipyrine derivatives formed by reacting 4-aminoantipyrine with benzaldehyde, cinnamaldehyde and 2-chlorobenzaldehyde respectively, along with 1,10-phenonthroline co-ligand. All the compounds were thoroughly characterized and examined for their DNA cleaving ability and antimicrobial activity against *B. subtilis, S. aureus, E. coli, P. putita* and *P. chrysosporium, R. stolinifer*. All the three complexes were found to have a square pyramidal geometry with two nitrogen donors of the 4-aminoantipyrine derivatives and two nitrogen donors of phenanthroline ring making the base and the oxygen

ligand sitting on the tip. All the complexes exhibited higher antibacterial and antifungal activity compared to the organic ligand and standard used (penicillin). Among the three redox active complexes **9** was found to exhibit higher order of oxidative DNA (CT-DNA) cleavage activity than its other two counterparts.



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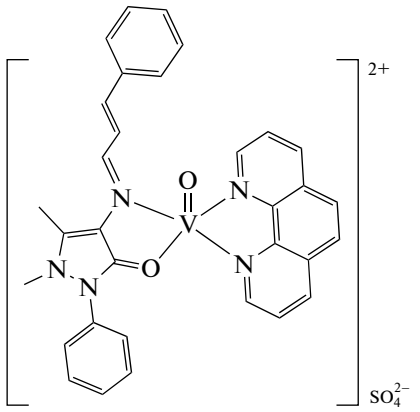

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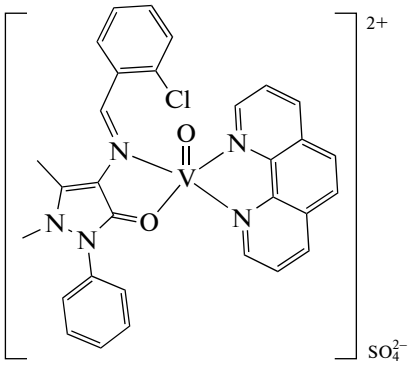
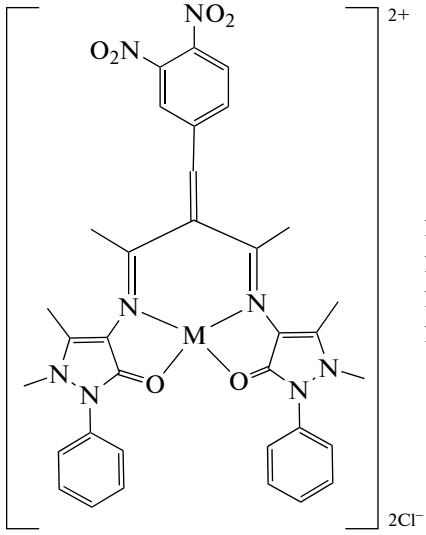


11

Raman group [18] developed another ligand system using acetyl acetone and 3-hydroxy-4-nitrobenzaldehyde with 4-aminoantipyrine via Knoevenagel condensation followed by Schiff base formation. A series of four complexes **12**–**15** was developed by reacting the ligand with the corresponding metal precursors and characterized thoroughly. All the complexes were found to have square planar structure except the vanadyl(II) complex **12**, which attained a square pyramidal structure. All the complexes exhibited better antifungal (against *A. niger, A. flavus* and *R. bataicola*) and antibacterial (against *S. typhi, P. aeruginosa, E. coli* and *B. subtilis*) activity than the organic ligand with the copper(II) complex **14** being the best. However, the activity of these complexes was found to be lower as compared to the standard, Streptomycin. Only the copper(II) complex **14** was found to facilitate oxidative cleavage in CT-DNA.



12 M = VO(IV)
13 M = Ni(II)
14 M = Cu(II)
15 M = Zn(II)

Chandra et al. [19] synthesized a chelating ligand system by treating 4-aminoantipyrine with 3,3'-

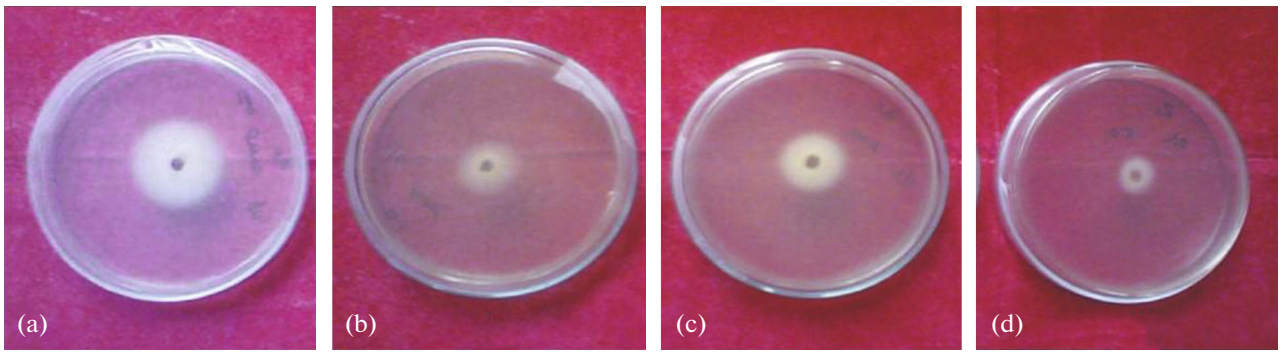
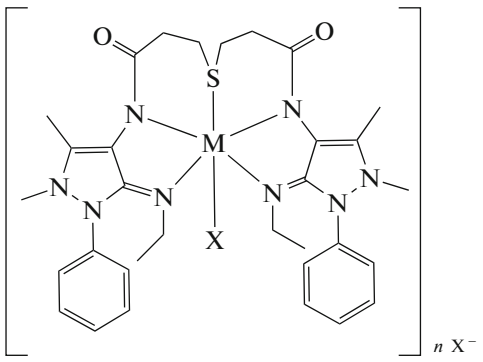


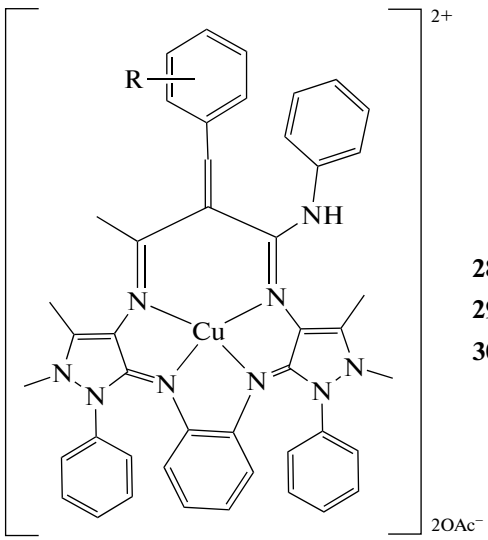
Fig. 1. Antifungal activity of the complexes against *F. oxysporum*: (a) ligand, (b) complex **21**, (c) complex **16**, (d) complex **25** (adapted from [19]).

thiodipropionicacid and ethylamine in a stepwise manner with 2 : 1 : 2 stochiometric ratio. They reacted this ligand with various cobalt(II), nickel(II) and copper(II) precursors to obtain a series of twelve complexes **16**–**27**. All the compounds were thoroughly characterized by various spectro-analytical techniques and found to have octahedral geometry. All the complexes exhibited greater inhibitory activity against the fungi (*A. brassicae*, *A. niger* and *F. oxysporum*) and the bacteria (*X. compestris* and *P. aeruginosa*) compared to the organic ligand, with the copper(II) complex **25** being the best among all (Fig. 1).



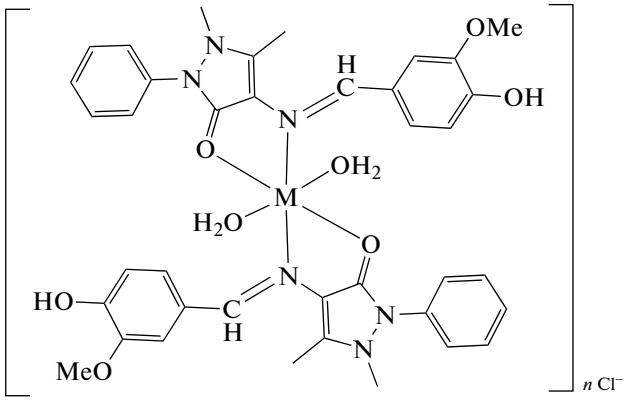
16 M = Co(II); X = Cl^-; $n = 1$
17 M = Co(II); X = NO_3^-; $n = 1$
18 M = Co(II); X = OAc^-; $n = 1$
19 M = Co(II); X = SO_4^{2-}; $n = 0$
20 M = Ni(II); X = Cl^-; $n = 1$
21 M = Ni(II); X = NO_3^-; $n = 1$
22 M = Ni(II); X = OAc^-; $n = 1$
23 M = Co(II); X = SO_4^{2-}; $n = 0$
24 M = Cu(II); X = Cl^-; $n = 1$
25 M = Cu(II); X = NO_3^-; $n = 1$
26 M = Cu(II); X = OAc^-; $n = 1$
27 M = Cu(II); X = SO_4^{2-}; $n = 0$

Gopalakrishnan et al. [20] synthesized a series of Schiff base ligands by treating 4-aminoantipyrine with a β-ketoanilide motifs obtained from the reaction of acetoacetanilide with *p*-hydroxybenzaldehyde, benzaldehyde and *p*-nitrobenzaldehyde respectively. The Schiff base ligands were treated with *o*-phenylene diamine to obtain three novel macrocyclic ligands, which were then reacted with copper acetate to produce the complexes **28**–**30**. The copper complexes exhibited superior inhibitory activity against bacterial species (*S. aureus, E. coli, K. pneumoniae, P. vulgaris,* and *P. aeruginosa*) and fungal species (*A. niger, R. stolonifer, A. flavus, R. bataicola* and *C. albicans*) over the organic ligands. Interestingly, the substituent on the aromatic ring was found to have a key effect on the antimicrobial activity of the complexes and the order of activity was found to be NO_2 (**30**) > H (**28**) > OH (**29**).



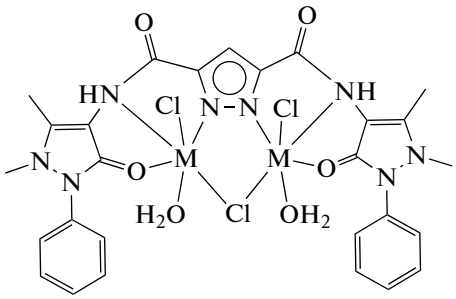
28 R = H
29 R = OH
30 R = NO_2

Suresh et al. [21] synthesized a novel ligand system by treating 4-aminoantipyrine and vanillin. This ligand was utilized in the preparation of metal complexes by treating with suitable metal precursor in a 2 : 1 stochiometric ratio. All the seven complexes **31**–**37** were characterized by spectral and analytical methods and were found to have octahedral geometry with two coordinated water molecules. All the complexes were tested for their antibacterial efficacy against *S. aureus* and *E. coli*, the zinc(II) complex **36** and cadmium(II) complex **37** were found to have better antibacterial activity as compared to the other complexes and organic ligand.



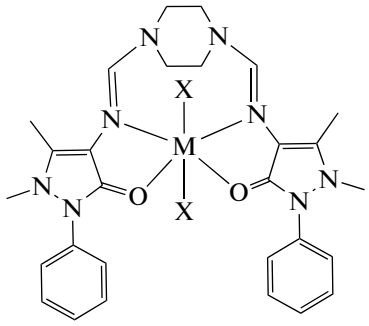
31 M = Cr(III); $n = 3$
32 M = Mn(II); $n = 2$
33 M = Co(II); $n = 2$
34 M = Ni(II); $n = 2$
35 M = Cu(II); $n = 2$
36 M = Zn(II); $n = 2$
37 M = Cd(II); $n = 2$

Budagumpi et al. [22] developed a novel ligand system by treating 4-aminoantipyrine with 3,5-dichloroformyl-1H-pyrazole. The ligand was reacted with late *3d*-transition metal chlorides in 1 : 2 stoichiometric ratio to obtain pyrazole and chloro bridged binuclear octahedral complexes **38**–**41**. All the compounds were duly characterized by analytical and spectroscopic methods. The ligand and complexes were tested for their DNA binding and cleaving ability. All the compounds were found to bind to the *E. coli* DNA through intercalative mode with the zinc(II) complex **41** exhibiting higher binding affinity. However, the cobalt(II) complex **38** and nickel(II) complex **39** were found to have the ability to cleave DNA strand. Due to their efficient nuclease activity these metal complexes were anticipated to be excellent inhibitors against bacteria, however direct antibacterial analyses are not reported in this study.



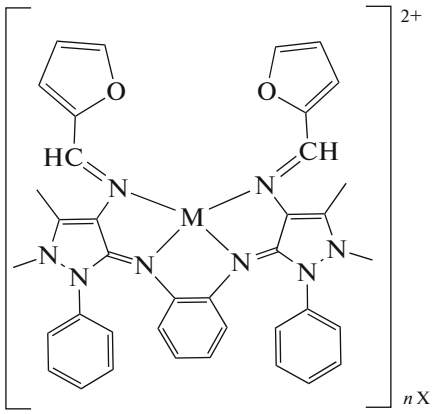
38 M = Co(II)
39 M = Ni(II)
40 M = Cu(II)
41 M = Zn(II)

Sharma et al. [23] developed a novel ligand system by reacting 4-aminoantipyrine with 1,4-diformylpiperazine in the presence of an acid. The ligand was treated with late 3*d*-transition metal salts to prepare six metal complexes **42**–**47**. The cobalt(II) complexes **42** and **43** and copper(II) complexes **46** and **47** were found to have tetragonal geometry, while the nickel(II) complexes **44** and **45** were found to have an octahedral structure. The biochemical study of the complexes against fungi *A. brassicae, A. niger* and *F. oxysporum* showed that the complexes have considerable fungicidal activity and their antipathogenic ability rises with concentration. The copper(II) complexes **46** and **47** were found to have highest fungicidal activity among the compounds tested.



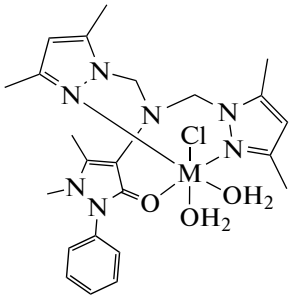
42 M = Co(II); X = Cl^-
43 M = Co(II); X = NO_3^-
44 M = Ni(II); X = Cl^-
45 M = Ni(II); X = NO_3^-
46 M = Cu(II); X = Cl^-
47 M = Cu(II); X = NO_3^-

Prakash et al. [24] developed a new ligand system by reacting 4-aminoantipyrene with furfural and *o*-phenylenediamine in a stepwise manner with 2 : 2 : 1 stochiometric ratio. This ligand was treated with transition metal chlorides and sulphates to obtain as series of ten monometallic complexes **48**–**57**. By the through structural analysis, square planar geometry of all the complexes was confirmed. All the compounds were investigated for their antibacterial efficacy against *S. aureus, E. coli, B. subtilis* and *P. aeruginosa*. The zinc(II) complexes **56** and **57** were found to exhibit higher antibacterial activity than the other complexes and ligand.



48 M = Mn(II); X = Cl^-; $n = 2$
49 M = Mn(II); X = SO_4^{2-}; $n = 1$
50 M = Co(II); X = Cl^-; $n = 2$
51 M = Co(II); X = SO_4^{2-}; $n = 1$
52 M = Ni(II); X = Cl^-; $n = 2$
53 M = Ni(II); X = SO_4^{2-}; $n = 1$
54 M = Cu(II); X = Cl^-; $n = 2$
55 M = Cu(II); X = SO_4^{2-}; $n = 1$
56 M = Zn(II); X = Cl^-; $n = 2$
57 M = Zn(II); X = SO_4^{2-}; $n = 1$

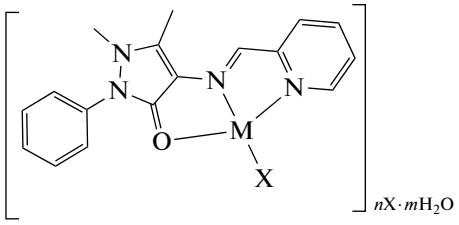
Kalanithi et al. [25] synthesized a scorpionate ligand system by reacting 4-aminoantipyrine with 3,5-dimethyl-1-(hydroxymethyl)-pyrazole. The ligand was treated with metal salts to synthesize the metal complexes **58**–**60**. The octahedral complexes were duly characterized and their antimicrobial activities were investigated against the bacteria *X. maltophilia, C. violaceum, Acientobacter, Staphylococci* and *Streptococci* as well as the fungus *C. albicans*. The ligand and three complexes exhibited good antimicrobial activity with the cobalt(II) complex **58** being the best. All the three metal complexes were found to have the ability to cleave DNA in the presence of hydrogen peroxide.



58 M = Co(II)
59 M = Ni(II)
60 M = Cu(II)

Mishra et al. [26] developed a 4-aminoantipyrine derivative by treating 2-pyridine carboxaldehyde with 4-aminoantipyrine. Four complexes **61**–**64**, were prepared by reacting the ligand with metal chloride/sul-

phate and were studied for antimicrobial activities against the microorganisms *E. coli, S. aureus, S. fecalis, A. niger, T. polysporum, C. albicans,* and *A. flavus*. Streptomycin, Nystatin and Miconazole were used as standards. The study indicated that the complexes can act as both bactericide and fungicide.



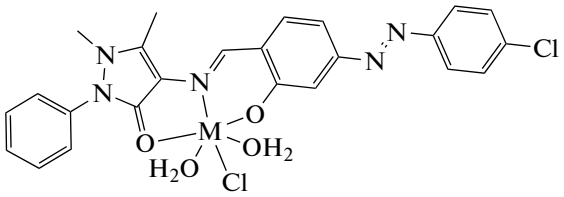
61 M = VO(II); X = SO_4^{2-}; $n = 0$; $m = 3$

62 M = Co(II); X = Cl^-; $n = 1$; $m = 1$

63 M = Ni(II); X = Cl^-; $n = 1$; $m = 3$

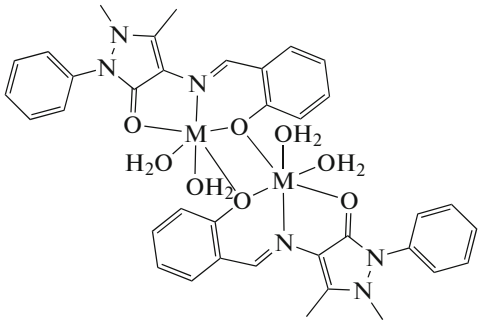
64 M = Cu(II); X = Cl^-; $n = 1$; $m = 1$

Anitha et al. [27] synthesized a 4-aminoantipyrine derivative by refluxing 5-((4-chlorophenyl)diazenyl)-2-hydroxybenzaldehyde with 4-aminoantipyrine. A series of five complexes **65**–**69** was prepared using this ligand and all the compounds were duly characterized using spectral, analytical and microscopic techniques. All the complexes were found to have octahedral geometry with three coordination places occupied by ONO donors of the monoionic tridentate ligand and other three vertices by two water molecules and a chloride ligand. All the complexes exhibited higher inhibitory activity against the bacteria (*S. aureus, S. typhi, E. coli, B. subtilis, S. sonnie*) and fungi (*C. albicans, A. niger* and *R. bataicola*) as compared to the ligand. Among all the compounds, only the cobalt(II) complex, **66** and copper(II) complex **68** were found to efficiently cleave the CT-DNA under oxidative conditions (Fig. 2).

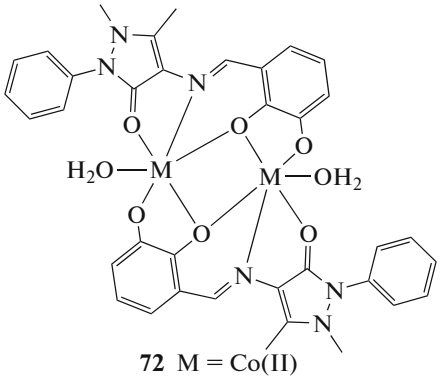


65 M = VO(II)
66 M = Co(II)
67 M = Ni(II)
68 M = Cu(II)
69 M = Zn(II)

Al-Obaidi et al. [28] developed two Schiff base derivatives of 4-aminoantipyrine treated them with hydrated cobalt(II) chloride and copper(II) chloride to produce binuclear metal complexes **70**–**73**. Both the metal centers in the complex were found to acquire octahedral geometry with one ligand coordinating in tridentate ONO fashion and the other ligand in monodentate (**70**–**71**) or bidentate (**72**–**73**) fashion. Rest of the coordination positions were occupied by water molecules. The bridging hydroxy groups were expected to instigate spin exchange between the two metal centers and provide unique properties to the complexes. The complexes and ligands were tested for their antibacterial efficacy against *S. aureus* and *E. coli*. The study revealed that the complexes have excellent antibacterial activity with the copper(II) complex **71** exhibiting highest activity.



70 M = Co(II)
71 M = Cu(II)



72 M = Co(II)
73 M = Cu(II)

Tyagi et al. [29] derived a ligand system by reacting 4-aminoantipyrine with dibenzoyl methane and ethylenediamine in 2 : 1 : 1 stoichiometric ratio. The ligand was then treated with first row transition metal

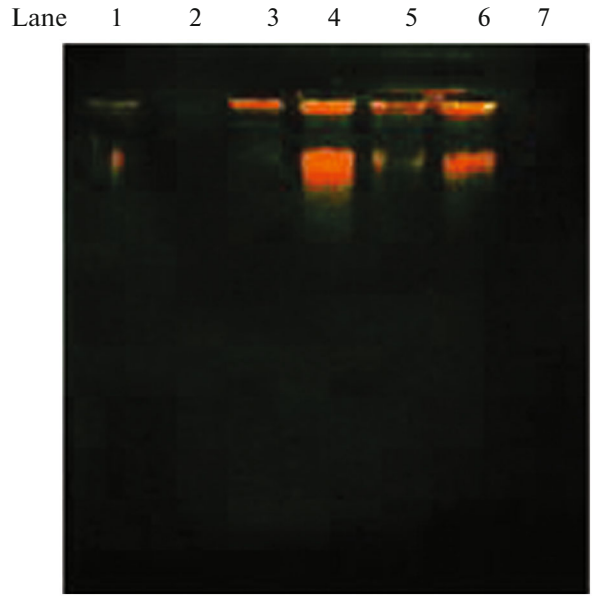
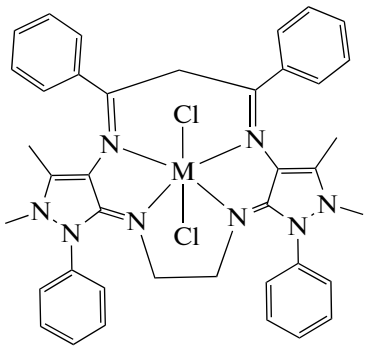
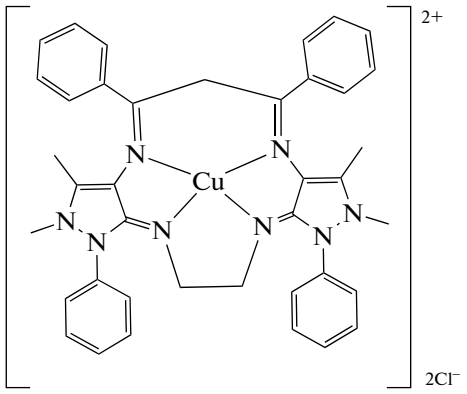


Fig. 2. CT-DNA cleavage study: Gel electrophoresis experiment; Lane 1: CT-DNA alone, Lane 2: CT-DNA + Ligand, Lane 3: CT-DNA + complex **65**, Lane 4: CT-DNA + complex **66**, Lane 5: CT-DNA + complex **67**, Lane 6: CT-DNA + complex **68**, Lane 7: CT-DNA + complex **69** (adapted from [27]). .

chlorides to produce a series of three metal complexes **74**–**76**. All the complexes were characterized by spectro-analytical techniques. The copper(II) complex **76** was found to have a tetragonal geometry whereas the cobalt(II) complex **73** and nickel(II) complex **75** have octahedral geometry. The antimicrobial study of the ligand and complexes against *M. phaseolina* and *F. solani* revealed that the complexes have better antifungal activity than the free ligand and among the complexes copper(II) complex **76** has greater radical growth inhibition activity against the fungal strains.



74 M = Co(II)
75 M = Ni(II)



76

Kumaran et al. [30] prepared a Schiff base ligand by reacting 4-aminoantipyrine with vanillin and 2-aminophenol in 1 : 1 : 1 stochiometric ratio. A series of four transition metal complexes **77**–**80** was prepared using this derivative and all the compounds were thoroughly characterized. All the complexes were found to have an octahedral geometry with the two mono-ionic ligand molecules binding in NNO tridentate fashion. Antimicrobial efficacy of the compounds was investigated against bacteria (*S. aureus, B. subtilis,* and *P. vulgaris*) and fungi (*C. albicans*) and compared with the standard antibacterial (tetracycline) and antifungal (amphotericin) drugs. All the complexes exhibited moderate antimicrobial activity, which was found to be dose dependent. The zinc(II) complex **80** showed relatively better antimicrobial effi-

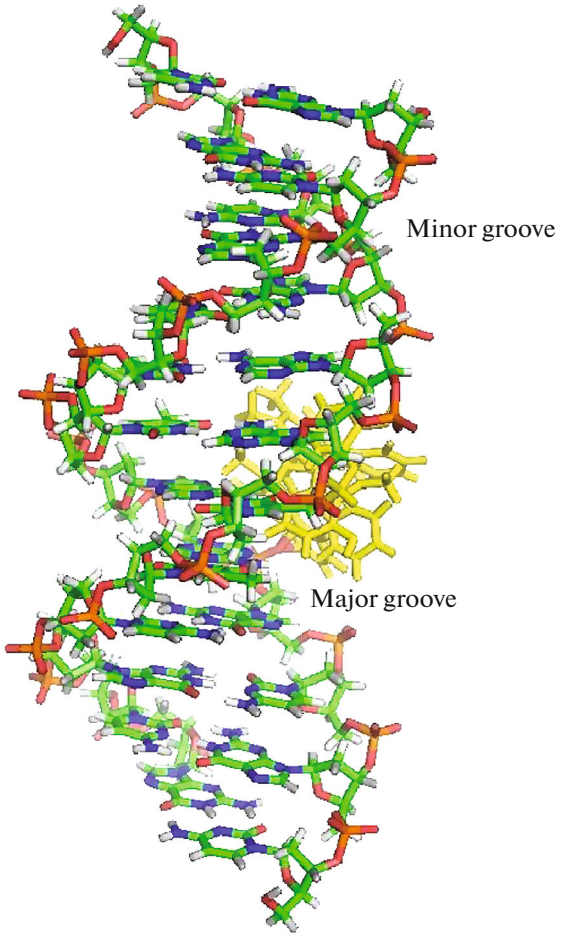


Fig. 3. *In silico* molecular docking studies showing binding of copper complex **79** to the major groove of CT-DNA (adapted from [30]).

cacy than the other compounds. *In silico* molecular docking studies indicated that all the complexes can efficiently interact with CT-DNA and would bind to the major groove of the CT-DNA, with the copper(II) complex **79** exhibiting stable and stronger interactions compared to others (Fig. 3).

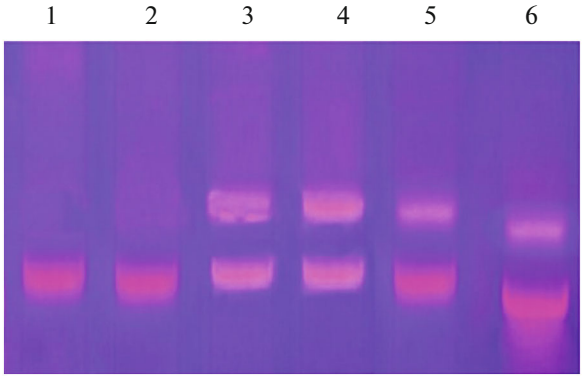
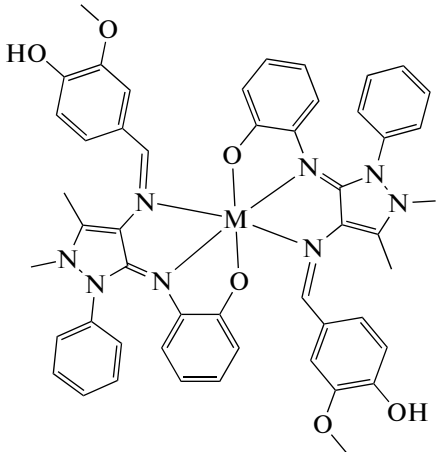
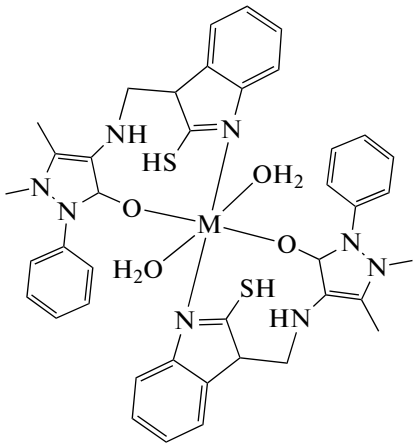


Fig. 4. Gel electrophorsis pattern of CT-DNA with cleavege induced by the compounds and H_2O_2. Lane 1: CT-DNA alone, Lane 2: CT-DNA + H_2O_2, Lane 3: CT-DNA + H_2O_2 + complex **83**, Lane 4: CT-DNA + H_2O_2 + complex **81**, Lane 5: CT-DNA + H_2O_2 + complex **82**, Lane 6: CT-DNA + H_2O_2 + complex **84** (adapted from [31]).

Bhava et al. [31] prepared a series of first row transition metal complexes **81**–**84** using derivative of 4-amioatipyrine produced by refluxing 4-amioantipyrine with 2-mercaptobenimdazole and formaldehyde in 1 : 1 : 1 stochiometric ratio. All the complexes were fully characterized by spectro-analytical methods and found to exhibit distorted octahedral structures with two ligand molecules binding in ON bidentate mode. Interestingly the mercapto and amine functionalities were found not to participate in the coordination. The fifth and sixth coordination positions were occupied by water molecules. All the compounds were investigated for their antibacterial activity against *Streptococci*, *S. aureus*, *Pseudomonas, K. pneumoniae, C. bacterium* and the antifungal activity against *C. albicans*. These studies showed that the complexes have higher antibacterial activity than the free ligand and can strongly interact with CT-DNA in an intercalation mode. All the complexes were found to cleave the CT-DNA by producing hydroxyl free radicals in presence of H_2O_2 (Fig. 4).

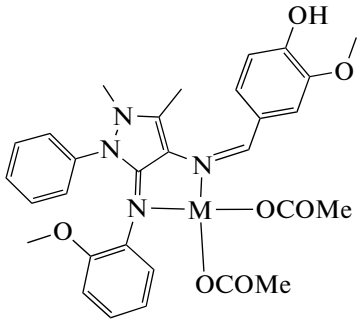


77 M = Co(II)
78 M = Ni(II)
79 M = Cu(II)
80 M = Zn(II)



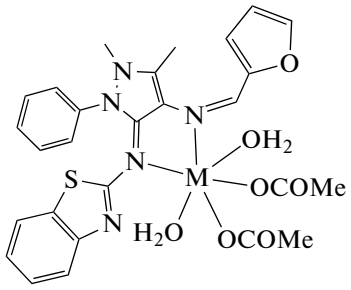
81 M = Co(II)
82 M = Ni(II)
83 M = Cu(II)
84 M = Zn(II)

Manjula et al. [32] developed a series of metal complexes derived from a Schiff base derivative of 4-aminoantipyrine. The bidentate ligand was prepared by reacting 4-aminoantipyrine with vanillin and o-anisidine. The ligand was refluxed with the transition metal acetates to form the complexes **85**–**88**. The ligand was found to bind to the metal ions in a bidentate mode forming the copper(II) complex **87** was found to have a square planar geometry, while all the other complexes were found to be tetrahedral in structure. All the compounds were found to act as excellent antimicrobial agents against bacteria (*P. aeruginosa, P. mirabilis, E. coli*) and fungi (*A. niger, A. fumigatus, C. albicans*) with the nickel(II) complex **86** exhibiting the greater toxicity towards the microbes.



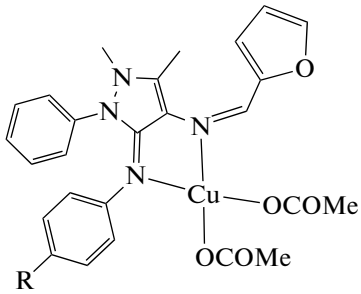
85 M = Co(II)
86 M = Ni(II)
87 M = Cu(II)
88 M = Zn(II)

Leelavathy et al. [33] synthesized a series of four transition metal complexes **89**–**92** using a 4-aminoantipyrine derivative. The ligand was prepared by treating 4-aminoantipyrine with furfuraldehyde and 2-aminobenzothiazole in 1 : 1 : 1 stoichiometric ratio. This novel ligand was reacted with 3*d*-transition metal acetates to obtain the complexes. All the complexes were thoroughly characterized and found to have a distorted octahedral geometry. Antimicrobial studies against bacterial species (*S. aureus, E. coli, K. pneumoniae, P. vulgaris, P. aeruginosa*) and fungal species (*A. niger, R. stolonifer, A. flavus, R. bataicola, C. albicans*) revealed all the compounds exhibit antibacterial and antifungal activities. The metal complexes showed better inhibitory action than the organic ligand, with the zinc(II) complex **92**, exhibiting highest activity. The complexes were also tested for superoxide dismutase (SOD) activity and DNA binding ability. The copper(II) complex **91** exhibited greater SOD activity compared to all the other compounds and showed remarkable DNA intercalating ability.



89 M = Co(II)
90 M = Ni(II)
91 M = Cu(II)
92 M = Zn(II)

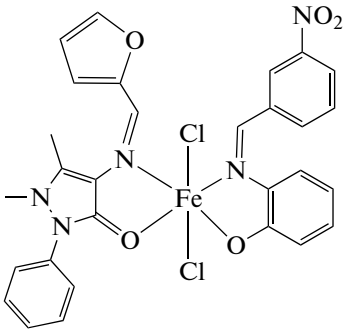
Joseph et al. [34] developed a series of copper complexes **93**–**95** using a set of new ligand systems derived from 4-aminoantipyrine. Three novel ligands were prepared by reacting 4-aminoantipyrine with furfuraldehyde and aniline, *p*-nitroaniline or *p*-hydroxy aniline, respectively, in equal stochiometric ratio. The ligands treated with copper(II) acetate under ambient conditions to obtain the complexes. All the three complexes were completely characterized and found to have square planar geometry. All the three ligands and their corresponding complexes were investigated for their antimicrobial efficacy against the bacterial species (*S. aureus, E. coli, K. pneumoniae, P. vulgaris, P. aeruginosa*) and fungal species (*A. niger, R. stolonifer, A. flavus, R. bataicola, C. albicans*) using well diffusion method. All the copper(II) complexes **93**–**95** exhibited higher bactericidal and fungicidal activity than the parent ligands as well as copper(II) acetate. These complexes were also found to exhibit excellent SOD mimetic abilities.



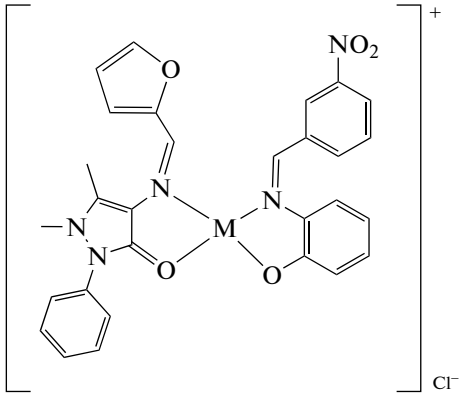
93 R = H
94 R = NO_2
95 R = OH

Using one of the above ligand systems and a Schiff base ligand prepared by condensing 3-nitrobenzaldehyde with 2-aminophenol, the same group synthesized a series of five mixed ligand complexes **96**–**100** and evaluated their biochemical activities [35]. All the synthesized complexes except the iron(III) complex were found to have square planar geometry, while the iron(III) complex **96** was found to have an octahedral structure. The biological studies of the complexes and the ligands revealed a prominent antifungal (against *A. niger, R. stolonifera, A. flavus, R. bataicola* and *C. albicans*) and antibacterial (against *E. coli, K. pneu-*

monia, S. typhi, P. aeruginosa and *S. aureus*) activity of the compounds. The complexes exhibited higher antimicrobial activity than the ligands. The copper(II) complex **99** was found to strongly interact with the CT-DNA via intercalative mode and exhibited superior SOD activity over other complexes.

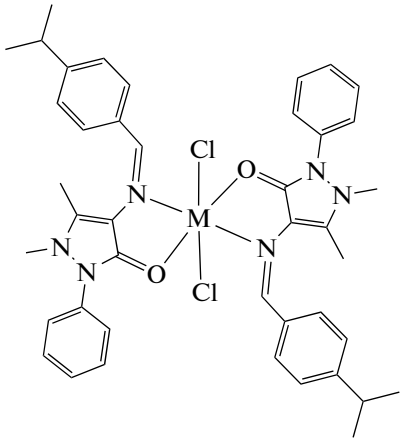


96



97 M = Co(II)
98 M = Ni(II)
99 M = Cu(II)
100 M = Zn(II)

Bennie et al. [36] prepared a series of transition metal complexes **101**–**104** using a Schiff base ligand prepared by treating cuminaldehyde with 4-aminoantipyrine. The ligand was reacted with late transition metal chlorides to obtain the complexes in pure form. All the complexes were found to have octahedral geometry with two ligands to one metal ion, stochiometric ratio. The ligand and the complexes were tested for their biological activities against *S. aures, E. coli, K. pneumonia, P. vulgaris, C. albicans,* and *A. nigers*. Meatal complexes exhibited better antifungal and antibacterial activity compared to the free ligand, with the copper(II) complex **103** showing the highest activity.



101 M = Co(II)
102 M = Ni(II)
103 M = Cu(II)
104 M = Zn(II)

Dhanaraj et al. [37] prepared a series of four complexes **105**–**108** by treating 3*d*-transition metal acetates with a 4-aminoantipyrine derivative synthesized by refluxing quinoxaline-2,3-(1,4 H)-dione with 4-aminoantipyrine. Among the complexes, cobalt(II) complex **105** was found to have tetrahedral geometry, copper(II) complex **108** was found to have square planar geometry, while the nickel(II) complex **106** and zinc(II) complex **107** were found to have octahedral structures. The study of biological activity of ligand and complexes against bacteria (*S. aureus, E. coli* and *P. aeruginosa* and fungi *C. albicans, A. flavus* and *A. niger*) showed that the complexes synthesized have better antimicrobial activity than the ligand and among all the complexes, the copper(II) complex **108** exhibited highest activity. Except the free ligand and the zinc(II) complex **107**, other complexes showed remarkable nuclease activity with CT-DNA (Fig. 5).

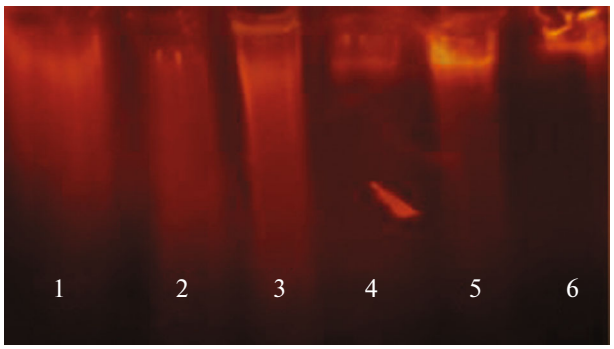


Fig. 5. Electrophoretic pattern of CT-DNA induced by H_2O_2 and compounds: (1) DNA alone, (2) DNA + Ligand + H_2O_2, (3) DNA + complex **105** + H_2O_2, (4) DNA + complex **106** + H_2O_2, (5) DNA + complex **108** + H_2O_2 and (6) DNA + complex **107** + H_2O_2 (adapted from [37]).

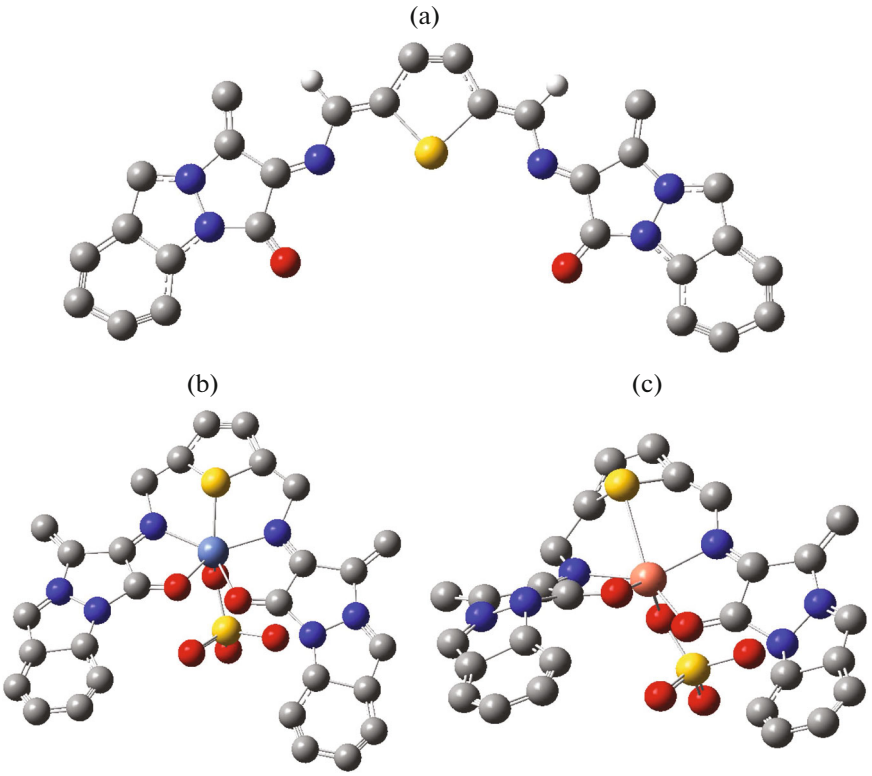
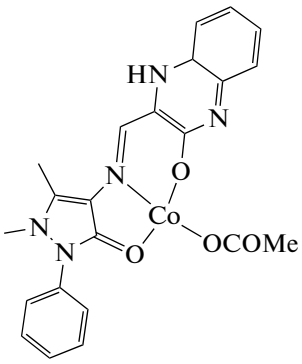
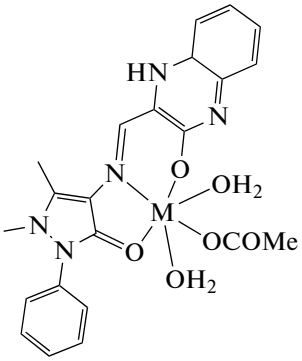


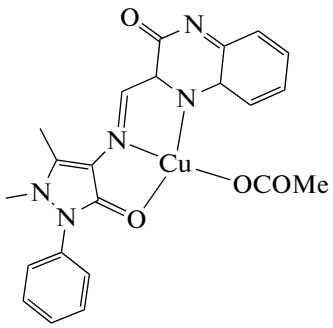
Fig. 6. DFT optimized structures of (a) ligand, (b) complex **111** and (c) complex **114** (colour code: H—white, C—grey, N—blue, O—red, N—silver grey, Cu—pink) (adapted from [38]).



105

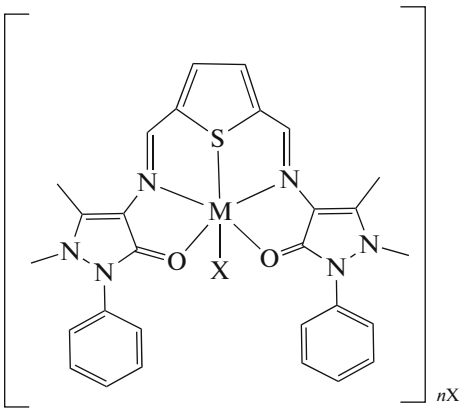


106 M = Ni(II)
107 M = Zn(II)



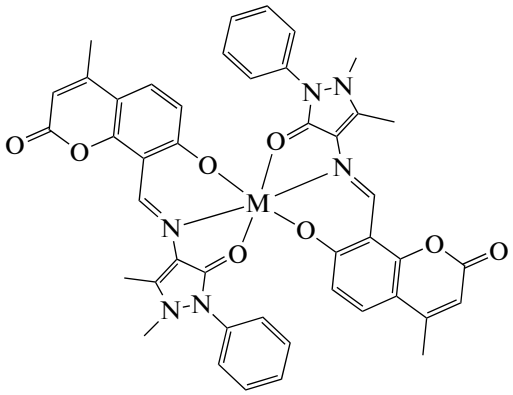
108

Tyagi et al. [38] synthesized a series of nickel(II) complexes **109**–**111** and copper(II) complexes **112**–**114** by treating the corresponding metal salts with a novel 4-aminoantipyrine derivative. The derivative was prepared by reacting 4-aminoantipyrine with 2,5-thiophenedicarboxaldehyde in a 1 : 2 stochiometric ratio. The octahedral complexes were duly characterized by various spectral and analytical methods and the structures were optimized using B3LYP three-parameter DFT method (Fig. 6). All the compounds were tested for their biological activity against the pathogens (*P. sorghina, F. oxysporum* and *A. niger*). The metal complexes were found to exhibit better antifungal activity than the ligand, with the copper(II) complexes showing higher inhibitory activity than the corresponding nickel(II) complexes.

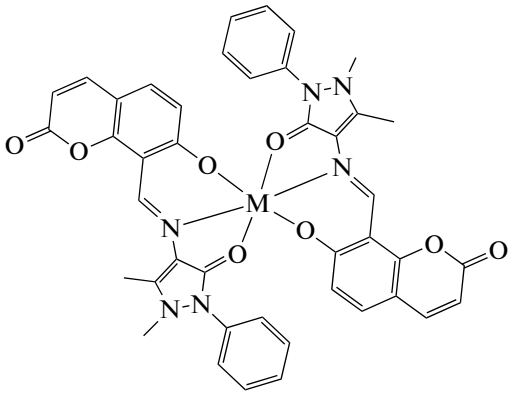


109 M = Ni(II); X = Cl^-; $n = 1$
110 M = Ni(II); X = NO_3^-; $n = 1$
111 M = Ni(II); X = SO_4^{2-}; $n = 0$
112 M = Cu(II); X = Cl^-; $n = 1$
113 M = Cu(II); X = NO_3^-; $n = 1$
114 M = Cu(II); X = SO_4^{2-}; $n = 0$

Manjunath et al. [39] developed two 4-aminoantipyrine derivatives and used them to synthesize a series of six metal complexes **115**–**120**. One of the derivatives was prepared by reacting 4-aminoantipyrine with 8-formyl-7-hydroxy-4-methylcoumarin and the other by reacting 4-aminoantipyrine with 5-formyl-6-hydroxycoumarin. The ligand was found to bind the metal center in an ONO tridentate mode and act as monoanionic upon deprotonation of the hydroxy group of the coumarin motif. All the complexes were thoroughly characterized and found to have octahedral structure with 2 : 1 ligand to metal stoichiometry. All the compounds were tested for their antimicrobial efficacy against *E. coli, S. aureus, P. aeruginosa, S. typhi* and *A. niger, A. flavus, Cladosporium*. The complexes were found to be better antibacterial and antifungal agents over the free organic ligands, with the corresponding copper(II) complexes **117** and **120** exhibiting superior activity over others. All the complexes exhibited promising anthelmintic activity and notable CT-DNA cleaving ability in the presence of hydrogen peroxide.



115 M = Co(II)
116 M = Ni(II)
117 M = Cu(II)



118 M = Co(II)
119 M = Ni(II)
120 M = Cu(II)

Mahmoud et al. [40] synthesized a series of transition metal complexes **121**–**127** utilizing the Schiff base derived from 4-aminoantipyrine. The Schiff base ligand was prepared by reacting *o*-nenzoylbenzoic acid with 4-aminoantipyrine. The ligand was treated with metal chlorides to obtain the stable metal complexes. All the complexes were found to have octahedral geometry with the main ligand binding in a ON bidentate mode and other coordination positions occupied by chloride and/or water ligands. All these structures were duly characterized by various spectral and analytical methods including thermal methods and optimized by DFT calculations (Fig. 7). The antimicrobial analysis showed that all the complexes, except the manganese(II) complex **121** and iron(III) complex **122**, possess excellent antimicrobial activity against the bacterial species (*S. aureus, B. subtilis, E. coli, N. gonorrhoeae*) as well as fungal species *C. albicans* with the cadmium(II) complex **127** exhibiting the superior activity. Same complex exhibited highest anticancer activity against breast cancer cell line (MCF-7) in comparison with the other complexes. From the molecular docking studies, it was found that the ligand can efficiently interact with the RNA (4p20) of *E. coli* bacterium through hydrogen bond and π-interactions (Fig. 8).

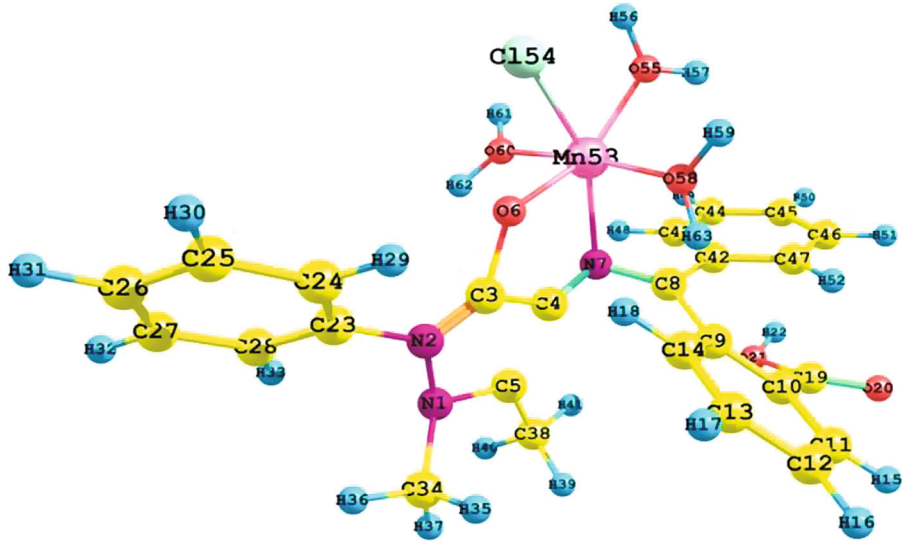
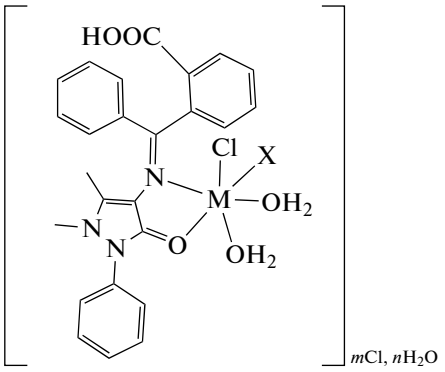
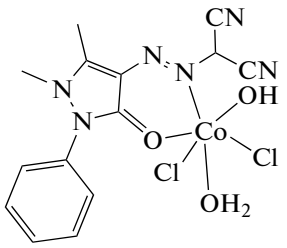


Fig. 7. DFT optimized structure of complex **121** (adapted from [40]).

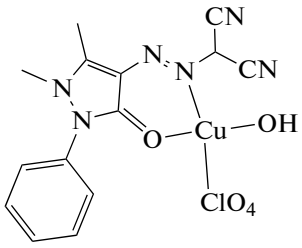


121 M = Mn(II); X = H_2O; $m = 1$; $n = 0$
122 M = Fe(III); X = H_2O; $m = 2$; $n = 0$
123 M = Co(II); X = H_2O; $m = 1$; $n = 1$
124 M = Ni(II); X = H_2O; $m = 1$; $n = 1$
125 M = Cu(II); X = Cl; $m = 0$; $n = 1$
126 M = Zn(II); X = Cl; $m = 0$; $n = 1$
127 M = Cd(II); X = Cl; $m = 0$; $n = 1$

Aly [41] synthesized a cobalt(II) complex **128** and copper(II) complex **129** using a Schiff base derivative prepared by reacting diazonium salt of 4-aminoantipyrine with malononitrile. The structural features of the complexes were studied by the use of spectroscopic techniques. The octahedral cobalt(II) complex **128** was found to be thermally more stable than the tetrahedral copper(II) complex **129**. The ligand and both the complexes were found to exhibit antibacterial activities against *S. pyogenes* and *E. coli* with the copper(II) complex **129** being the superior over other complex. Both the complexes were found to strongly interact with CT-DNA through intercalation mode.



128



129

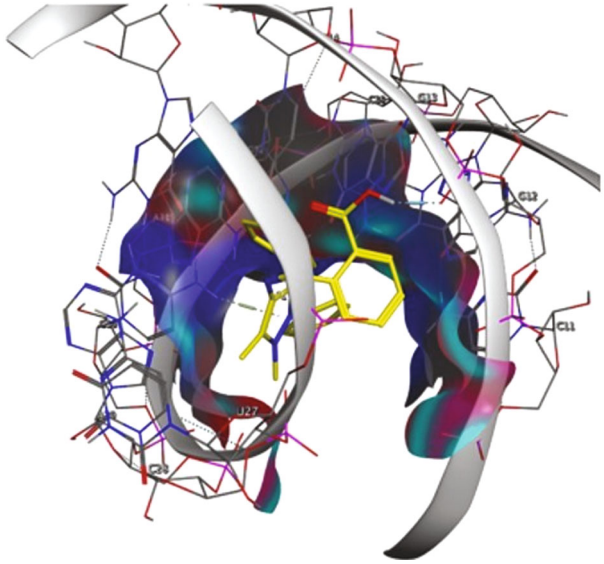
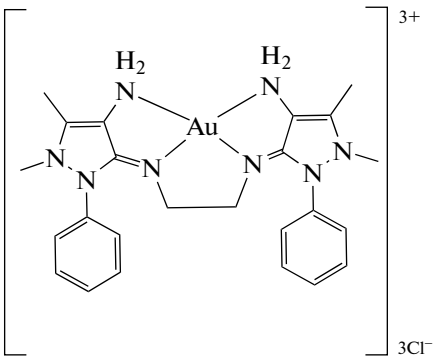
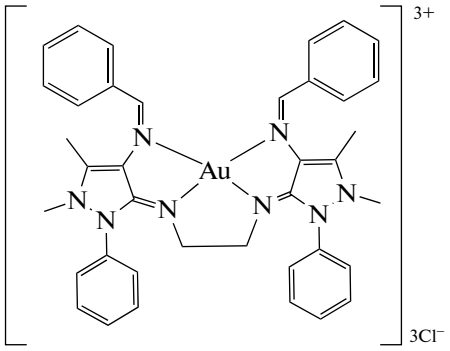


Fig. 8. Binding model of the ligand to the RNA of *E. coli* bacterium (adapted from [40]).

Abou Melha et al. [42] synthesized two gold(III) complexes **130** and **131** using two ligands derived from 4-aminoantipyrine. The first ligand was prepared by refluxing 4-aminoantipyrine with ethylenediamine in 1 : 1 stochiometric ratio and the second ligand was prepared by first reacting 4-aminoantipyrine with benzaldehyde and then refluxing with ethylenediamine. The ligands were refluxed with gold(III) chloride to produce the square planar gold(III) complexes **130** and **131**. All the compounds were characterized by spectral and analytical techniques as well as microscopy. All the compounds were tested for their antimicrobial and cytotoxic activity. Both the gold(III) complexes exhibited superior antibacterial activity against *E. coli, Klebsiella, S. aureus,* and *S. epidermidis* than the free ligands. In addition, these gold(III) complexes were found to exhibit remarkable cytotoxic effect on human hepatocellular carcinoma (HepG-2) than the MCF-7 cell lines.

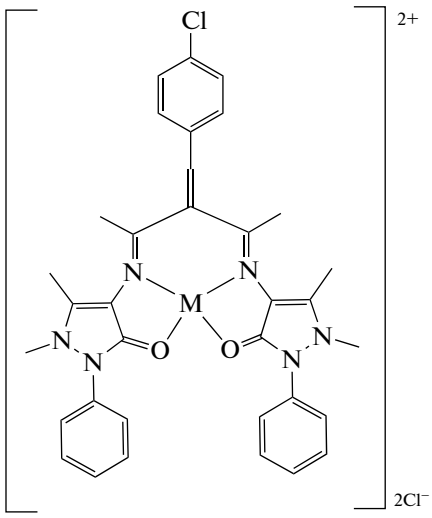


130



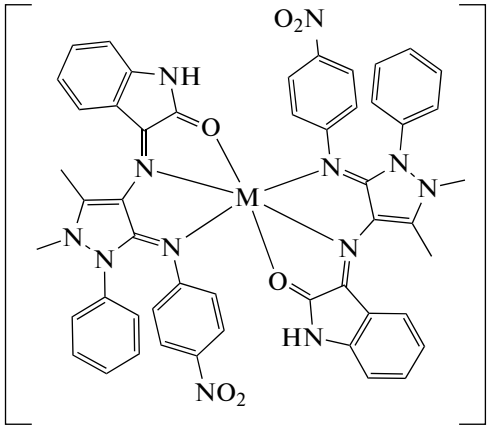
131

Ibatte et al. [43] synthesized a series of late 3*d*-transtion metal complexes **132**–**135** by reacting the corresponding metal chlorides with a novel 4-aminoantipyrine derived ligand. The ligand was obtained by treating 4-aminoantipyrine with acetylacetone and 4-chlorobenzaldehyde. All the complexes were found to form square planar structure. The complexes showed higher antibacterial activity against *S. typhi, S. aureus, E. coli* and *B. subtilis,* with the copper(II) complex **134** being superior.



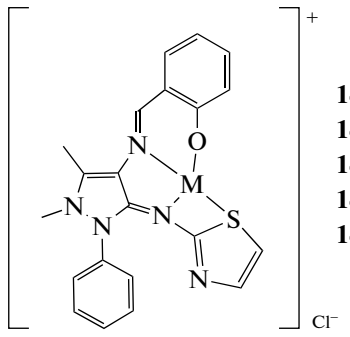
132 M = Co(II)
133 M = Ni(II)
134 M = Cu(II)
135 M = Zn(II)

Ali Jaafar [44] prepared a series of metal complexes **136**–**140** using a 4-aminoantipyrine derivative and studied their biological activities. The ligand was synthesized by refluxing 4-aminoantipyrine first with isatin and then with *p*-nitroaniline. The ligand was then reacted with hydrated metal chlorides to produce the corresponding metal complexes. All the complexes were thoroughly characterized and found to have distorted octahedral geometry with two molecules of the ligands binding to the metal center in a NNO tridentate fashion. All the compounds were investigated for their antibacterial ability against *S. aureus, E. coli, Pseudomonase* and *Proteus,* complexes exhibited higher order of activity than the ligand, with the manganese(II) complex **137** showing superior activity.



136 M = Cr(III); *n* = 3
137 M = Mn(II); *n* = 2
138 M = Zn(II); *n* = 2
139 M = Cd(II); *n* = 2
140 M = Hg(II); *n* = 2

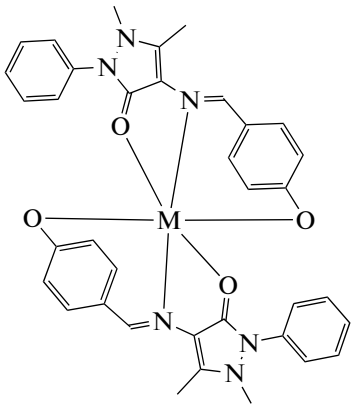
Palanimurugan et al. [45] synthesized a series of four transition metal complexes **141**–**145** using 4-aminoantipyrine derivative prepared by reacting 4-aminoantipyrine with salicylaldehyde and 2-aminothiazole. The ligand was refluxed with various metal chlorides to produce the metal complexes. All the compounds were duly characterized by using various analytical, spectroscopy and microscopy methods. Among the complexes the vanadyl(II) complex **141** was found to have a square pyramidal structure, while the other complexes have square planar geometry. The antimicrobial activity of all the compounds was investigated against *E. coli, K. pneumoniae, S. typhi, S. aureus* and *B. subtilis* bacterial strains and *R. bataicola, C. albicans, A. flavus, R. stolonifer* and *A. niger* fungi. All the complexes were found to exhibit better activity than the organic derivative, and among the complexes the vanadyl(II) complex **141** showed greater activity. The copper(II) complex **144** was also found to strongly bind to the CT-DNA via intercalation mode. It was also found to exhibit higher anticancer activity against the MCF-7 cell line.



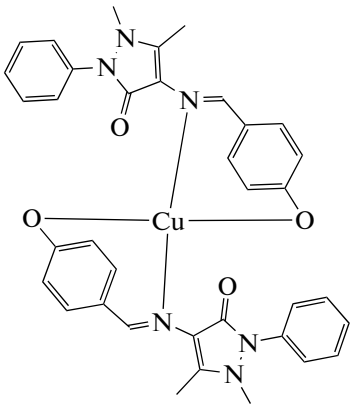
141 M = VO(II)
142 M = Co(II)
143 M = Ni(II)
144 M = Cu(II)
145 M = Zn(II)

Kashyap et al. [46] developed a series of three metal complexes **146**–**149** using the Schiff base ligand produced by treating 4-amioatipyrine with *m*-hydroxybenzaldehyde. The ligand was reacted with metal chlorides to obtain the metal complexes in high yield. All the complexes were found to have ligand : metal ratio of 2 : 1. Interestingly, in the case of copper(II)

complex **149**, the ligands acted as bidentate donors yielding a distorted tetrahedral complex, while in the case of other complexes **146**–**148** ligands coordinated in ONO tridentate mode forming the octahedral complexes. The biological studies revealed that among the all complexes, the copper(II) complex **149** and zinc(II) complex **148** exhibit remarkable antifungal (against *C. albicans* and *A. niger*) and antibacterial (against *S. aureus, E. coli, K. pneumonia* and *S. typhi*) activity. The copper(II) complex **149** also exhibited superior cytotoxic activity against the human colorectal carcinoma (HCT116) cancer cell lines. On the other hand, the nickel(II) complex was found to have better anticorrosion property than the other complexes.

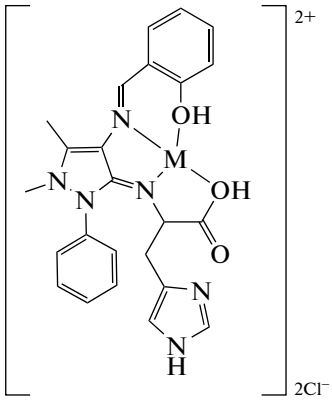


146 M = Co(II)
147 M = Ni(II)
148 M = Zn(II)



149

Palanimurugan et al. [47] prepared another 4-aminoantipyrine derivative by reacting 4-aminoantipyrine with salicylaldehyde and histidine. The Schiff base ligand was then treated with various metal chloride salts to synthesize metal complexes **150**–**154**. The ligand acts as a four dentate compartmental ligand with ONNO coordinating sites for the metal center. All the complexes except the vanadyl(II) complex **150** exhibited square planar geometry, while it was found to have square pyramidal structure. All the compounds were thoroughly characterized using various techniques including atomic force microscopy (AFM) and investigated for their antimicrobial activity against a set of bacteria (*S. aureus, B. subtilis, E. coli, K. pneumoniae, S. typhi*) and fungi (*A. flavus, A. niger, C. albicans, R. bataicola, R. stolonifer*). Among all the compounds, the vanadyl(II) complex **150** showed higher antimicrobial activity. All the complexes were found to interact with the CT-DNA via intercalation mode and the copper(II) complex **153** was found to have higher affinity.



150 M = VO(II)
151 M = Co(II)
152 M = Ni(II)
153 M = Cu(II)
154 M = Zn(II)

Kareem et al. [48] synthesized a series of metal complexes derived from Schiff base prepared using 4-aminoantipyrine. The ligand was synthesized by treating 4-aminoantipyrine in equal stochiometric ratio with benzoin and 3-aminoacetophenone. The ligand was reacted with various metal chlorides to produce the metal complexes **155**–**157**. All the metal complexes were thoroughly characterized by spectro-

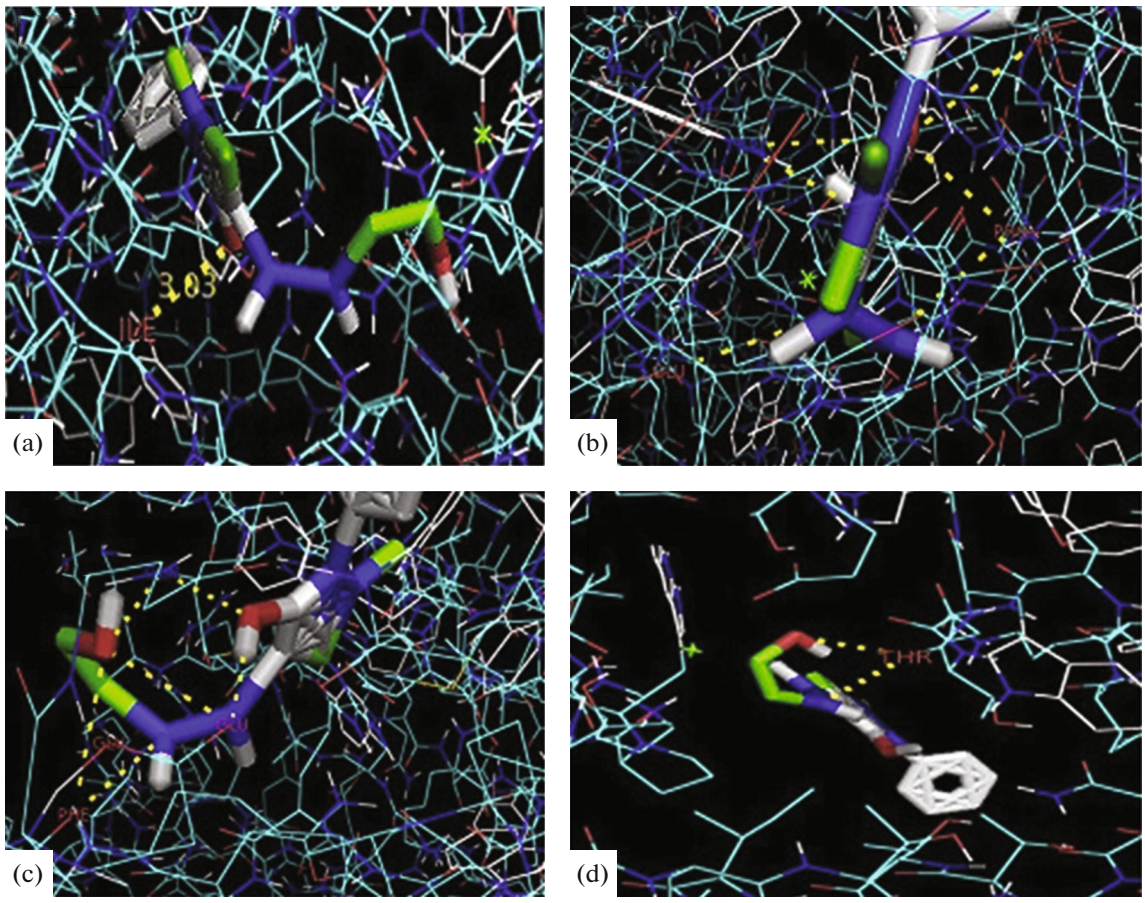
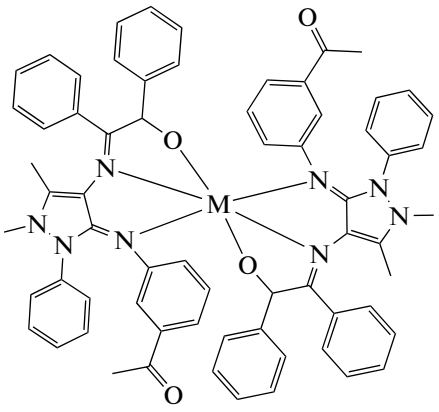


Fig. 9. Interaction of the ligand with native form of HIV Reverse Transcriptase with PDB ID (a) 1RT2 and (b) 1FK9; mutant form of HIV Reverse Transcriptase with PDB ID (c) 3BGR and (d) 1JLB (adapted from [49]).

analytical tools and found to have octahedral geometry with the ligand to metal ratio 2 : 1. All the compounds were tested for the antibacterial activity against *S. aureus, S. pyogenes, E. coli* and *K. pneumonia,* among all the compounds, the copper(II) complex **157** exhibited better activity.



155 M = Co(II)
156 M = Ni(II)
157 M = Cu(II)

Sreepriya et al. [49] prepared a series of manganese(II) complex **158**, cobalt(II) complex **159** and iron(III) complex **160** by reacting the respective metal chlorides with a 4-aminoantipyrine derivative. The ligand was prepared by treating the diazonium salt of 4-aminoantipyrine with 3-oxobutanoic acid. Two ligand molecules were found to bind the metal ion in ON bidentate mode to form octahedral complexes. The complexes and ligand were evaluated for their biological activity. The complexes showed better antibacterial (against *S. aureus* and *E. coli*) and antifungal (against *C. albicans*) activity than the free ligand, with the manganese(II) complex **158** as a lead compound. However, no compound was found to be active against the fungus *A. niger*. On the other hand, the ligand was found to have better antioxidant activity than the complexes. Among the three complexes the cobalt(II) complex **159** was found to have higher antitumor activity. Molecular docking studies indicated that the ligand can act as lead compounds for designing effective drug for treatment of AIDS (Fig. 9).

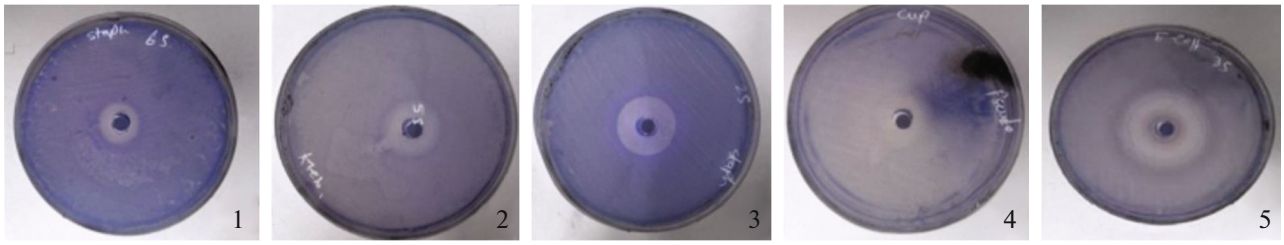
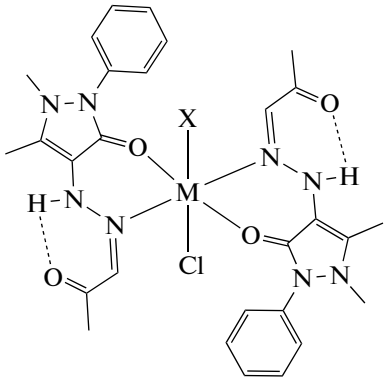
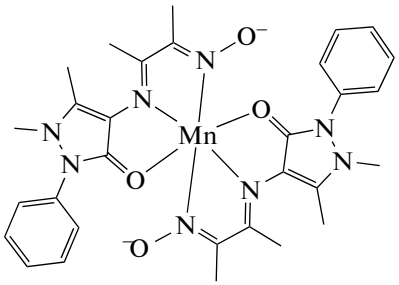


Fig. 10. Agar plates showing the antibacterial action of the complexes: (1) complex **161** on *S. aureus,* (2) complex **160** on *K. pneumonia*, (3) complex **165** on *S. aureus,* (4) complex **163** on *P. aeruginosa,* (5) complex **163** on *E. coli* (adapted from [50]).

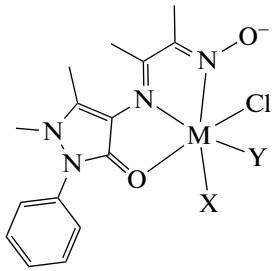


158 M = Mn(II); X = H_2O
159 M = Co(II); X = H_2O
160 M = Fe(III); X = Cl

Hassan et al. [50] produced a series of six metal complexes **161**–**166** derived from a Schiff base ligand, prepared by reacting 4-aminoantipyrine and 2,3-butanedionemonoxime. The complexes were synthesized by treating the ligand with metal chlorides. All the metal complexes except the palladium(II) complex **166**, were found to have octahedral geometry, while complex **166** was found to be square planar in structure. The manganese complex **161** was found to have two ligands coordinated to the single manganese center in ONN tridentate fashion, while all other complexes bear only one tridentate ligand bound to the metal center with the other coordination places occupied by water or chloride ligands. The antimicrobial activities of the ligand and the metal complexes were evaluated against the bacteria *E. coli, K. pneumonia, P. aeruginosa, S. aureus, S. mutans* and fungus *C. albicans*. Among all the complexes, the cadmium(II) complex **164** showed better antibacterial and antifungal activity (Fig. 10). The cadmium(II) complex **164** and palladium(II) complex **166** were found to have higher antitumor activity against human liver cancer (HepG-2) cell lines. Palladium(II) complex **166** and rhodium(III) complex **165** showed higher antioxidant activity and the palladium(II) complex **166** and nickel(II) complex **162** exhibited higher anti-inflammatory activity. Molecular docking studies were also employed to probe the antimicrobial and anticancer activity of the compounds.



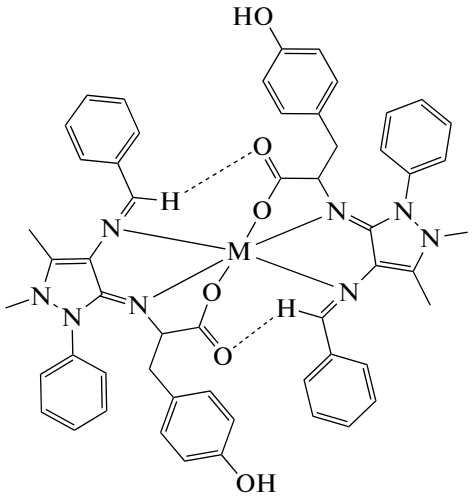
161



162 M = Ni(II); X = H_2O; Y = H_2O
163 M = Cu(II); X = H_2O; Y = H_2O
164 M = Cd(II); X = H_2O; Y = H_2O
165 M = Rh(III); X = Cl; Y = H_2O
166 M = Pd(II); X = Cl; Y = NA

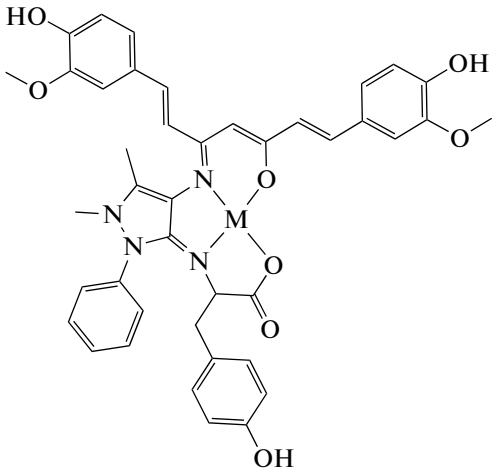
Soundaranayaki et al. [51] developed a series of transition metal complexes **167**–**171** by reacting metal chlorides with a Schiff base derivative of 4-aminoantipyrine. The ligand was prepared by refluxing benzalidene-4-iminoantipyrine with tyrosine. All the five complexes exhibited octahedral geometry with two

NNO tridentate ligands binding to the metal center in a facial manner. All the compounds were duly characterized by analytical, spectral and microscopic methods. Biological analysis of ligand and complexes showed that complexes exhibit better antimicrobial, analgesic, anti-inflammatory and antipyretic activity than the free ligand. Among the compounds tested, the manganese(II) complex **167** showed higher antibacterial activity against *E. coli*, *S. typhi*, *S. aureus*, *K. pneumoniae* and *B. subtilis*. While, copper(II) complex **170** exhibited superior activity against the fungi, *C. albicans, R. bataicola, A. flavus, A. niger,* and *R. stolonifera*. The copper(II) complex **170** also exhibited superior antipyretic activity over other compounds. The zinc(II) complex **171** was found to have better CNS depressant activity than other metal complexes and ligand. All the metal complexes were found to interact with the CT-DNA efficiently through intercalation mode.

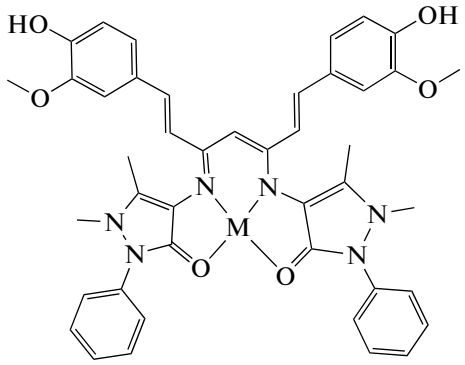


167 M = Mn(II)
168 M = Co(II)
169 M = Ni(II)
170 M = Cu(II)
171 M = Zn(II)

Sager et al. [52] developed six metal complexes **172**–**177** using two novel ligands derived from 4-aminoantipyrine. The first ligand was prepared by treating 4-aminoantipyrine with curcumin and tyrosine in 1 : 1 : 1 ration and the second ligand was prepared by treating 4-aminoantipyrine with curcumin in 2 : 1 ratio. Both the ligands formed tetrahedral complexes with cobalt(II), nickel(II) and copper(II) ions, binding in a tetradentate ONNO fashion. All the compounds were evaluated for their biological applications. The complexes **172**–**174** showed better antibacterial activity against *E. coli, S. aureus* and *S. typhi,* while the complexes **175**–**177** exhibited better antioxidant activity. In both the cases, the corresponding copper(II) complexes (viz. **174** and **177)** were found to be superior to other complexes.



172 M = Co(II)
173 M = Ni(II)
174 M = Cu(II)



175 M = Co(II)
176 M = Ni(II)
177 M = Cu(II)

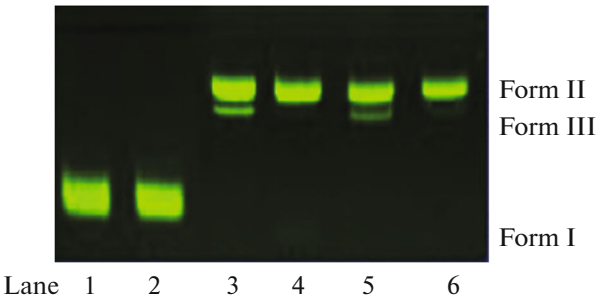
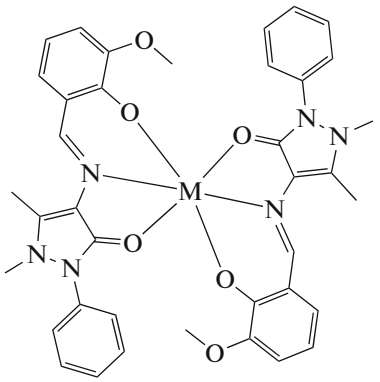
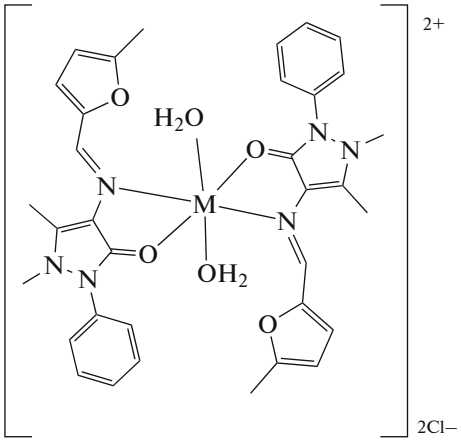


Fig. 11. Electrophoretic pattern of pUC 19-DNA induced by H_2O_2 and compounds: (1) DNA alone, (2) DNA + Ligand + H_2O_2, (3) DNA + complex **184** + H_2O_2, (4) DNA + complex **182** + H_2O_2, (5) DNA + complex **183** + H_2O_2 and (6) DNA + complex **185** + H_2O_2 (adapted from [54]).

Sherif et al. [53] recently prepared a series of transition metal complexes **178**–**182** using 4-aminoantipyrine derivatives as ligands. The ligands were synthesized by treating 4-aminoantipyrine with two different aldehydes, ortho-vanillin and 5-methyl furfural. All the compounds were thoroughly characterized by spectro-analytical techniques. The complexes were found to have octahedral geometry with 2 : 1 ligand to metal proportion. The metal complexes were found to exhibit higher order antibacterial activity against *S. aureus, E. coli,* and *P. aeruginosa* over the ligands. The cobalt(II) complex **178** exhibited superior activity over the other complexes of the series.



178 M = Co(II)
179 M = Ni(II)
180 M = Cu(II)



181 M = Ni(II)
182 M = Cu(II)

Fathima et al. [54] synthesized a bidentate Schiff-base ligand using 4-aminoantipyrine and 9-anthraldehyde. The ligand was reacted with transition metal chlorides to obtain the respective metal complexes **183**–**186**. All the complexes were dully characterized by multispectral techniques as well as ESI-mass analysis and scanning electron microscopy. All the complexes were found to have a distorted octahedral geometry with N and O donors of two ligands occupying the four vertices and two chlorides positioned at the other two. These compounds were screened for various biological activities including DNA interaction, antimicrobial, anticancer and antioxidant properties. Against the bacteria *S. aureus, B. subtilis, S. typhi* and *E. coli* and fungi *A. niger*, *A. flavus*, *C. lunata* and *C. albicans* tested, the copper(II) complex **185** was found to be more active compared to other complexes. All the complexes exhibited efficient free radical scavenging activity, cytotoxic activity (against MCF-7, HepG2 and HBL-100 cell lines), as well as CT-DNA binding and pUC19 DNA cleavage activity with the copper(II) complex **185** as a lead compound (Fig. 11).

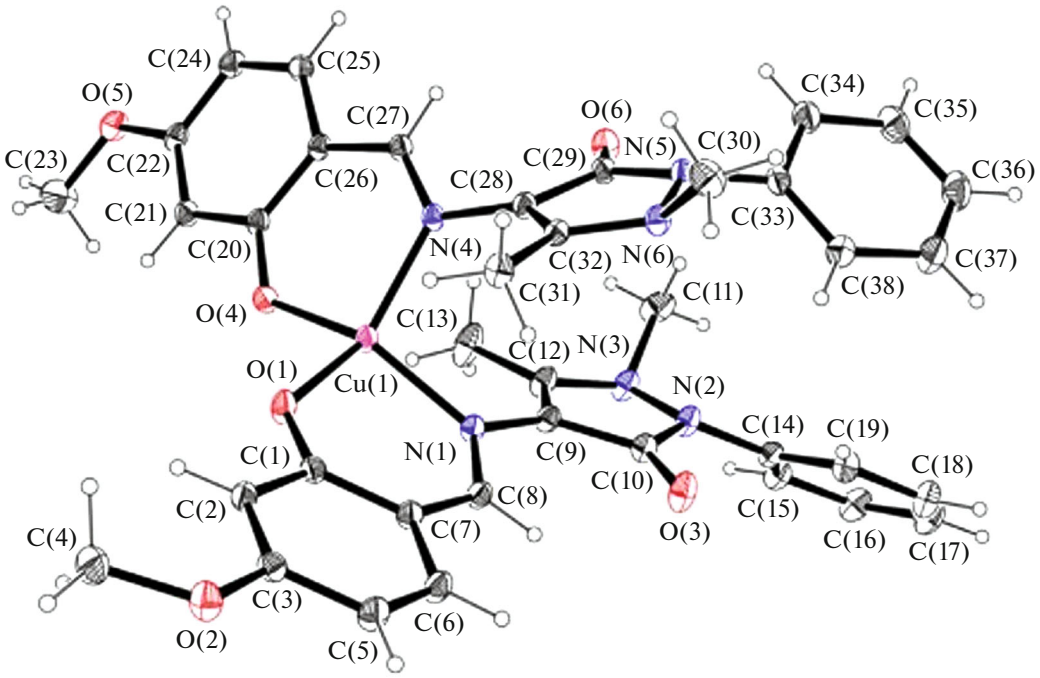
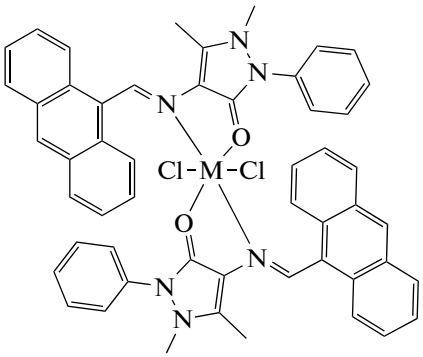
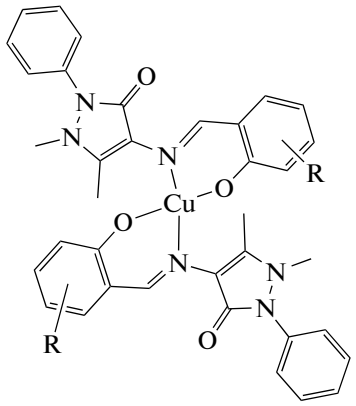


Fig. 12. ORTEP diagram of solid-state structure of complex **187** (adapted from [55]).



183 M = Co(II)
184 M = Ni(II)
185 M = Cu(II)
186 M = Zn(II)



187 R = 3-OMe
188 R = 4-OMe
189 R = 5-OMe
190 R = 6-OMe

Kargar et al. [55] synthesized a new series of copper(II) complexes using four N,O-bidentate Schiff base ligands derived from 4-aminoantipyrine and methoxy substituted salicylaldehydes. All the compounds were characterized by various spectro-analytical methods including single crystal X-ray analysis (Fig. 12) as well as optimized by theoretical calculations. All the four copper(II) complexes **187**–**190** exhibited a distorted tetrahedral geometry with the central copper ion coordinated by two bidentate ligands. The in vitro antibacterial activities of the synthesized compounds were evaluated against *S. aureus* and *E. coli*. All the complexes exhibited better activity compared to their respective ligands. The position of the methoxy substituent was found to have a significant influence on the antibacterial activity of the ligands, while in the case of complexes, no notable difference in the activity was observed.

CONCLUSIONS

Availability of a free amine group and cyclic ketonic group makes 4-aminoantipyrine an attractive substrate to build a library of Schifbase ligands. We see that varieties of aldehydes, ketones as well as amines have been condensed with the 4-aminoantipyrine motif to derive the Schiff base ligands of versatile coordination behaviour and functional applications. 4-Aminoantipyrine by itself can act as a bidentate neutral ligand, coordinating via ketonic oxygen donor and nitrogen donor of the primary amine group. However, the Schiff bases derived from 4-aminoantipyrine upon condensation with suitable reagents have exhibited variable denticity and versatile coordination behaviour. This versatility is found to be mainly depends upon the steric and electronic factors of the

Table 1. Summary table containing the data of the referenced research work

Sl no.	Complexes	Antibacterial activity		Antifungal activity		Other bioactivity reported	Reference
		bacteria tested	complex exhibiting best activity (MIC, μg/mL*)	fungi tested	complex exhibiting best activity (MIC, μg/mL*)		
1	**1–8**	*S. typhi*, *S. aureus*, *E. coli* and *B. subtilis*	**5** (3800–4100)	*A. niger*, *A. flavus* and *R. bataicola*	**5** (4600–5000)	CT-DNA cleavage activity	16
2	**9–11**	*B. subtilis, S. aureus, E. coli,* and *P. putita*	**9** (NA)	*P. chrysosporium* and *R. stolinifer*	**9** (NA)	CT-DNA cleavage activity	17
3	**12–15**	*S. typhi, P. aeruginosa, E. coli* and *B. subtilis*	**14** (3800–7100)	*A. niger, A. flavus* and *R. bataicola*	**14** (4100–7300)	CT-DNA cleavage activity	18
4	**16–27**	*X. compestris* and *P. aeruginosa*	**25** (250)	*A. brassicae*, *A. niger* and *F. oxysporum*	**25** (100 μg/mL)	NIL	19
5	**28–30**	*S. aureus, E. coli, K. pneumoniae, P. vulgaris,* and *P. aeruginosa*	**30** (18–32)	*A. niger, R. stolonifer, A. flavus, R. bataicola* and *C. albicans*	**30** (18–34)	NIL	20
6	**31–37**	*S. aureus* and *E. coli*	**37** (NA)	NIL	NIL	NIL	21
7	**38–41**	NIL	NIL	NIL	NIL	*E. coli* DNA binding and cleavage activity	22
8	**42–47**	NIL	NIL	*A. brassicae, A. niger* and *F. oxysporum*	**46** and **47** (200)	NIL	23
9	**48–57**	*S. aureus, E. coli, B. subtilis* and *P. aeruginosa*	**56** and **57** (NA)	NIL	NIL	NIL	24
10	**58–60**	*X. maltophilia, C. violaceum, Acientobacter, Staphylococci* and *Streptococci*	**58** (14–30)	*C. albicans*	**58** (35)	CT-DNA cleavage activity	25
11	**61–64**	*E. coli, S. aureus,* and *S. fecalis*	**64** (12–18)	*A. niger, T. polysporum, C. albicans,* and *A. flavus*	**64** (11–16)	NIL	26
12	**65–69**	*S. aureus, S. typhi, E. coli, B. subtilis,* and *S. sonnie*	**66** and **69** (100)	*C. albicans, A. niger,* and *R. bataicola*	**66** and **68** (100)	CT-DNA cleavage activity	27
13	**70–73**	*S. aureus* and *E. coli*	**71** (1000)	NIL	NIL	NIL	28
14	**74–76**	NIL	NIL	*M. phaseolina* and *F. solani*	**76** (200–1000)	NIL	29

Table 1. (Contd.)

Sl no.	Complexes	Antibacterial activity		Antifungal activity		Other bioactivity reported	Reference
		bacteria tested	complex exhibiting best activity (MIC, μg/mL*)	fungi tested	complex exhibiting best activity (MIC, μg/mL*)		
15	**77–80**	*S. aureus, B. subtilis,* and *P. vulgaris*	**80** (60)	*C. albicans*	**80** (60)	*In silico* molecular docking studies with CT-DNA	30
16	**81–84**	*Streptococci*, *S. aureus*, *Pseudomonas, K. pneumoniae,* and *C. bacterium*	**81** and **83** (NA)	*C. albicans*	**81** and **83** (NA)	CT-DNA binding and cleavage activity	31
17	**85–88**	*P. aeruginosa, P. mirabilis,* and *E. coli*	**86** (NA)	*A. niger, A. fumigatus,* and *C. albicans*	**86** (NA)	NIL	32
18	**89–92**	*S. aureus, E. coli, K. pneumoniae, P. vulgaris,* and *P. aeruginosa*	**92** (20–75 μg/mL)	*A. niger, R. stolonifer, A. flavus, R. bataicola,* and *C. albicans*	**92** (20–50 μg/mL)	Superoxide dismutase (SOD) activity and DNA binding activity	33
19	**93–95**	*S. aureus, E. coli, K. pneumoniae, P. vulgaris,* and *P. aeruginosa*	**94** (26–48)	*A. niger, R. stolonifer, A. flavus, R. bataicola, C. albicans*	**94** (6–46)	Superoxide dismutase (SOD) activity	34
20	**96–100**	*E. coli, K. pneumonia, S. typhi, P. aeruginosa* and *S. aureus*	**96** (43–62)	*A. niger, R. stolonifera, A. flavus, R. bataicola* and *C. albicans*	**97** (15–31)	Superoxide dismutase (SOD) activity and DNA binding activity	35
21	**101–104**	*S. aures, E. coli, K. pneumonia* and *P. vulgaris*	**103** (4–12)	*C. albicans,* and *A. nigers*	**103** (4–12)	NIL	36
22	**105–108**	*S. aureus, E. coli* and *P. aeruginosa*	**108** (12.2–12.5)	*C. albicans, A. flavus* and *A. niger*	**106** and **108** (10.5–11.5)	CT-DNA cleavage activity	37
23	**109–114**	NIL	NIL	*P. sorghina, F. oxysporum* and *A. niger*	**114** (1.875–3.75 μg/mL)	NIL	38
24	**115–120**	*E. coli, S. aureus, P. aeruginosa,* and *S. typhi*	**117** and **120** (25–100)	*A. niger, A. flavus* and *Cladosporium*	**117** and **120** (25–100)	Anthelmintic and CT-DNA cleavage activity	39
25	**121–127**	*S. aureus, B. subtilis, E. coli,* and *N. gonorrhoeae*	**127** (NA)	*C. albicans*	**127** (NA)	Anticancer activity against breast cancer cell line (MCF-7) and molecular docking studies with *E. coli* RNA	40

Table 1. (Contd.)

Sl no.	Complexes	Antibacterial activity		Antifungal activity		Other bioactivity reported	Reference
		bacteria tested	complex exhibiting best activity (MIC, μg/mL*)	fungi tested	complex exhibiting best activity (MIC, μg/mL*)		
26	**128–129**	*S. pyogenes* and *E. coli*	**129** (1000)	NIL	NIL	Heparin DNA binding studies	41
27	**130–131**	*E. coli, Klebsiella, S. aureus,* and *S. epidermidis*	**130** (NA)	NIL	NIL	Anticancer activity against human hepatocellular carcinoma (HepG-2) and human breast cancer (MCF-7) cell lines	42
28	**132–135**	*S. typhi, S. aureus,* and *E. coli*	**134** (100)	NIL	NIL	NIL	43
29	**136–140**	*S. aureus, E. coli, Pseudomonase* and *Proteus*	**137** (1)	NIL	NIL	NIL	44
30	**141–145**	*E. coli, K. pneumoniae, S. typhi, S. aureus* and *B. subtilis*	**141** (14–21)	*R. bataicola, C. albicans, A. flavus, R. stolonifer,* and *A. niger*	**141** (6–14)	CT-DNA binding studies and anticancer activity against human breast cancer cell line (MCF-7)	45
31	**146–149**	*S. aureus, E. coli, K. pneumonia* and *S. typhi*	**149** (9.24–18.48)	*C. albicans* and *A. niger*	**149** (4.62–9.24)	Anticancer activity against the human colorectal carcinoma (HCT116) cancer cell lines	46
32	**150–154**	*S. aureus, B. subtilis, E. coli, K. pneumoniae,* and *S. typhi*	**150** (15–21)	*A. flavus, A. niger, C. albicans, R. bataicola,* and *R. stolonifer*	**150** (12–17)	CT-DNA binding studies	47
33	**155–157**	*S. aureus, S. pyogenes, E. coli* and *K. pneumonia*	**157** (100)	NIL	NIL	NIL	48
34	**158–160**	*S. aureus* and *E. coli*	**158** (14–15)	*C. albicans*	**158** (9)	Antioxidant activity, anticancer activity against HeLa cells and molecular docking studies to probe as potential HIV drug	49

Table 1. (Contd.)

Sl no.	Complexes	Antibacterial activity		Antifungal activity		Other bioactivity reported	Reference
		bacteria tested	complex exhibiting best activity (MIC, μg/mL*)	fungi tested	complex exhibiting best activity (MIC, μg/mL*)		
35	**161–166**	*E. coli, K. pneumonia, P. aeruginosa, S. aureus,* and *S. mutans*	**164** (15000)	*C. albicans*	**164** (15000)	Anticancer activity against human liver (HEPG2) cancer cell lines. antioxidant activity. anti-inflammatory activity. Computational studies to probe bio-activity.	50
36	**167–171**	*E. coli*, *S. typhi*, *S. aureus*, *K. pneumoniae* and *B. subtilis*	**167** (40–65)	*C. albicans, R. bataicola, A. flavus, A. niger,* and *R. stolonifer*	**170** (10–16)	Analgesic activity, antipyretic activity, anti-inflammatory activity, antioxidant assay, CNS depressant activity, CT-DNA binding studies and molecular docking studies	51
37	**172–177**	*E. coli, S. aureus* and *S. typhi*	**174** (NA)	NIL	NIL	Antioxidant activity	52
38	**178–182**	*S. aureus, E. coli,* and *P. aeruginosa*	**178** (10000)	NIL	NIL	NIL	53
39	**183–186**	*S. aureus, B. subtilis, S. typhi* and *E. coli*	**185** (8.1–9.5)	*A. niger*, *A. flavus*, *C. lunata* and *C. albicans*	**185** (10.2–11.5)	Antioxidant activity, anticancer activity against MCF-7, HepG2 and HBL-100 cell lines, CT-DNA binding and pUC19 DNA cleavage activity, Computational studies to probe bio-activity	54
40	**187–190**	*S. aureus* and *E. coli*	**187–190** (32–128)	NIL	NIL	NIL	55

* MI— minimum inhibitory concentration.

substituents of the motifs that have been attached by condensation as well as the availability of the extra donor atoms. A range of bidentate to tetradentate ligands of end-off compartmental type to scorpionate type to macrocyclic type mode of coordination have been developed using 4-aminoantipyrine. The coordination cavities offered by the 4-aminoantipyrine Schiff base derivatives, which mostly consist of N, O and/or S donor atoms were found to be most suitable for the transition metal ions [56, 57]. A range of unique transition metal complexes have been developed using these derivatives, with the majority being late 3*d*-transtion metal complexes (viz. cobalt, nickel, copper and zinc). The steric and electronic parameters of the ligands were found to govern the geometry and stoichiometry of the metal complexes. Tetrahedral and octahedral structures were found to be the most common geometries with some complexes exhibiting square planar or square pyramidal molecular geometry. Most of the complexes were found to have 1 : 1 or 2 : 1 ligand to metal stoichiometry, while the polymeric complexes were not been observed. All the metal complexes were found to have the metal ions stabilized in high-spin states. The strong ligand to metal charge transfer transitions observed in the electronic spectra of most of the complexes reported is another common feature of these compounds.

Due to the proven antioxidant property of the 4-aminoantipyrine motif, the Schiff base derivatives as well as the respective metal complexes have been explored for biological applications. While targeting the antibacterial and antifungal efficacy it's been seen that tethering of two molecule with proven antimicrobial potential together to get a new motif with enhanced antimicrobial properties is a common strategy used. Here in this case of the 4-aminoantipyrine derivatives, various biologically important motifs like coumarin, pyrazole, quinoline, quinoxaline, isatin, etc. have been clubbed to obtain the molecules with improved antimicrobial activities. These added motifs were also found to contribute in the coordination with metal centers, in most cases by providing additional donor atoms, hence leading to the formation of stable metal complexes with unique structural features [58, 59]. It is seen that the metal complexes exhibited better antimicrobial activities compared to the organic 4-aminoantipyrine derivatives, which can be rationalized with the chelation effect and/or combined effect of metal ion and organic ligand functionalities. Among the metal complexes, the copper(II) complexes have generally been found to show higher order of antimicrobial activity [60–64]. Interestingly, 4-aminoantipyrine derivatives and their metal complexes exhibited better antifungal activity as compared to their antibacterial action. Although the mechanism of action of the antibacterial or antifungal activity of any of the derivatives is not been studied thoroughly, but the parallel DNA interaction/cleavage studies indicate a strong correlation between the antimicrobial action and the DNA binding/cleavage ability of the complexes. We believe that, this review provides an overall idea about the development of the field and will encourage innovative ideas and methodologies in creating new and improvised transition metal complexes of 4-amioantipyrinne derivatives with potential antibacterial and antifungal applications. A summary of the reviewed literature data is provided in Table 1.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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