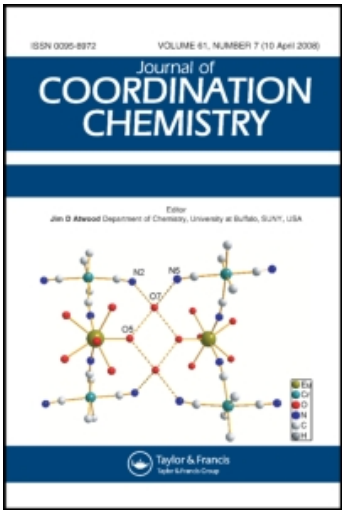

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Triazoles as complexing agents: synthesis, characterization and pharmacological activities of copper complexes of 4-amino-3-mercapto-5-substituted aryl-1,2,4-triazoles

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Triazoles as complexing agents: synthesis, characterization and pharmacological activities of copper complexes of 4-amino-3-mercapto-5-substituted aryl-1,2,4-triazoles

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Copper complexes of 4-amino-3-mercapto-5-substituted aryl-1,2,4-triazoles **2**(**a**–**j**) have been prepared in the ethanolic medium and characterized by elemental analysis, IR, TGA, ^{1}H NMR and magnetic susceptibility studies. The ligand is bidentate with SN donors of the mercapto S and amino N. Some compounds show significant anti-inflammatory and analgesic activities.

Keywords: Synthesis; Amino triazoles; Copper complexes; Pharmacological activities

1. Introduction

A significant rising interest in the design [1] is currently observed in the area of scientific inquiry appropriately termed medicinal inorganic chemistry. Investigations of metal compounds as drugs and diagnostic agents focus on speciation of metal species in biological media, based on possible interactions of these metal ions with diverse biomolecules [2–4]. A wide range of metal complexes are already in clinical use [5] and encourage further studies for new metallodrugs, such as metal-mediated antibiotics, antibacterial, antiviral, antiparasitic, radiosensitizing agents, and anticancer compounds [6]. Mechanisms of action are often still unknown, but recently, more than a thousand potential anticancer metal compounds, from the National Cancer Institute (NCI) tumor-screening database, were analyzed based on putative mechanisms of action, and classified into four broad classes according to their preference for binding to sulfhydryl groups, chelation, generation of reactive oxygen species, and production of lipophilic ions [7].

Increasing knowledge of the biological activities of simple metal complexes may guide researchers to the development of promising chemotherapeutic compounds to target specific physiological or pathological processes. Many potential antitumoral agents have been investigated based on their anti-angiogenesis or pro-apoptotic behavior.

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These studies involve both designed and natural products, in association with essential metal ions such as copper or iron [8, 9].

4-Amino-5-substituted-4H-1,2,4-triazole-3-thiols are multidentate sulfur and nitrogen donor ligands through the sulfur of thiol group, nitrogen of the primary and tertiary amino groups, and nitrogen atoms at positions 1 and 2 in the triazole ring system.

Many quantitative studies have revealed that metal chelates are more stable than those of related metal complexes derived from unidentate ligands [10]. Five- or six-membered chelates are by far the most common and, in general, the most stable [11, 12]. Triazole ligands contain both hard nitrogen and soft sulfur as donors. Substituted 4-amino-5-mercapto-1,2,4-triazole possesses chelating ability and has been used as an analytical agent. Coordination through thiol sulfur and amine nitrogen should result in formation of a five-membered stable chelate.

Various researchers have reviewed the synthesis, reactions and characterization of complexes of substituted 4-amino-5-mercapto-1,2,4-triazoles [13–17].

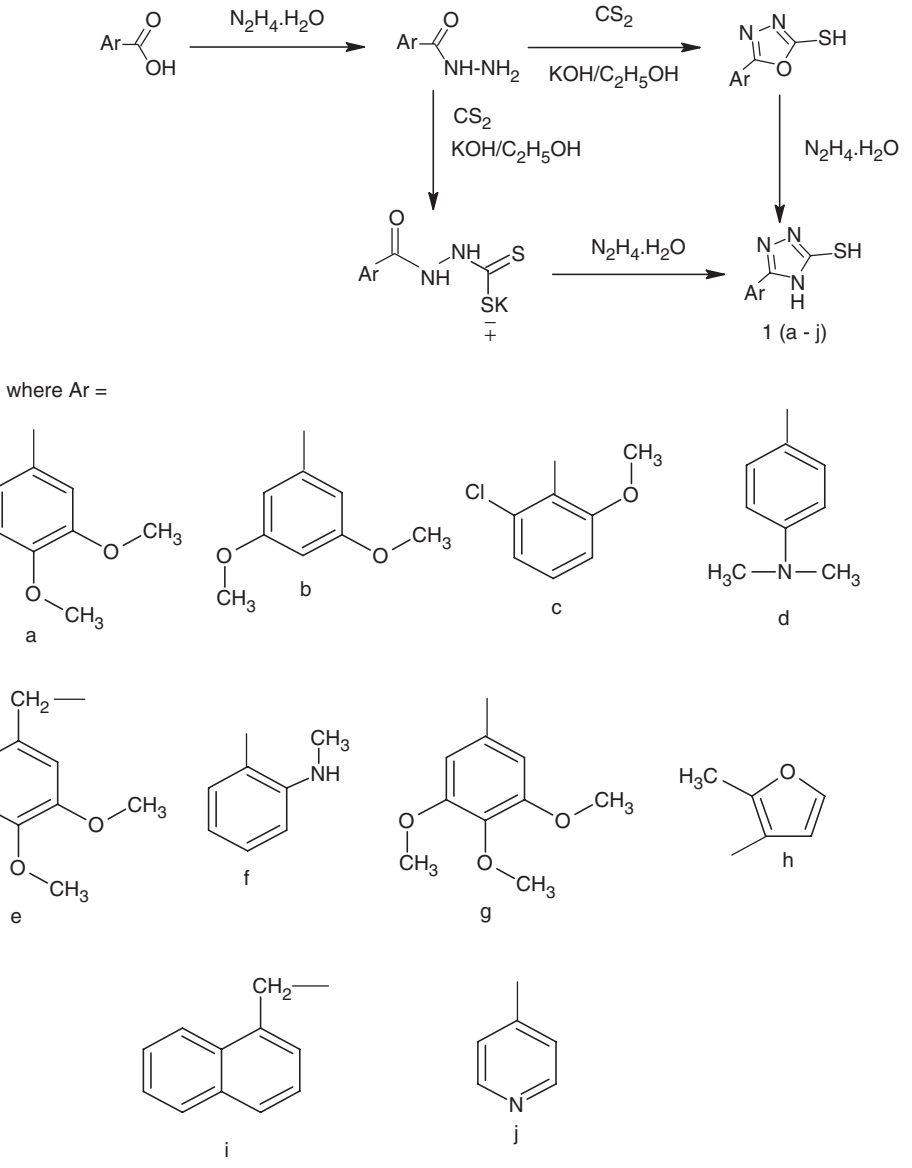
Amine and thione substituted triazoles are part of the larger family of sulfur and nitrogen containing organic compounds and their metal complexes display a broad range of biological activity, finding applications as antiproliferative agents [18], antifungal [l9], antibacterial agents [20], cytotoxic property [21], etc. The S=C–N–N unit allows bidentate coordination to a metal ion through the amine and thione substituents to form a stable five-membered ring. The importance of heterocyclic thiones in biological systems provides the impetus for the preparation and characterization of a series of copper complexes of various substituted triazoles. The synthesized compounds were studied for their anti-inflammatory and analgesic activities.

2. Experimental

Melting points were determined in open capillaries in melting point apparatus and are uncorrected. IR absorption spectra of the complexes were recorded as KBr pellets on a Shimadzu-8400 FTIR spectrophotometer; ^{1}H-NMR spectra were measured on a Bruker Avance 300 spectrometer operating at 300 MHz (DMSO-d6 solutions using TMS as internal reference). The electronic spectra were recorded using Shimadzu 2000; magnetic susceptibility was carried out at room temperature by using the Gouy magnetic balance consisting of NP-53 electromagnet with an MP-1053 DC power supply unit and semi micro electronic balance supplied by AND Electronics, Japan. [Hg(Co(SCN)$_4$)] was used as calibrant. A Mettler Toledo TGA unit, module TGA/SDTA.851e/SF1100/HT1/057, was used for recording TG curves in air and nitrogen at a heating rate of 10°C min^{-1} by taking 8–10 mg of the complexes in the temperature range of 20–800°C using heated alumina as the standard. Elemental analyses were carried out with a Flash-EA 1112 elemental analyzer.

2.1. *Materials*

All chemicals were purchased from Merck Chemicals and used without purification, except 4-amino-3-mercapto-5-substituted aryl-1,2,4-triazole **1**(**a**–**j**), prepared by literature methods [22] (scheme 1).



Scheme 1. Synthesis of 4-amino-3-mercapto-1,2,4-triazole.

2.2. *Synthesis of Cu(II) complexes 2(a–e)*

To a stirring ethanolic solution (40 mL) containing triazole, **1(a–e)** (0.02 mol) and $Cu(OAc)_2 \cdot H_2O$ (0.01 mol) was added dropwise an ethanolic solution of sodium hydroxide (0.01N). The resulting solution was refluxed on a water bath for 6 h. The contents of the reaction mixture were cooled and the pH of the solution adjusted to 10.0 by adding a few drops of 0.01N sodium hydroxide solution giving precipitate. The precipitate obtained was aged by digestion on a water bath for 30 min, filtered, washed with excess water, hot ethanol and dried under vacuum.

2.3. *Synthesis of Cu(II) complexes 2(f–g)*

To a stirring aqueous solution of triazole, **1(f–g)** (0.02 mol) was added an ethanolic solution of $Cu(OAc)_2 \cdot H_2O$ (0.01 mol), followed by a solution of NaOH (0.01N) in ethanol dropwise, and the resulting solution was stirred at 50°C for 10–12 h; the solution was set aside for precipitation. After several days, precipitates obtained were harvested by slow evaporation of the filtrate at room temperature. Precipitated complex was filtered and washed with excess water, hot ethanol and dried in a desiccator over fused calcium chloride.

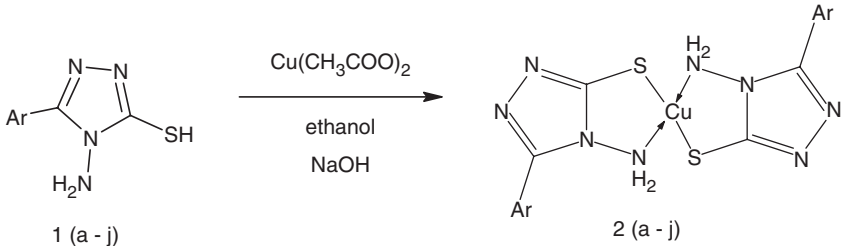
2.4. *Synthesis of Cu(II) complexes 2(h–j)*

Ethanolic solution of copper acetate (0.01 mol) was added to a hot ethanolic solution of triazole, **1(h–j)** (0.02) in 1 : 2 molar ratio with stirring. The mixture was refluxed for 30 min and after cooling, the pH of the mixture was raised to 8.0 by adding 0.01N sodium hydroxide. Refluxing was continued for 4–6 h and the solution was cooled. The colored complexes were filtered and washed with water, hot ethanol and dried.

The general route for synthesis of complexes was depicted in scheme 2; characterization data are presented in table 1.

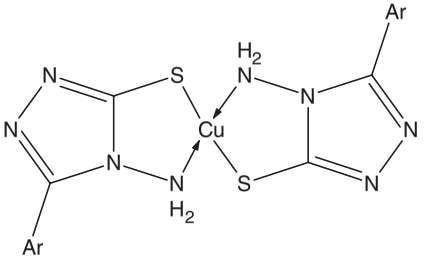
3. Results and discussion

Microanalytical measurements and metal determination data (table 1) suggest a 2 : 1 ratio for ligand to copper(II), in good agreement with the chemical formulas of the complexes. The complexes are sparingly soluble in common organic solvents and decompose above 300°C. Analyses of metal ions were carried out by digesting a known amount of each complex using concentrated nitric acid followed by evaporation to dryness, extraction with distilled water and estimation of the metal ions by standard methods [23]. Carbon, hydrogen and nitrogen were analyzed by STIC, Cochin; the results are given in table 1. Few of the synthesized copper complexes are soluble in common organic solvents and hence ^{1}H NMR spectra of only three complexes were taken. The copper complex contains two independent triazole ligands arranged in such a way to form a square plane around the copper



Scheme 2. Synthesis of copper complexes of 4-amino-3-mercapto-1,2,4-triazole.

Table 1. Physical characterization of copper complexes of 4-amino-3-mercapto-5-substituted aryl-1,2,4-triazole.



Compound number	Molecular formula	Ar	Color and nature of the compound	Yield (%)	Elemental analysis Calcd (Found) C	H	N	S	Cu
2a	$C_{20}H_{22}CuN_8O_4S_2$	3,4-Dimethoxy phenyl	Black crystalline	57	42.43 (42.57)	3.92 (3.96)	19.79 (19.84)	11.33 (11.26)	11.22 (11.09)
2b	$C_{20}H_{22}CuN_8O_4S_2$	3,5-Dimethoxy phenyl	Black crystalline	61	42.43 (42.59)	3.92 (3.87)	19.79 (19.82)	11.33 (11.29)	11.22 (11.03)
2c	$C_{18}H_{16}Cl_2CuN_8O_2\ S_2$	2-Chloro-5-methoxy phenyl	Light green amorphous powder	53	37.60 (37.69)	2.80 (2.85)	19.49 (19.37)	11.15 (11.09)	11.05 (10.84)
2d	$C_{20}\ H_{24}CuN_{10}S_2$	4-(*N*,*N*-Dimethyl amino) phenyl	Green amorphous powder	51	45.14 (45.21)	4.55 (4.59)	26.32 (26.41)	12.05 (11.97)	11.94 (11.82)
2e	$C_{22}H_{26}CuN_8O_4S_2$	3,4-Dimethoxy benzyl	Black crystalline	52	44.47 (44.61)	4.41 (4.34)	18.86 (18.95)	10.79 (10.63)	10.70 (10.56)
2f	$C_{18}H_{20}CuN_{10}S_2$	2-(*N*-Methyl amino) phenyl	Black crystalline	57	42.89 (43.12)	4.00 (3.87)	27.79 (27.65)	2.72 (12.63)	12.61 (12.54)
2g	$C_{22}H_{26}CuN_8O_6S_2$	3,4,5-Trimethoxy phenyl	Brown amorphous powder	54	42.20 (42.17)	4.19 (4.25)	17.90 (17.94)	10.24 (10.21)	10.15 (10.02)
2h	$C_{14}H_{14}CuN_8O_2S_2$	2-Methyl-3-furanyl	Pale blue amorphous powder	48	37.04 (37.11)	3.11 (3.13)	24.68 (24.60)	14.13 (14.09)	14.00 (13.87)
2i	$C_{26}H_{22}CuN_8S_2$	1-Naphthyl methyl	Blue amorphous powder	59	54.39 (54.41)	3.86 (3.87)	19.52 (19.55)	11.17 (11.13)	11.07 (10.96)
2j	$C_{14}H_{12}CuN_{10}S_2$	4-Pyridinyl	Golden yellow powder	55	37.53 (37.46)	2.70 (2.73)	31.27 (31.21)	14.32 (14.28)	14.18 (14.03)

ion with the donor atoms N and S *trans* to one another due to steric as well as electronic factors [24, 25].

3.1. *IR spectra*

The IR spectra of the complexes are expected to be complex impeding unambiguous assignments of bands. However, we focused on bands which furnish information on the probable coordination of the ligand with the metal ions. The spectra of complexes with various ligands exhibit an identical pattern.

IR spectra of the ligands show characteristic bands due to ν(N–H) and ν(S–H) at 3300 cm^{-1} and 2575–2580 cm^{-1}, respectively. Deprotonation of thiol is indicated by absence of the band in metal complexes due to ν(S–H), indicating complexation through sulfur.

IR spectra of ligands show bands at 1550, 1200, 1090 and 775 cm^{-1}, which are assigned to thioamide-I, -II, -III and -IV vibrations, respectively, and indicate thione form of ligands. The thioamide-IV band has been found to have maximum C=S contribution. In complexes, this band shifts to lower frequency (about 70 cm^{-1}) suggesting coordination of sulfur.

If bonding occurs through sulfur of the thiol or thione group, the charge delocalized between N, C and S would result in shifting of the IR band due to ν(C=N) towards higher wavenumber on complexation. The band due to ν(C=S) would shift towards lower wavenumber on complexation. Both these effects are observed. The thioamide band which has major contribution from ν(C=N) and minor contribution from ν(C–N), at 1295 cm^{-1} in the spectra of the ligands, shifts by 45 cm^{-1} towards higher wavenumber. The thioamide band around 750 cm^{-1} in the ligands due to ν(C=S), shifts by 70 cm^{-1} to lower wavenumber on complexation.

Stretching frequency of C=S (1150 cm^{-1}) shifts to 1075 cm^{-1}, further indicating conversion of C=S into C–S and coordination through sulfur atom.

Bands occurring at 3300, 1650 and 830 cm^{-1} assigned to NH_2 vibrations slightly shift to lower wavenumber and the intensity of the 830 cm^{-1} band diminishes, suggesting coordination of nitrogen to copper, resulting in a stable five-membered chelate.

Thus, infrared spectra reveal that both ligands are bidentate, chelating through thioketo sulfur and hydrazinic nitrogen.

On the basis of IR spectral studies a square-planar geometry has been assigned to the copper complexes.

3.2. *^{1}H NMR spectra*

NMR spectra of the complexes show a shift of electron density from the ligands to metal. The characteristic downfield signal at δ 13.82 ppm attributed to –N=C–SH (–NH–C=S of the tautomer) in **1**(**a**–**j**) is absent, supporting deprotonation of the thiol.

The N–NH_2 protons in metal complexes occur in the range 6.24–6.29 ppm, as compared to triazoles at 5.46–5.78 ppm, indicating coordination through nitrogen. The remaining protons are multiplets in the aromatic region and unchanged in the metal chelates. ^{1}H NMR spectra of two complexes are presented in supplemental data; values are depicted in table 2.

IR and ^{1}H NMR spectral studies suggest chelation through deprotonated sulfur of the thiol group and the nitrogen of the primary amino group.

3.3. *Magnetic moments and electronic spectra*

The magnetic moments (μ_{eff}) of the Cu(II) complexes lie in the range 1.9–2.6 B.M., well within the range expected for square-planar geometry (table 3). The effective magnetic moment, μ_{eff} (B.M.), was computed from the equation

$$\mu_{eff} = 2.84[\chi_M^{corr.} \cdot T]^{1/2}$$

where T = absolute temperature at which the measurement is made and χ_M = corrected molar susceptibility.

The electronic spectra of Cu(II) complexes show bands in the regions 19000–19500 and 21500–22000 which may be assigned to the transitions $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_g$, respectively, assuming a square-planar geometry. The third band around 24000–25000 cm^{-1} may be attributed to charge transfer.

3.4. *Thermal analysis*

Thermal studies of the Cu(II) complexes of triazoles show higher thermal stability in **2d** and **2f**, where initial decomposition started at 220°C. The TG curves of all these

Table 2. ^{1}H NMR spectral characterization data of ligand and complexes.

Sl.No	Comp.*	SH	NH_2	Ar–H	Other peaks
1	1c (2c)	13.92 (Absent)	5.46 s, 2H, NH_2, (6.26)	6.81–7.94 (6.80–7.97)	3.83 s, 3H, OCH_3 (3.89)
2	1d (2d)	13.65 (Absent)	5.73 s, 2H, NH_2, (6.29)	6.81, 7.90 (d, 4H, Ar–H), (6.84, 7.89)	2.99 s, H of $N(CH_3)_2$, (3.00)
3	1h (2h)	13.80	5.60 s, 2H, NH_2, (6.24)	7.17, 7.69 (2d, 2H of furan ring), (7.12 & 7.65)	2.45 s, 3H, CH_3, (2.48)

*δ ppm for complex is enclosed in the bracket.

Table 3. Magnetic susceptibility data and electronic spectral data of the complexes.

Compound	μ_{eff} (B.M.)	Max in cm^{-1}
2a	1.973	18400
2b	1.986	18700
2c	1.929	19400
2d	1.819	21800
2e	2.232	19600
2f	2.066	19200
2g	1.987	19700
2h	1.915	19300
2i	2.065	18900
2j	2.359	19500

complexes indicate decomposition takes place in two identical stages. The complexes start decomposition after 220°C, corresponding to degradation of the aromatic substituent of the triazole. The onset of the second decomposition step occurs in the range 320–580°C, involving loss of triazole ligand. The experimental values are in agreement with the percent weight calculated on the basis of stoichiometry proposed for the complexes. The terminal solid residue was copper oxide in all cases in conformity with the percentage losses of mass obtained from TG curves.

3.5. *Thermal degradation kinetic and thermodynamic parameters*

The graph of [ln(ln $1/y$) *vs.* $1/T$] (where y is the fraction not yet decomposed) for the first and second stages of thermal degradation was plotted by treating the TGA data in terms of Broido's method [26], and is presented in Supplemental data. Thermogravimetric analytical curves obtained for complexes are provided in Supplemental data. From the slope of the graph, the kinetic parameters such as activation energy E_a and pre-exponential factor $\ln A$ were evaluated (Supplemental data). The activation energies are low in first stage transition (0.86–3.94 kJ mol^{-1}) and high in the second stage (5.03–9.82 kJ mol^{-1}).

Enthalpy of reaction (ΔH), entropy (ΔS) and free energy (ΔG) for all the complexes evaluated from thermal degradation data are also presented in Supplemental data. The enthalpy values observed for all the steps compared with those of T_0 show that with decrease of enthalpy, the decomposition temperature also decreases. In both stages the free energy is positive. Low entropy is observed for first step degradation and high for second step. The entropy is negative [(−)115.87–(−)139.52 JK^{-1}] for the first step and positive [157.61–230.35 JK^{-1}] for second degradation. However, the negative values of entropies of activation are compensated for by the value of enthalpies of activation, leading to almost the same values (00.12–12.15 kJ mol^{-1}) for the free energies of activation. Activation energies for thermal decomposition of the same complexes in the nitrogen are further decreased indicating high stability.

On the basis of IR, ^{1}H NMR and magnetic susceptibility data, the square-planar structure shown in scheme 2 is proposed.

3.6. *Pharmacological results and discussion*

Anti-inflammatory and analgesic activity studies revealed that copper complexes of triazole showed significant anti-inflammatory and analgesic activities. Compounds **2c, 2h** and **2j** showed highest activity among the synthesized complexes. Other compounds had moderate anti-inflammatory and analgesic activities. Maximum protection was shown in compounds having electron-withdrawing substituents on the aromatic and heterocyclic ring at the 5th position of triazole ring. Maximum activity is observed in **2b** with 3,5 methoxy groups, while 3,4 produced less activity. Introduction of more methoxy groups, as in **2g**, produced the least active compound in the series. Replacement of methoxy by alkyl substituted amino gave reduction in the activity. Introduction of a bulky aromatic substituent to the triazole produced the least active copper complex. Although the conversion of triazoles to copper complexes produced good anti-inflammatory and analgesic activities, their efficacy is not enough to develop clinically useful agents. Hence, structural modifications have to be made to improve the potency of these compounds as anti-inflammatory and analgesic agents.

4. Pharmacological evaluation

4.1. *Anti-inflammatory activity*

All the synthesized compounds were tested for their anti-inflammatory activity using the carrageenan-induced rat hind paw edema method of Winter *et al.* [27, 28]. Albino rats (Wistar strain) of either sex, weighing between 150 and 200 g, were divided into groups consisting of six animals. One group served as control and received 0.1 mL of 1% gum acacia suspension orally. Group II served as standard and received phenylbutazone at $20\,mg\,kg^{-1}$ as suspension in gum acacia orally. One hour after administration of test compounds, 0.1 mL of 1% carrageenan in normal saline was given subcutaneously to the sub plantar region of right hind paw. The paw volume was measured immediately ('0' h) and after 1, 2, 3 and 4th h, respectively, by using a plethysmometer. The difference between the paw volume at 4th and '0' h measurement was calculated and taken as edema volume. Percentage inhibition in the paw edema was calculated by using the formula,

$$\text{Percentage inhibition} = 100\left(1 - \frac{V_t}{V_c}\right)$$

where V_t = mean increase in paw volume of test and V_c = mean increase in paw volume of control. Percentage inhibition of the triazoles were 12–18% and the complexes were 24–34%. Tables of data are given in the Supplementary material.

4.2. *Analgesic activity*

All the compounds were tested for their analgesic activity by using Eddy's hot plate technique [29]. Mice (Swiss strain) of either sex weighing between 25 and 35 g were used for the experiment. Diclofenac sodium at $20\,mg\,kg^{-1}$ body weight as suspension in 1% gum acacia was used as standard, which showed percentage analgesic activity of 46%. In this method heat is used as a source of pain. Animals were individually placed on a hot plate maintained at constant temperature (55°C) and the reaction of animals, such as paw licking or jump response (whichever appears first) was taken as the end point. Tested compounds at $20\,mg\,kg^{-1}$ body weight were given as suspension in 1% gum acacia orally to animals and reaction time of animals on the hot plate observed at 15, 30, 60, 90 and 120 min after administration. A cut off time of 15 sec was taken as maximum analgesic response to avoid injury to the paws. Percentage analgesic activity of the ligands were 14–18% and the copper complexes 25–38%. Tables of data are given in the Supplementary material.

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