ORIGINAL RESEARCH



# Transition metal complexes of *s*-triazine derivative: new class of anticonvulsant, anti-inflammatory, and neuroprotective agents

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Received: 23 January 2013/Accepted: 20 May 2013 © Springer Science+Business Media New York 2013

**Abstract** A new series of transition metal complexes of 2,4-bis(indolin-3-one-2-ylimino)-6-phenyl-1,3,5-triazine) (BIPTZ) have been synthesized. The structural features of BIPTZ and metal(II) complexes were investigated using elemental analyses, magnetic susceptibility, molar conductance, mass, IR, UV-Vis, <sup>1</sup>H NMR, <sup>13</sup>C NMR, CV, and ESR spectral studies. Electronic absorption spectra and magnetic susceptibility measurements of the complexes predict their geometry. The redox behavior of the copper(II) complexes has been studied by cyclic voltammetry. All the synthesized compounds may serve as potential photoactive materials as indicated from their characteristic fluorescence spectrum. The Schiff base and its metal complexes were screened for anticonvulsant and antiinflammatory activities in vivo. The metal(II) complexes are potent agents in treating neurochemical and behavioral abnormalities seen in Parkinson's diseased (PD) mice than free ligand.

**Keywords** *s*-Triazine · Metal complexes · Anticonvulsant · Anti-inflammatory · Neuroprotectivity

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#### Introduction

Medicinal inorganic chemistry is arousing a significant interest in the design of metal complexes as potential diagnostic and therapeutic agents (Cerchiaro and Ferreira, 2006). A comprehensive list of metal complexes which are already in use, encourage further studies for new metallodrugs such as metal-mediated antibiotics, antibacterial, antiviral, and anticancer compounds. While possessing a unique characteristic esteem in the heterocyclic compounds due to its wide range of therapeutic activities, s-triazine exhibits a seminal value in antibacterial (Chohan et al., 2004), antiviral (Davidson and Boyki, 1978), anti-HIV, and anti-inflammatory activities (Hielman et al., 1980; Sun et al., 2011). Recently, triazine derivatives have been disclosed as a potent inhibitor of tyrosine kinase and have demonstrated antiangiogenic property in vivo (Baindur et al., 2005). A large number of structurally novel triazine derivatives have been reported to be a suitable lead compound for the possible development of new antitumor agents, (Chohan et al., 2010). Several triazine derivatives are well known in the context of anticancer drugs (Porter et al., 2002), estrogen receptor modulators (Henke et al., 2002), inhibitors of sorbitol dehydrogenase (Mylari et al., 2003), anti-trypanosomal agent (Klenke et al., 2001), antitrypanosomal drugs, and antimalarial agents (Katiyar et al., 2005). For instance, carbamazepine and lamotrigine which are currently used anticonvulsant drugs contain a triazine ring in their structures. In harmony with the aforementioned study, we herein report the synthesis and characterization of Schiff base derived from condensation of 2,4-diamino-6-phenyl-1,3,5triazine and indoline-2,3-dione and its metal complexes. Furthermore, the synthesized compounds were evaluated for anticonvulsant activity, anti-inflammatory activity, and neuroprotectivity on albino mice.

# Materials and methods

# Materials

All the chemicals used were of reagent grade and used without further purification.

# 2,4-Bis(2,4-bis(indolin-3-one-2-ylimino)-6-phenyl-1,3,5triazine (BIPTZ)

This compound was prepared by refluxing a mixture of 2,4diamino-6-phenyl-1,3,5-triazine (0.01 mol) and indoline-2,3-dione (0.02 mol) in ethanol for a period of 6 h. The reaction was monitored by TLC and the resulting solution was slowly evaporated. The product was obtained as a reddish brown crystal. Yield: 75 %. m.p.: 185-187 °C. IR (KBr, cm<sup>-1</sup>): 1616, 1458 and 3190. <sup>1</sup>H NMR (DMSO- $d_6$ 300 MHz) (ppm): 9.607 (s, 2H, NH), 5.7-7.06 (m, 13H, Ar-H). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) (ppm): 117.38–143.24 (aromatic carbon), 155.57 (C=N of triazine ring), 164.42 (C=O), 167.50–172.18 (isatin ring carbon). EI-mass: m/z445. Analysis Found. C, 67.45; H, 3.33; N, 22.07 %. The synthesis of BIPTZ is shown in Fig. 1.

# Preparation of metal(II) complexes

An ethanolic solution of metal(II) chloride (MCl<sub>2</sub>, M=Cu(II), Ni(II), Co(II)) was stirred under reflux with hot ethanolic solution of the Schiff base in 1:1 and 1:2 M ratios for 4 h. During refluxation, the metal chelates were separated out. The metal chelates thus separated were filtered, washed with ethanol, and dried over CaCl<sub>2</sub> in vacuum. All the complexes obtained are colored and are listed in Table 1.

# Characterization

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), neurotoxin was obtained from Sigma Chemicals & Co. All other chemicals and solvents were purchased from Aldrich Chemicals & Co. and the solvents were distilled before use as per the standard procedure. The elemental analyses were done at Central Drug Research Institute, Lucknow. The

#### Fig. 1 Synthesis of BIPTZ

infrared (IR) spectra of Schiff base and its metal(II) complexes were recorded on a Jasco FT-IR spectrophotometer in KBr disks. <sup>1</sup>H NMR spectra of the Schiff base was recorded in DMSO-d<sub>6</sub> on Bruker 300 MHz spectrometer at room temperature using TMS as an internal reference. <sup>13</sup>C NMR spectrum of the Schiff base was recorded in DMSO $d^6$  at room temperature. EI-mass spectrum of the Schiff base was performed on JEOL-CGC MATE-2 instrument. Cyclic voltammetry measurements of Cu(II) complexes were carried out at room temperature in DMSO under N2 atmosphere on BAS-50 voltammograph using a threeelectrode cell containing a reference Ag/AgCl electrode, Pt wire auxiliary electrode, and glassy carbon working electrode in DMSO with tetrabutylammonium perchlorate (TBAP) as supporting electrolyte. The electronic absorption spectra of the complexes were recorded in DMSO on a JASCO V-530 spectrophotometer in the region 200-1100 nm. Fluorescence spectra were recorded on ELICO SL-174 spectrofluorometer. The ESR spectra of Cu(II) complexes were recorded in solid state at 300 and 77 K on JEOL 100 ESR spectrometer using DPPH as "g" marker. Magnetic susceptibility of the complexes was obtained on a Sherwood Magnetic susceptibility balance Mk1 at room temperature. Effective magnetic moments were calculated using the formula  $\mu_{eff} = 2.28 (\chi_M T)^{1/2}$ , where  $\chi_M$  is the corrected molar susceptibility. Molar conductivity measurements of the complexes were recorded on Systronics conductivity bridge type (OSWAL) in DMSO  $(10^{-3} \text{ M})$  at room temperature. The synthesized Schiff base and its metal complexes were screened for anticonvulsant, anti-inflammatory, and neuroprotective activity in K.M. College of Pharmacy, Madurai.

#### Pharmacology

Schiff base (BIPTZ) and its metal(II) complexes were evaluated for in vivo anticonvulsant, anti-inflammatory, and neuroprotective activities. Maximal electroshock method was used for establishing anticonvulsant activity, and carrageenan-induced rat paw edema method was used for evaluating anti-inflammatory activity. Behavioral parameter, antioxidants like lipid peroxidation, reduced glutathione and superoxide dismutase, and oxidative stress



2,4-diamino-6-phenyl triazine Indoline-2,3-dione

Compound	Empirical formula	Color	C % found (calc)	H % found (calc)	N % found (calc)	M % found (calc)	$\Lambda \text{ Ohm}^{-1} \text{ cm}^2 \text{mol}^{-1}$	$\mu_{\rm eff}$ (BM)
BIPTZ	$C_{25}H_{15}N_7O_2$	Red	67.45 (67.41)	3.33 (3.37)	22.07 (22.02)	-	-	_
(1)	$[Cu(C_{25}H_{15}N_7O_2)Cl_2]$	Brown	51.85 (51.81)	2.53 (2.59)	16.90 (16.92)	10.95 (10.92)	10.5	1.94
(2)	[Ni(C <sub>25</sub> H <sub>15</sub> N <sub>7</sub> O <sub>2</sub> )Cl <sub>2</sub> ]	Green	51.95 (51.99)	2.54 (2.59)	16.90 (16.98)	11.16 (10.57)	5.3	3.04
(3)	$[Co(C_{25}H_{15}N_7O_2)Cl_2]$	Violet	52.13 (52.17)	2.65 (2.60)	17.09 (17.04)	10.23 (10.26)	8.6	4.96
(4)	$[Cu(C_{25}H_{15}N_7O_2)_2]Cl_2$	Dark blue	58.56 (58.59)	2.96 (2.92)	19.17 (19.14)	6.24 (6.20)	160	1.82
(5)	[Ni(C <sub>25</sub> H <sub>15</sub> N <sub>7</sub> O <sub>2</sub> ) <sub>2</sub> ]Cl <sub>2</sub>	Brown	58.70 (58.70)	2.95 (2.93)	19.19 (19.17)	5.93 (5.96)	156	2.95
(6)	$[Co(C_{25}H_{15}N_7O_2)_2]Cl_2$	Dark violet	58.85 (58.82)	2.93 (2.94)	19.24 (19.21)	5.72 5.78)	201	4.75

Table 1 Elemental analysis, molar conductance, and magnetic moment measurements

Fig. 2 Proposed structure of metal(II) complexes



(1), (2), (3)



parameters such as nitrite level and myeloperoxidase level were also measured on albino mice.

#### Anticonvulsant activity

The anticonvulsant activity was studied by Supra maximal electrical shock method. Healthy male albino wistar mice weighing from 200–250 g were selected and housed in separate cages with 12/12 h light/dark cycle at 21 + 2 °C and fed with balanced diet, water ad libitum. The animals were divided into nine groups of six each. The first groups of animals were served as control, received 10 ml/kg normal saline. Second group served as standard which received 25 mg/kg phenytoin sodium. The Schiff base (BIPTZ) and its metal complexes (1-6) (10 mg/kg) were administered by IP injection to rest of the seven groups. The evaluation was started 30 min after administration of the synthesized compounds and Pinna electrodes with the intensity of 150 mA current were used to deliver the

stimuli. The time needed for the development of unequivocal sustained clonic seizure activity involving the limbs was carefully noted. The onset of a general clonus was used as the end point. The general clonus was characterized by forelimb clonus followed by full clonus of the body. The duration of clonic convulsions was also noted. Seizure-free interval in 1 h was considered as protection. The number of animals protected in each group was recorded and percentage protection was calculated.

#### Anti-inflammatory activity

The anti-inflammatory activity was studied by carrageenan-induced rat paw edema method. Albino mice of either sex (200-220 g) were selected and kept in animal house under standard laboratory conditions. The animals were divided into nine groups of six animals each. Group I served as control and received 10 ml/kg normal saline. Group II served as standard and received Diclofenac sodium (10 mg/kg) through IP route and the remaining seven groups served as test groups and received Schiff base (BIPTZ) and metal(II) complexes (1-6) (10 mg/kg) 30 min prior to carrageenan injection. The initial left hind paw volume of the rats was measured using a digital plethysmometer. The volume of the left hind paw of the test group, standard, and control groups were measured at 60, 240, and 360 min after carrageenan injection. Mean increase in paw volume was measured and percentage of inhibition was calculated.

# Neuroprotective activity

Male wistar mice weighing from 250-280 g were selected and kept in animal house under standard laboratory conditions at  $25 \pm 2^{\circ}$  C with light-dark cycles of 12 h. The animals were acclimatized to laboratory conditions before the experiment starts. The animals had free access to pellet diet and water ad libitum. The animals were divided into nine groups, each consisting of six mice. Group I served as vehicle control and received equivalent volume of vehicle of drug for 12 days, Group II received equivalent volume of vehicle of drugs for 7 days and on 7th day received intrastriatal injection of MPTP (32 µmol in 2 µl) and vehicle for further 5 days. Group III-IX received the synthesized Schiff base (BIPTZ) and its metal complexes (1-6), respectively, for 7 days and on 7th day received intrastriatal injection of MPTP (32 µmol in 2 µl) and again treatment for 5 days. At the end of experimental period, the animals were fasted overnight and sacrificed by cervical decapitation. The brains were excised immediately and the brain tissue was homogenized in ice-cold butanol solution and used for further analysis.

# Locomotor activity

The locomotor activity was measured using Actophotometer. It consists of cage which has  $30 \times 30 \times 30$  cm, and at the bottom six lights and six photocells were placed in the outer periphery of the bottom in such a way that a single mouse blocks only one beam. Photocell is activated when the rays of light falls on photocells. The beam of light is interrupted as and when animal crosses the light beam, number of cut interruptions was recorded for 10 min.

# Antioxidant studies

Brain tissue was homogenized in 50 mmol phosphate buffer (pH 7.0) containing 0.1 mmol of ethylenediamine tetraacetic acid (EDTA) to give 5 % (w/v) homogenate. The homogenate was centrifuged at 10,000 rpm for 10 min at 0 °C in cold centrifuge and the resulting supernatant was used for further studies.

# Lipid peroxidation

MDA level was measured according to the standard method at room temperature. 200  $\mu$ l of supernatant was added to 50  $\mu$ l of 8.1 % sodium dodecyl sulfate, vortexed, and incubated for 10 min at room temperature. 375  $\mu$ l of thiobarbituric acid (0.6 %) was added and placed in a boiling water bath for 60 min and then the sample was allowed to cool to room temperature. A mixture of 1.25 ml of butanol: pyridine (1.5:1) was added, vortexed, and centrifuged at 1000 rpm for 5 min. The colored layer (500  $\mu$ l) was measured at 532 nm on a ELICO 171 Spectrophotometer and the values were expressed in mmoles of MDA formed per mg protein/min (Ohkawa *et al.*, 1979).

# Reduced glutathione

Reduced glutathione levels were measured according to the standard procedure (Ellman, 1959) at room temperature. 0.75 ml of supernatant was mixed with 0.75 ml of 4 % sulfosalicylic acid and then centrifuged at 1,200 rpm for 5 min at 4 °C, from this 0.5 ml of supernatant was taken and added to 4.5 ml of 0.01 M 5,5-dithiobis-(2-nitrobenzoic acid) (DTNB) and absorbance was measured at 412 nm by using a ELICO 171 UV–Vis Spectrophotometer.

# Statistical analysis

All experimental results are expressed as mean  $\pm$  SEM. Behavioral parameters were analyzed using one-way ANOVA followed by Newman's keul's multiple range tests. The criterion for statistical significance was considered as P < 0.01.

# **Results and discussion**

All the complexes are colored, stable, and hygroscopic in nature. The complexes are insoluble in common organic solvents but soluble in DMF and DMSO. The elemental analyses (Table 1) support that the Schiff base forms metal complexes of the type [MLCl<sub>2</sub>] and [ML<sub>2</sub>] Cl<sub>2</sub>. The geometry of the metal complexes was elucidated using spectral studies. The proposed structure of the metal complexes is shown in Fig. 2.

# Molar conductance measurements

The molar conductivity measurement of metal(II) complexes of [ML] type (**1–3**) indicates the non-ionic nature of these complexes (5.3–10.5  $\Omega^{-1}$ cm<sup>-1</sup>mol<sup>-1</sup>) and hence they are considered as non-electrolytes (Sharaby, 2007). Metal complexes of [ML<sub>2</sub>] type (**4–6**) were found to have molar conductance values in the range of 156–201  $\Omega^{-1}$ cm<sup>-1</sup>mol<sup>-1</sup> suggesting their ionic nature and that of the type 1:2 electrolytes (Geary, 1971).

# Infrared spectra

The important infrared spectral data of the Schiff base and its metal complexes are listed in Table 2. The IR spectra of the Schiff base exhibited a characteristic high intensity band at 1616 cm<sup>-1</sup>, assigned to v(C=N). In comparison with the spectra of the Schiff base, all the complexes exhibited the band of v(C=N) in the region of 1654–1681 cm<sup>-1</sup> indicating that the ketimine nitrogen atom is coordinated to the metal ion (Murukan et al., 2007). A characteristic strong band observed around 1728 cm<sup>-1</sup> ascribed to v(C=O) of isatin was observed at similar positions in the spectra of metal complexes, suggesting the noninvolvement of carbonyl oxygen in coordination (Akinchan et al., 2002). The Schiff base exhibits a strong band at 1458  $\text{cm}^{-1}$  which is attributed to v(C=N) group in s-triazine. This band is shifted to lower frequency of 1404–1419 cm<sup>-1</sup> upon complexation which indicates that (C=N) of triazine ring is one of the coordinating atoms in the ligand (Solankee and Thakor, 2006). The band at 3190  $\text{cm}^{-1}$  assigned for v(NH) group was almost unchanged in the metal complexes, suggesting that this group is not participating in coordination (Bhusan subudhi et al., 2007). New bands are found in the spectra of metal complexes in the region 428–464  $\text{cm}^{-1}$  assigned to v(M-N)(Kulkarni et al., 2011). Proof of chloride coordination in 1:1 metal complexes is demonstrated by new bands at  $328-345 \text{ cm}^{-1}$  assigned to v(M-Cl) (Tharmaraj *et al.*, 2009). Therefore, from the IR spectra, it is concluded that the Schiff base behaves as a neutral tridentate coordinating to the metal ion via the triazine ring nitrogen and ketimine nitrogen.

## NMR spectra

The <sup>1</sup>H NMR spectrum of the Schiff base under study showed the characteristic resonance at 9.6 ppm due to –NH proton of isatin ring. The sharp multiplet signals of the phenyl protons are found in the region 5.7–7.06 ppm. <sup>13</sup>C NMR spectrum of Shciff base exhibits singlet at 155 ppm which is attributed to three equivalent carbon of triazine ring and aromatic carbons observed in the region 117–172 ppm. The equivalency of C<sub>2</sub>, C<sub>4</sub>, and C<sub>6</sub> indicates the symmetric nature of the ligand. Carbonyl carbon is observed at 164 ppm and isatin ring carbons are observed in the region 167–172 ppm. Figs. 3, 4, 5.

Electronic absorption spectral studies and magnetic susceptibility

The electronic spectrum of copper(II) complex (1) shows three bands at 10,964; 14,792; and 17,094  $\text{cm}^{-1}$  assignable

to  ${}^{2}B_{1} \rightarrow {}^{2}A_{1}$  (v<sub>1</sub>),  ${}^{2}B_{1} \rightarrow {}^{2}B_{2}$  (v<sub>2</sub>), and  ${}^{2}B_{1} \rightarrow {}^{2}E$  (v<sub>3</sub>) transitions, respectively; which are characteristic of square pyramidal geometry. The magnetic moment of (1) is found to be 1.94 BM, which is interpreted as suggestive of a fivecoordinate square pyramidal geometry around copper(II) ion (Yamada et al., 2002; Acuria Cueva et al., 2003). The nickel(II) complex (2) exhibits three d-d bands at 9,756; 14.619; and 20.661  $\text{cm}^{-1}$  and these bands may be tentatively assigned to  ${}^{3}B_{1}(F) \rightarrow {}^{3}E(F), {}^{3}B_{1}(F) \rightarrow {}^{3}A_{2}(P)$ , and  ${}^{3}B_{1}(F) \rightarrow {}^{3}E(P)$  transitions, respectively, suggesting square pyramidal geometry. The spectra resemble those spectra reported for five-coordinate square pyramidal nickel(II) complexes (Khalil, 2003; Yang et al., 2009). The electronic absorption spectrum of (3) displayed three bands at 10,050; 15,432; and 20,703  $\text{cm}^{-1}$  which can be assigned to the transitions  ${}^{4}A_{2} + {}^{4}E \rightarrow {}^{4}B_{1}$ ,  ${}^{4}A_{2} + {}^{4}E \rightarrow {}^{4}E(P)$ , and  ${}^{4}A_{2} + {}^{4}E \rightarrow {}^{4}A_{2}(P)$ , respectively, which are characteristic of square pyramidal geometry. Thus the electronic spectral data of (3) are in good agreement with the already reported square pyramidal complexes (Gupta and Chandra, 2006). The metal complexes (2) and (3) have magnetic moment values 3.04 and 4.96 BM, respectively, which further confirms the square pyramidal geometry (Dahl, 1969).

The electronic spectrum of (4) gives two bands at 17,543 and 21,739 cm<sup>-1</sup> which are assignable to ligand-to-metal charge transfer and intra-ligand charge transfer, respectively. A broad band at 11,061 cm<sup>-1</sup> is characteristic of d–d transition due to  ${}^{2}E_{g} \rightarrow {}^{2}T_{2g}$  transition (Ram Agarwal *et al.*, 2006). This band strongly favors an octahedral geometry and the same is further supported by the magnetic moment 1.82 BM (Thakurta *et al.*, 2009; Hazell *et al.*, 2000). The  $d^{9}$  configuration makes Cu(II) ion susceptible to John–Teller distortion. As a result, the above complex is found to be tetragonally distorted which can give rise to three types of electronic transitions. These may not be resolved into three bands due to the fact that d orbitals lie closer to each other. The nickel(II) complex (**5**) exhibits three d–d bands at 9,881; 12,738; and 21,645 cm<sup>-1</sup> which are tentatively assigned to  ${}^{3}A_{2g} \rightarrow {}^{3}T_{2g}$ ,  ${}^{3}A_{2g} \rightarrow {}^{3}T_{1g}(F)$ , and  ${}^{3}A_{2g} \rightarrow {}^{3}T_{1g}(P)$  transitions,

Table 2 Important IR frequencies of Schiff base and metal(II) complexes

Compound	v(C=N) ketimine	v(C=N) triazine	v(NH)	v(M–N)
BIPTZ	1616	1458	3190	_
(1)	1681	1412	3296	435
(2)	1681	1419	3213	453
(3)	1678	1419	3271	464
(4)	1662	1404	3282	428
(5)	1666	1415	3262	445
(6)	1654	1412	3225	438



respectively, which arises from octahedral geometry (Chandra *et al.*, 2009). The measured magnetic moment value is found to be 2.95 BM; this also supports the octahedral geometry (Emaraa and Abou-Hussen, 2006). The electronic spectrum of Co(II) complex (**6**) consists of three absorption bands at 9,980; 12,437; and 21,186 cm<sup>-1</sup> which may be assigned to  ${}^{4}T_{1g}(F) \rightarrow {}^{4}T_{2g}(F)$ ,  ${}^{4}T_{1g}(F) \rightarrow {}^{4}A_{2g}$ , and  ${}^{4}T_{1g}(F) \rightarrow {}^{4}T_{1g}(P)$  transitions, respectively, suggesting that there is an octahedral geometry around Co(II) ion (Omar and Mohamed, 2005). The magnetic moment value is found to be

4.75 BM which is an indicative of octahedral geometry (Singh *et al.*, 2006).

## ESR spectral studies

The ESR spectra of Cu(II) complexes (1) and (4) were recorded in solid state at 300 and 77 K, and the spin Hamiltonian parameters are listed in Table 3. The ESR spectrum of (1) exhibits anisotropic signals with  $g_{\parallel} = 2.227$  and  $g_{\perp} = 2.042$ . The  $g_{\parallel}$  and  $g_{\perp}$  values are



Fig. 5<sup>13</sup>C NMR spectrum of Schiff base

closer to 2 and  $g_{\parallel} > g_{\perp}$ , suggesting an axially elongated square pyramidal geometry (Ray and Kauffman, 1990). The covalent character of metal–ligand bond is inferred from the  $g_{iso}$  value 2.10. The trend,  $g_{\parallel} > g_{\perp} > g_e$  (2.0023) shows that the unpaired electron lies predominantly in the  $d_{x2-y2}$  orbital of the copper(II) ion (Gudasi *et al.*, 2006). The calculated magnetic moment for the copper(II) complex (1.96 BM) as per the relation  $\mu^2 = 3/4 [g]^2$  is indicative of an unpaired electron. The  $\alpha^2$  value (0.74) suggestive of in-plane covalency and the poor in-plane  $\pi$ -bonding in the complex is reflected in their  $\beta^2$  values. The molecular orbital coefficients  $\alpha^2$  and  $\beta^2$  were calculated using the following equations.

$$\begin{split} \alpha^2 = \ A_{||}/p \ + \ \left(g_{||} - 2.0023\right) + 3/7(g_{\perp} - 2.0023) \ + \ 0.04 \\ \beta^2 = \ \left(g_{||} - 2.0023\right) \ E \ /8\lambda \, \alpha^2 \end{split}$$

The calculated value of  $g_{\parallel}/A_{\parallel}$  is 138.7 cm characteristic of distorted structure. The geometric parameter *G* is estimated from the expression  $G = (g_{\parallel}-2.0023)/(g_{\perp}-2.0023)$ . The observed value *G* for the Cu(II) complex is 5.65 suggesting no appreciable coupling (Fouda *et al.*, 2008).

The observed  $g_{\parallel}$ ,  $g_{\perp}$ , and  $A_{\parallel}$  values for copper(II) complex (4) are characteristic of octahedral geometry

(Kasumov and Koksal, 2004). The observed value of *G* is 2.83, characteristic of mononuclear configuration which also suggests that the exchange coupling is present and misalignment is appreciable. The  $\alpha^2$  value (0.713) pointed out appreciable in-plane covalency. The calculated value of  $g_{\parallel}/A_{\parallel}$  (170.3 cm) reveals slightly distorted structure. The orbital reduction factors such as  $K_{\parallel}$  and  $K_{\perp}$  are estimated from the equation  $K_{\parallel} = (g_{\parallel}-2.0023) \Delta E/8\lambda$ ,  $K_{\perp} = (g_{\perp}-2.0023) \Delta E/2\lambda$  and  $K_{\parallel}$  (0.43) >  $K_{\perp}$  (0.15) show poor in-plane  $\pi$ -bonding which is also reflected in  $\beta^2$  values.

## Electrochemical behavior

Cyclicvoltammetry is a highly versatile electro-analytical technique. In recent years, it has become the most popular technique for studying electrochemical reactions. The cyclicvoltammogram of Schiff base (BIPTZ) in nitrogen atmosphere does not show any oxidation or reduction peak. Controlled potential electrolysis of the copper(II) complex (1) (Fig. 6a) exhibits well-defined irreversible redox peak corresponding to the formation of  $Cu^{II} \rightarrow Cu^{III}$  with anodic peak at 46.38 mV ( $E_{pa}$ ), followed by the respective cathodic waves in the reversible scan at -400 mV ( $E_{pc}$ ) due to  $Cu^{III} \rightarrow Cu^{II}$  reduction. The ratio of cathodic to anodic peak currents

<b>Table 3</b> ESR spectral data of copper(II) complexes									
Complex	g∥	$g_{\perp}$	$g_{\rm iso}$	$\alpha^2$	$\beta^2$	$A_\parallel X 10^{-4} \ cm^{-1}$	$A_\perp X 10^{-4} \ \text{cm}^{-1}$	$g_{\parallel}/A_{\parallel}~cm$	G
(1)	2.227	2.042	2.10	0.740	0.783	160.5	112.3	138.7	5.65
(4)	2.265	2.095	2.15	0.713	1.206	133.7	69.5	170.3	2.83





 $I_{\rm pc}/I_{\rm pa} = 1.075$  corresponds to one-electron process. The peak separation between  $E_{\rm pa}$  and  $E_{\rm pc}$  is 446.38 mV, larger than the value required for a reversible process (59 mV), which indicates that the electron transfer process is irreversible in nature (Kannappan *et al.*, 2003). The cyclicvoltammogram of Cu(II) complex (4) displays one reduction peak at ( $E_{\rm pc}$ ) -300 mV

with a corresponding anodic peak at  $(E_{pa})$  4.67 mV (Fig. 6b). The peak separation  $\Delta E_p = 304.67$  mV, which indicates that the reduction process is irreversible in nature and the ratio of cathodic to anodic peak currents corresponding to the chemical change occurs with one-electron transfer as Cu(II)  $\rightarrow$  Cu(III)  $\rightarrow$  Cu(II).

#### Fluorescence studies

The fluorescence studies are carried out for Schiff base and its metal complexes in DMSO. The spectral data are listed in Table 4 and the overlapping spectrum of the Schiff base and its metal complexes are presented in Fig. 7. The Schiff base exhibits a broad emission band with a maximum wavelength of 560 nm upon photo excitation at 550 nm. Similarly, all the above complexes were characterized by the emission bands around 458-575 nm. Significant differences in positions of emission maximum of Schiff base and its complexes establish the complexation process (Majumder et al., 2006). The excitation and emission spectra of metal complexes in DMSO at room temperature are similar and these excitation wavelength match the absorption spectra of the corresponding metal complexes. The most increased fluorescence intensity of Schiff base was observed in cobalt(II) complex (3). The maximum emission of the nickel(II) complex (2) was observed when the complex was excited at 558 nm, suggesting that ligandto-Ni(II) complex energy transfer is mainly mediated by the Schiff base. The strong emissions of metal complexes indicate that the Schiff base is a good chelating agent to absorb and transfer energy to metal(II) ions. The efficient energy transfer from Schiff base to metal ion is one of the key factor to achieve characteristic fluorescence. Among the six metal complexes, the excitation and emission intensities of Ni(II) complex (2) are relatively weak and the fluorescence intensity of Co(II) complex (3) is the strongest among the complexes. This enhancement of fluorescence through complexation is of much interest as it opens up the opportunity for photochemical applications of these complexes.

# Pharmacological study

# Anticonvulsant activity

Anticonvulsant activity data of the Schiff base and its metal complexes are presented in Table 5 and the graphical representation is shown in Fig. 8. The results were statistically analyzed by one-way ANOVA followed by Newman keul's multiple range tests and expressed as mean  $\pm$  SEM (Poojary *et al.*, 2012). The satisfactory results of the Schiff base and its metal(II) complexes are quite long and comparable to phenytoin which is used as the standard anticonvulsant drug. It has been reported that the existence of a hydrophobic unit, an electron donor group, and hydrogen bonding domain are essential for anticonvulsant activity. As evidenced by the active drugs, such as carbamazepine and lamotrigine, the synthesized Schiff base fulfills these demands. All the metal(II) complexes showed considerable effect on animals for a longer

Table 4 Fluorescence data of Schiff base and metal(II) complexes

Compound	Excitation wavelength $\lambda_{\max}$ (nm)	Fluorescence wavelength $\lambda_{\max}$ (nm)
BIPTZ	550	561
(1)	446	458
(2)	558	575
(3)	476	483
(4)	458	469
(5)	445	459
(6)	469	471



Fig. 7 Fluorescence spectrum of metal(II) complexes

duration when compared to Schiff base. Such increased activity of the metal complexes is of tremendous importance in pharmaceutical field. Procedures employed for evaluation of anticonvulsant and anti-inflammatory activity were reviewed and approved by the Institutional Animal Ethical Committee (IAEC).

## Anti-inflammatory activity

Anti-inflammatory activity data of the Schiff base and its metal complexes were evaluated by carrageenan-induced rat paw edema method and the results are shown in Table 6. Injection of carrageenan into the rat paw produces inflammation resulting from metabolism of arachidonic acid. From the observation, it is found that the Schiff base and metal(II) complexes possess higher anti-inflammatory activity compared to the standard. Among all the metal complexes, the percentage inhibition shown by the complex (6) was 64 % and it was significant and comparable

 Table 5
 Anticonvulsant activity data of Schiff base and metal(II) complexes

Compound	Dose mg/kg	Duration of seizure mean $\pm$ SEM	% inhibition of extension phase
Control	10	$13.52 \pm 2.12$	-
Phenytoin sodium	10	$2.22\pm0.45$	83.72
BIPTZ	10	$4.56\pm0.92$	66.27
(1)	10	$4.32\pm0.88$	68.04
(2)	10	$4.20\pm0.71$	68.93
(3)	10	$4.22\pm0.65$	68.78
(4)	10	$4.24\pm0.90$	68.63
(5)	10	$4.06\pm0.55$	69.97
(6)	10	$4.34\pm0.75$	68.63



Fig. 8 Anticonvulsant activity of Schiff base and metal(II) complexes

with the standard drug Diclofenac sodium (71 %) (Fig. 9). The enhanced anti-inflammatory activity of the complexes may be explained on the basis of enhanced penetration through cellular membranes due to complexation (Stefancich *et al.*, 1991).

#### Anti-parkinsonian activity

Neurodegeneration refers to a condition of neuronal death occurring as a result of progressive disease of long term. Among hundreds of different neurodegenerative disorders, much attention has been given to Parkinson's disease. Parkinson's disease (PD) is a chronic progressive neurodegenerative movement disorder characterized by a profound loss of nigrostriatal dopaminergic neurons. Neuroprotection is a broad term to cover any therapeutic strategy to prevent nerve cells called neurons from dying, and it usually involves an intervention, either a drug or treatment. The goal of neuroprotection is to limit neuronal dysfunction after injury and attempt to maintain the

Table 6	Anti-inflammatory	activity	data	of	Schiff	base	and	its
metal(II)	complexes							

Compounds	Dose (mg/ kg)	Paw volume (ml)	% inhibition of paw edema
Control	10	$5.92\pm0.96$	-
Diclofenac sodium	10	$1.70 \pm 0.48$	71.28
BIPTZ	10	$2.62\pm0.72$	55.74
(1)	10	$2.47\pm0.46$	58.27
(2)	10	$2.40\pm0.40$	59.45
(3)	10	$2.52\pm0.53$	57.43
(4)	10	$2.50\pm0.55$	57.77
(5)	10	$2.48\pm0.45$	58.10
(6)	10	$2.12\pm0.33$	64.18





Fig. 9 Anti-inflammatory activity of Schiff base and metal(II) complexes

possible integrity of cellular interactions in the brain resulting in undisturbed neural function.

## Evaluation of behavioral activity in MPTP-treated mice

The locomotor activity data of the Schiff base and metal complexes given in (Table 7) reveal that there was no significant difference between the locomotor activities in MPTP-treated mice and control group when accessed on 1st and 5th day. The administration of MPTP significantly decreases the locomotor activity and motor function in association with a significant oxidative damage induced in striatal region of the brain on 8th and 12th day. Alcoholic extract of Schiff base and its metal complexes (1-6) also display no significant difference in locomotor activity on 1st and 5th day. But it was significantly increased on 8th and 12th day of treatment with the Schiff base and its metal complexes (1-6) as compared to MPTP-treated group (Fig. 10). Thus it is plausible that the administration of Schiff base and metal complexes (1-6) produces a significant neuroprotective effect in MPTP-induced striatal lesions in mice.

Groups	1st day	5th day	8th day	12th day
Control	$296 \pm 10.62$	$257.66 \pm 9.6$	$259 \pm 3.12$	$252.16 \pm 2.10$
MPTP	$282\pm9.77$	$259.66 \pm 9.27$	133.16 ± 3.38*	136.33 ± 3.56*
BIPTZ	$291.16 \pm 11.42$	$259.32 \pm 3.13$	$260 \pm 2.73$	$263.66 \pm 3.49$
(1)	$281 \pm 10.63$	$260.83 \pm 3.22$	$255.66 \pm 2.71$	$240.66 \pm 2.87$
(2)	$270 \pm 10.63$	$257.16 \pm 2.18$	$258.33 \pm 1.4$	$287.33 \pm 2.30$
(3)	$277.66 \pm 10.11$	$256.16 \pm 2.24$	$212.33 \pm 2.82$	$245.52 \pm 2.97$
(4)	$266.12 \pm 9.25$	$250.40 \pm 10.20$	$260.05 \pm 10.82$	$248.6\pm8.97$
(5)	$257.22 \pm 8.68$	$248.22 \pm 9.30$	$226.55 \pm 8.60$	$246.5\pm9.25$
(6)	$260.32\pm9.57$	$252.30 \pm 9.18$	$235.45\pm9.34$	$232.8\pm9.24$

Table 7 Effect of Schiff base and metal(II) complexes on locomotor activity in MPTP-treated mice

Values are expressed as mean  $\pm$  SEM (n = 6)

\* Values were significantly different from control group at P < 0.01



Fig. 10 Effect of Schiff base and metal(II) complexes on Locomotor activity



Fig. 11 Effect on SOD level and oxidative stress parameters

## Antioxidant studies

Among the most prominent internal antioxidants, the enzyme glutathione peroxidase (GSH) and superoxide

dismutase (SOD) constitute the major intracellular antioxidant protection systems by removing superoxide anion and hydrogen peroxide. An effect of Schiff base and metal complexes on level of antioxidants of MPTP-induced mice is presented in Fig. 11. Glutathione (GSH), a potent antioxidant plays an important role in the dopamine turnover. It is a well-known fact that there is a reduced level of Dopamine occurring in dopaminergic neuronal damaged brain. Dopamine metabolism results in the formation of cellular oxidant, hydrogen peroxide, and at this stage glutathione peroxidase is not sufficiently enough to alternate the oxidative alterations. The lowering of reduced glutathione level is observed in MPTP-treated mice (Table 8) getting restored when treated with Schiff base and metal complexes which help to preserve the normal cellular glutathione level.

The damaging effects of MPTP are partly due to the formation of hydroxyl radical during the MPTP metabolism, dopamine and its metabolite. Superoxide dismutase (SOD) is a class of enzyme which majorly defense against the oxygen and hydroxyl radical. An effect of Schiff base and metal(II) complexes on superoxide dismutase in MPTP-treated mice are studied. From the observation, it is concluded that there is a significant reduction in the SOD level in Parkinson's diseased mice, which shows restoration upon treatment with Schiff base and metal complexes. Among all the metal complexes, (6) exhibits promising results.

An effect of Schiff base and metal complexes on level of lipid peroxides given in Table 8, confirmed that among the complexes, (2) showed promising increase in lipid peroxide level as compared to MPTP-treated mice.

The nitrite salt, NaNO<sub>2</sub> (sodium nitrite) has the ability to convert hemoglobin to methemoglobin. This causes reduction in oxygen carrying capacity of blood, leading to memory impairment. In the present study, it was observed that the nitrite levels were significantly increased in mice

Table 8 Effect of Schiff base and metal(II) complexes on antioxidant levels in MPTP-treated mice

Groups	Lipid peroxidation nmol/mg protein	Reduced glutathione µmol/mg protein	Superoxide dismutase
Control	$1.10 \pm 0.12$	$0.056 \pm 0.004$	$32.65 \pm 2.36$
MPTP	$2.56 \pm 0.25^{a^*}$	$0.020 \pm 0.002^{a^*}$	$8.65 \pm 0.92^{a^*}$
BIPTZ	$1.60 \pm 0.16^{b^*}$	$0.048 \pm 0.003^{b^*}$	$16.85 \pm 1.22^{b^*}$
(1)	$1.54 \pm 0.14^{b^*}$	$0.042 \pm 0.003^{b^*}$	$14.26 \pm 1.36^{b^*}$
(2)	$1.50 \pm 0.15^{b^*}$	$0.040 \pm 0.002^{b^*}$	$15.62 \pm 1.58^{b^*}$
(3)	$1.62 \pm 0.18^{b^*}$	$0.044 \pm 0.003^{b^*}$	$14.24 \pm 1.30^{b^*}$
(4)	$1.54 \pm 0.20^{b^*}$	$0.041 \pm 0.005^{b^*}$	$18.30 \pm 1.22^{b^*}$
(5)	$1.60 \pm 0.22^{b^*}$	$0.045 \pm 0.006^{b^*}$	$13.20 \pm 1.32^{b^*}$
(6)	$1.64 \pm 0.26^{b^*}$	$0.043 \pm 0.003^{b^*}$	$18.35 \pm 1.22^{b^*}$

Values are expressed as mean  $\pm$  SEM (n = 6)

<sup>a\*</sup> Values were significantly different from control group at P < 0.01

<sup>b\*</sup> Values were significantly different from MPTP-induced group at P < 0.01

 Table 9 Effect of Schiff base and metal(II) complexes on oxidative stress parameters in MPTP-treated mice

Groups	Nitrite level	Myeloperoxidase OD/min
Control	$120.4 \pm 3.54$	$205.62 \pm 5.30$
MPTP	$210.45\pm7.45^{a^*}$	$320.24 \pm 8.30^{a^*}$
BIPTZ	$148.65 \pm 4.23^{b^*}$	$232.40 \pm 5.98^{b^*}$
(1)	$172.25 \pm 4.56^{b^*}$	$245.32 \pm 6.25^{b^*}$
(2)	$158.32 \pm 4.05^{b^*}$	$230.15\pm5.98^{b^*}$
(3)	$162.10 \pm 4.52^{b^*}$	$238.20 \pm 6.05^{\mathrm{b}*}$
(4)	$165.16 \pm 4.22^{b^*}$	$242.18\pm5.65^{b^*}$
(5)	$160.22 \pm 4.26^{b^*}$	$240.28 \pm 5.13^{b^*}$
(6)	$165.14 \pm 4.42^{b^*}$	$236.25 \pm 5.45^{b^*}$

Values are expressed as mean  $\pm$  SEM (n = 6)

<sup>a\*</sup> Values were significantly different from control group at P < 0.01<sup>b\*</sup> Values were significantly different from MPTP-induced group at P < 0.01

challenged with MPTP as compared to control group. Treatment with Schiff base (BIPTZ) and its metal complexes (1-6) decreases the nitrite level significantly as compared to MPTP-challenged mice. Myeloperoxidase (MPO) is an important marker of tissue damage involving inflammatory cells. Table 9.

Administration of MPTP increases the myeloperoxidase activity in the striatum which indicates the increase in inflammatory pathway in the striatum. Therefore, it can be speculated that treatment with Schiff base (BIPTZ) and its metal complexes (1–6) reversed the myeloperoxidase activity as compared to MPTP-challenged mice.

# Conclusion

Transition metal complexes of type [ML] and [ML<sub>2</sub>] of 2,4-bis(indolin-3-one-2-ylimino)-6-phenyl-1,3,5-triazine)

have been synthesized and characterized with the help of spectral and analytical methods. On the basis of the above techniques the geometry of the metal(II) complexes were proposed as square pyramidal for [ML] type and octahedral for  $[ML_2]$  type complexes. Schiff base and its metal(II) complexes are highly fluorescent in nature. They were found to exhibit promising in vivo anticonvulsant and antiinflammatory activity. The synthesized Schiff base and its metal(II) complexes exert neuroprotective effect by restoring the neurotransmitters and antioxidants in the corpus striatum of PD mouse. Our findings suggest that the newly designed Schiff base and its metal(II) complexes prevent impairments within the confines of the MPTP model of Parkinson's disease. Hence the synthesized compounds may be utilized for further investigations to be formulated as an useful drug for Parkinson's disease.

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