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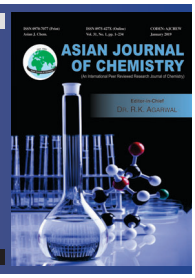

Synthesis, Characterization and Biological Studies of Novel Schiff Base *viz. Bis*-1,1'-(pyridine-2,6-diyldieth-1-yl-1-ylidene) biguanidine and Their Transition Metal Complexes

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Novel Schiff base and its two transition metal complexes derived from the condensation reaction of 2,6-diacetylpyridine with biguanide, characterized by ^{1}H NMR, IR and elemental analysis. The ligand and its cobalt(II) and nickel(II) complexes showed potent DNA photo-cleavage activity. Antimicrobial activity of this Schiff base and its cobalt(II) and nickel(II) complexes against bacteria and fungi *viz. S. aureus, K. pneumoniaae* and *A. niger, Trichophyton rubrum*, respectively was evaluated in terms of zone of inhibition.

Keywords: Cobalt(II), Nickel(II), Complexes, 2,6-Diacetylpyridine, Biguanide, DNA Photo-cleavage.

INTRODUCTION

Schiff bases are the compounds having azomethine (–C=N-) group which are easily synthesized by condensation of primary amine with active carbonyl group. Schiff bases made an important group of ligands having a number of donor atoms possessing fascinating mode of linkage with a variety of metals. Nitrogen atom of azomethine group having the lone pair of electron in its sp^2 hybridized orbital is considered responsible for the chemical and biological properties, as reported by several studies, therefore, Schiff bases form the major class of compounds in several fields, like medicinal, pharmaceutical, analytical, organic reagents and in various other industries [1-7]. Schiff bases emerged as an important part in the growth of coordination chemistry, which proved that they placed a great role for the progress in inorganic biochemistry also. It is evident from literature that the complexation of metals particularly transition metals with Schiff bases increases their biological properties. Schiff bases of biguanide had also been widely studied due to their broad biological spectrum and wide therapeutic applications like anticancerous, antimalarial and anti-infective. Mumtaz *et al.* [8] synthesize the novel Schiff bases of transition metal complexes using condensation between sulphadizine and 2-carboxybenzaldehyde and their antimicrobial activity was screened against *Enterobacter aerogenes, Escherichia coli*, *Staphylococcus aureus*, *Bacillus pumilus*, *Clostridium butyrium* and *Klebsiella oxytoca*. Hossain and Zakaria [9] synthesized the Cu(II) complexes *i.e.* $[C_{15}H_{11}N_3O_3Cu]$ and $[C_{15}H_{11}N_3O_2SCu]$ and evaluated their antimicrobial properties against *Escherichia coli, Shigella sonnei*, *Bacillus cereus, Shigella boydii, Salmonella typhinium* and *Enerobacter*. Rani *et al.* [10] explore the application of a number of noval Schiff bases as antimicrobial agents. Bridges *et al.* [11] delve into the uses of biguanide as antimalarial and antidiabetic and antineoplastic agents[11]. Olar *et al.* [12] prepared the Cu, Ni, Zn and Mn complexes of $(N,N\text{-dimethylbiguanide})_2(ClO_4)_2$ and describe their anti-infective and antimicrobial properties against *Pseudomonas aeruginosa* and *Staphylococcus aureus* strains and their ability to inhibit the colonization at inert surface. Similarly, biguanide salts were also conventionally engrossed and their applications were interpreted as preservatives, antiseptics and disinfectants [13]. The substituted biguanides were extensively used to control hyperglycemia and the complexes having biguanide moieties are also universally used in the treatment of non-insulin dependent diabetes mellitus (NIDDM) [14] and also as a antimetabolite for those microorganism whose folic acid metabolism found hindered [15]. A biguanide polymer *i.e.* poly(hexamethylene biguanide hydrochloride) (PHMB) is the

most successful biopolymer and frequently used in practice, as the synthetic polymers gain much more regard due to their biological activities but more achievements have also been attained to study the structural–activity relationship of naturally arise biopolymers and synthesize synthetic biopolymers which were in comparable with natural ones in their biological activities. Synthetic biopolymers have also been remembered as formidable antimicrobial agent towards a broad range of microorganisms like fungi, bacteria and yeast, but it is remarkably effective against both Gram-negative and Gram-positive bacteria with less mammalian toxicity and large killing rates [16]. The interaction with DNA can be used the way which recognize the biological property of the molecules and such molecules which have an excellent binding harmony with DNA can be serve as eminent chemotherapeutic reagents and posses their biological activity through the interaction with DNA, but the mode of the molecule through which they bind with the DNA is also important. Recently it is reported that the interaction of the platinum complex of metformin with calf thymus DNA is occurred though groove binding mode and it is also disclosed that the vanadyl complex of metformin express the potential synergistic insulin mimics. Despite this, platinum(IV) complex shows antitumor activity [17]. Literature reveals that the Schiff bases and their transition metal complexes obtained from 2,6-diacetylpyridine are also of considerable interest due to strong biological properties such as antibacterial, antifungal, antiviral and anticancer. Gudasi *et al.* [18] synthesize the Schiff base, 2,6-diacetylpyridine *bis*(3-methylsulfhydryl-4-amino-5-mercapto-1,2,4-triazole) and its transition metal complexes. Koksal *et al.* [19] prepared the Cu(II), Co(III), Ni(II), Pd(II) and Zn(II) complexes of the two ligands *i.e.* N,N-*bis*[2-hydroxy-3-methoxy-N-(pyridyl)benzylamine]-2,6-diacetylidenepyridine and N,N-*bis*[2-hydroxy-3-methoxy-N-(pyridyl)benzylamine]-1,2-phthaldialdimine and reported their antimicrobial properties against microorganisms, *B. megaterium B. subtilis E. aerogenes C. albicans* and yeast, *Candida albicans*. Dhanakodi *et al.* [20] synthesize the ligands, 2,6-diacetylpyridine*bis*(benzoylhydrazone) and 2,6-diacetylpyridinebis (benzenesulfonylhydrazide) and their Cu complexes and explains their application in pharmaceutical and medicinal field. Kumar *et al.* [21] reported the synthesis of Ni and Cu complexes of substituted biguanides and investigated their antimicrobial activities. Gup *et al.* [22] describe the synthesis of Co complexes of ligands, 2,6-diacetylpyridine *bis*(4-hydroxybenzoylhydrazone) and uncovered their antiviral and anticancer properties. The Schiff ligands of 2,6-diacetylpyridine have also been reported as catalyst in many chemical activities and also as biological models to recognize the structure of biomolecules [23]. Heterobimetallic complexes, the chelating agents having 2,6-diacetylpyridine moieties have been widely used to construct drugs regarding antibiotic resistant species in alikeness of the platinum and gold complexes possessing antitumor activity [24]. Likely zinc complexes of 2,6-diacetylpyridine have been studied for cell proliferation and inhibition [25]. It is evident from earlier published work that in most of the therapies DNA is the primary target molecule because of two reasons first any mutation in genes is the main cause of severity of human diseases and second DNA shows remarkable interaction with transition metal complexes. Thus it is intensively studied to design the new types of pharmaceutical compounds [26,27]. The present study reports the synthesis and characterization of Schiff base derived by condensation of biguanide with 2,6-diacetylpyridine and its transition metal complexes. Their antimicrobial and DNA photo-cleavage properties has been explored.

EXPERIMENTAL

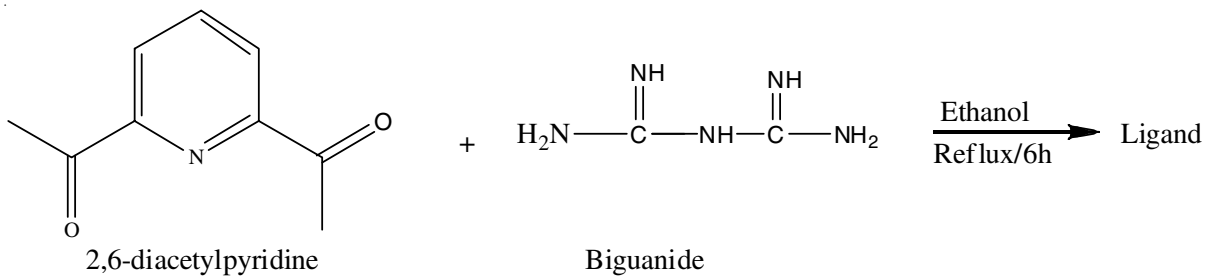
All the chemicals used were of analytical grade and procured from Loba, Emerk and Otto. Solvents were distilled before use.

Physical measurements: IR spectra were recorded as KBr pallets on Perkin-Elemer-spectrometer RX-1FTIR spectrophotometer. NMR spectra were taken down on Bruker Avance II 400 MHz NMR spectrometer taking TMS as internal standard. All spectroscopic studies were done in SAIF Punjab University, Chandigarh.

Preparation of ligand: Biguanide was synthesized by well known reported method [28]. Hot ethanolic solution of 0.2 g (2 mol) of biguanide was added to the ethanolic solution of 0.33 g (2 mol) of 2,6-diacytylpyridine followed by refluxing for 6 h on water bath. This solution was kept overnight followed by filtration on suction pump the uniform solid obtained on Buckner funnel and labeled as ligand (L) (**Scheme-I**).

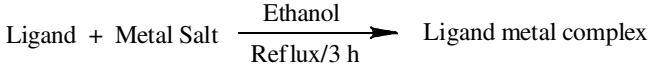
Ligand (L): Yield: 70-75 %; Yellow in colour, IR (KBr, ν_{max}, cm^{-1}): 1694 (C=N), 3100 (–NH), 1453 (C=C)$_{aromatic}$, 1360 $(CH_3)_{in\text{-}plane\ bend}$, 812 $(CH_3)_{out\text{-}of\text{-}plane\ bend}$. ^1H NMR (400 MHz, DMSO, ppm) δ: 1 (s, 12H, CH_3), 2.50-2.51 (s, 2H, –NH), 7.5-8.0 (t, 2H, *p*-ArH), 7.0 (s, 4H, *m*-ArH). Anal. calcd. for $C_{22}H_{24}N_{12}$: C, 57.89; H, 5.26; N, 36.89 %. Found: C, 57.50; H, 5.29; N, 36.51 %. m.p. > 360 °C.

Preparation of nickel complex [NiL]: 0.45 g (2 mol) of ligand and 0.23 g (1 mol) of metal salts ($NiCl_2{\cdot}6H_2O$) were dissolved in 20 mL ethanol separately. Both the solutions were mixed in round bottom flask followed by refluxing for 3 h on water bath. The crude product was separate out by keeping



Scheme-I: Synthesis of ligand

the solution overnight undisturbed followed by filtration on suction pump and dried in vacuum desiccators (**Scheme-II**).



Metal salt = $NiCl_2 \cdot 6H_2O$ and $CoCl_2 \cdot 6H_2O$

Scheme-II: Synthesis of transition metal complex

[NiL]: Yield: 70-77 %; IR (KBr, ν_{max}, cm^{-1}): 1625 (C=N), 727 (Ni-N), 3309 (–NH), 1145 $(C=C)_{aromatic}$. ^1H NMR (400 MHz, DMSO, ppm) δ: 1.3 (s, 12H, CH_3), 2.51 (s, 2H, –NH), 7.5-8.0 (t, 2H, *p*-ArH), 7.0 (s, 4H, *m*-ArH). Anal. calcd. for $C_{22}H_{28}N_{12}O_2Ni$: C, 42.9; H, 5.08; N, 30.49 %. Found: C, 50.2; H, 5.10; N, 30.54 %. m.p. > 360 °C.

Preparation of cobalt complex [CoL]: 0.45 g (2 mol) of ligand was dissolved in 20 mL of hot ethanol and 0.25 g (1 mol) of metal salts ($CoCl_2 \cdot 6H_2O$) was also dissolved in ethanol and both the solutions were mixed in round bottom flask followed by refluxing for 3 h on water bath. The crude product was obtained by keeping the solution undisturbed preferably overnight and filtration was done on suction pump and dried in vacuum desiccators (**Scheme-II**).

[CoL]: Yield: 73 %; IR (KBr, ν_{max}, cm^{-1}): 1620 (C=N), 720 (Co-N), 3300 (–NH), 1139 $(C=C)_{aromatic}$. ^1H NMR (400 MHz, DMSO, ppm) δ: 1.31 (s, 12H, CH_3), 2.45 (s, 2H, –NH), 7.5-8.0 (t, 2H, *p*-ArH), 7.0 (s, 4H, *m*-ArH). Anal. calcd. for $C_{22}H_{28}N_{12}O_2Co$: C, 47.91; H, 5.08; N, 30.49 %. Found: C, 47.80; H, 4.89; N, 30.55 %; m.p. > 360 °C.

Antimicrobial activity: Antibacterial activity of the synthesized ligand and their metal complexes against the selected bacteria were investigated by well plate diffusion method. The sterilized petri plates (150 mm in diameter) were used throughout the investigation. To make pour plates sterilized melted nutrient agar was used. After the solidification of pour plates bacteria under investigation were separately spreaded uniformly over the plates with the help of sterilized glass spreader. In each case, control plate was also maintained with DMSO. Firstly the plates were kept at low temperature for about 4 h and in this time the test chemicals were diffused from the well to the surrounding medium. Than the plates were incubated at (27 ± 2)°C for growth of bacteria under investigation and were observed at 24 and 48 h intervals. The activity was expressed in terms of the zone of inhibition in mm. *in vitro* antifungal activity was evaluated for the synthesized ligand and their transition metal complexes against selected fungus were assessed by poisoned food technique. Potato dextrose agar was prepared for fungal growth under sterilized condition. The various concentrations of ligand *viz.* 100, 250, 400 and 500 µg/mL were loaded in wells followed by incubation at 30 °C for 24 and 72 h to evaluate the effect of compound on fungal growth. Commercial antifungal Fluconazole were used as standard antimicrobial agents for fungal study [29,30].

DNA photo-cleavage assay: DNA cleavage activity of the synthesized ligands was studied by agarose gel electrophoresis using supercoiled pUC19 plasmid DNA [31]. The total volume of reaction mixture was 10 µL containing 0.5 µg of plasmid DNA in TE (*Tris* 10 mM, EDTA 0.01 mM, pH 8.0) buffer with various concentrations of synthesized ligands. The Eppendorfs carrying reaction mixture were placed directly on the surface of a trans-illuminator (8000 mW/cm), at 360 nm for 30 min. After irradiation, samples were further incubated at 37 °C for 1 h. Irradiated samples were mixed with 6X loading dye containing 0.25 % bromophenol blue and 30 % glycerol. The samples were then analyzed by electrophoresis on a 0.8 % agarose horizontal slab gel in *Tris*-Acetate EDTA buffer (40 mM *Tris*, 20 mM acetic acid, 1 mM EDTA, pH: 8.0) with comparison to untreated plasmid DNA as a control. Gel was stained with ethidium bromide (1 µg/mL) and photographed under UV light.

RESULTS AND DISCUSSION

In the synthesis of Schiff base, the selection of the reactant is of substantial importance. Earlier work on the 2,6-diacetylpyridine and biguanide shown to exhibit marked activity against a range of pathogenic fungi and some metal complexes shown significant antitumor and antidiabetic activity and also important in many protein-DNA-(RNA) interactions [32-35].

Characterization of ligand and its metal complexes

Infrared: In the IR spectra of ligand, the C=O stretching at 1760 cm^{-1} and NH_2 stretching at 3300 cm^{-1} of 2,6-diacetylpyridine and biguanide disappeared and a new bond observed at 1694 cm^{-1} which clearly indicates that the condensation indeed occurred and attributed to C=N stretching in ligand [36]. In the spectra of complex this stretching is appears at 1625 cm^{-1} [37] indicate the formation of metal- N bond that confirms the complexation. Whereas the absorption at 3309 and 3100 cm^{-1} shows the –NH stretching is there in ligand and complex [38] which inclines with proposed structure. Whereas the absorption at 1453 and 1145 cm^{-1} is the indication of presence of aromatic alkenes in the ligand and complex respectively [39] and the absorption at 1360 and 812 cm^{-1} attributed to the in and out of plane bend of CH_3 bend.

^1H NMR: The proton nuclear magnetic resonance of the complex was recorded in DMSO solvent. A singlet peak at δ (1-1.3) indicates the presence of - CH_3 group in the ligand and a peak at δ (1.3) is also observed in the complex due to - CH_3 group [40]. A singlet peak at δ (2.50-2.51) shows the presence of –NH group and this peak is observed at δ (2.51) in the complex, which favours the proposed structure. A triplet peak at δ (7.5-8.0) is clearly indicates the presence of para proton of pyridine ring and similar peak is also observed in the complex. The peak for imine proton was not observable probably because of rapid exchange of this proton with deuterium of solvent and *vice-versa*.

Structure description of ligand and its metal complexes: Spectroscopic and elemental analysis study indicate the structure of ligand and its transition metal complexes given under Figs. 1 and 2.

Antimicrobial study: It has been found that both the fungi *viz. A. niger* and *Trichophyton rubrum* were sensitive towards all of the test compounds. It was observed that by the application of the all test compounds the growth was inhibited with some variations [41]. Either the impermeability of the cells of the fungus or the difference of the ribosomes of fungal cells may be the cause of the variation in the effectiveness of different compounds against different fungi [42]. It has been observed

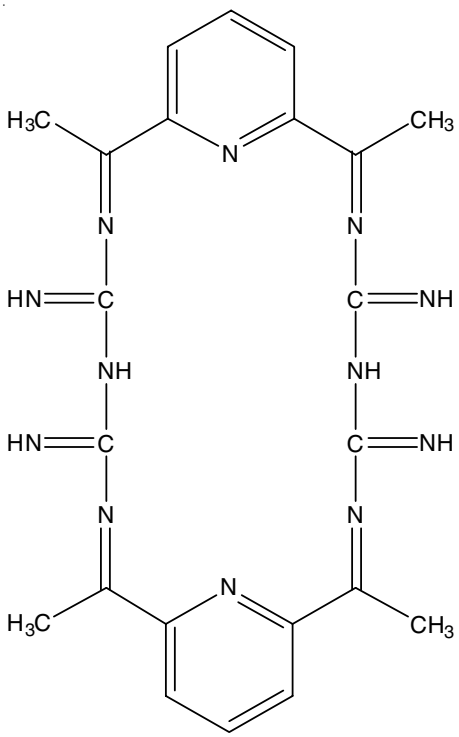
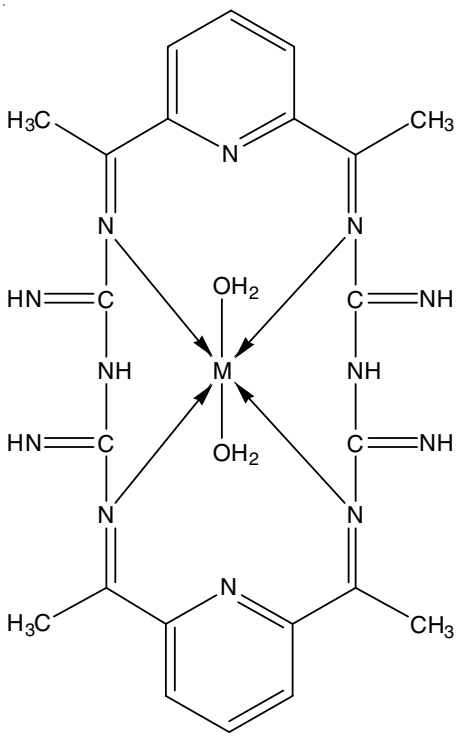


Fig. 1. Structure of ligand



where M = Co(II), Ni(II)

Fig. 2. Structure of metal complexes

that the metal complexes were more active against antifungal activity then the parent ligand. All the synthesized compounds were screened for their antibacterial activity against selected bacterias *viz. S. aureus, K. pneumoniaae*. Ligand and its metal complexes were found very potent against bacteria. The study revealed that the zone of inhibition of complexes are more than ligand. It was observed that the concentration also play a vital role in the degree of inhibition, the activity was found maximum up to 500 ppm. Carcelli *et al.* [43] have investigated the antibacterial and antifungal application of 2,6-diacetylpyridine and its metal complexes. Similarly, in other study, the complexes of 2,6-diacetylpyridine with pentagonal-bipyramidal associated metals (Zn and Cd) have shown promising antimicrobial activities against Gram-positive and Gram-negative strains of bacteria in the range of 62.5 to 1000 µg/mL [6]. A number of studies using metal complexes of N,N-dimethyl-biguanide reported their antimicrobial activities in the range of 4 to 1024 µg/mL [12,44]. In present study, we have also found the promising antimicrobial effects of *bis*-1,1'-(pyridine-2,6-diyldieth-1-yl-1-ylidene) biguanidine and their transition metal complexes in the range of 100 to 500 µg/mL. The antimicrobial result of ligand and its transition metal complexes are summarized in Table-1. Data represented as the average mean of three values with ± 0.5 to ± 0.7 standard deviation.

DNA photo-cleavage assay: The photo-induced DNA cleavage has been carried out using super coiled plasmid DNA by gel electrophoresis. The super coiled DNA (form I) migrate relatively fast with comparison to nicked DNA (form II and III). The conversion of form I to form II and III were observed with the treatment of synthesized ligand and its metal complexes in comparison to untreated plasmid DNA which indicates that ligand and its metal complexes have active DNA-cleavage potential.

Previous mechanistic reports have revealed that bigunanide or pyridine based ligand may exhibit type 1 and II DNA-photo

TABLE-1
ANTIMICROBIAL ACTIVITY DATA OF LIGAND AND ITS NICKEL(II) AND COBALT(II) COMPLEXES

Compd.	Bacterial strains								Fungal strains							
	S. aureus				*K. pneumoniaae*				*A. niger*				*Trichophyton rubrum*			
	Dosage (ppm)				Dosage (ppm)				Dosage (ppm)				Dosage (ppm)			
	100	250	400	500	100	250	400	500	100	250	400	500	100	250	400	500
Ligand	11± 0.6	16± 0.8	18± 0.7	19± 0.7	12± 0.6	13± 0.6	16± 0.6	19± 0.8	13± 0.6	16± 0.6	18± 0.6	21± 0.7	12± 0.7	14± 0.5	15± 0.6	17± 0.8
Nickel complex	13± 0.7	18± 0.9	20± 0.8	22± 0.8	14± 0.7	15± 0.7	18± 0.7	21± 0.9	15± 0.7	18± 0.7	20± 0.6	23± 0.8	14± 0.9	16± 0.6	17± 0.7	19± 0.8
Cobalt complex	12± 0.6	17± 0.8	19± 0.7	21± 0.7	13± 0.6	14± 0.6	17± 0.6	20± 0.8	14± 0.6	17± 0.6	19± 0.6	22± 0.7	13± 0.8	15± 0.5	16± 0.6	18± 0.7
Standards	250 ppm 21 mm (neomycin)				250 ppm 23 mm (neomycin)				250 ppm 24 mm (fluconazole)				250 ppm 19 mm (fluconazole)			
Solvent	3 mm				2 mm				Not observable				3 mm			

Zone of inhibition in mm

cleavage activities *i.e.* photo induced oxidation-reduction and singlet oxygen photosensitization mechanism. Miao *et al.* [45] designed a complex of Ru(II) polypyridyl with excellent DNA-photocleavage activity. Furthermore DNA photo cleaving activity can also be associated with DNA binding and nuclease activity of ligand [45,46]. Similarly, derivatives of pyridyl ligands have been reported to cause DNA photocleavage by reactive oxygen species [47]. Triazolopyridopyrimidines mechanistic insights have also revealed the reactive oxygen species productions upon irradiation. The complexes of *bis*(maltolato) vanadium(III)-polypyridyl and 2,6-diacetylpyridine *bis*(4-hydroxybenzoylhydrazone) have been found to cleave plasmid pBR322 DNA without the addition of any external agents. Vasantha *et al.* [48], also investigated the DNA photocleaving activity of copper-metformin (biguanide) ternary complexes. Therefore, the results of present studies are in well agreement with published reports on bigunanide or pyridine based ligands and could be utilized as promising DNA photo cleaving agent.

Conclusion

The Schiff base ligands were prepared by refluxing biguanide and 2,6-diacetylpyridine in ethanol and were characterized by elemental analysis and spectroscopy techniques. The biological activities of the ligand and its metal complexes were evaluated using well plate diffusion assay. In future there is scope that more metal complex of this ligand may be prepared and may be used as model for biological system. The DNA photo cleavage study indicated that proposed ligand and its metal complexes could be utilized as promising DNA photo cleaving agent.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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