Chemistry and Materials Research
ISSN 2224- 3224 (Print) ISSN 2225- 0956 (Online)
Vol.14 No.1, 2022

Synthesis of Complex from Nickel(II) salt and 2-imino-3-(2-hydroxy phenyl)-1-thiazolidin-4-one and Study of its Structure and Antimicrobial activity

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Abstract
The ligand 2-imino-3-(2-hydroxy phenyl)-1-thiazolidin-4-one was synthesized by condensation of 2-hydroxy-N-chloroacetylaniline with potassium thiocyanate. The nickel(II) metal complex of the ligand was prepared by refluxing the ligand with hydrated nickel(II)chloride ($NiCl_26H_2O$) salt under ethanol. Complex of Ni(II) with heterocyclic ligand has been characterized with the help of elemental analysis, magnetic, ^{1}H-NMR, ^{13}C-NMR, IR and electronic spectral data. IR spectra exhibit the coordination of the ligands to the metal ion through deprotonated phenolic oxygen and heterocyclic nitrogen. All these studies reveal square planar geometry of Ni(II)complex. Synthesized ligand and its complex have also been screened against two bacterial strains, *Escherichia coli* and *Salmonella-typhi* and two fungal strains, *Aspergillus niger* and *Penicillum chrysogenum* by 'paper disc' technique. It has been observed that the antimicrobial activity of metal complex was higher than that of the free ligands.
Keywords: Hetrocyclic ligand, thiazolidinone, (Nickel II) complexes, anti-microbial studies, electronic spectra
DOI: 10.7176/CMR/14-1-01
Publication date: January 31st 2022

1. Introduction

Metals have been used in the treatment of diseases in humans since ancient times. In more recent times, stable metal coordination complex based on the element platinum, cisplatin, has become the most well-known of all metal based drugs and hundreds of articles have been published on the synthesis and activity of complexes derived from the parent cis-platin molecule. Since Rosenberg's initial discovery of cis-platin in 1969 many more examples of metal-containing drugs have been reported in the literatures. For instance, gold containing complexes such as auranofin are commonly used to treat rheumatoid arthritis (Akhtar, Chohar & Zahid, 2007).

Complexes containing nickel, cobalt, lithium, bismuth, iron, calcium, lanthanum, gallium, tin, arsenic, rhodium, copper, zinc, aluminum and lutetium have all been used in medicine (Bertini, Grad, & Stiefel, 2007). The rapid growth of microbial infection has become an extremely serious threat to the health and economic prosperity of the world and it is highly manifested in the developing countries which cannot afford to pay for the high cost of research. With the existence of this phenomenon, there is growing interest in the discovery of substantial new antibacterial agents(Golkur & Bagazra, 2014). Heterocyclic ligands and their derivatives are one of the most important classes of compounds with wide spectrum of antimicrobial activities that have drawn attention due to their increasing importance in the field of pharmaceuticals (Bekhit, Sayed, & Aboulmagd, 2004). Numerous attempts have been made to synthesize heterocyclic-based molecules in effort to solve problems of pathogenic bacteria and fungi resistance drugs. For instance thiazolidinones, which is a fundamental structure of many synthetic pharmaceuticals, have showed a broad spectrum of biological activities. In recent years several new methods have been reported for preparing thiazolidinone derivatives (Gaikmar &Tripude, 1994; Cacic, Trkovnik, Cacic, & Scloon, 2006). Heterocyclic compounds with one, two or three coumarin cores contain thiazolidinone moieties and thiazolidinone coumarin derivatives have been proven to have significant biological activities like anticonvulsant (Amin, Rahman, & Eryani, 2008). Cytotoxic (Hafez, Khrisy, Badria, Fathy, 2003). antioxidant activity (Maples, Haffert, Parsell, Asselt, Silversides, 2009). Antiviralagents (Rawal,Tripathi, Katti, Pannecouque, & Clercq, 2007). antifungal and antibacterial activities and as well as anticarcinogenic agent(Omar-Geronikali et al.,2010). Reports have recently indicated that substituted thiozolidinone and oxazolidinones inhibit the enzyme, integral component in bacterial peptidoglycan biosynthesis even at low molar level(Donawade, Raghu,&Gadaginmath,2007).

Nickel is one of the transition metal which exists in wide variety of oxidation states such as (II) and (III) and reacts with many naturally occurring ligands particularly with those that contain N, O and/or S donor atoms to form several isomeric complexes (Singh,1986). Although a large number of complexes of transition metals with different Schiff's bases of heterocyclic, macro cyclic and other ligands have been studied for their structures and various properties to the best of our knowledge, there is no any report on the synthesis and properties of complexes of Ni(II) with heterocyclic ligands like 2-Imino-3-(2-hydroxyaryl)-1-thiozolidine-4-one. In this article, we present the synthesis, characterization and antimicrobial study of the ligand and their Ni(II) complex.

2. Materials and Methods

2.1. Chemical and Reagents

All chemicals and reagents were purchased and used without further purification. Chloroacetyl chloride, o-aminophenol and KCNS (Blulux Laboratory(p) Ltd) were used without purification. Hexa hydrated Nickel Chloride ($NiCl_26H_2O$) was purchased from Nice Lab reagent Ltd, were purchased from BDH Chemicals Ltd Poole England, other chemicals such as acetone, absolute methanol, ethanol and concentrated aqueous ammonia were purchased from LOBA Chemie Ltd Company. All solvents such as benzene, acetone, ether used in TLC studies were HPLC grade.

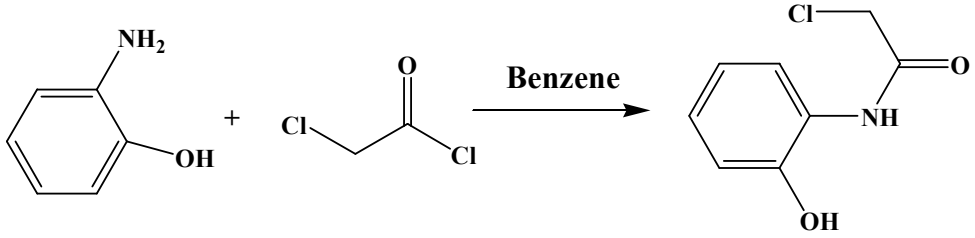
2.2. Instruments and Apparatus

The ^1H and ^{13}C NMR spectrum of the ligand was recorded in DMSO on Bruker Ultra shield TM 400 spectrometer using TMS as internal standard at Addis Ababa University. The infrared spectra were recorded on Fourier Transform Infrared (FT-IR) spectrophotometer (Prestige- 21) in the range [4000- 400]cm^{-1} in KBr medium; C, H, N and S elemental analyses using, EA1112 Flash CHNS/O-analyzer. The atomic absorption of spectrum of ligand and Nickel complex was recorded on ZEF nit 700p(anaytikjenu). Electronic spectral measurements were done using UV/Vis-SP65 SYANO spectrophotometer in 200-900nm range. Magnetic susceptibility measurements were done on MSB-AUTO, (Sherwood Scientific) magnetic balance at Addis Ababa University. The molar conductivity measurements were carried out using Jenway digital conductivity meter (UK).

2.3. Experimental Procedures

2.3.1. Synthesis of 2-imino-3-(2-hydroxyphenyl)-1-thiazolidin-4-one ligand(L)

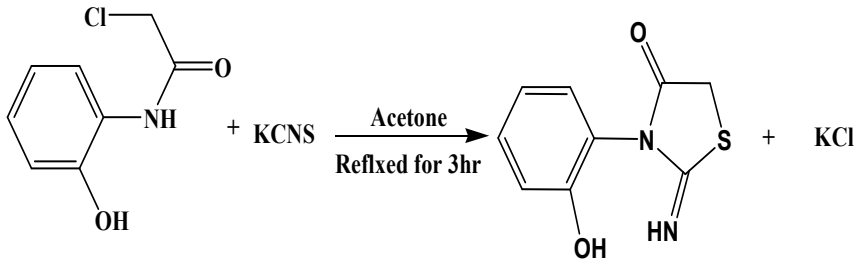
It has a two steps preparation; in first step 2-hydroxy-N-Chloroacetylaniline was prepared by mixing chloroacetylchloride (0.06mol,5.0mL) to the solution of o-hydroxyaniline (6.54g, 0.06mol) in 25mL ice cold benzene and the resulting solution was gently stirred until the precipitate obtained. The pale pink product was filtered off using Buchner filter paper and washed with benzene repeatedly to remove unreacted organic parts, and dried in air finally crystallized from alcohol (ethanol).



2-Hydroxy aniline **Chloroacetyl chloride** **2-Hydroxy- N- chloroacetyl aniline**

Scheme 1: Synthesis of 2-Hydroxy-N-Chloro acetylaniline

In the second step, a mixture containing 2-hydroxy–N-chloroacetyl aniline (0.02mol, 3.70g) and potassium thiocyanate(0.02mol, 1.95g) in acetone in 1:1 molar was refluxed for three hours and the resulting reaction mixture was filtered and the solvent was removed by rotary vapor. The product was washed with excess water and recrystallized from ethanol. Finally the air dried pale yellow product was collected.



2-hydroxy-N- chloroacetyl aniline **2-imino-3-(2-hydroxyphenyl)-1-thiazolidin-4-one ligand(L)**

Scheme 2: Synthesis of **2-imino-3-(2-hydroxyphenyl)-1-thiazolidin-4-one ligand(L)**

Preparation of Nickel (II) Complex

The nickel(II) complex was prepared by a common procedure. Mixture containing nickel(II) salt($NiCl_26H_2O$) and ligand [3-(2-hydroxyphenyl)-2-imino thiazolodin-4-one] in 1:2 molar ratio in acetone were refluxed for 2-3 h. The reaction mixtures were concentrated on water bath and allowed to cool at room temperature and the precipitate product was filtered out and washed with water and ethanol (small amount) successively and dried in air.

2.4. Test of Purity of the Product

The purity of the sample was checked by using thin layer chromatography (TLC) conducted on silica coated aluminum plates as stationary phase and ethanol as a mobile phase. A single spot were observed that showed both the ligand and the complex are pure.

2.5. Chloride Analysis

In order to know the presence of coordinated chlorine in the complex, 100 mg of complex was decomposed with concentrated HNO_3 and diluted and to the resultant solutions aqueous solution of $AgNO_3$ was added. In each case, no cruddy white precipitate was observed indicates the absence of chlorine in the coordination zone of the metal.

2.6. Determination of elemental Composition

2.6.1. Determination of metal content in the complex

The metal content in the complex was determined spectroscopically using Atomic Absorption Spectroscopy (AAS). The experimental percentage of the metal in the complex was obtained from the AAS data using the formula:

$$\mathrm{M}(\%) = \mathrm{Concentration(PPm)\ X}\ \frac{volume\ diluted\ in\ mL}{mass\ of\ sample\ taken(mg)} X \frac{100}{1000}$$

Four calibration points for every component and samples were run in triplicate and the average values have been taken100 mg each of Ni(II) complex was placed in clean and dry beaker to each of which 50mL of conc.

2.7. Antimicrobial Evaluation

Antimicrobial (antibacterial and antifungal) activity of the ligand and its complex was investigated *in-vitro* against bacteria and fungi using disc diffusion method. Growth zone of inhibition was measured to determine the antibacterial and antifungal activities of the synthesized ligands and complex and compared with the commercially available drug *gentamicin* (antibacterial) and *mancozeb* (antifungal)(Dorkov, Pantcheva, Sheldrick, Mayer,& Petrava, 2008)

2.7.1. Inoculums preparation

The test bacterial strains, Escherichia coli and Salmonella typhi were transferred from the stock cultures and streaked on Mueller Hinton agar (MHA) plates and incubated for about 24 hours Bacteria were transferred using bacteriological loop to autoclaved MHA that was cooled to about 45 ^{0}C in water bath and mixed with gentle swirling the flasks. The medium was then poured to sterile Petri dishes, allowed to solidify and used for the bio-test. Two fungi strains, Aspergillus niger *and* Penicillium chrysogenum, from the stock cultures were transferred to PDA plates and incubated for 72 hours. Then spores of the test fungi names were harvested by washing the surface of the colony using 10 mL sterile distilled water and transferred to 50 mL autoclaved PDA cooled to about 35^{0}C in a water bath. The medium containing spore suspension was poured to sterile plates, allowed to solidify and was used for the paper disc diffusion bioassay.

2.7.2. Antifungal Activity

Paper discs about 3 mm in diameter were cut from Watman-1filter paper with an office paper punch and placed in

a beaker covered with aluminum foil and sterilized in an oven at 121^{0}C for 1 h. Aliquots of 10µL of the sample solutions of ligand and its complex was pipetted to the discs. The paper discs impregnated with the sample solutions were then transferred using sterile forceps to PDA seeded with spore suspension of test fungi as described under inoculums preparation above. The petri dishes were incubated at 27^{0}C for 72hours. All the tests were performed in triplicate. The effectiveness of the samples was evaluated by measuring inhibition zone against the tested organisms.

2.7.3. Antibacterial Activity

Similar procedures were followed for testing antibacterial activities. Paper discs were transferred to Mueller Hinton agar (MHA) plate seeded with bacteria and incubated at 37^{0}C for 24hours. All the tests were performed in triplicate. Antibacterial activity was evaluated by measuring the zone of inhibition against the tested organisms**.**

3. Results and discussion

The reaction of 2-hydroxyaniline and chloroacetyl chloride in an ice bath was afforded 2-hydroxy aryl chloroacetanilide and subsequently the resulting aryl chloroacetanilide was refluxed with potassium thiocyanate to give 2-Imino-3-(2-hydroxyphenyl)-1-thiozolidine-4-one ligand. The reaction of hydrated nickel metal salt ($NiCl_26H_2O$) with this ligand yielded nickel complex in the molar ratio of (1:2).

All the synthesized ligand and complex were screened for their antibacterial and antifungals activities.

3.1. Elemental analysis of the Ligand and Metal Complex

Elemental analysis has been done for both the ligand and complex. And the values obtained are in the range of accepted values.

Table 1: Elemental analysis data of ligand and its complex

					Elemental Analysis (%)				
Compound	Color	M.p (^{0}C)	Yield(%)	M.Wt (g/mol)	C	H	N	S	Ni
L	Yellow brown	121-124	65.54	208	(51.92) 51.55	(3.85) 3.62	(13.46) 13.41	(15.38) 15.23	--
[NiL_2]	Pale green	168-172	71.23	472.71	(45.69) 45.54	(2.96) 2.81	(11.85) 11.60	(12.54) 12.52	12.42

* L = $C_9H_8N_2O_2S$ [NiL_2] = $C_{18}H_{14}N_4O_4S_2Ni$ In bracket: It is theoretical value

3.2. Determination of Metal Content by AAS

Four calibration points for every component and samples were run in triplicate and the average values have been taken. For nickel(II) complex 0.2 gram taken complex taken for analysis and 50mL, volume of solution.

Table 2**:** AAS data for Nickel Standard and the M-L complex

Concentration (ppm)	***Absorbance***
2	0.01071
2.5	0.01226
5	0.02516
7.5	0.0363
Nickel complex	1.953

$$\% \text{ Ni} = \frac{\text{Concentration(ppm) x Volume diluted(mL) X 100}}{\text{Mass of sample taken (mg) x 1000}} = \frac{\text{488 mg/L x 50 mL x 100}}{\text{200 mg x 1000}} = 12.2$$

Using Beer-Lambart Law the obtained absorbance values; the concentration of nickel calculated and becomes 488 ppm.

Table 3: Percent composition metal in complexes

Metal in complex	**Percentage due to theoretical value**	**Percentage due to AAS analysis**
Nickel (Ni)	12.42%	12.20 %

3.3. IR spectra studies

The infrared spectra of 3-(2-hydroxyphenyl)-2-imino thiazolodin-4-one and its complex shown in the table below reveal that *ν(C=O)* (ring), *ν(*C-S-C)(ring), *ν(*N-H), *ν*(C=N), *ν(*C=C) and *ν(*C-H) (benzene) and the distribution bands occurring in ligand spectrum are observed almost at same frequency in the complex spectra. Disappearance of band of *ν*(OH) and after complexation, the band of the ligand due to ν(C-N-C) showed substantial decreased which corresponding to ν(C-N-C) occurring at 1100cm^{-1} which clearly indicates coordination of pentacyclic ring

nitrogen with metal ion. And presence of new bands in low frequency region at 512 cm^{-1} and 467cm^{-1}, attributed to ν(Ni-N) and ν(Ni-O) confirm the coordination of deprotonated phenolic oxygen and heterocyclic nitrogen of the ligand with nickel. From the infrared studies, the ligand is bidentate and coordinated with the metal through their deprotonated phenolic oxygen and heterocyclic nitrogen. In the complex, Ni(II)salt chloride ion did not play any role in coordination (Kirube, 2012).

Table 4: Principal IR frequencies with their assignments for ligand and its complex

Cpd	**ν C=O (ring)**	**νC-S-C (ring)**	**ν N-H secondary ammine**	**ν C=N**	**νC-N-C ring**	**Phenolic**	**Benzene**		**νM-O**	**νM-N**
						ν OH	**ν C=C**	**ν C-H**		
$C_9H_8N_2O_2S$(L)	**1600**	**686d**	**3415 br**	**1642**	**1327**	**3200 br**	**1600 1597**	**2983**	**-**	**-**
[NiL_2]	**1605**	**700**	**3413 br**	**1625**	**1282**	**-**	**1957 1591**	**2974 br**	**512d**	**467d**

Where, L = $C_9H_8N_2O_2S$ (L), br =broad and d = doublet

3.4. Magnetic Susceptibility Measurements

Magnetic Susceptibility Measurements on complex was done at 20^0C and the observed Gram Susceptibility (χ_g) was (-0.277 x 10^{-6}) which confined that Nickel (II) complex is diamagnetic nature.

Table 5: Magnetic susceptibility value of nickel (II) complex

Sample	**Gram Susceptibility (χ_g)**	**Remark**
[NiL_2]	-0.277 x 10^{-6}	Diamagnetic

3.5. Electronic spectra studies of complex

In the complex band at 307nm which was assigned π→π* in (N=C) bond and the band observed at 428nm due to ligand to metal charge transfer. The obtained gram susceptibility value showed diamagnetic nature for nickel(II)complex confirm that square planar geometry and dsp^2 hybridization of this complex, this implies d-d transition not observed in the spectrum of nickel(II) complex.

Table 6: electronic spectra data of the ligand and its metal complex

Compounds	**λ max (nm)**	**Possible assignment**
L_1	323	π →π*
	372	n → π*
[NiL_2]	307	π → π*
	428	LMCT

3.6. ^{1}H-NMR and ^{13}C-NMR studies of ligand

^{1}H NMR (400MHz, DMSO) δ5.2 (1H), δ3.6(1H), δ(6.7-7.6)(4H), δ4.8(1H). ^{13}C NMR δ29.5 H_2C, δ163 (azomethine C), δ (116-129) for aromatic HC, δ173 carbonyl C and δ 149(phenolic group carbon);

Table 8 : ^{1}H NMR and ^{13}C NMR spectral data of the ligand

Compounds	^{1}H NMR		^{13}C NMR	
	Chemical shift (δ, ppm)	Assignment	Chemical shift (δ, ppm)	Assignment
$C_9H_7N_2O_2S$ (L)	6.7 -7.6	Benzene ring H	116-149	Carbons in benzene ring
	4.8	Phenolic OH	149	Benzene (C-OH)
	5.2	Imino group(C=NH)	163	C (C=NH)
	3.6	Methylene hydrogen(CH_2)	29.5	C(-CH_2-)

Structural Elucidation

Based on the combined analysis spectral, magnetic and conductance results the structure of all complexes in square planar geometry are proposed as shown below.

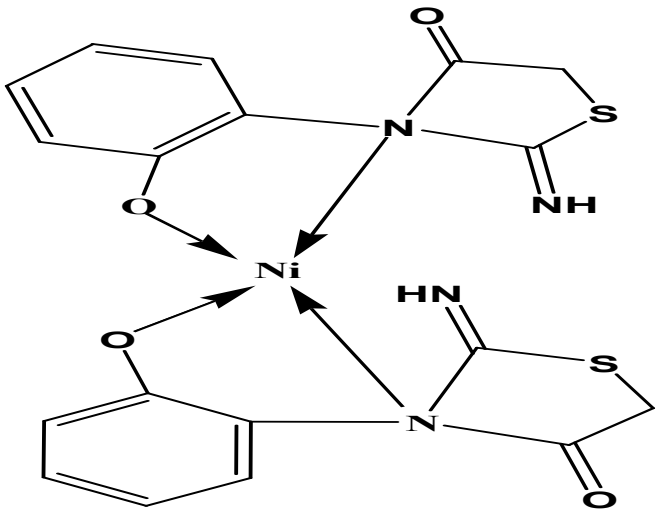
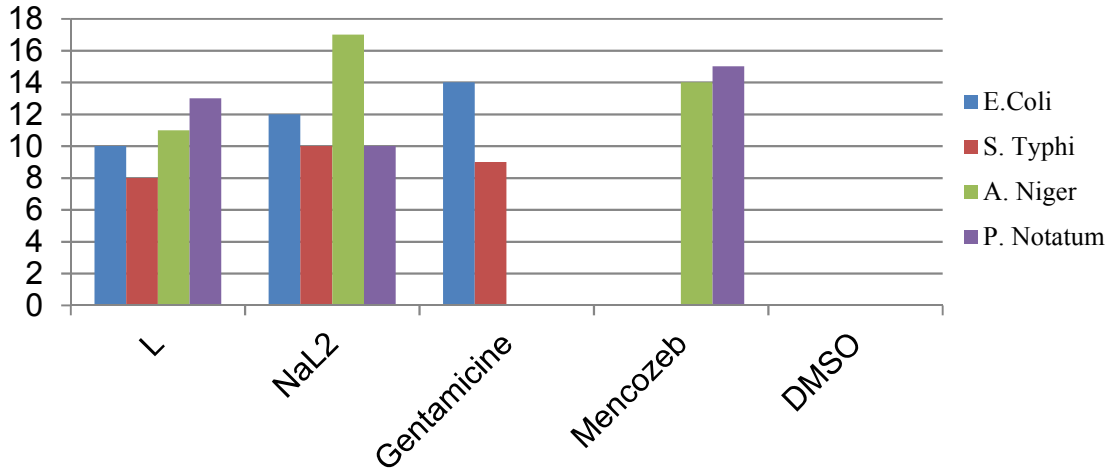


Figure 1 : Structure of 2-imino-3-(2-hydroxyaryl)-1-oxazolodin-4-one nickel(II) complex

3.7. Antimicrobial Activities

The result obtained from experiments the complex showed strong inhibition zone against two bacterial strains *Escherichia coli*, *Salmonella typhi* and one fungi strain (A. niger) than free ligand. On chelation the polarity of the metal ion reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of positive charge of metal ion with donor groups. It was further noted that the delocalization of electrons over the whole chelate ring enhanced the lipophillicity of the complex this increased lipophillicity enhanced the penetration of the complex into lipid membrane of microorganism thus retarding the normal cell processes.

Chart 1: Inhibition zone of bacterial and fungal growth in (mm)



L= $C_9H_8N_2O_2S$ [NiL_2] = $C_{18}H_{14}N_4O_4S_2Ni$ DMSO = Dimethyl sulfoxide

5. CONCLUSION

Heterocyclic ligand 2-imino-3-(2-hydroxy phenyl)-1-thiazolidin-4-one was synthesized by the cyclization of 2-hydroxychloro acetylaniline obtained by reaction o-aminophenol and chloroacetyl chloride, with KCNS. This ligand was fully characterized by elemental analysis, IR, ^{1}H-NMR and ^{13}C-NMR. This heterocyclic ligand was successfully coordinated to nickel (II) ion to form its corresponding complex. The comparison of the IR spectra of the synthesized ligand and its metal complex indicated bi-ligancy of the ligand through its deprotonated phenolic oxygen and heterocyclic nitrogen as exhibited by disappearance and lowering in frequencies of phenolic (OH) and heterocyclic C-N-C groups of ligand also gave additional evidence on the formation of this complex. Phenolic(OH) and heterocyclic C-N- group of ligand in its complex by appearance of new bands due to ν(M-N) and ν(M-O) in the spectra of metal complex. On the basis of magnetic susceptibility, electronic spectra, FT-IR

data, the complex was square planar geometry. In the antimicrobial study, it was revealed that complex has a much enhanced activity relative to synthesized ligand against selected bacteria and fungi strains. Therefore, further tests are needed to evaluate broad spectrum activities especially on complex against other (additional) microbial species to explore all possibilities to evaluate the potential of this complex in the development of pharmaceutical drugs.

Acknowledgment
The author would like to acknowledge Wolkite and Addis Abeba Universities for their financial and material support.

Conflict of Interest
The author declares that there is no conflict of interest.

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