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Research Article

# Synthesis of Metal Complexes of Substituted Isonicotinohydrazide and their Catalytic and Biological Activities

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**ABSTRACT**

Coordination chemistry has fascinated and inspired chemists all over the world due to an increasing academic, industrial, and biological interest in metal complexes of organic chelating ligands. Among the chelating ligands, Schiff bases have attracted the attention of chemists due to ease of preparation and complexation. Numerous reports showed that a large number of isatin and its Schiff base metal complexes have excellent catalytic activity in a variety of reactions at mild reaction conditions and are used as homogeneous catalysts. Copper-based isatin complexes have found much attention because of their biological relevance. In this study, we report the synthesis of Schiff base metal complexes of substituted isonicotinohydrazide. The Schiff base, ($C_{14}H_{10}N_4O_2$) is prepared by condensing isoniazid with isatin. The complexes were synthesized in good yield from easily available metal precursors and characterized by UV-visible and fourier-transform infrared spectroscopy (FTIR) spectroscopy. The Cu complex shows excellent activity for the C-N coupling reaction of the amination of aryl halides. All four complexes show better antibacterial activity as compared to their corresponding [M $(acac)_n$] complexes. In addition to this, the Co and Cu complexes such as [$Co(C_{14}H_{10}N_4O_2)_3$], and $Cu(C_{14}H_{10}N_4O_2)_3$] respectively show negative growth, towards *Fusarium, and Aspergillus,* i.e., showing antifungal activity. The results were compared with the standard acetyl-acetone complexes of the same metals.

**Keywords:** Isatin, Isonicotinohydrazide, Schiff Base, Complex, Catalyst, Amination, Antimicrobial, Antifungal.

## INTRODUCTION

The science of metal coordination plays a noteworthy part in catalysis and biology. There is an ever-increasing academic, commercial and biological interest in the metal complexes of organic chelating ligands. This has resulted in the emergence of allied fields like organometallic chemistry, homogeneous catalysis [1] and bioinorganic chemistry [2]. Many industrial catalysts are metal complexes and such catalysts are steadily becoming a more important way to control reactivity. The complexes of Fe, Zn, Cu and Mo that are crucial components of certain metalloenzymes are essential in biological systems. Hemoglobin, vitamin B12, and chlorophyll are some of the important examples [3].

Among the chelating ligands, Schiff bases have attracted the attention of chemists due to ease of preparation and complexation [4-5]. The activity of the metal chelates depends on the steric and electronic factors [6]. Amination (C-N coupling reaction) is the process by which an amine group is introduced into an organic molecule. Much cheaper copper complexes compared to expensive palladium complexes have boosted the search for new catalytic protocols in the formation of C–N bond formation reactions [7-10]. Schiff bases derived from isatin (1H-indole-2, 3-dione) exhibit many neurophysiological and neuropharmacological effects like antimicrobial, antiviral, anticonvulsant, anticancer, antimicobacterial, antimalarial, cysticidal, herbicidal and anti-inflammatory activity [11-14]. They also have anti-HIV, antiprotozoal antihelminthic and antitubercular activities and still expanding their pharmacological actions and beating the resistance [15-23].

The present work aims at the synthesis, characterization, catalytic and biological applications of a few transition metals chiff base complexes of substituted isonicotinohydrazide ($C_{14}H_{10}N_4O_2$). The transition metal complexes of Ru, Ni, Co and Cu were synthesized in good yield using easily available metal precursors and characterized by UV-visible and fourier-transform infrared spectroscopy (FTIR) spectroscopy. Cu complex shows excellent activity for the C-N coupling reaction of amination of aryl halides. These complexes also show antibacterial and antifungal activity. All four complexes show better antibacterial activity as compared to their corresponding acac complexes. On the other hand, Co and Cu complexes show antifungal activity against *Fusarium* and *Aspergillus*. The results were compared with the standard acetyl-acetone complexes of the same metals.

## MATERIAL AND METHODS

All the chemicals used were of analytical reagent (AR) grade. Metal salts such as $RuCl_3.6H_2O$, $NiCl_2.6H_2O$, $CoCl_2.6H_2O$, $CuCl_2.2H_2O$ were purchased from Loba Chemie India. Solvents were freshly

distilled and dried before use. FTIR spectra were recorded on Shimadzu FTIR- 8400S, (spectrophotometer). The electronic spectra ($\lambda$(200–1100) nm) in different solvents were recorded on Shimadzu (UV-Vis)-160 spectrophotometer.

## Syntheses of (E)N'–(2-oxoindolin-3-ylidene) isonicotinohydrazide ($C_{14}H_{10}N_4O_2$)

Isatin, (0.88 g, 0.006 moles) and isoniazid (0.96 g, 0.007 moles) was dissolved separately in 25 mL ethanol. A round bottom flask containing an ethanolic solution of isatin was placed in an oil bath to attain the desired temperature. A solution of isoniazid was added drop by drop to the above isatin solution in the required proportion (1:1 ratio). The reaction mixture was refluxed for 8 to 9 hours with constant stirring at 110°C. After the completion of the reaction yellow color precipitate was formed, which was filtered, washed and finally dried in the oven (Scheme 1).

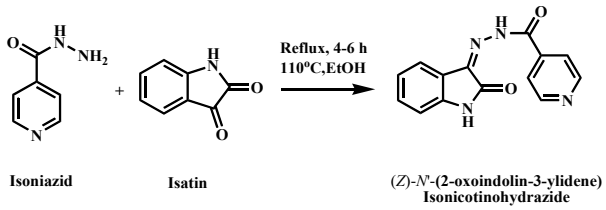
## General Procedure for the Synthesis of Metal Complexes of (Z)-N'-(2-oxoindolin-3-ylidene) Ison icotinohydrazide($C_{14}H_{10}N_4O_2$)

The desired metal salt (0.006 moles) and ligand (3.46 g, 0.013 moles) in the required proportion (1:2.1) were prepared separately by dissolving metal salt in 15 mL acetone and ligand in 15 mL DMF. The solution of metal salt was placed in an oil bath to attain the desired temperature. A solution of ligand was added drop by drop to the above solution of a metal salt by maintaining a temperature at 120°C. The reaction mixture was constantly stirred and refluxed for 4 to 5 hours. After the completion of the reaction, the complex was precipitated out as a colored residue. It was then filtered, washed and dried in an oven at 90°C. The dried precipitate was weighed, and the practical yield was calculated. By following the above procedure,the transition metal complexes of [(E)N'–(2-oxoindolin-3-ylidene)] isonicotinohydrazide were synthesized as shown in Scheme 2. There molecular formula can be represented as $[Ru(C_{14}H_{10}N_4O_2)_2Cl_2]$, $[Co(C_{14}H_{10}N_4O_2)_2Cl_2]$, $[Ni(C_{14}H_{10}N_4O_2)_2Cl_2]$ and $[Cu(C_{14}H_{10}N_4O_2)_2Cl_2]$.

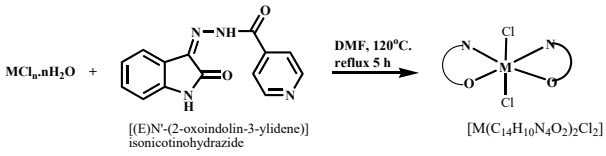
The acetylacetone complexes of the same metals, i.e., $[M(acac)_n]$ were prepared by literature reported method [24].

## General Procedures for Amination Reaction

Aniline (0.3725 g, 0.004 moles), bromobenzene (1.884 g, 0.012 moles) and potassium tertiary butoxide (0.012 moles) were taken in a round bottom flask along with 10 to 12 mL toluene as a solvent. The 0.025 g $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$ complex (M = Ru, Co, Ni, Cu ) was added as a catalyst in the above mixture. The content was then refluxed for 4 to 5 hours at 120°C with constant stirring. The progress of the reaction was monitored by using thin layer chromatography (TLC). After the completion, the reaction mixture was filtered and the catalyst was




**Scheme 1:** Synthesis of (Z)-N'-(2-oxoindolin-3-ylidene)isonicotinohydrazide




**Scheme 2:** General synthesis of metal complexes $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$

separated. The product was separated from filtrate by using column chromatography and further analyzed by gas chromatography–mass spectrometry (GC–MS) technique.

## Antibacterial Activity

The prepared complexes were dissolved in a solvent DMF. The 10 $\mu$L of the complex solution was poured into the well of the seeded medium. Each well contained 100 $\mu$g complexes and was tested against gram-positive and gram-negative bacteria *Pseudomonas, and Klebsiella pneumonia*. The antimicrobial assay plates were incubated at 37°C for 24 hours. The zone inhibition around each of the wells was measured and was noted down as the antimicrobial activity

## Test for Antifungal Activity

The fungi chosen for the study purpose were *Aspergillus and Fusarium.* The test fungal strains used in this experiment are *Fusarium and Aspergillus.*

## Culture Medium

To inoculate fungal spores' potato dextrose agar was prepared. Soft agar was prepared by 1-gm of agar dissolved in 100 mL of distilled water and sterilized in an autoclave. The activity was carried out with the help of the food poisoning method. In 100 $\mu$g of the metal complex was poured on sterile petri plates on which potato dextrose agar was poured of equal thickness. Cooled it to solidify. Then fungal spot was inoculated. The plates were incubated for 48 hours at 37°C. The growth was compared with copper sulphate ($CuSO_4$) which was used as a standard.

## RESULTS AND DISCUSSION

The physical properties of the above-prepared complexes are shown in Table 1. All The complexes were prepared in good yields and are coloured and octahedral in geometry.

## Characterization

*UV-vis spectra*

In the case of the metal complexes, they exhibit the absorption bands generally in two regions. The absorption bands in the region of wavelength 210 to 350 nm correspond to the $\pi$-$\pi$* transitions of the ligands and of wavelength 500 to 800 nm corresponds to the d-d transition. Similarly for the complexes $[Ru(C_{14}H_{10}N_4O_2)_2Cl_2]$ where M = Ru, Co, Cu, Ni, the $\lambda_{max}$ near 400 to 600 nm is due to MLCT and near 200 to 300 nm is due to ligand-to-ligand charge transfer. The corresponding values of each transition in the ligand and metal are shown in Fig. 1

The photo-physical data table containing the$\lambda_{max}$ and type of possible transitions is shown in Table 2. Every metal shows a characteristic MLCT band in the visible region of the spectrum. As

Table1: Physical properties of the prepared $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$ complexes

| *Sr. No* | *Complex* | *Colour* | *Practical Yield* |
|---|---|---|---|
| 1 | $[Ru(C_{14}H_{10}N_4O_2)_2Cl_2]$ | Black | 80. 7 % |
| 2 | $[Ni(C_{14}H_{10}N_4O_2)_2Cl_2]$ | Yellowish orange | 82.7 % |
| 3 | $[Co(C_{14}H_{10}N_4O_2)_2Cl_2]$ | Yellowish orange | 73.2 % |
| 4 | $[Cu(C_{14}H_{10}N_4O_2)_2Cl_2]$ | Yellowish orange | 91.1 % |
| 5 | $[Ru(acac)_3]$ | Greyish Black | 38.5 % |
| 6 | $[Ni(acac)_2]$ | Dark Green | 92.3 % |
| 7 | $[Co(acac)_3]$ | Pink | 78.1 % |
| 8 | $[Cu(acac)_2]$ | Brown | 82.3 % |

***Reaction Conditions:*** *For [M* $(C_{14}H_{10}N_4O_2)_2Cl_2$*]: T: 120 °C, Solvent: DMF, Reaction Time: 4–5 hrs.For[M(acac)$_n$]: T: 80° C, Solvent: $H_2O$, Reaction Time: 2–3 hrs.*

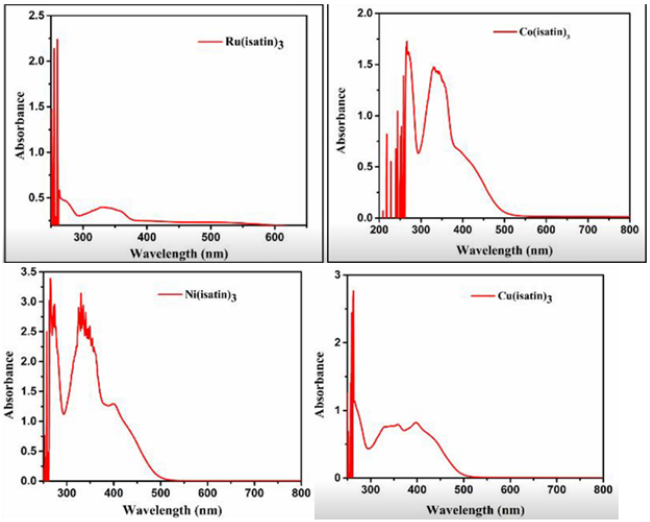



**Figure 1:** UV-vis spectra of $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$ complexes

the ligand environment around the complex changes, it leads to a change in wavelength. The change in the wavelength in the visible region is due to the d-d transition of metal complexes which indicates the formation of complex.

### *FTIR spectra*

The FTIR spectrum of ligands and their complexes shows that the respective metal-ligand bonding indicates the formation of the desired complex. The corresponding IR stretching frequencies for complexes are shown in Table 3.

The IR frequencies for the metal coordination (M-ligand) are generally shown in the region of 400 to 550 $cm^{-1}$. In all of the complexes peaks around 400 to 550 $cm^{-1}$ region are due to M-Cl, M-O and M-N stretching frequency. The other frequencies tabulated in Table 3 are due to the various functional groups present in the ligand of the complex. From these frequencies, we can easily distinguish between any two compounds and this is also the evidence for the formation of complexes between metal and ligand.

**Table 2:** Photo-physical data table for $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$ complexes

| *Complex* | *Absorbance* | |
|---|---|---|
| | *Ligand transitions* $l_{max}$ *(nm)* | *MLCT* $l_{max}$ *(nm)* |
| $[Run(C_{14}H_{10}N_4O_2)_2Cl_2]$ | 265 | 340 |
| $[Ni(C_{14}H_{10}N_4O_2)_2Cl_2]$ | 270<br>345 | 315 |
| $[Co(C_{14}H_{10}N_4O_2)_2Cl_2]$ | 250<br>265 | 345 |
| $[Cu(C_{14}H_{10}N_4O_2)_2Cl_2]$ | 265 | 350<br>400 |

## Catalytic activity $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$complexes foramination of aryl halides

This type of reaction is important in organic synthesis as well and organo nitrogen compounds are pervasive [25-26]. Among the prepared complexes, it was observed that $[Cu(C_{14}H_{10}N_4O_2)_2Cl_2]$ complex shows good activity for the amination of arylhalides. The amination of aniline with bromobenzene using Cu complex selectively gives diphenylamine as a product (Scheme 3). The quantification and identification of the product were confirmed using GC using an external standard method. The result indicates that $[Cu(C_{14}H_{10}N_4O_2)_2Cl_2]$complex shows better catalytic activity as compared to the other copper complexes.

## Biological Activities

There are reports regarding some isatin based complexes that can act as antifungal and antibacterial against bacteria such as *Pseudomonas,*and *Klebsiella pneumonia*[27].

### *Test of antibacterial activity*

The well diffusion method was used to test the antimicrobial activity. It was tested against gram-positive and gram-negative bacteria which are mentioned. The zone inhibition around each of the wells was measured and was noted down as the antimicrobial activity (Fig. 2). The activity was compared with standard $[M(acac)_3]$ complexes.

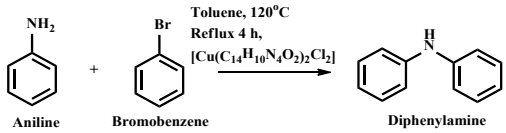
## *Pseudomonas* Bacteria

**a) Zone of clearance for $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$complexes**

1)$[Co(C_{14}H_{10}N_4O_2)_2Cl_2]$= 0.2 cm, (2)

**Table 3:** FTIR spectral data table for $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$ complexes

| *Sr. No.* | *Complex* | *Observed frequencies* ($cm^{-1}$) | *Information obtained* |
|---|---|---|---|
| 1 | $[Run(C_{14}H_{10}N_4O_2)_2Cl_2]$ | 860 – 680, 1590 – 1690, 1680 - 1700 | Aromatic C-H stretching, C=N, Amide C=O, |
| 2 | $[Ni(C_{14}H_{10}N_4O_2)_2Cl_2]$ | 860 - 680, 1690 – 1630, 3200 - 3350 | Aromatic C-H stretching, Amide C=O stretching, N-Hstretching |
| 3 | $[Co(C_{14}H_{10}N_4O_2)_2Cl_2]$ | 1590 – 1670, 1680 – 1700, 3200- 3350 | C=N, Amide C=O stretch, N-H stretching |
| 4 | $[Cu(C_{14}H_{10}N_4O_2)_2Cl_2]$ | 860 – 680, 1680 – 1700, 1590- 1690 | Aromatic C-H stretching, Amide C=O stretching |




**Scheme 3:** C-N coupling reaction of aniline with bromobenzene using $[Cu(C_{14}H_{10}N_4O_2)_2Cl_2]$complex

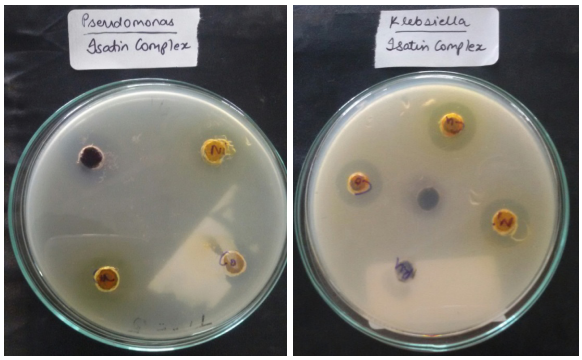



**Fig. 2:** Antibacterial activities of $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$ complexes

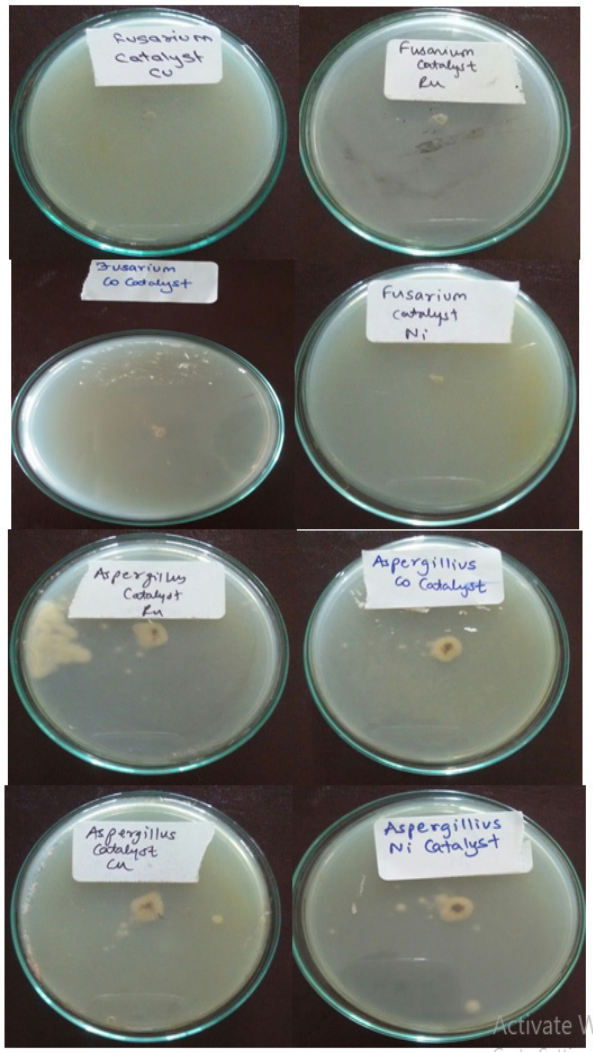



**Fig. 3:** Antifungal activity of$[M(C_{14}H_{10}N_4O_2)_2Cl_2]$ complexes

**Table 4:** Antifungal activity of$[M(C_{14}H_{10}N_4O_2)_2Cl_2]$ complexes

| *Complex* | *Conc. of complexes* | | *Observed growth against Fungal spp.* | |
|---|---|---|---|---|
| | *(µl)* | *(µg)* | *Fusarium* | *Aspergillus* |
| $[Ru(C_{14}H_{10}N_4O_2)_2Cl_2]$ | 10 | 100 | + | + |
| $[Ni(C_{14}H_{10}N_4O_2)_2Cl_2]$ | 10 | 100 | + | + |
| $[Co(C_{14}H_{10}N_4O_2)_2Cl_2]$ | 10 | 100 | - | + |
| $[Cu(C_{14}H_{10}N_4O_2)_2Cl_2]$ | 10 | 100 | - | + |

$[Ni(C_{14}H_{10}N_4O_2)_2Cl_2]$= 0.2 cm,
3) $[Ru(C_{14}H_{10}N_4O_2)_2Cl_2]$= 0.5 cm, (4)
$[Cu(C_{14}H_{10}N_4O_2)_2Cl_2]$= 0.5 cm

**b) Zone of clearance for $[M(acac)_3]$ complexes**

1) $[Co(acac)_3]$= 0.1 cm, 2) $[Ni(acac)_2]$= 0.18 cm,
3) $[Ru(acac)_3]$= 0.6 cm, 4) $[Cu(acac)_2]$= 0.8 cm

### *Klebsiella pneumonia Bacteria*

**a) Zone of clearance for $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$complexes**

1)$[Co(C_{14}H_{10}N_4O_2)_2Cl_2]$= 0.6 cm, 2) $[Ni(C_{14}H_{10}N_4O_2)_2Cl_2]$= 0.5 cm,
3) $[Ru(C_{14}H_{10}N_4O_2)_2Cl_2]$= 0.2 cm, 4) $[Cu(C_{14}H_{10}N_4O_2)_2Cl_2]$= 0.4 cm

**b) Zone of clearance for $[M(acac)_3]$ complexes**

1) $[Co(acac)_3]$ = 1.0 cm, 2) $[Ni(acac)_2]$= 2.0 cm,
3) $[Ru(acac)_3]$= 1.2 cm, 4) $[Cu(acac)_2]$= 1.5 cm

The zone of clearance on the agar plate shows the susceptibility of bacterial stain against the antibacterial agent. In general, larger the diameter of the zone of clearance, the more effective the antibacterial agent against bacteria. The result shows that $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$ complexes are more effective than $[M(acac)_n]$ complexes and show good antibacterial activity.

### *Antifungal activity*

All the prepared four $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$complexes were subjected to study their antifungal activity against fungicide *Fusarium* and *Aspergillus.* The results of antifungal activity showed that some $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$complexes $[Co(C_{14}H_{10}N_4O_2)_2Cl_2]$ and $[Cu(C_{14}H_{10}N_4O_2)_2Cl_2]$ inhibit the growth of fungal colony in the agar plate indicating the complexes are effective to resist the growth of fungus, *i.e.,* negative growth (Fig. 3). So they are the most effective complexes showing antifungal activity. It seems that Co and Cu complexes are effective bioactive compounds for growth inhibition of the fungi. The complexes of Ru and Ni do not show antifungal activity.

All the results of antifungal activity are tabulated in Table 4.

## CONCLUSION

Schiff base ligand substituted isonicotinohydrazide and its corresponding metal complexes with Ru, Ni, Co and Cu were prepared in good yield. The above-prepared complexes were characterized by using UV and IR spectroscopic techniques. The copper complex shows good catalytic activity, towards the amination of aniline with bromobenzene. All $[M(C_{14}H_{10}N_4O_2)_2Cl_2]$ complexes show better antibacterial activity than corresponding $[M(acac)_n]$ complexes. $[Cu(C_{14}H_{10}N_4O_2)_2Cl_2]$ and $[Co(C_{14}H_{10}N_4O_2)_2Cl_2]$complex show negative growth, and act as an antifungal agent against *Fusarium, and Aspergillus*.

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## CONFLICTS OF INTEREST

All authors declare that there is no conflict of interest about the publication of this manuscript

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