Synthesis and fungitoxic activity of 5-aryl-1formyl-4,5-dihydro-3-(2-hydroxyphenyl)-1*H*pyrazoles and their complexes

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Abstract: Cyclization of 3-aryl-1-(2-hydroxyphenyl)prop-2-en-1-ones with hydrazine hydrate in refluxing formic acid afforded the title ligands, 5-aryl-1-formyl-4,5-dihydro-3-(2-hydroxyphenyl)-1*H*-pyrazoles (HL¹-HL⁴, Ar=Ph, 4-CH₃O-C₆H₄-, 2-furyl, 2-thienyl). Reaction of HL¹-HL⁴ with the divalent metal ions, Mn^{2+} , Co^{2+} , Ni^{2+} , Cu^{2+} , and Zn^{2+} , afforded novel complexes of the type [ML₂] (M=metal ion; L=deprotonated ligand) which were characterized by elemental analyses, molecular weight determinations, molar conductances, magnetic moments and electronic and infrared spectral data. The ligands behaved as tridentate, coordinating through the phenolic oxygen after deprotonation, N-2 of the pyrazole ring and oxygen of the 1-formyl group. The ligands and their complexes were evaluated for growth-inhibiting activity against four phytopathogenic fungi. *Macrophomina phaseoli* was generally most sensitive followed by *Alternaria alternata* and *Colletotrichum falcatum* while *Fusarium oxysporum* was least sensitive to the tested compounds. The ligand HL¹ and its complexes showed the best activity against the fungi tested.

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1 INTRODUCTION

Hydrazones and acid hydrazides have been frequently used as useful ligands for complexation with transition metal ions and several of these complexes with useful biological activities have been studied extensively.¹⁻⁵ The substituted 1-acyl-4,5-dihydro-1H-pyrazoles possess structural features of both hydrazones and acid hydrazides in a rigid cyclic framework which can provide the added advantage of certain restricted conformations suitable for complexation. Moreover, these pyrazoles have been reported as showing enzyme-inhibiting,⁶ pharmacological,⁷ molluscicidal,⁸ antibacterial,⁹ antifungal,¹⁰ insecticidal,^{11–13} herbici-dal,¹⁴ herbicide safener¹⁵ and antifertility activities.¹⁶ Recently, we have reported¹⁷ improved antifungal activity of 4,5-dihydropyrazoles as a consequence of their coordination with transition metal ions. Continuing these studies and our interest in development of newer pesticides,^{18,19} we report herein the synthesis of 5-aryl-1-formyl-4,5-dihydro-3-(2-hydroxyphenyl)-1H-pyrazoles, their coordination with transition metal ions and the effect of such complexation on in vitro mycelial growth-inhibitory activity against some economically important phytopathogenic fungal pests.

2 MATERIALS AND METHODS

2.1 General

1-(2-Hydroxyphenyl)-3-phenylprop-2-en-1-one, (1), 1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (2), 3-furyl-1-(2-hydroxyphenyl)prop-2-en-1one (3) and 1-(2-hydroxyphenyl)-3-(thienyl)prop-2en-1-one (4) (Fig 1) were available from our earlier studies.¹⁷ All other chemicals were procured from commercial suppliers. The solvents were distilled prior to use.

2.2 Synthesis of ligands

The 5-aryl-1-formyl-4,5-dihydro-3-(2-hydroxyphenyl)-1*H*-pyrazole ligands (HL¹-HL⁴), were synthesized by refluxing a mixture of the appropriate propenone 1–4 (0.1 mole) and hydrazine hydrate (2 ml, excess) in formic acid (50 ml) for 20 h. The reaction mixture was cooled and poured onto icewater with stirring. The separated solid was filtered, washed with water and crystallized from methanol to give the corresponding ligands HL¹-HL⁴ in 74–87% yield. The synthesis is outlined in Fig 1.



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2.3 Synthesis of complexes

A solution of metal^{II} chloride (0.01 mole) in a minimum amount of ethanol was added slowly at ambient temperature to an alkaline solution (pH adjusted between 8 and 10 by adding few drops of saturated aqueous sodium hydroxide solution) of the corresponding ligand (0.02 mole) in ethanol (50 ml) with stirring. The reaction mixture was refluxed for 2h during which a solid was precipitated. The reaction mixture was cooled, the separated solid filtered off, washed successively with water and ethanol and dried under vacuum to give the complex in 51–65% yield.

2.4 Physicochemical measurements

The melting points were determined in open capillaries in a sulfuric acid bath and are uncorrected. ^{[1}H]NMR spectra were recorded on a Bruker AC 300F instrument (300MHz) in deuterochloroform using trimethylsilane as internal reference. Infrared spectra were recorded on a Perkin Elmer spectrophotometer, model 621 in the range $4000-200 \,\mathrm{cm}^{-1}$ using potassium bromide pellets. Electronic spectra of the metal complexes were recorded on a Beckmann DU-64 spectrophotometer in dimethylsulfoxide (DMSO). Conductance measurements were made on freshly prepared 1×10^{-3} M solutions in dry DMSO at 25°C using a Digital Conductivity Meter, model NDS-732. All ligands and complexes were analysed for C, H and N on a Carlo Erba Strumentazion automatic elemental analyser, model 1106. Metal contents were determined on a Varian Techtron atomic absorption spectrophotometer, model AA 120. Molecular masses of the complexes were determined by the cryoscopic method in dry DMSO. Magnetic susceptibility was determined at $25(\pm 1)^{\circ}C$ using a magnetic susceptibility balance (Sherwood Scientific, England).

2.5 Bioassay

2.5.1 Test solutions

Stock solutions of the compounds (1 mg ml^{-1}) were prepared in DMSO and stored in a refrigerator until needed.

2.5.2 Standard fungicide

The commercial fungicide carbendazim was used as a standard for comparing the activity of the test compounds. It was used as a commercial 500 g kg^{-1} WP (Bavistin, BASF).

2.5.3 Test organisms

The phytopathogenic fungi Alternaria alternata (Fr) Keissler from radish siliqua, Coletotricum falcatum Went from sugar cane, Fusarium oxysporum Schlecht emend Snyd and Hans f sp ciceri (Padwick) Snyd and Hans from chick pea and Macrophomina phaseoli (Maubl) Ashby from green gram were maintained on Czapek's Dox Agar Slants at $5(\pm 1)$ °C.

2.5.4 Growth-inhibitory activity

For determination of in vitro fungicidal activity, loopfuls of the test organisms from the slants were introduced aseptically into sterilized conical flasks containing 100 ml of Czapek's Dox broths. The flasks were incubated with intermittent shaking at $28(\pm 1)$ °C for 24h. The inoculated broths were used as such for testing the growth-inhibitory activity of the test compounds by a two-fold serial-dilution technique.²⁰ For this purpose, 1.8ml of the inoculated broth was taken in a test tube and 0.2 ml of the stock solution of the test compound was added to it to form the first dilution. This solution (1ml) was diluted further with the inoculated broth (1 ml) to produce the second dilution. The process was repeated to give a set of eight dilutions containing test compound concentrations of 100, 50, 25, 12.5, 6.25, 3.13, 1.56 and $0.78 \,\mathrm{mg}$ litre⁻¹. A set of tubes containing the inoculated broths with equivalent quantity of DMSO was kept as control. Each test was replicated twice. The tubes were incubated for 72h at $28(\pm 1)^{\circ}$ C. Results are reported as minimum inhibitory concentration limits (MIC, mg litre $^{-1}$), ie the minimum concentration of the compound where no growth of the mycelia could be observed.

3 RESULTS AND DISCUSSION

3.1 Chemistry

3.1.1 Characterization of ligands

The ligands displayed characteristic IR and [¹H]NMR spectra. The two protons at C4, which were adjacent to a chiral center at C₅, showed magnetic non-equivalence and, therefore, appeared at different chemical shifts. These protons were assigned in the [¹H]NMR spectra on the basis of their characteristic chemical shifts rather than coupling constants²¹ which are known to be influenced by the nature of the N-1 substituent.²² The proton at C_4 resonating upfield (δ 3.33-3.63) was assigned trans to C5-H and that resonating downfield (& 3.75-3.90) was assigned cis to C₅-H. The coupling constant $\mathcal{J}_{4,5}$ -trans was found to be 4–5Hz, whereas, $\mathcal{J}_{4,5}$ -cis was 11–12Hz. These values of the coupling constants are in agreement with those described earlier.^{21,22} The proton at C_5 appeared at δ 5.46–5.83. The structures were further supported by elemental analysis data. The characterization, analytical and ['H]NMR spectral data of the ligands HL^1 - HL^4 are given in Table 1.

3.1.2 Characterization of complexes

The complexes were characterized on the basis of their elemental analyses, molecular mass determinations, molar conductances, magnetic moments, infrared and electronic spectral data.

The complexes were stable under atmospheric conditions, decomposed only on heating and were insoluble in most of the common organic solvents except polar solvents such as DMSO and nitrobenzene. The low molar conductance values (0.40–19.50,

Table 1. Characterization, analytical and [¹H]NMR spectral data of 5-aryl-1-formyl-4,5-dihydro-3-(2-hydroxyphenyl)-IH-pyrazoles

Compd	Мр (°C)	Yield (%)	Mol formula (Mol mass)	Analysis (%): found (calcd)					
				С	Н	Ν	[¹ H]NMR (CDCl ₃ , δppm)		
HL ¹	151	74	C ₁₆ H ₁₄ N ₂ O ₂ (266.3)	72.3 (72.2)	5.5 (5.3)	10.7 (10.5)	3.33 (dd, 1H, <i>trans</i> C ₄ -H, <i>J</i> = 5 and 18Hz), 3.90 (dd, 1H, <i>cis</i> C ₄ -H, <i>J</i> = 11 and 18Hz), 5.50 (dd, 1H, C ₅ -H, <i>J</i> = 5 and 11Hz), 6.93–7.95 (m, 9H, aromatic H), 8.91 (s, 1H, CHO), 10.12 (s, 1H, OH, D ₂ O exchangeable).		
HL ²	168	87	C ₁₇ H ₁₆ N ₂ O ₃ (296.3)	68.7 (68.9)	5.5 (5.4)	9.4 (9.5)	 3.34 (dd, 1H, <i>trans</i> C₄-H, <i>J</i> = 5 and 18Hz), 3.78 (d, 3H, OCH₃), 3.88 (dd, 1H, <i>cis</i> C₄-H, <i>J</i> = 12 and 18Hz), 5.46 (dd, 1H, C₅-H, <i>J</i> = 5 and 12Hz), 6.85–7.40 (m, 8H, aromatic H), 8.90 (s, 1H, CHO), 10.14 (s, 1H, OH, D₂O exchangeable). 		
HL ³	170	76	C ₁₄ H ₁₂ N ₂ O ₃ (256.3)	65.6 (65.6)	4.6 (4.7)	10.9 (10.9)	3.63 (dd, 1H, <i>trans</i> C ₄ -H, <i>J</i> = 5 and 18Hz), 3.75 (dd, 1H, <i>cis</i> C ₄ -H, <i>J</i> = 11 and 18Hz), 5.62 (dd, 1H, C ₅ -H, <i>J</i> = 5 and 11Hz), 6.34–7.78 (m, 7H, aromatic H), 8.86 (s, 1H, CHO), 10.05 (s, 1H, OH, D ₂ O exchangeable).		
HL ⁴	120	79	C ₁₄ H ₁₂ N ₂ O ₂ S (272.3)	61.2 (61.7)	4.3 (4.4)	10.0 (10.3)	3.53 (dd, 1H, <i>trans</i> C_4 -H, $J = 4$ and 18Hz), 3.88 (dd, 1H, <i>cis</i> C_4 -H, $J = 11$ and 18Hz), 5.83 (dd, 1H, C_6 -H, $J = 4$ and 11Hz), 6.93–7.42 (m, 7H, aromatic H), 8.88 (s, 1H, CHO), 10.05 (s, 1H, OH, D_2O exchangeable).		

ohm⁻¹ cm²mol⁻¹) of the complexes in dry DMSO at 25 °C indicated their non-electrolytic nature. The results of elemental analyses and molecular mass determinations (Table 2) indicated 1:2 metal:ligand stoichiometry in the complexes with the general formula [ML₂] where L is the appropriate deprotonated ligand HL¹-HL⁴ and M is Mn^{II}, Co^{II}, Ni^{II}, Cu^{II} and Zn^{II}.

3.1.2.1 Infrared spectra. All the ligands²³ and complexes²⁴ displayed characteristic IR absorptions which support the coordination of the ligand through the phenolic oxygen after deprotonation and N-2 of the pyrazole ring. In addition, a negative shift (20- $30 \,\mathrm{cm}^{-1}$) for the carbonyl group indicated the participation of this group in coordination.²⁵ The furan and thiophene ring stretching vibrations remained unaltered in the spectra of the complexes of the ligands HL³ and HL⁴ respectively, suggesting non-participation of their oxygen and sulfur in the coordination. The participation of N-2, the phenolic oxygen after deprotonation and the carbonyl group was also supported by the appearance of new absorption bands in the far-IR region at 500–460 and $440-400\,\mathrm{cm}^{-1}$ assigned to v(M-O) and v(M-N), respectively.²⁶

3.1.2.2 Magnetic moments and electronic spectra. The effective magnetic moment (μ_{eff}) values of the complexes calculated from the corrected magnetic susceptibilities are presented in Table 2. Those of the Mn^{II} complexes were found to be in the range of 5.87–6.12 BM which are characteristic of high-spin Mn^{II} complexes. The electronic spectra of the complexes showed weak absorption bands in the regions 18520–19350, 21460–22321, 24681–25542 and 28060–28927 cm⁻¹ assigned to ${}^{6}A_{1g} \rightarrow {}^{4}T_{1g}(G)$, ${}^{6}A_{1g} \rightarrow {}^{4}T_{2g}(D)$ transitions, respectively, suggesting a distorted octahedral geometry for the Mn^{II} complexes.²⁷

The Co^{II} complexes displayed magnetic moments in the range of 4.89–5.35 BM which indicates the presence of three unpaired electrons with significant orbital contribution and a high spin octahedral stereochemistry.²⁷ The electronic spectra of the complexes exhibited three bands in the regions 8520–8950, 17560–17980 and 21620–22130 cm⁻¹ which were assigned to ${}^{4}T_{1g}(F) \rightarrow {}^{4}T_{2g}(F) (v_{1})$, ${}^{4}T_{1g}(F) \rightarrow {}^{4}A_{2g}(F) (v_{2})$ and ${}^{4}T_{1g}(F) \rightarrow {}^{4}T_{1g}(P) (v_{3})$ transitions, respectively. The appearance of these bands, energy ratio v_{2}/v_{1} of the complexes (2.01–

Table 2. Analytical data and magnetic moment values of the metal complexes of 5-aryl-1-formyl-4,5-dihydro-3-(2-hydroxyphenyl)-1H-pyrazoles

	Molecular	Melting/Decomp	Vield	Molmass	Analysis (%): found (calcd)				
Complex	formula	(D) point (°C)	(%)	Found (Calcd)	С	Н	Ν	Metal	μ _{eff.} (BM)
$[Mn(L^1)_2]$	$C_{32}H_{26}MnN_4O_4$	> 220	55	608 (585.5)	66.1 (65.6)	4.3 (4.5)	10.0 (9.6)	9.9 (9.4)	6.10
$[Mn(L^2)_2]$	$C_{34}H_{30}MnN_4O_6$	165 (D)	55	660 (645.6)	62.9 (63.3)	5.1 (4.7)	9.2 (8.7)	9.0 (8.5)	5.87
$[Mn(L^3)_2]$	$C_{28}H_{22}MnN_4O_6$	190	54	580 (565.4)	60.0 (59.5)	3.8 (3.9)	10.4 (9.9)	10.1 (9.7)	5.99
$[Mn(L^4)_2]$	$C_{28}H_{22}MnN_4O_4S_2$	140 (D)	55	620 (597.6)	55.9 (56.3)	4.6 (3.7)	10.3 (9.4)	9.3 (9.2)	6.12
$[Co(L^{1})_{2}]$	C ₃₂ H ₂₆ CoN ₄ O ₄	> 220	55	617 (589.5)	65.7 (65.2)	4.3 (4.4)	10.0 (9.5)	9.6 (10.0)	5.15
$[Co(L^2)_2]$	C ₃₄ H ₃₀ CoN ₄ O ₆	175 (D)	55	675 (649.6)	63.4 (62.9)	5.1 (4.7)	9.1 (8.6)	8.7 (9.1)	5.20
$[Co(L^3)_2]$	C ₂₈ H ₂₂ CoN ₄ O ₆	> 220	55	590 (569.4)	59.3 (59.1)	3.8 (3.9)	9.4 (9.8)	10.4 (10.3)	5.35
$[Co(L^4)_2]$	$C_{28}H_{22}CoN_4O_4S_2$	140	55	626 (601.6)	56.4 (55.9)	4.1 (3.7)	9.2 (9.3)	10.3 (9.8)	4.89
$[Ni(L^1)_2]$	C ₃₂ H ₂₆ NiN ₄ O ₄	> 220	52	605 (589.3)	65.6 (65.2)	4.2 (4.4)	9.9 (9.5)	10.4 (10.0)	3.00
$[Ni(L^2)_2]$	C ₃₄ H ₃₀ NiN ₄ O ₆	170 (D)	51	674 (649.3)	62.6 (62.9)	5.0 (4.7)	9.0 (8.6)	9.5 (9.0)	3.33
$[Ni(L^3)_2]$	C ₂₈ H ₂₂ NiN ₄ O ₆	> 220	52	585 (569.2)	59.5 (59.1)	4.0 (3.9)	10.3 (9.8)	10.6 (10.3)	3.09
$[Ni(L^4)_2]$	$C_{28}H_{22}NiN_4O_4S_2$	> 220	52	627 (601.3)	56.4 (55.9)	4.1 (3.7)	9.0 (9.3)	10.2 (9.8)	3.20
$[Cu(L^1)_2]$	$C_{32}H_{26}CuN_4O_4$	> 220	55	615 (594.1)	64.4 (64.7)	4.8 (4.4)	9.2 (9.4)	11.2 (10.7)	2.11
$[Cu(L^2)_2]$	$C_{34}H_{30}CuN_4O_6$	> 220	55	678 (654.2)	62.0 (62.4)	5.0 (4.6)	9.0 (8.6)	9.6 (9.7)	2.12
[Cu(L ³) ₂]	$C_{28}H_{22}CuN_4O_6$	190	55	588 (574.1)	59.1 (58.6)	3.7 (3.9)	10.2 (9.8)	11.5 (11.1)	1.92
$[Cu(L^4)_2]$	$C_{28}H_{22}CuN_4O_4S_2$	> 220	55	620 (606.2)	56.9 (55.5)	4.1 (3.7)	9.4 (9.2)	10.8 (10.5)	1.96
$[Zn(L^1)_2]$	$C_{39}H_{26}ZnN_4O_4$	220 (D)	52	623 (596.0)	65.0 (64.5)	4.7 (4.4)	9.9 (9.4)	11.2 (11.0)	_
$[Zn(L^2)_2]$	$C_{34}H_{30}ZnN_4O_6$	150 (D)	52	681 (656.0)	62.0 (62.3)	5.0 (4.6)	9.0 (8.5)	10.5 (10.0)	-
$[Zn(L^3)_2]$	$C_{28}H_{22}ZnN_4O_6$	> 220	56	600 (575.9)	58.7 (58.4)	3.7 (3.9)	9.9 (9.7)	11.3 (11.4)	-
$[Zn(L^4)_2]$	$C_{28}H_{22}ZnN_4O_4S_2$	124 (D)	56	633 (608.0)	55.6 (55.3)	4.1 (3.6)	9.7 (9.2)	11.2 (10.8)	-

2.06),²⁸ nephelauxetic ratio (0.910–0.935), 10 Dq (9030–9060 cm⁻¹) and LFSE (86.41–86.69 kJ mol⁻¹) were all in agreement with an octahedral configuration around Co^{II}. The Racah interelectronic repulsion parameter 'B' was found to be less ($884-908 \text{ cm}^{-1}$) than the free ion value (971 cm^{-1}), suggesting a weak covalent character of the metal–ligand bond.²⁹

The effective magnetic moment values of 3.00–3.33 BM for the Ni^{II} complexes suggested octahedral geometry around Ni^{II} which was further supported by the electronic spectra where three bands in the regions 10050–10240, 15600–15825 and 24420–24660 cm⁻¹ were observed. These were assigned to ${}^{3}A_{2g}(F) \rightarrow {}^{3}T_{2g}(F) (v_1)$, ${}^{3}A_{2g}(F) \rightarrow {}^{3}T_{1g}(F) (v_2)$ and ${}^{3}A_{2g}(F) \rightarrow {}^{3}T_{1g}(P) (v_3)$ transitions, respectively. The various ligand field parameters, such as 10Dq, B, β and LFSE, for the Ni^{II} complexes were found to be in the range 10050–10240 cm⁻¹, 651–658 cm⁻¹, 0.625–0.631 and 144.26–146.98 kJ mol⁻¹, respectively. The energy ratio v_2/v_1 for the complexes was within the range of 1.52–1.56 as required for octahedral complexes.³⁰ The Racah interelectronic repulsion parameter 'B' (651–658 cm⁻¹) value was less than the free ion value because of decreased interelectronic repulsion resulting from electron delocalization.³¹

The magnetic moment of the Cu^{II} complexes was observed in the range of 1.92–2.12 BM which corresponds to a single unpaired electron with significant orbital contribution. The increase from the spin-only value (1.73 BM) might be due to Jahn– Teller distortion.³² The electronic spectra displayed a broad band in the region 15500–16000 cm⁻¹ pertaining to the ${}^{2}E_{g} \rightarrow {}^{2}T_{2g}$ transition, suggesting a distorted octahedral configuration for the complexes. The possibility of a tetrahedral structure³³ was excluded by the absence of any band below 10000 cm⁻¹. The observed values of 10Dq (15500–16000 cm⁻¹) and LFSE (111.24–114.83 kJ mol⁻¹) supported the proposed geometry.

The Zn^{II} complexes were diamagnetic. On the basis of their elemental analyses, infrared spectra, molecular weight determinations and molar conductance studies octahedral structures have been proposed for these Zn^{II} complexes.³⁴

3.2 Fungicidal activity

The growth-inhibitory activity *in vitro* of the ligands (HL^1-HL^4) and their metal complexes against four test fungi are shown in Table 3, with data for carbendazim included for comparison.

The data indicate no clear trends with respect to the influence of coordination on fungitoxicity and little or no activity against F oxysporum in any case. The HL¹ ligand and its complexes gave the most promising results with the other three fungi and M phaseoli tended to be the most sensitive fungus to both ligands and complexes.

Although no ligand or complex showed activity comparable to that of carbendazim, nevertheless some

	Minimum inhibitory concentration (mg litre ⁻¹					
Ligand	Complex with ^a	A alternata	C falcatum	F oxysporum	M phaseoli	
HL ¹	None	25	>100	>100	3.13	
	Mn ^{II}	6.25	12.5	>100	6.25	
	Co ^{II}	12.5	25	>100	6.25	
	Ni ^{II}	25	12.5	>100	6.25	
	Cu ^{II}	6.25	25	>100	3.13	
	Zn ^{II}	25	50	>100	12.5	
HL ²	None	50	50	>100	3.13	
	Mn ^{II}	50	50	>100	50	
	Co ^{II}	50	50	>100	6.25	
	Ni ^{II}	50	50	>100	3.13	
	Cu ^{II}	100	100	>100	>100	
	Zn ^{II}	50	50	>100	<3.13	
HL ³	None	100	100	>100	100	
	Mn ^{II}	100	50	>100	100	
	Co ^{II}	100	50	>100	100	
	Ni ^{II}	25	25	>100	<3.13	
	Cu ^{II}	25	25	>100	25	
	Zn ^{II}	100	100	>100	100	
HL^4	None	50	100	>100	50	
	Mn ^{II}	25	25	>100	6.25	
	Co ^{II}	100	100	>100	50	
	Ni ^{II}	50	25	>100	12.5	
	Cu ^{II}	50	50	>100	6.25	
	Zn ^{II}	50	50	>100	50	
Carbendazim ^b	None	0.78	1.56	3.13	0.78	

Table 3. Activities *in vitro* of the ligands and

 their metal complexes against four test fungi

^a Complexes were of the type [ML₂] where M is metal ion and L is deprotanated ligand.

^b Included for comparison.

showed promising activity and could serve as lead structures for future work.

ACKNOWLEDGEMENT

Instrumental facilities provided by Regional Sophisticated Instrumentation Centre, Punjab University, Chandigarh are acknowledged.

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