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Synthesis, Characterization and Anti Tuberculosis Activity of Substituted Indole-3-Carboxaldehyde Thiosemicarbazonesand Their Ni(II) Complexes

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Abstract:Nickel acetatereacted withtwo moles of substituted indole-3-carboxaldehydethiosemicarbazones (HIntsc, H^1L; HIntscN^{1}Me, H^2L and HIntscN^{1}Ph, H^3L) to form complexes of stiochiometry, $[Ni(L)_2]$ (^1L, **1**; ^2L, **2**; ^3L, **3**). All the complexes (**1-3**) have been characterized using elemental analysis, IR,^{1}HNMR spectroscopy. Spectroscopic data is suggesting binding of ligand to nickel center through azomethine nitrogen and thiolate and formation of square planar geometry in **1-3.** Ligands and their complexes have been tested for anti-TB activity using Micro Plate Alamar Blue assaymethod. Ligands (H^1L and H^2L) are active at MIC 12.5 µg/ml and H^3L at MIC 25 µg/ml. Complexes **1-3**showed less activity than their corresponding ligands.

Keywords: Indole-3-carboxaldehyde, Ligand, Thiosemicatbazones, Nickel acetate,^{1}HNMR, Anti-tuberculosis

Introduction:

Tuberculosis (TB) is one of the deadly infectious diseases mainly caused by the bacteria named Mycobacterium tuberculosis. This deadly bacterium has infectedlarge population worldwide per year [1-3]. According to World Health Organization (WHO) this number will increase drastically between 2000 and 2020 [4]. Looking at this scenario, it is the need of hour to make new anti-mycobacterial drugs which will be effective against multidrug resistance, having less toxicity, quick action and many more [5-7].

Thiosemicarbazones are among such molecules that have wide range of applications such as antiviral [8-9], antifungal [10], antibacterial [11-12], antitumor [13-14], anticarcinogenic [15-16], antioxidant [17] activities, insulin mimetic effects [18] and antiamoebic activity [19].

Looking at the biological application of thiosemicarbazones, in present research work focused on synthesis of three thiosemicarbazones, indole-3-carboxaldehyde thiosemicarbazone (HIntsc, H^1L), indole-3-carboxaldehyde-N^1-methy thiosemicarbazone (HIntscN^1Me, H^2L), indole-3-carboxaldehyde-N^1-phenyl thiosemicarbazone (HIntscN^1Ph, H^3L) (Scheme 1) and their complexes with nickel(II). Structure establishment of these compounds has been done through elemental analysis, IR and ^{1}H NMR spectroscopy.

Experimental:

Chemicals:

$Ni(OAc)_2$, Indole-3-Carboxaldehyde, thiosemicarbazide, N-methylthiosemicarbazide and N-phenyl thiosemicarbazides are of AR grades and purchased from Aldrich Chemicals Ltd. SHIMADZU FTIR 8400S spectrophotometer was used to take Infrared spectra of ligands and their complexes. The base used to make pallets is KBr. Electrically heated Gallenkamp apparatus was used to check the melting point of compounds. For recording ^{1}H NMR AV500 FT spectrometer was used at a frequency of 500 MHz. Solvent used is d^6-dmso/$CDCl_3$ with TMS as the internal standard. Thermoelectron FLASHEA1112 CHNS analyzer was used for C, H and N analysis of complexes.

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Synthesis:

Indole-3-carboxaldehyde thiosemicarbazones (HIntsc, H^1L):

To a solution of Indole-3-carboxaldehyde (1.59 g, 10.9 mmol) in 50ml methanol was addedthiosemicarbazide(1g, 10.9 mmol). The reaction contents was refluxed for 6-7 hrs and filtered to remove any insoluble impurity. After 2-days brown precipitates thus obtained were separated out and dried in vaco.M.P. 138-140°C; yield, 87%;Main IR peaks:ν(N-H), 3448, 3331; ν(-NH-), 3146; ν(C=C)+ν(C=N)+δ(NH_2), 1614, 1539, 1442; ν(C=S), 839:^{1}H NMR signal: 10.07s (1H, N^2H), 7.86s (1H, C^4H),7.83s (2H, N^1H),8.33s (1H, C^2H), 7.46d (2H, $C^{6,9}$H, 8 Hz), 7.29d (2H, $C^{7,8}$H, 8 Hz).

Indole-3-carboxaldehyde-N^1-Me thiosemicarbazones (HIntsc-N^1-Me, H^2L):

To a solution ofIndole-3-carboxaldehyde (1.38g, 9.5 mmol)in 50ml methanol was added N^1-methylthiosemicarbazide (1g, 9.5 mmol). The contents were refluxed for 6-7 hrs and filtered to remove any insoluble impurity. After 2-days brown precipitates obtained were separated out and dried in vaco.M.P. 150-152°C, yield, 84%. IR peaks: ν(N-H), 3362; ν(-NH-), 3155; ν(C=C)+ν(C=N)+δ(NH_2), 1608, 1546, 1498; ν(C=S), 833.^{1}H NMR: 11.24s (1H, N^4H), 10.95s (1H, N^2H), 8.12s (1H, C^2H), 7.83s (1H, C^4H), 7.46d (2H, $C^{7,8}$ H, 7.2 Hz), 7.39s (1H, N^1H),7.14d (2H, $C^{6,9}$H, 8 Hz),3.16m (3H, CH_3).

Indole-3-carboxaldehyde-N^1-Ph thiosemicarbazones (HIntsc-N^1-Ph, H^3L):

To a solution of Indole-3-carboxaldehyde (0.86g, 5.9 mmol) in 50 ml methanol was added N^1-phenyl thiosemicarbazide (1g, 5.9 mmol). The contents were refluxed for 6-7 hrs and then filtered to remove any insoluble impurity. After 2-days brown precipitates thus obtained were separated out and dried in vaco.M.P. 166-168°C, yield, 82%.IR peaks: ν(N-H), 3410, 3317; ν(-NH-), 3139; ν(C=C)+ν(C=N)+ δ(NH_2), 1600, 1543, 1496; ν(C=S), 845.^{1}H NMR:11.71s (1H, N^2H), 11.62s (1H, N^4H),9.63s (1H, C^2H), 8.42s (1H, N^1H), 8.24d (2H, $C^{6,9}$H, 8 Hz),7.93s (1H, C^4H), 7.66d (2H, $C^{7,8}$H, 8Hz), 7.15-7.46m (5H, phenyl ring)

Synthesis of complexes:

[Ni(^{1}L)$_2$] 1:

Nickel acetate (0.05g, 0.20 mmol)was dissolved in 20 ml ethanol and to it was added HIntsc,(0.08g, 0.38 mmol). The contents were refluxed for 3 hrs and filtered to remove any insoluble impurity. After 2-daysDark red microcrystals were obtained. M.P. 237- 240 °C, yield 76%. Analysis found: C, 48.70; H, 3.67; N, 22.74 %. Calculated for $C_{20}H_{18}N_8S_2Ni$: C, 48.71; H, 3.65; N, 22.73 %; IR peaks:ν(N-H), 3255; ν(C=C)+ν(C=N)+δ(NH_2), 1615, 1567, 1532; ν(C=S), 816.^{1}H NMR: 12.00s (N^4H), 8.63s (C^2H), 7.60s(C^4H), 7.46d (2H, $C^{7,8}$H), 7.22d (2H, $C^{6,9}$H),6.92s (2H, NH_2)

[Ni(^{2}L)$_2$] 2:

Nickel acetate (0.05 g, 0.20 mmol) was dissolved in 20 ml ethanol and to it was added HIntsc-N^1-Me(0.09 g, 0.38 mmol). Contents were refluxed for 3 hrs. andfiltered to remove any insoluble impurity. After 2-days dark red microcrystal were obtained.M.P. 248- 250°C; yield 73%; Analysis found: C, 50.68; H, 4.23; N, 21.51 %. Calculated for $C_{22}H_{22}N_8S_2Ni$: C, 50.70; H, 4.22; N, 21.52 %. IR peaks: ν(N-H), 3340; ν(C=C)+ν(C=N)+ δ(NH_2), 1588, 1545, 1483; ν(C=S), 812.^{1}H NMR: 12.16s (N^4H), 9.94s (C^2H), 8.30s(C^4H), 7.51d ($C^{7,8}$H),7.24d ($C^{6,9}$H), 3.16m (3H, CH_3).

[Ni(^{3}L)$_2$] 3:

Nickel acetate (0.05 g, 0.20 mmol) was dissolved in 20 ml ethanol and to it was added HIntsc-N^1-Ph(0.05 g, 0.20 mmol). The contents wererefluxed for 3 hrs. andfiltered to remove any insoluble impurity. After 2-days dark red microcrystal were obtained. M.P. 265- 267 °C; yield 71%; Analysis found: C, 59.54; H, 4.04; N, 17.38 %. Calculated for $C_{32}H_{26}N_8S_2Ni$: C, 59.56; H, 4.03; N, 17.37 %.IR peaks: ν(N-H), 3315; ν(C=C)+ν(C=N)+ δ(NH_2), 1691, 1618, 1599; ν(C=S), 804.^{1}H NMR: 11.59s (N^4H), 8.10s (C^2H), 7.36s(C^4H), 6.87-7.20m (Ring protons).

Anti-tuberculosis activityH^1L-H^3L, 1-3:

Anti-tubercular assay of all synthesized compounds were carried out using Micro Plate Alamar Blue assay. A standard solution containing 1000 ppm of each compound was prepared. From standard solution, test solutions were prepared in the increasing concentration from 0.8 μg/ml to 100 μg/ml. In sterile 96 well plate, mixture of test solution, de-ionized water (200 μl) and

Middlebrook 7H9 Broth (100 µl), were taken. This plate was sealed and hatched at 37°C over aperiod of five days. Further, 25µl of Tween 10% and 80% and Almar Blue (1:1 ratio) was dispensed in each well and incubated for one day. Minimum Inhibitory Concentration (MIC) was reported as pink coloration for the growth of Mycobacterium while blue coloration was considered as no bacterial growth in the well.

Results and Discussion

Reaction of indole-3-carboxaldehyde thiosemicarbazones (H^1L) or indole-3-carboxaldehyde-N^1-methyl thiosemicarbazones (H^2L) or indole-3-carboxaldehyde-N^1-phenyl thiosemicarbazones (H^3L) with nickel(II) acetate in 1:2 (M:L) molar ratio yielded complexes of stiochiometry, $[Ni(L)_2]$ (^1L, **1**; ^2L, **2**; ^3L, **3**) (Scheme 2).

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Discussion on IR Spectrum

Table 1 shows characteristic bands (stretching and bending) obtained in IR spectra of ligands and their complexes.The IR band due to asymmetric and symmetric stretching of N-H obtained between 3450–3315 cm^{-1}. The amide (-NH-) stretching appeared in the ranges, 3130–3160 cm^{-1} The absence of band in the range,3130–3160 cm^{-1} in the complexes **1-3**, suggested that acidic proton at nitrogen (N^2H) atom get removed thus thiosemicarbazone ligand is in the anionic form [20, 21]. The thio ν(C=S) band appeared at 816 cm^{-1} (1), 812 cm^{-1} (2), and 804 cm^{-1} (3) showed shifted to low energy as compare to free ligands (H^1L- H^3L). This low energy shift of C=S band suggests decrease in double bond character and binding of ligand in thiolate form [20, 21].

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Table 2. CharacteristicIR peaks of ligands (H^1L-H^3L) and complexes (**1-3**)

Compounds	ν(N-H)	ν(-NH-)	ν(C=C)	ν(C=N)	δ(NH_2)	ν(C=S)
H^1L	3448, 3331	3146	1614	1539	1442	839
1	3255		1615	1567	1532	816
H^2L	3362	3155	1608	1546	1498	833
2	3340		1588	1545	1483	812
H^3L	3410, 3317	3139	1600	1543	1496	845
3	3315		1691	1618	1599	804

Discussion on ^{1}H NMR spectra

Important signals in ^{1}H NMR of ligands and their complexes are table 2. The -N^2H- proton in ligands appeared at δ 10.07 ppm (H^1L), δ 10.95 ppm (H^2L) and δ 11.71 ppm (H^3L). The disappearance of this peak in complexes **1-3**, ensures deprotonation of –N^2H- and binding of ligand in anionic form [20, 21]. The C^2H proton in complexes **1-3** appeared in the range, δ8.10-9.94 ppm and has shown downfield shift vis-à-vis free ligands except in **3** [20].Signal due to methyl protons at N^1 atom appeared atδ3.16 ppm and δ 3.22 ppm in H^2L and complex **2** respectively.

Table 3. Important ^{1}H NMR peaks of ligands (**H^1L-H^3L**) and their complexes (**1-3**).

Compounds	N^4H	N^2H	C^2H	Ring Protons	CH_3	Phenyl Group
H^1L	-	10.07s	8.33s	7.46d($C^{6,9}$H) 7.29d($C^{7,8}$H)		
1	12.00s	-	8.63s	7.22d($C^{6,9}$H) 7.46d($C^{7,8}$H)		
H^2L	11.24s	10.95s	8.10s	7.14d($C^{6,9}$H) 7.51d($C^{7,8}$H)	3.16m	

2	12.16s	-	9.94s	7.24d($C^{6,9}H$) 7.46d($C^{7,8}H$)	3.22m	
H^3L	11.62	11.71s	9.63s	8.24d($C^{6,9}H$) 7.66d($C^{7,8}H$)		7.15-7.46m
3	11.59	-	8.10s	6.87-7.20m		Obscured by ring proton

Antitubercular Activities

Anti TB activity of compounds H^1L-H^3L and complexes **1-3** was evaluated and MIC was given in Table 3. Standard drugs taken are Pyrazinamide (MIC = 3.125 µg/ml), ciprofloxacin (3.125 µg/ml) and streptomycin (6.25 µg/ml. All compounds were found active against M. tuberculosis as shown in Table 3. It is observed that ligands H^1L andH^2L exhibit more anti-TB activity (12.5 µg/ml) as compare to H^3L (25 µg/ml).Low activity of **H^3L** may be attributed to the increase in hydrophobicity at N^1 atom of thiosemicarbazone due to presence of phenyl ring. The activity of H1L-H3L was found to decreased on formation of complexes, which is in contrast to complexation of the ligands with copper (I) [22].

Table 3. Anti-TB activity of **H^1L-H^3L** and complexes **1-3**

Compound	**H37RV Strain MIC(µg/ml)**							
	100	**50**	**25**	**12.5**	**6.25**	**3.12**	**1.6**	**0.8**
H^1L	S	S	S	S	R	R	R	R
1	S	S	R	R	R	R	R	R
H^2L	S	S	S	S	R	R	R	R
2	S	S	R	R	R	R	R	R
H^3L	S	S	S	R	R	R	R	R
3	S	S	R	R	R	R	R	R

Conclusion

Three Indole-3-carboxaldehyde substituted thiosemicarbazones and their Ni(II) complexes were synthesized and characterized by various spectroscopic techniques. The physical and spectral

data revealed monobasic bidentate nature of Schiff base and ligand to metal ratio of 2:1 for complex chelates. Square planar geometry for nickel complexes has been predicted. Ligands (H^1L-H^3L) exhibit more anti-tubercular activity than its complexes (**1-3**).

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