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In silico and *in vitro* Antibacterial Assessment of Newly Synthesized Ni(II) Complexes of Thiosemicarbazone

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Nowadays, most anti-infective agents or antibiotics are becoming resistant to several uropathogenic microorganisms. Thus, there is an urgent need of new potent candidates for treating infectious diseases and overcome the antibiotic resistance. Nickel(II) complexes of composition $[Ni(Lig_2)\cdot 2H_2O]X_2$ have been synthesized with the ligand substituted benzaldehyde thiosemicarbazone (X = Cl). These obtained products were structurally interpreted by several spectroscopic studies includes FTIR for functional group detection, ^1H & ^{13}C NMR for the structural number of environment protons and carbons frame. The proposed Ni^{2+} complexes are octahedral structure and all ligands are coordinated with thiols or thiones and behaves as a bidentate manner. All the nickel(II) complexes were further screened *in vitro* antibacterial action against *E. coli* and *S. aureus*. The antibacterial activity of all the tested compounds, Ni(II) complex bearing 4-nitrobenzylidene thiosemicarbazone (**4e**) had shown significant inhibition against *E. coli* whereas overall assessment of antibacterial action indicates that all the compounds have been exhibited moderate to good inhibition growth bacterial with *E. coli*. Moreover, the binding affinity of the ligands had also been predicted through the molecular docking and physico-chemical properties were calculated. The synthesized nickel complexes could be more potent bacterial target inhibitor.

Keywords: Schiff base, Thiosemicarbazone, Molecular docking, Antibacterial activity.

INTRODUCTION

Nowadays, most anti-infective agents or antibiotics are becoming resistant to several uropathogenic microorganisms. Generally, antibiotics resistant causes may be due to either alteration of the target structure through mutations or reduced access to the target structure or inactivation of the therapeutic agent by modifying enzymes. Since resistance is increasing and "major drug companies are pulling out of antibiotic development", there is the urgent need to improve existing drugs or even better, the researchers have investigated to develop potent candidates for overcome resistivity patterns and increase the efficacy of antibacterial action with uropathogenic infectious diseases and also decrease the adverse effect [1-3]. The manifestation of bacterial UTI (urinary tract infection) has been predominantly endemic, globally; eventually, the development of new UTI antibacterial agent(s) remains the call of the day [4].

Aryl thiosemicarbazone derivatives are well-known established pharmacophore group and important chemical entity for the metal complexation. Thiosemicarbazones have ONS coordinating sites, which are unique in the coordinating chemistry due to their strong ability to bind with transitional metal ions. These thiosemicarbazones are also more potent due to remarkable biological activities including antibacterial [5], anticancer [6], anticonvulsant [7,8] and antifungal [9,10], *etc*. Thiosemicarbazone analogs and their related benzoyl pyridine derivatives have been shown significant antimalarial and cytotoxicity action against HepG2, A549 and MOLT-3 human cancer cell lines [11]. Organic Schiff base bearing thiosemicarbazone is a unique chemical class that has received more

attention, owing to its remarkable biological and pharmacological properties [12].

The oxygen, nitrogen and sulphur donors have been known to attract the focus of researchers due to some following reasons: (i) as the nitrogen donors create a strength of crystal-field to medium than the sulphur donors, hence the incorporation of such ligands may form unusual metal complexes with remarkable stereochemistry and spectroscopical behaviour; (ii) compounds with sulphur and nitrogen had always been popular for possessing a wide range of biological properties, which could be enhanced by incorporation of metals, nickel as bioorganic metal complex has been explored the most due to its vast avail-ability as a co-factor for various enzymes *viz.*, urease, glyoxalase I- Glx-I (*Escherichia coli*), hydrogenases containing both nickel and iron [Ni-Fe] and CO dehydrogenase carried by methanogens, acetyl-CoA synthetase (ACS), also some reductases have been reported well using crystographically [13].

Ligands bearing sulphur group have always been explored the most, for example the sulphonamides [14]. This functionality has since been shown to be related to their metal complexing ability and expression of their wide range of biological activity from antileukemic, antimalarial, antibacterial, antifungal and anti-inflammatory activities [15]. The commercial drug bearing semicarbazone/thiosemicarbazone class of antimicrobial drugs are thiacetazone, ambazone and nitrofurazone. Among these drugs, nitrofurazone metabolically cleaved the azomethine linkage (-CH=N-) of the structure and produced a reactive species, which can bind to cellular macromolecules by the covalent bond. It is well known that the metals present in complexes generally accelerate the drug action and drug-based metal complexes; the pharmacological efciencies depend upon the nature of the metal ions. Recently reported that coumarin based transitional metal complexes have been shown to be potent antibacterial against a wide range of uropathogenic bacteria [16-18]. Keeping interest in the biological action in the thiosemicarbazones entity; we designed and developed the nickel complexes of thiosemicarbazone derivatives and investigated their *in vitro* antibacterial action against urinary tract infection (UTI) bacteria. The predicted binding affinity of desired molecules against specific bacterial enzyme dihydropteroate synthetase (DHPS) was performed by molecular docking and also being carried out their physiological and drug likeness properties [19].

EXPERIMENTAL

All chemicals used were of synthetic grade and procured from Merck company Ltd. The UV λ_{max} was recorded on JASCO V-360 UV-visible spectrophotometer. The functional groups of the synthesized compouds were characterized by FT/IR (JASCO FT/IR4600 spectrophotometer) and the number of environmental protons/carbons was detected $^{1}H/^{13}C$ NMR (Bruckner ^{1}H NMR 400 MHz) using TMS as an internal standard. The melting points were measured by using the Elico melting point apparatus. These synthesized compounds were screened for antibacterial activity by using the agar disc diffusion method. All the designed molecules were carried out their molecular docking with specific target bacterial dihydrofolate synthetase PDB: 1AJO of *Staphylococcus aureus* and PDB: 1AD1 of *Escherichia coli*.

Molecular docking: The designed thiosemicarbazones **3a-l** was structurally drawn by ChemDraw Ultra12v. and ACD-Chemsketch and clarified neatly with the principle of stereochemistry. Subsequently, 2D structures were reinstated as 3D structures saved in mol2 format. Furthermore, those formats were converted to PDB lay-out by PyMol-program [20]. The desired thiosemicarbazones ligands **3a-l** were optimized and validated through molecular docking studies using two specific bacterial targets. These crystal structures of targets are (PDB ID: 1AJ0 of *E. coli* and 1AD1 of *S. aureus*) were retrieved from protein data bank (PDB) (www.rscb.org/pdb) and the heteroatoms were removes along with the attached ligands or drug molecules. The docking study was carried out by Auto Dock suite 4.0 with the addition of the grid parameter, Lamarckian genetic algorithm followed for energy minimization of the desired structures, which were thoroughly monitored. After completion of docking, the visualization of the ligand-protein interaction was carried out by Discovery studio v17 and LigPlot+ V.2.2. [21]. The physico-chemical profile of these derivatives was predicted with Lipinski's role of five (RO5) by Molinsperation software.

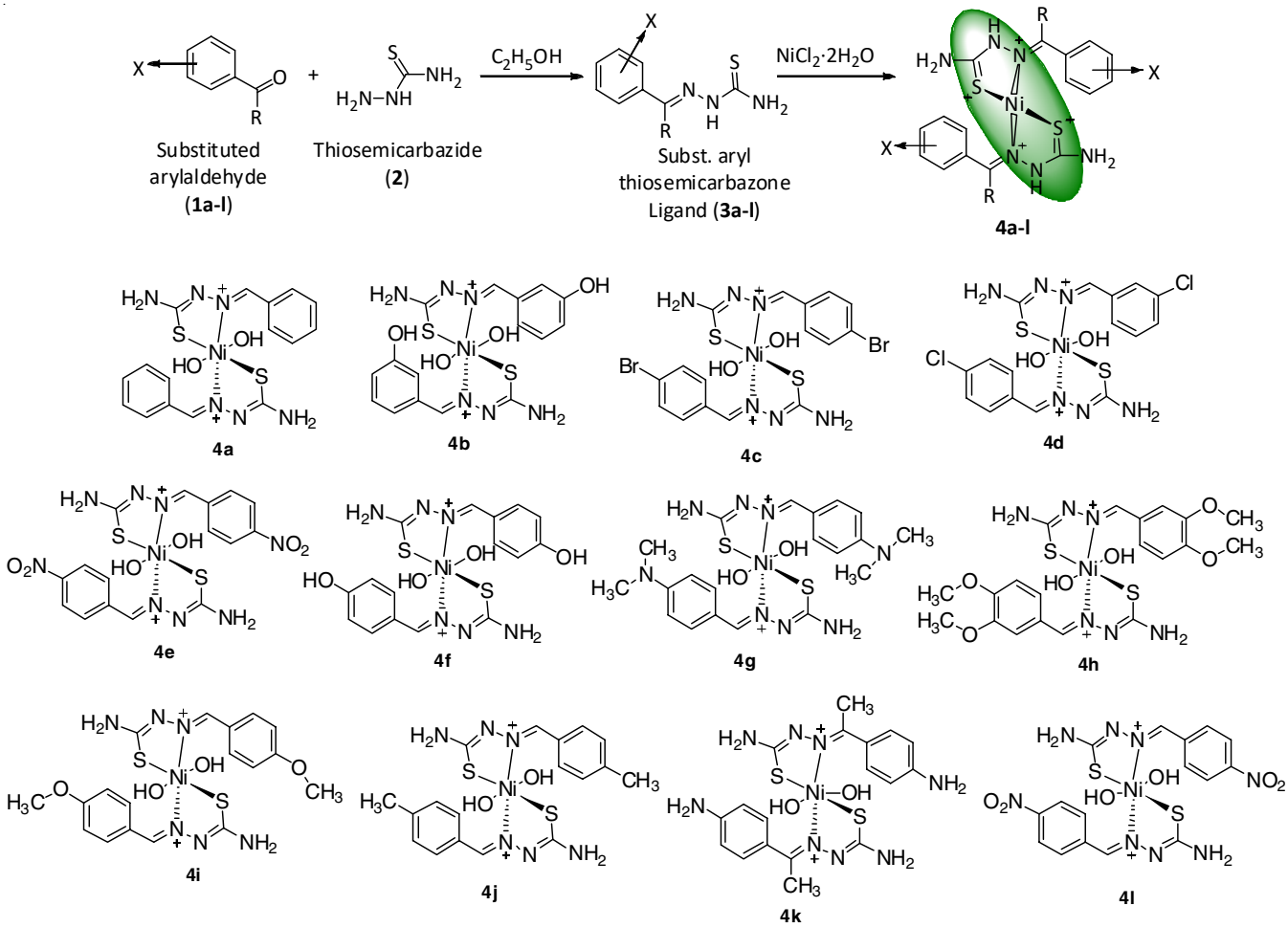
General synthetic procedure

Synthesis of aryl thiosemicarbazone congeners (3a-l): Arylthiosemicarbazone derivatives (**3a-l**) were synthesized by the condensation of equimolar of ethanolic solution of aryl aldehyde/ketone and thiosemicarbazide in glacial acetic acid and the reaction mixture was stirred at ambient temperature and refluxed the mixture for ~2 h. The reaction is progressed by TLC Plate with using suitable solvents (*n*-hexane:ethyl acetate) and the reaction mixture was kept overnight in the refrigerator, the formed fine crystals were filtered, dried in anhydrous calcium chloride and recrystallized from hot ethanol [22].

Synthesis of Ni(II) complexes (4a-l): A mixture of equimolar corresponding arylthiosemicarbazone (**3a-l**) and hydrated nickel chloride in methanolic solution was heated under refluxed for ~4 h. The resultant reaction mixture was kept overnight in the refrigerator and the precipitated solid mass product was filtered and dried at ambient temperature and recrystallized from hot ethanol (**Scheme-I**).

***Bis-N′*-benzylidenecarbamohydrazonoyl)thio)nickel (4a):** The obtained product was synthesized by mixing 2-benzylidene hydrazinecarbothioamide and nickel(II) chloride in ethanol. IR (ATR, ν_{max}, cm^{-1}): 3418, 3251 (NH *str.*), 3154 (OH *str.*), 3026 (ArCH *str.*), 1651 (CH=N *str.*), 1589 (ArCH *str.*), 1297 (C=S *str.*), 956 (N-N *str.*), 485 (Ni-N *str.*), 454 (Ni-S *str.*); ^{1}H NMR (DMSO-d_6, δ ppm, 500 MHz): 11.47 (br, 1H, OH), 8.24 (s, 1H, CH=N), 8.07 (s, 1H, NH_2), 8.02 (s, 1H, NH), 7.40-7.82 (m, 5H, ArH); ^{13}C NMR: 178.43, 142.76, 134.61, 130.31, 129.15, 129.05, 127.75, 127.72; ESI-HRMS (*m/z*): Anal. calcd. for $C_{16}H_{16}N_6NiS_2$414.33; found: 415.21 (M+1).

***Bis-N′*-(4-bromobenzylidene)carbamohydrazonoyl)-thio)nickel (4c):** The obtained product was synthesized by mixing 2-(4-bromobenzylidene)hydrazine carbothioamide and



Scheme-I: Schematic representation of Ni(II) complexes of thiosemicarbazone (**4a-l**)

nickel(II) chloride in ethanol. IR (ATR, ν_{max}, cm^{-1}): 3438, 3285 (NH *str.*), 3164 (OH *str.*), 1653 (CH=N *str.*), 1599 (ArCH *str.*), 1284 (C=S *str.*), 1010 (N-N *str.*), 924 (C-S) 471 (Ni-N), 463 (Ni-S); ^{1}H NMR (DMSO-d_6, δ ppm, 500 MHz): 11.50 (br, 1H, OH), 8.26 (s, 1H, CH=N), 8.09 (s, 2H, NH_2), 8.02 (s, 1H, NH), 7.59-7.78 (m, 8H, ArH); ^{13}C NMR: 178.54, 141.98, 134.00, 132.06, 129.15, 129.65, 123.50; ESI-HRMS (*m/z*): Anal. calcd. $C_{16}H_{14}Br_2N_6NiS_2$ 572.05; found: 571.38 (M+1).

***Bis-N′*-(4-chlorobenzylidene)carbamohydrazonoyl)-thio)nickel (4d):** The obtained product was synthesized by mixing 2-(4-chlorobenzylidene)hydrazine carbothioamide and nickel(II) chloride in ethanol. IR (ATR, ν_{max}, cm^{-1}): 3490, 3362 (NH *str.*), 3154 (OH *str.*), 1653 (CH=N *str.*), 1577 (ArCH *str.*), 1266 (C=S *str.*), 1020 (N-N *str.*), 926 (C-S), 468 (Ni-N), 458 (Ni-S); ^{1}H NMR (DMSO-d_6, δ ppm, 500 MHz): 11.77 (br, 1H, OH), 8.27 (s, 1H, CH=N), 8.10 (s, 2H, NH_2), 8.05 (s, 1H, NH), 7.45-7.86 (m, 8H, ArH); ^{13}C NMR: 178.56, 141.31, 134.70, 133.60, 129.40, 129.15, 123.42; ESI-HRMS (*m/z*): Anal. calcd. $C_{16}H_{14}Cl_2N_6NiS_2$: 484.05; found: 485.38 (M+1).

***Bis-N′*-(4-nitrobenzylidene)carbamohydrazonoyl)-thio)nickel (4e):** The obtained product was synthesized by mixing 2-(4-nitrobenzylidene) hydrazine carbothioamide and nickel(II) chloride in ethanol. IR (ATR, ν_{max}, cm^{-1}): 3436, 3268 (NH *str.*), 3164 (OH *str.*), 1653 (CH=N *str.*), 1587 (ArCH *str.*), 1455, 1366 (NO_2 *str.*), 1267 (C=S *str.*), 1090 (N-N *str.*), 924 (N-N), 488 (Ni-N), 452 (Ni-S); ^{1}H NMR (DMSO-d_6, δ ppm, 500 MHz): 11.73 (br, 1H, OH), 8.43 (s, 1H, CH=N), 8.28 (s, 2H, NH2), 8.23 (s, 1H, NH), 8.11-8.22 (m, 8H, ArH); ^{13}C NMR: 178.95, 148.02, 141.20, 139.99, 128.61, 124.23; ESI-HRMS (*m/z*): Anal. calcd. $C_{16}H_{14}N_8NiO_4S_2$: 505.05; found: 506.18 (M+1).

***Bis-N′*-(4-hydroxybenzylidene)carbamohydrazonoyl)-thio)nickel (4f):** The obtained product was synthesized by mixing 2-(4-hydroxybenzylidene)hydrazine carbothioamide and nickel(II) chloride in ethanol. IR (ATR, ν_{max}, cm^{-1}): 3359, 3261 (NH *str.*), 3160 (OH *str.*), 1653 (CH=N *str.*), 1597 (ArCH *str.*), 1266 (C=S *str.*), 1029 (N-N *str.*), 935 (C-S), 487 (Ni-N), 453 (Ni-S); ^{1}H NMR (DMSO-d_6, δ ppm, 500 MHz): 8.27 (s, 1H, CH=N), 8.10 (s, 2H, NH2), 8.05 (s, 1H, NH), 7.45-7.86 (m, 8H, ArH); ^{13}C NMR: 178.55, 141.31, 134.70, 133.65, 129.40, 129.15, 125.50; ESI-HRMS (*m/z*): Anal. calcd. $C_{16}H_{16}N_6NiO_2S_2$447.05; found: 448.18 (M+1).

***Bis-N′*-(4-(dimethylamino)benzylidene)carbamohydrazonoyl)thio)nickel (4g):** The obtained product was synthesized by mixing *N′*-(dimethylaminobenzylidene)hydrazine carbothioamide and nickel(II) chloride in ethanol. IR (ATR, ν_{max}, cm^{-1}): 3448, 3326 (NH *str.*), 3169 (OH *str.*), 2835 (CH_2 *str.*), 1653 (CH=N *str.*), 1598 (ArCH *str.*), 1281 (C=S *str.*), 1043 (N-N *str.*), 936 (C-S), 477 (Ni-N), 454 (Ni-S); ^{1}H NMR (DMSO-

d_6, δ ppm, 500 MHz): 11.27 (br, 1H, OH), 8.18 (s, 1H, CH=N), 8.10 (s, 2H, NH_2), 7.91 (s, 1H, NH), 7.42-7.73 (m, 8H, ArH), 3.91 {(s, 6H, N(CH_3), 2}; ^{13}C NMR: 177.89, 159.71, 143.21, 129.52, 116.02, 63.54; ESI-HRMS (*m/z*): Anal. calcd. $C_{20}H_{26}N_8NiS_2$ 501.05; found: 502.38 (M+1).

***Bis-N′*-(3,4-dimethoxy)benzylidene)carbamohydrazonoyl)thio)nickel (4h):** The obtained product was synthesized by mixing 2-(3,4-dimethoxybenzylidene)hydrazine carbothioamide and nickel(II) chloride in ethanol. IR (ATR, ν_{max}, cm^{-1}): 3357, 3264 (NH *str.*), 3169 (OH *str.*), 1653 (CH=N *str.*), 1581 (ArCH *str.*), 1266 (C=S *str.*), 955 (N-N *str.*), 473 (Co-N), 460 (Co-S); ^{1}H NMR (DMSO-d_6, δ ppm, 500 MHz): 11.37 (br, 1H, OH), 8.18 (s, 1H, CH=N), 8.10 (s, 2H, NH_2), 7.91 (s, 1H, NH), 7.42-7.73 (m, 6H, ArH), 3.91{(s, 6H, (3,4-di-OCH_3), 2}; ^{13}C NMR: 178.10, 150.31, 149.46, 145.94, 129.34, 124.80, 110.03, 109.46, 56.91, 56.81; ESI-HRMS (*m/z*): Anal. calcd. $C_{20}H_{24}N_6NiO_4S_2$: 535.05; found: 536.18 (M+1).

***Bis-N′*-(4-methoxybenzylidene)carbamohydrazonoyl)thio)nickel (4i):** The obtained product was synthesized by mixing *N′*-(4-methoxybenzylidene)hydrazine carbothioamide and nickel(II) chloride in ethanol. IR (ATR, ν_{max}, cm^{-1}): 3356, 3262 (NH *str.*), 3163 (OH *str.*), 2835 (CH_2 *str.*), 1651 (CH=N *str.*), 1598 (ArCH *str.*), 1254 (C=S *str.*), 1019 (N-N *str.*), 961 (C-S), 470 (Co-N), 458 (Co-S); ^{1}H NMR (DMSO-d_6, δ ppm, 500 MHz): 1133 (br, 1H, OH), 8.64 (s, 1H, CH=N), 8.17 (s, 2H, NH_2), 8.03 (s, 1H, NH), 7.12-7.52 (m, 8H, ArH), 3.83 (s, 3H, Ar-OCH_3); ^{13}C NMR: 178.01, 161.22, 149.61, 149.46, 142.98, 127.39, 127.16, 111.95, 111.69, 56.15; ESI-HRMS (*m/z*): Anal. calcd. $C_{18}H_{20}N_6NiO_2S_2$: 475.05; found: 476.38 (M+1).

***Bis-N′*-(4-methylbenzylidene)carbamohydrazonoyl)thio)nickel (4j):** The obtained product was synthesized by mixing *N′*-(4-methylbenzylidene)hydrazine carbothioamide and nickel(II) chloride in ethanol. IR (ATR, ν_{max}, cm^{-1}): 3396, 3259 (NH *str.*), 3155 (OH *str.*), 2835 (CH_2 *str.*), 1648 (CH=N *str.*), 1598 (ArCH *str.*), 1271 (C=S *str.*), 1030 (N-N *str.*), 930 (C-S), 470 (Co-N), 452 (Co-S); ^{1}H NMR (DMSO-d_6, δ ppm, 500 MHz): 8.26 (s, 1H, CH=N), 8.13 (s, 2H, NH_2), 8.03 (s, 1H, NH), 7.12-7.28 (m, 8H, ArH), 2.51 (s, 3H, Ar-CH_3); ^{13}C NMR: 178.47, 168.70, 151.70, 142.01, 141.13, 133.58, 121.33, 121.13, 20, 86.; ESI-HRMS (*m/z*): Anal. calcd. $C_{18}H_{20}N_6NiS_2$443.05; found: 444.38 (M+1).

***Bis-N′*-(1-(4-aminophenyl)ethylidene)carbamohydrazonoyl)thio)nickel (4k):** The obtained product was synthesized by mixing *N′*-(4-methylbenzylidene)hydrazine carbothioamide and nickel(II) chloride in ethanol. IR (ATR, ν_{max}, cm^{-1}): 3371, 3209 (NH *str.*), 3143 (OH *str.*), 1650 (CH=N *str.*), 1598 (ArCH *str.*), 1289 (C=S *str.*), 1091 (N-N *str.*), 961 (C-S), 476 (Co-N), 457 (Co-S); ^{1}H NMR (DMSO-d_6, δ ppm, 500 MHz): 8.56 (s, 2H, NH_2), 7.83 (s, 1H, NH), 6.68-7.53 (m, 8H, ArH), 2.45 (s, 6H, 2CH_3); ^{13}C NMR: 179.47, 151.70, 148.70, 130.33, 130.13, 127.58, 115.33, 115.13, 18.86.; ESI-HRMS (*m/z*): Anal. calcd. $C_{18}H_{22}N_8NiS_2$: 473.05; found: 474.38 (M+1).

***Bis-N′*-(1-(4-nitrophenyl)ethylidene)carbamohydrazonoyl)thio)nickel (4l):** The obtained product was synthesized by mixing *N′*-(4-methylbenzylidene)hydrazine carbothioamide and nickel(II) chloride in ethanol. IR (ATR, ν_{max}, cm^{-1}): 3387, 3202 (NH *str.*), 1650 (CH=N *str.*), 1583 (ArCH *str.*), 1277 (C=S *str.*), 1093 (N-N *str.*), 966 (C-S), 471 (Co-N), 455 (Co-S); ^{1}H NMR (DMSO-d_6, δ ppm, 500 MHz): 8.55 (s, 2H, NH_2), 8.02 (s, 1H, NH), 7.56-7.88 (m, 8H, ArH), 2.34 (s, 6H, 2CH_3); ^{13}C NMR: 179.37, 150.70, 148.22, 127.88, 127.56, 127.08, 126.83, 17.86.; ESI-HRMS (*m/z*): Anal. calcd. $C_{16}H_{14}N_8NiO_4S_2$: 505.05; found: 506.38 (M+1).

Antibacterial screening: The antibacterial activity of the synthesized nickel(II) complexes of aryl thiosemicarbazones (**4a-l**) was investigated by *in vitro* agar well diffusion method. The antimicrobial diffusion test was performed using a cell suspension of about 1.5×10^6 CFU mL^{-1} employing a McFarland turbidity standard No. 0.5 [23]. In this assessment, *Escherichia coli* and *Staphylococcus aureus* were used and amoxicillin was used as reference antibiotics against both bacterial strains. Test solutions of the synthesized compounds were prepared by two-fold dilution method at a concentration level ranging from 125-3.125 μg/mL using DMSO to evaluate the MIC.

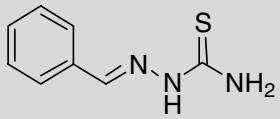
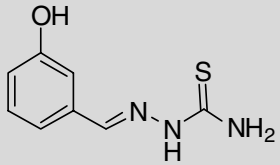
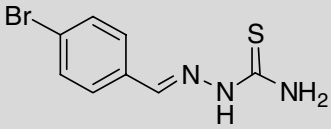
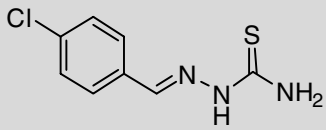
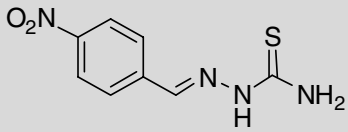
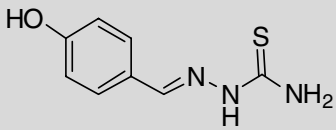
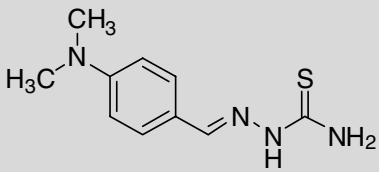
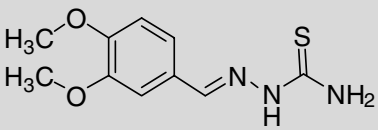
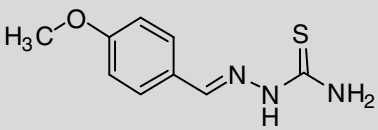
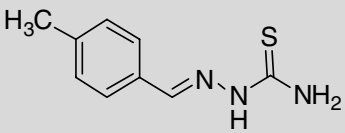
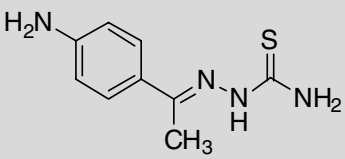
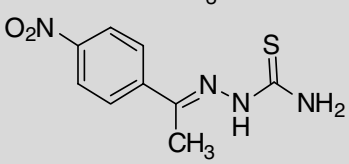
RESULTS AND DISCUSSION

Among four transitional metals, nickel is more potent bacterial inhibitor and less toxic than zinc and copper; for this inspiration, we developed nickel complexes from thiosemicarbazone. A series of nickel(II) ion complexes of aryl-substituted thiosemicarbazone derivatives (**4a-l**) were synthesized and characterized their structures using different spectral techniques. Initially, the formation of respective thiosemicarbazone **3a-l** from different aryl aldehyde by the simple condensation reaction with thiosemicarbazone in ethanol solvent. These compounds acted as an intermediate bidentate ligand, which further converted into corresponding nickel(II) complexes (**4a-l**) by treatment with hydrated nickel chloride in methanolic solution (**Scheme-I**). All the complexes are quite soluble in DMSO but insoluble in the most of all organic solvents.

The synthesized compounds were structurally confirmed by different spectral data. In FTIR spectrum of the complex **4a** had shown frequency at 1651, 1297, 956, 485 and 454 cm^{-1} which attribute to the presence of -C=N *str.* -N-N- *str.*, -Ni-N and Ni-S, respectively. The moderate absorption band ~1621 cm^{-1} that was indicated to ν(CH=N) in the thiosemicarbazone **3a-l** represented that free -NH_2 group of thiosemicarbazide was converted to azomethine group. During complexation the absorption band ~1621 cm^{-1} for ν(CH=N) shifted to the lower frequency, which suggested that azomethine group was coordinated to central nickel metal atom. Also the appearance of new absorption bands at 488-471 cm^{-1}, 460-445 cm^{-1} region were assigned to ν(Ni-N), ν(Ni-S), respectively in which further confirmed that N and S atoms are coordinated to nickel atom. The magnetic susceptibility of Ni(II) complex is 2.94 B.M. which is nearer to the reported value for octahedral symmetry [15]. Compounds **3a-l** act as bidentate ligands in which coordinating to the Ni(II) ions through their thiols or thioketone and azomethine group of thiosemicarbazone. FTIR spectrum of complex **4a** had also shown frequencies at 1651, 1297, 956, 485 and 454 cm^{-1}, which attribute to the presence of ν(CH=N), ν(N-N), ν(Ni-N) and ν(Ni-S), respectively.

Moreover, the carbonyl stretching of aldehyde frequency Ni(II) was vanished in thiosemicarbazone derivatives and also

TABLE-1
PHYSIO-CHEMICAL CHARACTERISTICS OF ARYL THIOSEMICARBAZONE (**3a-l**)

Compounds	Chemical structure	Lipinski rule of five (RO5)				
		MW	HA	HD	cLogP	tPSA
3a		179	2	3	1.90	42
3b		195	3	4	2.09	58.5
3c		195	3	4	2.09	58.5
3d		213	2	3	2.49	42
3e		224	5	4	1.25	62.5
3f		195	3	4	2.09	58.5
3g		222	2	3	1.96	44.8
3h		239	3	4	1.58	68.87
3i		209	3	3	1.85	49.5
3j		193	3	2	2.36	50.41
3k		208	3	3	1.85	49.5
3l		238	3	4	2.32	102.22

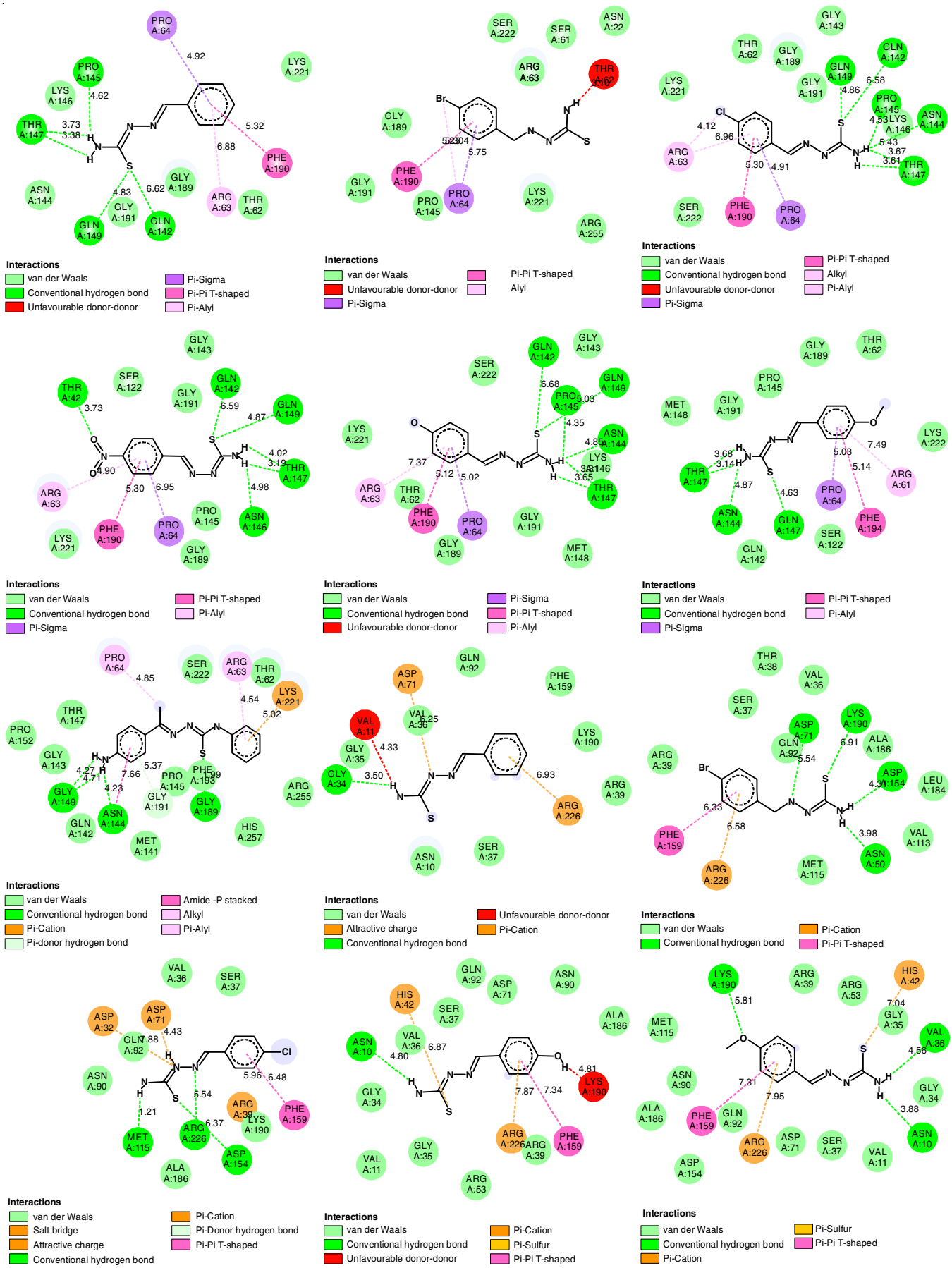


Fig. 1. Ligplot of the docked complexes with PDB ID: 1AJ0 and 1AD1

TABLE-2
MOLECULAR DOCKING INTERACTIONS WITH PDB ID: 1AJ0 AND 1AD1

Compounds	Docking score of *E. coli* with 1AJ0 (kcal/mol)	Protein-ligand binding interactions	Docking score of *S. aureus* with 1AD1 (kcal/mol)	Protein-ligand binding interactions
3a	-5.9	P145, T147, Q149, Q142	-5.9	G34, G35
3b	-5.9	T62, N22, Q60, R255	-6.1	V36, G34, N10
3c	-5.1	No H-bonding found	-6.5	N154, N90, N71, K190
3d	-6.2	Q149, Q142, P145, N144, T147	-6.3	D154, R226, M115
3e	-6.7	T147, N144, E149, E142, T62	-6.9	R189, N10, V136
3f	-5.7	Q149, N144, T147, Q142, P145	-5.8	T147, N144, Q149
3g	-6.0	P145, T147, Q149	-6.0	N10
3i	-5.8	T147, N144, Q149	-6.3	K190, N10, V36
3j	-5.8	T147, N144, Q149	-6.3	D154, R226, M115
3k	-7.2	Q149, N144, G189	-6.9	R189, N10, V36
3l	-6.2	T62, Q142, Q144, , T147, N144	-6.4	R226, K190, M115

its complex analog. The structural environmental proton of complex **4a** has been shown multiplet peaks at a range of δ 7.40-7.82 ppm, two singlet peaks observed at δ 8.24 and 8.02 ppm concerning the presence of aldimine and amines of thiosemicarbazone proton respectively. In addition to that, there is board peak at δ 11.47 ppm in the NMR spectra, which associate to hydrate hydroxyl group of nickel complex and also being appeared frequency at 3154 cm^{-1}. These spectral data indicates that Ni^{2+} ions were coordinated with a sulfur atom of thiocarbonyl, the nitrogen of thiosemicarbazone and functional group of thiols through deprotonation in each complex and possess octahedral geometries.

Molecular docking: These derivatives were performed their molecular docking with two different bacterial strains with the same target dihydropteroate synthetase (DHPS). The predicted physico-chemical properties of the compounds was also determined (Table-1). Among all docked derivatives, the compound **3k** have been shown the lowest binding energy with more binding affinity with target bacterial dihydropteroate DHPS enzyme at value of -7.2 Kcal/mol and -6.9 Kcal/mol concerning PDBID: 1AJ0 and PDBID: 1AD1, whereas the compound **3l** was the second-highest docked score at the value of -6.3 Kcal/mol and -6.2 Kcal/mol with same bacterial targets. These ligplot and bonding interaction between the desired ligand (**4a-l**) with specific bacterial targets depicted in Fig. 1. The antibacterial action of the resultant of tested compounds (**4e**, **4g**, **4k** and **4l**) has shown good to excellent inhibition against *E. coli*, whereas less significant inhibition with *S. aureus*. The reason is attributed due to the complexation, which decreases the polarity of the metal ion by coordinating with ligands and increases the lipophilicity of the metals. Thus, it facililates the peneration of the desired complexes into the lipoid cell membrane of bacteria and leads to increase growth inhibition.

Among all the designed candidates, compound **3k** had shown good binding affinity with the DHPS target of *E. coli* (1AJ0) at ΔH (Kcal/mol) -7.2, whereas the same compound showed -6.9 kcal/mol for the 1AD1 the DHPS target of *S. aureus*. Compound **3k** (*p*-amino acetophenone containing compound) had ineractions with the thiol of semithiocarbazone with G189 and other interactions occurred with the amine group of *p*-amino acetophenone residue at Q149 and N144, other hydrophobic interactions had also occurred and due to its active amine and thiol group the docking score could have been the highest with both the target of DHPS. Compound **3k** had shown the interactions at N10 of nitrogen of thiohydrazinoyl and the amine of semithiocarbazone interact with V36 and R189 with good binding score.

Compound **3e** had shown the second highest docking score at ΔH (Kcal/mol) -6.9 with three numbers of conventional hydrogen bonding at M115, K190 and R226. Each of this hydrogen bonding had significant activity against the pathogen as semithiocarbazone interacted with M115 and K190 whereas R226 had interacted with *p*-nitro benzylidiene imino nitrogen. The docking score and interactions of all the docked compounds have been reported in Table-2.

***In vitro* antibacterial assay:** The synthesized compound was screened against *S. aureus* and *E. coli*, the urinary tract infection (UTI) bacterial strains. The resultant of all the tested complexes has shown moderate to good inhibition against *E. coli* whereas less significant inhibition with *S. aureus* (Table-3). The nickel complexed **4g** had shown a significant inhibition against *E. coli* at MIC 6.25 μg/mL when compared to standard amoxycillin whereas, compound **4e** exhibited an excellent inhibition against both of the microorganisms with a zone of inhibition at 24 mm against *S. aureus* and 25 mm against *E. coli*. The SARs indicates that compound **4e** bearing substituted

TABLE-3
ANTIMICROBIAL ACTIVITY OF Ni(II) METAL COMPLEXES IN TERMS OF ZONE OF INHIBITION AND MIC VALUES (**4a-l**)

Compd.	*S. aureus*		*E. coli*	
	ZOI (mm)	MIC (μg mL^{-1})	ZOI (mm)	MIC (μg mL^{-1})
4a	ND	50	ND	50
4b	ND	50	ND	50
4c	ND	50	11	50
4d	11	50	13	50
4e	24	3.12	25	3.12
4f	15	50	18	25
4g	22	6.25	26	6.25
4h	ND	25	16	25
4i	ND	25	13	50
4j	17	25	14	25
4k	20	12.5	25	12.5
4l	21	12.5	26	12.5
Amox. (Std.)	19	–	22	–

nitro group, bonded nickel and thiosemicarbazone in a same structural frame whose presence may potentiate more bacterial inhibition among all.

Physico-chemical properties: The aryl thiosemicarbazones were analyzed for their druggable properties by observing their RO5 parameters. All the compounds obeyed the rules of RO5 indicating the achievement of compounds for the first line of compound synthesis towards drug synthesis (Table-1). The molecular weight should not exceed 500 Dalton and the compounds do not exceeded 300 Dalton. Likewise, other parameters such as high lipophilicity were expressed as cLogP, whose value should not surpass the value of 5. Therefore, we have proceed for the synthesis of the compounds and screening of the same, further these compounds after required validation could be proposed for a future drug prospective.

Conclusion

The research executed a simple and easy method for the single-step synthesis of nickel(II) complexes and their structures were well interpreted. The antibacterial activities of all the complexes have shown good inhibition against *E. coli* than respective ligands. Compounds **4e** and **4g** had exhibited more potent antibacterial activity, which could be possible due to higher binding activity towards bacterial dihydropteroate synthetase. Finally, it was concluded that nickel may have better synergistic action with thiosemicarbazone entity for antibacterial action against uropathogenic *E. coli* strains.

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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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