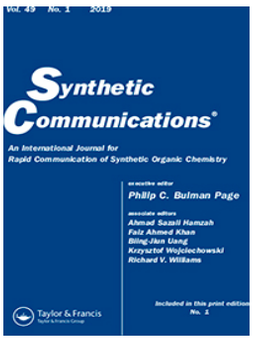

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Palladium(II) complexes of 5-substituted isatin thiosemicarbazones: Synthesis, spectroscopic characterization, biological evaluation and *in silico* docking studies

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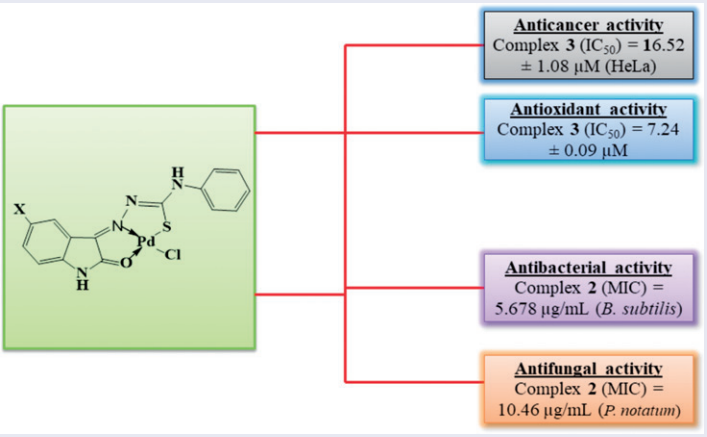
ABSTRACT

Substituted heterocyclic (isatin) appended thiosemicarbazone ligands (**L1**–**L3**) are synthesized by condensation of substituted isatin molecule with *N*(4)-phenyl-3-thiosemicarbazide in good yields. The palladium(II) complexes are synthesized from ligands (**L1**–**L3**) and $PdCl_2$, with a general formula [PdCl(X-$C_{15}H_{10}N_4OS$)] where X = 5-chloro (**1**), 5-bromo (**2**), and 5-nitro (**3**). Both analytical and spectroscopic methods have been used for the analysis and characterization of the synthesized compounds. The antimicrobial activity results observed that complexes, **1** and **2** have registered potent antibacterial activity against *B. subtilis* and *K. pneumonia*e and also complex **2** has shown good antifungal activity against the micro organisms. The antioxidant activity analysis revealed that the complex **3** showed significant activity with IC_{50} values 7.24 ± 0.09 μM. Moreover, the *in vitro* antiproliferative activity results suggested that complex **3** exhibited high activity against HeLa cell line compared with the standard with the IC_{50} value 16.52 ± 1.08 μM. The docking results correlate well.

GRAPHICAL ABSTRACT



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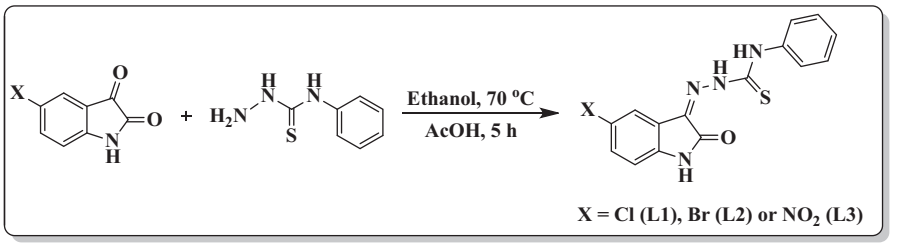
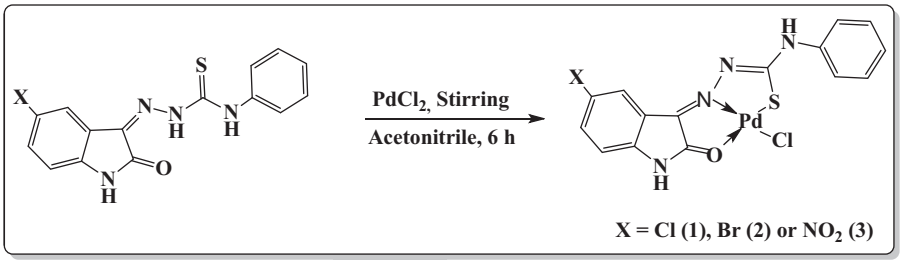
Introduction

Cisplatin is one of the most potent antitumor drugs, accessible for the therapeutic management of solid tumors, such as germ cell tumors, ovarian, lung, head, neck, and bladder cancers.[1,2] Bioinorganic chemistry provides surplus opportunities for the synthesis of pharmaceutical drugs that are not accessible to organic compounds.[3–6] Cisplatin, stilboestro, fulvestrant, carboplatin, goserelin, and oxaliplatin are some of the metal-based drugs which show significant antitumor activity and have been widely used in clinics.[7] However, these drugs have some limitations like drug resistance over a period of time and adverse side effects.[8–11] Since, the origin and development of the cytotoxic activity of cisplatin, several metal complexes have been investigated for therapeutic activity.[12,13] The chemistry of the transition metal complexes of thiosemicarbazones has become an interesting research field owing to their extensive pharmacological significance that provides an assorted array of compounds with various activities.[14–22] Among the transition metal complexes, Pd(II) complexes are extremely appealing applicants because of their similarity to Pt(II) complexes in coordination geometry and complex-forming processes,[23] which makes them a good alternative for metal-based drugs. Palladium complexes show about 10^4 to 10^5 times greater reactivity, though their structural and equilibrium behaviors are extremely comparable to those of Platinum(II) complexes.[24] The similar coordination nature of Pt(II) and Pd(II) also seconds the fact that palladium complexes can also exhibit anticancer properties.[25] Thiosemicarbazone derivatives of glucosyl and chitosan have significant antioxidant and oxygen free-radical scavenging activities. Because the –NH and C = S groups in the thiosemicarbazone react with free radicals, thereby increasing the antioxidant activity of these compounds.[26,27] Isatin is an interesting compound and its skeleton, present in the structure of natural compounds, has been inaccessible from the aquatic organisms with the high antifouling activity against fouling bacteria.[28–31] A number of palladium(II) thiosemicarbazone complexes have been synthesized and examined for their potential as antitumor agents.[32] Synthesis and characterization of a Pd(II) complexes of phenanthrenequinone thiosemicarbazone and its cytotoxic property in MCF-7 (breast cancer) and normal cells have been reported.[33] In the recent past, Ashok N. P. et al. have reported the synthesis and antimicrobial properties of Pd(II) complexes of thiosemicarbazones derived from 5-bromo isatin.[34] Amna Qasem Ali et al. have reported synthesis, characterization and *in vitro* anticancer, DNA binding and cleavage activity of Pd(II) complexes based on isatin thiosemicarbazone derivatives which clearly revealed the anticancer potency of the compounds against the human colorectal carcinoma cell line HCT116.[24] Muralisankar et al. have synthesized SNO pincer type palladium(II) complexes with *N*–substituted isatin thiosemicarbazone ligands and investigated their DNA cleavage, protein binding and *in vitro* cytotoxic properties. They found that the complexes possess significant *in vitro* antiproliferative activity against MCF-7 and A549 cancer cell lines.[35] All these reports prompted us to further investigate and improve the biological properties complexes with isatin based thiosemicarbazones containing Pd(II) as its central metal ion.

In the present work, we have demonstrated the synthesis of substituted (5-chloro/bromo/nitro) isatin thiosemicarbazones (**L1**–**L3**) and their respective palladium(II)



Scheme 1. Synthetic route of isatin based thiosemicarbazones ligands



Scheme 2. Synthetic route of pincer palladium(II) complexes

complexes (**1**–**3**). Further, the compounds were also thoroughly evaluated for their antimicrobial, antioxidant and *in vitro* antiproliferative activities.

Results and discussion

The isatin based thiosemicarbazone ligands (**L1**–**L3**) were synthesized by the condensation between substituted isatin and 4-phenyl thiosemicarbazide in the presence of acetic acid under reflux condition (Scheme 1). The corresponding palladium(II) complexes (**1**-**3**) were obtained in good yields from the reaction of Pd(II) chloride with appropriate thiosemicarbazone ligands in acetonitrile with stirring for 6 h (Scheme 2) at room temperature. The characterization of the ligands and complexes was achieved by the aid of elemental analysis presented in Table 1 and various spectroscopic (UV-Visible, FT-IR, ^{1}H and ^{13}C{^{1}H} NMR) tools. The ligands and complexes were soluble in DMF and DMSO and partially soluble in methanol, ethanol, chloroform, benzene, and dichloromethane.

Spectral characterization

The UV-Visible spectra of the synthesized compounds (ligands and its complexes) are shown in Figure S1 (Supplementary information) and were recorded from 800–200 nm using DMF as solvent at room temperature. Two absorption bands with varying intensities can be observed in the ligands. The absorption bands at 273–257 and 370–366 nm assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, respectively.[35] In the spectra of Pd(II) complexes showed three prominent bands. Low-intensity broad bands around 268–267 nm and 370–366 nm which assigned to $\pi \rightarrow \pi$ and $n \rightarrow \pi^*$ transitions. In addition, the band at 424–412 nm can be assigned to ligand-to-metal charge transfer (LMCT) transitions from sulfur to palladium ion. The S→M (LMCT) bands are relatively common in

Table 1. Analytical and physical properties of the ligands (**L1–L3**) and their complexes (**1–3**).

Molecular formula	Formula weight	Colour (Yield %)	Melting point (°C)	Elemental analyses Calculated (Found)			
				C	N	H	S
$C_{15}H_{11}N_4OSCl$ **(L1)**	330.79	Yellow (90)	310-312	54.46 (54.53)	16.94 (16.83)	3.35 (3.25)	9.69 (9.56)
$C_{15}H_{11}N_4OSBr$ **(L2)**	375.24	Yellow orange (92)	280-282	48.01 (48.11)	14.93 (14.83)	2.95 (2.85)	8.55 (8.50)
$C_{15}H_{11}N_5O_3S$ **(L3)**	341.24	Yellow (90)	268-270	52.78 (52.68)	20.52 (20.42)	3.25 (3.20)	9.39 (9.30)
$C_{15}H_{10}Cl_2N_4OP$-dS **(1)**	471.66	Dark brown (90)	308-310	38.20 (38.28)	11.88 (11.80)	2.14 (2.10)	6.80 (6.75)
$C_{15}H_{10}BrClN_4O$-PdS **(2)**	516.11	Reddish brown (92)	320-322	34.91 (34.81)	10.86 (10.80)	1.95 (1.90)	6.21 (6.18)
$C_{15}H_{10}N_5O_3ClP$-dS **(3)**	482.21	Brown (85)	326-328	37.36 (37.30)	14.52 (14.48)	2.09 (2.15)	6.65 (6.60)

Table 2. The important IR frequencies (in cm^{-1}) of ligands (**L1–L3**) and their complexes (**1–3**).

Compound	υ(N – H)	υ(H – N–C = S)	υ(C = N)	υ(C = O)	υ(C = S)
L1	3406, 3330	3230	1537	1700	1154
L2	3440, 3243	3170	1559	1690	1152
L3	3437, 3330	3239	1564	1692	1218
1	3405, 3374	–	1501	1633	1107
2	3438, 3318	–	1505	1648	1114
3	3431, 3307	–	1521	1639	1172

electronic spectra of complexes of thiosemicarbazones,[36–40] which clearly indicated the formation of palladium(II) complexes. The important FT-IR spectra of the compounds are presented in Table 2. The ligands (**L1–L3**) showed a broadband in the range 3440–3300 cm^{-1}, which was due to the isatin and terminal NH group stretching frequency, respectively. In the spectra of the complexes (**1–3**), the NH band stretching was unaltered. The thiocarbonyl attached NH stretching frequency band of the ligand was exhibited at 3243–3230 cm^{-1} and the stretching frequency of carbonyl (C = O), imine (C = N), and thiocarbonyl (C = S) were observed in the region 1700–1690 cm^{-1}, 1564–1537 cm^{-1}, and 1218–1152 cm^{-1}, respectively. After complexation, the thiocarbonyl attached NH band was disappeared while the carbonyl (C = O), imine (C = N) and thiocarbonyl (C = S) bands were decreased (1648–1633 cm^{-1}, 1521–1501 cm^{-1}, and 1172–1107 cm^{-1}) which clearly suggested that the coordination of ligand through carbonyl oxygen (neutral), imine nitrogen (neutral), and thiocarbonyl sulfur (anion) donor atoms with Pd(II) ion.

^{1}H NMR spectra of the ligands, the thiocarbonyl, isatin attached NH and terminal N–H protons appeared in the regions 11.50–12.62 ppm, 11.36–11.87 ppm, and 10.91–11.11 ppm, respectively. In the Pd(II) complexes spectra, the thiocarbonyl attached N–H proton signal disappeared, which clearly suggested the coordination of the ligand in the monobasic fashion after enolization and other two NH (isatin and terminal attached) protons observed at 11.33–11.87 ppm. The signal aromatic protons in the ligands and complexes were observed around 6.96–8.72 ppm and 6.61–9.31 ppm, respectively. $^{13}C\{^1H\}$ NMR spectrum of the ligands appeared resonances due to C = S, C = O and C = N carbons in the regions 176.54–176.93 ppm, 162.95–163.68 ppm, and 147.50–149.66 ppm, whereas same carbon signals in the complexes spectra appeared

Table 3. MIC values of antibacterial activity of synthesized ligands (**L1–L3**) and their corresponding complexes (**1–3**) presented in (μg/mL).

Compound	*B. subtilis*	*S. aureus*	*E. coli*	*K. pneumoniae*
L1	>100	>100	>100	25
L2	>100	>100	>100	>100
L3	50	>100	>100	>100
1	>100	>100	>100	6.1745
2	5.6785	25	50	9.3751
3	50	25	>100	25
Streptomycin	2.128	12.5	12.5	2.128

around 174.30–180.12 ppm, 163.42–164.14 ppm, and 144.18–147.45 ppm, respectively. The chemical shift of other protons and carbons was observed in the expected range.

Biological evaluation

Antibacterial activity

The antibacterial activity of the synthesized compounds was carried out against selected bacterial strains such as two gram-positive (*Bacillus subtilis* and *Staphylococcus aureus*) and two gram-negative (*Escherichia coli*, *Klebsiella pneumoniae*) bacteria by the disc diffusion method.[41,42] Streptomycin was used as a positive control. Experiments for each condition were performed in triplicate. The results were showed in terms of the minimum inhibitory concentration (MIC) and expressed in μg/ml, and the average values were depicted in Table 3. The results revealed that the complex **1** against *K. pneumoniae* (MIC: 6.1745 μg/mL) and complex **2** against *B. subtilis* (MIC: 5.6785 μg/mL) have shown good inhibition, respectively against the strains compared to the reference drug. And also complex **2** has shown moderate activity against *K. pneumoniae* (MIC: 9.3751 μg/mL) remaining complexes showed poor activity against the microorganisms. In conclusion, the ligands exhibited poor activity against all the four strains although good activity reported by complexes **1** and **2** because may be due to the presence of chloro and bromo substituted thiosemicarbazone ligands coordinated to palladium.

Antifungal activity

The antifungal activity of the free ligands (L1-L3) and their corresponding complexes (**1–3**) was tested against the strains *Pencillium notatum* and *Aspergillus niger*. The antifungal drug Ketoconazole was chosen as a reference drug. The results of the synthesized compounds in MIC are shown in Table 4. From the results, the complex **2** has registered good activity against both the strains *Pencillium notatum* and *Aspergillus niger* with MIC values of 10.46 μg/mL and 10.58 μg/mL, respectively. And also complex **3** exhibits good activity against *Aspergillus niger* with MIC value 11.87 μg/mL. Remaining compounds showed moderate to poor activity against the fungal strains. In conclusion, compared to the metal complexes, ligands have shown lesser activity against the organisms.

Table 4. MIC values of antifungal activity of synthesized ligands (**L1**–**L3**) and their corresponding complexes (**1**–**3**) presented in (μg/mL).

Compound	*Pencillium notatum*	*Asperegillus niger*
L1	18.68	50
L2	17.44	25
L3	25	>100
1	50	>100
2	10.46	10.58
3	18.46	11.87
Ketoconazole	4.25	4.25

Table 5. IC_{50} (μM) values of DPPH scavenging activity of ligands (**L1**–**L3**) and their corresponding complexes (**1**–**3**).

Compound	IC_{50} (μM)
L1	30.58 ± 0.35
L2	24.46 ± 1.04
L3	31.47 ± 0.73
1	17.29 ± 0.22
2	23.08 ± 0.58
3	7.24 ± 0.09
Ascorbic acid	3.25 ± 0.68

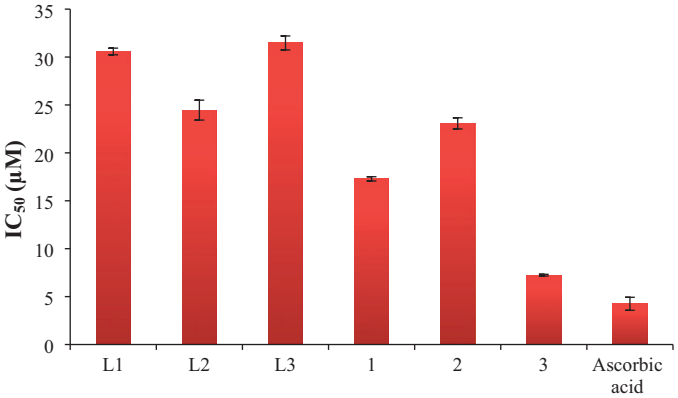


Figure 1. Scavenging activity of the ligands and its complexes (**1**-**3**).

Antioxidant activity

The scavenging activity of the ligands and their palladium(II) complexes results are presented in Table 5 and Figure 1. The Figure shows the antioxidant potential of the synthesized compounds in comparison with the standard Ascorbic acid. Among the free ligands and their palladium complexes, the complex **3** is found to be a most potent antioxidant with IC_{50} value of 7.24 ± 0.09 μM compared to standard ascorbic acid. Complex **1** has shown moderate activity with IC_{50} value of 17.29 ± 0.22 μM. The mechanism of action of these complexes on neutralizing the free DPPH radical is yet to be established. Based on the IC_{50} values the order of activity is **3** > **1** >**2**>**L2**>**L1**>**L3**.

In vitro antiproliferative activity

In order to understand the *in vitro* antiproliferative activity of the compounds, an MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)[43,44] was carried

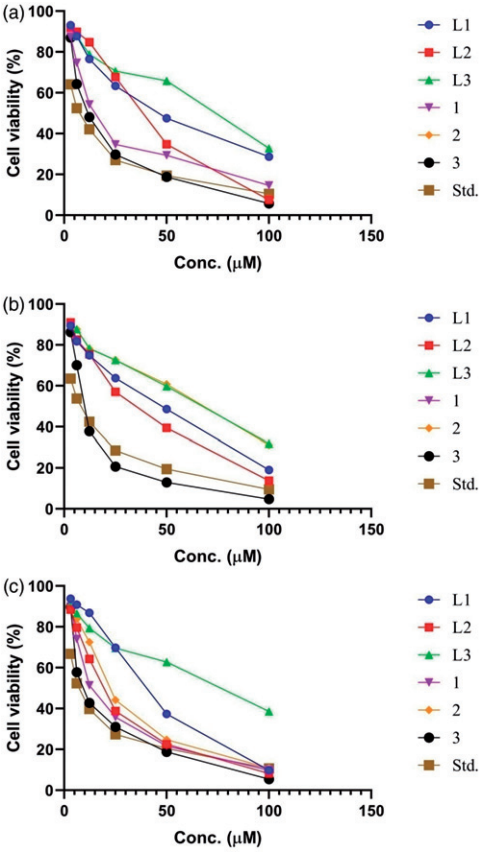


Figure 2. Survival curves of (a) COLO-205, (b) HeLa, and (c) MCF-7 of the compounds.

Table 6. IC_{50} (μM) values of *in vitro* antiproliferative activity of the compounds (μM/mL).

Compound	COLO-205	HeLa	MCF-7	HEK 293
L1	58.14 ± 0.6	51.40 ± 1.3	49.12 ± 1.4	ND
L2	46.10 ± 1.2	45.60 ± 0.8	33.10 ± 1.7	31.45 ± 1.6
L3	70.72 ± 1.3	67.20 ± 1.9	74.90 ± 0.2	ND
1	31.69 ± 0.69	45.72 ± 1.7	28.25 ± 1.2	ND
2	46.65 ± 1.1	67.17 ± 1.6	38.30 ± 1.0	56.82 ± 0.32
3	21.83 ± 1.85	16.52 ± 1.08	19.30 ± 1.0	33.20 ± 1.7
Cisplatin	3.72 ± 0.3	4.21 ± 0.1	4.36 ± 0.1	ND

ND: Not determined.

out by using cisplatin as a positive control. The relation between the surviving fraction and drug concentration was plotted to obtain the survival curves for MCF-7, HeLa and IMR-32 cancer cell lines as shown in Figure 2. The results of the synthesized compounds are summarized in Table 6. From the Table, it was observed that the complex **3** is unmistakable influences on HeLa and MCF-7 cancer cell lines with the IC_{50} values of 16.52 ± 1.08 μM and 19.30 ± 1.0 μM, respectively. The complex **1** showed moderate activity with IC_{50} values of 28.25 ± 1.2 μM against MCF-7. The ligand **L2** and complex **2** exhibits similar IC_{50} values [46.10 ± 1.2 μM and 46.65 ± 1.1 μM, respectively] against COLO-205 cell line, whereas the **L3** and **2** exhibits similar IC_{50} values [67.20 ± 1.9 μM and 67.17 ± 1.6 μM, respectively] against HeLa cell line. The remaining compounds

Table 7. Binding energy, bond length, hydrogen bonds, and residues involved in hydrogen bonding of ligands and their corresponding Pd(II) complexes inhibitors against EGFR protein receptor.

Compound	Binding energy (kcal/mol)	No. of hydrogen bonds	Residues involved in hydrogen bonding	Bond length (Å)
L1	−5.77	3	ARG817	1.64
			ASP813	1.95
			ASN818	2.41
L2	−6.60	5	ARG817	1.97
			ASN818	2.05
			ASP813	2.12
			LYS721	2.61 3.03
L3	−5.16	3	LYS721	1.86
			ASP813	2.72
			ASP831	3.33
1	−7.05	1	ASP813	2.89
3	−8.08	2	ARG817	2.08, 2.36

exhibited poor activity with the IC_{50} values ranging from 31.69 ± 0.69 μM to 74.90 ± 0.2μM against the four cancer cell lines.

In silico molecular docking studies

The main aim of this work was to examine the plausible binding modes and molecular interaction mechanism of ligands (**L1**–**L3**) and complexes (**1**–**3**) with target epidermal growth factor (EGFR) protein receptor through the molecular docking studies. The EGFR protein is an attractive target for various cancer inhibitors because it plays a prominent role in the cancer disease. Mutations of EGFR leads to several types of cancer disease like anal cancers, squamous-cell carcinoma of the lung and epithelial tumors of the head and neck. The molecular docking studies were carried out with ligands and metal complexes on the EGFR protein receptor. The Crystal structure of EGFR protein (PDB ID: 4hjo) was retrieved from RSC protein data bank.

The ligands and their metal complexes strongly bind to epidermal growth factor protein receptor, which was inferred by their least binding energies of −5.77, −6.60, −5.16, −7.05 and −8.08 kcal/mol, respectively. The metal complexes exhibited effective interactions with the protein receptor when compared to the corresponding ligands. The docking results were well correlated with the *in vitro* antiproliferative activity results as shown in Table 7. The assessment of molecular docking studies of ligands and their corresponding complexes unveil that, several hydrogen bond interactions and hydrophobic interactions existed in between the target molecules and EGFR protein receptor. Figure 3 shows the best docking conformations of ligands and their corresponding metal complexes. Among all the ligands, the ligand **L2** exhibited strong interactions with the selected protein receptor which was unambiguous from its minimum binding energy –6.60 kcal/mol and five hydrogen bonds were observed with the amino acid residues ARG817, ASN818, ASP813 and LYS721 having bond lengths 1.97 Å, 2.05 Å, 2.12 Å, 2.61 Å and 3.03 Å. among the complexes, the complex **3** interacts strongly with the EGFR protein which was inferred by its minimum binding energy –8.08 kcal/mol and formed two hydrogen bonds with the amino acid residues ARG817 having bond lengths 2.08 Å, 2.36 Å.

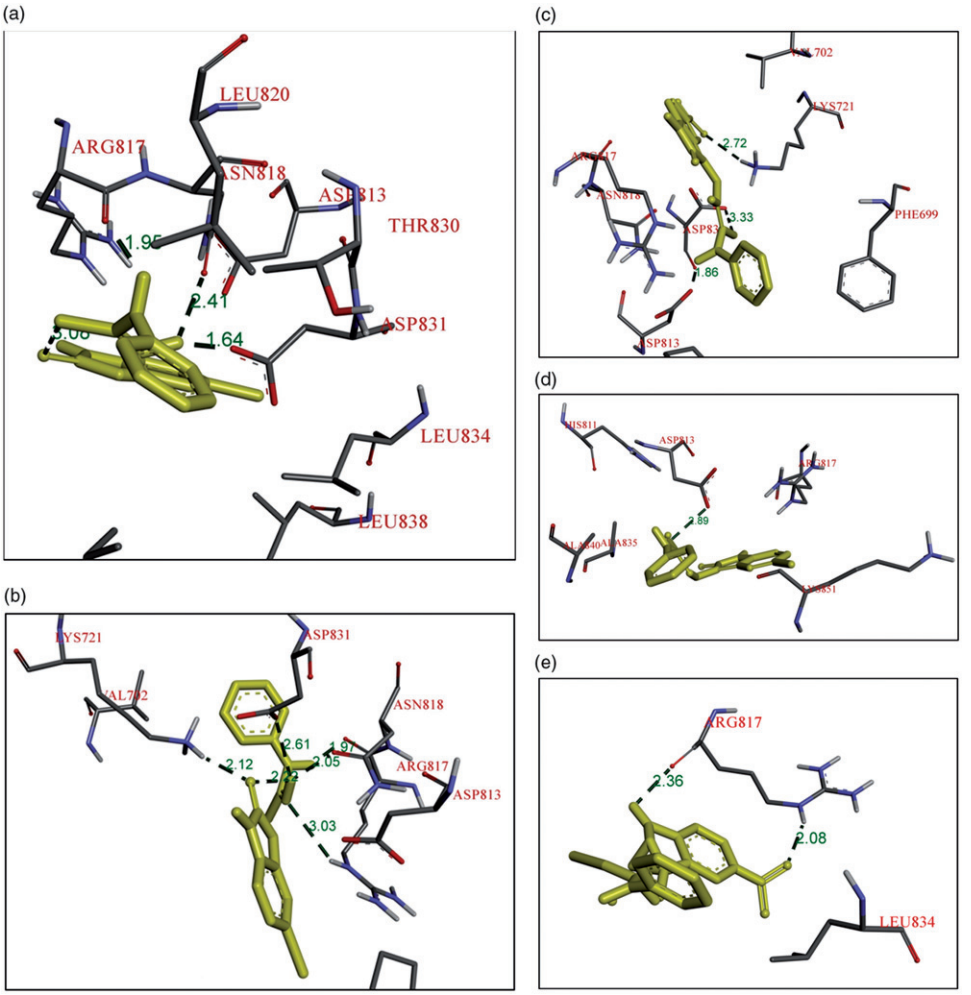


Figure 3. Docking interactions of (a) ligand **L1**, (b) **L2**, (c) **L3**, (d) complex **1**, (e) complex **3** to the binding sites of target protein EGFR (PDB ID: 4hjo).

Conclusion

In the present paper, the ligands and their corresponding Palladium complexes have been synthesized and characterized. The compounds were also examined for their antimicrobial, antioxidant, *in vitro* antiproliferative activities and *in silico* docking studies against EGFR protein receptor. The molecular structures of the complexes were confirmed by using various spectroscopic (UV-Visible, FT-IR, and NMR) and analytical techniques. Based on the spectral data the complexes (**1–3**) may be tentatively proposed as square planar geometry around Pd. In the biological applications, the complex **2** has shown good antimicrobial activity compared to Streptomycin and Ketoconazole standard drugs. The compounds were investigated to their antioxidant activity, the results showed that the complex **3** displayed excellent antioxidant agent with the IC_{50} values of 7.24 ± 0.09 µM, in comparison with the standard Ascorbic acid. The *in vitro* antiproliferative activity results revealed that complex **3** exhibited potent activity against HeLa

and MCF-7 with the IC_{50} values of 16.52 ± 1.08 μM and 19.30 ± 1.0 μM, respectively. Moreover, the molecular docking studies results show that the complex **3** gets minimum binding energies of −8.08 kcal mol^{-1} with EGFR target receptor. Importantly, complexes having the lowest binding energies are also displaying the highest cytotoxicity against the tested human cancer cell lines.

Experimental

Synthesis of isatin based thiosemicarbazone ligands (L1–L3)

The ligands (**L1**–**L3**) are prepared by using the standard procedure.[45] Equimolar (0.001 mol) quantities of 4-phenyl-3-thiosemicarbazide with the appropriately substituted isatin in ethanol (20 mL) and 0.5 mL of acetic acid were added. The contents were condensed for 5 h. The colored products were filtered, washed with cold ethanol and dried in *vacuo*.

Synthesis of pincer Pd(II) complexes (1–3)

The acetonitrile solution of $PdCl_2$ (0.001 mol) was added into an appropriately substituted isatin thiosemicarbazone ligands (0.001 mol) in acetonitrile. The reaction mixture was stirred for 6 h at room temperature, and then the precipitate formed was filtered and washed with acetonitrile and dried in *vacuo*.

Acknowledgments

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