International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 9, Issue 4, 2017

Original Article

FACILE SYNTHESIS, SPECTRAL STUDIES, DFT CALCULATIONS AND BIOLOGICAL ACTIVITIES OF NOVEL NI (II), CU (II), AND PD (II) COMPLEXES OF THIADIAZOLE ANALOGS

PRIYANKA BHATT[a], S. DEEPTHI[b], CH. RAVI SHANKAR KUMAR[b], ANJALI JHA[a]*

[a]Department of Chemistry, [b]Department of Physics, GIS, GITAM University, Rushikonda, Visakhapatnam 530045, India
Email: anjalimanishjha@yahoo.com

Received: 17 Jan 2017 Revised and Accepted: 27 Feb 2017

ABSTRACT

Objective: A facile synthesis of some novel Schiff base derivatives of 2-substituted-5-amino-thiadiazoles along with their Ni (II), Cu (II), and Pd (II) complexes were achieved by sonication and the conventional method. In addition to establish the structure by DFT studies and to explore antimicrobial and anticancer activities of these novel compounds.

Methods: The precursor 2-substituted-5-amino-thiadiazoles (T1-T3), target ligands and their metal complexes were synthesized by ultra-sonication and conventional means. The isolated products were thoroughly characterized by physical and spectroscopic techniques including ^{1}H-NMR, ^{13}C-NMR and IR spectroscopy. All characterized compounds were screened for antimicrobial activities using well diffusion method, and MTT assay was performed for cytotoxicity.

Results: All novel compounds were synthesized by a green route i.e. ultra sonication and a noticeable improvement in yield with shorter reaction time than the conventional method were observed. The octahedral geometry was proposed for Ni (II)/Cu (II) complexes whereas square planar for Pd (II) complexes on the basis of the spectral techniques which were supported by DFT analysis by Gaussian03. On the analysis of antimicrobial activities, the compound T7 and T10 showed maximum antibacterial and antifungal activities respectively. However, compounds T25, T37, T31 found to be a potential cytotoxic compound with IC_{50} value 0.469, 0.865 and 1.131 µM respectively.

Conclusion: Analysis of synthetic protocol, it could be concluded that ultra-sonication is the better method to synthesize these potential biological active moiety. On the whole Cu (II) and Ni (II) complexes showed promising activity towards all microorganisms while Pd (II) complex emerged an excellent moiety in carcinoma cell line.

Keywords: Ultrasonication, Substituted-thiadiazoles, Ketones (5-bromo-isatin/chalcone/acridone), DFT calculations, Antimicrobial and anticancer studies

DOI: http://dx.doi.org/10.22159/ijpps.2017v9i4.17130

INTRODUCTION

The nitrogen, sulphur bearing heterocyclic systems constitutes the core structure of a number of biologically interesting compounds in living organisms, natural products, drugs and many more substances useful to mankind. Their synthesis and evaluation have always drawn the attention of chemists and biologists over the years. Among them, 1, 3, 4-thiadiazoles is a promising structure in medicinal chemistry and drug discovery [1] due to their diverse biological activities such as antihypertensive, anti-inflammatory, anti-bacterial, anti-amoebic [2], anti-HIV [3], antitumor and cytotoxic [4] activity. Moreover, they acts as a building block for the synthesis of various biologically active intermediates and derivatives [5, 6]. Additionally, Schiff bases derived from amino-thiazoles have been shown to possess promising applications in various biological modeling and activities [7].

With the ever-increasing problem of microbe resistance to current antimicrobial drugs, there is an urgent need for new classes of compounds that will efficiently inhibit the growth of pathogenic microorganisms. So designing molecules bearing suitable functionalities for the creation of well-defined structural design is one of the major goals in chemistry. Additionally, increase in high throughputs biological screening and accelerated development of new biological targets has increased the demand on synthetic chemists to produce a new compound for testing in less time in sync with environment-friendly technique. In this context, the use of ultrasonic irradiation [8-12] to activate organic reactions in the heterogeneous/homogeneous system has recently taken on a new dimension. The prominent features of ultrasound approach are to enhance reaction rates, the formation of purer products in high yields, shorter reaction time and milder conditions as compared with traditional methods.

Structure-based pharmacophore approaches have become widely used in drug discovery and design. A survey of the literature reveals that isatin [13], chalcone [14, 15] and acridone [16] are versatile compounds and used as a raw material for synthesis of various drugs and heterocyclic compounds. Because of the excellent chelating behaviour of Schiff bases, the importance of their metal complexes are well documented in the literature [17]. Additionally, the Density functional theory (DFT) was used by the various researcher to optimize the structure of synthesized metal-ligand complexes [18-20]. Keeping all these observations in mind, some 2-substituted-5-amino-thiadiazoles (T1-T4) were synthesized by sonochemical as well as conventional method. These characterized products were further condensed with 5-bromoisatin/ chalcone/ acridone, with an aim to achieve the compounds (ligands, T5-T16) having better antimicrobial activity and lesser cytotoxicity. As metal complexes were found to be more active against various microbes and pathogen, these isolated ligands (T5-T16) were further complexed with Ni, Cu, Pd chlorides to get their metal complexes. All novel compounds were characterized by spectral techniques. The paper reports the synthesis and characterization studies of the novel complexes for antimicrobial activities, anticancer and computational studies using a B3LYP/3-21G basis set for geometrical optimization of complexes.

MATERIALS AND METHODS

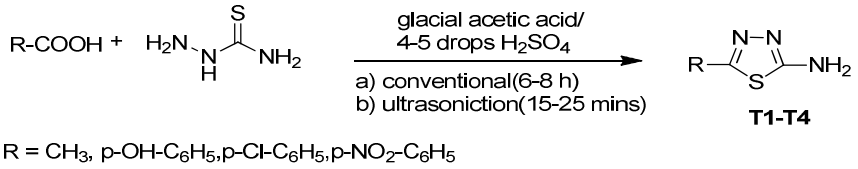
Reagents such as thiosemicarbazide hydrochloride, acetic acid, p-chlorobenzoic acid, p-nitrobenzoic acid and 5-bromoisatin were purchased from Across Ltd and used as received. However, chalcone [14] and acridone [16] were synthesized by following reported methods. All the solvents were of analytical grade and were distilled before used. Melting points are uncorrected. The solid IR (Infrared spectroscopy). spectra were recorded in KBr on Perkin Elmer-Spectrum-Lambda-25 spectrophotometer at GITAM University, Visakhapatnam; however, ^{1}H-NMR (proton nuclear magnetic resonance) and ^{13}C-NMR (Carbon-13 Nuclear Magnetic Resonance) spectra were obtained using Bruker 400 MHz NMR facility at IISc,

Bangalore. Chemical shift values were reported in parts per million (ppm) using TMS as an internal standard and DMSO-d_6/$CDCl_3$ as NMR solvents. Ultra sonication (US) experiments were performed on a probe sonicator (12/20 mm probe) with an ultrasonic processor (250 W) operating at a fixed frequency of 50 Hz with speed 238 rpm. Quantum chemical calculations were carried with the Gaussian 03v package using DFT/B3LYP/3-21G basis set to understand the electronic structure and to correlate with the experimental findings. The structural studies were drawn with Avogadro and the structures were visualized with Gauss view for optimisation.

Synthesis of 2-substituted-5-amino-thiadiazoles

2-substituted-5-amino-thiadiazoles was synthesised accordance to the literature reported procedure [21] and by an alternative greener method, ultra sonication in which pleasing similar outcomes was found. The progress of the reaction was monitored by TLC plates.

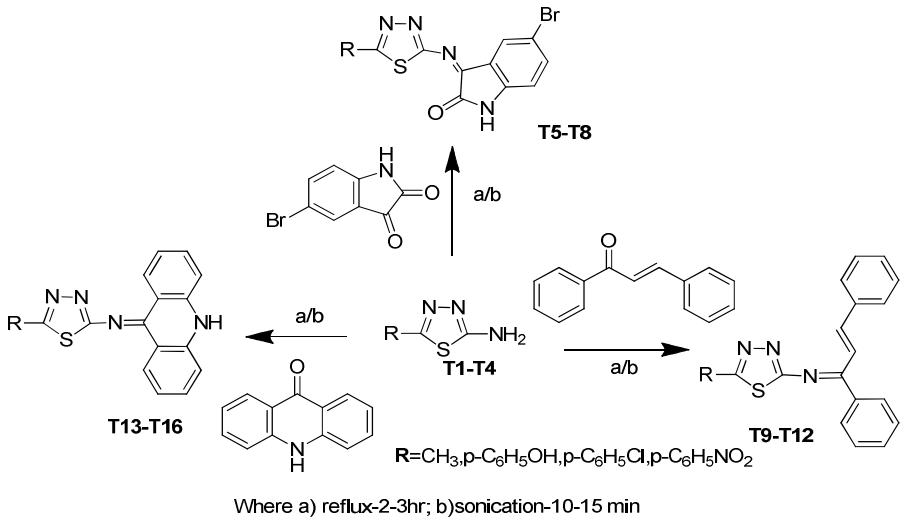
The final product was recrystallized from boiling water (Scheme 1). The isolated product was characterized by spectral means and found congruity structurally with the expected structure.



Scheme 1

Synthesis of substituted thiadiazole schiff's bases (T5-T16) by conventional/ultra-sonication method

A mixture of substituted thiadiazole (T1-T4, 1 mmol) and ketones (5-bromoisatin, chalcone, acridone, 1.0 mmol) was refluxed/ ultrasonicated under probe sonicator (table 1). The completion of the reaction was monitored by TLC. The solid mixture from both the methods was filtered, dried, recrystallized. The synthesized compounds were characterized by ^1H NMR, ^{13}C NMR and mass analysis.



Scheme 2

Table 1: Comparison of reaction kinetics of conventional and ultrasonic irradiation methods for synthesis of compounds T5-T16

S. No.	Compound	Reaction time		% Yield	
		US(min)	Conv.(h)	US*	Conv.*
1	T-5	10	8	82	70
2	T-6	20	6	91	72
3	T-7	25	9	80	59
4	T-8	25	8	82	71
5	T-9	20	10	88	65
6	T-10	15	12	74	54
7	T-11	20	12	89	74
8	T-12	20	8	81	70
9	T-13	20	9	92	80
10	T-14	15	7	82	76
11	T-15	25	7	90	82
12	T-16	20	10	91	79

T5: [*5-bromo-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)indolin-3-one*] ($C_{11}H_7BrN_4OS$)321.95: IR(cm^{-1}): 3390 (NH), 3105(Ar-H),2989(CH_3), 1670(C=O),1627,1520(C=N);^{1}HNMR(δ ppm):6.7-6.9(Ar-H),3.3(NH), 2.3(CH_3);^{13}CNMR(δppm):26.3(CH_3),113.6,115.6,120.3,129.8, 145.1,

147.8(Ar-C),159,150(thiazole carbons);m/e: 323.95; Analysis: Calcd C, 40.88; H, 2.18; N, 17.34 Found: C, 40.89; H, 2.20; N, 17.35.

T6: [5-bromo-2-((5-(4-hydroxyphenyl)-1,3,4-thiadiazol-2-yl)imino) indolin-3-one] ($C_{16}H_9BrN_4O_2S$);401.24;IR(cm^{-1}):3610 (OH), 3316 (NH),3108(Ar-H),1672(C=O),1626,1514 (C=N);^{1}HNMR(δppm):7.4-7.8(Ar-H),3.4(NH),^{13}CNMR (δppm):126.1, 126.7,129.5,130(Ar-C), 160,168 (Oxazole carbons); m/e: 401.96;Analysis: Calcd C, 47.89; H, 2.26; N, 13.96; Found: C, 47.92; H, 2.18; N, 13.98.

T7: [5-bromo-2-((5-(4-chlorophenyl)-1,3,4-thiadiazol-2-yl)imino) indolin-3-one] ($C_{16}H_8BrClN_4OS$);419.68;IR(cm^{-1}):3226 (NH),3130 (ArH),1669(C=O),1602(N=CH), 1514(C=N);^{1}HNMR(δppm): 9.9(O-H); 8.05(N=CH),6.7-7.3(Ar-H),3.5(NH),^{13}CNMR(δppm):116,118,130 (Ar-C),154,162,172(Oxazole Carbons),167.3(azomethine carbon); m/e: 419.93; Analysis: Calcd C, 45.79; H, 1.92; N, 13.35;Found: C, 45.80; H, 1.90; N, 13.33.

T8: [5-bromo-2-((5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)imino) indolin-3-one] ($C_{16}H_8BrN_5O_3S$);430.24;IR(cm^{-1}):3301(NH),3120(Ar-H),1671(C=O),1605(N=CH),1545(C=N);^{1}HNMR: (δppm): 8.05 (N=CH),7.5-7.8(Ar-H),6.7-6.8(Ar-H), 3.2(NH), ^{13}CNMR (δppm): 111.53, 125,132(Ar-C), 150, 154.68(thiazole carbons),163.3 (azomethine carbon); m/e: 430.24; Analysis: C, 44.67; H, 1.87; N, 16.28; Found: C, 44.69; H, 1.86; N, 16.29.

T9: [N-((E)-1,3-diphenylallylidene)-5-methyl-1,3,4-thiadiazol-2-amine] ($C_{18}H_{15}N_3S$);305.10**:** IR (cm^{-1}): 3130(Ar-H), 2987(-CH_3), 1626(HC=CH),1514(C=N), 1465; ^{1}HNMR(δ ppm):7.5-7.9 (Ar-H),6.1-6.0(HC=CH),2.3(CH_3);^{13}CNMR(δppm):110.1-111.9(HC=CH); 119, 126.5,128.7,130.3 (Ar-C), 152(C=C),162,169 (Oxazole carbons);m/e: 305.40; Analysis: Calcd C, 70.79; H, 4.95; N, 13.76; Found: C, 69.19; H, 4.86; N, 12.47.

T10: [4-(5-((E)-((E)-1,3-diphenylallylidene)amino)-1,3,4-thiadiazol-2-yl)phenol] ($C_{23}H_{17}N_3OS$); 383.11;IR(cm^{-1}):3469(-OH),3128(Ar-H),1536(C=N);^{1}HNMR (δ ppm):9.66(OH),8.1(N=CH),7.6-7.9(Ar-H), 6.1-5.9(HC=CH);^{13}CNMR(δppm):109.1-110.9(HC=CH); 111.4,125, 132(Ar-C),154.6, 159(thiazole carbons),165.3(azomethine carbon); m/e: 383.09; Analysis: Calcd C, 72.04; H, 4.47; N, 10.96;Found: C, 72.92; H, 4.95; N, 11.22.

T11: [(E)-5-(4-chlorophenyl)-N-((E)-1,3-diphenylallylidene)-1,3,4-thiadiazol-2-amine] ($C_{23}H_{16}ClN_3S$);401.08;IR (cm^{-1}): 3658(-OH), 3140 (Ar-H),1610(N=CH),1514(C=N);^{1}HNMR(δ ppm):8.2(N=CH),7.2-7.6(Ar-H),6.1-6.0(HC=CH),^{13}CNMR(δppm):109.5-110.8(HC=CH); 128.4, 129.4, 133.8,134.6(Ar-C);161,170(Oxazole Carbons),168(azomethine carbon); m/e: 401.05; Analysis: Calcd C, 68.73; H, 4.01; N, 10.46; Found: C, 67.51; H, 4.68; N, 10.21.

T12: [(E)-N-((E)-1,3-diphenylallylidene)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine] ($C_{23}H_{16}N_4O_2S$);412.10;IR(cm^{-1}):3610 (OH), 3130(ArH),1602(N=CH),1514(C=N);^{1}HNMR(δppm):9.9(O-H);8.05 (N=CH),6.7-7.3(Ar-H),6.1-6.0(HC=CH),^{13}CNMR(δ ppm): 109.4-111.6(HC=CH); 116,118,130(Ar-C),154,162,172 (Oxazole Carbons), 167.3(azomethine carbon); m/e: 412.08; Analysis: Calcd C, 66.97; H, 3.91; N, 13.58; O, 7.76; Found: C, 67.19; H, 3.21; N, 14.22.

T13: [N-(9,10-dihydroacridin-9-yl)-5-methyl-1,3,4-thiadiazol-2-amine]($C_{16}H_{14}N_4S$);292.08;IR (cm^{-1}):3325(NH),3130(Ar-H),2985 (CH_3),1626,1514(C=N);^{1}HNMR(δppm):6.7-7.3(Ar-H),3.8(NH),^{13}CNMR(δ ppm): 116,118,130,134,(Ar-C), 162,170 (Oxazole carbons); m/e: 294.08; Analysis: Calcd C, 65.28; H, 4.79; N, 19.03;Found: C, 65.20; H, 4.89; N, 19.09.

T14: [*4-(5-((9,10-dihydroacridin-9-yl)amino)-1,3,4-thiadiazol-2-yl) phenol*] ($C_{21}H_{16}N_4OS$);370.09;IR(cm^{-1}):3690(-OH),3128(Ar-H),610 (N=CH),1549-1536(C=N),1335-1064(C-O);^{1}HNMR (δ ppm): 9.15(OH),7.6-7.9(Ar-H),6.79-6.77(Ar-H),3.3(-NH),^{13}CNMR(δ ppm):111.5,125,132(Ar-C),153.67,158 (thiazole carbons), 164.31 (azomethine carbon); m/e: 372.10; Analysis: Calcd C, 67.72; H, 4.33; N, 15.04; Found: C, 67.79; H, 4.67; N, 15.11.

T15: [5-(4-chlorophenyl)-N-(9,10-dihydroacridin-9-yl)-1,3,4-thiadiazol-2-amine]($C_{21}H_{13}ClN_4S$) 388.05: IR (cm^{-1}): 3120(Ar-H),1615(N=CH),1514(C=N);^{1}HNMR(δ ppm):7.4-7.8(Ar-H),6.7-6.8(Ar-H),3.31(-NH),^{13}CNMR(δ ppm):126,126.7,129.5,130(Ar-C)160,169 (Oxazole Carbons), 165.3(azomethine carbon); m/e: 390.07; Analysis: Calcd C, 64.53; H, 3.87; N, 14.33; Found: C, 64.41; H, 3.82; N, 14.20.

T16: [N-(9,10-dihydroacridin-9-yl)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine]($C_{21}H_{15}N_5O_2S$);399.08;IR (cm^{-1}): 3140(Ar-H), 1610(N=CH), 1514(C=N);^{1}HNMR(δ ppm): 8.2(N=CH),7.2-7.6(Ar-H),3.35(-NH), ^{13}CNMR(δ ppm):128.4,129.4,133.8,134.6(Ar-C);161,170, (Oxazole Carbons),168(azomethine carbon); m/e: 401.09;Analysis: Calcd C, 62.83; H, 3.77; N, 17.45; Found: C, 62.91; H, 3.68; N, 17.55.

General procedure for the preparation of metal complexes

The Ni, Cu and Pd complexes of the above novel ligands (T5-T16) were prepared by the literature reported conventional method [22]. Further, the promising utility of ultrasonic radiation was also explored and found that 25 min of ultrasonication were sufficient to get similar results.

The complexes isolated from both the methods were compared by identical TLC spots and melting point. The isolated complexes were characterized by various spectral methods and gave satisfactory results for expected structure fig. 1.

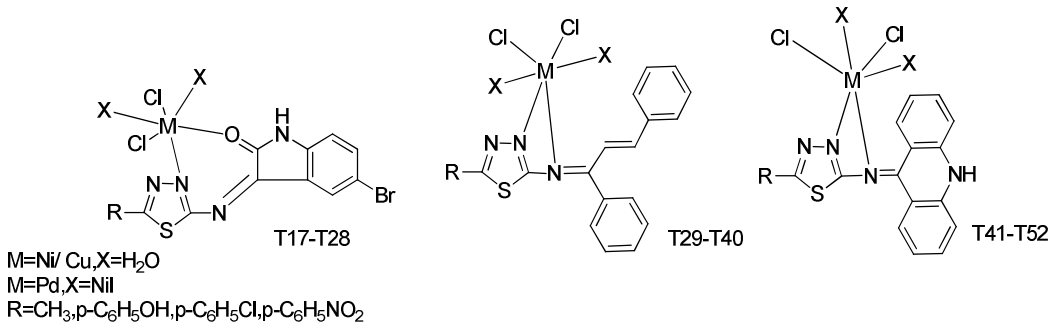


Fig. 1: Structure of metal complexes

T_5-Ni/[Ni$T_5Cl_2.(H_2O)_2$] (T17) $C_{11}H_{11}BrCl_2N_4NiO_3S$; 488.80;IR($cm^{-1}$): 3610 (OH),3114(Ar-H), 2988(CH_3),1666(C=O),1545(C=C),1543 (C=N); Analysis: Calcd C,27.03; H,2.27; N, 11.46; Ni, 12.01; Found: C, C, 27.00; H, 2.25; N, 11.47;Ni,12.25.

T_5-Cu/[Cu$T_5Cl_2.(H_2O)_2$] (T18) $C_{11}H_{11}BrCl_2N_4CuO_3S$; 493.65;IR($cm^{-1}$):3609(OH),3113(Ar-H), 2987(CH_3),1664(C=O),1542(C=C),1542(C=N); Analysis: Calcd C, 26.76; H, 2.25; N, 11.35; Cu, 12.87;Found: C, 26.74; H, 2.26; N, 11.34; Cu, 12.85.

T_5-Pd/[PdT_5Cl_2] (T19) ($C_{11}H_7BrCl_2N_4OPdS$); 500.49;IR(cm^{-1}): 3115(Ar-H), 2988(CH_3), 1665 (C=O),1544 (C=C),1542(C=N); Analysis: C, 26.40; H, 1.41; N, 11.19;Pd, 21.26; Found: C, 26.39; H, 1.40; N, 11.17;Pd, 21.24

T_6-Ni/[Ni$T_6Cl_2.(H_2O)_2$] (T20) $C_{16}H_{13}BrCl_2NiN_4O_4S$; 566.87;IR($cm^{-1}$): 3105(Ar-H),3611(OH), 1632(C=O),1510(C=N); Analysis: Calcd C, 33.90; H, 2.31; N, 9.88; Ni, 10.35; Found: C, 33.89; H, 2.30; N, 9.87; Ni, 10.34

T_6-Cu/[Cu$T_6Cl_2.(H_2O)_2$] (T21) $C_{16}H_{13}BrCl_2CuN_4O_4S$; 571.72;IR($cm^{-1}$):3103(Ar-H),3609(OH),1630(C=O),1512(C=N); Analysis: Calcd C, 33.61; H, 2.29; N, 9.80; Cu, 11.11; Found: C, 33.60; H, 2.28; N, 9.78; Cu, 11.09

T_6-Pd/[PdT_6Cl_2] (T22) $C_{16}H_9BrCl_2N_4O_2PdS$; 578.56;IR(cm^{-1}): 3101(Ar-H), 3612(OH), 1630 (C=O),1512(C=N); Analysis: Calcd C, 33.22; H, 1.57; N, 9.68; Pd, 18.39; Found: C, 33.20; H, 1.55; N, 9.67; Pd, 18.48

T_7-Ni/[Ni$T_7Cl_2.(H_2O)_2$] (T23) $C_{16}H_{12}BrCl_3N_4NiO_3S$; 585.31; IR($cm^{-1}$):3607(OH),3129(Ar-H), 1607(N=CH),1517(C=N);Analysis: Calcd C, 32.83; H, 2.07; N, 9.57; Ni, 10.03; Found: C, 32.82; H, 2.06; N, 9.55; Ni, 10.00

T_7-Cu/[Cu$T_7Cl_2.(H_2O)_2$] (T24) $C_{16}H_{12}BrCl_3N_4CuO_3S$; 590.17; IR($cm^{-1}$):3608(OH),3133(Ar-H),1610(N=CH),1515(C=N);Analysis: Calcd C, 32.56; H, 2.05; N, 9.49**;** Cu, 10.77; Found: C, 32.54; H, 2.04; N, 9.47**;** Cu, 10.96

T_7-Pd/[PdT_7Cl_2] (T25) $C_{16}H_8BrCl_3N_4PdO_3S$; 593.01;IR(cm^{-1}):3609(OH),3130(Ar-H),1611(N=CH),1519(C=N):Analysis: Calcd C, 32.19; H, 1.35;N, 9.38; Pd, 17.83; Found: C, 32.17; H, 1.34; N, 9.36; Pd, 17.82

T_8-Ni/[Ni$T_8Cl_2.(H_2O)_2$] (T26) $C_{16}H_{12}BrCl_2N_5NiO_5S$; 595.87;IR($cm^{-1}$):3613(OH),3118(Ar-H), 1603(N=CH),1540(C=N);Analysis: Calcd C, 32.25; H, 2.03; Br, 13.41; Cl, 11.90; N, 11.75; Ni, 9.85; Found: C, 32.24; H, 2.00; Br, 13.40; Cl, 11.87; N, 11.72; Ni, 9.82

T_8-Cu/[Cu$T_8Cl_2.(H_2O)_2$] (T27) $C_{16}H_{12}BrCl_2N_5CuO_5S$; 600.72;IR($cm^{-1}$):3612(OH),3116(Ar-H),1607(N= CH),1543(C=N); Analysis: Calcd C, 31.99; H, 2.01; N, 11.66; Cu, 10.58; Found: C, C, 31.97; H, 2.00; N, 11.64; Cu, 10.57

T_8-Pd/[PdT_8Cl_2] (T28) $C_{16}H_8BrCl_2N_5O_3PdS$; 607.56; IR(cm^{-1}):3118(Ar-H),1609(N=CH), 1547(C=N);Analysis: Calcd C, 31.63; H, 1.33;N, 11.53;Pd, 17.52; Found: C, 31.62; H, 1.32;N, 11.50;Pd, 17.51

T_9-Ni/[Ni$T_9Cl_2.(H_2O)_2$] (T29) $C_{18}H_{19}Cl_2N_3NiO_2S$; 471.03;IR ($cm^{-1}$):3615(OH),3128(Ar-H), 2989(CH_3),1622(HC=CH),1510(C=N),1463; Analysis: Calcd C, 45.90; H, 4.07; N, 8.92; Ni, 12.46; Found: C, 45.89; H, 4.05; N, 8.90; Ni, 12.44

T_9-Cu/[Cu$T_9Cl_2.(H_2O)_2$] (T30) $C_{18}H_{19}Cl_2N_3CuO_2S$; 475.88;IR ($cm^{-1}$):3614(OH),3127(Ar-H), 2985(CH_3), 1624(HC=CH),1512(C=N), 1464; Analysis: Calcd C, 45.43; H, 4.02; N, 8.83; Cu, 13.35; Found: C, 45.41; H, 4.00; N, 8.82; Cu, 13.33

T_9-Pd/[PdT_9Cl_2] (T31) $C_{18}H_{15}Cl_2N_3PdS$; 480.72;IR(cm^{-1}):3129(Ar-H),2986(CH_3),1622 (HC=CH),1510(C=N), 1466;Analysis: Calcd C, 44.79; H, 3.13; N, 8.70; Pd, 22.05; Found: C, 44.76; H, 3.12; N, 8.69; Pd, 22.02

T_{10}-Ni/[Ni$T_{11}Cl_2.(H_2O)_2$] (T32) $C_{23}H_{21}Cl_2N_3CuO_3S$; 549.10; IR($cm^{-1}$):3610(OH), 3466(-OH), 3125(Ar-H),1534(C=N); Analysis: Calcd C, 50.31; H, 3.85; N, 7.65; Ni, 10.69; Found: C, 50.30; H, 3.83; N, 7.64; Ni, 10.67

T_{10}-Cu/[Cu$T_{11}Cl_2.(H_2O)_2$] (T33) $C_{23}H_{21}Cl_2N_3CuO_3S$; 553.95;IR($cm^{-1}$):3610(OH),3467(-OH), 3124(Ar-H),1532(C=N);Analysis: Calcd C, 49.87; H, 3.82; N, 7.59; Cu, 11.47; Found: C, 49.86; H, 3.80; N, 7.58; Cu, 11.45.

T_{10}-Pd/[Pd$T_{11}Cl_2$] (T34) $C_{23}H_{17}Cl_2N_3PdOS$; 560.79;IR(cm^{-1}):3608(OH),3465(-OH),3123(Ar-H),1534(C=N); Analysis: Calcd C, 49.26; H, 3.06; N, 7.49;Pd, 18.98; Found: C, C, 49.24; H, 3.03; N, 7.48;Pd, 18.97

T_{11}-Ni/[Ni$T_{12}Cl_2.(H_2O)_2$] (T35) $C_{23}H_{20}Cl_3N_3NiO_2S$; 567.54;IR($cm^{-1}$):3658(-OH),3138(Ar-H), 1608(N=CH),1515(C=N); Analysis: Calcd C, 48.67; H, 3.55; N, 7.40; Ni, 10.34; Found: C, 48.66; H, 3.54; N, 7.39; Ni, 10.78

T_{11}Cu/[Cu$T_{12}Cl_2.(H_2O)_2$] (T36) $C_{23}H_{20}Cl_3N_3CuO_2S$; 572.39;IR($cm^{-1}$):3656(-OH),3136(Ar-H), 1605(N=CH),1512(C=N); Analysis: Calcd C, 48.26; H, 3.52;Cu, 11.10; N, 7.34; Found: C, 48.25; H, 3.51;Cu, 11.08; N, 7.33

T_{11}-Pd/[Pd$T_{12}Cl_2$] (T37) $C_{23}H_{16}Cl_3N_3PdS$; 579.24;IR(cm^{-1}):3137(Ar-H),1606(N=CH),1514 (C=N);Analysis: Calcd C, 47.69; H, 2.78; N, 7.25; Pd, 18.37; Found: C, 47.68; H, 2.77; N, 7.23; Pd, 18.36

T_{12}-Ni/[Ni$T_{12}Cl_2.(H_2O)_2$] (T38) $C_{23}H_{20}Cl_2N_4NiO_4S$; 578.09;IR($cm^{-1}$):3608(OH),3128(Ar-H), 1605(N=CH),1514(C=N); Analysis: Calcd C, 47.79; H, 3.49; N, 9.69; Ni, 10.15; Found: C,, 47.78; H, 3.46; N, 9.66; Ni, 10.14

T_{12}-Cu/[Cu$T_{12}Cl_2.(H_2O)_2$] (T39) $C_{23}H_{20}Cl_2N_4CuO_4S$; 582.95; IR ($cm^{-1}$): 3618(OH),3126(Ar-H), 1604(N=CH),1512(C=N); Analysis: Calcd C, 47.39; H, 3.46; N, 9.61;Cu, 10.90; Found: C,, 47.37; H, 3.44; N, 9.60;Cu, 10.88

T_{12}-Pd/[Pd$T_{12}Cl_2$] (T40) $C_{23}H_{16}Cl_2N_4O_2PdS$; 589.79;IR($cm^{-1}$):3128(Ar-H),1607(N=CH),1516 (C=N); Analysis: Calcd C, 46.84; H, 2.73;N, 9.50; Pd, 18.04; Found: C, 46.83; H, 2.72;N, 9.48; Pd, 18.00

T_{13}-Ni/[Ni$T_{13}Cl_2.(H_2O)_2$] (T41) $C_{16}H_{16}Cl_2N_4NiO_2S$; 457.99;IR($cm^{-1}$):3678(-OH),3322($NH_2$), 3133(Ar-H), 2989($CH_3$),1628,1516(C=N); Analysis: Calcd C, 41.96; H, 3.52; N, 12.23; Ni, 12.82; Found: C, 41.94; H, 3.50; N, 12.20; Ni, 12.80

T_{13}-Cu/[Cu$T_{13}Cl_2.(H_2O)_2$] (T42) $C_{16}H_{16}Cl_2N_3CuO_2S$; 462.84;IR($cm^{-1}$):3679(-OH),3326($NH_2$), 3134(Ar-H), 2990($CH_3$),1628,1515 (C=N); Analysis: Calcd C, 41.52; H, 3.48; N, 12.10;Cu, 13.73; Found: C, 41.50; H, 3.47; N, 12.08;Cu, 13.72

T_{13}-Pd/[Pd$T_{13}Cl_2$] (T43) $C_{16}H_{16}N_4O_2PdS$; 434.81;IR(cm^{-1}):3327 (NH_2),3132(Ar-H),2989 (CH_3),1629,1518(C=N);Analysis: Calcd C, 44.20; H, 3.71; N, 12.89; Pd, 24.48; Found: C, 44.19; H, 3.69; N, 12.88; Pd, 24.45

T_{14}-Ni/[Ni$T_{14}Cl_2.(H_2O)_2$] (T44) $C_{21}H_{18}Cl_2N_4NiO_3S$; 536.06;IR($cm^{-1}$):3686(-OH),3126(Ar-H), 612(N=CH),1545-1535(C=N),1332-1060 (C-O) Analysis: Calcd C, 47.05; H, 3.38;N, 10.45; Ni, 10.95; Found: C, 47.03; H, 3.37;N, 10.44; Ni, 10.94

T_{14}-Cu/[Cu$T_{14}Cl_2.(H_2O)_2$] (T45) $C_{21}H_{18}Cl_2N_4CuO_3S$; 540.91;IR($cm^{-1}$):3688(-OH),3124(Ar-H),613(N=CH),1546-1535(C=N),1335-1060 (C-O) Analysis: Calcd C, 46.63; H, 3.35; N, 10.36; Cu, 11.75; Found: C, 46.62; H, 3.33; N, 10.34; Cu, 11.72

T_{14}-Pd/[Pd$T_{14}Cl_2$] (T46) $C_{23}H_{18}N_4O_3PdS$; 512.88;IR(cm^{-1}):3686(-OH),3122(Ar-H),610(N= CH),1545-1533(C=N),1333-1062(C-O): Analysis: Calcd C, 49.18; H, 3.54; N, 10.92; Pd, 20.75; Found: C, 49.16; H, 3.55; N, 10.90; Pd, 20.73

T_{15}-Ni/[Ni$T_{15}Cl_2.(H_2O)_2$] (T47) $C_{21}H_{17}Cl_3N_4NiO_2S$; 554.50; IR ($cm^{-1}$):3675(-OH),3118(Ar-H), 1612(N=CH),1510(C=N); Analysis: Calcd C, 45.49; H, 3.09; N, 10.10; Ni, 10.58; Found: C, 45.48; H, 3.05; N, 10.08; Ni, 10.57

T_{15}-Cu/[Cu$T_{15}Cl_2.(H_2O)_2$] (T48) $C_{21}H_{17}Cl_3N_4CuO_2S$; 559.36;IR ($cm^{-1}$): 3677(-OH),3115(Ar-H),1609(N=CH),1508(C=N); Analysis: Calcd C, 45.09; H, 3.06; N, 10.02; Cu, 11.36; Found: C, 45.08; H, 3.05; N, 10.00; Cu, 11.33

T_{15}-Pd/[Pd$T_{15}Cl_2$] (T49) $C_{21}H_{13}Cl_3N_4PdS$; 566.20;IR (cm^{-1}):3117(Ar-H),1607(N=CH), 1506 (C=N); Analysis: Calcd C, 44.55; H, 2.31;N, 9.90; Pd, 18.80; Found: C, 44.54; H, 2.29;N, 9.88; Pd, 18.79

T_{16}-Ni/[Ni$T_{16}Cl_2.(H_2O)_2$] (T50) $C_{21}H_{17}Cl_2N_5NiO_4S$; 565.06;IR($cm^{-1}$):3655(-OH),3137(Ar-H), 1609(N=CH),1512(C=N); Analysis: Calcd C, 44.64; H, 3.03;N, 12.39; Ni, 10.39; Found: C, 44.63; H, 3.00;N, 12.37; Ni, 10.37

T_{16}-Cu/[Cu$T_{16}Cl_2.(H_2O)_2$] (T51) $C_{21}H_{17}Cl_2N_5CuO_4S$; 569.91;IR ($cm^{-1}$):3653(-OH),3136(Ar-H),1612(N=CH),1509(C=N); Analysis: Calcd C, 44.26; H, 3.01; N, 12.29; Cu, 11.15; Found: C, 44.24; H, 3.00; N, 12.28; Cu, 11.12

T_{16}-Pd/[Pd$T_{16}Cl_2$] (T52) $C_{21}H_{13}Cl_2N_5PdO_2S$; 576.75;IR($cm^{-1}$):3138(Ar-H),1614(N=CH), 1510(C=N);Analysis: Calcd C, 43.73; H, 2.27;Pd, 18.45; Found: C, 43.71; H, 2.25;Pd, 18.42

Antimicrobial assay

The synthesized compounds (T5–T52) were assessed for antimicrobial assay (Ansari, *et al.*, 2005) against gram negative

bacteria EC-*Escherichia coli* (MTCC 1687), PA-*Pseudomonas aeruginosa* (MTCC 1688) and gram positive bacteria BS-*Bacillus subtilis* (MTCC 441),SA-*Staphylococcus aureus* (MTCC 96), along with a fungus CA-*Candida albicans* (MTCC 227) using the well diffusion method. The compounds were dissolved in DMSO and activity was determined using serial dilution method. The whole procedure was carried out as reported [23]. Ciprofloxacin and ketaconazole were used as antibacterial and antifungal reference drugs,respectively. The zone of inhibition (mm) was determined at 10 µg/ml concentration for each compound in triplicate experiments; the values were averaged and are presented in table 2.

Table 2: Antimicrobial activity of synthesized compounds (zone of inhibition* in mm at concentration 10 µg/ml)

Compounds	Bacteria				Fungus
	EC	PA	BS	SA	CA
T5	19	25	13	15	16
T6	24	16	22	20	12
T7	24	27	19	25	14
T8	17	24	20	15	-
T9	15	18	17	23	17
T10	12	22	15	17	24
T11	22	20	18	19	23
T12	21	21	14	14	10
T13	-	14	18	18	11
T14	16	19	16	-	20
T15	14	17	-	17	19
T16	16	-	17	13	8
T21	25	20	19	14	15
T22	15	15	16	13	11
T23	28	25	21	20	18
T24	15	15	18	16	21
T26	16	-	-	-	-
T29	16	18	18	16	21
T33	28	23	19	16	15
T38	20	17	18	13	12
T44	18	16	17	12	11
T47	20	16	22	17	19
Cephaloflaxin	35	30	28	35	-
Ketoconazole	-	-	-	-	28

*Results are the mean of triplicate experiments, (-) no inhibition was observed, EC-*Escherichia coli*, PA-*Pseudomonas aeruginosa,* BS-*Bacillus subtilis,* SA-*Staphylococcus aureus*, CA-*Candida albicans*

Molecular DFT calculations

Quantum chemical calculations were carried with the Gaussian 03v package using DFT with geometry optimization in the gaseous state of complexes was carried out at the B3LYP level of theory 3-21G (d) basis set [20]. The structural studies were drawn with Avogadro and visualized with Gauss view for optimization. The analysis of frontier molecular orbitals was also performed at the same level of theory. The optimized geometrical parameters (bond lengths, bond angles and dihedral angles), dipole movement, electrophilicity index, wavelength and energy difference of the ground state for the ligand (T9) and its Cu (II) complexes were estimated and similar results were obtained for Ni (II) and Pd (II) complexes.

Cytotoxicity assay

The cytotoxicity of the Schiff base and its metal complexes were evaluated by MTT assay [22] against breast adenocarcinoma cells (MDA-MB231). The cells were pre-incubated at a concentration of 1 × 10^4 cells/well and incubated with L-15 medium containing different concentrations (10, 1, 0.1, 0.01 and 0.001 µM) of compounds for 24 and 48 h at 37 °C. The cell proliferation is based on the ability of the mitochondrial succinate-terazolium reductase system to convert 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) to a blue coloured formazan [25]. The test denotes the survival cells after toxic exposure. Then, 20 µl MTT mixture was added and incubated for next 3 h. Each experiment was done in triplicates and Cisplatin was used as a standard drug. The formazen crystals were dissolved in DMSO and spectrophotometric absorbance was measured using an ELISA microplate reader at 570 nm. Finally, the efficacy of the test compounds was evaluated by determining IC_{50} values by using Graph Pad Prism software (table 3).

Table 3: IC_{50} of tested compounds for antitumor screening against MDA-MB231 cancer cells

Compounds	IC_{50}(µM)*
T6	1.58
T8	1.948
T11	2.325
T14	2.286
T15	2.965
T25	0.469
T31	1.131
T37	0.865
T46	1.272
Standard (Cisplatin)	1.20

*IC_{50}: values indicate the effective concentration of a compound required to achieve 50 % growth inhibition in µg/ml.

RESULTS AND DISCUSSION

Several modified methods for synthesis of novel biologically active molecules including environmental-friendly methods were mentioned in the literature. Among them, the use of ultrasonic waves in organic synthesis came in light recently [26]. In the sonochemistry, due to cavitation very high local temperatures and pressures generated and consequently, products formed. As compared with traditional methods, this technique is more convenient, easily controllable and high producibility. Considering these facts and our interest to develop a new synthetic route, synthesis of substituted thiadiazoles (T1-T4) and their Schiff bases (T5-T16) with various ketones (5-bromoisatin, chalcone, acridone) by ultrasonication/conventional method were accomplished as depicted in Scheme 2 and 3 respectively.

Table 4: Moment of inertia of the studied compounds

Name of the compound	Moment of inertia 1×10^{-45} Kgm^2		
	I_x	I_y	I_z
T1	0.53	4.83	5.26
TC	4.86	42.4	47.1
T9	15.8	59.6	64.3
T30	53.2	76.3	106.3

The structures of the all synthesized compounds were established on the basis of their FTIR and NMR data. Identical TLC and melting points were observed for the product obtained from both the methods. The IR of substituted thiadiazole (1-4) showed characteristic peaks at 3312 and 3245 cm^{-1}, attributed to a primary amine group. Apart from major functional groups observed in the IR spectra of the compounds 5-16 showed a stretching band at 1620-1605 cm^{-1} corresponding to azomethine [27] group. The disappearances of NH_2 and CO (carbonyl) peaks in the IR spectra of 9-12; 13-16 were further supportive of condensation of the amino group of substituted thiadiazole with the carbonyl group of ketone. This was further confirmed by their 1HNMR spectra. The azomethine proton peak was clearly observed [28] in the Schiff bases (5-16) at δ 8.5-7.9 ppm. Other protons peaks were found to be well consistent with the expected structures.

To establish the expected structure of synthesized ligands and their metal complexes, DFT study of the novel synthesized complexes (T1, TC, T9 and T30) were performed to study for (i) comparison of wave numbers (ii) optimized structural geometry (iii) frontier orbital with energy differences (iv) Dipole moment and wavelength. The experimental wavenumbers for these complexes (T1, TC, T9 and T30) are comparable with the computed wave numbers (fig. 2). These wavenumbers exhibit bathochromic and hypsochromic shifts of complexes in functional group regions as shown in fig. 3(a, b). The optimize structure of ligand and its Cu complex corresponding to frontier contours was given in fig. 3(c). There is an increase in dipole moment and moment of inertia (table 4) from T1 to T30 and energy gap is reduced indicating the ability of ease of bonding activity and structure indicates the high donor activity.

Although the IR spectra were recorded in the solid state and DFT-calculated frequencies in gas phase, the proposed relatively simplified model provides a good agreement for the functional group and metal–ligand bonding frequencies in novel compounds. However, the significant variations were observed for the metal complexes indicating the octahedral geometry of the metal complexes due to the involvement of chelation. The responsible spectral properties i.e. dipole movement, electrophilicity index wavelength and energy difference for the formation of the structure due to electron transfer depicted in fig. 4.

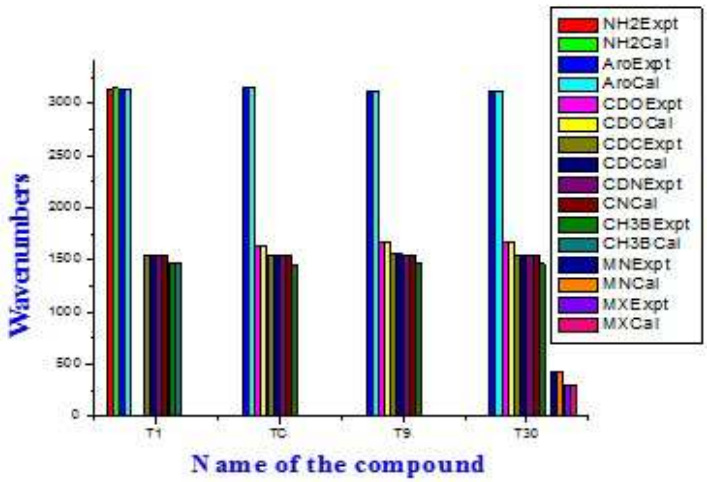


Fig. 2: Experimental and computed wave numbers of the T1, T9, T30 compound

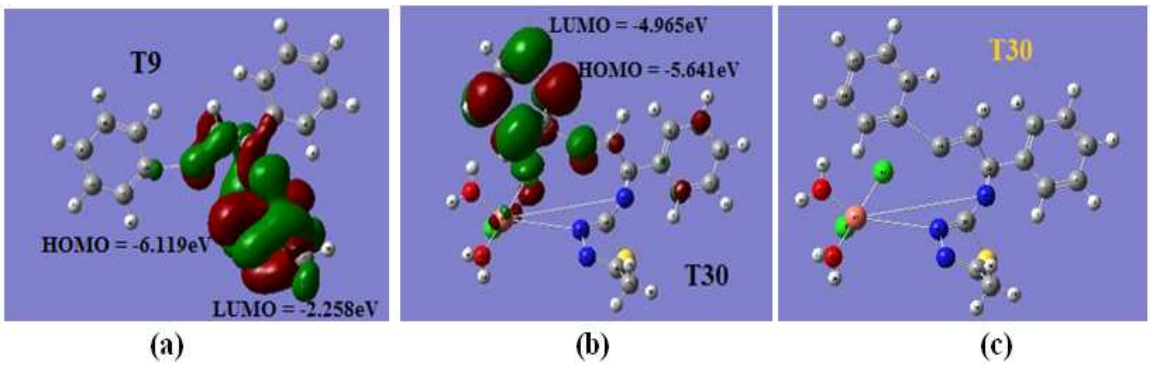


Fig. 3: Frontier contour of studied ligand T9 and its Cu complex (T30) with optimized its structures

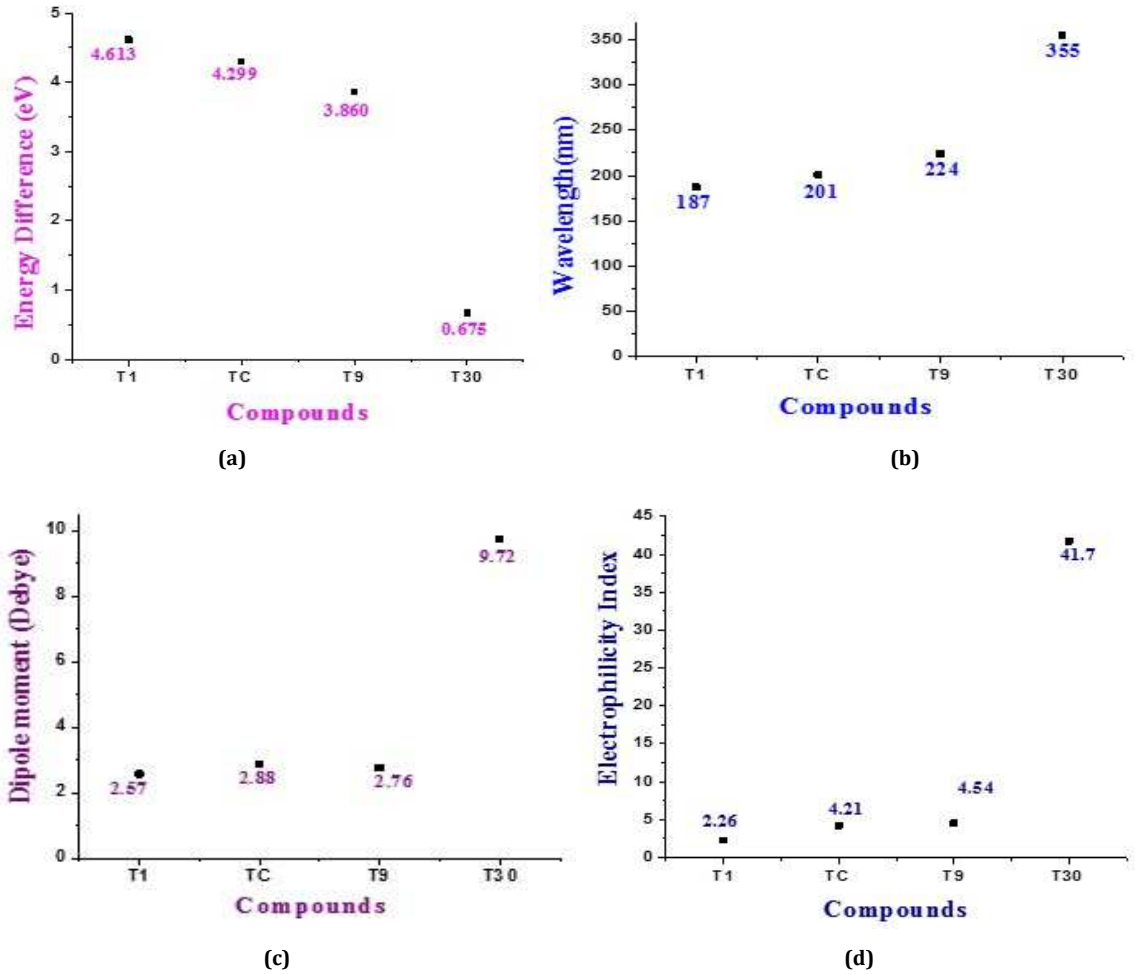


Fig. 4: Computed energy difference, wavelength, dipole moment and electrophilicity index profile of studied complex

Antimicrobial evaluation results of all novel compounds against bacteria and fungi are encouraging. The analysis of Schiff bases and their complexes (T5-T52) revealed that the isatin containing ligands showed significant activity against all bacterial strain. However, chalcone ligands shows better activity than acridone ligands in the case of gram-positive bacteria (BS and SA), while in the case of fungus the followed trend was chalcone> acidone> isatin. Among the *in vitro* antibacterial and antifungal studies Cu (II) and Ni (II) complexes showed better activities then their parent ligands thus advocating that the metal-ligand complexes shows a significant role in developing the lead drug molecule. Designing more polar compounds may overcome solubility problems of synthesized compounds, and might achieve more active compounds. However, Pd (II) complexes were emerged better candidate for antitumor agents [23] with IC_{50} values of 0.469 and 0.865 µM.

CONCLUSION

The present work reports greener approach ultrasonication (US) for the synthesis of thiadiazole analogs along with their metal complexes. It was observed that ultrasonication based method provides a better yield in relatively less amount of time. Moreover, this method (US) is more energy efficient, operationally simple and environmentally benign and hence is a worthwhile addition to the existing methods. All the synthesized compounds were characterized well by routine spectral methods. DFT analysis of few ligands and their metal complexes were also done to establish their expected structure and found consistent to experimental values. On the basis of spectral and DFT analysis, octahedral geometry was ascertained for metal complexes. All compounds were also evaluated for *in vitro* antimicrobial activities and few potential metal complexes with ligands *in vitro* anticancer activities. In general, complexes exhibited higher antimicrobial activity than respective free ligands. Furthermore, the chalcone and isatin containing compounds were found more active than acridone. However, its metal complexes displayed better activity in all the cases. Ni and Cu complexes exhibited better antimicrobial activities, however, Pd complexes as better cytotoxic compounds. We hope that our findings will be helpful in the design and synthesis of more effective but safe anticancer/antimicrobial drugs.

ACKNOWLEDGEMENT

The authors are thankful to the GITAM University for providing necessary facility to do this work and University Grants Commission (UGC, Government of India) for providing financial assistance [F. No. 42-239/2013 (SR)].

AUTHOR CONTRIBUTION

A. J. conceived the study and designed the experiments. P. B. performed the experimental synthesis. Computational experiments along and analysis were carried out by SD and CH. R. K. All the authors made contributions to the writing of the manuscript and approved the final version.

CONFLICT OF INTERESTS

Declared none

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How to cite this article

- Priyanka Bhatt, S Deepthi, Ch Ravi Shankar Kumar, Anjali Jha. Facile synthesis, spectral studies, dft calculations and biological activities of novel NI(II), CU(II), and PD(II) complexes of thiadiazole analogs. Int J Pharm Pharm Sci 2017;9(4):185-192.