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FULL PAPER

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Synthesis, spectral analysis and *in vitro* cytotoxicity of diorganotin (IV) complexes derived from indole-3-butyric hydrazide

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A series (**1–20**) of diorganotin (IV) complexes with general formula R_2SnL were formed by the reaction of R_2SnCl_2 (where R = Me, Et, Bu and Ph) with Schiff base ligands ($\mathbf{H_2L^{1-4}}$) derived from the reaction of indole-3-butyric hydrazide with the salicylaldehyde and its derivatives. The structure elucidation of compounds were done by using UV–Vis, FT-IR, NMR (^1H, ^{13}C, ^{119}Sn), Mass spectrometry and thermal gravimetric analysis. Spectroscopic evidences suggested tridentate nature (ONO) of Schiff base ligands and coordinated to the dialkyl/diaryltin (IV) moieties through nitrogen and oxygen donor sites giving pentacoordinated geometry to complexes. The compounds were tested for the antimicrobial activity against bacterial and fungal strains which showed promising biological activity with compound **20** (Ph_2SnL^4) as most active against microbes. The *in silico* study of the compounds was carried and observed that the compounds are used as orally active drugs and promote the formation of different hydrazide based drugs. The synthesized compounds were tested against human carcinoma cell lines namely A549, MCF7 and one normal cell line IMR 90 using MTT assay. The diethyl and dibutyltin complexes of Schiff bases displayed good cytotoxic activities. Compound **3** (H_2L^3) and **10** (Et_2SnL^2) were most potent against cancer cell lines with lowest IC_{50} values and 7–8 times less toxic against the normal cell line.

KEYWORDS
anticancer, antimicrobial, hydrazides, indole, pentacoordianted

1 | INTRODUCTION

Cancer is an imminent "human disaster" which causes human mortality and morbidity. It is the unconditional growth of tissues with manifold etiologies and constant combination of genetics or epigenetic alterations.[1,2] The study of cancer treatments hold promises for budding effective cancer therapies. From the last few years, medicinal chemistry has gained attention due to momentous achievements in cancer therapeutics and diagnostics.[3] The predominant treatment for cancer include chemotherapy, surgery, radiation, immunotherapy etc. but the fundamental treatment for cancer is based on chemotherapy that include the use of different natural and synthetic chemical entities.[4–7] In this context, Pt (II) metallodrugs are recognized anticancer drugs which attained world-wide clinical approval but these drugs have some limitations including high toxicity, different side effects, narrow range of activity and resistance problem.[8,9] So to improve the clinical efficacy and undesirable side effects,

a huge number of organometallic compounds have been assessed for anticancer activity.

Organotin (IV) complexes have established themselves as an effective candidates in oncology with amazingly good IC_{50} values.[10–14] Earlier, organotin (IV) complexes received appreciable attention due to their potent biological activities, industrial, catalytic and agriculture applications. Recently, a large number of organotins have been synthesized and tested for anticancer activities. The organotin moiety is decisive for cytotoxicity, DNA cleavage, antimicrobial, anti-inflammatory, analgesic, antioxidant, antiHIV etc.[15–20]

The ligand scaffolds also play a key role in the chemotherapy. Schiff base ligands having hydrazide groups are considered as "privileged ligands" and used widely due to their easy synthetic procedure, good solubility and their novel structural features.[21–24] Schiff base ligands with indole hydrazide unit have proven to possess good biological application like antimicrobial, anticonvulsant, antihypertensive, antiplatelet aggregation, and HIV-1 reverse transcriptase inhibitor activities.[25–34] Indoles are widely distributed heterocyclic compounds having medicinal importance e.g.- Tryptophan, a natural occurring essential amino acid which is used as precursor for auxin (indole-3-acetic acid-IAA), a plant regulating hormone and used as secondary metabolites, vincristine and vindesine, natural indole alkaloids is used in treatment of leukemia and as antitumor agent, brassinin which is used against microorganism and mitomycin is natural antibiotic used as anticancer and DNA cross linking agents.[35–39]

Keeping in view the medicinal and biological activities of indole hydrazides and the impending application of organotins, here we join both the moieties in the search for designing biologically active candidates that could belligerently work against microbes and have some potential application in pharmacology. In the present study, we have synthesized diorganotin (IV) complexes of indole-3-butyric hydrazide. Characterization the compounds were done by IR, ^{1}H NMR, ^{13}C NMR, ^{119}Sn NMR, Mass, UV–vis and TGA methods. The *in vitro* antimicrobial activity of compounds was investigated with four bacterial and two fungal cultures. Antitumor activity of synthesized compounds against two human cancer cell lines (A549 and MCF7) and one normal human cell line (IMR90) is evaluated and discussed.

2 | EXPERIMENTAL

2.1 | Material and instrumentation

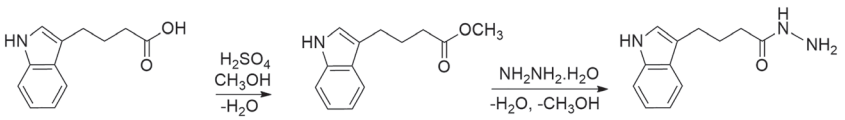
All the chemical reaction was carried out in anhydrous condition. The reagents - diorganotindichloride, indole-3-butyric acid, salicylaldehyde, 5-nitrosalicylaldehyde, 4-N,N-diethylsalicylaldehyde and 3,5-dibromosalicylaldehyde were commercially available from Sigma Aldrich and were used without purification. The solvents obtained were dried according to the literature procedure.[40] The melting points were determined by capillary method using electrical heating coil apparatus. Shimadzu IR affinity-I 8000 FT-IR spectrophotometer was used for recording the IR spectra using KBr pellets in the range of 400–4,000 cm^{-1}. ^{1}H, ^{13}C and ^{119}Sn NMR were recorded on a Bruker Avance II 400 MHz Spectrometer by using $CDCl_3$ and DMSO as solvent with tetramethylsilane and tetramethyltin as standard. The value of chemical shifts (δ) are reported in ppm and coupling constants (J) values in Hz and the multiplicities of signals are given as s = singlet, d = doublet, t = triplet, m = multiplet. The chemical shift value for the solvents $CDCl_3$ and DMSO in ^{1}H NMR appeared at δ 7.25 and δ 3.0, 2.5 ppm and ^{13}C NMR were present at δ 77.0 and 40.0 ppm. Absorption spectra were measured in DMSO on UV- Vis–NIR Varian Cary – 5,000 spectrometer at room temperature. The electrical conductance was recorded in conductivity bridge type model- 306 Systronic at room temperature by using DMF as solvent. Mass spectra were recorded in methanol and DMSO solvent by using SCIEX-QTOF instrument. Thermal gravimetric analysis (TGA) was measured by using EXSTAR TG/DTG 6300 at a heating rate of 10 °C/min under high purity nitrogen atmosphere.

2.2 | Synthesis of indole-3-butyric hydrazide precursor

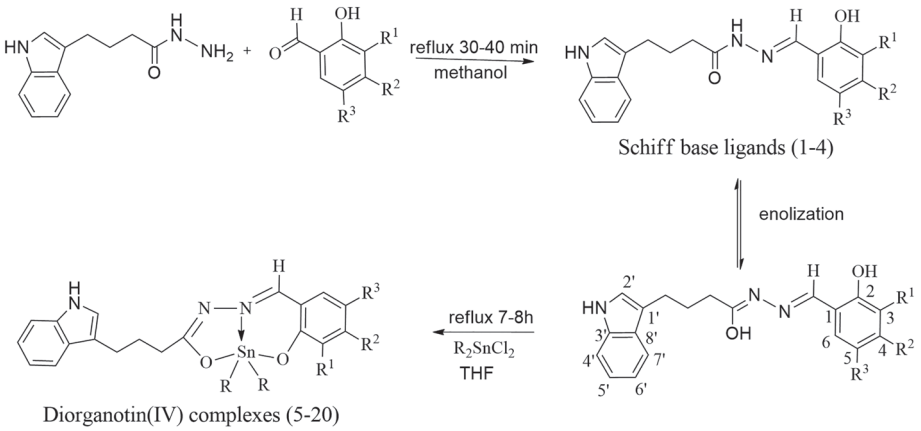
The methanolic solution (35 ml) of indole-3-butyric acid (5 g) was refluxed with 5 ml of concentrated sulphuric acid for 5 hr by using the dean stark apparatus to remove excess of water obtained during the reaction. The ester formed was extracted by using the dichloromethane and then refluxed with the methanolic solution of hydrazine hydrated for 2 hr, which resulted in the formation of indole-3-butyric hydrazide (Scheme 1). The reddish black color hydrazide formed was recrystallized from hot methanol to get the pure product.

Synthesis of Schiff base ligands (1–4): The 35 ml of hot methanolic solution of indole-3-butyric hydrazide (0.651 g, 3 mmol) was refluxed with methanolic solution of salicyaldehyde (0.3 ml, 3 mmol) $\mathbf{H_2L^1}$/5-nitrosalicaldehyde (0.501 g, 3 mmol) $\mathbf{H_2L^2}$/4-(N,N diethyl)salicaldehyde (0.579 g, 3 mmol) $\mathbf{H_2L^3}$/3,5-dibromosalicaldehyde (0.83 g, 3 mmol) $\mathbf{H_2L^4}$ (Scheme 2). The colored product was obtained after refluxing the above solution for 30–40 min. The product

SCHEME 1 Synthesis of Indole-3-butyric hydrazide from indole-3-butyric acid



SCHEME 2 Synthesis of hydrazide Schiff base ligands (**1–4**) and their diorganotin (IV) complexes (**5–20**)



	R^1	R^2	R^3
(1) H_2L^1 =	H	H	H
(2) H_2L^2 =	H	H	NO_2
(3) H_2L^3 =	H	$N(C_2H_5)_2$	H
(4) H_2L^4 =	Br	H	Br

(5)	R^1 = H	R^2 = H	R^3 = H	R= Me	(13)	R^1 = H	R^2 = $N(C_2H_5)_2$	R^3 = H	R= Me
(6)	R^1 = H	R^2 = H	R^3 = H	R= Et	(14)	R^1 = H	R^2 = $N(C_2H_5)_2$	R^3 = H	R= Et
(7)	R^1 = H	R^2 = H	R^3 = H	R= Bu	(15)	R^1 = H	R^2 = $N(C_2H_5)_2$	R^3 = H	R= Bu
(8)	R^1 = H	R^2 = H	R^3 = H	R= Ph	(16)	R^1 = H	R^2 = $N(C_2H_5)_2$	R^3 = H	R= Ph
(9)	R^1 = H	R^2 = H	R^3 = NO_2	R= Me	(17)	R^1 = Br	R^2 = H	R^3 = Br	R= Me
(10)	R^1 = H	R^2 = H	R^3 = NO_2	R= Et	(18)	R^1 = Br	R^2 = H	R^3 = Br	R= Et
(11)	R^1 = H	R^2 = H	R^3 = NO_2	R= Bu	(19)	R^1 = Br	R^2 = H	R^3 = Br	R= Bu
(12)	R^1 = H	R^2 = H	R^3 = NO_2	R= Ph	(20)	R^1 = Br	R^2 = H	R^3 = Br	R= Ph

were recrystallised from chloroform and methanol to obtain the pure ligands.

[1] N′-(2-hydroxybenzylidene)-4-(1H-indole-3-yl) butanehydrazide, H_2L^1 - Yield: 91%, yellow solid; M.p.: 170-174 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 13.05, MS: m/z (M^+) Cacld. for $C_{19}H_{19}N_3O_2$: 321.14; found: 322.15 $(M + H)^+$. ^1H NMR [400 MHz, $CDCl_3$ δ (ppm)]: 11.59 (s, 1H, N-H), 11.22 (s, 1H, N-H), 10.78 (s, 1H, O-H) 8.33 (s, 1H,- N=C-H), 7.54–7.47 (3H, m, $C_{3,4,4'}$-Ar-H), 7.34–7.32 (1H, d, $C_{7'}$-Ar-H), 7.13–7.12 (1H, d, $C_{2'}$-Ar-H), 7.08–7.04 (1H, m, $C_{6'}$-Ar-H), 6.99–6.95 (1H, t, $C_{5'}$-Ar-H), 6.91–6.89 (2H, d, $C_{5,6}$-Ar-H, $^3J_{H,H}$ = 7.84 Hz), 2.77–2.71 (3H, m), 2.67–2.63 (1H, t, $^3J_{H,H}$ = 7.46 Hz), 2.30–2.27 (2H, t, $^3J_{H,H}$ = 7.44 Hz): ^{13}C NMR [100 MHz, $CDCl_3$, δ (ppm)]: 174.22 (C=O), 168.53 (HC=N), 157.30 (C-OH), 34.16, 26.27, 25.62 (aliphatic carbon). FT-IR (ν, cm^{-1}): 3390 (N-H, indole ring), 3,287 (N-H), 3,065 (O-H, br), 1,708 (C=O), 1,609 (C=N, m), 1,260 (C-OH).

[2] N′-(2-hydroxy-5-nitrobenzylidene)-4-(1H-indole-3-yl)butanehydrazide, H_2L^2 - Yield: 93%, yellow solid; M. p.: 172-175°C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 13.65, MS: m/z (M^+) Cacld. for $C_{19}H_{18}N_4O_4$: 366.13; found: 367.15 $(M + H)^+$. ^1H NMR [400 MHz, $CDCl_3$ δ (ppm)]: 12.06 (s, 1H, N-H), 11.98 (s, 1H, N-H), 10.88 (s, 1H, O-H) 9.39 (s, 1H,- N=C-H), 7.80–7.81 (1H, d, C_4-Ar-H, $^3J_{H,H}$ = 7.71 Hz), 7.77–7.76 (1H, d, C_6-Ar-H, $^4J_{H,H}$ = 2.24 Hz), 7.63–7.60 (1H, d, C_3-Ar-H, $^3J_{H,H}$ = 7.7 Hz), 7.53–7.51 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.67 Hz), 7.34–7.32 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.07 Hz), 7.14–7.13 (1H, d, $C_{2'}$-Ar-H, $^4J_{H,H}$ = 2.34 Hz), 7.08–7.04 (1H, t, $C_{6'}$-Ar-H, $^3J_{H,H}$ = 6.98 Hz), 6.99–6.95 (1H, t, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 6.98 Hz), 2.75–2.71 (2H, m), 2.67–2.64 (2H, t, $^3J_{H,H}$ = 7.47 Hz), 2.50–2.47 (2H, t, $^3J_{H,H}$ = 7.50 Hz): ^{13}C NMR [100 MHz, $CDCl_3$, δ (ppm)]: 174.40 (C=O), 168.91 (HC=N), 157.75 (C-OH), 34.19, 26.18, 25.64 (aliphatic carbon). FT-IR (ν, cm^{-1}): 3394 (N-H, indole ring), 3,292 (N-H), 3,062 (O-H, br), 1,703 (C=O), 1,610 (C=N, m), 1,265 (C-OH).

[3] N′-(5-diethylamino)-2-hydroxybenzylidene-4-(1H-indole-3-yl)butanehydrazide, H_2L^3 - Yield: 89%, red solid; M.p.: 167-169 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in

DMF: 12.48, MS: m/z (M^+) Cacld. for $C_{23}H_{28}N_4O_2$: 393.22; found: 394.23 $(M + H)^+$. ^{1}H NMR [400 MHz, $CDCl_3$ δ (ppm)]: 11.36 (s, 1H, N-H), 11.27 (s, 1H, N-H), 10.78 (s, 1H, O-H) 8.11 (s, 1H,- N=C-H), 7.53–7.51 (d, 1H, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.76 Hz), 7.34–7.32 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.04 Hz), 7.15–7.12 (2H, m, $C_{6,2'}$-Ar-H), 7.08–7.04 (1H, t, $C_{6'}$-Ar-H, $^3J_{H,H}$ = 8.04 Hz), 6.99–6.95 (1H, m, $C_{5'}$-Ar-H), 6.25–6.22 (1H, dd, C_5-Ar-H, J = 8.76, 2.4 Hz), 6.09–6.091 (1H, d, C_3-Ar-H, $^4J_{H,H}$ = 2.2 Hz), 2.74–2.70 (2H, m), 2.58–2.55 (1H, t, $^3J_{H,H}$ = 7.44 Hz), 2.26–2.22 (2H, t, $^3J_{H,H}$ = 7.44 Hz), 1.98–1.92 (2H, m), 1.11–1.07 (9H, t, $^3J_{H,H}$ = 7 Hz): ^{13}C NMR [100 MHz, $CDCl_3$, δ (ppm)]: 172.13 (C=O), 168.14 (HC=N), 159.96 (C-OH), 44.22, 44.27, 97.94 ($N(C_2H_5)_2$), 34.16, 26.33, 24.79 (aliphatic carbon). FT-IR (ν, cm^{-1}): 3382 (N-H, indole ring), 3,205 (N-H), 3,054 (O-H, br), 1,695 (C=O), 1,614 (C=N, m), 1,253 (C-OH).

[4] N′-(3,5-dibromo-2-hydroxybenzylidene)-4-(1H-indole-3-yl)butanehydrazide, H_2L^4 - Yield: 93%, yellow solid; M.p.: 172-174°C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 14.01, MS: m/z (M^+) Cacld. for $C_{19}H_{17}Br_2N_3O_2$: 476.96; found: 477.98 $(M + H)^+$.^{1}H NMR [400 MHz, $CDCl_3$ δ (ppm)]: 12.65 (s, 1H, N-H), 12.00 (s, 1H, N-H), 10.79 (s, 1H, O-H) 8.25 (s, 1H,- N=C-H), 7.808–7.803 (1H, d, C_4-Ar-H, $^4J_{H,H}$ = 2.36 Hz), 7.77–7.76 (1H, d, C_6-Ar-H, $^4J_{H,H}$ = 2.36 Hz), 7.53–7.51 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.53 Hz), 7.34–7.32 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.04 Hz), 7.14–7.13 (1H, d, $C_{2'}$-Ar-H, $^4J_{H,H}$ = 2.12 Hz), 7.08–7.04 (1H, t, $C_{6'}$-Ar-H, $^3J_{H,H}$ = 7 Hz), 6.99–6.95 (1H, t, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 7 Hz), 2.75–2.71 (3H, t, $^3J_{H,H}$ = 7.52 Hz), 2.34–2.31 (3H, t, $^3J_{H,H}$ = 7.52 Hz): ^{13}C NMR [100 MHz, $CDCl_3$, δ (ppm)]: 176.42 (C=O), 169.35 (HC=N), 159.87 (C-OH), 34.02, 26.04, 24.71 (aliphatic carbon). FT-IR (ν, cm^{-1}): 3403 (N-H, indole ring), 3,308 (N-H), 3,087 (O-H, br), 1,724 (C=O), 1,617(C=N, m), 1,281 (C-OH).

2.3 | Synthesis of diorganotin (IV) complexes (5–20)

The Schiff base ligand (0.963 g, 3 mmol) **H_2L^1**/ (1.098 g, 3 mmol) **H_2L^2**/ (1.176 g, 3 mmol) **H_2L^3**/ (1.430 g, 3 mmol) **H_2L^4** was dissolved in tetrahydrofuran solvent (20 ml) and stirred for 20–30 min by adding ethylamine (0.3 ml) as base. The above solution was then refluxed with methyl (0.659 g, 3 mmol), ethyl (0.743 g, 3 mmol), butyl (0.911 g, 3 mmol) and phenyl (1.031 g, 3 mmol) derivatives of diorganotindichloride (IV) for 7–8 h where white colored Et_3NHCl salt was filtered and solvent was evaporated on the rotary evaporator to get the purified product (Scheme 2). The different colored solid products isolated were washed and recrystallized with dried hexane.

[5] Me_2SnL^1: Yield: 78%, yellow solid; M.p.: 160-162 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 12.33, MS: m/z (M^+) Cacld. for $C_{21}H_{23}N_3O_2Sn$: 469.00; found: 470.01 $(M + H)^+$. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 11.99 (s, 1H, N-H), 8.60 (s, 1H,- N=C-H), 7.65–7.63 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.84 Hz), 7.38–7.31 (2H, m, $C_{3,4}$-Ar-H), 7.22–7.18 (1H, m, $C_{7'}$-Ar-H), 7.16–7.13 (1H, m, $C_{2'}$-Ar-H), 7.04–7.03 (1H, d, $C_{6'}$-Ar-H, $^4J_{H,H}$ = 1.4 Hz), 6.93–6.91 (1H, m, $C_{5,6}$-Ar-H), 6.77–6.74 (1H, m, $C_{5'}$-Ar-H), 2.86–2.83 (2H, t, $^3J_{H,H}$ = 7.6 Hz), 2.43–2.40 (2H, t, $^3J_{H,H}$ = 7.44 Hz), 2.12–2.05 (2H, m), 0.79 (s, 6H, Me). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 169.03 (HC=N), 166.27 (N=C-OH), 159.86 (C-OH), 34.33, 26.23, 25.67 (aliphatic carbon), 8.51 (Me). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −130.43. FT-IR (ν, cm^{-1}): 3392 (N-H, indole ring, br), 1,601 (C=N, m), 1,240 (C-O), 712 (Sn-O), 526 (Sn-N), 423 (Sn-C).

[6] Et_2SnL^1: Yield: 75%, yellow solid; M.p.: 161-163 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 12.06, MS: m/z (M^+) Cacld. for $C_{23}H_{27}N_3O_2Sn$: 497.11; found: 598.13 $(M + H)^+$. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 11.95 (s, 1H, N-H), 8.62 (s, 1H,- N=C-H), 7.63–7.61 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.84 Hz), 7.38–7.31 (2H, m, $C_{3,4}$-Ar-H), 7.22–7.18 (1H, m, $C_{7'}$-Ar-H), 7.16–7.13 (1H, m, $C_{2'}$-Ar-H), 7.03–7.02 (1H, d, $C_{6'}$-Ar-H, $^4J_{H,H}$ = 1.4 Hz), 6.97–6.95 (1H, m, $C_{5,6}$-Ar-H), 6.89–6.85 (1H, m, $C_{5'}$-Ar-H), 2.86–2.83 (2H, t, $^3J_{H,H}$ = 7.6 Hz), 2.45–2.42 (2H, t, $^3J_{H,H}$ = 7.34 Hz), 2.15–2.10 (2H, m), 1.23–1.27 (m, 4H), 0.83–0.85 (t, 6H, $^3J_{H,H}$ = 7.56 Hz). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 169.37 (HC=N), 166.33 (N=C-OH), 159.91 (C-OH), 35.22, 27.27, 26.54 (aliphatic carbon), 23.34 (Et-C), 7.98 ((Et-C). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −150.78. FT-IR (ν, cm^{-1}): 3393 (N-H, indole ring, br), 1,598 (C=N, m), 1,241 (C-O), 714 (Sn-O), 524 (Sn-N), 426 (Sn-C).

[7] Bu_2SnL^1: Yield: 65%, yellow solid; M.p.: 170.172 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 12.74, MS: m/z (M^+) Cacld. for $C_{27}H_{35}N_3O_2Sn$: 552.17; found: 553.19 $(M + H)^+$. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 11.98 (s, 1H, N-H), 8.60 (s, 1H,- N=C-H), 7.65–7.63 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.84 Hz), 7.36–7.30 (2H, m, $C_{3,4}$-Ar-H), 7.24–7.19 (1H, m, $C_{7'}$-Ar-H), 7.15–7.12 (1H, m, $C_{2'}$-Ar-H), 7.10–7.09 (1H, d, $C_{6'}$-Ar-H, $^4J_{H,H}$ = 1.4 Hz), 6.97–6.95 (1H, m, $C_{5,6}$-Ar-H), 6.89–6.85 (1H, m, $C_{5'}$-Ar-H), 2.85–2.81 (2H, t, $^3J_{H,H}$ = 7.6 Hz), 2.45–2.42 (2H, t, $^3J_{H,H}$ = 7.34 Hz), 2.15–2.10 (2H, m), 1.76–1.71 (m, 4H), 1.39–1.34 (m, 4H), 1.21–1.24 (m, 4H), 0.91–0.88 (6H, t, $^3J_{H,H}$ = 7.83 Hz). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 169.56 (HC=N), 166.54 (N=C-OH), 159.34 (C-OH), 35.21, 28.23, 26.42 (aliphatic carbon), 27.72 (Bu-C), 22.19 (Bu-C), 8.31 (Bu-C). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −214.49. FT-IR (ν, cm^{-1}): 3392 (N-H, indole ring, br), 1,600 (C=N, m), 1,244 (C-O), 709 (Sn-O), 526 (Sn-N), 418 (Sn-C).

[8] Ph_2SnL^1: Yield: 65%, yellow solid; M.p.: 169-171 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 13, MS:

m/z (M^+) Cacld. for $C_{31}H_{27}N_3O_2Sn$: 593.11; found: 594.13 $(M + H)^+$. ^1H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 11.93 (s, 1H, N-H), 8.62 (s, 1H,- N=C-H), 7.69–7.66 (3H, m, $C_{3,4,4'}$-Ar-H), 7.57–7.54 (2H, m, $C_{2',7'}$-Ar-H), 7.45–7.41 (8H, Sn-Ar-H, m), 7.30–7.26 (2H, m, $C_{5,6}$-Ar-H), 7.19–7.17 (2H, m, $C_{6',5'}$-Ar-H, $^4J_{H,H}$ = 1.4 Hz), 7.09–7.07 (2H, m Sn-Ar-H), 2.86–2.83 (2H, t, $^3J_{H,H}$ = 7.6 Hz), 2.43–2.40 (2H, t, $^3J_{H,H}$ = 7.44 Hz), 2.12–2.05 (2H, m). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 169.34 (HC=N), 166.12 (N=C-OH), 159.46 (C-OH), 115–110 (Sn-aromatic carbon), 35.34, 28.37, 26.42 (aliphatic carbon). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −312.04. FT-IR (ν, cm^{-1}): 3394 (N-H, indole ring, br), 1,602 (C=N, m), 1,240 (C-O), 711 (Sn-O), 520 (Sn-N), 419 (Sn-C).

[9] Me_2SnL^2: Yield: 70%, yellow solid; M.p.: 161.159 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 11.48, MS: m/z (M^+) Cacld. for $C_{21}H_{22}N_4O_4Sn$: 514.06; found: 515.09 $(M + H)^+$. ^1H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 12.26 (s, 1H, N-H), 9.45 (s, 1H,- N=C-H), 7.95–7.94 (1H, dd, C_4-Ar-H, $^3J_{H,H}$ = 7.83, 1.96 Hz), 7.86–7.85 (1H, d, C_6-Ar-H, $^4J_{H,H}$ = 1.96 Hz), 7.70–7.72 (1H, d, C_3-Ar-H, $^3J_{H,H}$ = 7.8 Hz), 7.62–7.60 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.14 Hz), 7.44–7.42 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.14 Hz), 7.20–7.21 (1H, d, $C_{2'}$-Ar-H, $^4J_{H,H}$ = 2.10 Hz), 7.10–7.13 (1H, t, $C_{6'}$-Ar-H, $^3J_{H,H}$ = 8.13 Hz), 7.01–6.98 (1H, t, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 7.16 Hz), 2.80–2.77 (2H, m), 2.71–2.69 (2H, t, $^3J_{H,H}$ = 7.84 Hz), 2.53–2.51 (2H, t, $^3J_{H,H}$ = 7.81 Hz), 0.87 (s, 6H, Me). ^{13}C NMR [100 MHz, $CDCl_3$, δ (ppm)]: 170.34 (HC=N), 166.23 (N=C-OH), 160.92 (C-OH), 34.26, 30.33, 26.81, (aliphatic carbon), 8.61 (Sn-C). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −129.81. FT-IR (ν, cm^{-1}): 3396 (N-H, indole ring, br), 1,606 (C=N, m), 1,238 (C-O), 709 (Sn-O), 528 (Sn-N), 426 (Sn-C).

[10] Et_2SnL^2: Yield: 68%, yellow solid; M.p.: 162-159 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 12.13. MS: m/z (M^+) Cacld. for $C_{23}H_{26}N_4O_4Sn$: 542.09; found: 543.11 $(M + H)^+$. ^1H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 12.23 (s, 1H, N-H), 9.48 (s, 1H,- N=C-H), 7.95–7.94 (1H, dd, C_4-Ar-H, $^3J_{H,H}$, $^4J_{H,H}$ = 7.83, 1.96 Hz), 7.86–7.85 (1H, d, C_6-Ar-H, $^4J_{H,H}$ = 1.96 Hz), 7.71–7.73 (1H, d, C_3-Ar-H, $^3J_{H,H}$ = 7.8 Hz), 7.61–7.59 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.16 Hz), 7.43–7.40 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.04 Hz), 7.23–7.24 (1H, d, $C_{2'}$-Ar-H, $^4J_{H,H}$ = 2.2 Hz), 7.11–7.14 (1H, t, $C_{6'}$-Ar-H, $^3J_{H,H}$ = 8.03 Hz), 7.03–6.98 (1H, t, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 7.16 Hz), 2.83–2.79 (2H, m), 2.74–2.70 (2H, t, $^3J_{H,H}$ = 7.76 Hz), 2.62–2.58 (2H, t, $^3J_{H,H}$ = 7.73 Hz), 1.58–1.54 (6H, t, $^3J_{H,H}$ = 7.31 Hz), 0.84–0.80 (m, 4H). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 170.21 (HC=N), 166.68 (N=C-OH), 160.84 (C-OH), 34.26, 30.33, 26.80, (aliphatic carbon), 26.11 (Et-C), 8.61 (Et-C). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: 159.51. FT-IR (ν, cm^{-1}): 3397 (N-H, indole ring, br), 1,604 (C=N, m), 1,234 (C-O), 705 (Sn-O), 525 (Sn-N), 420 (Sn-C).

[11] Bu_2SnL^2: Yield: 64%, yellow solid; M.p.: 160-162 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 13.79, MS: m/z (M^+) Cacld. for $C_{27}H_{34}N_4O_4Sn$: 598.16; found: 599.17 $(M + H)^+$. ^1H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 12.47 (s, 1H, N-H), 9.51 (s, 1H,- N=C-H), 7.99–8.02 (1H, dd, C_4-Ar-H, $^3J_{H,H}$, $^4J_{H,H}$ = 7.62, 2.34 Hz), 7.89–7.90 (1H, d, C_6-Ar-H, $^4J_{H,H}$ = 2.2 Hz), 7.76–7.78 (1H, d, C_3-Ar-H, $^3J_{H,H}$ = 7.62 Hz), 7.63–7.61 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.52 Hz), 7.52–7.50 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.34 Hz), 7.37–7.36 (1H, d, $C_{2'}$-Ar-H, $^4J_{H,H}$ = 1.93 Hz), 7.17–7.14 (1H, t, $C_{6'}$-Ar-H, $^3J_{H,H}$ = 8.31 Hz), 7.04–7.01 (1H, t, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 7.52 Hz), 3.11–3.07 (4H, m), 2.82–2.76 (2H, m), 1.50–1.47 (10H,m), 1.10–1.07 (4H, m), 0.83–0.77 (4H, m). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 170.34 (HC=N), 166.65 (N=C-OH), 161.02 (C-OH), 37.26, 32.51, 28.17 (aliphatic carbon), 27.98 (Bu-C), 25.18 (Bu-C), 20.18 (Bu-C), 9.23 (Bu-C). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: -242.28. FT-IR (ν, cm^{-1}): 3396 (N-H, indole ring, br), 1,603 (C=N, m), 1,232 (C-O), 711 (Sn-O), 520 (Sn-N), 422 (Sn-C).

[12] Ph_2SnL^2: Yield: 65%, yellow solid; M.p.: 165-168 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 14.04, MS: m/z (M^+) Cacld. for $C_{31}H_{26}N_4O_4Sn$: 638.09; found: 639.11 $(M + H)^+$. ^1H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 12.43 (s, 1H, N-H), 9.46 (s, 1H,- N=C-H), 7.95–7.89 (3H, m, $C_{3,4,6}$-Ar-H, $^3J_{H,H}$, $^4J_{H,H}$ = 7.62, 2.34 Hz), 7.71–7.69 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.6 Hz), 7.51–7.49 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.09 Hz), 7.34–7.33 (1H, d, $C_{2'}$-Ar-H, $^4J_{H,H}$ = 2.2 Hz), 7.18–7.16 (1H, t, $C_{6'}$-Ar-H, $^3J_{H,H}$ = 8.07 Hz), 7.03–7.00 (1H, t, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 7.6 Hz), 6.95–6.92 (8H, m), 6.84–6.81 (2H, m), 2.83–2.81 (4H, m), 1.94–1.91 (2H, m). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 170.68 (HC=N), 165.85 (N=C-OH), 160.38 (C-OH), 112–108 (Sn-Ph-C), 35.18, 32.97, 26.81 (aliphatic carbon). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −315. FT-IR (ν, cm^{-1}): 3396 (N-H, indole ring, br), 1,601 (C=N, m), 1,235 (C-O), 709 (Sn-O), 521 (Sn-N), 424 (Sn-C).

[13] Me_2SnL^3: Yield: 78%, reddish black solid; M.p.: 160-162 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 12.79, MS: m/z (M^+) Cacld. for $C_{25}H_{32}N_4O_2Sn$: 540.15; found: 541.16 $(M + H)^+$.^1H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 12.03 (s, 1H, N-H), 8.36 (s, 1H,- N=C-H), 7.65–7.63 (d, 1H, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.8 Hz), 7.38–7.36 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.00 Hz), 7.21–7.18 (1H, m, $C_{2'}$-Ar-H), 7.14–7.10 (1H, m, C_6 –Ar-H), 7.03 (1H, m, $C_{6'}$-Ar-H), 6.95–6.93 (1H, d, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 8.8 Hz), 6.169–6.163 (1H, d, C_5-Ar-H, $^4J_{H,H}$ = 2.2 Hz), 6.147–6.141 (1H, d, C_3-Ar-H, $^4J_{H,H}$ = 2.2 Hz), 3.41–3.37 (4H, q, $^3J_{H,H}$ = 7 Hz), 3.15–3.10 (2H, m), 2.85–2.81 (2H, m), 2.40–2.36 (2H, m), 1.22–1.18 (6H, m), 0.75 (s, 6H, Me).

^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 170.64 (HC=N), 167.21(N=C-OH), 159.84 (C-OH), 98.94, 45.80, 44.37 ($N(C_2H_5)_2$), 34.38, 31.36, 27.36 (aliphatic carbon), 7.98 (Me). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −135.02. FT-IR (ν, cm^{-1}): 3384 (N-H, indole ring, br), 1,610 (C=N, m), 1,248 (C-O), 697 (Sn-O), 510 (Sn-N), 418 (Sn-C).

[14] Et_2SnL^3: Yield: 73%, black solid; M.p.: 164-166 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 12.53, MS: m/z (M^+) Cacld. for $C_{27}H_{36}N_4O_2Sn$: 568.18; found: 569.19 $(M + H)^+$. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 11.88 (s, 1H, N-H), 8.38 (s, 1H,- N=C-H), 7.64–7.62 (d, 1H, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.6 Hz), 7.38–7.36 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.00 Hz), 7.25–7.20 (1H, m, $C_{2'}$-Ar-H), 7.12–7.08 (1H, m, C_6 –Ar-H), 7.02 (1H, m, $C_{6'}$-Ar-H), 6.95–6.93 (1H, d, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 8.8 Hz), 6.17–6.16 (1H, d, C_5-Ar-H, $^4J_{H,H}$ = 2.2 Hz), 6.15–6.14 (1H, d, C_3-Ar-H, $^4J_{H,H}$ = 2.2 Hz), 3.38–3.35 (4H, q, $^3J_{H,H}$ = 7.32 Hz), 3.22–3.18 (2H, m), 2.73–2.67 (2H, m), 2.40–2.36 (2H, m), 1.34–1.28 (6H, m), 1.18–1.13 (6H, t, $^3J_{H,H}$ = 7.68 Hz), 0.80–0.76 (4H, m). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 170.91 (HC=N), 168.41(N=C-OH), 159.83 (C-OH), 99.03, 45.91, 44.63 ($N(C_2H_5)_2$, 37.28, 33.59, 28.95 (aliphatic carbon), 24.19 (Et-C), 8.37 (Et-C). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −162.73. FT-IR (ν, cm^{-1}): 3385 (N-H, indole ring, br), 1,612 (C=N, m), 1,243 (C-O), 691 (Sn-O), 512 (Sn-N), 419 (Sn-C).

[15] Bu_2SnL^3: Yield: 63%, red solid; M.p.: 165-167 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 13, MS: m/z (M^+) Cacld. for $C_{31}H_{44}N_4O_2Sn$: 624.24; found: 625.26 $(M + H)^+$. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 11.72 (s, 1H, N-H), 8.37 (s, 1H,- N=C-H), 7.65–7.64 (d, 1H, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.6 Hz), 7.38–7.34 (2H, m, $C_{7',\ 2'}$-Ar-H), 7.10–7.07 (1H, m, C_6 –Ar-H), 7.05 (1H, m, $C_{6'}$-Ar-H), 6.97–6.95 (1H, d, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 8.8 Hz), 6.25–6.24 (1H, d, C_5-Ar-H, $^4J_{H,H}$ = 2.4 Hz), 6.18–6.17 (1H, d, C_3-Ar-H, $^4J_{H,H}$ = 2.4 Hz), 3.43–3.39 (4H, q, $^3J_{H,H}$ = 7.76 Hz), 3.30–3.25 (2H, m), 2.84–2.80 (2H, m), 2.45–2.40 (2H, m), 1.85–1.79 (6H, m), 1.47–1.40 (10H, m), 1.08–1.04 (4H, m), 0.73–0.69 (4H, m). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 170.93 (HC=N), 168.45(N=C-OH), 159.96 (C-OH), 101.37, 51.37, 47.39 ($N(C_2H_5)_2$, 41.28, 35.19, 31.86 (aliphatic carbon), 29.77 (Bu-C), 25.35 (Bu-C), 20.29 (Bu-C), 8.94 (Bu-C). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −223.45. FT-IR (ν, cm^{-1}): 3384 (N-H, indole ring, br), 1,614 (C=N, m), 1,240 (C-O), 695 (Sn-O), 510 (Sn-N), 422 (Sn-C).

[16] Ph_2SnL^3: Yield: 68%, reddish black solid; M.p.: 163-165 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 12.42, MS: m/z (M^+) Cacld. for $C_{35}H_{36}N_4O_2Sn$: 664.18; found: 665.19 $(M + H)^+$. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 11.42 (s, 1H, N-H), 8.51 (s, 1H,- N=C-H), 7.63–7.60 (m, 2H, $C_{4',\ 5'}$-Ar-H), 7.54–7.52 (2H, m, $C_{2',7'}$-Ar-H), 7.42–7.39 (8H, m, Sn-Ar-H), 7.21–7.17 (1H, m, $C_{6'}$-Ar-H), 7.07–7.04 (2H, m, Sn-Ar-H), 7.02–7.00 (1H, s, C_3-Ar-H), 6.88–6.85 (2H, d, $C_{5,6}$-Ar-H, $^3J_{H,H}$ = 7.8 Hz), 3.48–3.42 (2H, m), 3.33–3.27 (4H, q, $^3J_{H,H}$ = 7.2 Hz), 2.76–2.72 (2H, t, J = 7.6 Hz), 2.44–2.40 (2H, m), 1.13–1.10 (6H, t, $^3J_{H,H}$ = 7.2 Hz). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 170.68 (HC=N), 167.54(N=C-OH), 159.70 (C-OH), 112–104 (Sn-Ph-C), 101.90, 45.86, 44.51 ($N(C_2H_5)_2$, 34.23, 30.33, 26.67 (aliphatic carbon). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −314.37. FT-IR (ν, cm^{-1}): 3387 (N-H, indole ring, br), 1,617 (C=N, m), 1,241 (C-O), 701 (Sn-N) (Sn-O), 513 (Sn-N), 424 (Sn-C).

[17] Me_2SnL^4: Yield: 70%, yellow solid; M.p.: 162-164 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 14.05, MS: m/z (M^+) Cacld. for $C_{21}H_{21}Br_2N_3O_2Sn$: 624.90; found: 625.93 $(M + H)^+$.^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 12.73 (s, 1H, N-H), 8.48 (s, 1H,- N=C-H), 8.03–8.02 (1H, d, C_4-Ar-H, $^4J_{H,H}$ = 2.4 Hz), 7.91–7.90 (1H, d, C_6-Ar-H, $^4J_{H,H}$ = 2.4 Hz), 7.68–7.67 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.74 Hz), 7.43–7.41 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.01 Hz), 7.21–7.19 (1H, d, $C_{2'}$-Ar-H, $^4J_{H,H}$ = 2.3 Hz), 7.08–7.04 (1H, t, $C_{6'}$-Ar-H, $^3J_{H,H}$ = 7 Hz), 6.97–6.93 (1H, t, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 7.2 Hz), 2.87–2.84 (3H, t, $^3J_{H,H}$ = 7.6 Hz), 2.45–2.41 (3H, t, $^3J_{H,H}$ = 7.6 Hz), 0.81 (s, 6H, Me). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 171.72 (HC=N), 169.28 (N=C-OH), 161.65 (C-OH), 35.71, 31.28, 26.18 (aliphatic carbon) 8.47 (Me). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −135.60. FT-IR (ν, cm^{-1}): 3408 (N-H, indole ring, br), 1,610 (C=N, m), 1,272 (C-O), 720 (Sn-O), 542 (Sn-N), 431 (Sn-C).

[18] Et_2SnL^4: Yield: 63%, yellow solid; M.p.: 165-168 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 13.97, MS: m/z (M^+) Cacld. for $C_{23}H_{25}Br_2N_3O_2Sn$: 652.93; found: 653.92 $(M + H)^+$. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 12.75 (s, 1H, N-H), 8.47 (s, 1H,- N=C-H), 7.99–7.98 (1H, d, C_4-Ar-H, $^4J_{H,H}$ = 2.34 Hz), 7.91–7.90 (1H, d, C_6-Ar-H, $^4J_{H,H}$ = 2.34 Hz), 7.70–7.72 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 7.8 Hz), 7.45–7.43 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.20 Hz), 7.21–7.19 (1H, d, $C_{2'}$-Ar-H, $^4J_{H,H}$ = 2.3 Hz), 7.07–7.05 (1H, t, $C_{6'}$-Ar-H, $^3J_{H,H}$ = 7.2 Hz), 6.97–6.93 (1H, t, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 7.2 Hz), 2.88–2.84 (3H, t, $^3J_{H,H}$ = 8 Hz), 2.45–2.40 (3H, t, $^3J_{H,H}$ = 8 Hz), 1.43–1.41 (6H, m), 0.82–0.79 (q, 4H, $^3J_{H,H}$ = 8.27 Hz). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 171.66 (HC=N), 169.64 (N=C-OH), 161.04 (C-OH), 35.20, 31.33, 26.13 (aliphatic carbon), 24.72 (Et-C), 8.83 (Et-C). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −167.86. FT-IR (ν, cm^{-1}): 3408 (N-H, indole ring, br), 1,611 (C=N, m), 1,270 (C-O), 719 (Sn-O), 540 (Sn-N), 428 (Sn-C).

[19] Bu_2SnL^4: Yield: 71%, whitish yellow solid; M.p.: 167-169 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 13.76, MS: m/z (M^+) Cacld. for $C_{27}H_{33}Br_2N_3O_2Sn$: 708.99; found: 710.02 $(M + H)^+$.^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 12.55 (s, 1H, N-H), 8.53 (s, 1H,- N=C-H),

8.05–8.04 (1H, d, C_4-Ar-H, $^4J_{H,H}$ = 2.12 Hz), 7.93–7.94 (1H, d, C_6-Ar-H, $^4J_{H,H}$ = 2.12 Hz), 7.74–7.72 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 8 Hz), 7.47–7.45 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.34 Hz), 7.21–7.19 (1H, d, $C_{2'}$-Ar-H, $^4J_{H,H}$ = 2.3 Hz), 7.15–7.13 (1H, t, $C_{6'}$-Ar-H, $^3J_{H,H}$ = 7.53 Hz), 6.99–6.97 (1H, t, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 7.6 Hz), 3.04–3.02 (3H, t, $^3J_{H,H}$ = 7.95 Hz), 2.77–2.75 (3H, t, $^3J_{H,H}$ = 7.95 Hz), 1.72–1.70 (t, 6H, $^3J_{H,H}$ = 7.34 Hz), 1.34–1.30 (8H, m), 0.75–0.72 (t, 4H, $^3J_{H,H}$ = 8.14 Hz Hz). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 171.89 (HC=N), 169.04 (N=C-OH), 161.47 (C-OH), 37.17, 34.49, 28.85 (aliphatic carbon), 26.29 (Bu-C), 24.69 (Bu-C), 19.90 (Bu-C), 8.52 (Bu-C). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −247.55. FT-IR (ν, cm^{-1}): 3406 (N-H, indole ring, br), 1,613 (C=N, m), 1,269 (C-O), 715 (Sn-O), 538 (Sn-N), 433 (Sn-C).

[20] Ph_2SnL^4: Yield: 61%, red solid; M.p.: 163-164 °C, Conductivity: (ohm^{-1} cm^2 mol^{-1}) in DMF: 14.38, MS: m/z (M^+) Cacld. for $C_{31}H_{25}Br_2N_3O_2Sn$: 748.93; found: 749.95 $(M + H)^+$. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 12.52 (s, 1H, N-H), 8.60 (s, 1H,- N=C-H), 7.99–7.91 (2H, m), 7.74–7.72 (1H, d, $C_{4'}$-Ar-H, $^3J_{H,H}$ = 8 Hz), 7.45–7.38 (8H, m, Sn-Ar-H), 7.34–7.31 (1H, d, $C_{7'}$-Ar-H, $^3J_{H,H}$ = 8.05 Hz), 7.28–7.26 (2H, t, Sn-Ar-H, $^3J_{H,H}$ = 8.46 Hz), 7.20–7.19 (1H, d, $C_{2'}$-Ar-H, $^4J_{H,H}$ = 2.0 Hz), 7.10–7.08 (1H, t, $C_{6'}$-Ar-H, $^3J_{H,H}$ = 7.62 Hz), 6.99–6.97 (1H, t, $C_{5'}$-Ar-H, $^3J_{H,H}$ = 7.6 Hz), 2.89–2.86 (3H, t, $^3J_{H,H}$ = 8 Hz), 2.74–2.72 (3H, t, $^3J_{H,H}$ = 8 Hz). ^{13}C NMR [100 MHz, $CDCl_3$. δ (ppm)]: 171.67 (HC=N), 168.72 (N=C-OH), 161.12 (C-OH), 112–104 (Ph-C), 34.18, 32.72, 26.61 (aliphatic carbon). ^{119}Sn NMR [400 MHz, $CDCl_3$, δ (ppm)]: −324.47. FT-IR (ν, cm^{-1}): 3410 (N-H, indole ring, br), 1,615 (C=N, m), 1,269 (C-O), 716 (Sn-O), 538 (Sn-N), 431 (Sn-C).

2.4 | Biological application

2.4.1 | Antimicrobial activity

The synthesized compounds (**1–20**) were evaluated for the *in vitro* antibacterial and antifungal activity choosing four bacterial and two fungal cultures. Ciprofloxacin and fluconazole were used as positive control and DMSO as negative control for antibacterial and antifungal activity.

2.4.2 | Microbes used

For carrying out the antibacterial activity of synthesized compounds, two gram positive bacteria -*Staphylococcus aureus* (MTCC 2901) (causes food poisoning and skin syndrome) *and Bacillus subtilis* (NCIM 2063) (causes food poisoning) and two gram negative bacteria - *Escherichia coli* (MTCC 732) (causes dysentery and infection in urinary tract) *and Pseudomonas aeruginosa* (MTCC 424) (causes soft tissue infection and dermatitis) were used. The fungal strains used were - *Aspergillus niger* (MTCC 9933) (weaker immune system and lungs) and *Candida albicans* (MTCC 227) (causes tongue piercing).

2.4.3 | Compounds concentration

The compounds were prepared by dissolving 5 mg in 5 ml of DMSO as a stock solution. Then 1 ml of stock solutions was diluted with the 9 ml of DMSO to form concentration up to 100 μg/ml.[41]

2.4.4 | Culture and preservation of microbes

Different conditions were used for growth of bacterial and fungal strains. The bacteria were subcultured on the nutrient broth (1.3 g) and fungus on Potato dextrose broth (2.4 g) in the 100 ml of distilled water and autoclaved at 15 psi for 30–35 min. The cultures were incubated at 37 °C for 24 hr and 48 hr at 27 °C for bacterial and fungal culture. Then transferred 1 ml of the above bacterial/fungal culture to the saline solution and used it for the antibacterial and antifungal activity.[42]

2.4.5 | Determination of antibacterial and antifungal assay

Serial dilution method was used for carrying the antimicrobial activity and minimum inhibitory concentrations (MIC) of the compounds were calculated. In serial dilution method, 1 ml of stock solution was added to the test tube containing 1 ml of broth and serially diluted it to 3.125 μg/ml concentration. After serial dilution of each test tube, above prepared microbes culture was inoculated and plugged with the cotton. Then the test tubes were put in the incubator at controlled temperature for fixed time. The MICs of the compounds were calculated after the definite interval of time. The activity was performed in duplicate to minimize the error and their mean value is represented here.

2.4.6 | Cytotoxicity assay

Anticancer activity of the synthesized compounds **(1–20)** was evaluated by measurement of *in vitro* growth

inhibition of tumor cells in 96 well plates by cell mediated reduction of tetrazolium salt to water insoluble formazan crystals using doxorubicin as a standard drug. The cytotoxicity was tested against a panel of three different human cell lines: A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185); MCF7 derived from human breast adenocarcinoma cells (ATCC No. HTB-22) and IMR90 derived from human normal lung cells (ATCC No. CCL-186), using the MTT colorimetric assay.[43] For the evaluation of effect of synthesized compounds on the viability of tumor as well as normal cell lines, the absorbance was observed at wavelength of 540 nm on a multimode reader (InfiniteM200, Tecan, Mannedorf, Switzerland), followed by plotting of dose response curves for the synthesized compounds and standard after making correction by subtracting the background absorbance with that of the blanks. IC_{50} values were calculated from the plotted absorbance data of the dose response curves. All the experiments were carried out in triplicate and the results were reported as IC_{50} values (in μM) expressed as the mean ± SD.

2.4.7 | *In Silico* study

ADME study was carried out *in silico* for the prediction of drug likeness of synthesized compounds. For *in silico* study molinspiration online study toolkit (http: //www. Molinspiration. com/cgi-bin/properties)[44] was used and bioactivity scores are calculated which are summarized in Table 2.

3 | RESULTS AND DISCUSSION

3.1 | Chemistry

In the present work, hydrazide Schiff base ligands (**1–4**) were synthesized by the reaction of indole-3-butyric hydrazide with the salicylaldehyde and its derivatives in methanol solvent. Sixteen new diorganotin (IV) complexes (**5–20**) were prepared by reaction of hydrazide Schiff base ligands with R_2SnCl_2 in 1:1 molar ratio by adding triethylamine as base. The spectroscopic data describes the synthesized diorganotin (IV) complexes to have pentacoordinated geometry with the tridentate ligands (ONO). All diorganotin (IV) complexes were stable in air, obtained in good yield, non-volatile, non-electrolytic in nature and are soluble in DMSO, DMF, THF and $CHCl_3$ solvent.

3.2 | Electronic spectra

The electronic transition involved in the Schiff base ligands and their diorganotin (IV) complexes was studied with the help of UV–vis spectra. The electronic spectra of the ligands showed π → π* and n → π* transitions around 254–262 and 348–367 nm. These bands were slightly shifted to higher wavelength on complexation. A new band on complexation appeared at the 415–400 nm due to the ligand to metal charge transfer which confirmed the complexation of Schiff base ligands with the metal centre.[45,46]

3.3 | IR spectra

The most explicit band in the IR spectrum which ascertain about the complexation was the disappearance of the ν(N–H) and ν(O–H) stretching bands present in the ligands at 3205–3308 cm^{-1} and 3,059–3,087 cm^{-1}, respectively. The binding in the complexes was studied by comparing the ν(C=N) and ν(N–N) stretching frequency of complexes and ligands. In Schiff base ligands, the ν(C=N) and ν(N–N) stretching bands appeared at 1609–1617 cm^{-1} and 987–1,009 cm^{-1} but in complexes, they slightly got shifted to lower frequency which supported the coordination of azomethine nitrogen to the tin (IV) metal centre.[47,48] In ligands ν(C=O) stretching band was present at 1695–1724 cm^{-1}, got disappeared in the complexes which suggested the tautomerisation of the Schiff bases on complexation. The stretching vibration band due to the ν(C–O) at 1253–1281 cm^{-1} got displaced to lower frequency in complexes, postulates the formation of Sn-O bond in the complexes. The vibration stretching band in complexes at 691–720 cm^{-1}, 510–542 cm^{-1} and 418–433 cm^{-1} due to the Sn-O, Sn-N and Sn-C bond confirmed coordination of tin metal with oxygen, nitrogen and carbon atom (Fig. S1, S2).[49] After studying all the vibration bands of IR spectra, it was suggested that the complexes have pentacoordinated geometry around the tin metal and Schiff bases have tridentate (ONO) nature.

3.4 | ^{1}H NMR spectra

In the ^{1}H NMR spectra of Schiff base ligands, the most prominent signal is present at δ 11.22–12.00 ppm and 10.78–10.88 ppm due to O=C-NH and OH proton, respectively, which got disappeared on complexation. The tautomerization of Schiff base ligands and coordination of enolic oxygen with the tin (IV) metal center was suggested in the IR spectra but the confirmation was

given by the disappearance of O=C-NH signal in proton NMR.[50,51] The signal at δ 8.11–9.39 ppm due to azomethine proton (N=CH) got shifted downfield on complexation due to the donation of electron density from azomethine nitrogen to tin (IV) metal atom. The $^{3}J(^{119}Sn\text{-}^{1}H)$ coupling gives tin satellite peaks with the azomethine proton signals due to coupling of azomethine proton with tin metal and comes in the range of 43–48 Hz, confirms the coordination of nitrogen with tin (IV) metal and formation of Sn-N bond. The N-H proton of the indole ring display signal at δ 11.36–12.65 ppm that remains unaffected on complexation, established its non-coordination with the metal centre.[52] The aromatic protons of the Schiff base ligands at δ 6.09–7.80 ppm were unaffected or very less affected on the complex formation. Aliphatic signals present at δ 2.22–2.75 ppm gets shifted downfield during the complex formation (Fig. S3-S6).

The ^{1}H NMR of diorganotin (IV) complexes show some additional signals due to the presence of alkyl/aryl groups directly attached to the tin (IV) metal. A singlet of Sn-CH_3 at δ 0.75–0.81 ppm with tin satellite peaks due to $^{2}J(^{119}Sn\text{-}^{1}H)$ coupling has values in range of 72–76 Hz, which is indicative of the five coordinated tin (IV) species.[53,54] The methyl proton in the diethyl complexes appears as triplet at δ 1.13–1.43 ppm and methylene protons as multiplets in the range of δ 0.76–0.85 ppm. The butyl protons in the dibutyl complexes resonates as multiplet and triplet in the range of δ 1.04–1.76 ppm and δ 0.69–0.91 ppm, respectively. In the diphenyl complexes, the phenyl protons appear at δ 6.22–7.26 ppm (Fig. S7-S10).

The ^{1}H NMR data confirms the tridenticity of the hydrazide Schiff base ligands (ONO) and their pentacoordinated environment around the central metal atom. The NMR data is in good agreement with the expected molecular structure.

3.5 | ^{13}C NMR spectra

^{13}C NMR spectral data also supports the authenticity of the proposed structures. The signals for C=O carbon atom resonate at δ 172.12–176.42 ppm in ligands which shifted upfield in the complexes supports further the tautomerization of Schiff base ligands on complexation.[55] The coordination of Schiff base ligands were further strengthened by the azomethine carbon signals at δ 168.14–169.35 ppm in ligands which undergoes downfield shift in their position on complexation (Fig. S11).[56]

Some new signals in complexes additionally describe the further coordination of tin metal with alkyl/aryl groups. The carbon of methyl group in dimethyltin (IV) derivative is present at δ 7.98–8.61 ppm. The chemical shift value of diethyl and dibutyl carbon falls in the range of δ 23.34–26.11 ppm, δ 7.98–8.83 ppm and δ 20.18–27.72 ppm, δ 8.31–9.23 ppm. The carbon signals of phenyl group appended to tin atom at δ 104–115 ppm (Fig. S13-S16). These new signals confirm the Sn-C bond in the complexes.

3.6 | ^{119} Sn NMR

The chemical shift value of ^{119}Sn NMR describes the coordination number of tin metal. The methyl complexes in the ^{119}Sn NMR gives the signal at δ − 129.81 to −135.60 ppm, ethyl complexes resonate at - δ 150.78 t0–167.86 ppm, butyl complexes at δ − 214.75 to −274.55 ppm and phenyl complexes give signals at δ − 312.04 to −324.47 ppm (Fig. S17-S19). These values of chemical shift lie in the penta coordinated environment and all the signals appear as the singlet which confirms the existence of one isomer or mononuclear complex of the tin (IV) metal.[57]

3.7 | Mass spectra

The molecular weight determination, possible fragmentation pattern, stability of fragments and isotopic studies was done with the help of mass spectra. In Figure 1 represents the mass spectra of compound **3** and **16**. In the mass spectra of (H_2L^3) **3** the M + H ion peak and base peak was observed at m/z 393.22 which was same as the calculated value. The medium intensity peak at m/z 394.23 was due to the isotopes of nitrogen [M + H + ^{15}N]. In the mass spectra of complex **16** (Ph_2SnL^3), the molecular ion peak of [M + H + ^{119}Sn] is observed at m/z 665.19 and another peak with the a gap of 2 m/z units at m/z 663.19 is attributed to [M + H + ^{117}Sn] molecular ion and agrees with the isotopic abundance of tin. One additional peak at m/z 664.19 is due to [M + ^{119}Sn]$^{+\cdot}$. The molecular ion peaks observed at m/z 394.23 and 393.22 was due to ligand entity which confirmed the coordination of tin metal with Schiff base ligands.

Molecular ion peak and other characterized peaks indicate the mononuclear nature of the complexes in 1:1 metal ligand ratio.

3.8 | Thermal studies

Thermogravimetric curve for the diorganotin (IV) complexes in the temperature range 28–800 °C highlights the percentage mass loss with the temperature which indicates the volatility and stability of

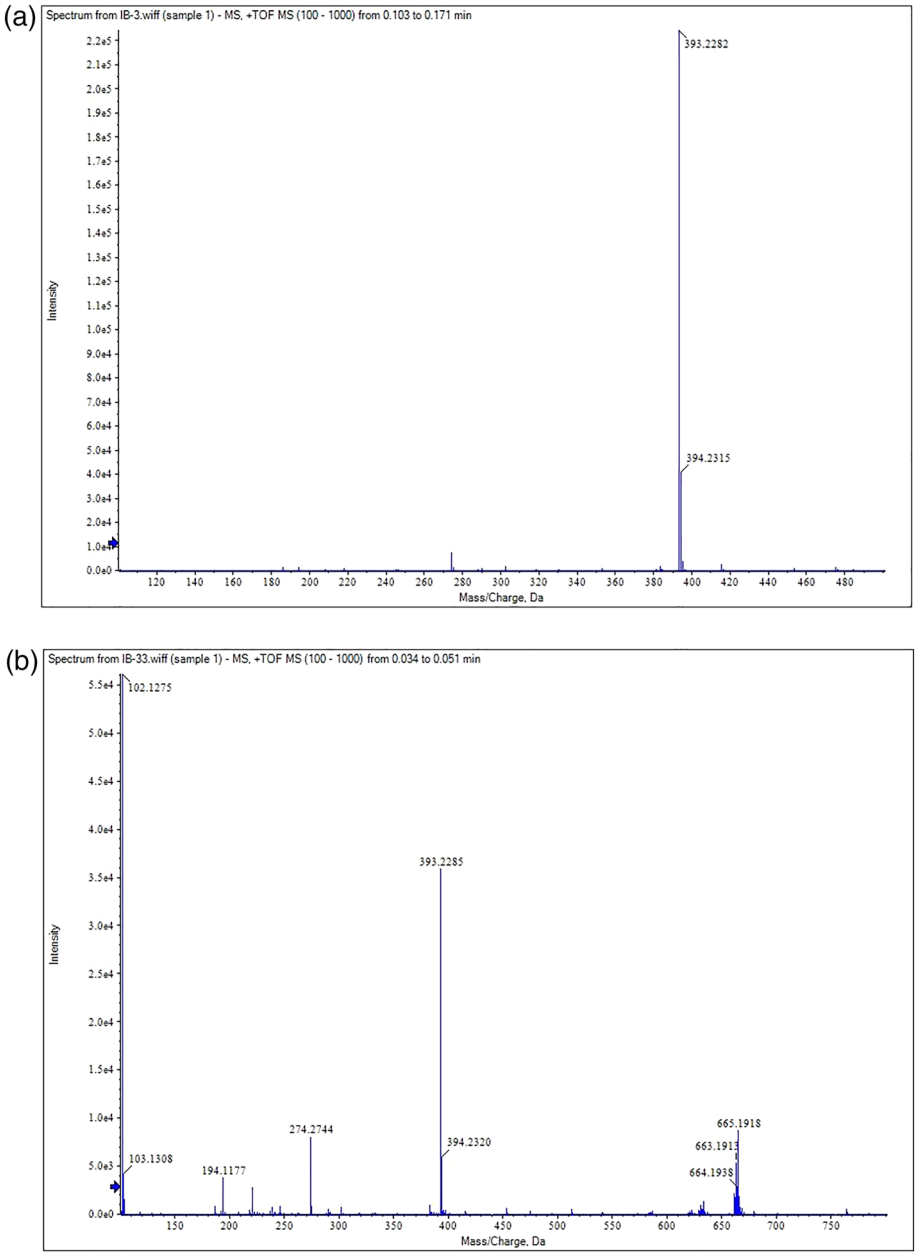


FIGURE 1 Mass spectra of compounds a) H_2L^3 (**3**) and b) Ph_2SnL^3 (**16**)

compounds.[58] From the TGA curve of Me_2SnL^2 **(9)**, three successive mass loss steps take place Figure 2. In the first step mass loss of 5.57% (calculated 5.34%) at temperature 201-232 °C due to removal of methyl groups directly attached to the tin (IV) which suggests that the compound was stable up to 200 °C and complex does not contain the coordinated as well as lattice water molecule and the complex was free of moisture. In the second step a gradual weight loss of 75.79% was noticed at temperature 234–398 °C due to ligand moiety, agreed with the estimated mass loss of the calculated value 75.32%. In the last step, tin oxide remains as residue having 20% mass which verified tin oxides as the precursor of the complexes. All the complexes follow the same pattern of decomposition as described above.

3.9 | Antimicrobial activity

Hydrazide Schiff bases and their diorganotin (IV) complexes (**1–20**) were screened for the antimicrobial activity against four bacterial strain *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli, Pseudomonas aeruginosa* and two fungal strains *Aspergillus niger* and *Candida albicans*. The experiments were performed in duplicate by serial dilution method using ciprofloxacin and fluconazole as positive standard and DMSO as negative standard for antibacterial and antifungal activity. The MIC values were calculated and results are summarized in the Table 1 and Figure 3.

The pentacoordinated diorganotin (IV) complexes have more growth inhibition effect than the free Schiff

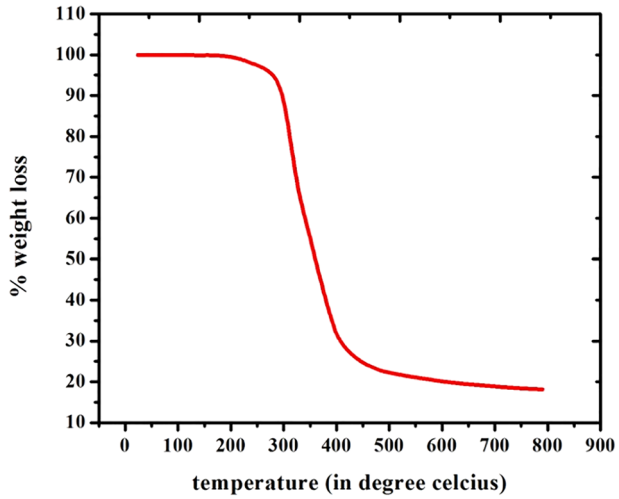


FIGURE 2 Thermal decomposition curve of complex Me_2SnL^2 (**9**)

base ligands which have greater than respective starting precursors. The growth inhibition of microbes increases with the increase in the concentration of complexes. Generally, structure activity relationship of the compounds are discussed on the basis of coordination number, chelate effects of ligands, substituent attached to the ring, presence and absence of electron withdrawing and releasing groups, alkyl/aryl groups attached to tin metal, total charge on the complexes and molecular mass of the compounds.[59,60] The conclusions drawn from the current activity data is summarised below:

1 By comparing the antimicrobial activity of Schiff base ligands (**1–4**) it was found that the H_2L^4 **(4)** was most active (MIC = 0.026 μm/ml) than the other ligands. The higher activity of the H_2L^4 was due to the presence of the electron withdrawing group (bromo) on the ring and H_2L^3 **(3)** was less active (MIC = 0.127 μm/ml) due to the presence of the electron releasing group (diethylamine). When no

TABLE 1 Minimum inhibitory concentration (MIC in μM/ml) of compounds (**1–20**) against antibacterial and antifungal strains

		MIC in μM/ml					
		Gram +ve bacteria		Gram –ve bacteria		Fungi	
Comp. no.	compounds	*S.aureus*	*B.*subtilis	*E. coli*	*P.aeruginosa*	*A.niger*	*C.albicans*
1	H_2L^1	0.077	0.077	0.077	0.077	0.077	0.077
2	H_2L^2	0.034	0.034	0.068	0.034	0.068	0.034
3	H_2L^3	0.127	0.127	0.127	0.127	0.063	0.063
4	H_2L^4	0.026	0.026	0.026	0.026	0.026	0.026
5	Me_2SnL^1	0.026	0.026	0.026	0.026	0.026	0.026
6	Et_2SnL^1	0.025	0.025	0.025	0.025	0.050	0.050
7	Bu_2SnL^1	0.022	0.022	0.044	0.044	0.022	0.022
8	Ph_2SnL^1	0.021	0.042	0.021	0.021	0.042	0.021
9	Me_2SnL^2	0.024	0.024	0.048	0.024	0.024	0.024
10	Et_2SnL^2	0.023	0.023	0.023	0.023	0.023	0.023
11	Bu_2SnL^2	0.020	0.020	0.040	0.040	0.020	0.020
12	Ph_2SnL^2	0.019	0.019	0.019	0.019	0.009	0.009
13	Me_2SnL^3	0.046	0.046	0.046	0.092	0.046	0.046
14	Et_2SnL^3	0.044	0.088	0.088	0.044	0.044	0.044
15	Bu_2SnL^3	0.040	0.040	0.080	0.040	0.040	0.040
16	Ph_2SnL^3	0.037	0.037	0.037	0.037	0.074	0.037
17	Me_2SnL^4	0.020	0.020	0.020	0.020	0.010	0.010
18	Et_2SnL^4	0.019	0.019	0.038	0.019	0.019	0.019
19	Bu_2SnL^4	0.016	0.016	0.016	0.016	0.016	0.016
20	Ph_2SnL^4	0.008	0.008	0.008	0.008	0.008	0.008
21	**Ciprofloxacin**	0.0047	0.0047	0.0047	0.0047	-	-
22	**Fluconazole**	-	-	-	-	0.0102	0.0051

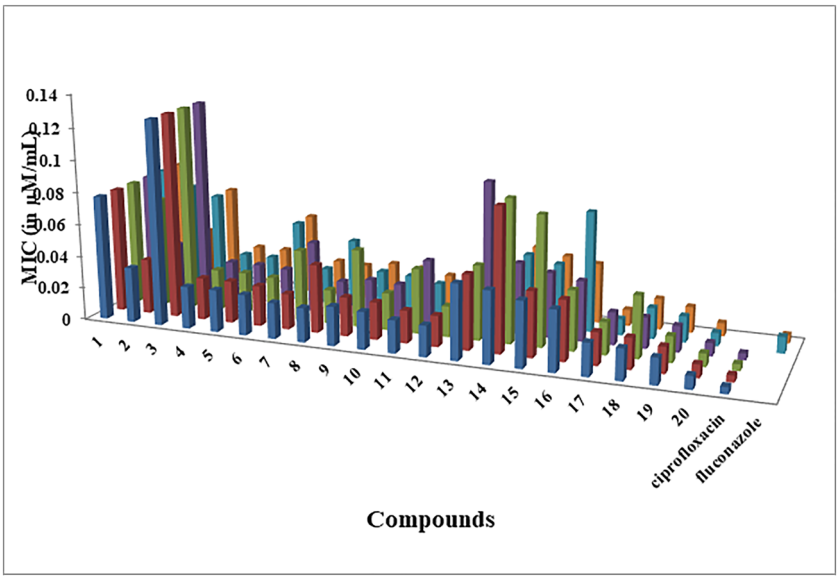


FIGURE 3 Graph showing antimicrobial activity of the synthesized compounds (**1–20**)

substituent is attached to the Schiff base ligand as in compound H_2L^1 **(1)**, the moderate activity (MIC = 0.077 μm/mL) or in between the compound **3** and **4**. The above data indicates that compounds having electronegative groups were more active than the compounds having the electron releasing groups. The general trend of the activity for the Schiff base ligands was: $\mathbf{H_2L^4 > H_2L^2 > H_2L^1 > H_2L^3}$

2 Activity of complexes increases as compared to the Schiff base ligands due to the chelation of metal which results in increase in lipophilic and hydrophobic character of the compounds as explained in the tweedy chelation theory. With the increase in the lipophilicity, complexes easily pass through the lipid bilayer of cell membrane and blocks the metal binding sites which results in the disruption of the cell, inhibit the protein synthesis machinery and biological process of the cell.[61,62]

3 On complexation, the effect of the alkyl/aryl group attached to tin metal is observed. Complexes having the phenyl ring have higher activity (MIC = 0.021–0.008 μm/ml) than the butyl, ethyl and methyl complexes. The higher activity of the phenyl complexes was due to the delocalisation of the Π electron cloud over the ring. The butyl complexes has higher activity (MIC = 0.022–0.016 μm/ml) than the ethyl and methyl complexes which was due to higher molecular mass of the compound. The above data signifies that the activity of these compounds were mainly affected by the presence of alkyl/aryl groups directly attached with the tin (IV) metal and molecular mass of compounds. The general order of activity of the complexes were **Ph > Bu > Et ≥ Me.**

4 Compounds **4, 5, 6, 10, 11, 12, 17, 18, 19** and **20** have higher activity among all compounds for gram positive bacteria with MIC value in the range of 0.026–-0.008 μm/ml. For gram negative bacteria, complexes **4, 5, 6, 8, 10, 12, 17, 19** and **20** were MIC in the range of MIC = 0.026–0.008 μm/ml. The results of antimicrobial activity also suggested that the compounds were more active for fungus as compared to the bacteria. Compounds **12, 17** and **20** (MIC = 0.010–0.008 μm/ml) were more active against the fungus. Compound **20** have highest activity (MIC = 0.008 μm/mL) in the entire series which was nearer to the standard drugs (ciprofloxacin MIC = 0.0047 μm/ml and fluconazole MIC = 0.0102 for *A. niger* and 0.0051 μm/ml for *C. albicans*).

The different physiochemical studies were done for the synthesis of any drugs which is based on their molecular properties. Orally active drug should follow the Lipinski's rule of five which describe the molecular and biological properties of the drugs and is essential for the ADME properties. The Lipinski's rules of five are: molecular weight of the compounds should be ≤500 dalton, the value of logP to be ≤5, the number of hydrogen bond donor is ≤5 and hydrogen bond acceptor ≤10. If the violation of more than 2 rules takes place than the drug is not an orally active drug.[63]

Molinspiration online (http:/molinspiration.com/cgi-bin/properties) was used to study the molecular properties and bioactivity of compounds. The ADME properties were calculated and presented in the Table **2** and concluded that the synthesized compounds are not violating more than two rules and can be used as orally active drugs according to the rule of five.

The value of log P describes about the lipophilicity of compounds. **4, 7, 11, 15, 16, 19** and **20** compounds does not show the lipophilic nature (log P) due to its value is

TABLE 2 Bioactivity Scores of compounds (**1–20**) by using the molinspiration

C.No	Compounds	% Abs	MW	C log P	TPSA	n-ON	n-OHNH	n-rot	Volume
1	H_2L^1	82.26	321.38	4.07	77.48	5	3	6	279.50
2	H_2L^2	66.45	366.38	4.00	123.31	8	3	7	320.83
3	H_2L^3	81.15	392.50	4.90	80.72	6	3	9	377.01
4	H_2L^4	82.26	479.17	5.38	77.48	5	3	6	333.27
5	Me_2SnL^1	88.68	468.14	2.47	58.99	5	1	4	360.76
6	Et_2SnL^1	88.68	496.20	3.22	58.99	5	1	6	394.36
7	Bu_2SnL^1	88.68	552.31	5.34	58.99	5	1	10	461.57
8	Ph_2SnL^1	88.68	592.29	5.86	58.99	5	1	6	470.45
9	Me_2SnL^2	72.84	513.14	2.40	104.81	8	1	5	384.09
10	Et_2SnL^2	72.84	541.20	3.16	104.81	8	1	7	417.70
11	Bu_2SnL^2	72.84	597.30	5.28	104.81	8	1	11	484.90
12	Ph_2SnL^2	72.84	637.28	5.80	104.81	8	1	7	493.79
13	Me_2SnL^3	87.53	539.27	3.30	62.23	6	1	7	440.27
14	Et_2SnL^3	87.53	567.32	4.05	62.23	6	1	9	473.87
15	Bu_2SnL^3	87.53	623.43	6.18	62.23	6	1	13	541.08
16	Ph_2SnL^3	87.53	663.41	6.69	62.23	6	1	9	549.96
17	Me_2SnL^4	88.64	625.94	3.99	58.99	5	1	4	396.53
18	Et_2SnL^4	88.64	653.99	4.74	58.99	5	1	6	430.13
19	Bu_2SnL^4	88.64	710.10	6.87	58.99	5	1	10	497.34
20	Ph_2SnL^4	88.64	750.08	7.39	58.99	5	1	6	506.23

-MW = Molecular weight
-ClogP = Logarithm of partition Coefficient
-TPSA = Topological polar surface area
-n-ON = Number of hydrogen bond acceptor
-n-OHNH = Number of hydrogen bond donor
- n-rot = Number of rotatable bond

more than 5 value.[64] The TPSA value of compounds was less than 130 $Å^2$ which shows good transport properties of compounds. The percentage absorption of the compounds was calculated by using the formula % Abs = 109-(0.345 × TPSA).[65] The value of % absorbance was high for the complexes as compared to the ligands which suggests better absorption of complexes than respective ligands.

3.10 | Cytotoxicity results

The efficiency of the hydrazide Schiff bases and their diorganotin (IV) complexes (**1–20**) as anticancer drug has been tested *in vitro* on two human cancer cell lines namely human alveolar adenocarcinoma epithelial cell line (A549), human breast adenocarcinoma cell line (MCF7), and human normal lung cell line (IMR90), using MTT assay. The results of IC_{50} values of compounds are summarized in Table 3 and Figure 4. The data was compared with the activity of the known anticancer drug doxorubicin which was used as a reference.

Activity data of Schiff base ligands (**1–4**) suggested compound **3** (H_2L^3) to be more potent with lowest IC_{50} value of 15.4 and 13.9 μM against A549 and MCF7 cell lines. Schiff base ligand **1** (H_2L^1) was found to be moderately active with IC_{50} value of 62.1 and 51.2 μM against human cancer cell lines and ligand **2** (H_2L^2) was least active in the entire series of the compounds.

The results of cytotoxic activity of diorganotin (IV) complexes (**5–20**) showed that compound **10** (Et_2SnL^2) displayed excellent activity with an IC_{50} value of 13.4 and 15.2 μM against A549 and MCF7 cell lines, respectively. The ethyl complexes **14** and **18** showed moderate anticancer activity with IC_{50} values 29.6, 27.8 and 23.8, 20.5 μM against A549 and MCF7 cell lines. The significant feature of ethyl complexes is about 8 fold less toxic as compared to standard drug doxorubicin against normal cell line IMR90. Compounds **1, 3, 7, 12, 16** and **19** showed the good cytotoxic activity with IC_{50} values

TABLE 3 Anticancer activity of synthesized compounds (**1–20**) against two cancer cell lines (A549, MCF7) and one normal cell line (IMR90)

		IC_{50} values (μM ± S.D.)		
C.No.	**Compounds**	**A549**	**MCF7**	**IMR90**
1	H_2L^1	62.1 ± 0.33	51.2 ± 0.21	106.8 ± 0.13
2	H_2L^2	190.5 ± 0.54	186.2 ± 0.22	198.6 ± 0.56
3	H_2L^3	15.4 ± 0.34	13.9 ± 0.12	90.6 ± 0.52
4	H_2L^4	102.5 ± 0.32	101.0 ± 0.18	120.3 ± 0.37
5	Me_2SnL^1	-	-	-
6	Et_2SnL^1	82.4 ± 0.14	79.7 ± 0.34	108.8 ± 0.43
7	Bu_2SnL^1	77.5 ± 0.34	74.2 ± 0.22	89.3 ± 0.12
8	Ph_2SnL^1	86.4 ± 0.71	95.7 ± 0.45	108.7 ± 0.38
9	Me_2SnL^2	94.1 ± 0.31	91.2 ± 0.61	98.9 ± 0.29
10	Et_2SnL^2	13.4 ± 0.23	15.2 ± 0.33	95.5 ± 0.43
11	Bu_2SnL^2	84.6 ± 0.37	83.2 ± 0.14	100.3 ± 0.28
12	Ph_2SnL^2	73.1 ± 0.15	71.2 ± 0.11	99.6 ± 0.32
13	Me_2SnL^3	85.7 ± 0.23	82.5 ± 0.22	102.4 ± 0.32
14	Et_2SnL^3	29.6 ± 0.34	27.8 ± 0.14	88.7 ± 0.25
15	Bu_2SnL^3	-	-	-
16	Ph_2SnL^3	80.5 ± 0.24	77.1 ± 0.72	100.8 ± 0.43
17	Me_2SnL^4	107.9 ± 0.32	103.2 ± 0.38	187.8 ± 0.31
18	Et_2SnL^4	23.8 ± 0.35	20.5 ± 0.28	85.7 ± 0.56
19	Bu_2SnL^4	33.6 ± 0.12	31.2 ± 0.25	96.7 ± 0.43
20	Ph_2SnL^4	106.7 ± 0.42	104.2 ± 0.34	167.8 ± 0.81
Doxorubicin		0.8 ± 0.08	0.7 ± 0.07	12.3 ± 0.12

– Not active
A549- Human lung carcinoma cell line
MCF7- Human breast carcinoma cell line
IMR90- Normal human lung cell line

<80 μM against cancer cell lines. Compounds **5** and **15** fail to preserve the cytotoxic activity against all the cancer cell lines. Compounds **2, 4, 17,** and **20** were least active against both the cancer cell lines but their toxicity is also less against IMR90.

The cytotoxicity of compounds against human normal lung cell line (I**MR90**) showed that all the compounds in the series were 7–16 times less toxic as compared with the reference drug doxorubicin, except compound **5** and **15** which did not provoke any toxicity (Figure 3).

From the data of compounds (**1–20**), it was concluded that the Schiff base ligand H_2L^3 **(3)** was found to be more active and its diorganotin (IV) complexes (**9–12**) was also found active against all the cancer cell line but its ethyl complex was most active and its methyl complex was least active. The ethyl complex of ligand **2** and **4** was also found to be more potent than the other complexes of that group against all the cancer cell lines. The trend of the cytotoxic activity of diorganotin (IV) complexes (**5–20**) is **Et > Bu > Ph > Me**.

The SAR of (1–20) compounds is studied to found out the effect of substituents on the biological activity. All the synthesized compounds (**1–20**) were found to be active against both the cancer cell lines (except compound 5 and 15), and compound **3** (H_2L^3) and **10** (Et_2SnL^2) were particularly more active against both the cancer cell lines. In compound **3** (H_2L^3), the benzene ring is substituted with diethylamino group at meta position with respect to hydroxyl group. The complexation of this ligand **(3)** with dibutyltin resulted in complete loss of anticancer activity **(15)** but complexation with methyl groups (**13**) and phenyl (**16**) groups resulted in about five-fold decrease in anticancer activity as compared to ligands. Although, its diethyl complex (**14**) resulted in decrease in anticancer activity, but still the activity was significantly good.

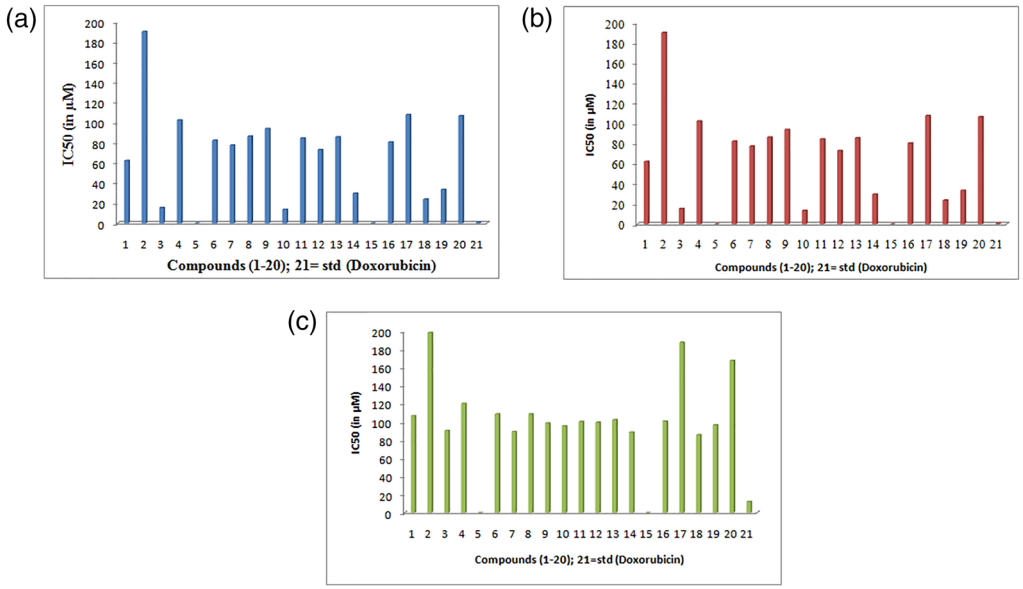
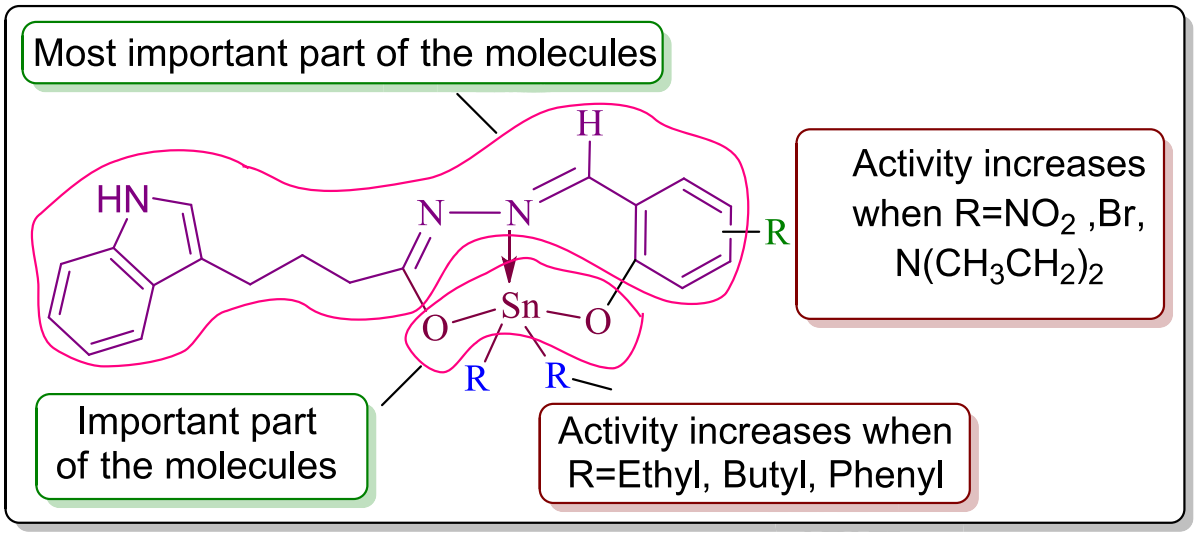


FIGURE 4 Cytotoxicities of synthesized compounds (**1–20**) against (a) Human lung carcinoma cell line (A549), (b) Human breast carcinoma cell line (MCF7), (c) Normal human lung cell line (IMR90)



Compound **10** having very good activity against both A549 and MCF7 cell lines is a coordination compound of ligand **2** (H_2L^2). Although, compound **2** (having nitro substitution on benzene ring) itself is very poorly active, but on complexation the activity is increased and diethyl complex (**10**) is 12–15 times more potent (one of the most active compound in the series). On the other hand, the complexation of ligand **2** with tin having methyl groups (**9**), butyl groups (**11**) and phenyl groups (**12**) resulted in almost two-fold enhancement of anticancer activity as compared to compound **2** itself.

In case of compound **1**, where no substitution on the benzene ring, the anticancer activity is moderate, but its methyl complex (**5**) resulted in complete abolishment of anticancer activity. However, the ethyl (**6**), butyl (**7**) and phenyl (**8**) complexes somewhat weakens the anticancer activity of ligand itself.

Ligand **4** having two bromo substitutions on the benzene ring was poorly active, but its complexation with ethyl (**18**) resulted in almost five times enhancement of anticancer activity. Similarly, its butyl complex (**19**) resulted in around three times enhancement of anticancer activity and methyl (**17**) and phenyl complex (**20**) has no effect on its anticancer activity.

The literature survey suggests that probable target for cytotoxic activity is DNA. The organotin (IV) complexes

attacks on the primary structure of DNA, induce long-lasting effects and gives variable response in cells which leads to cell death due to apoptosis or necrosis. Further, the complexes induce cytotoxicity through inhibition of macromolecules synthesis, decrease DNA synthesis and interaction with cells which increase cytosolic calcium ion concentration. Diorganotin (IV) dichloride induce the apoptosis by increase in concentration of calcium ions which results in release of cytochrome-c and activation of caspases leads to DNA fragmentation.[66–70] Hence, it is anticipated that diorganotin complexes of hydrazide Schiff bases exert the cytotoxic effects by involving above discussed pathways.

4 | CONCLUSION

Four new hydrazide Schiff bases (**1–4**) and diorganotin (IV) complexes (**5–20**) were successfully synthesized and well characterized by spectroscopic and physical analysis. Schiff bases were bound to tin (IV) metal *via* azomethine nitrogen and oxygen atom of phenolic and enolic groups (ONO) forming pentacoordinated complexes. The antimicrobial studies and ADME properties of the compounds displayed that tin complexes enhance the microbial activity as compared to the free Schiff base ligands. The results of cytotoxic activity of the compounds were promising and compound **3** (H_2L^3) and **10** (Et_2SnL^2) was most active against the cancer cell lines and their toxicity was 7 to 8 times lesser than the standard drug doxorubicin against normal cell lines IMR90. The interesting cytotoxic activity against cell lines, bioactivity scores and ease of synthesis makes the current series of compounds promising for the potential development of anticancer agents.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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REFERENCES

[1] M. Barcelo-Oliver, A. Garcia-Raso, A. Terron, E. Molins, M. J. Prieto, V. Moreno, J. Martinez, V. Llado, I. Lopez, A. Gutierrez, P. V. Escriba, *J. Inorg. Biochem.* **2007**, *101*, 649.
[2] I. Ali, M. N. Lone, Z. A. Al-Othman, A. Al-Warthan, M. Marsin Sanagi, *Curr. Drug Targets* **2015**, *16*, 711.
[3] M. Sirajuddin, S. Ali, V. McKee, N. Akhtar, S. Andleeb, A. Wadoo, *J. Photochem. Photobio. B: Bio.* **2019**, *197*, 111516.
[4] M. V. Blagosklonny, *Drug Discovery Today* **2003**, *8*, 1104.
[5] A. Alama, A. M. Orengo, S. Ferrini, R. Gangemi, *Drug Discovery Today* **2012**, *17*, 435.
[6] A. Dey, V. Tergaonkar, D. P. Lane, *Nat. Rev. Drug Discov.* **2008**, *7*, 1031.
[7] N. Hoti, D. Zhu, Z. Song, Z. Wu, S. Tabassum, M. Wu, N. Hoti, D. Zhu, Z. Song, Z. Wu, S. Tabassum, M. Wu, *J. Pharmacol. Exp. Ther.* **2004**, *311*, 22.
[8] B. Rosenberg, L. Vancamp, J. E. Trosko, V. H. Mansour, *Nature* **1969**, *222*, 385.
[9] H. Yu, Y. Tan, D. Kuang, F. Zhang, W. Jiang, *Inorg. Chim. Acta* **2019**, *496*, 119044.
[10] N. Đ. Pantelić, B. B. Zmejkovski, Ž. Žižak, N. R. Banjac, B. Đ. Božić, T. P. Stanojković, G. N. Kaluđerović, *J. Chem.* **2019**, *2019*, 1.
[11] A. F. Butt, M. N. Ahemad, M. H. Bhatti, M. A. Choudhary, K. Ayub, M. N. Tahir, T. Mahmood, *J. Mol. Struct.* **2019**, *1191*, 291.
[12] E. N. Md Yusof, M. A. M. Latif, M. I. M. Tahir, J. A. Sakoff, M. I. Simone, A. J. Page, A. Veerakumarasivam, E. R. T. Tiekink, T. B. S. A. Ravoof, *Int. J. Mol. Sci.* **2019**, *20*, 854.
[13] N. Naz, M. Sirajuddin, A. Haider, S. M. Abbas, S. Ali, A. Wadood, M. Ghufran, G. Rehman, B. Mirza, *J. Mol. Struct.* **2019**, *1179*, 662.
[14] J. Devi, J. Yadav, *Anticancer Agents Med. Chem. (Form. Curr. Med. Chem. - Anti-Cancer Agents)* **2018**, *18*, 335.
[15] J. Devi, S. Pachwania, *Inorg. Chem. Comm.* **2018**, *91*, 44.
[16] J. Devi, S. Devi, A. Kumar, *Med. Chem. Commun.* **2016**, *7*, 932.
[17] J. Devi, S. Devi, A. Kumar, *Hetero. Chem* **2016**, *27*, 361.
[18] J. Devi, S. Kumari, S. Devi, R. Malhotra, P. Kumar, B. Narasimhan, *Monatsh. Chem.* **2014**, *146*, 1995.
[19] C. N. Banti, S. K. Hadjikakou, T. Sismanoglu, N. Hadjiliadis, *J. Inorg. Biochem.* **2019**, *194*, 114.
[20] S. Eldin, H. EtaiwDina, M. Abd El-AzizElham, A. Ali, *J. Organomet. Chem.* **2019**, *30*, 43.
[21] J. Devi, N. Batra, *Spectrochim. Acta, Part a* **2015**, *135*, 710.
[22] J. Devi, M. Yadav, D. Kumar, L. S. Naik, D. K. Jindal, *Appl. Organomet. Chem.* **2019**, *33*, e4693.
[23] J. Devi, M. Yadav, A. Kumar, A. Kumar, *Chem. Pap.* **2018**, *72*, 2479.
[24] J. Devi, M. Yadav, D. Kumar, L. S. Naik, D. K. Jindal, Y. Poornachandra, *Appl. Organomet. Chem.* **2019**, e5154.*33*(10)
[25] J. Kaur, D. Utreja, N. Jain, S. Sharma, *Current Org. Synthesis* **2019**, *16*, 17.
[26] O. A. EL-Gammal, H. Alshater, H. A. El-Boraey, *J. Mol. Struct.* **2019**, *1195*, 220.
[27] M. A. Bhat, M. A. Al-Omar, M. Raish, M. A. Ansari, H. A. Abuelizz, A. H. Bakheit, A. M. Naglah, *Molecules* **2018**, *23*, 1250.

[28] S. Reddy, A. Reddy, A. Avuti, N. Boggula, V. Bakshi, R. Kyatham, *Pharma Innov. J.* **2018**, *7*, 355.
[29] L. Fan, J.-C. Qin, C.-R. Li, Z.-Y. Yang, *Spectrochim. Acta, Part a* **2019**, *218*, 342.
[30] K. Kaur, V. Jaitak, *Anticancer Agents Med. Chem. (Form. Curr. Med. Chem. - Anti-Cancer Agents)* **2018**, *19*, 962.
[31] M. Taha, M. S. Baharudin, N. H. Ismail, S. Imran, M. N. Khan, F. Rahim, M. Selvaraj, S. Chigurupati, M. Nawaz, F. Qureshi, S. Vijayabalan, *Bioorg. Chem.* **2018**, *80*, 36.
[32] R. Bhowmick, A. S. M. Islam, M. Sasmal, A. Katarkar, M. Ali, *J. Coord. Chem.* **2018**, *71*, 2065.
[33] R. Hajare, *Archive Org. Inorg. Chem. Sc.* **2018**, *3*, 366.
[34] A. Kumari, R. K. Singh, *Bioorg. Chem.* **2019**, *89*, 103021.
[35] J. E. Saxton, Monoterpenoid indole alkaloids, in *The Chemistry of Heterocyclic Compounds Part 4*, John Wiley & Sons, Hoboken, NJ **2008**.
[36] R. G. Mehta, J. Liu, A. Constantinou, C. F. Thomas, M. Hawthorne, M. You, C. Gerhüser, J. M. Pezzuto, R. C. Moon, R. M. Moriarty, *Carcinogenesis* **1995**, *16*, 399.
[37] I. S. Johnson, J. G. Armstrong, M. Gorman, J. P. Burnett, *Cancer Res.* **1963**, *23*, 1390.
[38] A. Duflos, A. Kruczynski, J. M. Barrat, *Curr. Med. Chem. Anticancer Agents* **2002**, *2*, 55.
[39] G. La Regina, R. Bai, A. Coluccia, V. Naccarato, V. Famiglini, M. Nalli, D. Masci, A. Verrico, P. Rovella, C. Mazzoccoli, E. Da Pozzo, *Eur. J. Med. Chem.* **2018**, *152*, 283.
[40] A. I. Vogel, *Text Book of Quantitative Chemical Analysis*, fifth ed., Longmans, Edison, Wesley, London **1999**.
[41] J. Devi, M. Yadav, D. Kumar, L. S. Naik, D. K. Jindal, *J. App. Organomet. Chem* **2019**, *33*, e4693.
[42] A. Sharma, A. Jain, S. Saxena, *Appl. Organomet. Chem.* **2015**, *29*, 499.
[43] T. Mosmann, *J. Immunol. Methods* **1983**, *65*, 55.
[44] Molinspiration Chemoinformatics Brastislava, Slovak Republic, available from: http://www.molinspiration.com/cgibin/properties, **2014**.
[45] A. P. Rebolledo, G. M. de Lima, L. N. Gambi, N. L. Speziali, D. F. Maia, C. B. Pinheiro, J. D. Ardisson, M. E. Cortes, H. Beraldo, *Appl. Organomet. Chem.* **2003**, *17*, 945.
[46] R. M. Maurya, M. N. Jayaswal, V. G. Puranik, P. Chakrabarti, S. Gopinathan, C. Gopinathan, *Polyhedron* **1997**, *16*, 3977.
[47] F. F. Costa, A. P. Rebolledo, T. Matencio, H. D. R. Calado, J. D. Ardisson, M. E. Cortes, B. L. Rodrigues, H. J. Beraldo, *Coord. Chem.* **2005**, *58*, 1307.
[48] O. A. Rajan, A. Chakravarthy, *Inorg. Chem.* **1981**, *20*, 660.
[49] S. G. Teoh, S. B. Teo, G. Y. Yeap, J. P. Declercq, *Polyhedron* **1991**, *10*, 2683.
[50] H. D. Yin, J. C. Cui, Y. L. Qiao, *Polyhedron* **2008**, *27*, 2157.
[51] T. S. Basu Baul, C. Masharing, S. Basu, C. Pettinari, E. Rivarola, S. Chantrapromma, H. Fun, *Appl. Organomet. Chem.* **2008**, *22*, 114.
[52] B.-L. Wang, Y.-Z. Zhan, L.-Y. Zhang, Y. Zhang, X. Zhang, Z.-M. Li, *Phosphorus Sulfur Silicon* **2016**, *191*, 48.
[53] T. P. Lockhart, W. F. Manders, *Inorg. Chem.* **1986**, *25*, 892.
[54] T. P. Lockhart, W. F. Manders, *J. Am. Chem. Soc.* **1987**, *109*, 7015.
[55] V. Barba, E. Vega, R. Luna, H. Hopfl, I. H. Beltran, S. L. Zamudio-Rivera, *J. Organomet. Chem.* **2007**, *692*, 731.
[56] C. Ma, Y. Han, R. Zhang, *Inorg. Chim. Acta* **2007**, *360*, 2439.
[57] M. Sirajuddin, S. Ali, F. A. Shah, M. Ahmad, M. N. Tahir, *J. Iran. Chem. Soc.* **2014**, *11*, 297.
[58] J. O. Adeyemi, D. C. Onwudiwe, A. C. Ekennia, C. R. Uwaoma, E. C. Hosten, *Inorg. Chim. Acta* **2018**, *477*, 148.
[59] P. Debnath, A. Das, K. S. Singha, T. Yama, S. S. K. Singh, R. J. Butcher, L. Sieroń, W. Maniukiewicz, *Inorg. Chim. Acta* **2019**, *498*, 119.
[60] T. Sedaghat, A. Tarassoli, Z. Ansari-Asl, H. Motamedi, *J. Coord. Chem.* **2013**, *66*, 2549.
[61] Y. Anjaneyula, R. P. Rao, *Synth. React. Inorg. Met. Org. Chem.* **1986**, *16*, 257.
[62] Z. H. Chohan, A. Scozzafava, C. T. Supuran, *J. Enzyme Inhib. Med. Chem.* **2003**, *18*, 259.
[63] A. Daina, O. Michielin, V. Zoete, *Sci. Rep.* **2017**, *7*, 42717.
[64] J. M. Pallicer, M. Rosés, C. Ràfol, E. Bosch, R. Pascual, A. Port, *ADMET & DMPK* **2014**, *2*, 107.
[65] Y. Zhao, M. H. Abraham, J. Lee, A. Hersey, N. C. Luscombe, G. Beck, B. Sherborne, I. Cooper, *Pharm. Res.* **2002**, *19*, 1446.
[66] R. Kadu, H. Roy, V. K. Singh, *Appl. Organomet. Chem.* **2015**, *29*, 746.
[67] M. Gielen, L. D. Clercq, R. Willem, E. Joosen, in *Tin and Malignant Cell Growth*, (Ed: J. J. Zuckerman), CRC Press, Boca Raton, FL **1988** 39.
[68] C. Pellerito, L. Nagy, L. Pellerito, A. Szorcsik, *J. Organomet. Chem.* **2006**, *691*, 1733.
[69] A. M. Pizarro, A. Habtemariam, P. J. Sadler, *Top Organometal. Chem* **2010**, *32*, 21.
[70] A. Gennari, R. Bleumink, B. Vivani, C. L. Galli, M. Marinovich, R. Pieters, E. Corsini, *Toxicol. Appl. Pharmacol.* **2000**, *169*, 185.

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