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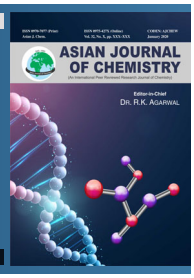

Synthesis, Characterization, Stability and Cytotoxic Evaluation of Novel Titanium(IV) Complexes of 8-Hydroxyquinoline and 2-Hydroxy-N-phenylbenzylamine Derivatives

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A new class of moisture stable heteroleptic titanium(IV) complexes, synthesized from 8-hydroxyquinoline of the type $[(Q)_2Ti(2\text{-}O\text{-}5\text{-}X\text{-}C_6H_3CH_2NC_6H_4R]$ (**3a-j**), was prepared by reacting the antecedent molecule $[(Q_2)Ti(OiPr)_2]$ (**2**) with various 2-hydroxy-*N*-phenylbenzylamine analogues in 1:1 molar ratios in dry toluene (where, HQ = 8-hydroxyquinoline; iPr = isopropyl; R = H, 4-CH_3, 4-OCH_3, 2-Cl, 4-Cl, 2-Br, 4-Br; X= H, Br). Moisture sensitive study disclosed that these new metal complexes were unreacted for 72 h. Mass spectral data were employed for proving the mono-nuclearity of the new derivatives. Thermal decomposition pattern of the new derivatives was explained by thermogravimetric analyses. Elemental analyses data are in concordance with their expected values. The hexa-coordinated way of titanium-ligand linkage is further proved through NMR, FTIR, and UV-visible spectral studies. The cytotoxic efficiency of new complexes was tested against MDA-MB-231 human breast carcinoma cell line. Complex **3a** exhibited the highest cytotoxic potential of 0.039 µM in comparison to all its analogues of this series by employing cisplatin as the standard.

Keywords: Cytotoxicity evaluation, 8-Hydroxyquinoline, Moisture Stability, Titanium complexes.

INTRODUCTION

Non-communicable diseases have become the leading causes of the ever-increasing mortality rate across the globe. Surprisingly, the vast majority of this decreasing life expectancy is due to cancer [1,2]. Though different kinds of drugs are using in the treatment of cancer, complete recovery from it is still a vexing issue. Metal-based drugs hold a strong history in the field of cancer research [3,4]. The success story of cisplatin, the first drug from the inorganic background, opened a new window for the scholars to initiate their research in the synthesis and biological evaluation of various metal complexes [5]. Among various metal complexes, titanium complexes become attractive to the researchers due to their low toxicity and fewer side effects [6].

A few titanium complexes such as budotitane and titanium dichloride have displayed substantial anticancer abilities against various cell lines [7]. However, their rapid hydrolysis in the moisture environment rendered failure in the clinical trial [8,9]. The Achilles heel in the titanium chemistry is the low stability of titanium complexes in the moisture enriched conditions [10]. The vulnerability of titanium complexes towards moisture is due to the oxophilicity of the titanium atom [11]. Moisture stable complexes are highly desirable for proper biological evaluations [12].

Based on our studies, we have found that Ti(IV) complexes with short Ti-N coordination bonds have exceptional stability in the hydrous environment [11,13,14]. In view of this, 8-hydroxyquinoline (8-HQ) is selected as a potential ligand for the synthesis process. In the present series, we have synthesized different metallacyclic heteroleptic titanium(IV) derivatives by employing 8-hydroxyquinoline and various derivatives of 2-hydroxy-*N*-phenylbenzylamines. Furthermore, we have systematically monitored the ability of all these complexes to withstand in hydrous conditions and found that all of them are stable for 4 days. Additionally, anticancer potential of all these complexes has evaluated against MDA-MB-231 human breast carcinoma cell line by using cisplatin as the standard drug.

EXPERIMENTAL

All the reagents were purified either by distillation or by re-crystallization and prior to the experiment were dried thoroughly. Toluene (S.D. Fine Chemicals, b.p., 110.6 ºC) was dried first by keeping over sodium wire for a night and later refluxed on the fractionating column for 24 h and finally, it was distilled off.

^{1}H NMR spectra: ^{1}H NMR data were obtained from a BRUKER Advance III NMR spectrometer in DMSO/$CDCl_3$ solution at 400 MHz frequency using TMS as an internal standard.

^{13}C NMR spectra: ^{13}C NMR spectral studies of the new titanium derivatives were performed in DMSO/$CDCl_3$ solution on a BRUKER Advance III NMR spectrometer at 100 MHz frequency.

FTIR analysis: FTIR spectra were taken on a Shimadzu IR affinity 1 spectrometer with anhydrous KBr pellets in the range of 4000-400 cm^{-1}.

Mass analysis: Mass spectral data of the new titanium(IV) complexes were recorded on HR-Q-Tof mass spectrometer.

Thermogravimetric analysis: Thermogravimetric analyses of the new complexes were performed on a TA instrument SDTQ 600, USA at a heating rate of 10 ºC/min from 25 ºC to 900 ºC under flowing nitrogen environment.

Elemental analysis: Elemental analyses of the complexes were carried out on an Elementar Vario EL III instrument.

UV analysis: The UV-visible spectra were taken over a range of 200-800 cm^{-1} using Jasco V-670 UV-Visible spectrophotometer.

Synthesis of 2-hydroxy-*N*-phenylbenzylamines: Previously reported method [15] was adopted for the synthesis of various derivatives of 2-hydroxy-*N*-phenylbenzylamines.

Synthesis of titanium(IV) derivatives: A previously reported [16] synthetic route was adopted for the synthesis of various new titanium(IV) derivatives.

Estimation of titanium and isopropanol: Estimation of titanium was carried out by a known method [17] and chromate oxidimetric method [18] employed for estimating the liberated isopropanol during the reactions.

Spectral data

[(*N*-(Phenyl)benzylamine-2-ato)-*bis*(8-quinolinato)-titanium(IV)] (3a): Colour: Reddish brown powder; m.p. = 178-180 °C; % Yield: 98.7 %; Alcohol estimation (Pr^iOH): Calcd. 0.46 g, Found: 0.45 g; UV (DMSO) λ_{max} (log ε, nm): 269 (5.45), 304 (5.51); IR (KBr, ν_{max}, cm^{-1}): 2937, 2912, 2861, 1815, 1749, 1600, 1573, 1494, 1463, 1448, 1373, 1319, 1257, 1105, 1064, 1051, 1010, 898, 821, 786, 740, 711, 628, 422; ^{1}H NMR (400 MHz, DMSO) δ: 8.47 (2H, dd, *J* = 1.6, 8.0 Hz, H-2, H-2′), 7.83 (2H, dd, *J* = 1.6, 8.0 Hz, H-4, H-4′), 7.45 (2H, dd, *J* = 1.6, 8.0 Hz, H-5, H-5′), 7.10 (2H, dd, *J* = 1.6, 8.0 Hz, H-6, H-6′), 7.06 (1H, t, H-4$^{\#}$), 7.02 (1H, t, H-4*), 6.99 (2H, dd, *J* = 1.6, 8.0 Hz, H-3, H-3′), 6.84 (2H, t, H-3$^{\#}$, H-5$^{\#}$), 6.75 (2H, dd, *J* = 1.6, 8.0 Hz, H-7, H-7′), 6.72 (1H, d, *J* = 6.0 Hz, H-6*), 6.67 (1H, t, H-5$^{\#}$), 6.58 (1H, d, *J* = 4.0 Hz, H-3*), 6.54 (1H, d, *J* = 4.8 Hz, H-2$^{\#}$), 6.50 (1H, d, *J* = 7.6 Hz, H-6$^{\#}$), 4.37 (2H, s, H-1**); ^{13}C NMR (100 MHz, DMSO) δ: 152.5 (C, C-2*), 151.0 (C, C-1$^{\#}$), 147.7 (C, C-8, C-8′), 142.0 (CH, C-3$^{\#}$), 135.9 (CH, C-2, C-2′), 134.8 (C, C-8a, C-8a′), 133.4 (CH, C-5$^{\#}$), 132.6 (CH, C-4, C-4′), 131.3 (C, C-1*), 130.4 (CH, C-4$^{\#}$), 129.6 (C, C-4a, C-4a′), 128.9 (CH, C-6, C-6′), 127.2 (CH, C-5*), 126.1 (CH, C-3*), 125.1 (CH, C-4*, C-5*), 124.9 (CH, C-2$^{\#}$, C-6$^{\#}$), 123.6 (CH, C-3, C-3′), 120.7 (CH, C-5, C-5′), 118.9 (CH, C-7, C-7′), 53.7 (CH_2, C-1**); HRMS: *m/z* (pos): 533.1222, $C_{31}H_{23}N_3O_3Ti$ (Calcd. 533.1219); Anal. calcd. (%) for $C_{31}H_{23}N_3O_3Ti$: C, 69.80; H, 4.35; N, 7.88; Ti, 8.97. Found (%). C, 69.92; H, 4.41; N, 7.93; Ti, 8.92.

[(*N*-(4-Methylphenyl)benzylamine-2-ato)-*bis*(8-quinolinato)titanium(IV)] (3b): Colour: Reddish brown powder; m.p. = 181-183 °C; % Yield: 98.1 %; Alcohol estimation (Pr^iOH): Calcd. 0.44 g, Found: 0.43 g; UV (DMSO) λ_{max} (log ε, nm): 267 (5.46), 325 (5.53); IR (KBr, ν_{max}, cm^{-1}): 2940, 2914, 2860, 1614, 1573, 1494, 1463, 1448, 1373, 1319, 1251, 1236, 1172, 1105, 1029, 1010, 950, 902, 821, 740, 713, 615, 432; ^{1}H NMR (400 MHz, DMSO) δ: 7.64 (2H, dd, *J* = 1.6, 8.0 Hz, H-2, H-2′), 7.47 (1H, d, *J* = 8.0 Hz, H-6*), 7.36 (1H, d, *J* = 8.0 Hz, H-3*), 7.21 (2H, dd, *J* = 1.6, 8.0 Hz, H-4, H-4′), 7.06 (2H, dd, *J* = 1.6, 8.0 Hz, H-5, H-5′), 6.88 (2H, dd, *J* = 1.6, 8.0 Hz, H-6, H-6′), 6.84 (2H, dd, *J* = 1.6, 8.0 Hz, H-3, H-3′), 6.75 (1H, t, H-4*), 6.60 (2H, dd, *J* = 1.6, 9.6 Hz, H-7, H-7′), 6.52 (1H, d, *J* = 8.4 Hz, H-3$^{\#}$), 6.36 (1H, d, *J* = 8.0 Hz, H-5$^{\#}$), 6.31 (1H, d, *J* = 8.0 Hz, H-2$^{\#}$), 6.22 (1H, d, *J* = 8.0 Hz, H-6$^{\#}$), 5.74 (1H, t, H-5*), 4.27 (2H, s, H-1**) 2.16 (3H, s, H-4$^{\#\#}$); ^{13}C NMR (100 MHz, DMSO) δ: 152.5 (C, C-8, C-8′), 151.0 (C, C-2*), 147.7 (CH, C-2, C-2′), 140.0 (C, C-1$^{\#}$), 137.2 (C, C-8a, C-8a′), 135.9 (CH, C-4, C-4′), 134.8 (C, C-4a, C-4a′), 133.5 (CH, C-3$^{\#}$), 132.2 (CH, C-5$^{\#}$), 131.6 (CH, C-6, C-6′), 130.6 (CH, C-3, C-3′), 129.5 (C, C-1*), 127.2 (C, C-4$^{\#}$), 125.5 (CH, C-6*), 125.0 (CH, C-5, C-5′), 123.2 (CH, C-4*), 122.6 (CH, C-7, C-7′), 120.7 (CH, C-3*, C-5*), 119.0 (CH, C-2$^{\#}$, C-6$^{\#}$), 53.8 (CH_2, C-1**), 20.3 (CH_3, C-4$^{\#\#}$); HRMS: *m/z* (pos): 547.1381, $C_{32}H_{25}N_3O_3Ti$ (Calcd. 547.1375); Anal. calcd. (%) for $C_{32}H_{25}N_3O_3Ti$: C, 70.36; H, 4.60; N, 7.68; Ti, 8.66. Found (%). C, 70.26; H, 4.61; N, 7.60; Ti, 8.71.

[(*N*-(4-Methoxyphenyl)benzylamine-2-ato)-*bis*(8-quinolinato)titanium(IV)] (3c): Colour: Reddish brown powder; m.p. = 187-189 °C; % Yield: 98.4 %; Alcohol estimation (Pr^iOH): Calcd. 0.46 g, Found: 0.45 g; UV (DMSO) λ_{max} (log ε, nm): 269 (5.48), 320 (5.55); IR (KBr, ν_{max}, cm^{-1}): 2928, 2905, 2859, 1591, 1573, 1510, 1494, 1463, 1446, 1373, 1319, 1230, 1105, 1004, 898, 821, 740, 711, 615, 430; ^{1}H NMR (400 MHz, DMSO) δ: 7.77 (2H, dd, *J* = 1.6, 8.0 Hz, H-2, H-2′), 7.43 (2H, dd, *J* = 1.6, 8.0 Hz, H-4, H-4′), 7.39 (2H, dd, *J* = 1.6, 8.0 Hz, H-5, H-5′), 7.16 (2H, dd, *J* = 1.6, 8.0 Hz, H-6, H-6′), 7.08 (1H, d, *J* = 7.6 Hz, H-6*), 7.04 (1H, d, *J* = 8.4 Hz, H-3*), 7.00 (1H, t, H-4*), 6.98 (1H, d, *J* = 7.6 Hz, H-3$^{\#}$), 6.80 (2H, dd, *J* = 1.6, 8.0 Hz, H-3, H-3′), 6.63 (1H, d, *J* = 7.6 Hz, H-5$^{\#}$), 6.58 (2H, dd, *J* = 1.6, 8.0 Hz, H-7, H-7′), 6.56 (1H, d, *J* = 3.6 Hz, H-2$^{\#}$), 6.49 (1H, t, H-5*), 6.42 (1H, d, *J* = 8.8 Hz, H-6$^{\#}$), 4.31 (2H, s, H-1**), 3.66 (3H, s, H-4$^{\#\#}$); ^{13}C NMR (100 MHz, DMSO) δ: 155.0 (C, C-2*), 152.5 (C, C-8, C-8′), 151.1 (C, C-4$^{\#}$), 147.7 (CH, C-2, C-2′), 136.6 (C, C-1$^{\#}$), 134.7 (C, C-8a, C-8a′), 132.6 (CH, C-4, C-4′), 131.7 (C, C-4a, C-4a′), 130.4 (CH, C-6, C-6′), 129.6 (CH, C-4*, C-6*), 128.5 (C, C-1*), 127.1 (CH, C-3*), 125.5 (CH, C-5*), 125.0 (CH, C-3, C-3′), 123.6 (CH, C-5, C-5′), 120.7 (CH, C-7, C-7′), 119.0 (CH, C-3$^{\#}$, C-5$^{\#}$), 116.9 (CH, C-2$^{\#}$, C-6#), 55.7 (CH_3, OCH_3), 53.9

(CH_2, C-1**); HRMS: *m/z* (pos): 563.1330, $C_{32}H_{25}N_3O_4Ti$ (Calcd. 563.1325); Anal. calcd. (%) for $C_{32}H_{25}N_3O_4Ti$: C, 68.22; H, 4.47; N, 7.46; Ti, 8.50. Found (%). C, 68.30; H, 4.44; N, 7.53; Ti, 8.54.

[(*N*-(2-Chlorophenyl)benzylamine-2-ato)-*bis*(8-quinolinato)titanium(IV)] (3d): Colour: Reddish brown powder; m.p. = 182-184 °C; % Yield: 98.2 %; Alcohol estimation (Pr^iOH): Calcd. 0.48 g, Found: 0.47 g; UV (DMSO) λ_{max} (log ε, nm): 262 (5.47), 308 (5.54); IR (KBr, ν_{max}, cm^{-1}): 2944, 2908, 2847, 1593, 1573, 1494, 1463, 1448, 1373, 1249, 1236, 1126, 1105, 1004, 894, 823, 785, 738, 711, 628, 432; ^{1}H NMR (400 MHz, DMSO) δ: 8.43 (1H, d, *J* = 7.6 Hz, H-3#), 7.86 (2H, dd, *J* = 1.6, 8.0 Hz, H-2, H-2′), 7.79 (1H, t, H-5#), 7.71 (1H, d, *J* = 8.0 Hz, H-6*), 7.37 (2H, t, H-4#, H-5*), 7.16 (2H, dd, *J* = 1.6, 8.0 Hz, H-4, H-4′), 7.07 (2H, dd, *J* = 1.6, 8.0 Hz, H-5, H-5′), 6.89 (2H, dd, *J* = 1.6, 8.0 Hz, H-6, H-6′), 6.84 (1H, d, *J* = 8.0 Hz, H-3*), 6.62 (1H, d, *J* = 8.0 Hz, H-6#), 6.46 (2H, dd, *J* = 1.6, 8.0 Hz, H-3, H-3′), 6.43 (1H, t, H-4*), 6.32 (2H, dd, *J* = 1.6, 8.0 Hz, H-7, H-7′), 4.21 (2H, s, H-1**); ^{13}C NMR (100 MHz, DMSO) δ: 152.7 (C, C-8, C-8′), 151.1 (C, C-2*), 147.7 (CH, C-2, C-2′), 142.2 (C, C-8a, C-8a′), 137.9 (C, C-1#), 136.7 (CH, C-3#), 135.2 (C, C-1*), 134.2 (CH, C-4, C-4′), 133.6 (C, C-4a, C-4a′), 132.2 (CH, C-6*), 131.3 (CH, C-4*), 130.3 (CH, C-5#), 129.6 (CH, C-6, C-6′), 127.3 (CH, C-4#), 126.3 (C, C-2#), 125.4 (CH, C-5*), 124.9 (CH, C-3, C-3′), 123.5 (CH, C-5, C-5′), 120.7 (CH, C-7, C-7′), 119.0 (CH, C-3*, C-6#), 53.6 (CH_2, C-1**); HRMS: *m/z* (pos): 567.0834, $C_{31}H_{22}ClN_3O_3Ti$ (Calcd. 567.0829); Anal. calcd. (%) for $C_{31}H_{22}ClN_3O_3Ti$: C, 65.57; H, 3.91; N, 7.40; Ti, 8.43. Found (%). C, 65.60; H, 3.92; N, 7.43; Ti, 8.41.

[(*N*-(4-Chlorophenyl)benzylamine-2-ato)-*bis*(8-quinolinato)titanium(IV)] (3e): Colour: Reddish brown powder; m.p. = 197-199 °C; % Yield: 98.6 %; Alcohol estimation (Pr^iOH): Calcd. 0.50 g, Found: 0.49 g; UV (DMSO) λ_{max} (log ε, nm): 268 (5.48), 314 (5.55); IR (KBr, ν_{max}, cm^{-1}): 2956, 2912, 2862, 1597, 1573, 1494, 1463, 1448, 1373, 1319, 1251, 1236, 1174, 1126, 1105, 1002, 896, 823, 785, 742, 709, 628, 438; ^{1}H NMR (400 MHz, DMSO) δ: 8.51 (2H, dd, *J* = 1.6, 8.0 Hz, H-2, H-2′), 7.98 (2H, dd, *J* = 1.6, 8.0 Hz, H-4, H-4′), 7.86 (2H, dd, *J* = 1.6, 8.0 Hz, H-5, H-5′), 7.74 (1H, t, H-4*), 7.42 (2H, dd, *J* = 1.6, 8.0 Hz, H-6, H-6′), 7.36 (2H, dd, *J* = 1.6, 8.0 Hz, H-3, H-3′), 7.23 (1H, t, H-5*), 7.15 (1H, d, *J* = 8.0 Hz, H-6*), 6.98 (2H, d, *J* = 8.0 Hz, H-3#, H-5#), 6.92 (1H, d, *J* = 8.0 Hz, H-3*), 6.86 (2H, dd, *J* = 1.6, 8.0 Hz, H-7, H-7′), 6.29 (2H, d, *J* = 8.4 Hz, H-2#, H-6#), 4.33 (2H, s, H-1**); ^{13}C NMR (100 MHz, DMSO) δ: 152.5 (C, C-8, C-8′), 151.1 (C, C-2*), 147.7 (CH, C-2, C-2′), 140.7 (C, C-1#), 135.7 (C, C-8a, C-8a′), 134.9 (CH, C-4, C-4′), 133.7 (C, C-4a, C-4a′), 132.7 (C, C-1*), 131.9 (CH, C-6, C-6′), 130.6 (CH, C-3#, C-5#), 129.5 (C, C-4#), 127.1 (CH, C-5*), 125.9 (CH, C-3*), 124.9 (CH, C-4*, C-6*), 123.6 (CH, C-3, C-3′), 122.6 (CH, C-5, C-5′), 120.7 (CH, C-7, C-7′), 119.0 (CH, C-2#, C-6#), 53.9 (CH_2, C-1**); HRMS: *m/z* (pos): 567.0832, $C_{31}H_{22}ClN_3O_3Ti$ (Calcd. 567.0829); Anal. calcd. (%) for $C_{31}H_{22}ClN_3O_3Ti$: C, 65.57; H, 3.91; N, 7.40; Ti, 8.43. Found (%). C, 65.78; H, 3.86; N, 7.54; Ti, 8.33.

[(*N*-(Phenyl)-5-bromobenzylamine-2-ato)-*bis*(8-quinolinato)titanium(IV)] (3f): Colour: Reddish brown powder; m.p. = 189-190 °C; % Yield: 98.1 %; Alcohol estimation (Pr^iOH): Calcd. 0.49 g, Found: 0.48 g; UV (DMSO) λ_{max} (log ε, nm): 263 (5.50), 322 (5.55); IR (KBr, ν_{max}, cm^{-1}): 2952, 2911, 2867, 1732, 1600, 1573, 1494, 1463, 1373, 1319, 1259, 1170, 1122, 1105, 1004, 902, 821, 785, 742, 717, 628, 465; ^{1}H NMR (400 MHz, DMSO) δ: 8.50 (2H, dd, *J* = 1.6, 8.0 Hz, H-2, H-2′), 8.40 (2H, dd, *J* = 1.6, 8.0 Hz, H-4, H-4′), 8.35 (2H, dd, *J* = 1.6, 8.0 Hz, H-5, H-5′), 7.98 (1H, d, *J* = 8.0 Hz, H-4*), 7.92 (1H, d, *J* = 8.0 Hz, H-3*), 7.84 (2H, dd, *J* = 1.6, 8.0 Hz, H-6, H-6′), 7.75 (1H, d, *J* = 8.0 Hz, H-2#), 7.43 (1H, t, H-3#), 7.38 (2H, dd, *J* = 1.6, 8.0 Hz, H-3, H-3′), 7.13 (1H, t, H-5#), 7.09 (1H, s, H-6*), 6.89 (1H, dt, H-4#), 6.56 (2H, dd, *J* = 1.6, 8.0 Hz, H-7, H-7′), 6.38 (1H, d, *J* = 7.6 Hz, H-6#), 4.2 (2H, s, H-1**); ^{13}C NMR (100 MHz, DMSO) δ: 152.5 (C, C-8, C-8′), 150.1 (C, C-2*), 147.7 (CH, C-2, C-2′), 142.1 (C, C-1#), 136.8 (C, C-1*), 135.3 (C, C-8a, C-8a′), 134.3 (CH, C-4*), 133.8 (CH, C-4, C-4′), 132.2 (CH, C-6*), 131.4 (C, C-4a, C-4a′), 129.6 (CH, C-3#, C-5#), 128.9 (CH, C-6, C-6′), 127.2 (CH, C-4#), 126.3 (CH, C-5*), 124.9 (CH, C-3, C-3′), 123.3 (CH, C-5, C-5′), 120.7 (CH, C-7, C-7′), 118.9 (CH, C-2#, C-6#), 112.4 (CH, C-3*), 55.2 (CH_2, C-1**); HRMS: *m/z* (pos): 611.0330, $C_{31}H_{22}BrN_3O_3Ti$ (Calcd. 611.0324); Anal. calcd. (%) for $C_{31}H_{22}BrN_3O_3Ti$: C, 60.81; H, 3.62; N, 6.86; Ti, 7.82. Found (%). C, 60.94; H, 3.51; N, 6.94; Ti, 7.93.

[(*N*-(4-Methylphenyl)-5-bromobenzylamine-2-ato)-*bis*(8-quinolinato)titanium(IV)] (3g): Colour: Reddish brown powder; m.p. = 192-194 °C; % Yield: 98.6 %; Alcohol estimation (Pr^iOH): Calcd. 0.50 g, Found: 0.49 g; UV (DMSO) λ_{max} (log ε, nm): 264 (5.51), 315 (5.59); IR (KBr, ν_{max}, cm^{-1}): 2944, 2900, 2845, 1815, 1724, 1614, 1573, 1519, 1494, 1462, 1373, 1319, 1257, 1236, 1122, 1105, 1082, 1002, 902, 823, 806, 785, 742, 715, 665, 430; ^{1}H NMR (400 MHz, DMSO) δ: 8.51 (2H, dd, *J* = 1.6, 8.0 Hz, H-2, H-2′), 8.41 (2H, dd, *J* = 1.6, 8.0 Hz, H-4, H-4′), 8.36 (1H, d, *J* = 8.0 Hz, H-3#), 7.99 (2H, dd, *J* = 1.6, 8.0 Hz, H-5, H-5′), 7.94 (2H, dd, *J* = 1.6, 8.0 Hz, H-6, H-6′), 7.86 (2H, dd, *J* = 1.6, 8.0 Hz, H-3, H-3′), 7.45 (2H, dd, *J* = 1.6, 8.0 Hz, H-7, H-7′), 7.41 (1H, d, *J* = 8.0 Hz, H-4*), 7.07 (1H, s, H-6*), 7.04 (1H, d, *J* = 8.8 Hz, H-5#), 6.77 (1H, d, *J* = 6.0 Hz, H-3*), 6.57 (1H, d, *J* = 8.0 Hz, H-2#), 6.31 (1H, d, *J* = 8.0 Hz, H-6#), 4.22 (2H, s, H-1**), 2.12 (3H, CH_3, H-4##); ^{13}C NMR (100 MHz, DMSO) δ: 152.5 (C, C-8, C-8′), 150.1 (C, C-2*), 147.7 (CH, C-2, C-2′), 140.0 (C, C-1#), 137.8 (C, C-1*), 136.3 (CH, C-4*), 135.7 (C, C-8a, C-8a′), 134.5 (CH, C-4, C-4′), 132.9 (C, C-4a, C-4a′), 131.5 (CH, C-6*), 130.6 (CH, C-6, C-6′), 129.6 (CH, C-3#, C-5#), 128.9 (C, C-4#), 126.3 (C, C-5*), 124.9 (CH, C-3, C-3′), 123.6 (CH, C-5, C-5′), 120.7 (CH, C-7, C-7′), 118.9 (CH, C-2#, C-6#), 112.4 (CH, C-3*), 55.4 (CH_2, C-1**), 20.3 (CH_3, C-4##); HRMS: *m/z* (pos): 625.0489, $C_{32}H_{24}BrN_3O_3Ti$ (Calcd. 625.0481); Anal. calcd. (%) for $C_{32}H_{24}BrN_3O_3Ti$: C, 61.36; H, 3.86; N, 6.71; Ti, 7.64. Found (%). C, 61.42; H, 3.90; N, 6.75; Ti, 7.67.

[(*N*-(4-Methoxyphenyl)-5-bromobenzylamine-2-ato)-*bis*(8-quinolinato)titanium(IV)] (3h): Colour: Reddish brown powder; m.p. = 195-197 °C; % Yield: 98.2 %; Alcohol estimation (Pr^iOH): Calcd. 0.44 g, Found: 0.43 g; UV (DMSO) λ_{max} (log ε, nm): 263 (5.52), 330 (5.61); IR (KBr, ν_{max}, cm^{-1}): 2932, 2904, 2856, 1573, 1462, 1373, 1319, 1259, 1230, 1172, 1105, 1002, 900, 819, 785, 742, 715, 628, 613, 484; ^{1}H NMR (400

MHz, DMSO) δ: 8.51 (2H, dd, *J* = 1.6, 8.0 Hz, H-2, H-2′), 8.42 (2H, dd, *J* = 1.6, 8.0 Hz, H-4, H-4′), 8.02 (2H, dd, *J* = 1.6, 8.0 Hz, H-5, H-5′), 7.97 (2H, dd, *J* = 1.6, 8.0 Hz, H-6, H-6′), 7.89 (2H, dd, *J* = 1.6, 8.0 Hz, H-3, H-3′), 7.79 (1H, d, *J* = 8.0 Hz, H-4*), 7.50 (2H, dd, *J* = 1.6, 8.0 Hz, H-7, H-7′), 7.46 (1H, d, *J* = 8.0 Hz, H-3*), 7.37 (1H, d, *J* = 8.0 Hz, H-3#), 7.17 (1H, s, H-6*), 7.03 (1H, d, *J* = 8.0Hz, H-5#), 6.57 (1H, d, *J* = 8.0 Hz, H-2#), 6.35 (1H, d, *J* = 8.0 Hz, H-6#), 4.09 (2H, s, H-1**), 3.63 (3H, OCH_3, H-4##); ^{13}C NMR (100 MHz, DMSO) δ: 153.7 (C, C-8, C-8′), 151.1 (C, C-2*), 148.7 (CH, C-2, C-2′), 140.2 (C, C-1#), 137.6 (C, C-1*), 136.5 (CH, C-4*), 135.6 (C, C-8a, C-8a′), 133.9 (CH, C-4, C-4′), 132.9 (C, C-4a, C-4a′), 131.5 (CH, C-6*), 130.9 (CH, C-6, C-6′), 129.6 (CH, C-3#, C-5#), 128.3 (C, C-4#), 125.9 (C, C-5*), 124.4 (CH, C-3, C-3′), 122.9 (CH, C-5, C-5′), 120.4 (CH, C-7, C-7′), 117.3 (CH, C-2#, C-6#), 111.8 (CH, C-3*), 55.7 (CH_2, C-1**), 21.9 (CH_3, C-4##); HRMS: *m/z* (pos): 641.0434, $C_{32}H_{24}BrN_3O_4Ti$ (Calcd. 641.0430); Anal. calcd. (%) for $C_{32}H_{24}BrN_3O_4Ti$: C, 59.84; H, 3.77; N, 6.54; Ti, 7.45. Found (%). C, 59.92; H, 3.81; N, 6.53; Ti, 7.57.

[(*N*-(2-Bromophenyl)-5-bromobenzylamine-2-ato)-*bis*(8-quinolinato)titanium(IV)] (3i): Colour: Reddish brown powder; m.p. = 189-191 °C; % Yield: 97.8 %; Alcohol estimation (Pr^iOH): Calcd. 0.47 g, Found: 0.46 g; UV (DMSO) λ_{max} (log ε, nm): 264 (5.53), 320 (5.58),; IR (KBr, ν_{max}, cm^{-1}): 2946, 2911, 2842, 1726, 1597, 1573, 1494, 1462, 1456, 1373, 1361, 1319, 1282, 1236, 1124, 1105, 1082, 1004, 898, 821, 785, 740, 717, 628, 461; ^{1}H NMR (400 MHz, DMSO) δ: 8.50 (2H, dd, *J* = 1.6, 8.0 Hz, H-2, H-2′), 8.41 (1H, d, *J* = 8.0 Hz, H-3#), 8.35 (2H, dd, *J* = 1.6, 8.0 Hz, H-4, H-4′), 7.98 (1H, d, *J* = 8.0 Hz, H-4*), 7.92 (1H, d, *J* = 8.0 Hz, H-3*), 7.42 (2H, dd, *J* = 1.6, 8.0 Hz, H-5, H-5′), 7.37 (2H, dd, *J* = 1.6, 8.0 Hz, H-6, H-6′), 7.17 (1H, s, H-6*), 7.09 (2H, dd, *J* = 1.6, 8.0 Hz, H-3, H-3′), 6.91 (2H, dd, *J* = 1.6, 8.0 Hz, H-7, H-7′), 6.72 (1H, t, H-5#), 6.60 (1H, dt, H-4#), 6.34 (1H, d, *J* = 8.0 Hz, H-6#), 4.12 (2H, s, CH_2, H-1**); ^{13}C NMR (100 MHz, DMSO) δ: 153.4 (C, C-8, C-8′), 151.1 (C, C-2*), 146.9 (CH, C-2, C-2′), 141.4 (C, C-1#), 136.1 (C, C-1*), 134.6 (CH, C-4*), 134.0 (C, C-8a, C-8a′), 132.9 (CH, C-6*), 132.5 (CH, C-4, C-4′), 131.2 (C, C-4a, C-4a′), 130.5 (CH, C-6, C-6′), 129.8 (CH, C-3#, C-5#), 128.5 (CH, C-4#), 126.6 (C, C-2#), 124.4 (CH, C-3, C-3′), 122.7 (CH, C-5, C-5′), 120.5 (CH, C-7, C-7′), 117.4 (CH, C-6#; C, C-5*), 112.9 (CH, C-3*), 53.2 (CH_2, C-1**); HRMS: *m/z* (pos): 688.9438, $C_{31}H_{21}Br_2N_3O_3Ti$ (Calcd. 688.9429); Anal. calcd. (%) for $C_{31}H_{21}Br_2N_3O_3Ti$: C, 53.87; H, 3.06; N, 6.08; Ti, 6.93. Found (%). C, 53.93; H, 3.15; N, 6.14; Ti, 7.02.

[(*N*-(4-Bromophenyl)-5-bromobenzylamine-2-ato)-*bis*(8-quinolinato)titanium(IV)] (3j): Colour: Reddish brown powder; m.p. = 185-187 °C; % Yield: 98.3 %; Alcohol estimation (Pr^iOH): Calcd. 0.49 g, Found: 0.48 g; UV (DMSO) λ_{max} (log ε, nm): 265 (5.53), 324 (5.60); IR (KBr, ν_{max}, cm^{-1}): 2967, 2919, 2859, 1726, 1598, 1573, 1494, 1462, 1456, 1373, 1361, 1319, 1259, 1236, 1172, 1122, 1105, 1078, 1002, 902, 806, 785, 742, 713, 628, 439; ^{1}H NMR (400 MHz, DMSO) δ: 8.51 (2H, dd, *J* = 1.6, 8.0 Hz, H-2, H-2′), 8.35 (2H, dd, *J* = 1.6, 8.0 Hz, H-4, H-4′), 8.02 (2H, dd, *J* = 1.6, 8.0 Hz, H-5, H-5′), 7.89 (2H, dd, *J* = 1.6, 8.0 Hz, H-6, H-6′), 7.80 (1H, d, *J* = 8.0 Hz, H-3#), 7.48 (2H, dd, *J* = 1.6, 8.0 Hz, H-3, H-3′), 7.44 (2H, dd, *J* = 1.6, 8.0 Hz, H-7, H-7′), 7.15 (1H, d, *J* = 8.0 Hz, H-5#), 7.13 (1H, s, H-6*), 6.88 (1H, d, *J* = 8.0 Hz, H-4*), 6.56 (1H, d, *J* = 8.0 Hz, H-3*), 6.43 (1H, d, *J* = 8.0 Hz, H-2#), 6.25 (1H, d, *J* = 8.0 Hz, H-6#), 4.28 (2H, s, CH_2, H-1**); ^{13}C NMR (100 MHz, DMSO) δ: 152.5 (C, C-8, C-8′), 150.2 (C, C-2*), 147.7 (CH, C-2, C-2′), 140.8 (C, C-1#), 137.3 (C, C-1*), 136.8 (CH, C-4*), 134.7 (C, C-8a, C-8a′), 133.3 (CH, C-6*), 132.2 (CH, C-4, C-4′), 131.7 (C, C-4a, C-4a′), 130.9 (CH, C-6, C-6′), 129.6 (CH, C-3#, C-5#), 128.9 (CH, C-4#), 126.3 (C, C-5*), 125.0 (CH, C-3, C-3′), 123.6 (CH, C-5, C-5′), 120.7 (CH, C-7, C-7′), 118.9 (CH, C-2#, C-6#), 112.4 (CH, C-3*), 55.4 (CH_2, C-1**); HRMS: *m/z* (pos): 688.9436, $C_{31}H_{21}Br_2N_3O_3Ti$ (Calcd. 688.9429); Anal. calcd. (%). for $C_{31}H_{21}Br_2N_3O_3Ti$: C, 53.87; H, 3.06; N, 6.08; Ti, 6.93. Found (%). C, 53.91; H, 3.11; N, 6.13; Ti, 7.01 (The numbering followed for the NMR interpretation is indicated in Fig. 1).

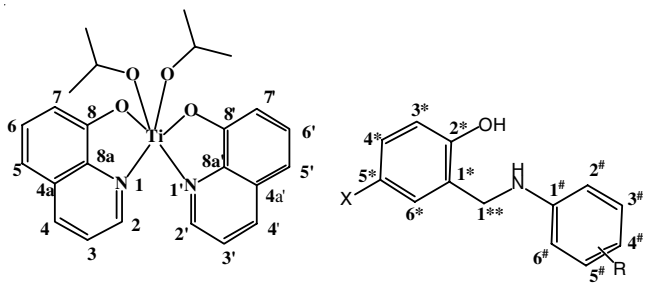


Fig. 1. Numbering followed for the NMR interpretation of the complexes

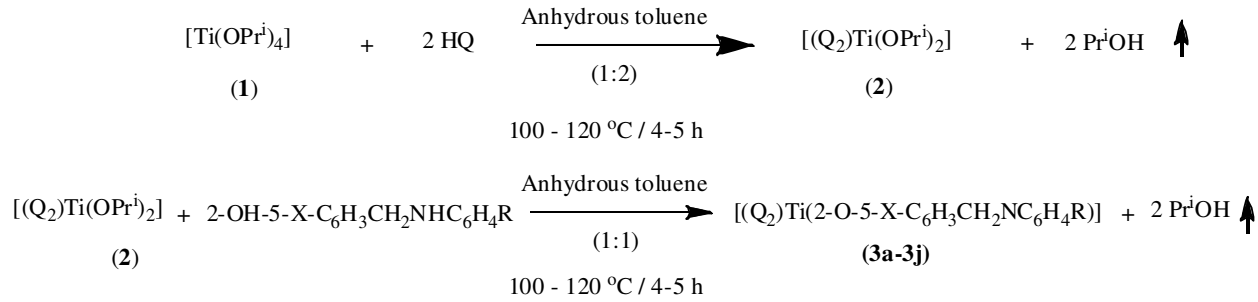
Cytotoxicity evaluation: The cytotoxicity ability of the newly synthesized derivatives was carried out on MDA-MB-231 human breast carcinoma cell line. The cell line was obtained from National Centre for Cell Science (Pune, India). Already existing procedures [19,20] were adopted for the evaluating cytotoxicity.

RESULTS AND DISCUSSION

The precursor titanium tetraisopropoxide [$Ti(OPri)_4$] (**1**) reacts with the bidentate ligand 8-hydroxyquinoline in 1:2 molar ratio in anhydrous toluene and produces the complex [$(Q_2)Ti(OPri)_2$] (**2**). Complex **2**, on treating further with 2-hydroxy-*N*-phenylbenzylamine in equimolar ratio produces titanium complexes of general formula [$(Q)_2Ti$(2-O-5-X-$C_6H_3CH_2NC_6H_4R$] (**3a-j**) as given in **Scheme-I**.

With the progress of the reaction, free isopropanol gets released in the reaction mixture. The reaction mixture containing toluene-isopropanol azeotrope was then subjected to iodometric titration for the evaluation of reaction advancement. All the reactions were very rapid and completed in 4-5 h. The newly synthesized derivatives were pale yellow in appearance with quantitative yields. These complexes are insoluble in most of the organic solvents except in DMSO and purified with anhydrous acetonitrile and toluene. Mono-nuclearity of all these complexes has been proved through mass spectra. Various substituents used for the synthesis of complexes are shown depicted in Table-1.

Elemental analysis: Elemental analyses have been carried out in order to identify the percentage of various elements present in the newly synthesized titanium complexes. The results were very close to their theoretical values. The analysis results reaffirmed the mono-nuclearity of these complexes.



[Where, HQ = 8-hydroxyquinoline; Pr^i = isopropyl; R = H, 4-CH_3, 2-Cl, 4-Cl, 2-Br, 4-Br and X= H, Br]

Scheme-I

TABLE-1
LIST OF SUBSTITUENTS USED FOR THE SYNTHESIS

Compd.	R	X	Compd.	R	X
3a	H	H	**3f**	H	Br
3b	4-CH_3	H	**3g**	4-CH_3	Br
3c	4-OCH_3	H	**3h**	4-OCH_3	Br
3d	2-Cl	H	**3i**	2-Br	Br
3e	4-Cl	H	**3j**	4-Br	Br

NMR spectral analysis: In order to explain the NMR spectra of all the newly synthesized derivatives, it had been compared with the spectra of the free ligand molecules, which were used for the synthesis of different derivatives [21-23]. The hydroxyl proton of phenols normally appears in the range δ 8.5-10.5 ppm and the -NH proton observed at the region of δ 4.5-6.5 ppm, respectively. Absence of -OH or -NH peak in the spectra of the complexes is the strong evidence for the removal of a proton from -OH and -NH groups as well as the formation of new Ti-O and Ti-N bonds. The δ values of other protons and carbons have appeared at their normal positions.

IR spectral analysis: IR interpretations have been made by matching the spectra of the complexes with that of free ligands employed for the preparation of the complexes [21-23]. The disappearance of a band in the range 3400-3100 cm^{-1} indicates the deprotonation of hydroxyl group and the subsequent formation of metal-hetero atom bonds. Two new peaks have been observed in the range 635-610 and 455-430 cm^{-1} were another proof of the removal of protons from -OH and -NH groups and the formation of Ti-O and Ti-N bonds.

Thermogravimetric analysis: In order to assess the thermal stability and the decomposition pathway, thermogravimetric analyses were performed up to 900 ºC for three complexes (**3c**, **3e** and **3h**). These molecules exhibited multiple decomposition patterns due to the pyrolysis of organic moieties at different temperatures. Complex **3c** undergoes two decompositions before it reaches the thermodynamically stable form. The first decomposition observed at 336.73 ºC is due to the pyrolysis of aromatic moieties present in the Schiff's base part of the complex. At this stage, the complex suffered a weight loss of 39.40 % against the expected value of 40.33 %. The next stage of dissociation appeared at 504.30 ºC and the molecule had undergone a weight loss of 45.80 % against its theoretical value of 45.48 %. This is due to the dissociation of quinoline moiety present in the complex. The amount of TiO_2 obtained at the end of the analysis was found as 14.80 % compared to the theoretical value of 14.10 %. The stable TiO_2 obtained for other complexes are 14.74 % (**3e**) and 13.18 % (**3h**) compared to their expected value of 14.57 % and 13.03 %, respectively.

UV-visible spectral analysis: Dimethyl sulfoxide was used for recording the UV-visible spectra of these derivatives. Each complex exhibited multiple absorption bands. The first λ-maximum is due to the n-π* transition and the absorption bands appeared in the range 310-330 nm are due to the ligand to titanium charge transfer [11,24].

Mass spectral analysis: High-resolution mass spectra were employed for recording the molecular weight of the newly synthesized titanium(IV) derivatives. Nuclearity of all these derivatives was found as one. Additionally, the mass spectral data are close to their expected molecular weight of the complexes.

Stability studies: The inability to stay in the hydrous condition is the Achilles heel of most of the titanium(IV) complexes. Though some of the titanium complexes displayed promising tumour-inhibiting potentials, their weak stability restrained them from further development. The inability of titanium complexes to withstand in water enriched environment is due to the oxophilicity of titanium. This results in the disintegration of the complex into various ligand fragments as well as thermodynamically stable titanium dioxide [11].

UV-visible spectroscopy was employed for the stability evaluation. In the case of titanium complexes, absorption band appeared in the range of 310-330 nm was the signature of the ligand-to-metal charge transfer band (LMCT). This signal was considered as a reference for the stability evaluation. The absorption band is neither turning to zero nor changing its position even after a period of 96 h in the hydrous environment. However, a small decrease noticed in the absorbance values in the course of measurements could be considered as the slow dissociation of the complexes in the moist medium. The enhanced stability of these titanium(IV) derivatives is due to the small Ti-N bond [11], which is missing in the case of well-known tumour inhibiting complexes like Budotitane and Titanocene dichloride. Fig. 2 represents the UV-visible absorption overtime for the complex **3h**.

Cytotoxicity evaluation: All the newly synthesized Ti(IV) derivatives were subjected to cytotoxicity evaluation. The cytotoxicity potential of titanium complexes was determined according to reported procedures [19,20]. The study was performed on MDA-MB-231 human breast carcinoma cell line and found that all these new complexes have moderate tumour inhibiting potentials.

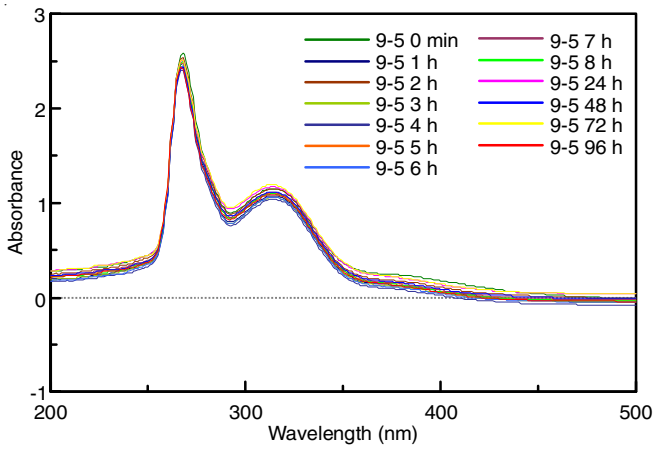


Fig. 2. UV-visible absorption overtime for [(*N*-(4-methoxyphenyl)-5-bromobenzylamine-2-ato)-*bis*(8-quinolinato)titanium(IV)] (**3h**) upon addition of water

It has been found from the *in-vitro* study that all these new derivatives (**3a-j**) have substantial antitumor activity against the cell line tested. Complex **3a** showed the highest potential of 0.039 µM against 0.017 µM of cisplatin [25]. The higher activity of this complex compared to all its analogues is due to the presence of smaller and potent Schiff's base ligands. Additionally, complex **3e** was found as the least active molecule in this series and its low antiproliferative activity presumably due to the presence of bulky electron-withdrawing group in the complex. Antitumor efficiency of 4-methyl substituted titanium(IV) derivative has been found as moderate. However, a decrease in activity was observed while replacing the methyl group with a methoxy moiety. This difference in activity is because of the larger methoxy group. Complex without any substitution on the aniline moiety exhibited more cytotoxic potential than complexes with various substitutions. The cytotoxicity potential of complexes (**3a-j**) is depicted in Table-2.

TABLE-2
CYTOTOXICITY VALUES OBTAINED FOR COMPLEXES **3a-j**

Compd.	IC_{50} (µM)	Compd.	IC_{50} (µM)
3a	0.0394 ± 0.0039	**3g**	0.1366 ± 0.0052
3b	0.0877 ± 0.0057	**3h**	0.1346 ± 0.0019
3c	0.1279 ± 0.0033	**3i**	0.1142 ± 0.0027
3d	0.0748 ± 0.0084	**3j**	0.1316 ± 0.0048
3e	0.1674 ± 0.0091	Cisplatin	0.0166 ± 0.0047
3f	0.0474 ± 0.0049	–	–

(± = Standard error)

Conclusion

The stability study confirms that all the newly synthesized titanium(IV) derivatives have an ability to withstand in a moist environment for a period of 96 h. The NMR and UV-visible spectra are the direct proof of their stability. The binding of titanium(IV) through nitrogen and oxygen atoms have been confirmed by IR and NMR spectroscopy. Elemental analyses and TGA results were in accordance with the theoretical values. Monomeric nature of all these derivatives had been confirmed through mass spectra. Therefore, based on the available literature and the characterization data, *cis*-octahedral geometry had been proposed around titanium(IV) with hexa-coordination for these newly synthesized titanium(IV) complexes, which were derived from various derivatives of 2-hydroxy-*N*-phenylbenzylamines. Fig. 3 represents the proposed tentative structure of the newly synthesized Ti(IV) derivatives.

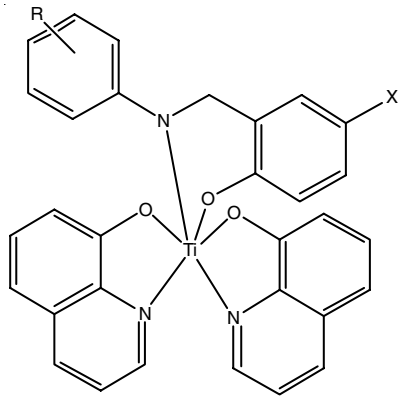


Fig. 3. Proposed structure of the titanium(IV) derivatives

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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