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A new series of moisture resistant metallacyclic titanium(IV) derivatives prepared from 8-hydroxyquinoline of the general formulae [(Q2)Ti{(L1)(L2OR)}] (3a-b, 3d-e), [(Q2)Ti{(L1)(L3)}] (3c) and [(Q2)Ti(L4)] (3g and 3h) is synthesized by interacting the precursor molecule [(Q2)Ti(OiPr)2] (2) with various 2-heteroaryl methyl ketone oximes and various alkoxyalkanols/2-hydroxypyridine or only with catechol/resorcinol in 1:1:1 or in 1:1 molar ratios in anhydrous boiling toluene (where, HQ = 8-hydroxyquinoline; iPr = isopropyl; L1H = HONC(Me)py-2/HONC(Me)fu-2; L2 = O-CH2-CH2-; R = CH3, C2H5; L3 = 2-hydroxypyridine and L4H = catechol/resorcinol). Stability study revealed that these molecules were stable for a period of 72 h. Mononuclear nature of the complexes was confirmed through mass spectral analysis. Thermogravimetric results explain the multistage fragmentation of the complexes at 900 °C. NMR, FTIR, and UV-visible spectral data suggested that titanium-ligands attachment is in a hexa-coordinated manner. Additionally, all these molecules were tested for their tumour inhibiting potential against MDA-MB-231 human breast carcinoma cell line.

Keywords: 8-Hydroxyquinoline, Titanium complexes, Cytotoxicity evaluation, Moisture stability, Metal-to-ligand charge transfer.

INTRODUCTION

The triumph of cisplatin as a metal-containing therapeutics has opened a new avenue for the researchers for the synthesis and activity evaluation of various metal-based drugs [1-3]. Among the various metal complexes, titanium based complexes have captured the attention of researchers due to their diverse applications including their potential cytotoxic efficiency [4]. Two titanium complexes namely, budotitane and titanocene dichloride have displayed substantial tumour inhibiting potential against different cell lines [5]. However, these complexes have extremely low stability in the moisture-enriched environment [6]. This undesirable attribute rendered them in failure in the clinical trial [7].

In order to prevail the achilles heel of titanium complexes we have selected 8-hydroxyquinoline (8-HQ) as a ligand. Though several titanium-HQ complexes have already been reported [8-10], their tumour inhibiting potential has never been an area of investigation. In the present series, we have synthesized different heteroleptic titanium derivatives which are prepared from 8-HQ and with different ketone oximes and various alkoxyalkanols or 2-hydroxypyridine or only with catechol or resorcinol. Additionally, we have studied the stability of all these molecules in the moisture-enriched environment and found that all these complexes are stable in hydrous condition for a period of 72 h.

Tumour has become one of the destructive diseases across the globe. Though various kinds of drugs are available in the market, the complete annihilation of this deadly disease is still a vexing issue [11]. Preparation of efficient cytotoxic drug is the only remedy for mitigating such a deleterious situation. Hence, we have decided to prepare various 8-HQ-titanium complexes and evaluate their tumour inhibiting efficiency against MDA-MB-231 human breast carcinoma cell line by employing cisplatin as the standard drug.

EXPERIMENTAL

All the reagents purified either by distillation or by recrystallization and prior to the experiment were dried thoroughly.
Spectra were taken over a range of 200-800 cm\(^{-1}\) using a JASCO spectrometer. Analyses of new complexes were performed on a TA instrument under flowing nitrogen environment.

Fourier transform infrared: FTIR spectra were taken on a SHIMADZU IR affinity 1 spectrometer with anhydrous KBr pellets in the range of 4000-400 cm\(^{-1}\).

Mass spectrometry: Mass spectral data of new titanium complexes were recorded on an HR-Q-TOF mass spectrometer.

Thermogravimetric analysis: Thermogravimetric analyses of new complexes were performed on a TA instrument.

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

Ultraviolet-visible spectrophotometry: The UV-visible spectra were taken over a range of 200-800 cm\(^{-1}\) using JASCO V-670 UV-Visible spectrophotometer.

Synthesis of oximes: Oximes were prepared by a reported method and all of them were recrystallized in hot water.

Estimation of titanium and isopropanol: Estimation of titanium was carried out by a known method and chromate was used for monitoring the progress of reaction by estimating the liberated isopropanol during the course of the reactions.

Synthesis of bis(8-quinolinolato)titanium(IV) (3b): Colour: Pale yellow powder; Yield: 97.9 %; Alcohol estimation (PrOH): calcld. (found): 0.47 g (0.46 g); UV (DMSO) \(\lambda_{\text{max}}\) (log e): 267 (5.72), 316 (5.80) nm; IR (KBr, \(v_{\text{max}}\) cm\(^{-1}\)):

4.72 (2H, t, -OCH\(_2\)), 4.25 (2H, t, -CH\(_2\)O), 3.36 (3H, s, -OCH\(_3\)), 2.91 (3H, s, \(\text{H}^1\)), \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 155.7 (C, C-2\(^\prime\)), 153.3 (C, C-2\(^\prime\)\(^\prime\)), 151.7 (C, C-8, C-8\(^\prime\)), 149.4 (CH, C-2, C-2\(^\prime\)), 148.3 (CH, C-6\(^\prime\)), 136.0 (CH, C-4\(^\prime\)), 132.1 (C, C-8a, C-8\(^\prime\)a), 130.5 (CH, C-4, C-4\(^\prime\)), 129.2 (C, C-4a, C-4\(^\prime\)a), 128.9 (CH, C-6, C-6\(^\prime\)), 126.5 (CH, C-3, C-3\(^\prime\)), 123.5 (CH, C-5\(^\prime\)), 122.9 (CH, C-3\(^\prime\)), 121.6 (CH, C-5, C-5\(^\prime\)), 117.1 (CH, C-7, C-7\(^\prime\)), 75.8 (CH\(_2\), -OCH\(_3\)), 72.8 (CH\(_2\), -CH\(_2\)O), 61.5 (CH\(_3\), -OCH\(_3\)), 15.7 (CH\(_3\), C-1\(^\prime\)); HRMS: \(m/z\) (pos): 546.1390, C\(_{23}\)H\(_{23}\)N\(_2\)O\(_{4}\)Ti (calcld. 546.1383); Anal. calcld. (found) % for C\(_{23}\)H\(_{23}\)N\(_2\)O\(_{4}\)Ti: C, 65.11 (65.72); H, 4.80 (4.73); N, 10.25 (10.30); Ti, 8.76 (8.51).

[2-Acetylpyridineoximato-2-ethoxyethanolo-bis(8-quinolinolato)titanium(IV)] (3b): Colour: Pale yellow powder; Yield: 97.9 %; Alcohol estimation (PrOH): calcld. (found): 0.47 g (0.46 g); UV (DMSO) \(\lambda_{\text{max}}\) (log e): 267 (5.72), 316 (5.80) nm; IR (KBr, \(v_{\text{max}}\) cm\(^{-1}\)):

4.72 (2H, t, -OCH\(_2\)), 4.25 (2H, t, -CH\(_2\)O), 3.36 (3H, s, -OCH\(_3\)), 2.91 (3H, s, \(\text{H}^1\)), \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 155.7 (C, C-2\(^\prime\)), 153.3 (C, C-2\(^\prime\)\(^\prime\)), 151.7 (C, C-8, C-8\(^\prime\)), 149.4 (CH, C-2, C-2\(^\prime\)), 148.3 (CH, C-6\(^\prime\)), 136.0 (CH, C-4\(^\prime\)), 132.1 (C, C-8a, C-8\(^\prime\)a), 130.5 (CH, C-4, C-4\(^\prime\)), 129.2 (C, C-4a, C-4\(^\prime\)a), 128.9 (CH, C-6, C-6\(^\prime\)), 126.5 (CH, C-3, C-3\(^\prime\)), 123.5 (CH, C-5\(^\prime\)), 122.9 (CH, C-3\(^\prime\)), 121.6 (CH, C-5, C-5\(^\prime\)), 117.1 (CH, C-7, C-7\(^\prime\)), 75.8 (CH\(_2\), -OCH\(_3\)), 72.8 (CH\(_2\), -CH\(_2\)O), 61.5 (CH\(_3\), -OCH\(_3\)), 15.7 (CH\(_3\), C-1\(^\prime\)); HRMS: \(m/z\) (pos): 546.1390, C\(_{23}\)H\(_{23}\)N\(_2\)O\(_{4}\)Ti (calcld. 546.1383); Anal. calcld. (found) % for C\(_{23}\)H\(_{23}\)N\(_2\)O\(_{4}\)Ti: C, 65.11 (65.72); H, 4.80 (4.73); N, 10.25 (10.30); Ti, 8.76 (8.51).
Hz, H-6*), 7.11 (1H, t, H-4*), 6.98 (1H, dd, J = 1.2, 7.6 Hz, H-4*), 6.36 (1H, d, J = 8.0 Hz, H-3*), 6.31 (1H, dd, J = 1.6, 8.0 Hz, H-5*), 6.17 (1H, t, H-5*), 2.36 (3H, s, H-1'); 13C NMR (100 MHz, CDCl3) δ: 156.5 (C, C-2*), 153.5 (C, C-2*), 151.4 (C, C-2*), 149.4 (CH, C-6*), 147.8 (C, C-8, C-8*), 146.0 (CH, C-4*), 145.2 (CH, C-2, C-2), 139.8 (C, C-8a, C-8*a), 136.0 (CH, C-4*), 133.3 (CH, C-5*), 131.6 (CH, C-4, C-4*), 128.9 (C, C-4a, C-4*a), 127.6 (CH, C-6, C-6*), 125.5 (CH, C-6), 123.6 (CH, C-3, C-3*), 122.6 (CH, C-3, C-3*), 121.7 (CH, C-5, C-5*), 119.2 (CH, C-4*), 117.8 (CH, C-7, C-7*), 102.3 (CH, C-5*), 15.9 (CH, C-1'); HRMS: m/z (pos): 565.1236, C36H27N5O4Ti (calcd. 565.1230); Anal. calc'd. (found) % for C36H27N5O4Ti: C, 63.73 (63.87); H, 4.11 (4.21); N, 12.39 (12.33); Ti, 8.47 (8.62).

[2-Acetylfuranoximato-2-methoxyethanolato-bis(8-quino-
linolato)titanium(IV)] (3d): Colour: pale yellow powder; Yield: 98.7 %; Alcohol estimation (PrOH); calcd. (found): 0.49 g (0.48 g); UV (DMSO) λmax (log ε): 266 (5.37), 315 (4.55) nm; IR (KBr, νmax, cm⁻¹): 2930, 2913, 2854, 1708, 1602, 1575, 1498, 1469, 1379, 1323, 1276, 1230, 1163, 1019, 981, 823, 745, 715, 624, 426; 1H NMR (400 MHz, CDCl3) δ: 8.30 (2H, dd, J = 1.6, 8.0 Hz, H-2'), 7.97 (2H, dd, J = 1.6, 8.0 Hz, H-4'), 7.60 (2H, dd, J = 1.6, 8.0 Hz, H-5*), 7.39 (2H, dd, J = 1.6, 8.0 Hz, H-6'), 7.09 (2H, dd, J = 1.6, 8.0 Hz, H-3'), 7.03 (2H, dd, J = 1.6, 8.0 Hz, H-7'), 6.48 (1H, d, J = 8.0 Hz, H-5*), 5.96 (1H, t, H-4*), 5.79 (1H, d, J = 8.0 Hz, H-3*), 3.66 (2H, t, -OCH3), 3.43 (2H, t, -CHO2), 3.32 (3H, s, -OCH3), 2.18 (3H, s, H-1'''); 13C NMR (100 MHz, CDCl3) δ: 155.3 (C, C-2*), 150.8 (C, C-8, C-8*), 149.4 (CH, C-2, C-2*), 146.7 (C, C-2*), 143.9 (CH, C-5*), 136.1 (C, C-8a, C-8*a), 133.1 (CH, C-4, C-4*), 131.5 (C, C-4a, C-4*a), 129.9 (CH, C-6, C-6*), 128.8 (CH, C-3, C-3*), 126.6 (CH, C-5, C-5*), 122.6 (CH, C-6), 121.1 (CH, C-7, C-7*), 117.2 (CH2, 78.0 (CH3, -OCH3), 72.9 (CH3, -CH2O), 61.6 (CH3, OCH3), 15.0 (CH3, C-1'''); HRMS: m/z (pos): 535.1225, C32H26N4O7Ti (calcd. 535.1223); Anal. calc'd. (found) % for C32H26N4O7Ti: C, 62.83 (62.63); H, 4.04 (4.22); N, 10.10 (10.03); Ti, 8.63 (8.95).

[Benzene-1,2-diolato-bis(8-quinolino- 
latinum(IV)) (3g): Colour: Chocolate brown powder; Yield: 98.3 %; Alcohol estimation (PrOH); calcd. (found): 0.47 g (0.46 g); UV (DMSO) λmax (log ε): 263 (5.37), 316 (5.45) nm; IR (KBr, νmax, cm⁻¹): 2940, 2921, 2856, 1602, 1573, 1496, 1463, 1375, 1315, 1109, 767, 750, 644, 422; 1H NMR (400 MHz, CDCl3) δ: 8.87 (2H, dd, J = 1.6, 8.0 Hz, H-2', H-2'), 8.38 (1H, d, J = 7.6 Hz, H-3*), 7.58 (2H, dd, J = 1.6, 8.0 Hz, H-4', H-4'), 7.47 (1H, t, H-4'), 7.42 (2H, dd, J = 1.6, 8.0 Hz, H-5', H-5'), 7.25 (1H, t, H-5'), 7.17 (1H, d, J = 7.6 Hz, H-6'), 7.12 (2H, dd, J = 1.6, 8.0 Hz, H-6', H-6*), 6.73 (2H, dd, J = 1.6, 8.0 Hz, H-3', H-3*), 6.60 (2H, dd, J = 1.6, 8.0 Hz, H-7', H-7*); 13C NMR (100 MHz, CDCl3) δ: 152.4 (C, C-8, C-8*), 148.2 (CH, C-2, C-2*), 145.2 (C, C-1', C-1''), 132.4 (C, C-8a, C-8*a), 130.9 (CH, C-4, C-4*), 129.9 (C, C-4a, C-4*a), 127.9 (CH, C-6, C-6*), 126.5 (CH, C-3, C-3*), 125.0 (CH, C-5, C-5*), 123.4 (CH, C-4, C-4*), 121.1 (CH, C-7, C-7*), 117.2 (CH, C-6', C-6*); HRMS: m/z (pos): 444.0594, C34H29N5O7Ti (calcd. 444.0590); Anal. calc'd. (found) % for C34H29N5O7Ti: C, 64.88 (64.90); H, 3.63 (3.64); N, 6.31 (6.61); Ti, 10.77 (10.74).

[Benzene-1,3-diolato-bis(8-quinolino- 
latinum(IV)) (3h): Colour: reddish brown powder; Yield: 98.6 %; Alcohol estimation (PrOH); calcd. (found): 0.44 g (0.43 g); UV (DMSO) λmax (log ε): 262 (5.37), 318 (5.46) nm; IR (KBr, νmax, cm⁻¹): 2946, 2926, 2861, 1573, 1496, 1463, 1375, 1321, 1301, 1269, 1166, 1134, 1077, 975, 782, 744, 630, 426; 1H NMR (400 MHz, CDCl3) δ: 8.50 (2H, dd, J = 1.6, 8.0 Hz, H-2', H-2*), 8.25 (2H, dd, J = 1.6, 8.0 Hz, H-4', H-4*), 7.24 (2H, dd, J = 1.6, 8.0 Hz, H-5', H-5*), 7.15 (2H, dd, J = 1.6, 8.0 Hz, H-6'), 7.06 (1H, d, J = 8.0 Hz, H-4*), 6.94 (1H, s, H-2*), 6.81 (2H, dd, J = 1.6, 8.0 Hz, H-3', H-3*), 6.23 (1H, d, J = 8.0 Hz, H-6'), 6.20 (1H, dd, J = 1.6, 8.0 Hz, H-5*), 6.13 (2H, dd, J = 1.6, 8.0 Hz, H-6').
Hz, H-7, H-7'); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$: 149.7 (C, C-8, C-8'), 147.6 (CH, C-2, C-2'), 145.9 (C, C-1', C-3'), 137.9 (C, C-8a, C-8a'), 136.3 (CH, C-4, C-4'), 135.3 (CH, C-5'), 130.8 (C, C-4a, C-4a'), 129.2 (CH, C-6, C-6'), 126.2 (CH, C-3, C-3'), 124.4 (CH, C-5, C-5'), 123.8 (CH, C-4', C-6), 120.9 (CH, C-7, C-7'), 95.9 (CH, C-2'), HRMS: $m/z$ (pos): 444.0598, C$_{24}$H$_{16}$N$_2$O$_4$Ti (calcd. 444.0590); Anal. calcd. (found) % for C$_2$: 124.4 (CH, C-5, C-5'), 123.8 (CH, C-4', C-6'), 120.9 (CH, C-7, C-7'), 95.9 (CH, C-2').

Cytotoxicity: The study was performed on MDA-MB-231 breast cancer cell line. The cell line was obtained from National Centre for Cell Science (Pune, India). The cells were maintained in L-15 (Leibovitz's) culture medium with 10% fetal bovine serum in a humidified atmosphere at 37 °C. The cell line was maintained in their growing phase at 70% confluency with regular passaging.

Cytotoxic potential of titanium derivatives was tested using MTT assay. MDA-MB-231 cells cultured in the culture medium (with 10% serum), were seeded (200 µL, 6 x 10$^3$ cells/well) in a 96-well plate and incubated at 37 °C for 24 h. After incubation, the control wells were replenished with fresh medium and the test wells were treated with 25, 50 and 100 µL of complexes. The cells were further incubated for 72 h maintaining the same conditions. After the treatment incubation period, medium in each well was replenished with 200 µL of fresh medium plus 50 µL of MTT (0.6 mg/mL containing 25 µL PMS). The plate was then re-incubated for 4 h in the same conditions after which the absorbance was measured at 450 nm (with a 630 nm reference filter) in a Dynex Opsys MRTM Microplate Reader (Dynex Technologies, VA, USA). All assays were carried out in duplicate. Percentage cytotoxicity was calculated by the following formula:

$$\text{Cytotoxicity (\%)} = \frac{A_c - A_t}{A_c} \times 100$$

where, $A_c$ is the mean absorbance of the control wells and $A_t$ is the mean absorbance of test wells with a particular extract dosage.

[Scheme-I]

RESULTS AND DISCUSSION

All the new titanium(IV) derivatives have been subjected for elemental analysis and their results are matched with the theoretical values. The elemental analyses results are the direct proof for the mononuclear nature of all these new complexes.

Treatment of titanium tetraisopropoxide [Ti(OPr)$_4$] (1) with 8-hydroxyquinoline (HQ) in 1:2 mole ratio in anhydrous toluene yields (Q$_2$)Ti(OPr)$_2$ (2). The precursor molecule (1) reacted with a mixture of 2-heteroaryl methyl ketone oximes and alkoxyalkanols or 2-hydroxypyridine in 1:1:1 molar ratios gives mononuclear titanium complexes of general formulae [(Q$_2$)Ti{(L$_1$)(L$_2$)OR}], [(Q$_2$)Ti{(L$_1$)(L$_3$)}] and [(Q$_2$)Ti(L$_4$)] as given in Scheme-I.

The reaction progress was assessed by determining the liberated isopropanol in toluene-isopropanol azeotrope by oxidimetric titration. The reactions were very rapid and got over in 4-5 h. The products obtained were orange/yellow powder in quantitative yield. All these derivatives are sparingly soluble in common organic solvents except in CHCl$_3$ and DMSO and can be purified with anhydrous n-hexane and toluene. Based on the mass spectra and elemental analysis data, the monomeric nature of all new derivatives has been confirmed (structure of different ligands used for the synthesis is presented in Table-1).

NMR analysis: The NMR data of the new derivatives have been explained by examining it with the free spectra of the ligands used for the preparation [16, 17]. The hydroxyl signal of oximes, alkoxyalkanols, dihydric phenols and 2-hydroxypyridine are observed in the region δ 8.35-10.50 ppm. The absence of these signals in the above region is the true evidence of deprotonation of hydroxyl group as well as the development of new Ti-O and Ti-N bond. The δ values of other protons as well as carbons are obtained in the expected range.

IR analysis: IR spectral interpretations of all new complexes have been carried out by matching it with the free ligand.
Table 1: Various ligands used for the synthesis of various derivatives

<table>
<thead>
<tr>
<th>Complex No.</th>
<th>L₁</th>
<th>L₂</th>
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</thead>
<tbody>
<tr>
<td>3a</td>
<td></td>
<td>OHCH₂CH₂OCH₃</td>
</tr>
<tr>
<td>3b</td>
<td></td>
<td>OHCH₂CH₂OC₂H₅</td>
</tr>
<tr>
<td>3c</td>
<td></td>
<td>OHCH₂CH₂OCH₃</td>
</tr>
<tr>
<td>3d</td>
<td></td>
<td>OHCH₂CH₂OC₂H₅</td>
</tr>
<tr>
<td>3e</td>
<td></td>
<td>OHCH₂CH₂OCH₃</td>
</tr>
<tr>
<td>3f</td>
<td></td>
<td>OHCH₂CH₂OC₂H₅</td>
</tr>
</tbody>
</table>

Complex No. L₄ -
3g -
3h -

spectra [8,16,18]. The appearance of a couple of peaks in the range 2931-2849 cm⁻¹ is due to the presence of alkoxyalkanol moiety in the complexes. Lack of any peak in the range 3500-3300 cm⁻¹ is the direct evidence for the deprotonation of hydroxyl groups from various ligands used for the process of synthesis. The existence of two new peaks in the region 630-618 and 485-435 cm⁻¹ confirmed the formation of Ti-O and Ti-N bonds. Additionally, just as our expectation, a peak has been observed at 1705-1695 cm⁻¹ for two molecules (3c & 3f) as the signature of ν(C=O) stretching frequency in the molecule.

Thermal analysis: Thermal stability as well as the decomposition pattern of new titanium derivatives has been evaluated by employing thermogravimetric analyses at 900 °C. Analyses have been carried out for three representative molecules (3b, 3g and 3h). All the molecules have undergone multiple stages of weight loss due to the decomposition of organic components. In case of complex 3b, aliphatic residue undergoes dissociation at 269.57 °C and the complex suffered a weight loss of 15.75 % against the theoretical value of 16.10 %. The second decomposition happened at a temperature of 392.73 °C and it is because of the dissociation of pyridine moiety present in the complex. Weight loss occurred at this stage was 22.85 % and the corresponding theoretical value was 24.10 %. The third and final decomposition of complex took place at 490.82 °C and this is due to the pyrolysis of quinoline rings of the complex. The weight loss observed at this stage was 46.20 % and the expected value at this stage was 45.73 %. Residual TiO₂ was found as 15.2 % and the corresponding theoretical value was 14.07 %. The residual TiO₂ values for other complexes are 16.84 % (complex 3g) and 16.65 (complex 3h) against their theoretical value of 17.98 %.

UV-visible analysis: Dimethyl sulfoxide was employed in order to record the UV-visible spectra of the complexes. Each and every derivative displayed multiple absorption bands. The first λ-maximum is due to the n-π* transition and the bands observed in the range of 305-325 nm arose due to the ligand to metal charge transfer (LMCT) band [19,20].

Mass analysis: High-resolution mass spectra were recorded for all the new titanium(IV) derivatives. The analysis report closely matches with their theoretical values and indicates the mono nuclearity of these derivatives.

Stability studies: One of the major limitations of Ti(IV) complexes including the well-known tumour inhibiting complexes such as budotitane and titanocene dichloride is their low stability in water enriched environment. The lack of stability of titanium complexes in a moisture environment is owing to the oxophilicity of titanium metal which causes the depletion of both inorganic as well as organic moieties [20]. UV-visible spectrometer was employed in order to assess the stability of the newly synthesized complexes. A band observed at 305-325 nm, indicates the LMCT band which does not turn to zero even after 72 h in hydrous condition. There was neither appearance of any new band nor slight shifting too in the existing peaks was observed during the course of the study. But, there were some visible changes in the absorbance, which is presumably due to the slow decomposition of the complex compared to rapid hydrolysis of other titanium complexes. The exceptional stability of titanium(IV) complexes is due to the formation of short Ti-N coordination bond [20] which is absent in the case of metallocene as well as β-diketonato complexes. Fig. 1 represents the UV-visible absorption overtime for the complex 3d.

Cytotoxicity evaluation: Newly synthesized titanium(IV) derivatives were subjected to cytotoxicity evaluation. The
cytotoxicity potential of titanium complexes was evaluated according to reported procedures [21,22]. The study was performed on MDA-MB-231 human breast carcinoma cell line. In this series, a few molecules displayed good antiproliferative activity. Moderate activity was observed for the remaining molecules. Complex 3h was identified as the highest tumour inhibiting molecule among all its derivatives and its cytotoxic potential was found to be 0.05 µM against 0.017 µM of a well-known tumour inhibiting drug cisplatin [23]. The highest cytotoxic property of this molecule is due to its excellent symmetric arrangement [24]. The lower cytotoxic potential of complexes 3a and 3b is probably due to the presence of large steric groups in the complex. Nevertheless, complex 3c exhibited good anti-tumor activity and its greater inhibiting potential is presumably due to the presence of one extra pyridine ring in the complex, which is absent in the former two complexes.

The tumour inhibiting potential of complexes 3d and 3e are also not promising. Because of bulkier groups, tumour inhibiting potentials of these complexes are decreased substantially. However, these complexes have more cytotoxic potential than their pyridine analogues. This variation in the cytotoxicity is presumably due to the lower steric strain of 5-membered cyclopentadienyl group compared to 6-membered pyridine moiety. Lower steric strain and the presence of a potential 5-membered furanyl ring make the complex 3f more potent than its other analogue molecules. Though complex 3h is the position isomer of molecule 3g, their symmetry difference caused complex 3h is more potent than its isomer. The cytotoxicity values obtained for the complexes (3a-h) are depicted in Table-2.

### Table-2

<table>
<thead>
<tr>
<th>Complex No.</th>
<th>IC(_{50}) (µM)</th>
<th>Complex No.</th>
<th>IC(_{50}) (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>0.2902 ± 0.0036</td>
<td>3f</td>
<td>0.0796 ± 0.0047</td>
</tr>
<tr>
<td>3b</td>
<td>0.3095 ± 0.0077</td>
<td>3g</td>
<td>0.0623 ± 0.0071</td>
</tr>
<tr>
<td>3c</td>
<td>0.1348 ± 0.0018</td>
<td>3h</td>
<td>0.0503 ± 0.0026</td>
</tr>
<tr>
<td>3d</td>
<td>0.2685 ± 0.0022</td>
<td></td>
<td>0.0166 ± 0.0047</td>
</tr>
<tr>
<td>3e</td>
<td>0.2869 ± 0.0039</td>
<td></td>
<td>–</td>
</tr>
</tbody>
</table>

**Conclusion**

The stability studies results confirm the enhanced stability of newly synthesized titanium complexes. Additionally, neither was there formation of any new peak nor decomposition of any band during the course of 72 h of study. Thus, a ligand to metal charge transfer theory has supported our results and was confirmed through UV-visible spectral studies. The deprotonation of ligands and bonding of titanium through heteroatoms have been identified by IR and NMR spectra. Elemental analyses results and the TGA fragmentation patterns are in agreement with the theoretical values. Mass spectral analyses results proposed mono-nuclearity for all these derivatives. Therefore, based on the spectral data and available literature [9,10], we have proposed a hexacoordinated cis octahedral geometry for these derivatives. Fig. 2 represents the proposed structures of the newly synthesized titanium(IV) complexes synthesized from 8-hydroxyquinoline, 2-hydroxypyridine, alkoxyalkanols and 2-heteroaryl methyl ketone oximes.

**CONFLICT OF INTEREST**

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

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