Electronic Supplementary Material (ESI) for Chemical Communications

Supporting information for

Synthesis and X-ray structure analysis of a heptacoordinate titanium(IV)-*bis*-chelate with enhanced *in vivo* antitumor efficacy

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Chemical Section

Materials and Methods

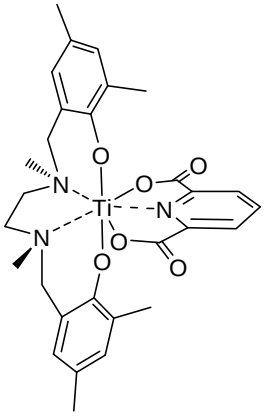
Syntheses of salan ligand **1** and complex [Ti($Ph^{Me}N^{Me}$)$_2$($O^{i\text{-}Pr}$)$_2$] (**1**) were achieved as described previously.[1] Titanium tetra*iso*propoxide (97%) was purchased from Aldrich Chemical Company and *N,N'*-dimethylethylenediamine (85%) was purchased from Acros Organics. Deuterated solvents were purchased from euriso-top in sealed ampoules and dried where necessary, other solvents were purified according to standard procedures.[2] All experiments requiring dry atmosphere were carried out under nitrogen atmosphere using standard Schlenk technique. NMR spectra were measured on *JEOL Eclipse-ECP 400* and *Bruker Avance DRX 600* spectrometers. Structure assignments were done based on 2D-NMR (COSY, HMBC, HSQC) experiments.

Data collection for X-ray structure-determination was performed at a *STOE IPDS-II* diffractometer equipped with a graphite monochromated radiation source (λ = 0.71073 Å), an image plate detection system and an *Oxford Cryostream 700* with nitrogen as coolant gas. The selection, integration, and averaging procedure of the measured reflex intensities, the determination of the unit cell by a least-squares fit of the 2Θ values, data reduction, LP correction, and the space group determination were performed using the *X-Area* software package delivered with the diffractometer. A semiempirical absorption correction method was performed after indexing of the crystal faces. The structures were solved by direct methods (*SHELXS-97*)[3] and refined by standard Fourier techniques against F square with a full-matrix leastsquares algorithm using *SHELXL-97* and the *WinGX* (1.80.05)[4] software package. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and refined with a riding model. Graphical representations were prepared with *ORTEP-III*.[5] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 804777 (**3**) and 804775 (**4**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. (fax: (+44)1223−336−033. e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Chemical Section

Synthesis and crystal structure analysis

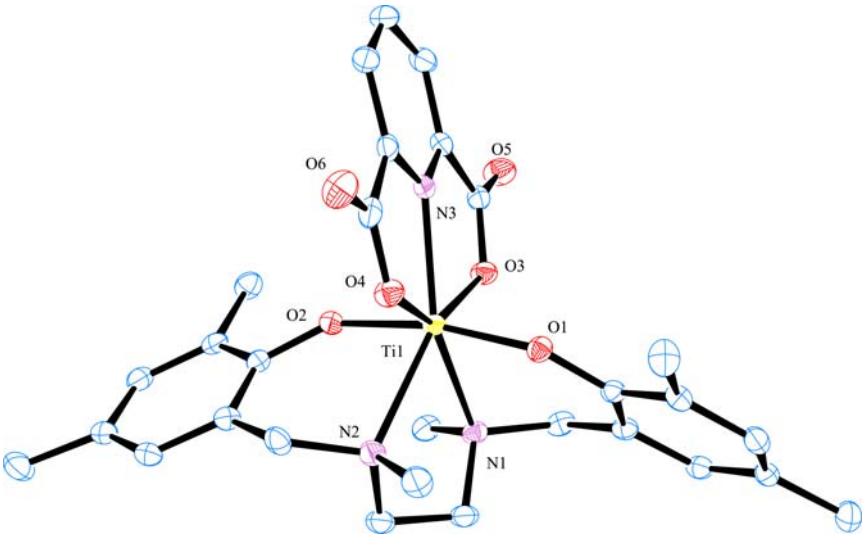
[Ti(Ph^{Me}N^{Me})$_2$(dipic)] (3)



To a mixture of [Ti(Ph^{Me}N^{Me})$_2$(O$^{i\text{-}Pr}$)$_2$] (**1**) (0.5 g, 0.96 mmol) and pyridine-2,6-dicarboxylic acid (0.16 g, 0.96 mmol) dry THF (25 ml) was added under nitrogen atmosphere. After 12 h stirring at room temperature, the solvent was evaporated and the crude product was recrystallized from dry toluene.

m.p. >350°C (toluene); ^{1}H-NMR (400 MHz, C_6D_6): δ = 7.54 (d, J = 7.6 Hz, 2H, H_{Pyr}), 6.70 (t, J = 7.6 Hz, 1H, H_{Pyr}), 6.64 (s, 2H, H_{ar}), 6.40 (s, 2H, H_{ar}), 5.39 (d, J = 14.0 Hz, 2H, $C_{ar}CH_2$), 2.82 (d, J = 9.2 Hz, 2H, NCH_2CH_2N), 2.61 (d, J = 14.0 Hz, 1H, $C_{ar}CH_2$), 2.42 (s, 6H, NCH_3), 2.10 (s, 6H, $ArCH_3$), 2.07 (s, 6H, $ArCH_3$), 1.17 ppm (d, J = 9.2 Hz, 2H, NCH_2CH_2N); ^{13}C-NMR (101 MHz, C_6D_6): δ = 169.1 (C=O), 156.1 (C_{ar}), 150.1 (C_{ar}), 143.3 (C_{ar}), 130.8 (C_{ar}), 130.8 (C_{ar}), 128.0 (C_{ar}), 127.6 (C_{ar}), 125.9 (C_{ar}), 125.2 (C_{ar}), 64.2 ($C_{ar}\underline{C}H_2$), 54.0 (NCH_2), 47.3 (NCH_3), 20.9 ($ArCH_3$), 16.42 ppm ($ArCH_3$); IR (ATR): ν = 2903, 2862, 1682, 1652, 1475, 1341, 1310, 1249, 1179), 1068, 998, 925, 852, 773, 740 cm^{-1}; UV/Vis ($CHCl_3$): λ_{max} (ε) = 410 nm (13948 M^{-1}cm^{-1}); elemental analysis calcd (%) for $C_{29}H_{33}N_3O_6Ti$: C 61.38, H 5.86, N 7.40; found: C 61.06, H 5.847, N 7.29.

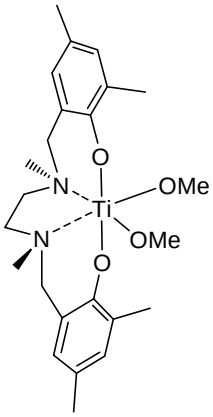
Crystal Data for 3 (CCDC 804777):



$C_{29}H_{33}N_3O_6Ti$, Mr = 567.46, monoclinic, p 21/c, a = 9.2989(6) Å, b = 22.7397(17) Å, c = 14.9120(10) Å, β = 122.978(4)°, V = 2645.2(3) Å^3, Z = 4, ρ(calcd.) = 1.425 g/cm^3, μ = 0.373 mm^{-1}, T = 100(2) K. A total of 25319 reflections were collected, of which 5643 were independent. The refinement on all data converged at $R1$ = 5.43%, $wR2$ = 8.39% and the goodness of fit was 1.020. All hydrogen atoms were included at calculated positions with fixed thermal parameters. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms are omitted for clarity.

Chemical Section

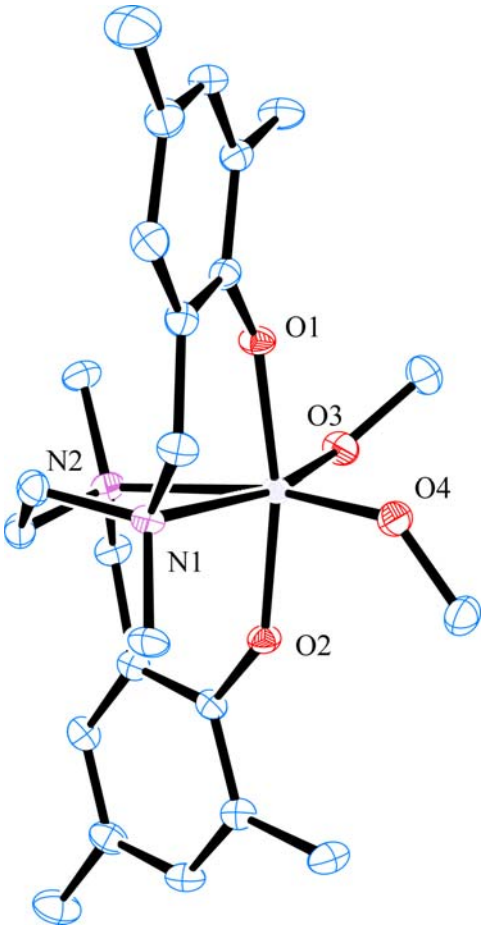
[Ti(Ph^{Me}N^{Me})$_2$(OMe)$_2$] (4)



[Ti(Ph^{Me}N^{Me})$_2$(O$^{i\text{-}Pr}$)$_2$] (**1**) (1 g, 1.92 mmol) was dissolved in dry methanol (60 ml) under a nitrogen atmosphere and kept stirring for 12h. The resulting yellow suspension was heated and cooled slowly during the course of several hours to yield yellow, crystalline [Ti(Ph^{Me}N^{Me})$_2$(O^{Me})$_2$] (360 mg, 0.77 mmol, 40 %).

m.p. 203.0 - 203.4°C (MeOH); ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.97 (d, J = 2.2 Hz, 2H, H_{ar}), 6.55 (d, J = 2,3 Hz, 2H, H_{ar}), 4.51 (d, J = 13.3 Hz, 2H, $C_{ar}CH_2$), 4.47 (s, 6H, OCH_3), 2.67 (d, J = 13.3 Hz, 2H, $C_{ar}CH_2$), 2.64 (d, J = 9.2 Hz, 2H, NCH_2CH_2N), 2.40 (s, 6H, $ArCH_3$), 2.27 (s, 6H, $ArCH_3$), 2.04 (s, 6H, NCH_3), 0.99 ppm (d, J = 9.2 Hz, 2H, NCH_2CH_2N); ^{13}C-NMR (151 MHz, $CDCl_3$): δ = 157.4 (C_{ar}), 131.1 (C_{ar}), 127.8 (C_{ar}), 126.9 (C_{ar}), 125.0 (C_{ar}), 123.8 (C_{ar}), 64.4 ($C_{ar}\underline{C}H_2$), 63.5 (OCH_3), 51.5 (NCH_2CH_2N), 46.8 ($C_{ar}\underline{C}H_3$), 20.5 ($C_{ar}\underline{C}H_3$), 17.2 ppm (NCH_3); elemental analysis calcd (%) for $C_{24}H_{36}NO_4Ti$: C 62.07, H 7.81, N 6.03; found: C 62.06, H 7.91, N 6.05.

Crystal Data for 4 (CCDC804775):



$C_{24}H_{36}N_2O_4Ti$, Mr = 464.45, triclinic, P -1, a = 11.2918 (7) Å, b = 11.8315 (8) Å, c = 18.3210 (12) Å, α = 98.082 (5)°, β = 102.992 (5)°, γ = 97.181 (5)°, V = 2330.0 (3) Å^3, Z = 4, ρ(calcd.) = 1.324 g/cm^3, μ = 0.400 mm^{-1}, T = 173(3) K. A total of 33475 reflections were collected, of which 9894 were independent. The refinement on all data converged at $R1$ = 4.38%, $wR2$ = 8.92% and the goodness of fit was 1.039. The asymmetric unit contains a pair of enantiomers, the unit cell contains four molecules. One methyl group was disordered over two positions and split in a 50:50 ratio over two positions rotated by 60 degree. (type 123 - shelxl file). All hydrogen atoms were included at calculated positions with fixed thermal parameters. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms are omitted for clarity.

Chemical Section

Table S1. Crystal data and structure refinement for [Ti($Ph^{Me}N^{Me}$)$_2$(dipic)] (**3**).

Empirical formula	$C_{29}H_{33}N_3O_6Ti$	
Formula weight	567.48	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	p 21/c	
Unit cell dimensions	a = 9.2989(6) Å	α = 90°.
	b = 22.7397(17) Å	β = 122.978(4)°.
	c = 14.9120(10) Å	γ = 90°.
Volume	2645.2(3) Å^3	
Z	4	
Density (calculated)	1.425 g/cm^3	
Absorption coefficient	0.373 mm^{-1}	
F(000)	1192	
Crystal size	0.380 x 0.270 x 0.150 mm^3	
Theta range for data collection	2.38 to 26.88°.	
Index ranges	-11<=h<=11, -28<=k<=28, -18<=l<=18	
Reflections collected	25319	
Independent reflections	5643 [R(int) = 0.0520]	
Completeness to theta = 26.88°	99.1 %	
Absorption correction	Integration	
Max. and min. transmission	0.9521 and 0.9112	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5643 / 0 / 358	
Goodness-of-fit on F^2	1.020	
Final R indices [I>2sigma(I)]	$R1$ = 0.0364, $wR2$ = 0.0794	
R indices (all data)	$R1$ = 0.0543, $wR2$ = 0.0839	
Largest diff. peak and hole	0.308 and -0.379 e·Å^{-3}	

Chemical Section

Table S2. Bond lengths [Å] for [Ti(Ph^{Me}N^{Me})$_2$(dipic)] (**3**).

C(1)-O(1)	1.348(2)	C(15)-C(16)	1.502(3)
C(1)-C(6)	1.402(2)	C(16)-N(2)	1.488(2)
C(1)-C(2)	1.402(3)	C(21)-N(1)	1.487(2)
C(2)-C(3)	1.395(3)	C(22)-N(2)	1.487(2)
C(2)-C(17)	1.502(3)	C(30)-N(3)	1.331(2)
C(3)-C(4)	1.394(3)	C(30)-C(31)	1.392(2)
C(4)-C(5)	1.388(3)	C(30)-C(36)	1.498(3)
C(4)-C(18)	1.511(3)	C(31)-C(32)	1.388(3)
C(5)-C(6)	1.387(3)	C(32)-C(33)	1.387(3)
C(6)-C(7)	1.503(2)	C(33)-C(34)	1.388(2)
C(7)-N(1)	1.490(2)	C(34)-N(3)	1.333(2)
C(8)-O(2)	1.346(2)	C(34)-C(35)	1.503(3)
C(8)-C(13)	1.399(2)	C(35)-O(6)	1.215(2)
C(8)-C(9)	1.401(3)	C(35)-O(4)	1.302(2)
C(9)-C(10)	1.390(3)	C(36)-O(5)	1.219(2)
C(9)-C(19)	1.506(2)	C(36)-O(3)	1.298(2)
C(10)-C(11)	1.390(3)	N(1)-Ti(1)	2.3504(15)
C(11)-C(12)	1.394(3)	N(2)-Ti(1)	2.3842(15)
C(11)-C(20)	1.505(3)	N(3)-Ti(1)	2.1850(14)
C(12)-C(13)	1.390(3)	O(1)-Ti(1)	1.8443(12)
C(13)-C(14)	1.513(3)	O(2)-Ti(1)	1.8497(13)
C(14)-N(2)	1.499(2)	O(3)-Ti(1)	2.0459(12)
C(15)-N(1)	1.486(2)	O(4)-Ti(1)	2.0428(13)

Chemical Section

Table S3. Bond angles [°] for [Ti($Ph^{Me}N^{Me}$)$_2$(dipic)] (**3**).

O(1)-C(1)-C(6)	120.52(16)	N(2)-C(14)-C(13)	114.05(15)	C(14)-N(2)-Ti(1)	110.93(10)
O(1)-C(1)-C(2)	118.98(16)	N(1)-C(15)-C(16)	109.84(14)	C(30)-N(3)-C(34)	120.70(15)
C(6)-C(1)-C(2)	120.50(16)	N(2)-C(16)-C(15)	109.48(14)	C(30)-N(3)-Ti(1)	119.20(12)
C(3)-C(2)-C(1)	118.57(17)	N(3)-C(30)-C(31)	121.47(17)	C(34)-N(3)-Ti(1)	119.37(12)
C(3)-C(2)-C(17)	121.93(17)	N(3)-C(30)-C(36)	111.15(15)	C(1)-O(1)-Ti(1)	144.34(11)
C(1)-C(2)-C(17)	119.50(16)	C(31)-C(30)-C(36)	127.36(16)	C(8)-O(2)-Ti(1)	145.58(11)
C(4)-C(3)-C(2)	121.91(17)	C(32)-C(31)-C(30)	117.90(17)	C(36)-O(3)-Ti(1)	125.69(11)
C(5)-C(4)-C(3)	117.92(16)	C(33)-C(32)-C(31)	120.34(17)	C(35)-O(4)-Ti(1)	126.12(11)
C(5)-C(4)-C(18)	120.10(17)	C(32)-C(33)-C(34)	117.91(17)	O(1)-Ti(1)-O(2)	168.92(5)
C(3)-C(4)-C(18)	121.98(17)	N(3)-C(34)-C(33)	121.65(17)	O(1)-Ti(1)-O(4)	88.53(5)
C(6)-C(5)-C(4)	122.26(17)	N(3)-C(34)-C(35)	111.18(15)	O(2)-Ti(1)-O(4)	95.94(5)
C(5)-C(6)-C(1)	118.76(16)	C(33)-C(34)-C(35)	127.12(17)	O(1)-Ti(1)-O(3)	93.10(5)
C(5)-C(6)-C(7)	119.57(16)	O(6)-C(35)-O(4)	126.18(17)	O(2)-Ti(1)-O(3)	89.73(5)
C(1)-C(6)-C(7)	121.65(16)	O(6)-C(35)-C(34)	122.34(16)	O(4)-Ti(1)-O(3)	141.37(5)
N(1)-C(7)-C(6)	114.53(14)	O(4)-C(35)-C(34)	111.48(15)	O(1)-Ti(1)-N(3)	103.77(5)
O(2)-C(8)-C(13)	120.01(16)	O(5)-C(36)-O(3)	126.24(17)	O(2)-Ti(1)-N(3)	87.28(5)
O(2)-C(8)-C(9)	119.14(16)	O(5)-C(36)-C(30)	122.14(16)	O(4)-Ti(1)-N(3)	71.23(5)
C(13)-C(8)-C(9)	120.85(17)	O(3)-C(36)-C(30)	111.62(15)	O(3)-Ti(1)-N(3)	70.92(5)
C(10)-C(9)-C(8)	118.63(16)	C(15)-N(1)-C(21)	109.03(14)	O(1)-Ti(1)-N(1)	80.29(5)
C(10)-C(9)-C(19)	121.97(16)	C(15)-N(1)-C(7)	108.50(13)	O(2)-Ti(1)-N(1)	90.29(5)
C(8)-C(9)-C(19)	119.35(16)	C(21)-N(1)-C(7)	106.58(14)	O(4)-Ti(1)-N(1)	144.54(5)
C(11)-C(10)-C(9)	121.89(17)	C(15)-N(1)-Ti(1)	111.13(11)	O(3)-Ti(1)-N(1)	73.26(5)
C(10)-C(11)-C(12)	118.14(17)	C(21)-N(1)-Ti(1)	109.73(11)	N(3)-Ti(1)-N(1)	144.10(5)
C(10)-C(11)-C(20)	120.79(17)	C(7)-N(1)-Ti(1)	111.74(11)	O(1)-Ti(1)-N(2)	91.84(5)
C(12)-C(11)-C(20)	121.03(17)	C(22)-N(2)-C(16)	108.85(14)	O(2)-Ti(1)-N(2)	79.81(5)
C(13)-C(12)-C(11)	121.86(17)	C(22)-N(2)-C(14)	107.17(14)	O(4)-Ti(1)-N(2)	73.36(5)
C(12)-C(13)-C(8)	118.56(17)	C(16)-N(2)-C(14)	108.63(14)	O(3)-Ti(1)-N(2)	145.00(5)
C(12)-C(13)-C(14)	120.86(16)	C(22)-N(2)-Ti(1)	109.92(11)	N(3)-Ti(1)-N(2)	140.66(6)
C(8)-C(13)-C(14)	120.56(16)	C(16)-N(2)-Ti(1)	111.23(11)	N(1)-Ti(1)-N(2)	73.48(5)

Chemical Section

Table S4. Crystal data and structure refinement for [Ti($Ph^{Me}N^{Me}$)$_2$(OMe)$_2$] (**4**).

Empirical formula	C_{24} H_{36} N_2 O_4 Ti	
Formula weight	464.45	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 11.2918(7) Å	α = 98.082(5)°.
	b = 11.8315(8) Å	β = 102.992(5)°.
	c = 18.3210(12) Å	γ = 97.181(5)°.
Volume	2330.0(3) $Å^3$	
Z	4	
Density (calculated)	1.324 g/cm^3	
Absorption coefficient	0.400 mm^{-1}	
F(000)	992	
Crystal size	0.400 x 0.300 x 0.200 mm^3	
Theta range for data collection	1.88 to 26.86°.	
Index ranges	-14<=h<=14, -14<=k<=14, -23<=l<=23	
Reflections collected	33475	
Independent reflections	9894 [R(int) = 0.0428]	
Completeness to theta = 26.86°	98.6 %	
Absorption correction	Integration	
Max. and min. transmission	0.9471 and 0.8507	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9894 / 0 / 570	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	$R1$ = 0.0333, $wR2$ = 0.0859	
R indices (all data)	$R1$ = 0.0438, $wR2$ = 0.0892	
Largest diff. peak and hole	0.576 and -0.490 e·$Å^{-3}$	

Chemical Section

Table S5. Bond lengths [Å] for [Ti($Ph^{Me}N^{Me}$)$_2$(OMe)$_2$] (**4**).

C(13)-N(2)	1.494(2)	C(2)-C(3)	1.397(2)	C(123)-O(104)	1.410(2)
C(13)-C(12)	1.508(2)	C(3)-C(4)	1.391(2)	C(124)-O(103)	1.409(2)
C(14)-N(1)	1.493(2)	C(4)-C(5)	1.394(2)	N(101)-Ti(1)	2.3373(14)
C(14)-C(2)	1.504(2)	C(5)-C(6)	1.393(2)	N(102)-Ti(1)	2.3239(13)
C(15)-N(1)	1.482(2)	C(7)-O(2)	1.3392(19)	O(101)-Ti(1)	1.9051(11)
C(15)-C(16)	1.518(2)	C(7)-C(12)	1.401(2)	O(102)-Ti(1)	1.8936(11)
C(16)-N(2)	1.484(2)	C(7)-C(8)	1.408(2)	O(103)-Ti(1)	1.8282(11)
C(17)-N(1)	1.486(2)	C(8)-C(9)	1.391(2)	O(104)-Ti(1)	1.8341(12)
C(18)-N(2)	1.487(2)	C(9)-C(10)	1.395(2)	C(101)-O(101)	1.3379(18)
C(19)-C(10)	1.510(2)	C(10)-C(11)	1.388(2)	C(101)-C(102)	1.401(2)
C(20)-C(8)	1.500(2)	C(11)-C(12)	1.399(2)	C(101)-C(106)	1.411(2)
C(21)-C(6)	1.506(2)	C(113)-N(101)	1.4971(19)	C(102)-C(103)	1.397(2)
C(22)-C(4)	1.509(2)	C(113)-C(112)	1.509(2)	C(103)-C(104)	1.393(2)
C(23)-O(4)	1.406(2)	C(114)-N(102)	1.498(2)	C(104)-C(105)	1.394(2)
C(24)-O(3)	1.408(2)	C(114)-C(102)	1.506(2)	C(105)-C(106)	1.387(2)
N(1)-Ti(2)	2.3320(14)	C(115)-N(102)	1.488(2)	C(107)-O(102)	1.3439(19)
N(2)-Ti(2)	2.3289(14)	C(115)-C(116)	1.518(2)	C(107)-C(112)	1.403(2)
O(1)-Ti(2)	1.8910(11)	C(116)-N(101)	1.486(2)	C(107)-C(108)	1.407(2)
O(2)-Ti(2)	1.8932(11)	C(117)-N(102)	1.4849(19)	C(108)-C(109)	1.393(2)
O(3)-Ti(2)	1.8393(12)	C(118)-N(101)	1.4839(19)	C(109)-C(110)	1.392(2)
O(4)-Ti(2)	1.8395(12)	C(119)-C(108)	1.505(2)	C(110)-C(111)	1.396(2)
C(1)-O(1)	1.3404(18)	C(120)-C(110)	1.513(2)	C(111)-C(112)	1.396(2)
C(1)-C(2)	1.401(2)	C(121)-C(106)	1.504(2)		
C(1)-C(6)	1.407(2)	C(122)-C(104)	1.509(2)		

Chemical Section

Table S6. Bond angles [°] for [Ti($Ph^{Me}N^{Me}$)$_2$(OMe)$_2$] (**4**).

N(2)-C(13)-C(12)	115.83(13)	O(1)-C(1)-C(6)	118.45(14)
N(1)-C(14)-C(2)	116.57(13)	C(2)-C(1)-C(6)	120.24(14)
N(1)-C(15)-C(16)	109.97(13)	C(3)-C(2)-C(1)	119.01(15)
N(2)-C(16)-C(15)	110.08(13)	C(3)-C(2)-C(14)	118.87(15)
N(101)-C(113)-C(112)	114.94(12)	C(1)-C(2)-C(14)	121.81(14)
N(102)-C(114)-C(102)	115.21(13)	C(4)-C(3)-C(2)	122.02(16)
N(102)-C(115)-C(116)	110.65(13)	C(3)-C(4)-C(5)	117.67(15)
N(101)-C(116)-C(115)	110.53(13)	C(3)-C(4)-C(22)	121.48(16)
C(15)-N(1)-C(17)	109.86(13)	C(5)-C(4)-C(22)	120.85(16)
C(15)-N(1)-C(14)	109.80(12)	C(6)-C(5)-C(4)	122.42(15)
C(17)-N(1)-C(14)	106.11(12)	C(5)-C(6)-C(1)	118.59(15)
C(15)-N(1)-Ti(2)	109.75(9)	C(5)-C(6)-C(21)	121.55(15)
C(17)-N(1)-Ti(2)	110.40(10)	C(1)-C(6)-C(21)	119.81(14)
C(14)-N(1)-Ti(2)	110.87(10)	O(2)-C(7)-C(12)	121.00(14)
C(16)-N(2)-C(18)	110.17(13)	O(2)-C(7)-C(8)	118.86(14)
C(16)-N(2)-C(13)	109.85(13)	C(12)-C(7)-C(8)	120.14(14)
C(18)-N(2)-C(13)	106.35(12)	C(9)-C(8)-C(7)	118.65(15)
C(16)-N(2)-Ti(2)	109.98(9)	C(9)-C(8)-C(20)	121.87(15)
C(18)-N(2)-Ti(2)	109.95(10)	C(7)-C(8)-C(20)	119.46(14)
C(13)-N(2)-Ti(2)	110.48(9)	C(8)-C(9)-C(10)	122.32(15)
C(118)-N(101)-C(116)	109.98(12)	C(11)-C(10)-C(9)	117.99(15)
C(118)-N(101)-C(113)	106.39(12)	C(11)-C(10)-C(19)	121.70(16)
C(116)-N(101)-C(113)	110.90(12)	C(9)-C(10)-C(19)	120.31(16)
C(118)-N(101)-Ti(1)	111.19(10)	C(10)-C(11)-C(12)	121.66(15)
C(116)-N(101)-Ti(1)	108.84(9)	C(11)-C(12)-C(7)	119.23(15)
C(113)-N(101)-Ti(1)	109.53(9)	C(11)-C(12)-C(13)	119.84(14)
C(117)-N(102)-C(115)	110.18(13)	C(7)-C(12)-C(13)	120.69(14)
C(117)-N(102)-C(114)	106.13(12)	O(101)-C(101)-C(102)	121.22(14)
C(115)-N(102)-C(114)	110.59(12)	O(101)-C(101)-C(106)	119.13(14)
C(117)-N(102)-Ti(1)	110.70(9)	C(102)-C(101)-C(106)	119.64(14)
C(115)-N(102)-Ti(1)	109.03(9)	C(103)-C(102)-C(101)	119.31(14)
C(114)-N(102)-Ti(1)	110.20(9)	C(103)-C(102)-C(114)	120.09(14)
C(24)-O(3)-Ti(2)	126.28(10)	C(101)-C(102)-C(114)	120.53(14)
C(23)-O(4)-Ti(2)	131.80(10)	C(104)-C(103)-C(102)	121.90(15)
C(124)-O(103)-Ti(1)	131.05(10)	C(103)-C(104)-C(105)	117.69(14)
C(123)-O(104)-Ti(1)	130.50(11)	C(103)-C(104)-C(122)	121.78(15)
O(1)-C(1)-C(2)	121.29(14)	C(105)-C(104)-C(122)	120.53(15)

Chemical Section

C(106)-C(105)-C(104)	122.29(15)	O(104)-Ti(1)-O(101)	96.44(5)
C(105)-C(106)-C(101)	119.13(14)	O(102)-Ti(1)-O(101)	166.16(5)
C(105)-C(106)-C(121)	121.81(14)	O(103)-Ti(1)-N(102)	163.95(5)
C(101)-C(106)-C(121)	119.04(14)	O(104)-Ti(1)-N(102)	89.57(5)
O(102)-C(107)-C(112)	120.78(14)	O(102)-Ti(1)-N(102)	89.05(5)
O(102)-C(107)-C(108)	119.26(14)	O(101)-Ti(1)-N(102)	80.36(5)
C(112)-C(107)-C(108)	119.96(15)	O(103)-Ti(1)-N(101)	89.53(5)
C(109)-C(108)-C(107)	118.54(15)	O(104)-Ti(1)-N(101)	164.63(5)
C(109)-C(108)-C(119)	121.33(14)	O(102)-Ti(1)-N(101)	80.98(5)
C(107)-C(108)-C(119)	120.10(15)	O(101)-Ti(1)-N(101)	87.85(5)
C(110)-C(109)-C(108)	122.76(15)	N(102)-Ti(1)-N(101)	76.56(5)
C(109)-C(110)-C(111)	117.52(15)	O(3)-Ti(2)-O(4)	104.05(6)
C(109)-C(110)-C(120)	120.77(14)	O(3)-Ti(2)-O(1)	91.39(5)
C(111)-C(110)-C(120)	121.70(15)	O(4)-Ti(2)-O(1)	95.12(5)
C(112)-C(111)-C(110)	121.70(15)	O(3)-Ti(2)-O(2)	96.00(5)
C(111)-C(112)-C(107)	119.47(14)	O(4)-Ti(2)-O(2)	91.77(5)
C(111)-C(112)-C(113)	120.03(14)	O(1)-Ti(2)-O(2)	168.38(5)
C(107)-C(112)-C(113)	120.43(14)	O(3)-Ti(2)-N(2)	91.06(5)
C(1)-O(1)-Ti(2)	141.77(10)	O(4)-Ti(2)-N(2)	163.92(5)
C(7)-O(2)-Ti(2)	142.78(10)	O(1)-Ti(2)-N(2)	89.88(5)
C(101)-O(101)-Ti(1)	142.35(10)	O(2)-Ti(2)-N(2)	81.05(5)
C(107)-O(102)-Ti(1)	142.65(10)	O(3)-Ti(2)-N(1)	164.77(5)
O(103)-Ti(1)-O(104)	105.07(6)	O(4)-Ti(2)-N(1)	89.97(5)
O(103)-Ti(1)-O(102)	96.73(5)	O(1)-Ti(2)-N(1)	81.33(5)
O(104)-Ti(1)-O(102)	92.35(5)	O(2)-Ti(2)-N(1)	89.35(5)
O(103)-Ti(1)-O(101)	91.30(5)	N(2)-Ti(2)-N(1)	75.66(5)

Chemical Section

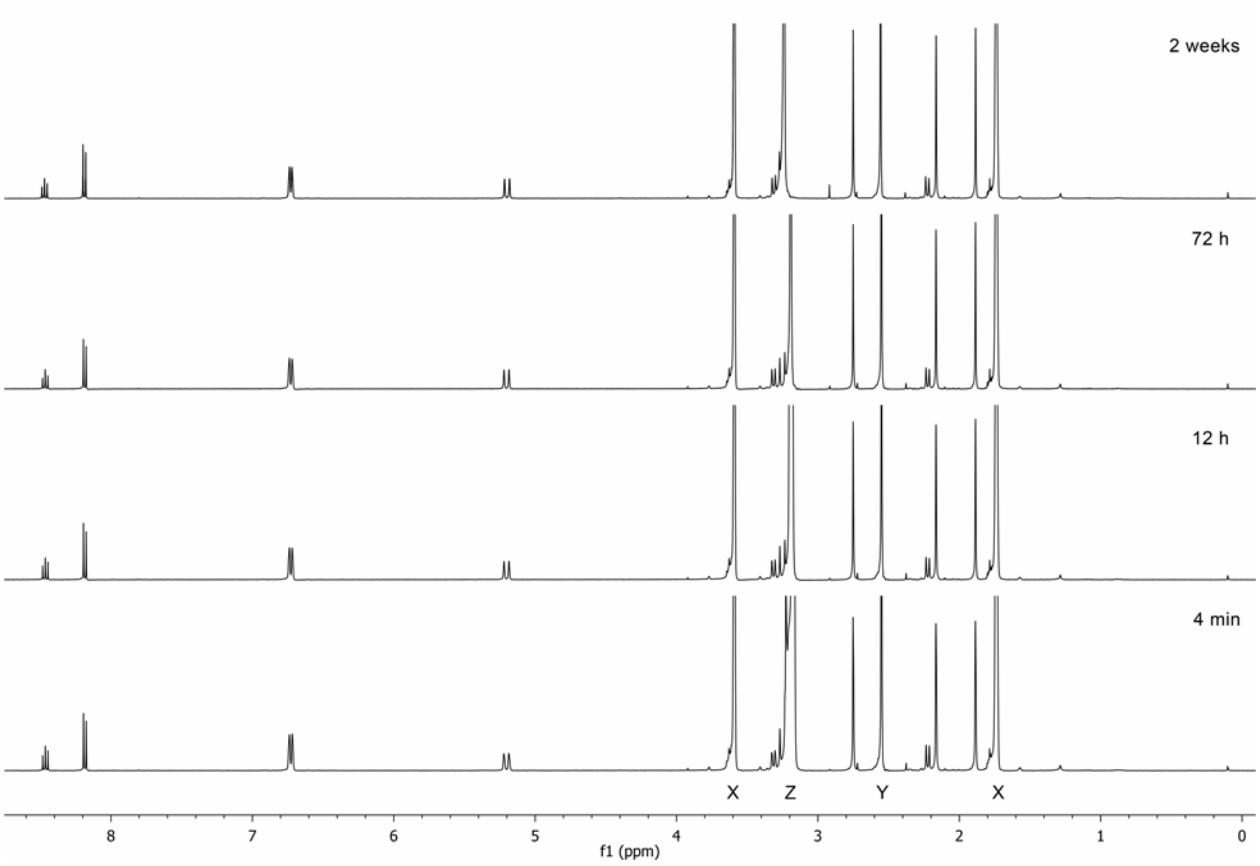


Figure S1: ^{1}H-NMR spectra of complex [Ti(Ph^{Me}N^{Me})$_2$(dipic)] (**3**) in [D$_8$]THF measured 4min, 12h and 72h after addition of 1000 equivalents D_2O and incubation at 37 °C (from bottom to top). Top panel shows final spectrum recorded after 2 weeks continued incubation at 37 °C, no precipitation or other signs of degradation were visible. Signals marked X, Y, and Z are THF, DMSO, and D_2O respectively.

Chemical Section

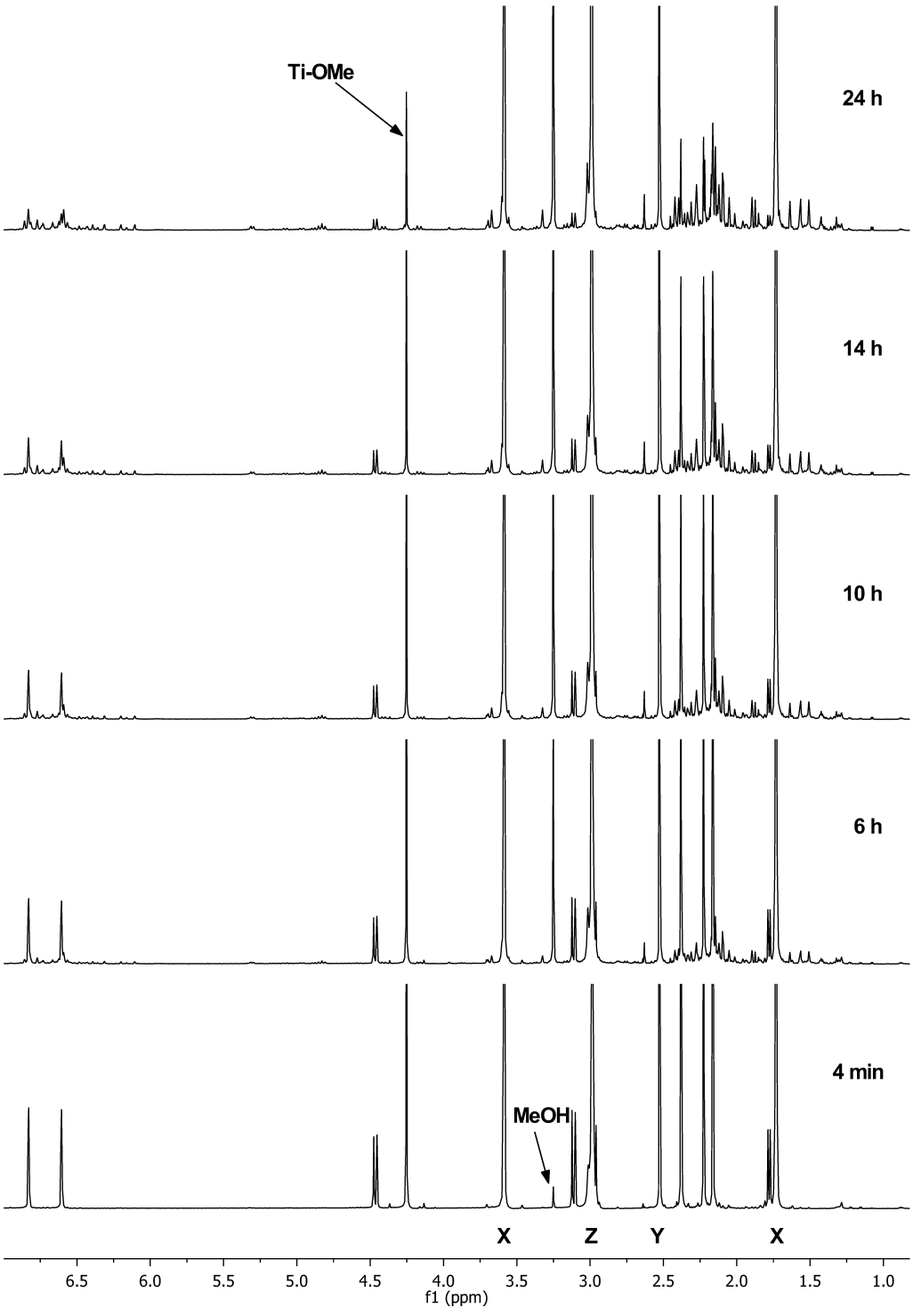


Figure S2: Hydrolytic stability at 37°C of [Ti($Ph^{Me}N^{Me}$)$_2$(OMe)$_2$] (**4**) investigated by time resolved ^{1}H-NMR in aqueous (1000 eq. D_2O) [D_8]THF and 0.2 % [D_6]DMSO as internal reference. Spectra shown are from bottom to top measured at t = 4min, 6h, 10h, 14h, and 24h after the addition of D_2O. Signals marked X, Y, and Z are THF, DMSO, and D_2O respectively. Methanol signals at δ = 3.25 ppm from hydrolysis. $t_{1/2}$ was estimated to 8.5h.

Biological Section

Materials and Methods

Cytotoxicity was measured on HeLa S3 and Hep G2 cells using an AlamarBlue assay. AlamarBlue was purchased from BioSource Europe.

Cell cultivation

Cells were cultivated at 37°C in humidified 5% CO_2 atmosphere using Dulbecco's DMEM-media (Invitrogen) containing 10% foetal calf serum, 1% penicillin and 1% streptomycin. Cells were split every three days. Both cell lines were tested for mycoplasma infections using a mycoplasma detection kit (Roche Applied Science).

AlamarBlue Assay[6]

Cells were seeded in 96-well plates (4,000 HeLa S3 cells/well or 8,000 Hep G2 cells/well) and allowed to attach and grow for 24 h. The cells were then treated with different concentrations of the reagent tested. Solutions of reagents were prepared by dissolving the respective complexes in a suitable amount of DMSO and diluting with medium to give final concentrations with a maximum DMSO content of 0.5 %. The cells were incubated for 48 h, AlamarBlue (10 µl) was added and the cells were incubated for another hour. After excitation at 530 nm, fluorescence at 590 nm was measured using a Synergy 2 HT Fluorescence Microplate Reader (BioTek). Cell viability is expressed in percent with respective to a control containing only pure medium and 0.5 % DMSO. All experiments were repeated for a minimum of three times with each experiment done in four replicates. The resulting curves were fitted using Sigma plot 10.0.[7]

Tumor regression studies [8]

Tumor regression studies were run in the well established C3 tumor model of cervical cancer.[9] C57BL/6 mice received 0.5 x 10^6 HPV-16 E7 expressing C3 cells in 100 µl of PBS subcutaneously (s.c.) in the right shaved flank (needles: 20G 1½'' BD Microlance 3). When small tumors were palpable in all animals (days 9–15) the first treatment (complexes **3** and **4**, respectively) was applied intraperitoneally (i.p.) in 100 µl DMSO/PBS/0.5% Tween 80 and control animals received DMSO/PBS/0.5% Tween 80 only. The treatment was repeated six times at given intervals. Tumor sizes were measured with a caliper and were determined every 2–4 days until mice had to be sacrificed (tumor size of 400 mm^2 or when tumors were bleeding).

Tumor sizes of the mice within a group (n= 10/group) were calculated as arithmetic means with standard error of the means (SEMs). All operations on live animals were performed under Isoflurane anesthesia (CuraMed Pharma, Karlsruhe, Germany).

Biological Section

Tumor regression I: A total of 30 mg/kg of compounds [Ti($Ph^{Me}N^{Me}$)$_2$(dipic)] (**3**) or [Ti($Ph^{Me}N^{Me}$)$_2$($OMe)_2$] (**4**) were administered at multiple applications (m.a.) (days 0, 3, 6, 9, 11, 14 (5 mg/kg)) and control animals received DMSO/PBS/Tween at the same intervals. Results are summarized in table S7.

Tumor regression II: In a second treatment scheme, animals (n= 10/group) were administered a total of 30 mg/kg of compounds [Ti($Ph^{Me}N^{Me}$)$_2$(dipic)] (**3**) and [Ti($Ph^{Me}N^{Me}$)$_2$($OMe)_2$] (**4**) m.a. but now at days 0, 2, 5, 8, 11, 14 (5 mg/kg) with control animals receiving DMSO/PBS/Tween at the same intervals. Results are summarized in table S8.

Table S7: Growth of established C3 tumors in mice after treatment with substances [Ti($Ph^{Me}N^{Me}$)$_2$(dipic)] (**3**) and [Ti($Ph^{Me}N^{Me}$)$_2$($OMe)_2$] (**4**) respectively (n=10/group).

Tumor regression I	DMSO/PBS/ 0.5% Tween 80	**3**[c] (30 mg/kg m.a.)	**4**[c] (30 mg/kg m.a.)
Average tumor size at day 0 (mm^2) ± S.E.M[a]	3 ± 2	2 ± 1	2 ± 1
Average tumor size at day 37 (mm^2) ± S.E.M[b]	288 ± 33	11 ± 5	72 ± 14
number of total regressors at day 37	0	3	0

[a] Tumors were established when palpable and tumor sizes were measured over time by a sliding caliper.

[b] Experiment was terminated at day 37.

[c] Treatments at multiple applications (m.a.) on days 0, 3, 6, 9, 11, 14 (5 mg/kg).

288 ± 33 vs 11 ± 5 → p-value: 0.0001;

288 ± 33 vs 72 ± 14 → p-value: 0.0001

11 ± 5 vs. 72 ± 14 → p-value: 0.0007

Biological Section

Table S8: Growth of established C3 tumors in mice after treatment with substances [Ti($Ph^{Me}N^{Me}$)$_2$(dipic)] (**3**) and [Ti($Ph^{Me}N^{Me}$)$_2$($OMe)_2$] (**4**) respectively (n=10/group).

Tumor regression II	DMSO/PBS/ 0.5% Tween 80	**3**[c] (30 mg/kg m.a.)	**4**[c] (30 mg/kg m.a.)
Average tumor size at day 0 (mm^2) ± S.E.M[a]	2 ± 1	4 ± 2	3 ± 1
Average tumor size at day 35 (mm^2) ± S.E.M[b]	267 ± 28	8 ± 3	63 ± 11
number of total regressors at day 35	0	4	0

[a] Tumors were established when palpable and tumor sizes were measured over time by a sliding caliper.

[b] Experiment was terminated at day 35.

[c] Treatments at multiple applications (m.a.) on days 0, 2, 5, 8, 11, 14 (5 mg/kg)

267 ± 28 vs 8 ± 3 → p-value: 0.0001

267 ± 28 vs 63 ± 11 → p-value: 0.0001

8 ± 3 vs 63 ± 11 → p-value: 0.0001

Biological Section

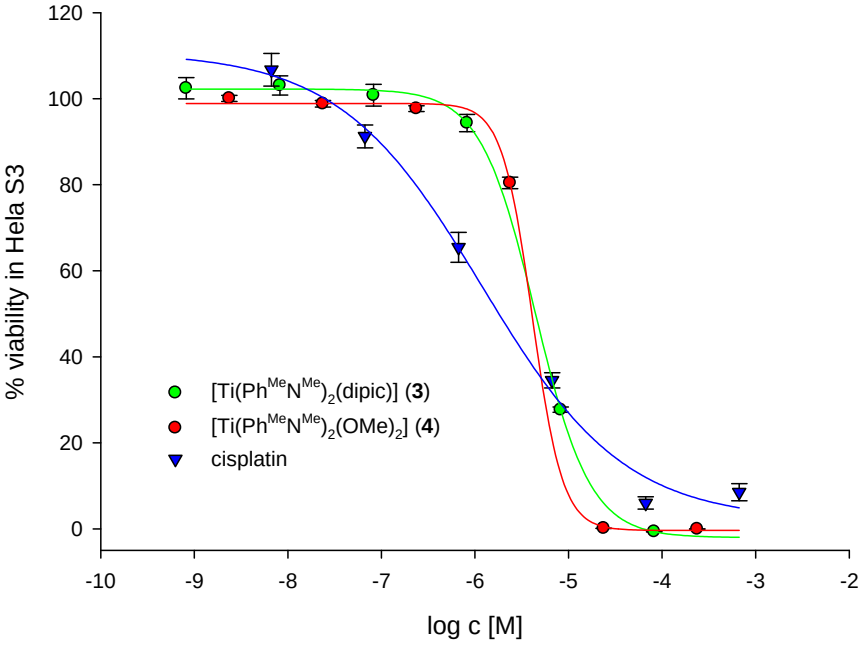


Figure S3. Comparison of viability of Hela S3 cells after treatment with different concentrations of [Ti(Ph^{Me}N^{Me})$_2$(dipic)] (**3**), [Ti(Ph^{Me}N^{Me})$_2$(OMe)$_2$] (**4**) and *cis*-platin after 48h of incubation.

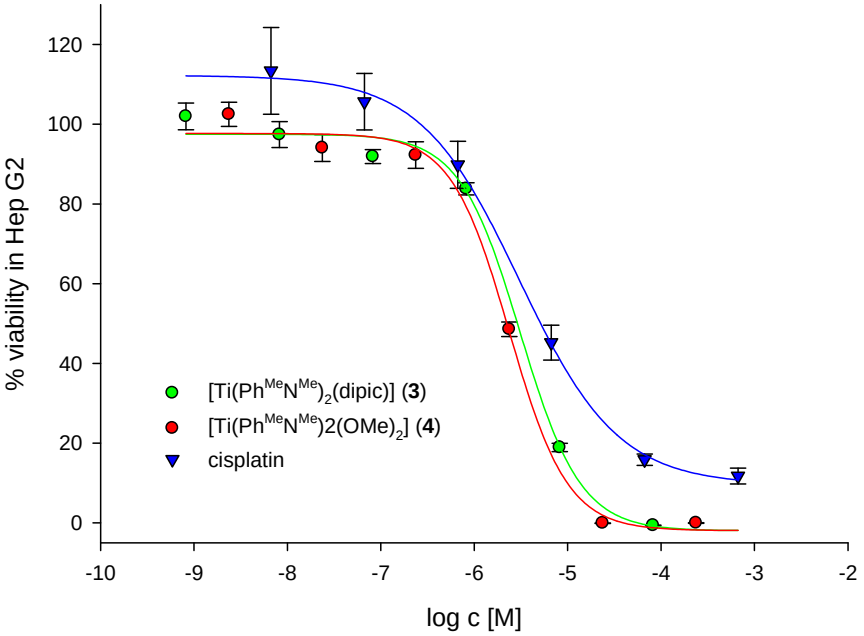


Figure S4. Comparison of viability of Hep G3 cells after treatment with different concentrations of [Ti(Ph^{Me}N^{Me})$_2$(dipic)] (**3**), [Ti(Ph^{Me}N^{Me})$_2$(OMe)$_2$] (**4**) and *cis*-platin after 48h of incubation.

Literature

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[8] All animal work has been conducted according to relevant national and international guidelines. The animal studies were reviewed and approved by the local ethical committee (Regierungspräsidium Freiburg, Freiburg, Germany, approval number: 35/9185.81/G-06/48 (2008), permission given to P. Öhlschläger).

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