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Synthesis and X-ray Structure Analysis of Cytotoxic Heptacoordinate Sulfonamide Salan Titanium(IV)-bis-Chelates

Tiankun Zhao,^a Martin Grützke,^b Kathrin H. Götz,^a Tetiana Druzhenko,^c and Thomas Huhn*^a

^a *Fachbereich Chemie and Konstanz Research School Chemical Biology, Universität Konstanz, Universitätsstr. 10, D-78457 Konstanz, Germany. E-mail: thomas.huhn@uni-konstanz.de;*

Fax: +49-7531-884424; Tel: +49-7531-882283

^b *Present address: MEET Battery Research Center, University of Münster, Corrensstr. 46, D 48149 Münster, Germany.*

^c *Department of Chemistry, Kyiv National Taras Shevchenko University, 64 Volodymyrska Street, Kyiv, 01601, Ukraine.*

† Electronic supplementary information (ESI) available: Copies of spectra of all compounds, crystallographic data for **[L4Ti(dipic)]** and supplementary figures. For ESI and crystallographic data in CIF or other electronic format see DOI:

Abstract

A series of novel sulfonamide substituted heteroleptic salan titanium(IV)-bis-chelates complexed to 2,6-pyridinedicarboxylic acid were synthesized, structurally characterized and evaluated for their anticancer activity against two human carcinoma cell lines. All cytotoxic complexes showed complete inhibition of cell growth at active concentration, two complexes based on pyrrolidine and azepane substituted sulfonamides displayed IC₅₀ values below 1.7 μM and are more cytotoxic than cisplatin in both tested cell lines. The azepane substituted complex [L3Ti(dipic)] exhibited excellent activity with an IC₅₀ value of 0.3 ± 0.2 μM in Hela S3 and 0.9 ± 0.1 in Hep G2.

Introduction

Cisplatin with its good antitumor activity was approved as the first metal anticancer drug in the early 1970s.¹ Since then it became the leading drug in chemotherapy of different solid tumors such as genitourinary, colorectal and non-small cell lung cancers for more than three decades.² However, platinum based drugs are usually associated with side effects and drug resistance.³ Consequently, there is a high demand for designing new non-platinum alternatives with improved pharmacological properties and better tolerability. Titanium complexes have been identified rather early as promising metal based anticancer drugs.⁴ Most of the titanium complexes reported as antitumor agents so far are derivatives of titanocene dichloride (Cp₂TiCl₂)⁵ and Budotitane [Ti(bzac)₂(OEt)₂] (Hbzac = 1-phenylbutane-1,3-dione),⁶

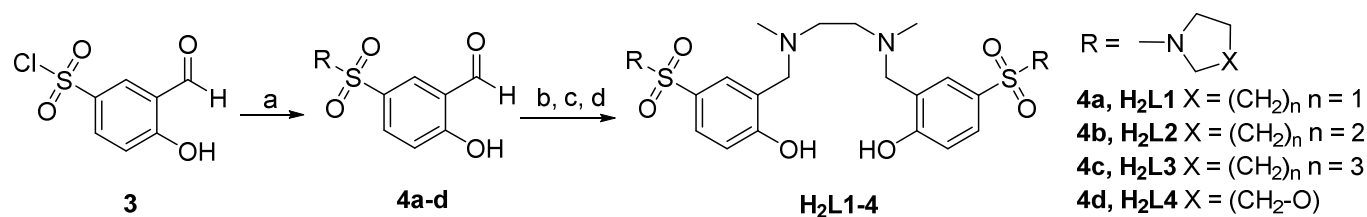
these complexes showed enhanced antitumor activity in various cell lines and reduced side effects compared to cisplatin. Unfortunately, their clinical trials are stagnant due to rapid hydrolysis in the range of minutes under physiological conditions.⁷ In comparison, diamino *bis*(phenolato) “salan” titanium(IV)-*bis*-alkoxides, a third class of anticancer active Ti(IV), proved to be less prone towards hydrolysis and highly active in different cell lines.⁸ Bioactivity and reactivity of salan-Ti(IV)-alkoxides are significantly influenced by the aromatic substitution pattern of the salan ligand. While halogen substitution improved cytotoxicity in favour of apoptosis^{8c} increasing the steric bulk resulted in a loss of cytotoxicity.^{8b, e} A polar nitro substituent resulted in decreased hydrolytic stability but had a beneficial influence on cytotoxicity, most probably by enhancing the solubility of the resulting complex in biological relevant medium.⁹ Replacement of the notorious labile alkoxides by the dianionic tridentate 2,6-pyridinedicarboxylic acid (dipic) let us recently developing an efficiently stabilized heptacoordinate salan Ti(IV)-*bis*-chelate.¹⁰ Even though, the reported complex is not redox-active and has a significantly increased aqueous stability in the range of several days, this complex is highly toxic *in vitro* and more importantly, has enhanced antitumor efficacy in an *in vivo* cervical cancer mouse model.^{8f}

Exploring scope and limitations of the stability enhancing effect of the additional dipic-chelator¹¹ we became interested in introducing the electron withdrawing sulfonamide motif which is known to be a privileged group in drug discovery.¹² A large number of structurally novel sulfonamide derivatives were reported to show substantial antitumor activities in a variety of processes such as carbonic anhydrase inhibition,¹³ cell cycle arrest,¹⁴ disruption of microtubular assembly,¹⁵ and angiogenesis inhibition.¹⁶ Several combinations of sulfonamide with metal-based chemotherapeutic agents have been reported to show synergistic effects in the treatment of cancer processes.¹⁷ However, Ti(IV) complexes with non-coordinating and thus potentially bioavailable sulfonamide groups are not known.¹⁸ Herein, we present the synthesis and preliminary cytotoxicity study of several heptacoordinate Ti(IV)-salan dipic hetero-*bis*-chelates with non-coordinating sulfonamide groups.

Results and Discussion

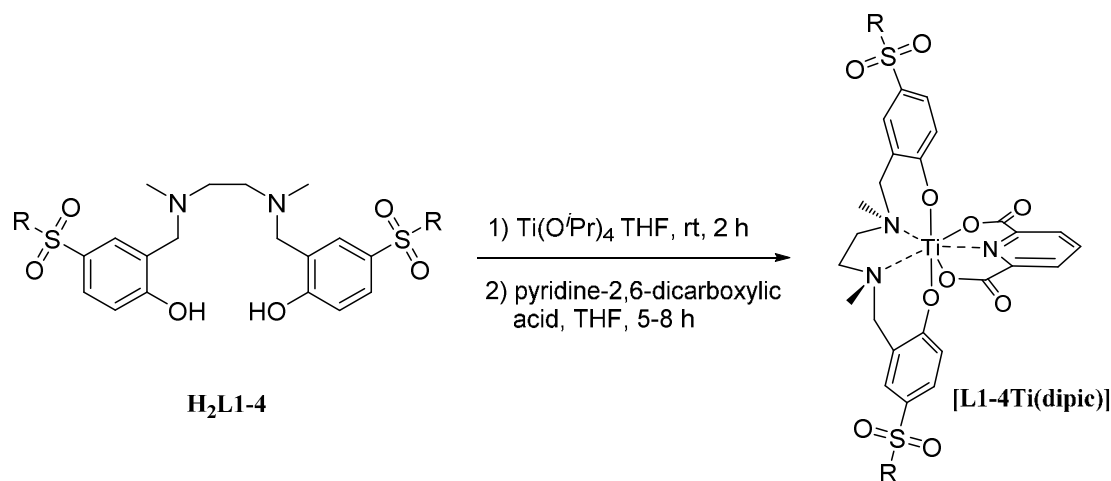
Complex synthesis

The synthetic route for the sulfonamide-based salan ligands is outlined in Scheme 1. Protection of salicylaldehyde (**1**) as anilide followed by chloro sulfonation and *in situ* deprotection during work up, afforded hitherto unknown sulfonylchloride **3** as common starting material in 81 % overall yield.¹⁹ **3** reacted smoothly with different cyclic secondary amines to give sulfonamide substituted salicylic aldehydes **4a-d**. The corresponding salan ligands **H₂L1-4** were prepared by reductive amination with ethylenediamine and reductive alkylation using aqueous formaldehyde in analogy to a known procedure.^{8f}

Scheme 1: Synthesis of sulfonamide bearing salan ligands H_2L1-4 ^a

^a Reagents and reaction conditions: (a) amine, CH_2Cl_2 , 0 °C to rt. (b) ethylene diamine, MeOH, rt. (c) $NaBH_4$, rt. CH_2Cl_2 , MeOH, rt. (d) HCHO, AcOH, CH_3CN , rt. then $NaBH_4$, 0 °C to rt.

The synthesis of the sulfonamido-salan Ti(IV) complexes [**L1-4Ti(dipic)**] is summarized in Scheme 2.

Scheme 2: Synthesis of sulfonamido-salan Ti(IV) complexes [**L1-4Ti(dipic)**]^a

Metalation of salans H_2L1-4 with titanium tetraisopropoxide in tetrahydrofuran resulted in the clean formation of the C_2 -symmetric cis- α -isomers in all cases as evident from the typical AB pattern of the diastereotopic benzylic protons ($Ar-CH_2-N$) in the 1H NMR spectra recorded from the crude. [**L1-4Ti(OiPr)₂**] were isolated in nearly quantitative yield as racemic mixtures of the Δ and Λ -isomers. In contrast to Ti(IV)-alkoxides of alkyl or halogen substituted salans which are dark orange to red colored and have their LMCT band accordingly in the UV-vis region, complexes [**L1-4Ti(OiPr)₂**] are virtually colourless. The strongly electron withdrawing sulfonamide distinctly blue shifted the spectrum compared to alkyl or halogen substituted salans.^{8c} In case of [**L4Ti(OiPr)₂**] the isopropoxide was isolated and the λ_{max} was determined to 308 nm. All sulfonamide substituted Ti(IV)-isopropoxides are quite sensitive in solution and decompose slowly over time. Consequently, they were directly converted to the corresponding dipic-derivatives.¹⁰ The ligand exchange reaction was initiated by the addition of THF to a mixture of crude [**L1-4Ti(OiPr)₂**] and dipic to afford analytical pure [**L1-4Ti(dipic)**] in yields between 33 – 45 % based on $Ti(OiPr)_4$. The progress of the reaction was conveniently monitored by TLC. In contrast to previous experiments with non-sulfonamide bearing complexes¹⁰⁻¹¹ the addition of less than 2 equiv. of dipic resulted in non-complete conversion even on prolonged reaction time. The excess dipic could be removed by carefully washing of a solution of [**L1-4Ti(dipic)**] in dichloromethane with dilute (1

mol/L) sodium hydroxide solution. Complexes were then purified by column chromatography on silica gel and recrystallization.

Solid state structure and NMR studies

In the $^1\text{H-NMR}$ spectra all complexes showed the characteristic signals for pseudo C_2 symmetrical complexes, namely a coincidence of the signals of both halves of the salan backbone. As expected for complexes with electron withdrawing substituents, all signals are low-field shifted compared to the non-sulfonamide substituted dipic complex **[L5Ti(dipic)]**. For instance, the NMe-resonance of the dipic-bound protons in the sulfonamide bearing complexes appears around 0.1 ppm down-field shifted with respect to **[L5Ti(dipic)]**. The effect on the diastereotopic methylene protons is with 0.15 ppm slightly stronger. This demonstrates clearly that the sulfamido group of the salan ligand communicates via the Ti(IV) centre with the dipic ligand. The symmetry found in solution was confirmed in the solid by X-ray diffraction of single crystals of **[L4Ti(dipic)]** and **[L5Ti(dipic)]** (Figure 1). Both crystallize in the monoclinic space group $C2/c$. In the asymmetric unit one molecule **[L4Ti(dipic)]** is accompanied by two molecules of acetone while **[L5Ti(dipic)]** crystalizes without additional solvent. In **[L5Ti(dipic)]** Ti(1), N(2) and C(12) are oriented on the two-fold axis which intersects the ethylenediamine bridge of the salan backbone between C(8) and C(8'). Consequently, the asymmetric unit contains only half a molecule. Selected bond length and angles are summarized in Table 1, crystallographic data are found in Table 4. With respect to the arrangement around the titanium centre **[L4Ti(dipic)]** and **[L5Ti(dipic)]** compare extremely well with the other known solid state structures of Ti(IV)-salan dipicolinates.¹⁰⁻¹¹ Both feature the pentagonal bipyramidal core structure of a heptacoordinate titanium centre with the phenolates in the apical position and the nitrogen atoms of the salan and the pyridine together with the carboxylates defining the equatorial plane. The bridging nitrogen atoms of the salan have the greatest deviation from the equatorial plane with 0.194(17) Å for N2 in **[L4Ti(dipic)]** and 0.284(8) Å for N1 in **[L5Ti(dipic)]**. The phenolate-Ti distance in **[L5Ti(dipic)]** (1.8672(11) Å) is comparable to that in **[L4Ti(dipic)]** (1.8586(15) Å and 1.8648(15) Å). In both complexes this distance is slightly elongated compared to the 1.84 Å found for the 2,4-dimethylsubstituted salan in ref. 10 indicating that the *p*-sulfonamido substituted **[L4Ti(dipic)]** as well as the unsubstituted homologue have a diminished donor strength compare with the 2,4-dimethylsubstituted complex. The MeN-Ti distance in both complexes is unaffected by the substitution in the vicinity of the salan and is with 2.3457(17) and 2.3757(18) for **[L4Ti(dipic)]** and 2.3695(14) Å for **[L5Ti(dipic)]** in the range of 2.350(2) Å and 2.384(2) of the previous characterized complex.¹⁰ Dipicolinic acid acts as bis-anionic tridentate coordinating to the titanium-salan fragment *via* two of the carboxylate oxygen atoms and its pyridine N atom. In **[L4Ti(dipic)]** both carboxylate groups of the dipic are pulled towards the Ti(IV) centre resulting in a twist out of plane with respect to the pyridine ring by 3.9(2)°. The Ti-carboxylate distances in **[L4Ti(dipic)]** differ with 2.0361(15) Å and

2.0551(14) Å quite strongly whereas the Ti–O distances in the previous characterized complex is more balanced (2.043(1) and 2.046(1) Å).¹⁰ In **[L5Ti(dipic)]** the Ti–carboxylate distance is with 2.0345(12) Å considerably shorter.

Table 1. Selected bond lengths and angles for **[L4Ti(dipic)]** and **[L5Ti(dipic)]**.

[L4Ti(dipic)]					
Distances [Å]			Angles [°]		
Ti–O(11)	1.8586(15)	O(11)–Ti–O(12)	170.21(7)	O(11)–Ti–N(2)	80.98(6)
Ti–O(12)	1.8648(15)	O(11)–Ti–O(4)	95.06(6)	O(12)–Ti–N(2)	92.01(6)
Ti–O(4)	2.0361(15)	O(12)–Ti–O(4)	89.38(6)	O(4)–Ti–N(2)	73.19(6)
Ti–O(2)	2.0551(14)	O(11)–Ti–O(2)	89.21(6)	O(2)–Ti–N(2)	145.08(6)
Ti–N(1)	2.1941(18)	O(12)–Ti–O(2)	92.75(6)	N(1)–Ti–N(2)	143.21(6)
Ti–N(2)	2.3457(17)	O(4)–Ti–O(2)	141.42(6)	O(11)–Ti–N(3)	91.22(6)
Ti–N(3)	2.3757(18)	O(11)–Ti–N(1)	94.33(7)	O(12)–Ti–N(3)	80.22(6)
		O(12)–Ti–N(1)	95.36(7)	O(4)–Ti–N(3)	144.99(6)
		O(4)–Ti–N(1)	70.91(6)	O(2)–Ti–N(3)	72.91(6)
		O(2)–Ti–N(1)	70.53(6)	N(1)–Ti–N(3)	142.91(6)
				N(2)–Ti–N(3)	73.88(6)

[L5Ti(dipic)]					
Distances [Å]			Angles [°]		
N(1)–Ti(1)	2.3695(14)	O(1)#1–Ti(1)–O(1)	171.17(7)	O(1)–Ti(1)–N(1)	80.46(5)
N(2)–Ti(1)	2.178(2)	O(1)#1–Ti(1)–O(2)	89.00(5)	O(2)–Ti(1)–N(1)	73.05(5)
O(1)–Ti(1)	1.8672(11)	O(1)–Ti(1)–O(2)	93.84(5)	O(2)#1–Ti(1)–N(1)	143.95(5)
O(2)–Ti(1)	2.0345(12)	O(2)–Ti(1)–O(2)#1	142.47(7)	N(2)–Ti(1)–N(1)	143.46(3)
		O(1)–Ti(1)–N(2)	94.41(4)	O(1)–Ti(1)–N(1)#1	92.41(5)
		O(2)–Ti(1)–N(2)	71.23(3)	N(1)–Ti(1)–N(1)#1	73.08(7)
		O(1)#1–Ti(1)–N(1)	92.41(5)		

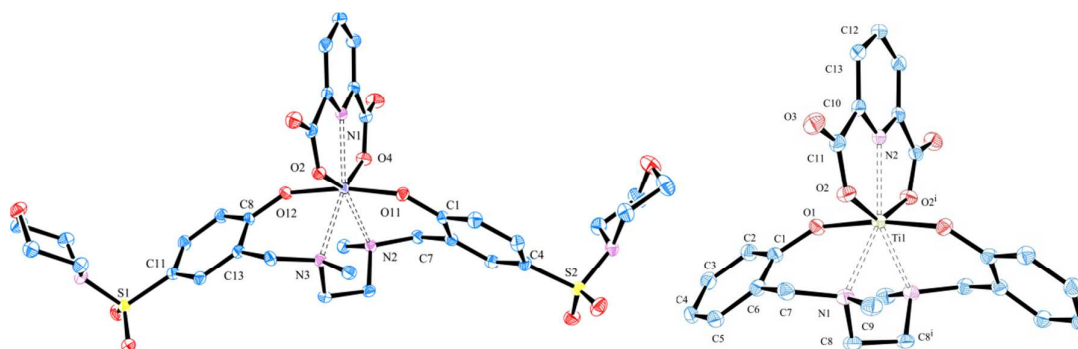


Figure 1: X-ray crystal structure of heptacoordinate **[L4Ti(dipic)]** (left) and **[L5Ti(dipic)]** (right). Both are exhibiting pseudo C_2 symmetry and a distorted pentagonal-bipyramidal conformation of the ligands

around the Ti(IV) center. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms and additional solvent molecules for **[L4Ti(dipic)]** are omitted for clarity.

Stability and Hydrolysis

Stability tests were carried out using time resolved ^1H NMR spectroscopy as previously reported.^{8b, e} Briefly, to solutions of 15 μmol complexes **[L1-4Ti(dipic)]** in d_8 -THF a ~ 1000 molar excess of D_2O was added ($t = 0$) and ^1H NMR spectra were recorded in certain time intervals. In case of **[L5Ti(dipic)]** the concentration was with 4.5 μmol much lower because of its very limited solubility in most solvents. The aim of the hydrolytic degradation study is to benchmark relative stability under controlled conditions which are certainly different from the hydrolysis in a biological environment. All complexes **[L1-4Ti(dipic)]** exhibit moderate hydrolytic stability with their half-lives ranging from 2 - 3.5 h (Table 2, Figure S1 in the ESI), and thus are more prone towards hydrolysis than is our previously reported Ti(IV)-*bis*-chelate with $t_{1/2} \gg 2$ weeks under the same conditions¹⁰ but well within the range of other complexes recently tested to be bioactive.²⁰ The non-sulfonamide bearing **[L5Ti(dipic)]** exhibited a much higher stability as evident from time resolved ^1H NMR spectra (Figure S9 of the ESI). The reduced stability of sulfonamide bearing salan dipicolinates **[L1-4Ti(dipic)]** compared with the non-sulfonamide bearing **[L5Ti(dipic)]** can be rationalized by the electron withdrawing nature of the sulfonamide which renders the titanium more electrophilic and hence more 'attractive' towards the attack of OD^- from the autoprotolysis of D_2O . The lack of the *ortho*-substituent of the salan in complexes **[L1-5Ti(dipic)]** makes those complexes less efficiently shielded compared to the first hetero-*bis*-chelate from ref. 10 whose salan features a 2,4-dimethyl substitution pattern. In contrast to the oligonuclear hydrolysis products of *bis*(alkoxo) salan Ti(IV) complexes,^{8f, 21} the hydrolysis of **[L1-5Ti(dipic)]** exclusively yields the corresponding salan ligands **H₂L1-5** as detected by NMR and HPLC (for a detailed one-to-one comparison see Fig. S1 and S2 in the ESI).¹¹ Figure 2 depicts a series of time resolved ^1H NMR spectra recorded during the incubation of **[L3Ti(dipic)]** with D_2O . After a total duration of 14 h only minute quantities of intact complex are detectable whereas the signals of the free ligands figure most prominently. For time resolved spectra recorded during the hydrolysis of the other complexes see Figures S3 – S5 of the ESI.

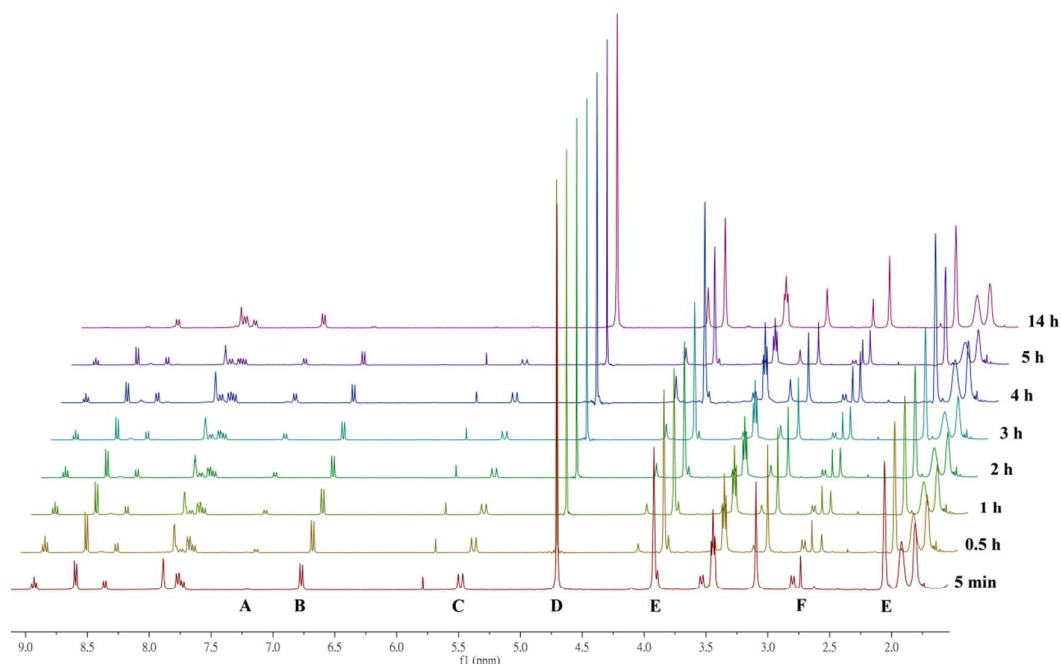


Figure 2: Example of a hydrolytic stability study of **[L3Ti(dipic)]** at 37 °C investigated by time resolved ¹H NMR in aqueous (1000 eq. D₂O), *d*₈-THF (0.4 ml) and 0.15 equiv of 4-nitrotoluene as an internal reference. Spectra shown are from bottom to top measured at *t* = 5 min, 0.5 h, 1 h-5 h and 14 h after the addition of D₂O. Signals marked are H_{ar} of free salan ligand **H₂L3** (A), H_{ar} of the **[L3Ti(dipic)]** (B), C_{ar}CH₂ of **[L3Ti(dipic)]** (C), D₂O (D), THF (E) and CH₃ of 4-nitrotoluene (F).

Biotest are run in DMEM medium which itself contains several inorganic salts, vitamins, amino acids and other constituents (see experimental for details). To study the influence of these electrolytes on the stability of **[L4Ti(dipic)]** a series of time resolved ¹H NMR with added medium was recorded. (cf. Figure S6 in the ESI). For this a solution of Dulbecco's Modified Eagle's Medium (dry formulation, Aldrich order no.: D5523-10X1L) with added sodium bicarbonate to make up for complete medium in D₂O was prepared. This aqueous solution now containing all salts, amino acids, vitamins and glucose of the original cell medium was added as before to a solution of **[L4Ti(dipic)]** in *d*₈-THF and NMR spectra measured immediately after. These measurements showed a slightly increased speed of hydrolysis which is well within the error margins (30 min) of those experiments (see Figure S7 in the ESI).

Next we investigated if the DMSO used for preparing stock solutions of complexes for the bio tests might interfere with the complex stability. Recently, McGowan et al. reported on the isolation of a biologically non active DMSO-coordinated titanium oxo species which forms upon the addition of the solvent to a 1,3-β-diketonato titanium(IV) complex during formulation of the drug for *in vitro* testing.²² As visible from time resolved ¹H NMR spectra of **[L4Ti(dipic)]** recorded in *d*₆-DMSO during 24 h at 37 °C (Figure S8 of ESI), no degradation or ligand exchange is detectable. Obviously, the heptacoordinate complex is

efficiently stabilized by its two chelating ligands and withstands a potential ligand exchange against DMSO under these conditions.

Table 2: Half-lives of **[L1-4Ti(dipic)]** at 37°C determined in aqueous (1000 eq. D₂O), *d*₈-THF by time resolved ¹H-NMR

Compound	<i>t</i> _{1/2} (h) ^a	Compound	<i>t</i> _{1/2} (h) ^a
[L1Ti(dipic)]	2.0	[L3Ti(dipic)]	2.2
[L2Ti(dipic)]	3.5	[L4Ti(dipic)]	3.0

^a Detailed NMR-spectra are given in the ESI; Error was estimated to be ± 0.5 h

Cytotoxicity assay

All compounds were tested for their cytotoxicity in the human cervix carcinoma cell line HeLa S3 and the human hepatocarcinoma cell line Hep G2 in a AlamarBlue-based cytotoxicity assay.²³ IC₅₀ values are given as mean values from three independent experiments each done in four replicates (further details of the assay are to be found in the experimental section). The IC₅₀ values of the synthesized compounds are summarized in Table 3. It was observed that compounds **[L1-3Ti(dipic)]** exhibited good to excellent bioactivity and reached maximum inhibition, that is a cell viability of 0 % (For IC₅₀-charts see Figures S12 and S13 in the ESI). Two of the most active complexes **[L2Ti(dipic)]** and **[L3Ti(dipic)]**, with IC₅₀ values below or close to 1 μmolar, are even more cytotoxic than cisplatin. Even though, the morpholinosulfonyl derivative **[L4Ti(dipic)]** showed the anticipated enhanced aqueous solubility, its bioactivity against HeLa S3 is greatly reduced when compared with **[L1-3Ti(dipic)]** and even completely vanished against Hep G2 cells.

The ligands **H₂L1-4** and dipic were investigated for their cytotoxicity as well to answer the question if the measured cytotoxicity might be an effect of liberated ligand. Dose-response curves for the ligands **H₂L1-5** were recorded in a concentration range comparable to that of the complexes. One obvious difference observed is the lower solubility of the ligand **H₂L1-4** compared to the corresponding complexes. While those were soluble close to the millimolar range during bio assays, the ligands showed limited solubility with the exception of **H₂L4**. As a result, the ligands dose-response plots did not follow a sigmoidal trend (A comparison of complex and ligand toxicity is given in Table S11 of the ESI). Instead, these curves show a shallow slope and monotonously approach towards some cytotoxicity. At the 100 μmolar regime bioactivity was detected albeit the maximum cell viability never reached below 30%. Raising the concentration even further leads to severe solubility problems. Only at this concentration regime where precipitation already was manifest highest cell viability was reached. Precipitation of **H₂L1-3** was detected during the assay when concentrations were higher than 100 μmolar by microscopic control of the cell assay. This precipitation might account for the found cytotoxicity of the ligands at highly elevated

concentrations. In contrast, complexes **[L1-3Ti(dipic)]** showed potent cytotoxicity already at concentration in the μ molar regime with an inhibition rate of greater than 90%. The ligands **H2L1-4** and **dipic**, however, showed a less pronounced cytotoxicity in this concentration regime. In contrast to the behaviour of the ligands, complexes **[L1-3Ti(dipic)]** lead to a complete loss of viability already at two orders of magnitude lower concentrations.

We have determined the half-lives of **[L1-4Ti(dipic)]** in the region of 2-3h. Upon hydrolysis only ligands were found. The cytotoxicity of ligands does not follow a sigmoidal trend and reaches maximum inhibition only at concentrations higher than 100 μ molar. However, complexes show complete inhibition at much lower concentrations and have their IC_{50} values in the 1-3 μ molar regime. Based on the assumption that the ligand is not modified during incubation whereas the complexes decompose within a certain time, the found cytotoxicity can be rationalized by the following way: If cellular uptake of the complex would be rather slow, most of the complex would decompose to yield the ligand. As a result, the cytotoxicity profile of free ligand and complex should become very similar or even identical, which our data proves to be incorrect. Previous studies on salan type-Ti(IV) complexes suggested a serum protein-independent rapid cell penetrating mechanism,²⁴ which recently was further corroborated by a high-resolution atomic absorption spectroscopy based study.²⁵ The authors showed the rapid increase of the intracellular titanium concentration within hours after drug exposure for a wide selection of different Ti(IV)-species. For heptacoordinate hetero-*bis*-chelates recently a fast cellular uptake of the intact complex was proposed.¹¹ Whether this obviously fast cellular uptake of **[L1-3Ti(dipic)]** results from the sulfonamide substitution by way of an active shuttling or if the solubility enhancing sulfonamide is making the complexes better accessible is debatable. Because the long-time stable **[L5Ti(dipic)]** showed a cytotoxicity in the low μ molar regime comparable to the other complexes, it does not necessarily has to rely on a fast uptake. What sets **[L1-4Ti(dipic)]** apart from complexes lacking the sulfonamide moiety are: (1) a greatly enhanced solubility and stability in DMSO facilitating the drug formulation, (2) a much enhanced aqueous solubility preventing precipitation of active drug from the media. Admittedly one has to note that the sulfonamide substitution reduces the long term stability of complexes in aqueous media. However, we could show that this does not necessarily limit the usefulness of those complexes because their cytotoxicity against Hela S3 and Hep G2 cells compares very well with other Ti(IV) based systems.

Table 3: IC_{50} -values obtained for **[L1-4Ti(dipic)]** by an AlamarBlue assay in Hela S3 and Hep G2 cells after 48h of incubation.

	Hela S3	Hep G2
	IC_{50}^a	
[L1Ti(dipic)]	3.1 \pm 0.2	9.3 \pm 0.2
[L2Ti(dipic)]	0.9 \pm 0.1	1.8 \pm 0.2
[L3Ti(dipic)]	0.5 \pm 0.1	1 \pm 0.1

[L4Ti(dipic)]	19 ± 4	nontoxic
[L5Ti(dipic)]	2.8 ± 0.5	3.7 ± 1.3
Cisplatin	2.0 ± 0.3	4.8 ± 1.2

^a Values determined after 48 h of incubation.

Conclusions

In summary, we have synthesized sulfonamide functionalised Ti(IV)-salan dipic *bis*-chelates with the sulfonamide being not part of the titanium's coordination sphere. Their structures were elucidated by means of NMR and by single crystal X-ray diffraction of **[L4Ti(dipic)]**, and **[L5Ti(dipic)]**. Preliminary *in vitro* biological evaluation against two human cell lines revealed that **[L2Ti(dipic)]** and **[L3Ti(dipic)]** have cytotoxicity in the sub μ molar range and are 5-7 times more cytotoxic than cisplatin. The contribution of the sulfonamide group to this observation might be twofold: (1) complexes **[L1-4Ti(dipic)]** are notably better soluble in DMSO than the non-sulfonamide bearing homologue. This results in a better distribution in media and hence a possible better bioavailability in the cell based assay. (2) A possible role of the sulfonamido group during the process of cellular uptake cannot be ruled out and demands further biological studies. These novel sulfonamide Ti(IV)-*bis*-chelate complexes have highly potent anticancer activities. Further studies on the explanation of structure-activity relation are currently underway.

Experimental Section

All reagents, metal catalysts and solvents were obtained from commercial sources and were purified before use by standard methods.²⁶ All experiments requiring dry atmosphere were carried out under nitrogen atmosphere using standard Schlenk technique. Silica gel 60 (40–63 μ m) for flash chromatography was purchased from Macherey & Nagel (Düren). NMR spectra were measured on Bruker Avance III 400 and Bruker Avance DRX 600 spectrometers. Structure assignments were done based on 2D-NMR (COSY, HMBC, HSQC) experiments. ¹H NMR chemical shifts are referenced with respect to the chemical shift of the residual protons present in the deuterated solvents (CDCl₃: δ H = 7.26 ppm, δ C = 77.16 ppm; *d*6-DMSO: δ H = 2.50 ppm, δ C = 39.52 ppm; *d*6-Acetone: δ H = 2.05 ppm, δ C = 29.84, 206.26 ppm). UV-vis spectra were recorded on a Varian Cary 50 spectrophotometer and a Perkin Elmer Lambda 18 (200 - 600 nm) in dilute ($\sim 10^{-5}$ M) THF solutions. IR spectra were recorded on a Perkin Elmer Spectrum 100 FTIR (ATR) spectrometer. Melting points are not corrected and were measured with a Krüss-Meltingpointmeter KFP I N. High resolution mass spectra were recorded of 1 μ M dilute samples in acetonitrile-acetone-water-solutions on a Bruker micrOTOF II mass spectrometer. Elemental analyses were carried out in the micro analytical lab of the University of Konstanz using an Elementar Vario EL CHN analyzer.

X-ray Crystallography. Suitable single crystals of **[L4Ti(dipic)]** and **[L5Ti(dipic)]** were grown by slow diffusion of hexane into a saturated solution of **[L4Ti(dipic)]** in acetone or of hexane into a saturated solution of **[L5Ti(dipic)]** in dichloromethane. Crystals were directly picked from solution and covered in an inert oil and immediately placed in the cold N₂-stream of the Oxford Cryostream 700 with nitrogen as coolant gas. Data collection for X-ray structure-determination was performed at a STOE IPDS-II diffractometer equipped with a graphite monochromated radiation source ($\lambda = 0.71073 \text{ \AA}$), an image plate detection system. 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 structure was solved by direct methods (SHELXS-97)²⁷ and refined by standard Fourier techniques against F square with a full-matrix leastsquares algorithm using SHELXL-97 and the WinGX (1.80.05)²⁸ 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.²⁹ Crystallographic data (excluding structure factors) of **[L4Ti(dipic)]** and **[L5Ti(dipic)]** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1031337 and 1410575. 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>).

Table 4: Crystallographic data of **[L4Ti(dipic)]** and **[L5Ti(dipic)]**.

Compound reference	[L4Ti(dipic)]	[L5Ti(dipic)]
Chemical formula	C ₃₃ H ₃₉ N ₅ O ₁₂ S ₂ Ti•2(C ₃ H ₆ O)	C ₂₅ H ₂₅ N ₃ O ₆ Ti
Formula Mass	925.86	511.38
Crystal system	Monoclinic	Monoclinic
<i>a</i> /Å	38.9176(16)	16.7824(13)
<i>b</i> /Å	10.0754(5)	14.9183(9)
<i>c</i> /Å	21.8768(8)	8.6437(7)
<i>α</i> /°	90.00	90.00
<i>β</i> /°	93.133(3)	91.497(6)
<i>γ</i> /°	90.00	90.00
Unit cell volume/Å ³	8565.3(6)	2163.3(3)
Temperature/K	100(2)	100(2)
Space group	<i>C2/c</i>	<i>C2/c</i>
No. of formula units per unit cell, <i>Z</i>	8	4
Absorption coefficient, <i>μ</i> /mm ⁻¹	0.370	0.447
No. of reflections measured	58758	14886
No. of independent reflections	9115	2181
<i>R</i> _{int}	0.1041	0.1342
Final <i>R</i> _{<i>I</i>} values (<i>I</i> > 2σ(<i>I</i>))	0.0436	0.0332
Final <i>wR</i> (<i>F</i> ²) values (<i>I</i> > 2σ(<i>I</i>))	0.0835	0.0893
Final <i>R</i> _{<i>I</i>} values (all data)	0.0689	0.0449
Final <i>wR</i> (<i>F</i> ²) values (all data)	0.0901	0.0916
Goodness of fit on <i>F</i> ²	1.022	1.043

Hydrolysis study. Hydrolysis tests were carried out by time-resolved ¹H-NMR spectroscopy under the following conditions: Ti complex (15 μmol) for **[L1-L4Ti(dipic)]**, 4-nitrotoluene as internal standard (0.3 mg, 2.25 μmol, 0.15 equiv), D₂O (0.27 ml, 1000 equiv), *d*₈-THF (0.4 ml). In case of **[L5Ti(dipic)]** the amounts were adjusted because of its lower solubility: (4.5 μmol) complex, D₂O (0.08 ml, 1000 equiv), and *d*₈-THF (0.5 ml). ¹H NMR were measured at 37 °C at given intervals and samples stored in-between at 37 °C. Data gathered by monitoring the decrease in isolated signals of the titanium-bound salan backbone and increase in the free salan ligand. Integrals are normalized against the internal standard. Control measurements were done in the absence of 4-nitrotoluene and showed no significant difference in the hydrolysis rate and products being formed. The hydrolysis experiments using cell medium were done in a similar manner with the exception of the amount of added D₂O. While keeping the volume ratio as before the amount of available D₂O is slightly diminished because of the added salts, amino acids,

vitamins and glucose of the DMEM medium. Since the constituents of the medium interfere with the above standard, we used 1,4-dinitrobenzene instead. For an exact content of the used dry medium refer to ref.³⁰

Cytotoxicity assay. Cytotoxicity was measured on HeLa S3 and Hep G2 cells using an AlamarBlue (Thermo Scientific) assay.³¹ Alamarblue was purchased from BioSource Europe. Cells were cultivated at 37 °C in humidified 5% CO₂ atmosphere using Dulbecco's DMEM-media (Invitrogen) containing 10 % foetal calf serum (Biochrome AG), 1 % penicillin and 1 % streptomycin (both GIBCO). Cells were split twice per week. Both cell lines were tested on mycoplasma infections using a mycoplasma detection kit (Roche Applied Science). The cells were seeded in 96-well plates (4.000 HeLa S3 cells/well or 8.000 Hep G2 cells/well) and allowed to attach for 24 h. The cells were then incubated with different concentrations of the reagent to be tested. Compounds to be tested were dissolved in a suitable amount of DMSO and different concentrations were prepared by serial dilution with DMSO. One part of each DMSO solution is then added to 99 parts of medium. Cells were then incubated for 48 h with 100 µl of above medium containing 1% DMSO and a certain concentration of compound. The medium was then replaced by 100 µL medium containing 10 % AlamarBlue (BioSource Europe) and the cells were incubated for 90 min. The fluorescence at 590 nm was measured after excitation at 530 nm using a Synergy HT Microplate Reader (BioTek). Raw readout data from the assay was corrected for background fluorescens by an "on-plate" blind containing only medium, 1 % DMSO and Alamarblue but no cells (0-value). The background corrected absolute read-outs were then expressed as relative values with regard to an "on-plate" 100 % standard containing untreated cells in medium with 1 % DMSO. All data was then fitted to a sigmoidal dose-response model with variable slope (4 parameter logistic nonlinear regression model) using Sigma plot 10.0.³² Upper and lower boundaries as well as the slope were allowed to refine freely. All experiments were repeated at least three times on three different days with each experiment done in four replicates on the same plate. Replicates are treated with equal statistical weight; Error-bars representing SEM. IC₅₀ values are given as means from independent experiments, error values of IC₅₀ are based on standard deviation of independent experiments.

Complex syntheses

3-Formyl-4-hydroxybenzene-1-sulfonyl chloride (3): Chlorosulfonic acid (147.7 g, 1.27 mol) was added slowly to 2-((phenylimino)methyl)phenol (25 g, 126.7 mmol) at 0 °C while stirring, the reaction was allowed to proceed for 20 h at r.t. The reaction mixture was added portionwise to ice (1000 g) and extracted with CH₂Cl₂ (3 × 100 mL), the combined organic phase was washed three times with 50% H₂SO₄ (100 ml). The organic layer was dried over Na₂SO₄, and the solvent was evaporated in vacuo to give **3** as yellow solid (19.4 g, 87.93 mmol, 70 %). M.p.121-122 °C; IR absorptions (cm⁻¹, ATR): 1682, 1665, 1567, 1468, 1379, 1291, 1174, 1078, 709; ¹H NMR (CDCl₃, 400 MHz): δ 11.71 (s, 1H, OH), 10.00

(s, 1H, HC=O), 8.32 (s, 1H, H_{ar}), 8.15 (d, $J = 6.4$ Hz, 1H, H_{ar}), 7.22 (d, $J = 6.4$ Hz, 1H, H_{ar}); ¹³C NMR (CDCl₃, 101 MHz): δ 195.4 (C=O), 166.6 (C_{ar}), 135.9 (C_{ar}), 134.9 (C_{ar}), 133.8 (C_{ar}), 120.0 (C_{ar}). HRMS (ESI-TOF) m/z Calcd for C₇H₆ClO₄S [M+H]⁺: 220.9670. Found: 220.9672.

2-Hydroxy-5-(pyrrolidin-1-ylsulfonyl)benzaldehyde (4a): To a solution of **3** (3.0 g, 13.5 mmol) in 40 ml CH₂Cl₂ was added portionwise pyrrolidine (1.19 g, 16.7 mmol) at 0 °C, the reaction was allowed to proceed for another 12 h and warm to r.t., the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/Petroleum ether = 2:1) to give **4a** as a yellow solid (2.85 g, 11.16 mmol, 83%). M.p. 158-159 °C; IR absorptions (cm⁻¹, ATR): 2981, 2878, 1642, 1617, 1469, 1320, 1191, 1088, 751; ¹H NMR (CDCl₃, 400 MHz): δ 11.37 (s, 1H, OH), 9.95 (s, 1H, HC=O), 8.10 (d, $J = 2.4$ Hz, 1H, H_{ar}), 7.92 (dd, $J = 2.4, 8.8$ Hz, 1H, H_{ar}), 7.09 (d, $J = 8.8$ Hz, 1H, H_{ar}), 3.24-3.20 (m, 4H, NCH₂), 1.78-1.76 (m, 4H, NCH₂CH₂); ¹³C NMR (CDCl₃, 101 MHz): δ 196.1 (C=O), 164.5 (C_{ar}), 135.4 (C_{ar}), 133.8 (C_{ar}), 129.0 (C_{ar}), 119.9 (C_{ar}), 118.9 (C_{ar}), 48.1 (NCH₂), 25.3 (NCH₂CH₂); ESI-MS m/z (%): 256 (90) [(M+H)⁺]; Anal. Calcd. for C₁₁H₁₃NO₄S: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.78; H, 5.28; N, 5.55.

2-Hydroxy-5-(piperidin-1-ylsulfonyl)benzaldehyde (4b): Following the same procedure as for **4a** with **3** (3.0 g, 13.5 mol), piperidine (5.78 g, 67.9 mmol) in 50 ml CH₂Cl₂ for 1 h to give **4b** as a yellow solid after column chromatography on silica gel (EtOAc/Petroleum ether = 2:1) (3.18 g, 11.8 mmol, 87 %). M.p. 168-170 °C; IR absorptions (cm⁻¹, ATR): 2927, 1662, 1292, 1154, 925, 742; ¹H NMR (CDCl₃, 400 MHz): δ 11.40 (s, 1H, OH), 9.96 (s, 1H, HC=O), 8.03 (d, $J = 2.4$ Hz, 1H, H_{ar}), 7.87 (dd, $J = 2.4, 8.8$ Hz, 1H, H_{ar}), 7.12 (d, $J = 8.8$ Hz, 1H, H_{ar}), 3.01 (t, $J = 4.0$ Hz, 4H, NCH₂), 1.68-1.63 (m, 4H, NCH₂CH₂), 1.47-1.41 (m, 2H, NCH₂CH₂CH₂); ¹³C NMR (CDCl₃, 101 MHz): δ 196.0 (C=O), 164.7 (C_{ar}), 135.6 (C_{ar}), 134.0 (C_{ar}), 128.4 (C_{ar}), 120.0 (C_{ar}), 118.9 (C_{ar}), 47.1 (NCH₂), 25.3 (NCH₂CH₂), 23.6 (NCH₂CH₂CH₂); ESI-MS m/z (%): 270 (100) [(M+H)⁺]; Anal. Calcd. for C₁₂H₁₅NO₄S: C, 53.52; H, 5.61; N, 5.20. Found: C, 53.61; H, 5.45; N, 5.34.

5-(Azepan-1-ylsulfonyl)-2-hydroxybenzaldehyde (4c): Following the same procedure as for **4a** with **3** (3.19 g, 14.4 mmol), azepane (2.85 g, 28.7 mmol) in 25 ml CH₂Cl₂ for 2.5 h to give **4c** as a light yellow solid after column chromatography on silica gel (EtOAc/Petroleum ether = 2:1) (1.35 g, 4.7 mmol, 33%); M.p. 152-154 °C; IR absorptions (cm⁻¹, ATR): 2915, 1661, 1321, 1086, 997, 875, 736; ¹H NMR (CDCl₃, 400 MHz): δ 11.37 (s, 1H, OH), 9.95 (s, 1H, HC=O), 8.08 (d, $J = 2.4$ Hz, 1H, H_{ar}), 7.90 (dd, $J = 2.4, 8.8$ Hz, 1H, H_{ar}), 7.10 (d, $J = 8.8$ Hz, 1H, H_{ar}), 3.29 (t, $J = 4.0$ Hz, 4H, NCH₂), 1.74-1.72 (m, 4H, NCH₂CH₂), 1.62-1.59 (m, 4H, NCH₂CH₂CH₂); ¹³C NMR (CDCl₃, 101 MHz): δ 196.0 (C=O), 164.4 (C_{ar}), 135.0 (C_{ar}), 133.3 (C_{ar}), 131.7 (C_{ar}), 120.0 (C_{ar}), 119.0 (C_{ar}), 48.4 (NCH₂), 29.3 (NCH₂CH₂), 27.1 (NCH₂CH₂CH₂); HRMS (ESI-TOF) m/z Calcd for C₁₃H₁₈NO₄S [M+H]⁺: 284.0951. Found: 284.0959.

2-Hydroxy-5-(morpholin-sulfonyl)benzaldehyde (4d): Following the same procedure as for **4a** with **3** (5.0 g, 22.7 mmol), morpholin (20.18 g, 231.7 mmol) in 50 ml CH₂Cl₂ for 2.5 h to give **4d** as a light

yellow solid after column chromatography on silica gel (EtOAc/Petroleum ether = 2:1) (5.37 g, 19.79 mmol, 88%); M.p. 187-188 °C; IR absorptions (cm⁻¹, ATR): 2993, 1685, 1668, 1348, 1328, 1260, 1225, 1150, 1111, 941, 742; ¹H NMR (*d*₆-DMSO, 400 MHz): δ 11.85 (s, 1H, OH), 10.32 (s, 1H, HC=O), 7.93 (d, *J* = 2.0 Hz, 1H, H_{ar}), 7.81 (dd, *J* = 2.0, 8.8 Hz, 1H, H_{ar}), 7.22 (d, *J* = 8.8 Hz, 1H, H_{ar}), 3.7 (t, *J* = 4.0 Hz, 4H, OCH₂), 2.85 (t, *J* = 4.0 Hz, 4H, NCH₂); ¹³C NMR (*d*₆-DMSO, 101 MHz): δ 189.6 (C=O), 164.2 (C_{ar}), 134.8 (C_{ar}), 128.7 (C_{ar}), 124.9 (C_{ar}), 122.3 (C_{ar}), 118.6 (C_{ar}), 65.2 (OCH₂), 45.8 (NCH₂); HRMS (ESI-TOF) *m/z* Calcd for C₁₁H₁₄NO₅S [M+H]⁺: 272.0587. Found: 272.0578.

2,2'-(Ethane-1,2-diylbis(methylazanediyl))bis(methylene))bis(4-(pyrrolidin-1-ylsulfonyl)phenol)

(H₂L1): To a solution of **4a** (1.7 g, 6.66 mmol) in CH₂Cl₂ (30 ml) was added ethane-1,2-diamine (198 mg, 3.3 mmol) at r.t., the reaction was allowed to proceed for another 12h at r.t. after which the yellow precipitates was collected by filtration and resuspended in fresh CH₂Cl₂ (30 ml), NaBH₄ (1.19 g, 31.45 mmol) was slowly added while maintaining the temperature at 0 °C. After the addition was complete the reaction was allowed to proceed for 12 h and warm to r.t. The reaction mixture was washed with saturated NH₄Cl aqueous solution (5 ml) and extracted with CH₂Cl₂ (2 × 20 ml). The organic layer was dried over MgSO₄, the solvent was evaporated in vacuo to give a crude solid which was used for the next step without further purification. To a stirred solution of the crude solid in CH₃CN (50 ml) and CH₃COOH (10 ml) was added formaldehyde 37 wt. % in H₂O (2.46 ml, 32.3 mmol). The resulting suspension was stirred at r.t. for 1.5 h and then cooled to 0 °C and NaBH₄ (610 mg, 16 mmol) was slowly added. After complete addition the reaction was allowed to warm to r. t. and monitored by TLC. After completion the pH was adjusted to 7 by aqueous NaOH (1N), the reaction mixture was washed with H₂O (15 ml) and extracted with CH₂Cl₂ (2 × 20 ml). The organic layer was dried over MgSO₄ and the solvent was evaporated in vacuo to give **H₂L1** as a yellow solid after recrystallization from ethyl acetate/pentane (1.33 g, 23.46 mmol 71 %). M.p. 205-207 °C; IR absorptions (cm⁻¹, ATR): 2967, 1582, 1482, 1472, 1329, 1145, 1007; ¹H NMR (CDCl₃, 400 MHz): δ 7.64 (dd, *J* = 2.0, 8.4 Hz, 2H, H_{ar}), 7.48 (d, *J* = 2.0 Hz, 2H, H_{ar}), 6.92 (d, *J* = 8.4 Hz, 2H, H_{ar}), 3.77 (s, 4H, C_{ar}CH₂), 3.19 (t, *J* = 4.0 Hz, 8H, NCH₂), 2.70 (s, 4H, NCH₂CH₂N), 2.30 (s, 6H, NCH₃), 1.76-1.73 (m, 8H, NCH₂CH₂); ¹³C NMR (CDCl₃, 101 MHz): δ 162.0 (C_{ar}), 129.2 (C_{ar}), 128.6 (C_{ar}), 127.3 (C_{ar}), 121.7 (C_{ar}), 116.9 (C_{ar}), 61.3 (C_{ar}CH₂), 53.8 (NCH₂CH₂N), 48.0 (NCH₂), 41.6 (NCH₃), 25.3 (NCH₂CH₂); ESI-MS *m/z* (%): 567 (95) [(M+H)⁺]; Anal. Calcd. for C₂₆H₃₈N₄O₆S₂: C, 55.10; H, 6.76; N, 9.89. Found: C, 54.64; H, 6.67; N, 9.81.

2,2'-(Ethane-1,2-diylbis(methylazanediyl))bis(methylene))bis(4-(piperidin-1-ylsulfonyl)phenol)

(H₂L2): Following the same procedure as for **H₂L1** with **4b** (3.1 g, 11.5 mmol), ethane-1,2-diamine (365 mg, 6.1 mmol) in MeOH (30 ml) for 2h, then NaBH₄ (1.32 g, 35 mmol) in CH₂Cl₂ (30 ml) for 12 h. Reductive amination was carried out using CH₃COOH (17.1 ml), formaldehyde 37 wt. % in H₂O (5 ml, 67 mmol), NaBH₄ (761 mg, 20 mmol) in CH₃CN (40 ml) to give **H₂L2** as a yellow solid after recrystallization from ethyl acetate/pentane (1.08 g, 1.82 mmol, 32 %). M.p. 190-191 °C; IR absorptions

(cm^{-1} , ATR): 2838, 1589, 1332, 1322, 1159, 931, 725; ^1H NMR (CDCl_3 , 400 MHz): δ 7.61 (d, $J = 6.8$ Hz, 2H, H_{ar}), 7.46 (s, 2H, H_{ar}), 7.00 (d, $J = 6.8$ Hz, 2H, H_{ar}), 3.83 (s, 4H, $\text{C}_{\text{ar}}\text{CH}_2$), 2.99 (t, $J = 8.0$ Hz, 8H, NCH_2), 2.77 (s, 4H, $\text{NCH}_2\text{CH}_2\text{N}$), 2.36 (s, 6H, NCH_3), 1.70-1.65 (m, 8H, NCH_2CH_2), 1.49-1.43 (m, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2$); ^{13}C NMR (CDCl_3 , 101 MHz): δ 162.0 (C_{ar}), 129.5 (C_{ar}), 128.7 (C_{ar}), 126.7 (C_{ar}), 121.7 (C_{ar}), 116.9 (C_{ar}), 61.4 ($\text{C}_{\text{ar}}\text{CH}_2$), 53.9 ($\text{NCH}_2\text{CH}_2\text{N}$), 47.1 (NCH_2), 41.7 (NCH_3), 25.3 (NCH_2CH_2), 23.7 ($\text{NCH}_2\text{CH}_2\text{CH}_2$); ESI-MS m/z (%): 595 (85) $[(\text{M}+\text{H})^+]$; Anal. Calcd. for $\text{C}_{28}\text{H}_{42}\text{N}_4\text{O}_6\text{S}_2$: C, 56.54; H, 7.12; N, 9.42. Found: C, 56.55; H, 6.88; N, 9.24.

2,2'-((Ethane-1,2-diylbis(methylazanediy))bis(methylene))bis(4-(azepan-1-ylsulfonyl)phenol)

(H₂L3): Following the same procedure as for **H₂L1** with **4c** (900 mg, 3.18 mmol), ethane-1,2-diamine (95 mg, 15.81 mmol), MeOH (15 ml) for 2 h then NaBH_4 (350 mg, 9.25 mmol), CH_2Cl_2 (25 ml) for 2 h followed by CH_3COOH (2.5 ml), formaldehyde 37 wt.% in H_2O (1.5 ml, 19.69 mmol), NaBH_4 (470 mg, 12.42 mmol), CH_3CN (20 ml) for 12 h to give **H₂L3** as a light yellow solid after recrystallization from ethyl acetate/pentane (370 mg, 0.59 mmol, 38 %). M.p. 170-172 °C; IR absorptions (cm^{-1} , ATR): 2930, 1683, 1582, 1479, 1332, 1036, 922; ^1H NMR (d_6 -DMSO, 400 MHz): δ 7.57 (d, $J = 2.0$ Hz, 2H, H_{ar}), 7.50 (dd, $J = 2.0, 8.8$ Hz, 2H, H_{ar}), 6.88 (d, $J = 8.8$ Hz, 2H, H_{ar}), 3.66 (s, 4H, $\text{C}_{\text{ar}}\text{CH}_2$), 3.59 (t, $J = 8.0$ Hz, 8H, SO_2NCH_2), 2.66 (s, 4H, $\text{NCH}_2\text{CH}_2\text{N}$), 2.18 (s, 6H, NCH_3), 1.57-1.53 (m, 8H, NCH_2CH_2), 1.47-1.43 (m, 8H, $\text{NCH}_2\text{CH}_2\text{CH}_2$); ^{13}C NMR (d_6 -DMSO, 101 MHz): δ 160.6 (C_{ar}), 128.5 (C_{ar}), 128.4 (C_{ar}), 127.5 (C_{ar}), 124.1 (C_{ar}), 115.7 (C_{ar}), 56.7 ($\text{C}_{\text{ar}}\text{CH}_2$), 53.4 ($\text{NCH}_2\text{CH}_2\text{N}$), 47.6 (NCH_2), 41.2 (NCH_3), 28.4 (NCH_2CH_2), 26.3 ($\text{NCH}_2\text{CH}_2\text{CH}_2$); HRMS (ESI-TOF) m/z Calcd for $\text{C}_{30}\text{H}_{47}\text{N}_4\text{O}_6\text{S}_2$ $[\text{M}+\text{H}]^+$: 623.2932. Found: 623.2912.

2,2'-((Ethane-1,2-diylbis(methylazanediy))bis(methylene))bis(4-(morpholinosulfonyl)phenol)

(H₂L4): Following the same procedure as for **H₂L1** with **4d** (2.22 g, 8.18 mmol), ethane-1,2-diamine (246 mg, 4.09 mmol), MeOH (25 ml) for 2 h then NaBH_4 (100 mg, 2.64 mmol), CH_2Cl_2 (50 ml) for 2 h followed by CH_3COOH (3.1 ml), formaldehyde 37 wt.% in H_2O (1.07 ml, 14.05 mmol), NaBH_4 (186 mg, 4.91 mmol), CH_3CN (25 ml) for 12 h to give **H₂L4** as a white solid after recrystallization from ethyl acetate/pentane (735 mg, 12.3 mmol, 28 %). M.p. 222-224 °C; IR absorptions (cm^{-1} , ATR): 2959, 1595, 1488, 136, 1108, 949 735; ^1H NMR (d_6 -DMSO, 400 MHz): δ 7.55 (d, $J = 2.0$ Hz, 2H, H_{ar}), 7.48 (dd, $J = 2.0, 8.8$ Hz, 2H, H_{ar}), 6.94 (d, $J = 8.8$ Hz, 2H, H_{ar}), 3.70 (s, 4H, $\text{C}_{\text{ar}}\text{CH}_2$), 3.59 (t, $J = 4.0$ Hz, 8H, OCH_2), 2.79 (t, $J = 4.0$ Hz, 8H, NCH_2), 2.66 (s, 4H, $\text{NCH}_2\text{CH}_2\text{N}$), 2.32 (s, 6H, NCH_3); ^{13}C NMR (d_6 -DMSO, 101 MHz): δ 161.5 (C_{ar}), 129.4 (C_{ar}), 128.6 (C_{ar}), 124.2 (C_{ar}), 123.5 (C_{ar}), 115.8 (C_{ar}), 65.2 ($\text{C}_{\text{ar}}\text{CH}_2$), 56.6 (OCH_2), 53.4 ($\text{NCH}_2\text{CH}_2\text{N}$), 45.9 (NCH_2), 41.2 (NCH_3); HRMS (ESI-TOF) m/z Calcd for $\text{C}_{26}\text{H}_{39}\text{N}_4\text{O}_8\text{S}_2$ $[\text{M}+\text{H}]^+$: 599.2204. Found: 599.2203.

[L4Ti(O^{*i*}Pr)₂]: To an oven-dried, N_2 -purged flask containing **H₂L4** (400 mg, 0.66 mmol), in anhydrous THF (15 ml), $\text{Ti}(\text{O}^i\text{Pr})_4$ (208 mg, 0.73 mmol) was added. The reaction mixture was stirred at r.t. for 2 h. Solvent removal under vacuo gave the raw product as colorless solid (489 mg, 0.64 mmol, 96 %).

Recrystallization of the raw product in anhydrous isopropanol and chloroform give pure **[L4Ti(O^{*i*}Pr)₂]** (226 mg, 0.30 mmol, 45 %). M.p. 210-212 °C; ¹H NMR (CDCl₃, 400 MHz): δ 7.55 (dd, *J* = 8.7, 2.5 Hz, 2H, H_{ar}), 7.39 (d, *J* = 2.5 Hz, 2H, H_{ar}), 6.74 (d, *J* = 8.7 Hz, 2H, H_{ar}), 4.95 (sept, *J* = 5.9 Hz, 2H, OCH(CH₃)₂), 4.60 (d, *J* = 14.4 Hz, 2H, C_{ar}CH₂), 3.74 (dt, *J* = 4.6 Hz, 8H, OCH₂CH₂N), 3.27 (d, *J* = 14.1 Hz, 2H, C_{ar}CH₂), 2.98 (dt, *J* = 4.6 Hz, 8H, OCH₂CH₂N), 2.90 (d, *J* = 9.4 Hz, 2H, NCH₂CH₂N), 2.46 (s, 6H, NCH₃), 1.94 (d, *J* = 9.4 Hz, 2H, NCH₂CH₂N), 1.25 (d, *J* = 6.5 Hz, 12H, OCH(CH₃)₂); ¹³C NMR (CDCl₃, 101 MHz): δ 166.3 (C_{ar}), 130.2 (C_{ar}), 130.0 (C_{ar}), 124.4 (C_{ar}), 122.6 (C_{ar}), 118.3 (C_{ar}), 79.6 (OCH(CH₃)₂), 66.3 (OCH₂CH₂N), 51.9 (C_{ar}CH₂), 47.5 (NCH₃), 46.2 (OCH₂CH₂N), 26.0 (NCH₂CH₂N), 25.7 (OCH(CH₃)), 25.5 (OCH(CH₃)); UV/Vis (THF): λ_{max} (ε) = 252 nm (8383 M⁻¹ cm⁻¹), 308 nm (10004 M⁻¹ cm⁻¹); Anal. Calcd. for C₃₂H₅₀N₄O₁₀S₂Ti: C, 50.39; H, 6.61; N, 7.35. Found: C, 49.90; H, 6.55; N, 7.38.

[L1Ti(dipic)]: Reactions were carried out using standard Schlenk techniques under a nitrogen atmosphere. To an oven-dried, N₂-purged flask containing **H₂L1** (200 mg, 0.35 mmol) in anhydrous THF (10 ml), Ti(O^{*i*}Pr)₄ (100 mg, 0.35 mmol) was added. After stirring overnight, the solvent was removed under vacuo, crude product was dissolved in 10 ml anhydrous THF, pyridine-2,6-dicarboxylic acid (118 mg, 0.70 mmol) was added under N₂ protection and the reaction was stirred for 24 h at r.t. and monitored by TLC. Upon completion, the solvent was evaporated, the residue was dissolved in CH₂Cl₂ (30 ml) and washed with 1N NaOH (2x10 ml) then with brine and the organic phase was dried over MgSO₄. After the solvent was evaporated in vacuo the crude product was purified by column chromatography on silica gel (DCM/MeOH = 10:1) to give **[L1Ti(dipic)]** as a yellow solid (90.4 mg, 0.12 mmol, 33 %). M.p. 250-251 °C; IR absorptions (cm⁻¹, ATR): 2933, 1644, 1592, 1475, 1298, 1111, 945, 908, 783; ¹H NMR (CDCl₃, 400 MHz): δ 8.34 (dd, *J* = 7.0, 8.0 Hz, 1H, H_{Pyr}), 8.24 (d, *J* = 7.0 Hz, 2H, H_{Pyr}), 7.58-7.54 (m, 4H, H_{ar}), 6.52 (d, *J* = 8.0 Hz, 2H, H_{ar}), 5.39 (d, *J* = 16.0 Hz, 2H, C_{ar}CH₂), 3.37 (d, *J* = 16.0 Hz, 2H, C_{ar}CH₂), 3.32 (d, *J* = 8.0 Hz, 2H, NCH₂CH₂N), 3.19-3.16 (m, 8H, NCH₂), 2.82 (s, 6H, NCH₃), 2.33 (d, *J* = 8.0 Hz, 2H, NCH₂CH₂N), 1.77-1.74 (m, 8H, NCH₂CH₂); ¹³C NMR (CDCl₃, 101 MHz): δ 169.1 (C=O), 162.7 (C_{ar}), 149.5 (C_{ar}), 144.2 (C_{ar}), 129.7 (C_{ar}), 129.6 (C_{ar}), 129.3 (C_{ar}), 128.2 (C_{ar}), 126.3 (C_{ar}), 117.1 (C_{ar}), 63.9 (C_{ar}CH₂), 54.3 (NCH₂CH₂N), 48.0 (NCH₂), 47.7 (NCH₃), 25.3 (NCH₂CH₂); UV/Vis (THF): λ_{max} (ε) = 210 nm (33120 M⁻¹cm⁻¹), 240 nm (28330 M⁻¹cm⁻¹), 375 nm (10340 M⁻¹cm⁻¹); Anal. Calcd. for C₃₃H₃₉N₅O₁₀S₂Ti: C, 50.97; H, 5.05; N, 9.01. Found: C, 51.16; H, 5.17; N, 8.92; HRMS (ESI-TOF) *m/z* Calcd for C₃₃H₄₀N₅O₁₀S₂Ti [M+H]⁺: 778.1691. Found: 778.1699.

[L2Ti(dipic)]: Following the same procedure as for **[L1Ti(dipic)]** reacting **H₂L2** (200 mg, 0.34 mmol), Ti(O^{*i*}Pr)₄ (105 mg, 0.37 mmol) in anhydrous THF (10 ml) for 2 h (TLC control) then adding pyridine-2,6-dicarboxylic acid (109 mg, 0.67 mmol) in anhydrous THF (10 ml) gives after purification by column chromatography **[L2Ti(dipic)]** as a yellow solid (108 mg, 0.133 mmol, 40 %). M.p. 210-212 °C; IR absorptions (cm⁻¹, ATR): 1682, 1478, 1337, 1264, 1144, 1050, 911, 796; ¹H NMR (CDCl₃, 400 MHz): δ

8.34 (t, $J = 8.0$ Hz, 1H, H_{pyr}), 8.24 (d, $J = 8.0$ Hz, 2H, H_{pyr}), 7.50-7.46 (m, 4H, H_{ar}), 6.51 (d, $J = 8.0$ Hz, 2H, H_{ar}), 5.40 (d, $J = 16.0$ Hz, 2H, $C_{\text{ar}}\text{CH}_2$), 3.37 (d, $J = 16.0$ Hz, 2H, $C_{\text{ar}}\text{CH}_2$), 3.32 (d, $J = 8.0$ Hz, 2H, $\text{NCH}_2\text{CH}_2\text{N}$), 2.96-2.88 (m, 8H, NCH_2), 2.82 (s, 6H, NCH_3), 2.33 (d, $J = 8.0$ Hz, 2H, $\text{NCH}_2\text{CH}_2\text{N}$), 1.62-1.59 (m, 8H, NCH_2CH_2), 1.41-1.38 (m, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2$); ^{13}C NMR (CDCl_3 , 101 MHz): δ 169.0 (C=O), 162.7 (C_{ar}), 149.5 (C_{ar}), 144.3 (C_{ar}), 129.6 (C_{ar}), 129.4 (C_{ar}), 128.9 (C_{ar}), 128.1 (C_{ar}), 126.3 (C_{ar}), 117.0 (C_{ar}), 63.9 ($C_{\text{ar}}\text{CH}_2$), 54.2 ($\text{NCH}_2\text{CH}_2\text{N}$), 47.7 (NCH_2), 47.0 (NCH_3), 25.3 (NCH_2CH_2), 23.5 ($\text{NCH}_2\text{CH}_2\text{CH}_2$). λ_{max} (ϵ) = 215 nm ($29690 \text{ M}^{-1}\text{cm}^{-1}$), 240 nm ($23870 \text{ M}^{-1}\text{cm}^{-1}$), 375 nm ($8640 \text{ M}^{-1}\text{cm}^{-1}$); Found: 806.1993; Anal. Calcd. for $\text{C}_{35}\text{H}_{43}\text{N}_5\text{O}_{10}\text{S}_2\text{Ti}$: C, 52.17; H, 5.38; N, 8.69. Found: C, 52.25; H, 5.42; N, 8.53; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{35}\text{H}_{44}\text{N}_5\text{O}_{10}\text{S}_2\text{Ti} [\text{M}+\text{H}]^+$: 806.2004.

[L3Ti(dipic)]: Following the same procedure as for **[L1Ti(dipic)]** reacting **H₂L3** (312 mg, 0.5 mmol), $\text{Ti}(\text{O}^i\text{Pr})_4$ (157 mg, 0.55 mmol) in anhydrous THF (15 ml) for 2 h (TLC control) then adding pyridine-2,6-dicarboxylic acid (162 mg, 1.0 mmol) in anhydrous THF (15 ml) gives after purification by column chromatography **[L3Ti(dipic)]** as a light yellow solid (165 mg, 0.20 mmol, 40 %). M.p. 225-227 °C; IR absorptions (cm^{-1} , ATR): 2930, 1689, 1478, 1337, 1308, 1146, 910, 795; ^1H NMR (CDCl_3 , 400 MHz): δ 8.33 (dd, $J = 7.2, 8.4$ Hz, 1H, H_{pyr}), 8.22 (d, $J = 7.2$ Hz, 2H, H_{pyr}), 7.51-7.49 (m, 4H, H_{ar}), 6.48 (d, $J = 8.8$ Hz, 2H, H_{ar}), 5.37 (d, $J = 14.6$ Hz, 2H, $C_{\text{ar}}\text{CH}_2$), 3.35 (d, $J = 14.6$ Hz, 2H, $C_{\text{ar}}\text{CH}_2$), 3.30 (d, $J = 8.0$ Hz, 2H, $\text{NCH}_2\text{CH}_2\text{N}$), 3.19 (t, $J = 4.0$ Hz, 8H, NCH_2), 2.80 (s, 6H, NCH_3), 2.31 (d, $J = 8.0$ Hz, 2H, $\text{NCH}_2\text{CH}_2\text{N}$), 1.71-1.65 (m, 8H, NCH_2CH_2), 1.57-1.55 (m, 8H, $\text{NCH}_2\text{CH}_2\text{CH}_2$); ^{13}C NMR (CDCl_3 , 101 MHz): δ 169.0 (C=O), 162.4 (C_{ar}), 149.5 (C_{ar}), 144.2 (C_{ar}), 132.2 (C_{ar}), 129.0 (C_{ar}), 128.6 (C_{ar}), 128.1 (C_{ar}), 126.3 (C_{ar}), 117.0 (C_{ar}), 63.9 ($C_{\text{ar}}\text{CH}_2$), 54.3 ($\text{NCH}_2\text{CH}_2\text{N}$), 48.2 (NCH_2), 47.7 (NCH_3), 29.2 (NCH_2CH_2), 27.0 ($\text{NCH}_2\text{CH}_2\text{CH}_2$); UV/Vis (THF): λ_{max} (ϵ) = 210 nm ($18360 \text{ M}^{-1}\text{cm}^{-1}$), 242 nm ($10180 \text{ M}^{-1}\text{cm}^{-1}$), 375 nm ($4054 \text{ M}^{-1}\text{cm}^{-1}$); Anal. Calcd. for $\text{C}_{37}\text{H}_{47}\text{N}_5\text{O}_{10}\text{S}_2\text{Ti}$: C, 53.30; H, 5.68; N, 8.40. Found: C, 53.43; H, 5.82; N, 8.30; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{37}\text{H}_{48}\text{N}_5\text{O}_{10}\text{S}_2\text{Ti} [\text{M}+\text{H}]^+$: 834.2317, found: 834.2279.

[L4Ti(dipic)]: Following the same procedure as for **[L1Ti(dipic)]** reacting **H₂L4** (300 mg, 0.5 mmol), $\text{Ti}(\text{O}^i\text{Pr})_4$ (157 mg, 0.55 mmol) in anhydrous THF (15 ml) for 2 h (TLC control) then adding pyridine-2,6-dicarboxylic acid (162 mg, 1.0 mmol) in anhydrous THF (15 ml) gives after purification by column chromatography **[L4Ti(dipic)]** as a yellow solid (179 mg, 0.22 mmol, 45 %). M.p. 267-268 °C; IR absorptions (cm^{-1} , ATR): 2929, 1591, 1480, 1299, 1110, 944, 909, 793; ^1H NMR (d_6 -acetone, 400 MHz): δ 8.63 (t, $J = 8.0$ Hz, 1H, H_{pyr}), 8.27 (d, $J = 8.0$ Hz, 2H, H_{pyr}), 7.59-7.49 (m, 4H, H_{ar}), 6.60 (d, $J = 8.0$ Hz, 2H, H_{ar}), 5.32 (d, $J = 16.0$ Hz, 2H, $C_{\text{ar}}\text{CH}_2$), 3.70 (d, $J = 16.0$ Hz, 2H, $C_{\text{ar}}\text{CH}_2$), 3.64 (t, $J = 4.0$ Hz, 8H, OCH_2), 3.41 (d, $J = 8.0$ Hz, 2H, $\text{NCH}_2\text{CH}_2\text{N}$), 2.89 (t, $J = 4.0$ Hz, 8H, NCH_2), 2.86 (s, 6H, NCH_3), 2.60 (d, $J = 8.0$ Hz, 2H, $\text{NCH}_2\text{CH}_2\text{N}$); ^{13}C NMR (d_6 -acetone, 101 MHz): δ 169.1 (C=O), 164.2 (C_{ar}), 150.1 (C_{ar}), 146.4 (C_{ar}), 131.0 (C_{ar}), 130.4 (C_{ar}), 129.7 (C_{ar}), 128.3 (C_{ar}), 127.1 (C_{ar}), 117.8 (C_{ar}), 66.7 (OCH_2), 63.9 ($C_{\text{ar}}\text{CH}_2$), 54.8 ($\text{NCH}_2\text{CH}_2\text{N}$), 47.9 (NCH_3), 47.1 ($\text{OCH}_2\text{CH}_2\text{N}$); UV/Vis (THF): λ_{max} (ϵ) = 210 nm

(27190 M⁻¹cm⁻¹), 245 nm (15900 M⁻¹cm⁻¹), 360 nm (5930 M⁻¹cm⁻¹); Anal. Calcd. for C₃₃H₃₉N₅O₁₂S₂Ti: C, 48.95; H, 4.86; N, 8.65. Found: C, 48.72; H, 4.75; N, 8.81; HRMS (ESI-TOF) m/z Calcd for C₃₃H₄₀N₅O₁₂S₂Ti [M+H]⁺: 810.1589. Found: 810.1608.

[L5Ti(dipic)]: Following the same procedure as for [L1Ti(dipic)] reacting H₂L5³³ (500 mg, 1.7 mmol), Ti(OⁱPr)₄ (567.9 mg, 2.0 mmol) in anhydrous THF (15 ml) for 2 h (TLC control) then adding pyridine-2,6-dicarboxylic acid (324 mg, 2.0 mmol) in anhydrous THF (20 ml) gives after purification by column chromatography **[L5Ti(dipic)]** as a red solid (368 mg, 0.7 mmol, 44 %). M.p. 221 °C (decomp.); IR absorptions (cm⁻¹, ATR): 1678, 1480, 1340, 1258, 1242, 1177, 1069, 893, 739; ¹H NMR (CDCl₃, 400 MHz): δ 8.27 (dd, *J* = 6.8, 8.8 Hz, 1H, H_{pyr}), 8.18 (d, *J* = 7.2 Hz, 2H, H_{pyr}), 7.08-7.04 (m, 4H, H_{ar}), 7.0 (d, *J* = 7.2 Hz, 2H, H_{ar}), 6.81 (td, *J* = 7.2, 0.8 Hz, 2H, H_{ar}), 6.4 (d, *J* = 8.8 Hz, 2H, H_{ar}), 5.37 (d, *J* = 14.4 Hz, 2H, CH_{ar}), 3.37 (d, *J* = 9.2 Hz, 2H, NCH₂CH₂N), 3.23 (d, *J* = 14.4 Hz, 2H, C_{ar}CH₂), 2.80 (s, 6H, NCH₃), 2.19 (d, *J* = 9.2 Hz, 2H, NCH₂CH₂N); ¹³C NMR (CDCl₃, 101 MHz): δ 169.0 (C=O), 159.6 (C_{ar}), 149.9 (C_{ar}), 143.5 (C_{ar}), 129.7 (C_{ar}), 129.0 (C_{ar}), 128.1 (C_{ar}), 128.1 (C_{ar}), 125.9 (C_{ar}), 121.7 (C_{ar}), 116.4 (C_{ar}), 64.2 (C_{ar}CH₂), 54.0 (NCH₂CH₂N), 47.7 (NCH₃); UV/Vis (THF): λ_{max} (ε) = 215 nm (23240 M⁻¹cm⁻¹), 380 nm (6350 M⁻¹cm⁻¹); HRMS (ESI-TOF) m/z Calcd for C₂₅H₂₆N₃O₆Ti [M+H]⁺: 512.1301, found: 512.1316.

Associated Content

Selected stability tests in different media, X-ray diffraction data of **[L4Ti(dipic)]** and **[L5Ti(dipic)]**, colored representations of the cell viability plots as well as ¹H and ¹³C NMR spectra are to be found in the ESI.

Notes

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