

Chapter 3

Titanocene derivatives with heteroaromatic thiolate ligands

3.1 Introduction

Metallo-intercalators, such as the complexes in Chapter 2, are designed to either intercalate or bond covalently, but not both and their antitumor activities are ascribed to a particular type of interaction with DNA. This was not the objective of the present study as the combined effects of intercalation and covalent bonding were to be investigated. The insertion of a spacer atom between the titanium fragment and the ring ligand will change the geometry of the molecule and allow the heteroaromatic ligand to be more flexible. Thus, both covalent bonding and intercalation are a possibility. This can readily be achieved by introducing a sulfur atom between the heteroaromatic rings and metal. Titanocene derivatives with the general formula $[\text{TiCp}_2(\text{SR})\text{Cl}]$ were synthesized ($\text{R} = \text{Dbt}, \text{Bt}, \text{Dbz}, \text{Thr}, \text{Dbf}$ and Bf) and are shown in Figure 3.1.

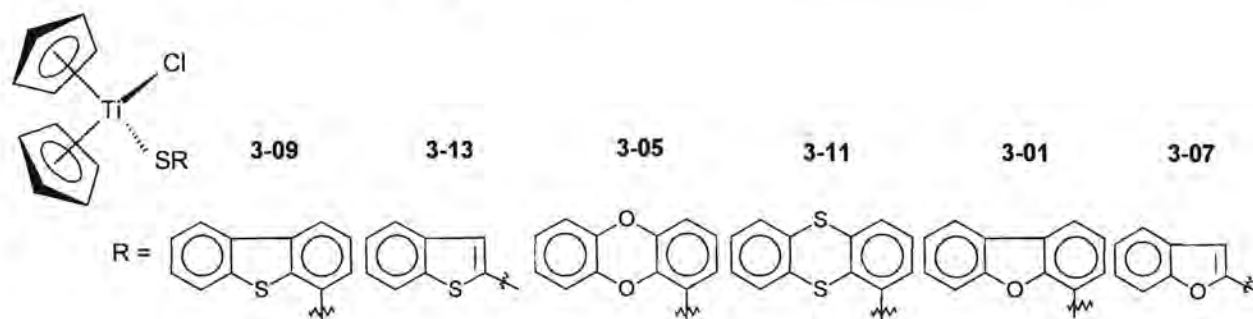
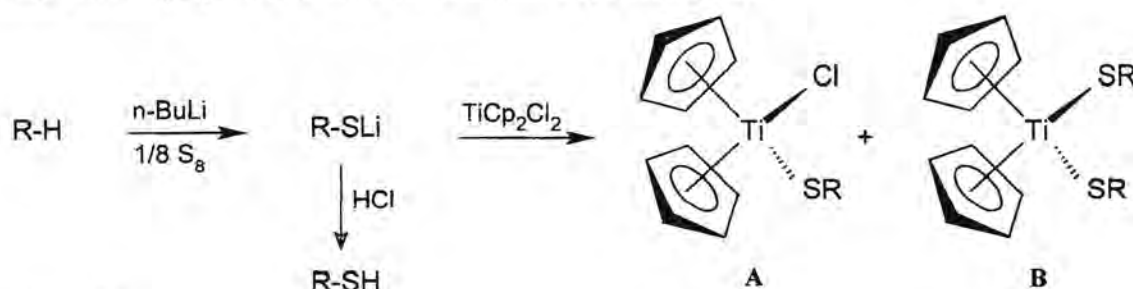


Figure 3.1 Titanocene thiolate complexes, $[\text{TiCp}_2(\text{SR})\text{Cl}]$.

The same heteroaromatic ligands used in Chapter 2 were investigated and their structure-antitumor activity relationships will be compared with that of the corresponding complexes where the ligand was bound directly to the metal.

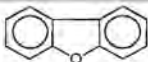
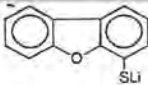
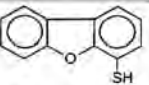
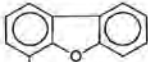
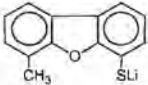
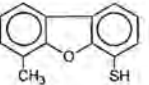
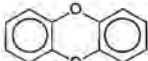
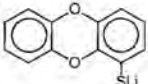
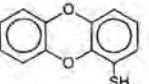
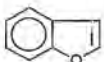
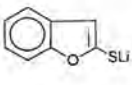
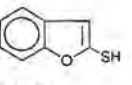
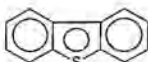
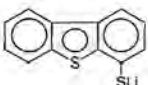
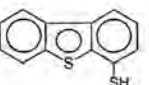
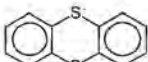
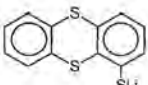
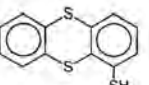
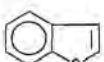
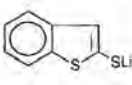
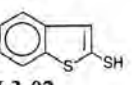
3.2 Synthesis

The synthesis of the complexes is given in Scheme 3.1 and the identification numbers of the compounds are listed in Table 3.1. Flowers of sulfur was added to the lithiated heteroaromatic ligand before reaction with titanocene dichloride. Lithiation and subsequent addition of sulfur afforded thiolates in high yields for all of the heteroarenes, **L2-01-L2-07**.



Scheme 3.1

Table 3.1 Identification numbers of the complexes in Scheme 3.1.

Heteroarene (R-H)	Thiolates(R-SLi)	Thiol(R-SH)	Product A	Product B
 L2-06	 L2-06	 L3-06	3-01	3-02
 L2-07	 L2-07	 L3-07	3-03	3-04
 L2-03	 L2-03	 L3-03	3-05	3-06
 L2-05	 L2-05	 L3-05	3-07	3-08
 L2-01	 L2-01	 L3-01	3-09	3-10
 L2-04	 L2-04	 L3-04	3-11	3-12
 L2-02	 L2-02	 L3-02	3-13	3-14

Reaction of L2-06 with butyllithium/sulfur and titanocene dichloride

Addition of sulfur to lithiated L2-06 at low temperature caused a colour change from yellow to orange due to the formation of lithiated dibenzofuran-4-thiolate. Protonation of the thiolate, by bubbling HCl gas through the solution, formed dibenzofuran-4-thiol, [HSDbf] L3-06. Addition of titanocene dichloride to the thiolate resulted in a colour change of the reaction mixture from red to purple. Chromatography yielded chlorobis(cyclopentadienyl)(dibenzofuran-4-ylsulfanyl)titanium(IV), [TiCp₂(SDBf)Cl] 3-01 and bis(cyclopentadienyl)bis(dibenzofuran-4-ylsulfanyl)titanium(IV), [TiCp₂(SDBf)₂] 3-02.

Reaction of L2-07 with butyllithium/sulfur and titanocene dichloride

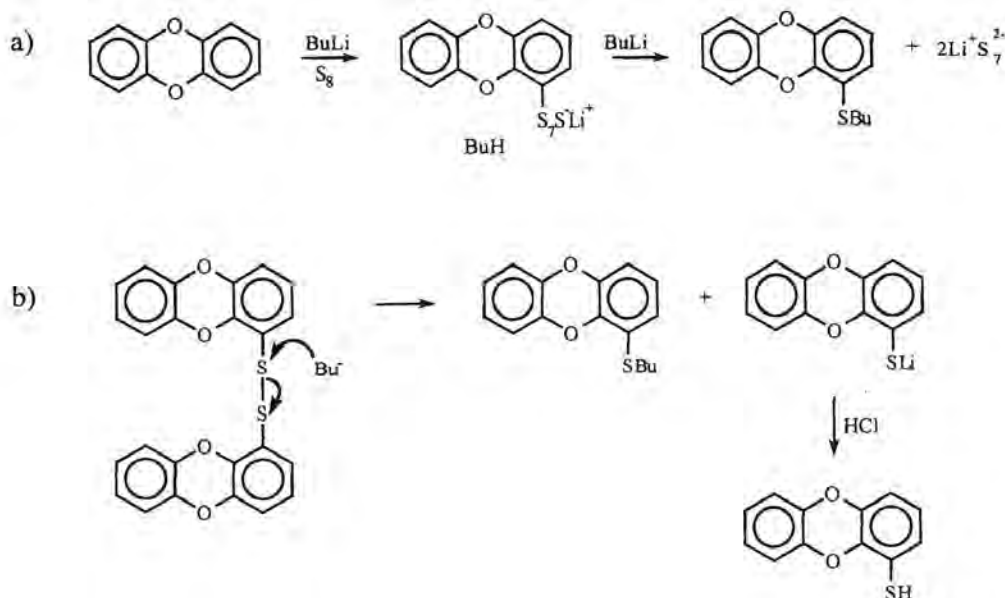
The ligand L2-07 was deprotonated at the 6-position. On addition of sulfur the reaction colour turned from yellow to orange and protonation of the lithiated 6-methyl dibenzofuran-4-thiolate formed 6-methyl dibenzofuran-4-thiol, [HSDbf-Me] L3-07. Addition of titanocene dichloride to the thiolate changed the colour of the reaction mixture from red to dark red. Purification by column chromatography gave chlorobis(cyclopentadienyl)(6-methyl dibenzofuran-4-ylsulfanyl)titanium(IV), [TiCp₂(SDBf-Me)Cl] 3-03 and bis(cyclopentadienyl)bis(6-methyl dibenzofuran-4-ylsulfanyl)titanium(IV), [TiCp₂(SDBf-Me)₂] 3-04.

Reaction of L2-03 with butyllithium/sulfur and titanocene dichloride

Addition of sulfur to the lithiated L2-03 at low temperature caused a colour change from yellow to orange-brown due to the formation of lithiated dibenzodioxin-1-thiolate. Protonation yielded dibenzodioxin-1-thiol, [HSDbz] L3-03. The formation of 1-butylsulfanyl dibenzodioxin, [BuSDBz] L3-03b during the reaction is difficult to explain, but a possible explanation for the formation is shown in Scheme 3.2. Initial attack of lithiated L2-03 on S₈ is followed by an attack of a second molecule BuLi resulting in the release of a S₇²⁻ molecule in (a). A second, more likely explanation takes a different route and involves the prior formation of bis(dibenzodioxin)disulfide. Interestingly, the disulfide is a fragment ion in the mass spectrometer of the complexes, [TiCp₂(SR)₂] (*vide infra*), and may have resulted from an elimination reaction of the two thiolate ligands. The disulfide is cleaved by BuLi resulting in the formation of the thioether and thiol according to (b).

The reaction of DbzSLi and titanocene dichloride was accompanied by a colour change from red to dark red-brown for the reaction mixture. On the silica gel column chlorobis(cyclopentadienyl)(dibenzodioxin-1-ylsulfanyl)titanium(IV), [TiCp₂(SDBz)Cl] 3-05 and bis(cyclopentadienyl)bis(dibenzodioxin-1-ylsulfanyl)titanium(IV), [TiCp₂(SDBz)₂] 3-06 were separated and collected. The

complexes were light sensitive and lost colour within a few hours after being exposed to normal daylight.



Scheme 3.2

Reaction of L2-05 with butyllithium/sulfur and titanocene dichloride

Addition of sulfur to lithiated benzofuran gave a colour change from yellow to light pink to yellow and the lithiated benzofuran-2-thiolate was protonated to form benzofuran-2-thiol [HSBf] **L3-05**. Addition of titanocene dichloride to the thiolate resulted in an immediate colour change from red to purple. The solvent was removed and separation and purification by column chromatography gave bis(cyclopentadienyl)bis(benzofuran-2-ylsulfanyl)titanium(IV), [TiCp₂(SBf)₂] **3-08** and (benzofuran-2-ylsulfanyl)chlorobis(cyclopentadienyl)titanium(IV), [TiCp₂(SBf)Cl] **3-07**.

Reaction of L2-01 with butyllithium/sulfur and titanocene dichloride

Addition of sulfur to DbtLi resulted in a colour change from green to yellow and protonation of lithiated dibenzothiophene-4-thiolate formed dibenzothiophene-4-thiol, [HSDbt] **L3-01**. The addition of titanocene dichloride to DbtSLi resulted in an immediate colour change from red to dark red. Purification by column chromatography gave bis(cyclopentadienyl) bis(cyclopentadienyl)bis(dibenzothien-4-ylsulfanyl)titanium(IV), [TiCp₂(SDbt)₂] **3-10** and chlorobis(cyclopentadienyl) (dibenzothien-4-ylsulfanyl)titanium(IV), [TiCp₂(SDbt)Cl] **3-09**. Complex **3-09** was crystallized from a dichloromethane-hexane solution and this yielded crystals suitable for a single crystal structure determination.

Reaction of L2-04 with butyllithium/sulfur and titanocene dichloride

The reaction of ThrLi with flowers of sulfur yielded thianthrene-1-thiolate, that was converted to thianthrene-1-thiol [HSThr] L3-04, when protonated with HCl gas. No information of this product could be found in literature and it was fully characterized. Unlike L2-03, the compound L2-04 did not react with butyllithium to give the corresponding thioether. The reaction of ThrLi with flowers of sulfur caused a colour change from yellow to orange-brown. The reaction of the thiolate and titanocene dichloride was accompanied by a colour change from red to dark red for the reaction mixture. The complexes chlorobis(cyclopentadienyl)(thianthren-1-ylsulfanyl)titanium(IV), [TiCp₂(SThr)Cl] 3-11 and bis(cyclopentadienyl)bis(thianthrenyl-1-ylsulfanyl)titanium(IV), [TiCp₂(SThr)₂] 3-12 were separated and collected by column chromatography. 3-12 is a light sensitive complex, which lost colour within a few hours after being exposed to light. 3-11 was very unstable and the ¹H NMR spectrum showed that it decomposed to L2-04 and the oxygen bridged dimer (μ-oxo)bis(chlorobis(cyclopentadienyl)titanium(IV))¹.

Reaction of L2-02 with butyllithium/sulfur and titanocene dichloride

Addition of sulfur to BtLi gave a colour change from yellow to orange and protonation of the lithiated benzothiophene-2-thiolate BtSLi yielded benzothiophene-2-thiol, [HSBt] L3-02. Addition of titanocene dichloride to the thiolate resulted in an immediate colour change from red to dark red. Column chromatography on silica gel afforded bis(cyclopentadienyl)bis(benzothien-2-ylsulfanyl)titanium(IV), [TiCp₂(SBt)₂] 3-14 and (benzothien-2-ylsulfanyl)chlorobis(cyclopentadienyl)titanium(IV), [TiCp₂(SBt)Cl] 3-13.

3.3 Characterization

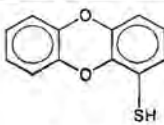
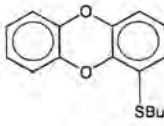
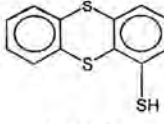
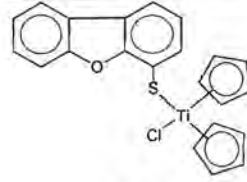
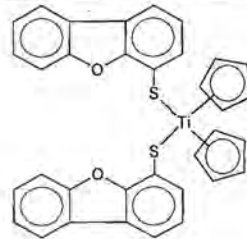
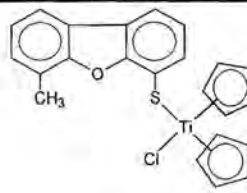
- *Mass spectrometry*

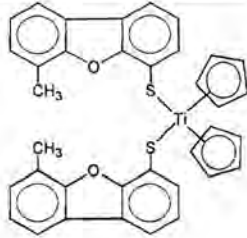
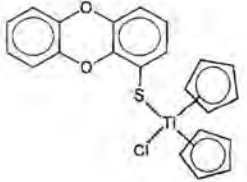
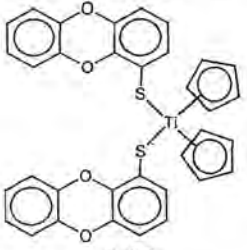
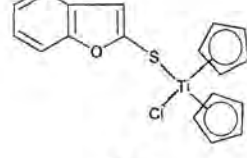
The mass spectral data for L3-01² was reported in literature. The data for the ligands L3-03, L3-04, L3-03b and the complexes 3-01 – 3-10 as well as for 3-12 – 3-14 are summarized in Table 3.2. Due to the instability of 3-11 a representative mass spectrum could not be obtained for the complex.

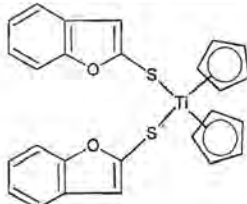
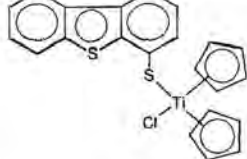
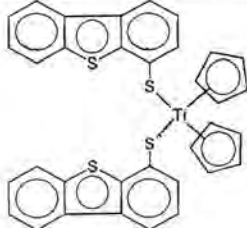
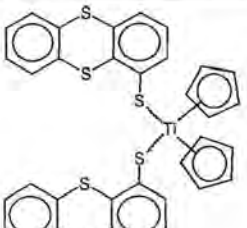
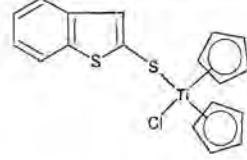
1. D. Nath, R. K. Sharma, A. N. Bhat, *Inorg. Chim. Acta*, **1976**, *20*, 109; S. A. Giddings, *Inorg. Chem.*, **1964**, *3*, 684.

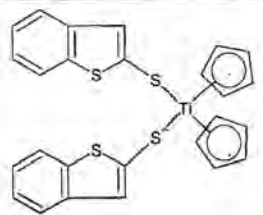
2. T. Kuster, H. Mändli, R. Robbani, J. Seibl, *Helv. Chem. Acta*, **1978**, *61*, 1017.

Table 3.2 Mass spectral data for complexes **L3-03**, **L3-03b**, **L3-04**, **3-01** – **3-10** and **3-12** – **3-14**.

Mass Peaks, m/z(I, %)		
 <p>L3-03</p>	216 (100) [M] ⁺ 184 (26) [DbzH] ⁺	183 (20) [Dbz] ⁺
 <p>L3-03b</p>	272 (2) [M] ⁺ 216 (5) [M-Bu] ⁺ 184 (5) [DbzH] ⁺	183 (5) [Dbz] ⁺ 57 (5) [Bu] ⁺
 <p>L3-04</p>	248 (100) [M] ⁺ 217 (13) [ThrH ₂] ⁺ 216 (11) [ThrH] ⁺ 184 (53) [ThrH-S] ⁺	171 (38) [Thr-CSH] ⁺ 152 (1) [Thr-2S] ⁺
 <p>3-01</p>	No [M] ⁺ 378 (3) [M-Cl] ⁺ 347 (2) [M-Cp] ⁺ 328 (1) [TiCp(SDbf)O] ⁺ 312 (1) [TiCp(SDbf)] ⁺ 282 (1) [Ti(SDbf)Cl] ⁺ 263 (1) [Ti(SDbf)O] ⁺ 247 (1) [Ti(SDbf)] ⁺	214 (4) [M-SDbf] ⁺ 200 (2) [HSDbf] ⁺ 199 (2) [SDbf] ⁺ 178 (72) [TiCp ₂] ⁺ 148 (9) [TiCpCl] ⁺ 113 (18) [TiCp] ⁺
 <p>3-02</p>	577 (100) [M] ⁺ 511 (38) [M-Cp] ⁺ 446 (10) [Ti(Dbff) ₂] ⁺ 398 (32) [Dbf S- SDbf] ⁺ 378 (95) [M-SDbf] ⁺ 312 (20) [TiCp(SDbf)] ⁺	280 (13) [TiCp(Dbff)] ⁺ 200 (100) [HSDbf] ⁺ 199 (100) [SDbf] ⁺ 178 (100) [TiCp ₂] ⁺ 113 (15) [TiCp] ⁺
 <p>3-03</p>	539 (1) [TiCp ₂ (SDbf-Me) ₂] ⁺ (3-04) 426 (5) [M] ⁺ or [Me-DbfS-SDbf-Me] ⁺ 391 (1) [TiCp ₂ (SDbf-Me)] ⁺ 361 (4) [TiCp(SDbf)Cl] ⁺ 326 (2) [TiCp(SDbf-Me)] ⁺ 296 (2) [Ti(SDbf-Me)Cl] ⁺ 261 (4) [Ti(SDbf-Me)] ⁺	214 (100) [TiCp ₂ Cl] ⁺ or [SDbf-Me] ⁺ 200 (52) [HSDbf] ⁺ 199 (52) [SDbf] ⁺ 181 (96) [Dbf-Me] ⁺ 178 (9) [TiCp ₂] ⁺ 148 (20) [TiCpCl] ⁺ 113 (12) [TiCp] ⁺

 <p style="text-align: center;">3-04</p>	<p>539 (1) [M]⁺ 426 (14) [Me-DbfS- SDbf-Me]⁺ 326 (4) [TiCp(SDbf-Me)]⁺ 277 (7) [Ti(SDbf-Me)O]⁺ 261 (2) [Ti(SDbf-Me)]⁺ 245 (9) [Ti(Db f -Me)O]⁺</p>	<p>214 (52) [HSDbf-Me]⁺ 213 (52) [SDbf-Me]⁺ 181 (100) [Dbf -Me]⁺ 178 (5) [TiCp₂]⁺ 113 (14) [TiCp]⁺</p>
 <p style="text-align: center;">3-05</p>	<p>428 (60) [M]⁺ 396 (11) [TiCp₂(Dbz)Cl]⁺ 393 (4) [M-Cl]⁺ 361 (4) [TiCp₂(Dbz)]⁺ 360 (6) [M-Cp]⁺ 328 (8) [TiCp(SDbz)]⁺ 298 (1) [Ti(SDbz)Cl]⁺</p>	<p>296 (1) [TiCp(Dbz)]⁺ 263 (1) [Ti(SDbz)]⁺ 231 (1) [Ti(Dbz)]⁺ 216 (13) [HSDbz]⁺ 215 (13) [SDbz]⁺ 184 (5) [DbzH]⁺ 183 (4) [Dbz]⁺ 178 (100) [TiCp₂]⁺</p>
 <p style="text-align: center;">3-06</p>	<p>610 (66) [M]⁺ 545 (1) [M-Cp]⁺ 426 (5) [DbzS-SDbz]⁺ 425 (5) [TiCp₂(SDbz)S]⁺ 393 (12) [M-SDbz]⁺ 360 (73) [TiCp(SDbz)S]⁺ 328 (27) [TiCp(SDbz)]⁺</p>	<p>295 (5) [Ti(SDbz)S]⁺ 263 (10) [Ti(SDbz)]⁺ 214 (100) [HSDbz]⁺ 213 (100) [SDbz]⁺ 184 (37) [DbzH]⁺ 183 (37) [Dbz]⁺ 178 (36) [TiCp₂]⁺</p>
 <p style="text-align: center;">3-07</p>	<p>477 (36) [TiCp₂(SBf)₂]⁺ (3-08) 411 (61) [TiCp(SBf)₂]⁺ 363 (4) [M]⁺ 360 (8) [TiCp₂(SBf)S]⁺ 328 (7) [M-Cl]⁺ 297 (56) [M-Cp]⁺ 265 (33) [TiCp(Bf)Cl]⁺ 262 (5) [TiCp(SBf)]⁺</p>	<p>236 (30) [TiCp₂(Bf)]⁺ 232 (6) [Ti(SBf)Cl]⁺ 210 (25) [TiSCp₂]⁺ 197 (12) [Ti(SBf)]⁺ 178 (27) [TiCp₂]⁺ 150 (94) [HSBf]⁺ 149 (94) [SBf]⁺ 113 (12) [TiCp]⁺</p>

 <p>3-08</p>	<p>477 (55) [M]⁺ 445 (4) [TiCp₂(SBf)(Bf)]⁺ 413 (13) [TiCp₂(Bf)₂]⁺ 411 (52) [M-Cp]⁺ 379 (5) [TiCp(SBf)(Bf)]⁺ 360 (8) [TiCp₂(SBf)S]⁺ 347 (6) [TiCp(Bf)₂]⁺ 346 (8) [Ti(SBf)₂]⁺ 328 (65) [M-SBf]⁺ 314 (4) [TiCp(SBf)(Bf)]⁺</p>	<p>300 (13) [BfS-SBf]⁺ 296 (20) [TiCp₂(Bf)]⁺ 262 (10) [TiCp(SBf)]⁺ 210 (11) [TiSCp₂]⁺ 197 (7) [Ti(SBf)]⁺ 178 (100) [TiCp₂]⁺ 150 (36) [HSBf]⁺ 149 (94) [SBf]⁺ 113 (19) [TiCp]⁺</p>
 <p>3-09</p>	<p>430 (36) [DbtS-SDbt]⁺ 428 (30) [M]⁺ 393 (36) [M-Cl]⁺ 363 (49) [M-Cp]⁺ 328 (17) [TiCp(SDbt)]⁺</p>	<p>263 (1) [Ti(SDbt)]⁺ 213 (100) [M-SDbt]⁺ 178 (10) [TiCp₂]⁺ 152 (7) [C₁₂H₈]⁺</p>
 <p>3-10</p>	<p>608 (48) [M]⁺ 543 (2) [M-Cp]⁺ 430 (9) [DbtS-SDbt]⁺ 393 (100) [M-SDbt]⁺ 366 (3) [Dbt-Dbt]⁺ 328 (20) [TiCp(SDbt)]⁺ 295 (2) [Ti(SDbt)S]⁺</p>	<p>263 (2) [Ti(SDbt)]⁺ 215 (13) [HSDbt]⁺ 214 (13) [SDbt]⁺ 178 (11) [TiCp₂]⁺ 152 (7) [C₁₂H₈]⁺ 113 (1) [TiCp]⁺</p>
 <p>3-12</p>	<p>674 (6) [M]⁺ 609 (66) [M-Cp]⁺ 544 (47) [Ti(SThr)₂]⁺ 496 (23) [ThrS-SThr] 457 (6) [TiCp₂(SThr)S]⁺ 425 (4) [M-Cl]⁺ 392 (100) [TiCp(SThr)S]⁺ 360 (5) [Ti(SThr)S]⁺</p>	<p>327 (6) [Ti(SThr)S]⁺ 295 (6) [Ti(SThr)]⁺ 263 (9) [Ti(Thr)]⁺ 248 (2) [HSThr]⁺ 247 (2) [SThr]⁺ 216 (22) [ThrH]⁺ 216 (22) [Thr]⁺ 178 (81) [TiCp₂]⁺ 113 (4) [TiCp]⁺</p>
 <p>3-13</p>	<p>378 (5) [M]⁺ 343 (52) [M-Cl]⁺ 213 (22) [M-SBt]⁺</p>	<p>166 (24) [HSBt]⁺ 165 (24) [SBt]⁺</p>

 <p style="text-align: center;">3-14</p>	508 (10) [M] ⁺	178 (100) [TiCp ₂] ⁺
	378 (5) [Ti(SBt) ₂] ⁺	166 (22) [HSBt] ⁺
	343 (52) [M-SBt] ⁺	165 (24) [SBt] ⁺
	330 (2) [BtS-SBt] ⁺	

The mass spectra of **L3-03** and **L3-04** show the molecular ion and fragments that correspond to the elimination of the thiol sulfur. In the spectrum of **L3-03b** additional fragment ions are observed due to a butyl group.

Although three different fragmentation routes look possible from the observed fragment ions of complex **3-01** the high intensity of the [TiCp₂]⁺ fragment is noteworthy. This indicates that either DbfS or the Cl ligand fragments first. The intensities of [TiCp₂(SDBf)]⁺ and [TiCp₂Cl]⁺ are almost the same which makes suggestions of a preferred fragmentation route risky. The fragment ions of highest intensities for **3-02** are again [TiCp₂]⁺ and [TiCp₂(SDBf)]⁺ which indicates that the fragmentation of the thiolato ligands dominates again and also explains the formation of (DbfS-SDBf)⁺ in the mass spectrometer. Noteworthy for complexes **3-03** and **3-07** are the formation of the bithiolato complexes **3-04** and **3-08**, respectively, which implies that the fragment ion [TiCp₂(SDBf)]⁺ or [TiCp₂(SBf)]⁺ exists for a long enough period of time to attached to a free thiolate from the environment in the mass spectrometer. This result represents the initial fragmentation of a chloro ligand. Unlike **3-04** and **3-06**, the complexes **3-02**, **3-08** and **3-14** again showed [TiCp₂]⁺ to be the principle fragment ion indicating initial fragmentation of the thiolate ligands. By contrast, the former compounds revealed irregular patterns of fragmentation representative of routes whereby any of the four ligands are fragmented. The intensities of the fragment ions however are very low. Many complexes display the fragment ion M⁺-Cp, sometimes of reasonably high intensity for bis-thiolato complexes which is not easy to explain in the light of very strong bonding between Cp-ligands and transition metals. Complex **3-10** gives a principle peak corresponding to the fragment ion [TiCp₂(SDBt)]⁺ which represents the initial fragmentation of a thiolate ligand. Thereafter fragmentation is again irregular. Generally it was found that the monothiolato or chloro containing complexes are very unstable under the conditions employed to measure the mass spectra. This is evident from the absence of molecular ion peaks in some instances and the many fragment ions observed in the spectra of which many are formed in the mass spectrometer. Some of the assignments for fragment ions may be incorrect, for example, in complex **3-05** the fragment ion of second highest m/z-value represents a loss of 32 units which could

be either the elimination of a sulfur of the thiolato ligand or the elimination of a molecule oxygen from the dibenzodioxim rings.

- *¹H NMR and ¹³C NMR spectroscopy*

The ¹H NMR chemical shifts and peak assignments for **L3-01**³, **L3-02**⁴ and **L3-05**⁴ agree with those reported in literature and a summary of the shift values (ppm) for **L3-03**, **L3-03b** and **L3-04** is given in Table 3.3. The ¹H NMR and ¹³C NMR spectral data for complexes **3-01** – **3-10** and **3-12** – **3-14** is summarized in Table 3.4. Due to instability of **3-11** in solution no useful spectrum was obtained and for **L3-01** and **L3-05** no useful ¹³C NMR spectral data could be recorded.

¹H NMR spectroscopy

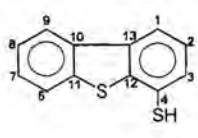
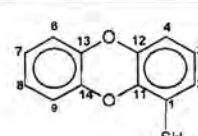
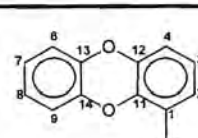
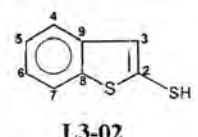
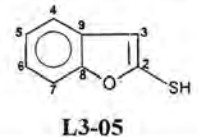
When comparing the chemical shifts of **L3-03**, with **L2-03** (Chapter 2), it is clear that the addition of the sulfur atom did not, with the exception of H2, influence the chemical shifts much. The same was observed for **L3-04** compared to **L2-04**. The chemical shifts of the protons of the ring without the thiol group are roughly the same as the corresponding resonances for the protons of **L2-06** or **L2-01**, but due to their overlapping signals the specific chemical shifts could not be assigned for H6-H9. The ring with the thiolate sulfur as substituent has a downfield shift of 0.34ppm (**L3-03**) and 0.24ppm (**L3-04**) for H2 compared to **L2-03** and **L2-04**, respectively, whereas the resonances of H3 and H4 are little affected. The proton closest to the substituent is shifted downfield because of the electron withdrawing effect of the sulfur atom. In the spectrum of **L3-03b** the presence of the butyl group is seen in resonances at ppm-values of 2.90, 1.44, and 0.89. The triplet at 2.9ppm is indicative of protons on a carbon attached to a sulfur atom and adjacent to a methylene carbon. This observation supports **L3-03b** being a thioether rather than a butyl substituent on the thiophenol ring of the dioxin molecule.

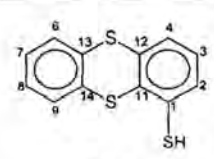
Sulfur atoms in **L2-04** tend to affect the chemical shifts of its adjacent protons in such a way that they are shifted further downfield compared to the same protons of an oxygen molecule such as **L2-03**. In the case of the thiolato complexes the proton closest to the substituent is downfield because of the electron withdrawing effect of the sulfur atom. Coordination of the thiolate to titanium results in a more shielded proton on C2, which indicates that the phenyl ring is shielded and not really affected by the coordination of the sulfur atom. The upfield shift of this proton can only be ascribed to π -resonance effects of the sulfur lone pair to the substituted phenyl ring. This will compete with π -

3. L. V. Dunkerton, B. C. Barot, A. Nigam, *J. Heterocycl. Chem.*, **1987**, *24*, 749.

4. P. C. Montevacchi, M. L. Navacchia, *J. Org. Chem.*, **1995**, *60*, 6455.

Table 3.3 ^1H and ^{13}C NMR spectroscopic data^a for L3-01 – L3-04.

Ligand	C	Chemical Shift (δ ppm)	H	Chemical Shift (δ ppm)	Splitting & Integration	Coupling Constant (J Hz)
 L3-01	Not recorded	-	1/9 2/7/8 3/6 SH	8.04-8.14 7.36-7.48 7.75-7.83 2.14	m 2H m 3H m 2H s 1H	- - - -
 L3-03	1 2 3 4 6/9 7/8 11 12/13/14	141.7 124.7 123.5 116.6 115.9/116.2 124.1/124.3 167.7 141.7/141.8 /142.4	2 3 4 6/7/8/9 SH	7.19 6.83 6.73 6.76-6.91 -	dd 1H t 1H dd 1H m 4H	7.9/1.6 8.1/7.9 8.1/1.6 -
 L3-03b	1 2 3 4 6/9 7/8 11 12/13/14 SBu	141.5 124.4 123.3 116.8 114.3/114.3 123.8/124.1 150.1 141.5-143.0 13.6/22.0/ 31.1/32.4	2 3 4 6/7/8/9 SBu	7.13 6.83 6.68 6.76-6.91 2.90 1.44 0.89	dd 1H t 1H dd 1H m 4H t 2H m 4H m 3H	7.1/1.9 7.7/7.1 7.7/1.9 - 5.6 - -
 L3-02	2 3 4 5 6 7 8 9	142.8 130.9 122.7 125.4 123.9 122.1 141.6 139.9	3 4/7 5/6 SH	7.29 7.64/7.69 7.31/7.27 3.67	s 1H m 2H m 2H s 1H	- - -
 L3-05	Not recorded	-	3 4/5/6/7 SH	6.80 7.17-7.50 3.70	s 1H m 4H s 1H	- -

 <p>L3-04</p>	1	136.9	2	7.48	dd	1H	7.8/1.4
	2	129.2	3	7.13	t	1H	7.7/7.8
	3	128.7	4	7.33	dd	1H	7.7/1.4
	4	123.5	6/9	7.18-7.29	m	2H	-
	6/9	126.2/127.7	7/8	7.43-7.57	m	2H	-
	7/8	127.8/128.2	SH	-			
	11	176.0					
	12/13/14	134.2/135.7					
		/136.2					

^a Recorded in CDCl₃

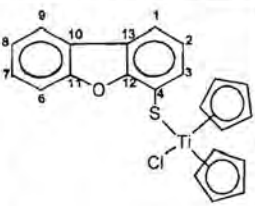
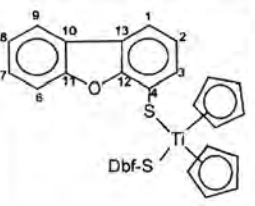
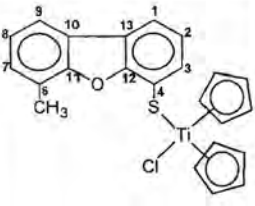
donation from the sulfur to the titanium. Notable is a significant downfield shift for H2 of 0.89ppm for **3-06** compared to **3-05**. A similar trend but smaller effect was observed for H3 of **3-10** and **3-09**. The chemical shifts of H3 and H4 are about the same for **L3-03**, **3-05** (shifted a little more upfield) and **3-06**.

In the cases where there is a methyl substituent on the ring we have all the protons influenced. In the case of **3-03** and **3-04** there is also a big upfield shift for H2 and H5, while H3 is shifted upfield compared to **L2-07**. An explanation can be that the methyl substituents have interaction with other parts of the molecule. The rest of the protons are also downfield but only moderately. The methyl protons in both cases are very much upfield.

The singlet observed in **3-07** and **3-08** shows that the titanium fragment is bound to the sulfur in the 2-position of **L3-05**. Since the H3 protons are the closest protons to the coordination site, it is expected that these protons be influenced most and in the case of **3-07** and **3-08** it is -0.4 and -0.03ppm, respectively. In the case of **3-07** and **3-08**, the protons in the substituted ring were shifted upfield and the H3 resonances were further downfield than expected. The H4 protons were most influenced, which is the opposite of the trend discussed Chapter 2.

In **3-09** and **3-10** the protons of the unsubstituted ring of the heteroaromatic ligand were shifted upfield by -0.01 on average. These shifts for the rest of the complexes were normally around -0.10. The greatest shifts were recorded for the ring coordinated to titanium. In **3-05**, **3-06** and **3-12** the unsubstituted ring's protons are assigned as a multiplet and the general tendency of the chemical shifts are slightly downfield.

Table 3.4 ¹H and ¹³C NMR spectroscopic data^a for 3-01 – 3-10 and 3-12 – 3-14.

Complex	C	Chemical Shift ^b (δ ppm)	H	Chemical Shift (δ ppm)	Splitting & Integration	Coupling Constant (J Hz)	
 <p>3-01</p>	1	115.3	1	7.48	Dd	1H	7.8/1.3
	2	120.4	2	7.35	t	1H	7.7/7.8
	3	139.0	3	7.83	dd	1H	7.7/1.3
	4	no	6	7.97	ddd	1H	7.8/7.5/0.8
	6	112.1	7	7.35	t	1H	7.5/7.8
	7	125.8	8	7.45	td	1H	8.3/7.5/0.8
	8	122.5	9	7.65	dd	1H	8.3
	9	119.8	Cp	6.31	s	10H	
	10/13	122.3					
	11	156.5					
	12	161.5					
	Cp	112.0/113.0					
	 <p>3-02</p>	1	118.3	1	7.97	dd	2H
2		123.3	2	7.34	t	2H	7.6
3		132.1	3	7.80	dd	2H	7.6/1.1
4		154.0	6	7.96	dd	2H	7.8/1.3
6		112.1	7	7.27	t	2H	7.4/7.8
7		127.0	8	7.44	td	2H	8.2/7.4/1.3
8		122.8	9	7.64	dt	2H	8.2/0.8
9		120.8	Cp	6.47	s	10H	
10		123.6					
11/12		no					
13		123.0					
Cp		113.1					
 <p>3-03</p>		1	118.2	1	7.73	dd	1H
	2	122.3	2	7.35	t	1H	7.1/6.7
	3	137.0	3	7.92	dd	1H	6.7/1.1
	4	147.2	7	7.34	m	1H	-
	6	116.0	8	7.45	td	1H	7.0/7.7
	7	127.0	9	7.54	dd	1H	7.7/1.0
	8	123.0	Me	1.53	s	3H	
	9	120.7	Cp	6.46	s	10H	
	10/13	123.8					
	11/12	no					
	Me	29.7					
	Cp	117.2					

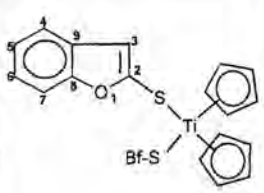
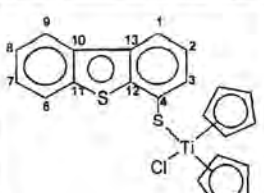
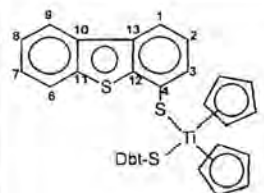


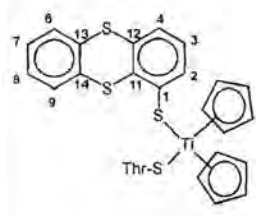
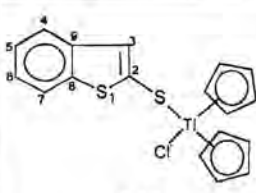
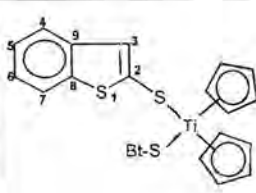
3. Titanocene derivatives with heteroaromatic thiolate ligands

<p style="text-align: center;">3-04</p>	<p>1 118.1 2 123.0 3 132.2 4 145.0 6 112.1 7 128.1 8 122.7 9 118.3 10 123.0 11/12 no 13 120.8 Me 15.6 Cp 113.0</p>	<p>1 7.77 dd 2H 7.5/1.0 2 7.31 t 2H 7.5/7.8 3 7.92 dd 2H 7.8/1.0 7 7.33 m 2H - 8 7.45 td 2H 7.5/7.2 9 7.97 dd 2H 7.2/0.8 Me 1.54 s 6H Cp 6.12 s 5H 6.13 s 5H</p>
<p style="text-align: center;">3-05</p>	<p>1 136.1 2 124.3 3 111.0 4 108.0 6 116.3 7 123.2 8 123.8 9 116.7 11 158.0 12/13/14 139.8/143.0 Cp 112.0/113.0</p>	<p>2 6.42 dd 1H 8.3/1.3 3 6.76 t 1H 8.3 4 6.57 dd 1H 8.3/1.3 6/7/8/9 6.83-6.96 m 4H - Cp 6.05 s 5H 6.33 s 5H</p>
<p style="text-align: center;">3-06</p>	<p>1 138.7 2 129.5 3 123.0 4 116.9 6/9 114.4/116.1 7/8 123.6/123.7 11 150.2 12/13/14 142.2/142.2/142.5 Cp 112.8</p>	<p>2 7.31 dd 1H 7.9/1.6 3 6.84 t 1H 8.0/7.9 4 6.69 dd 1H 8.0/1.6 6/7/8/9 6.71-6.94 m 4H - Cp 6.11 s 10H</p>
<p style="text-align: center;">3-07</p>	<p>2 137.0 3 110.6 4 120.5 5 123.0 6 123.8 7 111.0 8 no 9 131.0 Cp 114.1</p>	<p>3 6.77 s 1H 4 7.46 dd 1H 7.2/0.8 5 7.20 t 1H 7.2 6 7.19 td 1H 5.2/0.8 7 7.43 dd 1H 5.2/1.3 Cp 6.21 s 10H</p>

3. Titanocene derivatives with heteroaromatic thiolate ligands

66

 <p>3-08</p>	2	no	3	6.78	s	1H	
	3	110.8	4	7.43	dd	1H	6.3/1.0
	4	119.9	5	7.18	t	1H	6.2/6.3
	5	122.8	6	7.15	td	1H	7.5/1.0
	6	123.4	7	7.33	d	1H	7.5
	7	110.6	Cp	6.14	s	5H	
	8	156.0		6.21	s	5H	
	9	129.9					
	Cp	114.6					
	 <p>3-09</p>	1	119.5	1	8.00	dd	1H
2		124.9	2	7.46	t	1H	8.3
3		131.2	3	7.53	dd	1H	7.2/1.3
4		143.1	6	7.85	m	1H	-
6		122.7	7	7.45	m	1H	-
7		126.6	8	7.45	m	1H	-
8		124.4	9	8.14	m	1H	-
9		121.9	Cp	6.27	s	10H	
10		136.4					
11		139.8					
12		142.0					
13		134.7					
Cp		115.9					
 <p>3-10</p>		1	118.9	1	7.99	dd	2H
	2	125.0	2	7.48	t	2H	7.6
	3	130.7	3	7.96	dd	2H	6.4/1.0
	4	142.5	6	7.86	m	2H	-
	6	122.8	7	7.45	m	2H	-
	7	126.5	8	7.45	m	2H	-
	8	124.3	9	8.16	m	2H	-
	9	122.0	Cp	6.09	s	10H	
	10	136.6					
	11	139.7					
	12	142.3					
	13	134.5					
	Cp	112.8					

 <p>3-12</p>	1	148.0/148.0	2	7.72	dd	1H	7.8/1.4
	2	132.5/133.2	3	7.13	dd	1H	7.6/7.8
	3	128.7	4	7.27	dd	1H	7.6/1.4
	4	128.3	6/9	7.18-7.24	m	2H	-
	6/9	126.9/126.4	7/8	7.43-7.50	m	2H	-
	7/8	127.5/127.7	Cp	6.31	s	10H	
	11	no					
	12/13/14	135.7/135.9/137.4					
	Cp	112.8/113.4					
	 <p>3-13</p>	2	149.6	3	7.16	s	1H
3		127.7	4	7.69	d	1H	7.5
4		122.8	5	7.32	td	1H	7.5/1.2
5		124.2	6	7.24	td	1H	7.5/1.2
6		123.7	7	7.74	d	1H	8.8
7		121.5	Cp	6.35	s	10H	
8		141.9					
9		140.4					
Cp		116.3					
 <p>3-14</p>		2	149.9	3	7.34	s	2H
	3	126.8	4	7.66	dd	2H	7.4/0.8
	4	122.5	5	7.39	td	2H	7.5/1.1
	5	124.1	6	7.22	td	2H	7.5/1.3
	6	123.5	7	7.72	d	2H	7.9
	7	121.5	Cp	6.19	s	10H	
	8	141.6					
	9	140.6					
	Cp	113.6					

^a Recorded in CDCl₃ ^b no = not observed

The two Cp rings resonate as a singlet due to similar chemical environments for the protons on the rings. The resonances are shifted upfield in all instances compared to titanocene dichloride, which has a chemical shift value of 6.57ppm for its Cp ligands. This can be ascribed to the replacement of the chloro ligand in titanocene dichloride and a resulting increase in the electron density on the metal fragment. In most cases the shift is around -0.10 to -0.50ppm. It is interesting to note that there is a tendency for the Cp to split up in two singlets in the bis-thiolato complexes. The replacement of both chloro ligands caused even more electron density to reside on the metal fragment and the chemical shift of the Cp rings was even further upfield.

Two-dimensional homonuclear shift correlation spectroscopy (COSY) was used to aid in the unambiguous assignment of the different protons in **3-01** - **3-03**, **L3-03** and **L3-04**. In spite of this, it was still difficult to assign protons in the multiplets of **L3-03** and **L3-04**.

¹³C NMR spectroscopy

In **L3-03**, **L3-03b** and **L3-04** the chemical shift of C1 is observed downfield due to the electron withdrawing effect of the thiol/thioether substituent. The other carbons are little affected and have about the same chemical shifts compared to the corresponding carbons in the unsubstituted heteroaromatic compounds. The carbons C2 and C3 are downfield and this correlates with the results from the ¹H NMR spectrum.

The resonances of the *ipso* carbons of C1(C4) (*ca* 140ppm) of the thiolato complexes are shifted downfield but not as far as was observed for the complexes where this carbon was directly bonded to the titanium centre (*ca* 180 ppm). The values fall between those of the uncoordinated thiols and the titanium-C(heteroarene) complexes. This observation is supported by the ¹H NMR data. The neighbouring carbons, C2 (C3) and C12 (C11), also display resonances that represent downfield shifts, but much less than C1. Resonances of carbons, C11 and C12, are further downfield because of the effects of the neighbouring oxygen atoms. The rest of the chemical shifts are quite similar to those of the uncoordinated heteroaromatic molecules. The Cp signal is upfield (about 3 - 8 ppm) due to increased electron density on the metal fragment, when compared to titanocene dichloride. In **3-12** the Cp signals appear as two single peaks in a ratio of 3:1. This ratio is repeated for the rest of the spectrum and can be ascribed to two different isomers in solution.

The HETCOR spectra of **L3-03** and **3-04** were used to assign and correlate the specific proton resonances to the corresponding carbons resonances. Again it was impossible to assign the protons in the unsubstituted ring of **L3-03**.

• *X-ray crystallography*

Structure of complex 3-09

The final confirmation of **3-09** was obtained from a single crystal X-ray diffraction study. The complex was recrystallised from a 1:1 dichloromethane:hexane solution by using the layering technique. It gave dark red crystals suitable for data collection on the diffractometer. In Figure 3.2 the structure of the molecule is given as a ball and stick representation, which also indicates the atom-labelling scheme that was used. The most important bond lengths and angles are listed in Table 3.5 and Table 3.6 respectively. Other structural information is given in Chapter 6 and in Appendix C.

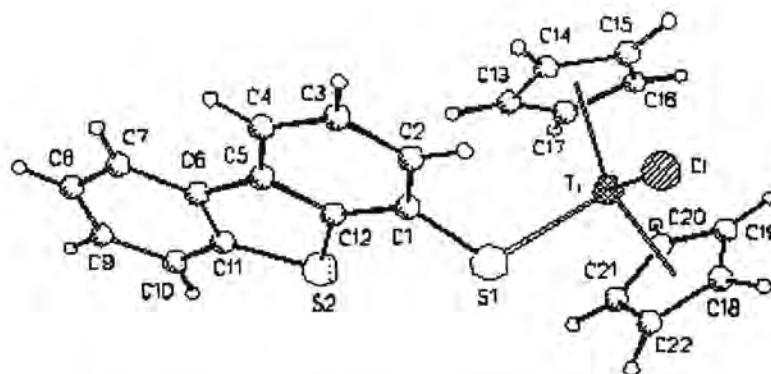


Figure 3.2. Ball and stick picture of the structure of **3-09**.

Table 3.5. Selected bond lengths of **3-09**.

	Bond length [Å]		Bond length [Å]
Ti-Cl	2.3948(7)	C(5)-C(12)	1.408(3)
Ti-S(1)	2.4068(7)	C(5)-C(6)	1.460(3)
S(1)-C(1)	1.782(2)	C(6)-C(7)	1.408(3)
S(2)-C(12)	1.757(2)	C(6)-C(11)	1.411(3)
S(2)-C(11)	1.762(2)	C(7)-C(8)	1.379(4)
C(1)-C(2)	1.394(3)	C(8)-C(9)	1.400(4)
C(1)-C(12)	1.400(3)	C(9)-C(10)	1.388(4)
C(2)-C(3)	1.404(4)	C(10)-C(11)	1.396(4)
C(3)-C(4)	1.389(4)	C(21)-C(22)	1.415(4)
C(4)-C(5)	1.403(3)		

Table 3.6. Selected bond angles of **3-09**.

	Bond angle [°]		Bond angle [°]
Cl-Ti-S(1)	96.13(3)	C(7)-C(6)-C(11)	118.2(2)
Cl-Ti-C(18)	77.39(7)	C(7)-C(6)-C(5)	129.7(2)
C(1)-S(1)-Ti	114.89(8)	C(11)-C(6)-C(5)	112.0(2)
C(12)-S(2)-C(11)	91.06(12)	C(8)-C(7)-C(6)	120.0(2)
C(2)-C(1)-C(12)	117.6(2)	C(7)-C(8)-C(9)	120.8(3)
C(2)-C(1)-S(1)	124.4(2)	C(10)-C(9)-C(8)	120.7(3)
C(12)-C(1)-S(1)	117.8(2)	C(9)-C(10)-C(11)	118.3(3)
C(1)-C(2)-C(3)	120.7(2)	C(10)-C(11)-C(6)	122.0(2)
C(4)-C(3)-C(2)	120.9(2)	C(10)-C(11)-S(2)	125.7(2)
C(3)-C(4)-C(5)	119.7(2)	C(6)-C(11)-S(2)	112.4(2)
C(4)-C(5)-C(12)	118.3(2)	C(1)-C(12)-C(5)	122.7(2)
C(4)-C(5)-C(6)	130.0(2)	C(1)-C(12)-S(2)	124.5(2)
C(12)-C(5)-C(6)	111.7(2)	C(5)-C(12)-S(2)	112.8(2)

The arrangement of the ligands is similar to complexes **2-02**, **2-05** (Chapter 2) and **2-08**⁵ displays a pseudo tetrahedral environment of ligands around titanium. The insertion of a sulfur atom between the bulky ring ligand and the metal center causes almost no change of the angle between the two non-Cp ligands Cl-Ti-S(1) of **3-09** (96.1°) compared to the Cl-Ti-Cl angle in titanocene dichloride⁶ which is 94.6°. This angle was significantly larger in **2-02** (105.0°), **2-05** (97.4°) and **2-08** (96.7°) with the bulky ligands directly bound to the metal. The dihedral angle, Cl-Ti-S(1)-C(1) of 73.16(9)° reveals that the chloro ligand is not in the plane of the rings. The dihedral angle of C(11)-S(2)-C(12)-C(1) is -179.2(2)°, which shows that the dibenzothiophene ring is planar.

If we compare the bond lengths of dibenzothiophene⁷ to those of **3-09**, we can see that they differ very little and that coordination to titanium has very little effect on the bond lengths. The average C-S bond distance 1.74(8)Å in the free ligand is similar to the bond distances for S(2)-C(11) 1.757(2)Å and S(2)-C(12) 1.76(2)Å in **3-09**. The C-S-C bond angle in the free ligand is 91.5(4)° is also similar to the

5. R. Meyer, *Titanium, Molybdenum and Platinum Complexes with Potential Antitumor Properties*, Ph. D. (Chemistry) Thesis, University of Pretoria, 1998, 73.

6. A. Clearfield, D. K. Warner, C. H. Salderiaga-Molina, R. Ropal, J. Bernal, *Can. J. Chem.*, 1975, 53, 1622.

7. R. M. Schaffrin, J. Trotter, *J. Chem. Soc. (A)*, 1970, 651.

C(12)-S(2)-C(11) angle of $91.1(1)^\circ$ in **3-09**. The structure reveals that the chloro and dibenzothiophene ligands does not share the same plane, unlike that found for **2-05**. In **3-09** the ring is more flexible to rotate and chances of covalent bond formation at the chloro site as well as intercalation by the dibenzothiophene ring ligand is greatly enhanced for this improved ligand orientations.

3.4 Conclusions

The aim was to synthesize a series of titanocene complexes where the heteroaromatic ligand is linked via a sulfur atom to the metal fragment. This was done by lithiation of the heteroaromatic ligand (compare Chapter 2), followed by the addition of a stoichiometric amount of sulfur to obtain the corresponding thiolates. The thiolates were then added to titanocene dichloride at low temperatures to give mono- and bis-thiolato complexes of titanium. The desired mono-thiolate complexes [TiCp₂(SDBf)Cl] **3-01**, [TiCp₂(SDBf-Me)Cl] **3-03**, [TiCp₂(SDBz)Cl] **3-05**, [TiCp₂(SBf)Cl] **3-07**, [TiCp₂(SDBt)Cl] **3-09**, [TiCp₂(SThr)Cl] **3-11** and [TiCp₂(SBt)Cl] **3-13** were isolated in high yields. In addition, the untargetted bis-thiolato complexes were obtained as by-products of the reaction and are [TiCp₂(SDBf)₂] **3-02**, [TiCp₂(SDBf-Me)₂] **3-04**, [TiCp₂(SDBz)₂] **3-06**, [TiCp₂(SBf)₂] **3-08**, [TiCp₂(SDBt)₂] **3-10**, [TiCp₂(SThr)₂] **3-12**, [TiCp₂(SBt)₂] **3-14**. The structure of complex **3-09** was confirmed by X-ray crystallography. The introduction of a linking sulfur atom greatly affects the electronic properties and geometric features of the complexes compared to the previously described titanium complexes with a direct bond between the metal and a carbon atom of the heteroaromatic ring ligand.

Thiolato complexes were selected for preclinical testing based on their stability, solubility and most importantly their structural features. Complexes **3-05**, **3-09** and **3-10** were selected for initial testing and complexes **3-01**, **3-02**, **3-03**, **3-05**, **3-06**, **3-07**, **3-09** and **3-13** were tested against antitumor activity in a later test series. Serious handling problems eliminated **3-11** and **3-12** as possible candidates for further testing in biological systems. Based on the assumptions of this study, the geometry of complexes **3-02**, **3-04**, **3-06**, **3-08**, **3-10** and **3-14** were not desirable for intercalation and covalent bonding. In hindsight, the lability of the thiolate ligands were much higher than generally expected and could in some instances be comparable with the very labile chloro ligands. This observation makes the requirement of a chloro ligand in the molecular design of these compounds for fast displacement and covalent bonding to DNA less important and also has consequences for intercalation. The antitumor properties of the selected complexes will be further investigated in Chapter 5.

Chapter 4

Bi- and trinuclear complexes of titanium(IV) and platinum(II)

4.1 Introduction

Recently some of the interest in the *cisplatin* area of research shifted towards complexes containing more than one Pt(II) center for various reasons, but also because they tend to display activity against some *cisplatin* resistant tumors¹. Figure 4.1 illustrates two examples of bifunctional binuclear platinum complexes with linear coordinating spermidine and spermine. Both these complexes exhibit high antitumor activity against *cisplatin* sensitive as well as *cisplatin* resistant cell lines. It is believed that complexes with more than one Pt(II) coordination center may take part in different intra- and interstrand interactions on each strand of the DNA double helix.

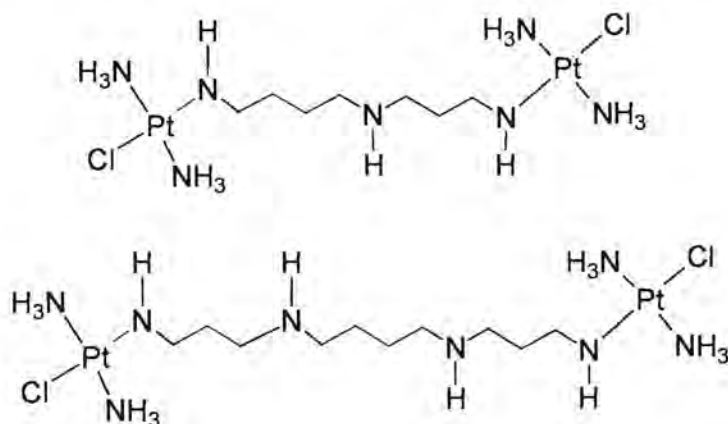


Figure 4.1 Bifunctional binuclear platinum complexes exhibiting antitumor activity.

Another approach is to combine non-platinum antitumor complexes into the framework of the *cisplatin* molecule to produce heteronuclear bimetallic complexes. Since NN donor ligands have been used in complexation with many transition metals, it is reasonably easy to synthesize such complexes.

1. H. Rauter, R. Di Domenico, E. Menta, A. Olivia, Y. Qu, N. Farrell, *Inorg. Chem.*, **1997**, *36*, 3919.

The example in Figure 4.2 combines ferrocenyl groups with *cis*-platin and the resulting complex was identified as a possible anticancer agent².

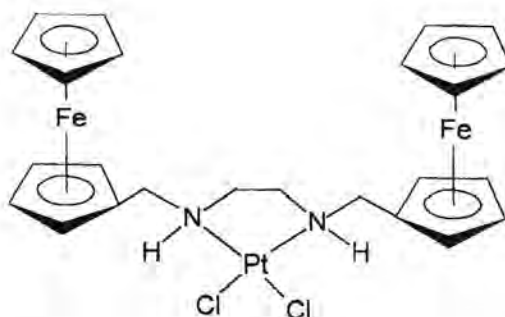


Figure 4.2 Platinum complex tested as a positive anticancer agent.

Figure 4.3 show examples of ferrocenyl and platinum fragments combined in one molecule and one or two platinum fragments were incorporated, producing bi- or trinuclear ferrocenyl complexes³.

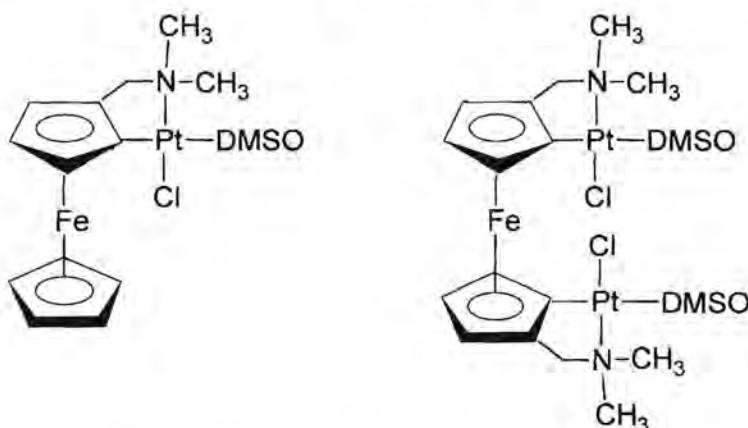


Figure 4.3 Platinum complexes tested as positive anticancer agents.

The antitumor active titanocene complexes are mainly mononuclear. Although binuclear titanocene complexes are mentioned in literature, they have mostly application as catalysts. So far no titanocene binuclear complexes were identified as antitumor agents. The product of the reaction in Figure 4.4 has attractive structural features that make it worthwhile to investigate the antitumor properties. This complex was mentioned in literature as the product of a ligand exchange process in a photochemical

2. E. N. Neuse, M. G. Meirim, N. F. Bolm, *Organometallics*, **1988**, *7*, 2562.

3. P. Ramani, R. Ranatunge-Bandarage, N. W. Duffy, S. M. Johnston, B. H. Robinson, J. Simpson, *Organometallics*, **1994**, *13*, 511.

reaction⁴. However, the yield for this reaction was very low and it was decided to use a different route for synthesizing the complex.

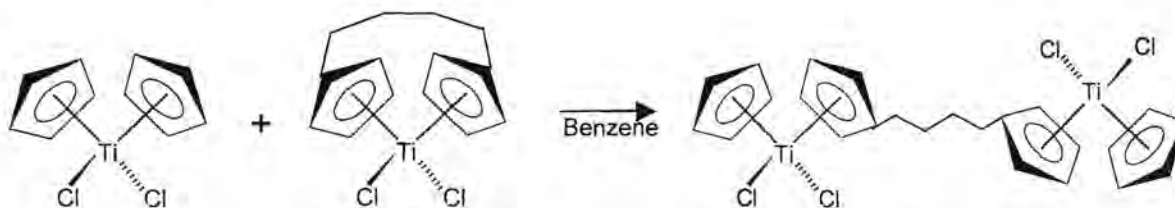


Figure 4.4 Photochemical reaction affording a binuclear titanocene complex.

In the context of this study it was decided to try and combine the best of the *cisplatin* and titanocene dichloride to synthesize new binuclear complexes with antitumor properties. The above examples demonstrated that a carefully chosen chain of atoms could act as a bridge between two metal centres.

In this chapter the focus is on combining ligand donor functions with linking atoms which will ultimately act as a bridge to incorporate titanocene and platinum in one molecule, as seen in Figure 4.5. On one end of the common ligand donor atoms are needed that could coordinate effectively to platinum such as amines and on the other end of the ligand a moiety that could be attached to titanium. For the latter, a heteroatom (class 1) or a cyclopentadiene that is readily convertible into a cyclopentadienyl ligand (class 2) was chosen. For the first class the reaction would mean the substitution of a chloro ligand in titanocene dichloride by a heteroatom whereas for the second class the substrate will be reacted with TiCpCl_3 to give a titanocene derivative.

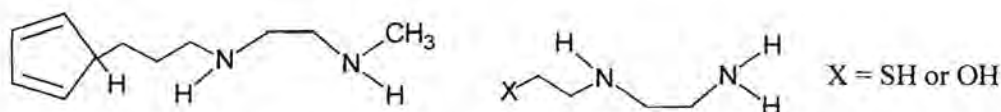


Figure 4.5 Typical substrates designed to be used as bridging ligands for binuclear complexes.

In this chapter the synthesis of two main types of Pt(II) complexes will be investigated. The first structure (Figure 4.6) represents a binuclear heterometallic complex with an early (Ti) and late (Pt) transition metal. In the first approach only one chloro ligand remain on the titanium and is available for further manipulation. In another method the two metals are bridged by an ethylene diamine on one end of the chain to coordinate to platinum and a cyclopentadienyl ring on the other end to coordinate to titanium. In the latter case two chloro ligands are available for manipulation or covalent bonding.

4. E. Vitz, C. H. Brubaker, *J. Organomet. Chem.*, 1976, 104, C33.

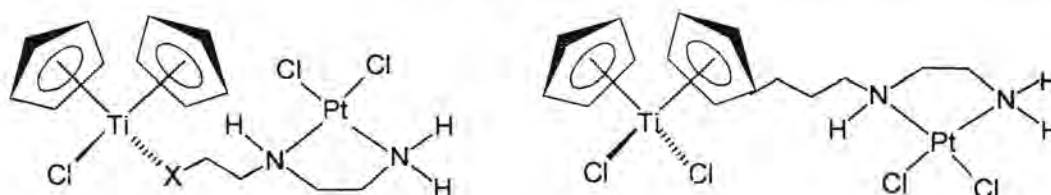


Figure 4.6 Binuclear heterometallic complexes of Ti(IV) and Pt(II).

The structures in Figure 4.7 represent binuclear complexes with two titanium metal moieties linked by donor atoms on the two ends of a chain of methylene fragments. The bridge can run between a cyclopentadienyl ligand of each fragment or directly between the metal centers by replacing a chloro ligand in each titanocene fragment by another donor atom.

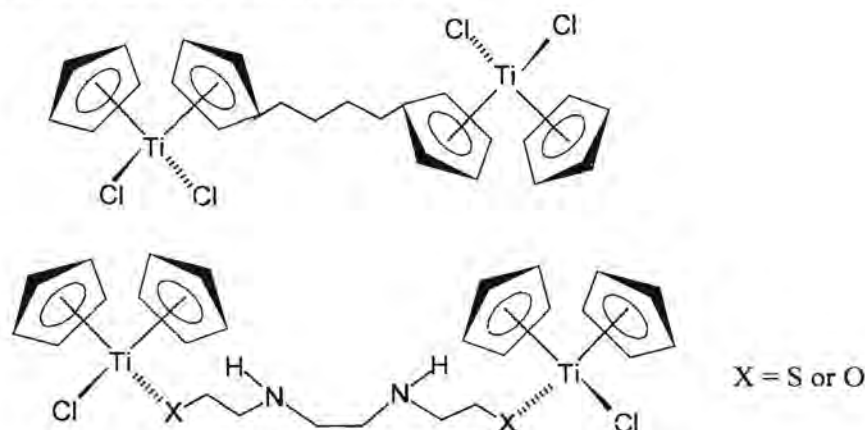
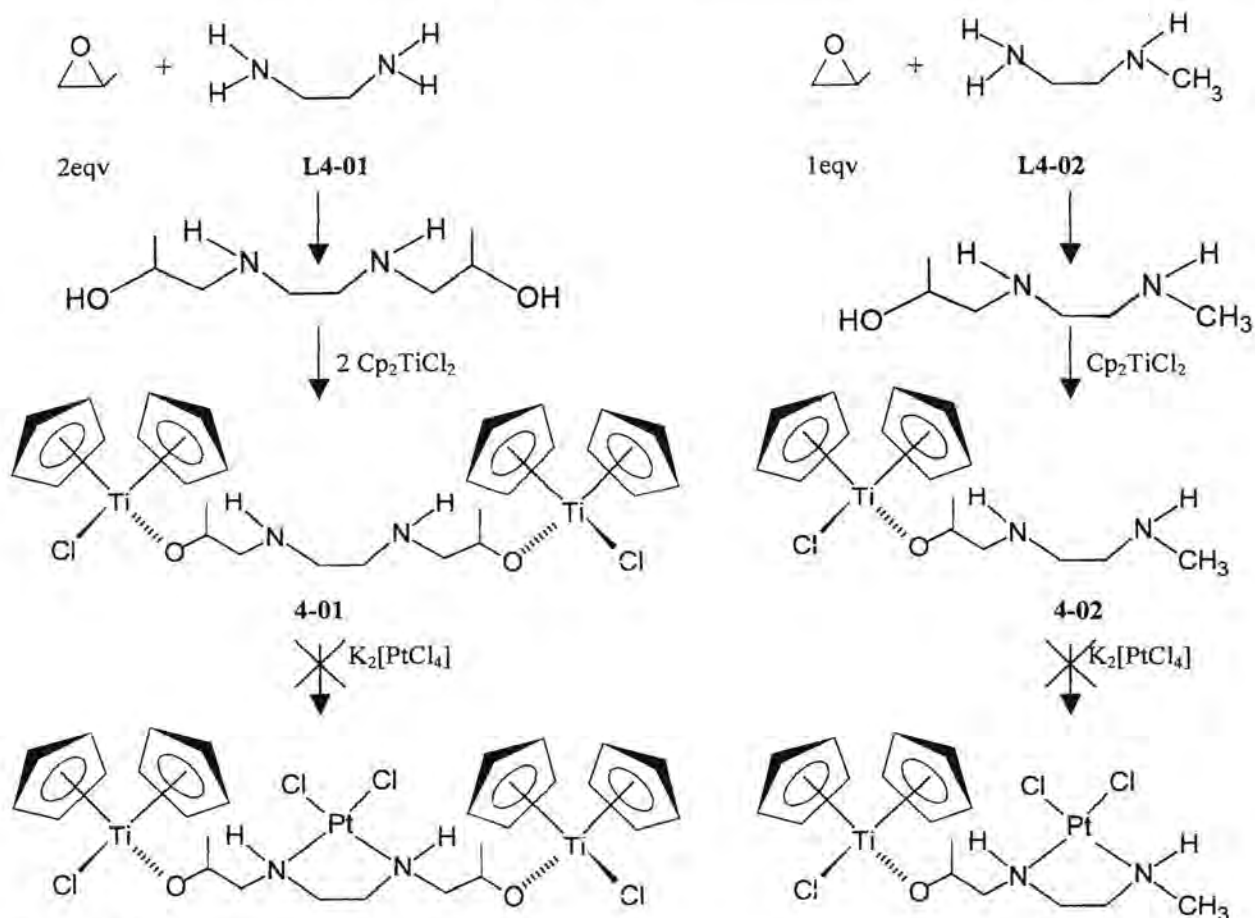


Figure 4.7 Binuclear homometallic complexes of Ti(IV).

4.2 Synthesis

Schemes 4.1 and 4.2 represent the planned syntheses of complexes where a heteroatom is used to replace a chloro ligand in the coordination sphere of titanium. Titanium has a strong affinity for sulfur and oxygen ligands and the introduction of thiolate and oxolate donor atoms were considered. The bridging ligands was to be constructed by either adding one or two equivalents of epoxide to ethylene diamine. When two equivalents of epoxide were added, two titanocene chloride fragments are found at the ends of the bridging ligand with the possibility to afterwards introduce a platinum fragment. For one equivalent epoxide the result would lead to a binuclear Ti-Pt complex. To enable the addition of only one equivalent of epoxide methyl ethylene diamine was chosen as starting substrate as the methyl group would effectively block one side of the molecule.

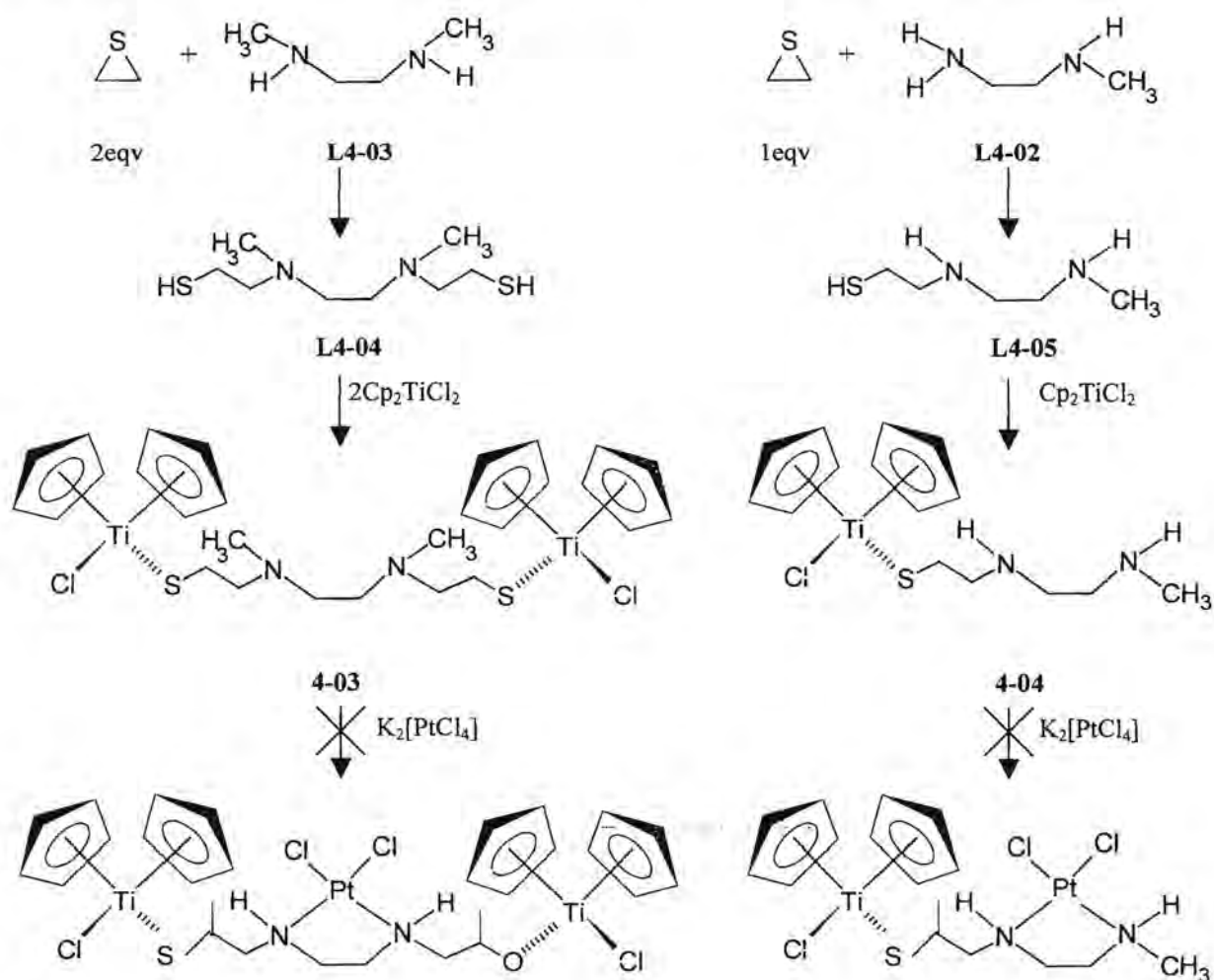


Scheme 4.1

In the first case of Scheme 4.1 methyl epoxide was added to ethylene diamine **L4-01** and to this colourless solution were added two equivalents of titanocene dichloride and the colour changed from red-orange to yellow. The product was extracted with hot toluene and precipitated with hexane to give a yellow product identified by mass spectrometry and ^1H NMR spectroscopy as $[\{\mu\text{-C}_8\text{H}_{18}\text{N}_2\text{O}_2\}\text{Ti}_2\text{Cp}_2\text{Cl}_2]$ **4-01**. Addition of **4-01** to $\text{K}_2[\text{PtCl}_4]$ in an aqueous acetonitrile solution afforded unreacted **4-01** as well as titanocene decomposition products. One of these being the oxygen bridged bis titanocene chloride dimer, $[(\mu\text{-O})\{\text{TiCp}_2\text{Cl}\}_2]$.

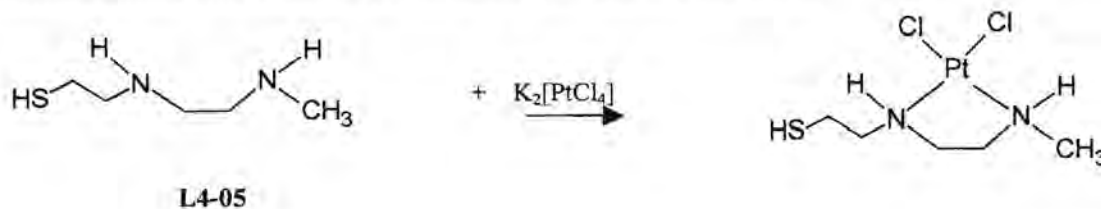
The same procedure was repeated with methyl epoxide and N-methyl ethylene diamine **L4-02** (Scheme 4.1) and adding titanocene dichloride changed the colour from red to orange. Extraction and precipitation gave a yellow product identified by mass spectrometry and ^1H NMR spectroscopy as $[\text{TiCp}_2(\text{OC}_6\text{H}_{15}\text{N}_2)\text{Cl}]$ **4-02**. Addition of **4-02** to $\text{K}_2[\text{PtCl}_4]$ in aqueous solution again did not lead to the desired product but afforded similar decomposition products.

The same basic procedure was followed for thiiran, as shown in Scheme 4.1 for epoxides, but in this case the bridge was built by adding two equivalents of thiiran to *N,N'*-dimethyl ethylene diamine **L4-03** and reacting at high temperature and pressure (Scheme 4.2). The product was purified by filtration and distillation to yield a colourless oil [$C_8H_{20}N_2S$] **L4-04**. The addition of this new ligand to two equivalents of titanocene caused a colour change from red to orange-red. The product was extracted with dichloromethane and addition of hexane precipitated [$\{\mu-C_8H_{18}N_2S_2\}Ti_2Cp_4Cl_2$] **4-03** as a red-orange product. The binuclear complex was characterized by 1H NMR spectroscopy. The addition of one equivalent of thiiran to **L4-02** and reaction at high pressure and temperature yielded an oily substance that was purified by filtration and distillation. The resulting colourless oil was identified as [$C_5H_{14}N_2S$] **L4-05**. Reaction of this substrate with titanocene dichloride changed the colour of the mixture from red to red-orange. Extraction with dichloromethane and precipitation with hexane yielded an orange product [$TiCp_2(SC_6H_{15}N_2)Cl$] **4-04**. Subsequent reactions of **4-03** and **4-04** with $K_2[PtCl_4]$ again did not afford the desired bi- and trinuclear complexes of platinum and titanium.



Scheme 4.2

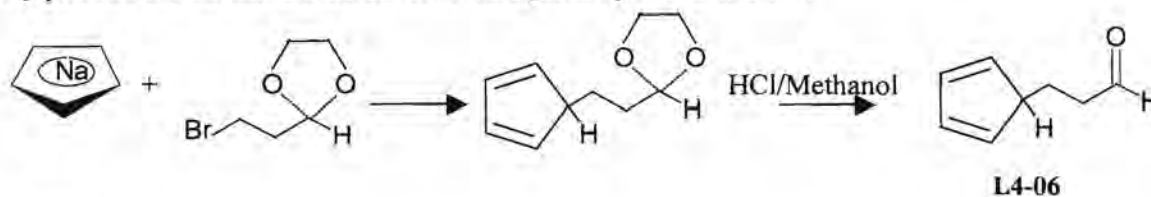
Scheme 4.3 represents an alternative approach where the order in which the metal fragments are introduced are being reversed. However, this was not a very good idea as a number of platinum complexes formed with different combinations of N and S donor atoms.



Scheme 4.3

A better method would undoubtedly be to start with a different platinum precursor. The most likely contender would be to use [Pt(COD)Cl₂] instead of [PtCl₄²⁻] as this compound has available a readily displaceable COD ligand. In the light of the instability of especially **4-01** and **4-03** in solution it was apparent that pursuing this line of research would defy the objectives of the study. Preparing useful compounds that displayed superior antitumor activities had to be supported by easy to handle, unambiguously characterizable compounds. The weakness of this approach was found in the relatively weak Ti-O/S bond in solution in bi- and trinuclear Pt-Ti complexes. To solve this problem it was decided to make use of a much stronger bonded ligand such as cyclopentadienyl.

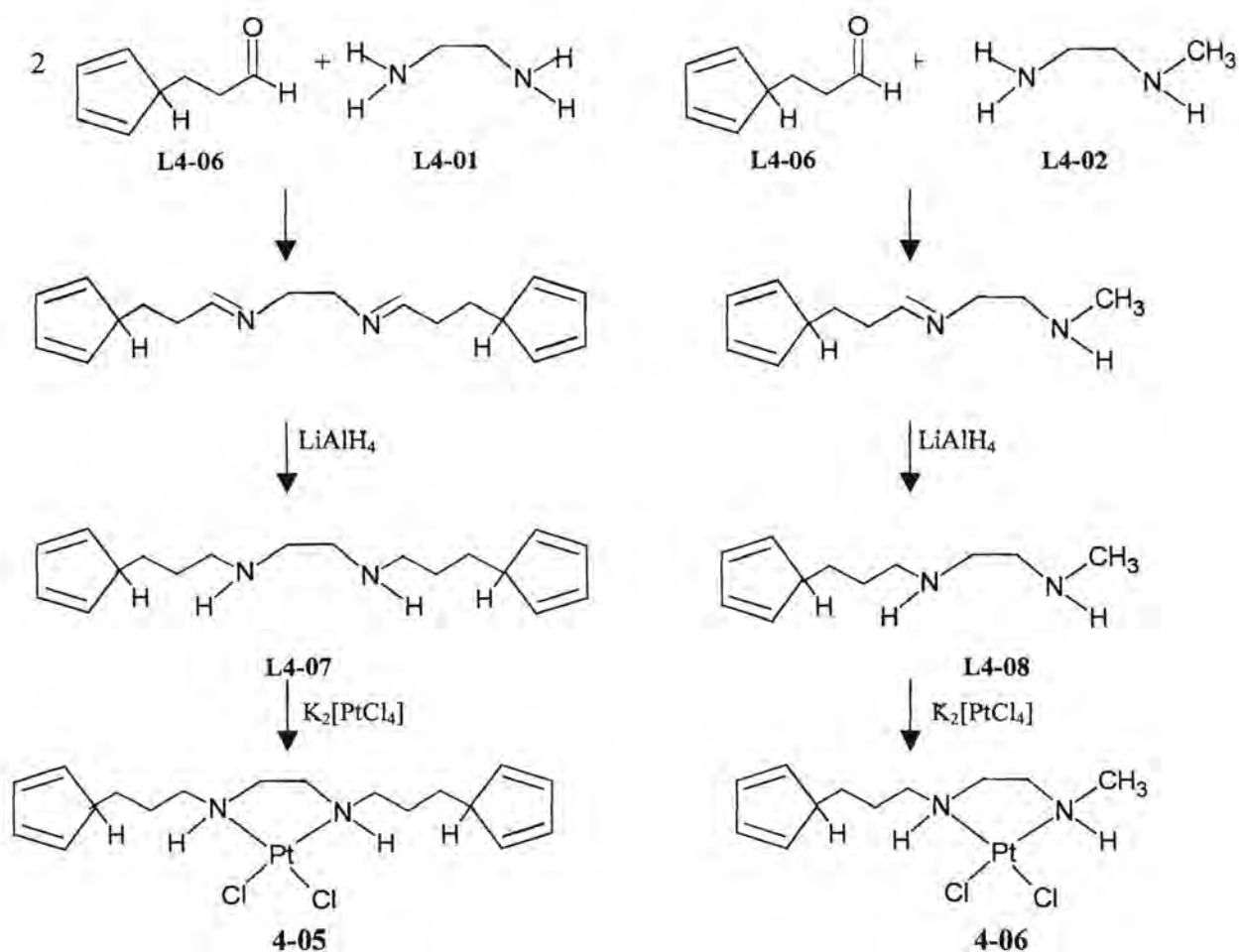
Scheme 4.4 shows the synthesis of 3-cyclopenta-2,4-dienyl propionaldehyde **L4-06**. 2-(2-Bromoethyl)-[1,3]dioxolan was added to NaCp (freshly prepared) and the colour of the mixture changed from purple to brown. The residue was treated with HCl to deprotect the acetal and a brown oily product **L4-06** was extracted from the aqueous phase with ether.



Scheme 4.4

Scheme 4.5 shows the synthesis of two ligands that were designed to bridge two heterobimetallic fragments. In the first example two equivalents of **L4-06** was refluxed overnight with **L4-01** in a Schiff Base reaction to give the unsaturated product. The product was subsequently reduced to give the desired bisdiene precursor. Purification by extraction and precipitation with a dichloromethane-hexane mixture yielded N,N'-bis-(3-cyclopenta-2,4-dienyl propyl) ethylene diamine **L4-07** as a yellow-brown oil. Addition of **L4-07** to K₂[PtCl₄] in an aqueous acetonitrile solution resulted in a

colour change of the reaction mixture from red to brown to yellow-brown. The product $[\text{Pt}(\mu\text{-N}_2\text{N}'\text{C}_{18}\text{H}_{28}\text{N}_2)\text{Cl}_2]$ **4-05** precipitated from the brown solution.

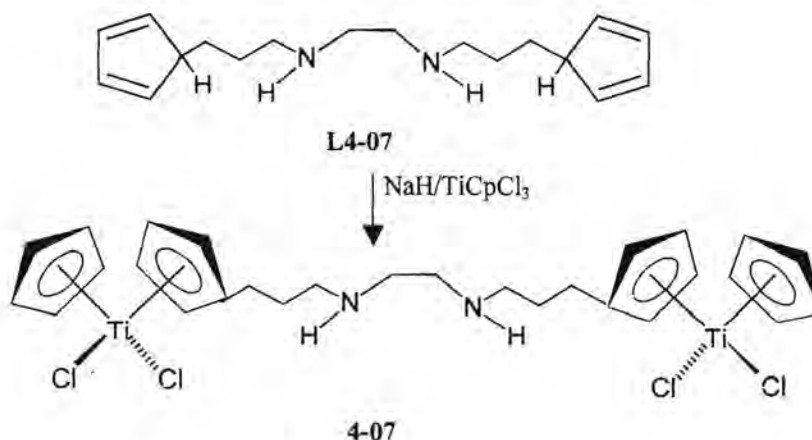


Scheme 4.5

Addition of one equivalent of **L4-06** to **L4-02** in refluxing benzene yielded a Schiff Base, which was subsequently reduced. Extraction with dichloromethane yielded *N*-(3-cyclopenta-2,4)dienyl propyl)-*N*'-methyl ethylene diamine **L4-08** as a yellow-brown oil. Treatment of **L4-08** with $\text{K}_2[\text{PtCl}_4]$ in an aqueous acetonitrile solution gave a brown product $[\text{Pt}(\mu\text{-N}_2\text{N}'\text{-C}_{11}\text{H}_{20}\text{N}_2)\text{Cl}_2]$ **4-06** after precipitation.

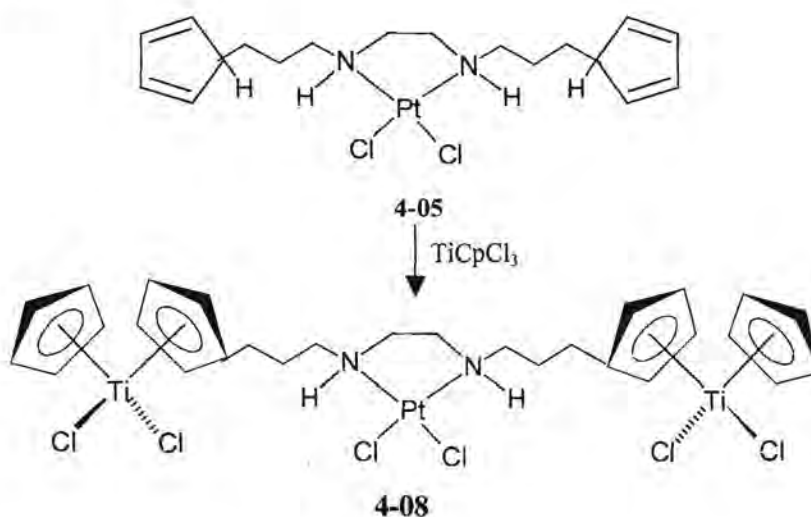
In Scheme 4.6 the cyclopentadiene rings on ligand **L4-07** was deprotonated with NaH and trichloro cyclopentadienyl titanium (IV) was added. The colour of the reaction mixture changed to dark brown and the product was extracted with toluene, concentrated and mixed with hexane causing unreacted $[\text{TiCpCl}_3]$ to precipitate. The yellow filtrate was evaporated and extracted into dichloromethane. Addition of hexane precipitated a black solid, which was insoluble and removed by filtration. The

filtrate was evaporated to give the desired product $[\{\mu\text{-}\eta^5, \eta^5\text{-C}_{18}\text{H}_{26}\text{N}_2\}\text{Ti}_2\text{Cp}_2\text{Cl}_4]$ **4-07**. This is an example of binuclear complexes displaying two titanocene fragments joined by a chain of methylene units and a central ethylene diamine moiety.



Scheme 4.6

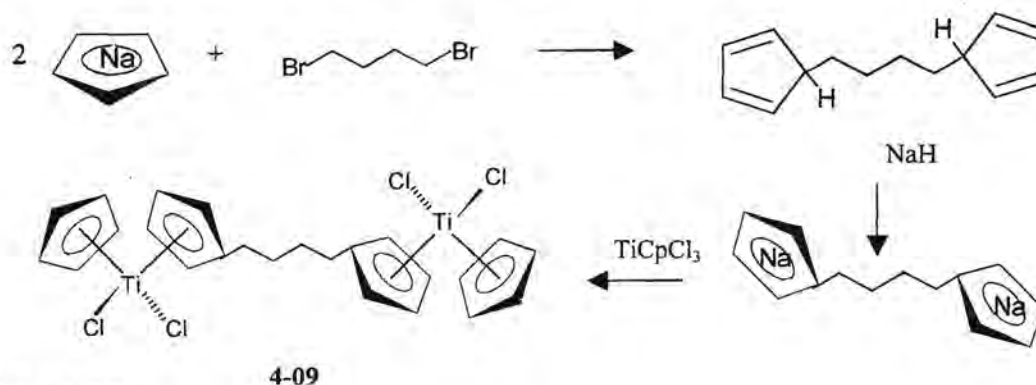
In Scheme 4.7 the synthesis of a mixed trinuclear complex is illustrated. The titanocene fragments are joined by a chain containing ethylene diamine which in turn is coordinated to a dichloro platinum fragment. The cyclopentadiene rings on product **4-05** were deprotonated (NaH) and two equivalents of trichloro cyclopentadienyl titanium (IV) were added in THF. The brown solution turned yellow and a cream-pink precipitate was isolated and identified as the trinuclear product $[\text{Ti}_2\{\mu\text{-}\eta^5, \eta^5\text{-}(\text{Pt}(\text{N}, \text{N}'\text{-C}_{18}\text{H}_{26}\text{N}_2)\text{Cl}_2)\}\text{Cp}_2\text{Cl}_4]$ **4-08**.



Scheme 4.7

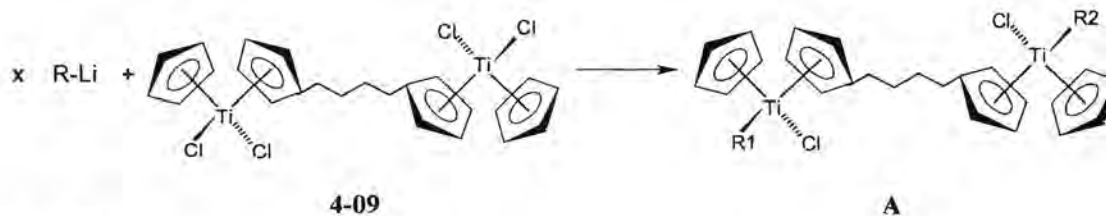
The method shown in Scheme 4.8 was used to synthesize a binuclear bistitanocene complex where the two metal fragments are coordinated to two cyclopentadienyl ligands connected by a butane chain.

Reacting NaCp and 1,4-dibromobutane accomplished this goal. After deprotonation the resulting brown solution was added to trichloro cyclopentadienyl titanium (IV) and evaporated to dryness. The residue gave a dark green product which was identified as $[\{\mu-\eta^5, \eta^5-C_{14}H_{16}\}Ti_2Cp_2Cl_4]$ **4-09**.



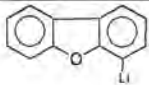
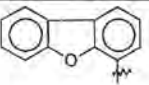
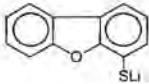
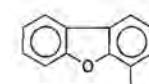
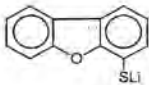
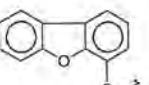
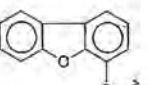
Scheme 4.8

Product **4-09** was treated with lithiated dibenzofuran precursors in ratios of 1:1 and 1:2 as shown in Scheme 4.9. The identification numbers of the isolated complexes are shown in Table 4.1



Scheme 4.9

Table 4.1

x	R-Li	R1	R2	Complex A
1			Cl	4-10
1			Cl	4-11
2				4-12

Addition of one equivalent of **4-09** to one equivalent [Dbf-Li] caused a colour change from dark green to green-yellow. Extraction with ether yielded a green product which was isolated and characterized to be $[\{\mu\text{-}\eta^5, \eta^5\text{-C}_{14}\text{H}_{16}\}\text{Ti}_2(\text{Dbf})\text{Cp}_2\text{Cl}_3]$ **4-10**. Similarly, the addition of one equivalent of **4-09** to one equivalent [DBF-SLi] yielded an orange-yellow product, $[\{\mu\text{-}\eta^5, \eta^5\text{-C}_{14}\text{H}_{16}\}\text{Ti}_2(\text{Dbf-S})\text{Cp}_2\text{Cl}_3]$ **4-11**. Addition of one equivalent of **4-09** to two equivalents lithiated dibenzofuranylthiolate caused a colour change from dark green to red. The red-purple residue was subjected to column chromatography and a purple fraction was collected and contained the product $[\{\mu\text{-}\eta^5, \eta^5\text{-C}_{14}\text{H}_{16}\}\{\text{Ti}(\text{Dbf-S})\text{CpCl}\}_2]$ **4-12**.

4.3 Characterization

- *Mass spectrometry*

The mass spectral data for thiiran⁵, methyl epoxide⁶, **L4-02**⁷ and **L4-03**⁸ are given in literature and the mass spectral data for **L4-07** and **L4-08** and complexes **4-01**, **4-02**, **4-05**, **4-09**, **4-10**, **4-11** and **4-12** are summarized in Table 4.2. The most prominent peaks for **L4-07** correspond to *m/z*-values that belong to fragments that result from C-N bond cleavage in the molecule. In **L4-08** the $[\text{M}^+]$ ion was observed and the principle ion corresponds to a fragment whereby the methyl on the nitrogen was fragmented first.

The molecular ions of **4-01** and **4-02** were observed and they fragmented in a similar way. Most fragmentation ions represent fragmentation patterns due to C-N bond cleavage. No molecular ion was observed for **4-05** and the peak of highest *m/z*-value corresponds to the fragment $\text{M}^+\text{-Cl}$. It is clear from the fragment ions that the chlorine and biscyclopentadiene ethylene diamine ligands were bonded to the platinum. Again the molecular ion was not observed for **4-09** in the spectrum and the peak of highest intensity at *m/z*=268 for a binuclear species is one that corresponds to a fragment ion where the two titanium metals are bridged only by the biscyclopentadienyl ligand, $[\text{Ti}_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$.

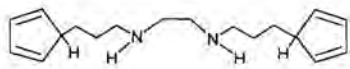
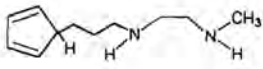
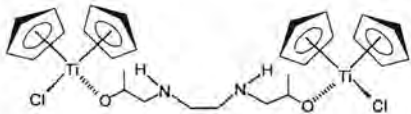
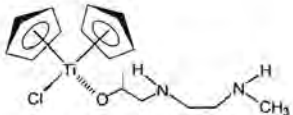
5. G. N. Merrill, U. Zoller, D. R. Reed, S. R. Kass, *J. Org. Chem.*, **1999**, *64*, 7395.

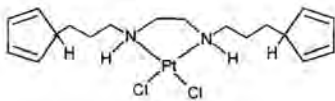
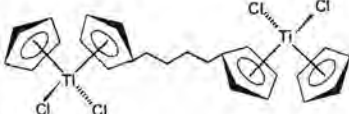
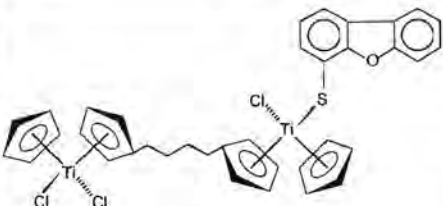
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7. M. Pykaelainen, A. Vianiotalo, T. A. Pakkenen, P. Vianiotalo, *J. Mass Spectrom.*, **1996**, *31*, 716.

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Table 4.2 Mass spectral data for L4-07, L4-08, 4-01, 4-02, 4-05 and 4-09 - 4-12.

Mass Peaks, m/z (I, %)		
 <p>L4-07</p>	<p>272 (30) [M⁺], 207 (7) [M⁺-Cp], 165 (51), 142 (9) [M⁺-2Cp], 120 (7), 107 (58), 100 (65)</p>	<p>71 (100) [(C₄H₉N)⁺], 66 (3) [CpH⁺], 58 (26), 57 (15), 42 (25), 42 (25), 28 (5)</p>
 <p>L4-08</p>	<p>180 (7) [M⁺], 165 (100) [M⁺-CH₃], 120 (1), 107 (18), 100 (9), 71 (11),</p>	<p>66 (3) [CpH⁺], 58 (17), 57 (15), 42 (14), 28 (7)</p>
 <p>4-01</p>	<p>352 (5) [TiCp₂(OC₃H₆)₂(C₂H₆N₂)⁺], 340 (9) [M⁺-4Cp], 335 (1) [M⁺-3Cp-2Cl], 322 (2) [TiCpCl(OC₃H₆)₂(C₂H₆N₂)⁺], 305 (1) [M⁺-4Cp-Cl], 294 (5) [TiCp₂(OC₃H₆)(C₂H₆N₂)⁺], 287 (6) [TiCp(OC₃H₆)₂(C₂H₆N₂)⁺], 271 (1) [TiCp₂Cl(OC₃H₆)⁺], 270 (1) [M⁺-4Cp-2Cl], 257 (6) [TiCl(OC₃H₆)₂(C₂H₆N₂)⁺], 246 (8) [TiCpCl(OC₃H₆)(C₂H₆N₂)⁺], 236 (25) [TiCp₂(OC₃H₆)⁺], 229 (2) [TiCp(OC₃H₆)(C₂H₆N₂)⁺], 222 (3) [Ti(OC₃H₆)₂(C₂H₆N₂)⁺],</p>	<p>213 (4) [TiCp₂Cl⁺], 206 (3) [TiCpCl(OC₃H₆)⁺], 178 (8) [TiCp₂⁺], 174 (2) [(OC₃H₆)₂(C₂H₆N₂)⁺], 171 (3) [TiCp(OC₃H₆)⁺], 164 (2) [Ti(OC₃H₆)(C₂H₆N₂)⁺], 148 (7) [TiCpCl⁺], 141 (5) [TiCl(OC₃H₆)⁺], 116 (1) [(OC₃H₆)(C₂H₆N₂)⁺], 113 (8) [TiCp⁺], 106 (5) [Ti(OC₃H₆)⁺], 58 (60) [C₂H₆N₂⁺], 42 (60) [C₂H₆N⁺], 28 (100) [C₂H₄⁺</p>
 <p>4-02</p>	<p>264 (1) [M⁺-Cp-Me], 243 (1) [M⁺-Cp-Cl], 236 (2) [TiCp₂(OC₃H₆)⁺], 229 (2) [M⁺-Cp-Cl-Me], 213 (17) [M⁺-2Cp], 213 (17) [TiCp₂Cl⁺], 206 (1) [TiCpCl(OC₃H₆)⁺], 199 (1) [M⁺-2Cp-Me], 178 (2) [M⁺-2Cp-Cl], 178 (2) [TiCp₂⁺], 171 (1) [TiCp(OC₃H₆)⁺],</p>	<p>164 (1) [M⁺-2Cp-Cl-Me], 148 (7) [TiCpCl⁺], 141 (1) [TiCl(OC₃H₆)⁺], 131 (1) [(OC₃H₆)(C₂H₆N₂)⁺], 116 (2) [(OC₃H₆)(C₂H₆N₂)⁺], 113 (5) [TiCp⁺], 106 (2) [Ti(OC₃H₆)⁺], 74 (7) [(C₃H₉N₂)⁺], 58 (16) [C₂H₆N₂⁺], 42 (100) [C₂H₆N⁺], 28 (20) [C₂H₄⁺</p>
<p>601 (5) [M⁺], 565 (6) [M⁺-Cl], 536 (4) [M⁺-Cp], 530 (1) [M⁺-2Cl], 435 (1) [M⁺-2Cp-Cl], 400 (1) [M⁺-2Cp-2Cl], 405 (4) [M⁺-3Cp],</p>	<p>343 (1) [M⁺], 294 (2) [M⁺-Cl-Me], 271 (1) [TiCp₂Cl(OC₃H₆)⁺],</p>	

	<p>537 not observed $[M^+]$ 502 (1) $[M^+-Cl]$, 467 (1) $[M^+-2Cl]$, 428 (2), 408 (2), 395 (1), 372 (1), 366 (2), 360 (1), 337 (1), 330 (5), 323 (5), 295 (1), 288 (2),</p>	<p>272 (4) $[(CpC_3H_6)_2(C_2H_5N_2)^+]$ 266 (2), 253 (5), 230 (15), 195 (10) $[Pt^+]$, 165 (4), 142 (6), 107 (8), 100 (2), 65 (15), 58 (100), 42 (94),</p>
	<p>552 not observed $[M^+]$ 345 (5) $[M^+-4Cl-Cp]$, 280 (54) $[Ti_2(Cp_2C_4H_8)^+]$, 268 (3) $[TiCl(Cp_2C_4H_8)^+]$, 238 (50), 203 (5),</p>	<p>184 (80) $[Cp_2C_4H_8]^+$, 183 (100) $[TiCpCl_2]^+$, 178 (12) $[TiCp_2]^+$, 168 (31), 148 (7), 120 (43), 113 (7) $[TiCp^+]$, 70 (10), 57 (35)</p>
	<p>480 (18) $[Ti_2Cp_2Cl_2(Cp_2C_4H_8)^+]$, $[Ti_2(Dbfs)(Cp_2C_4H_8)^+]$, 479 (36) $[Ti(Dbfs)Cl(Cp_2C_4H_8)^+]$, 445 (5) $[Ti_2Cp_2Cl(Cp_2C_4H_8)^+]$, 432 (14) $[Ti(Dbfs)(Cp_2C_4H_8)^+]$, 415 (14) $[Ti_2CpCl_2(Cp_2C_4H_8)^+]$, 412 (4) $[TiCp_2(Dbfs)Cl^+]$, 402 (17) $[Ti(Dbfs)Cl(CpC_4H_8)^+]$, 399 (2) $[Ti(Dbfs)(Cp_2C_4H_8)^+]$, 385 (1) $[Ti_2Cl_3(Cp_2C_4H_8)^+]$, 380 (1) $[Ti_2CpCl(Cp_2C_4H_8)^+]$, 377 (1) $[TiCp_2(Dbfs)^+]$, 370 (1) $[Ti(Dbfs)Cl(CpC_4H_8)^+]$, 367 (15) $[TiCpCl_2(Cp_2C_4H_8)^+]$, 350 (2) $[TiCl_2(Cp_2C_4H_8)^+]$, 347 (4) $[TiCp(Dbfs)Cl^+]$, 346 (5) $[Ti_2Cp(Cp_2C_4H_8)^+]$, 335 (1) $[Ti(Dbfs)(Cp_2C_4H_8)^+]$, 332 (32) $[TiCpCl(Cp_2C_4H_8)^+]$, 315 (2) $[Ti_2Cl(Cp_2C_4H_8)^+]$,</p>	<p>312 (2) $[TiCp(Dbfs)^+]$, 302 (2) $[TiCl_2(Cp_2C_4H_8)^+]$, 299 (1) $[TiCp(Cp_2C_4H_8)^+]$, 280 (1) $[Ti_2(Cp_2C_4H_8)^+]$, 267 (3) $[TiCl(Cp_2C_4H_8)^+]$, 248 (2) $[TiCp_2Cl_2^+]$, 238 (8) $[TiCl_2(CpC_4H_8)^+]$, 232 (12) $[Ti(Cp_2C_4H_8)^+]$, 213 (8) $[TiCp_2Cl^+]$, 203 (4) $[TiCl(CpC_4H_8)^+]$, 200 (100) $[Dbfs-SH^+]$, 186 (1) $[CpH-C_4H_8-CpH]$ 184 (12) $[Cp_2C_4H_8]^+$, 183 (12) $[TiCpCl_2^+]$, 178 (3) $[TiCp_2^+]$, 168 (55) $[Dbfs-H^+]$, $[Ti(CpC_4H_8)^+]$, 148 (5) $[TiCpCl^+]$, 120 (3) $[CpC_4H_8]^+$, 113 (6), 70 (10), 57 (3)</p>

716 (2) $[M^+]$,

680 (1) $[M^+-Cl]$

615 (7) $[M^+-Cp-Cl]$,

579 (4) $[M^+-Cp-2Cl]$,

550 (8) $[M^+-2Cp-Cl]$,

545 (3) $[M^+-Cp-3Cl]$,

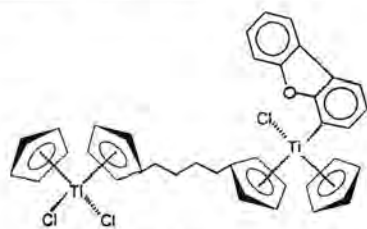
544 (8) $[Ti_2Cp(Dbfs)(Cp_2C_4H_8)^+]$,

531 (8) $[TiCp(Dbfs)Cl(Cp_2C_4H_8)^+]$,

516 (8) $[M^+-DbfsSH]$,

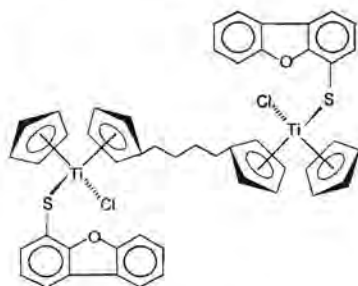
514 (8) $[Ti_2(Dbfs)Cl(Cp_2C_4H_8)^+]$,

496 (4) $[TiCp(Dbfs)(Cp_2C_4H_8)^+]$,



4-10

683 not observed $[M^+]$	267 (2) $[\text{TiCl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,
399 (2) $[\text{Ti}(\text{Dbf})(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	248 (1) $[\text{TiCp}_2\text{Cl}_2^+]$,
380 (1) $[\text{Ti}_2\text{CpCl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	232 (1) $[\text{Ti}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$, $[\text{Dbf-Cp}^+]$
370 (1) $[\text{Ti}(\text{Dbf})\text{Cl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	213 (3) $[\text{TiCp}_2\text{Cl}^+]$,
367 (1) $[\text{TiCpCl}_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	186 (1) $[\text{CpH-C}_4\text{H}_8\text{-CpH}]$
346 (1) $[\text{Ti}_2\text{Cp}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	184 (5) $[\text{Cp}_2\text{C}_4\text{H}_8]^+$,
345 (1) $[\text{TiCp}_2(\text{Dbf})^+]$,	183 (17), $[\text{TiCpCl}_2^+]$,
332 (1) $[\text{TiCpCl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	168 (100) $[\text{Dbf-H}^+]$,
315 (1) $[\text{TiCp}(\text{Dbf})\text{Cl}^+]$,	148 (1) $[\text{TiCpCl}^+]$,
$[\text{Ti}_2(\text{Cp}_2\text{C}_4\text{H}_8)\text{Cl}^+]$,	120 (1) $[\text{CpC}_4\text{H}_8]^+$,
302 (2) $[\text{TiCl}_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	113 (5) $[\text{TiCp}^+]$,
280 (1) $[\text{TiCp}(\text{Dbf})^+]$, $[\text{Ti}_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	70 (3), 57 (2)



4-12

881 (13) $[M^+]$,	610 (45) $[\text{Ti}_2\text{Cp}_2(\text{DbfS})(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	346 (75) $[\text{Ti}_2\text{Cp}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,
845 (28) $[M^+\text{-Cl}]$,	579 (4) $[\text{Ti}_2\text{CpCl}(\text{DbfS})(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	332 (14) $[\text{TiCpCl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,
815 (20) $[M^+\text{-CpH}]$,	576 (14) $[\text{TiCp}_2(\text{DbfS})_2^+]$,	315 (44) $[\text{Ti}_2\text{Cl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,
810 (6) $[M^+\text{-2Cl}]$,	550 (12) $[\text{Ti}_2\text{Cl}_2(\text{DbfS})(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	313 (25) $[\text{TiCp}(\text{DbfS})^+]$,
780 (23) $[M^+\text{-Cl-CpH}]$,	545 (17) $[\text{Ti}_2\text{Cp}(\text{DbfS})(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	303 (12) $[\text{TiCl}_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,
750 (14) $[M^+\text{-2Cp}]$,	544 (17) $[\text{Ti}_2\text{Cp}(\text{DbfS})(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	299 (10) $[\text{Ti}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,
745 (10) $[M^+\text{-2Cl-Cp}]$,	531 (12) $[\text{TiCp}(\text{DbfS})\text{Cl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	280 (20) $[\text{Ti}_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,
715 (14) $[M^+\text{-Cl-2Cp}]$,	514 (90) $[\text{Ti}_2\text{Cl}(\text{DbfS})(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	268 (18) $[\text{TiCl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,
696 (13) $[\text{TiCp}(\text{DbfS})_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	513 (85) $[\text{TiCp}(\text{DbfS})_2^+]$,	248 (14) $[\text{TiCp}_2\text{Cl}_2^+]$,
680 (8) $[\text{MH}^+\text{-2Cl-2Cp}]$,	496 (15) $[\text{TiCp}(\text{DbfS})(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	238 (20) $[\text{TiCl}_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,
$[M^+\text{-DbfSH}]$,	480 (10) $[\text{Ti}_2\text{Cp}_2\text{Cl}_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	233 (14) $[\text{Ti}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,
679 (8) $[\text{Ti}_2(\text{DbfS})_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	479 (17) $[\text{Ti}_2(\text{DbfS})(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	213 (32) $[\text{TiCp}_2\text{Cl}^+]$,
645 (42) $[\text{Ti}_2\text{Cp}_2\text{Cl}(\text{DbfS})(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	467 (13) $[\text{Ti}(\text{DbfS})\text{Cl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	203 (8) $[\text{TiCl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,
631 (3) $[\text{Ti}(\text{DbfS})_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	466 (10) $[\text{Ti}(\text{DbfS})\text{Cl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	200 (100) $[\text{Dbf-SH}^+]$,
615 (18) $[\text{Ti}_2\text{CpCl}_2(\text{DbfS})(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	445 (6) $[\text{Ti}_2\text{Cp}_2\text{Cl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	186 (1) $[\text{CpH-C}_4\text{H}_8\text{-CpH}]$
	432 (13) $[\text{Ti}(\text{DbfS})(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	184 (4) $[\text{Cp}_2\text{C}_4\text{H}_8]^+$,
	415 (8) $[\text{Ti}_2\text{CpCl}_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	183 (4) $[\text{TiCpCl}_2^+]$,
	413 (9) $[\text{TiCp}_2\text{Cl}(\text{DbfS})^+]$,	178 (10) $[\text{TiCp}_2^+]$,
	410 (15) $[\text{Ti}_2\text{Cp}_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	168 (17) $[\text{Dbf-H}^+]$,
	402 (12) $[\text{Ti}(\text{DbfS})\text{Cl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	168 (17) $[\text{Ti}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,
	380 (13) $[\text{Ti}_2\text{CpCl}(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	148 (5) $[\text{TiCpCl}^+]$,
	378 (96) $[\text{TiCp}_2(\text{DbfS})^+]$,	120 (13) $[\text{CpC}_4\text{H}_8]^+$,
	367 (45) $[\text{TiCpCl}_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	113 (8) $[\text{TiCp}^+]$,
	350 (11) $[\text{TiCl}_2(\text{Cp}_2\text{C}_4\text{H}_8)^+]$,	70 (18) $[\text{TiS}^+]$,
	348 (75) $[\text{TiCpCl}(\text{DbfS})^+]$,	57 (23)

The molecular ions of **4-11** and **4-12** were observed but in the case of **4-10** the peak of highest m/z -value was assigned to a mononuclear titanium fragment. Peaks of fragments containing two titaniums as well as the bridging biscyclopentadienyl ligand were observed but all of them without the Dbf ligand. The spectrum is of poor quality and this is ascribed to the instability of the complex. The dinuclear thiolate compounds are of higher stability and gave spectra of higher quality. There are two pathways for the fragmentation of the complexes **4-10** to **4-12**. In the first instance the two titanium atoms remain bonded to the bridging ligand and other ligands are fragmented randomly. Ultimately all ligands are lost except for the bridging biscyclopentadienyl ligand to give the fragment ion ($m/z=280$) which is present on all the spectra, all though not observed as a peak of high intensity. The second route represents the fragmentation of a titanium fragment by decomplexation from a cyclopentadienyl ligand. This leaves the bridging ligand in tact, but replaces the metal by a hydrogen atom to give a diene at the open end of the ligand. As a result, it is difficult to distinguish between the fragments DbfSH and $2Cp + 2Cl$ as they have very similar mass contributions. Whereas the intensity of fractions with the Dbf ligand is very low for **4-10**, higher intensities peaks assigned to fractions containing DbfS were observed in the spectra of **4-11** and **4-12**. It is not possible to write a general fragmentation sequence for the ligands

• *¹H NMR and ¹³C NMR spectroscopy*

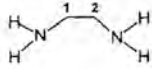
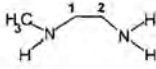
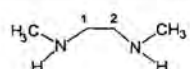


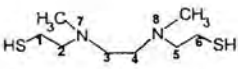
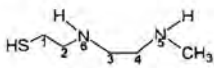
A summary of the ¹H NMR and ¹³C NMR data for thiiran^{9,10}, methyl epoxide^{11,12} **L4-01**^{13,14}, **L4-02**¹⁵, **L4-03**¹⁶ and **L4-04** - **L4-08** is given in Table 4.3. The values of the commercially available compounds were confirmed with the literature values. The ¹H NMR and ¹³C NMR spectral data for complexes **4-01**, **4-02**, **4-03**, **4-07** and **4-09** - **4-12** are summarized in Table 4.4.

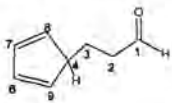
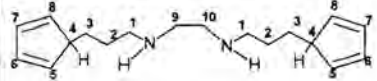
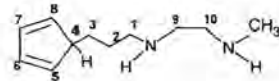
Table 4.3 ¹H and ¹³C NMR spectral data^a for the diamines, thiiran and methyl oxiran, **L4-01** - **L4-08**.

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4. Bi- and trinuclear complexes of titanium(IV) and platinum(II)

Ligand	C	Chemical Shift (δ ppm)	H	Chem. Shift (δ ppm)	Splitting/ Integration	Coupling Constant (J Hz)	
 L4-01	1,2	44.7	1,2 NH	2.66 1.17	s s	4H 4H	
 L4-02	1 2 N-Me	54.5 41.2 36.1	1 2 N-Me NH	2.49 2.66 2.30 1.29	t t s s	2H 2H 3H 3H	5.4/5.9 5.9/5.4
 L4-03	1,2 N-Me	51.5 36.2	1,2 N-Me NH	2.54 2.29 1.14	s s s	4H 6H 2H	
 L4-04	1,2	18.9	1,2	2.30	s	4H	
 L4-05	1 2 3	46.3 46.6 16.8	1/2 3	2.46-3.00 1.32	m br	3H 1H	-
 L4-06	1,6 2,5 3,4 N-Me	22.3 41.8 60.3 36.3/	1,6 2,5 3,4 N-Me SH	2.40 2.46-2.50 2.53 2.13 1.70	d m d s br	4H 4H 4H 6H 2H	5.7 - 5.9
 L4-07	1 2 3 4 N-Me	23.0 42.2 60.6 60.8 39.9	1 2/3 4 N-Me NH/SH	2.36 2.47-2.54 2.58-2.61 2.16/2.17 1.46/1.47	d m m s/s s/s	2H 4H 2H 3H 2H	5.43 - -

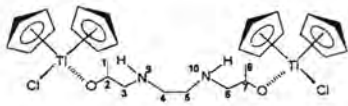
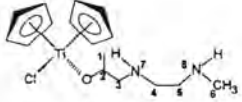
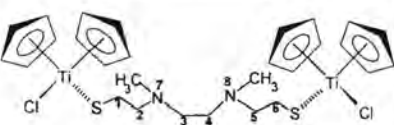
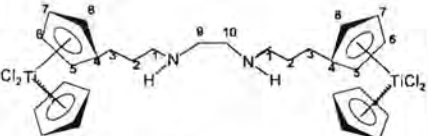
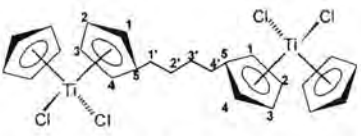
 <p>L4-06</p>	<p>1 199.1 2 35.8 3 28.5 4 45.9/50.8 5,8 102.9 6,7 102.9</p>	<p>1 9.71 s 1H 2 3.40 t 2H 6.7 3 2.10-2.12 m 2H - 4 2.59-2.61 m 1H - 5,8 3.05 t 2H 6.6 6,7 4.51-4.54 m 2H -</p>
 <p>L4-07</p>	<p>1 32.7 2 30.0 3 49.3 4 45.3 5,8 103.0 6,7 103.5 9,10 49.2</p>	<p>1 1.77-1.78 m 4H - 2 1.70-1.72 m 4H - 3 2.44 t 4H 6.7/7.2 4 2.60-2.63 m 2H - 5,8 4.38-4.40 m 4H - 6,7 4.34-4.35 m 4H - 9,10 2.68 s 4H NH 2.11 s 2H</p>
 <p>L4-08</p>	<p>1 32.9 2 30.4 3 49.2 4 45.4 5,8 103.1 6,7 104.2 9 51.5 10 42.16 N-Me 36.4</p>	<p>1 2.14 t 2H 5.9/5.9 2 1.59-1.61 m 2H - 3 1.69-1.70 m 2H - 4 2.58-2.60 m 1H - 5,8 4.30 d 2H 5.7 6,7 4.39 t 2H 5.7/5.7 9 2.58 d 2H 6.7 10 2.32 d 2H 6.7 N-Me 2.35 s 3H NH 1.18 s 2H</p>

^a Recorded in CDCl₃

¹H NMR spectroscopy

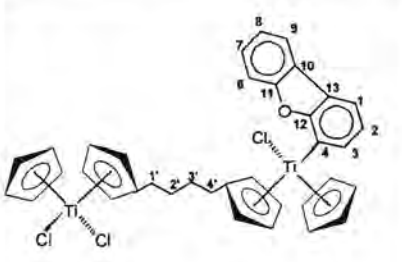
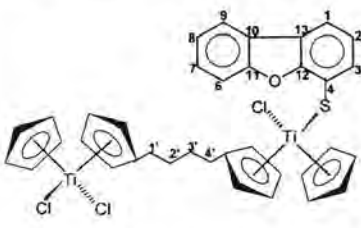
The NH signal of **L4-05** was broadened to such an extent that it coincided with the baseline and no meaningful assignment could be made. The characteristic -C(O)H peak for the aldehyde is observed at 9.71 ppm. Due to poor resolution of resonances it was difficult to get all the coupling constants for **L4-07** and **L4-08**.

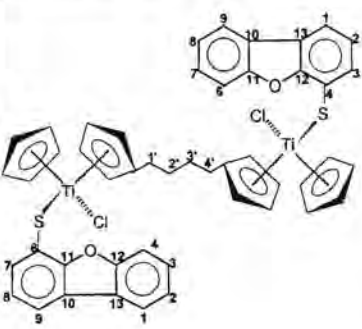
Table 4.4 ¹H and ¹³C NMR spectral data^a for 4-01, 4-02, 4-03, 4-07 and 4-09 - 4-12.

Complex	C	Chem. Shift ^b (δ ppm)	H	Chem. Shift (δ ppm)	Splitting/Integration	Coupling Constant (J Hz)	
 <p>4-01</p>	1/8 2/7 3/6 4/5 Cp	20.1 67.7 50.0 51.6 116.8	1/8 2/7 3/6 4/5 NH Cp	1.25 3.99-4.00 3.57-3.59 3.41/3.45 1.57 6.28	d m m d/d s s	6H 2H 4H 4H 2H 20H	6.4 - - 7.2/7.2 - -
 <p>4-02</p>	Not recorded	-	1 2 3 4/5 N-Me NH Cp	1.25 3.98-3.99 3.57-3.59 3.41/3.45 3.47 1.68 6.28/6.31	d m m d/d s br s,s	3H 1H 2H 4H 3H 2H 10H	6.2 - - 7.2/7.2 - -
 <p>4-03</p>	Not recorded	-	1,6 2,5 3,4 N-Me Cp	3.71 4.32-4.33 3.25 2.76 6.41/6.42	t m s s s/s	4H 4H 4H 6H 20H	6.2 - - -
 <p>4-07</p>	Not recorded	-	1 2 3 5-8 9/10 NH Cp	2.29 2.20-2.21 3.33-3.35 6.57-7.04 3.47 1.22 6.60	d m m m s s s	2H 2H 2H 8H 4H 2H 10H	6.0 - - -
 <p>4-09</p>	1/4 2/3 5 1'/4' 2'/3' Cp	119.5 119.7 122.2 23.9 41.0 115.8	1/4 2/3 5 1'/2'/3'/4' Cp	6.34-6.36 6.27-6.28 6.43 2.68-2.70 6.48	m m s m s	4H 4H 2H 8H 20H	- - - -



4. Bi- and trinuclear complexes of titanium(IV) and platinum(II)

 <p style="text-align: center;">4-10</p>	1	116.6	1	7.50	d	1H	7.5
	2	123.0	2	7.21	t	1H	7.5/8.0
	3	129.1	3	7.00	d	1H	8.0
	4	no	6	7.94	d	1H	7.5
	6	111.7	7	7.33	t	1H	7.5/7.2
	7	127.1	8	7.44	t	1H	7.2/7.2
	8	122.7	9	7.56	t	1H	7.2
	9	120.6	1'/4'	3.64	t	4H	6.5
	10/12/13	no	2'/3'	3.72-3.73	m	4H	-
	11	159.5	Cp	6.61/6.63	s/s	10H	
	1'/4'	23.7	Cp*	6.44/6.57	s/s	8H	
	2'/3'	39.0		6.62/6.65	s/s		
	Cp	119.2					
		119.4					
	Cp*	119.2					
	119.3						
	119.5						
	119.7						
 <p style="text-align: center;">4-11</p>	1	120.2	1	7.67/7.73	d	1H	7.8
	2	123.3	2	7.23/7.24	t	1H	7.8
	3	129.5	3	7.87/7.87	d	1H	7.8
	4	no	6	7.92/7.94	d	1H	7.5
	6	112.0	7	7.33/7.34	t	1H	7.5
	7	127.5	8	7.44/7.47	t	1H	7.5
	8	123.0	9	7.56/7.60	d	1H	7.5
	9	121.3	1'/4'	3.09	t	4H	7.5
	10-13	no	2'/3'	1.62-1.64	m	4H	-
	1'/4'	25.9	Cp	6.61	s	10H	
	2'/3'	38.9	Cp*	6.48/6.52	s/s	8H	
	Cp	120.8		6.56/6.64	s/s		
	Cp*	120.7					
		120.8					
		120.9					
	120.9						

 <p style="text-align: center;">4-12</p>	<p>Not recorded</p>	<table border="1"> <tr><td>1</td><td>7.77</td><td>d</td><td>2H</td><td>7.5</td></tr> <tr><td>2</td><td>7.31</td><td>t</td><td>2H</td><td>7.5</td></tr> <tr><td>3</td><td>7.93</td><td>d</td><td>2H</td><td>7.5</td></tr> <tr><td>6</td><td>7.94</td><td>d</td><td>2H</td><td>7.5</td></tr> <tr><td>7</td><td>7.32</td><td>t</td><td>2H</td><td>7.5/6.2</td></tr> <tr><td>8</td><td>7.39</td><td>t</td><td>2H</td><td>6.2/8.0</td></tr> <tr><td>9</td><td>7.59</td><td>d</td><td>2H</td><td>8.0</td></tr> <tr><td>1'/4'</td><td>3.73</td><td>t</td><td>4H</td><td>7.5</td></tr> <tr><td>2'/3'</td><td>1.82-1.84</td><td>m</td><td>4H</td><td>-</td></tr> <tr><td>Cp</td><td>6.01/6.08</td><td>s</td><td>10H</td><td></td></tr> <tr><td>Cp*</td><td>5.87/5.87</td><td>s/s</td><td>8H</td><td></td></tr> <tr><td></td><td>5.88/6.07</td><td>s/s</td><td></td><td></td></tr> </table>	1	7.77	d	2H	7.5	2	7.31	t	2H	7.5	3	7.93	d	2H	7.5	6	7.94	d	2H	7.5	7	7.32	t	2H	7.5/6.2	8	7.39	t	2H	6.2/8.0	9	7.59	d	2H	8.0	1'/4'	3.73	t	4H	7.5	2'/3'	1.82-1.84	m	4H	-	Cp	6.01/6.08	s	10H		Cp*	5.87/5.87	s/s	8H			5.88/6.07	s/s		
1	7.77	d	2H	7.5																																																										
2	7.31	t	2H	7.5																																																										
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7	7.32	t	2H	7.5/6.2																																																										
8	7.39	t	2H	6.2/8.0																																																										
9	7.59	d	2H	8.0																																																										
1'/4'	3.73	t	4H	7.5																																																										
2'/3'	1.82-1.84	m	4H	-																																																										
Cp	6.01/6.08	s	10H																																																											
Cp*	5.87/5.87	s/s	8H																																																											
	5.88/6.07	s/s																																																												

^a Recorded in CDCl₃ ^b no = not observed

A 2D-COSY experiment was used to confirm the assignments of the peaks for **4-01**. In complexes **4-02** and **4-03** two Cp peaks were observed. The ¹H NMR spectrum for **4-04** had very poor resolution and no definite assignments could be made. Overlapping of resonances in the ¹H NMR spectrum of **4-05** complicated assignments (all the peaks are stacked around 4.49 ppm) and unambiguous assignments could not be made. The data was omitted from Table 4.4, as well as the spectral data of **4-06** and **4-08** as no spectrum could be recorded due to very poor solubility. In **4-07** the unsubstituted cyclopentadienyl rings are seen as singlets and the substituted Cp's as multiplets. The intensity ratios between the unsubstituted Cp and substituted Cp's are, as expected, 1:1. The chemical shift values of the C₃H₆-link between the Cp and amine portions of the bridging ligand are downfield compared to **L4-07**. This is ascribed to the electron withdrawing effect of the titanium atoms once they are coordinated to the Cp rings.

In complex **4-09** all the chemical shifts for the substituted Cp ring were resolved, but the CH₂ protons overlap. In **4-10** the cyclopentadienyl rings of the bridging ligand are electronically not equivalent due to the presence of the dibenzofuranyl ligand on one of the titanium centres. In Table 4.4 the substituted cyclopentadienyl rings are indicated as Cp*. Complexes **4-11** and **4-12** also display electronically non-equivalent Cp rings, the latter being ascribed to restricted rotation because of the bulkiness of two dibenzofuranyl ligands in **4-12**. Assignments of resonances for complex **4-12** were achieved by performing a 2D-COSY experiment.

¹³C NMR spectroscopy

A 2D-HETCOR experiment was used to confirm assignments to chemical shift values of the peaks for **L4-07**. In **L4-06** two peaks are observed where H4 is expected and it is not clear which one is correct,

so both values were listed. No ^{13}C NMR was obtained for **4-02** - **4-08** due to poor solubility in deuterated solvents.

The substituted rings in complex **4-09** display, as expected, two resonances. In **4-10** the peaks for most of the quaternary carbons are not observed. In **4-11** the quaternary peaks were not observed. Excessive decomposition of **4-12** during the recording of the spectrum gave spectral data that was not useful due to the bad resolution of the spectrum. Complex **4-11** displayed the expected multiple signals for the Cp rings.

4.4 Conclusions

The screening and preclinical testing of the complexes in this chapter was not included in the study at this point of time. The first priority was to establish sound methods of synthesis of binuclear compounds with specific features that will have properties suitable for handling during preclinical testing. These properties include high stability in solution, fixed compositions, favorable geometrical features and high solubility. Many problems were identified with regard to the synthesis of binuclear complexes and the foundations have now been laid for sound and successful syntheses of bi- and trinuclear complexes of platinum and titanium. The binuclear complexes of choice are shown in Figure 4.8 and represent an example of a titanium-platinum and a titanium-titanium combination. Whereas a method is available to synthesize complexes of the second type, this problem has not yet been solved for the mixed Ti-Pt dinuclear complex. Deprotonation of **L4-08** and subsequent reactions, first with TiCpCl_3 , and thereafter with $[\text{Pt}(\text{COD})\text{Cl}_2]$ seems like the correct approach. A further aspect to be considered before testing the products is the appropriate length of the connecting carbon chains between the two ligating functions. This will also have implications on the procedures during the synthesis. Binuclear complexes are more stable in solution compared to trinuclear complexes which makes the use of **4-07** as an ideal precursor questionable.

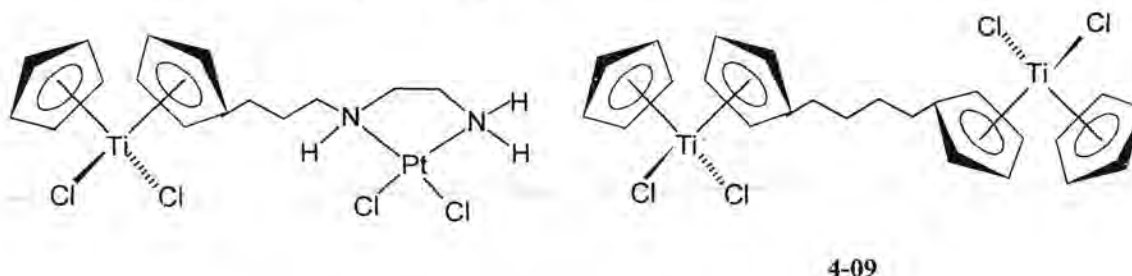


Figure 4.8 Model binuclear complexes chosen for future investigation.