

Novel Metallocene Anticancer Drug

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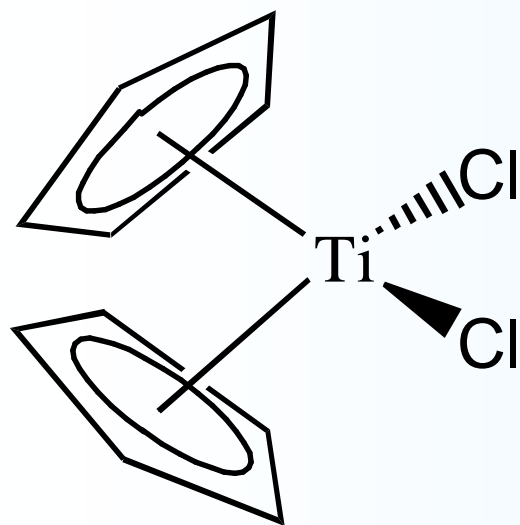
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€€€ CSCB, UCD, IRCSET, COST, CESAR

100 Years of Chemotherapy

The Nobel Laureate Dr. Paul Ehrlich in **1908**: We must search for magic bullets. We must learn to aim with chemical substances!”



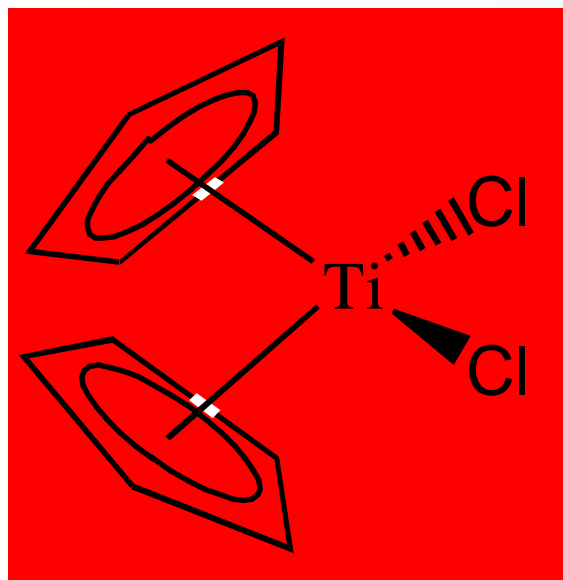
- First synthesis in **1954** by the Nobel Laureate Ernst Otto Fischer in München.
- Identified as a possible anticancer drug in **1979** by Petra Köpf-Maier in Berlin.
- Low cytotoxicity in vitro, but high efficacy in animal models (**1980s**).
- Phase I/II clinical trials against metastatic breast and renal-cell cancer (**1990s**).

Bioorganometallic Fulvene-Derived Titanocene Anticancer Drugs

K. Strohfeldt, M. Tacke, *Chem. Soc. Rev.*, **2008**, 37, 1174-1187.

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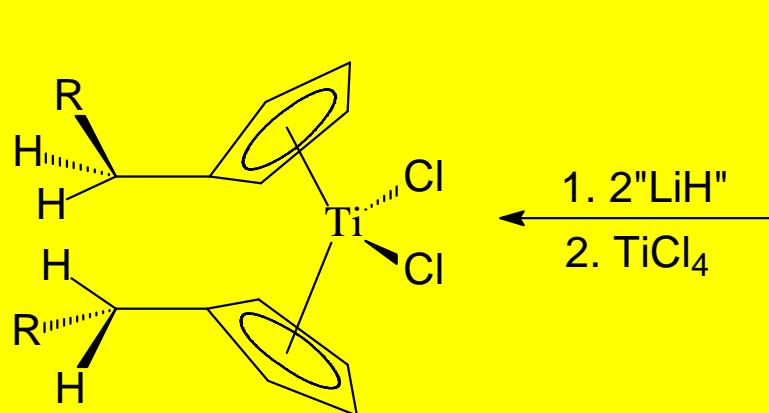
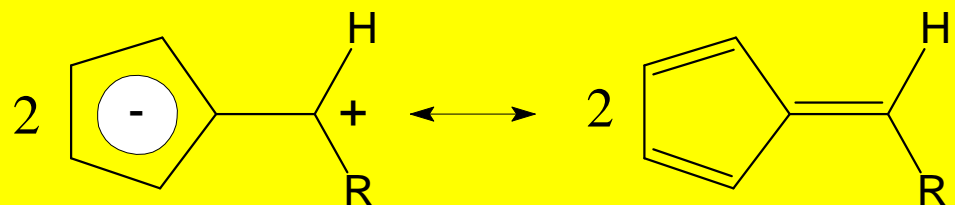
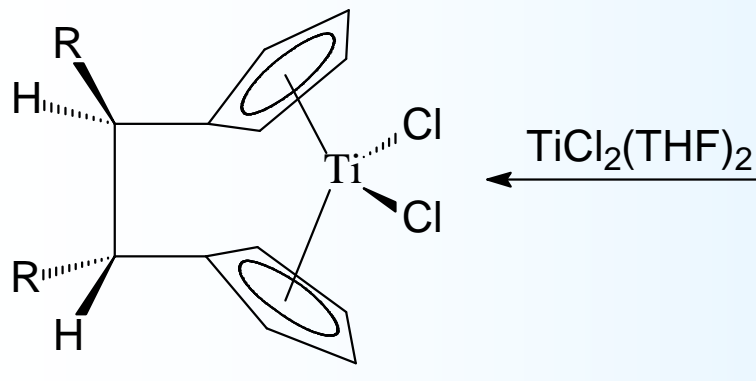
But the compound failed finally!

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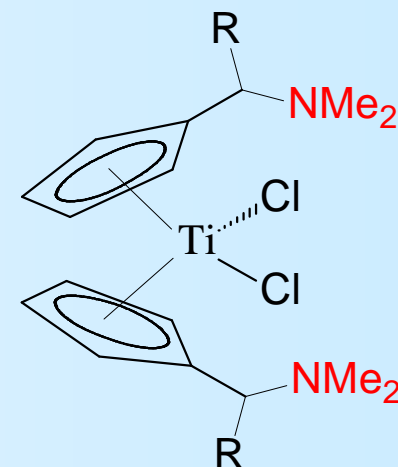
Synthesis of Titanocenes from Fulvenes

REDUCTIVE DIMERISATION



HYDRIDOLITHIATION

R = NMe₂

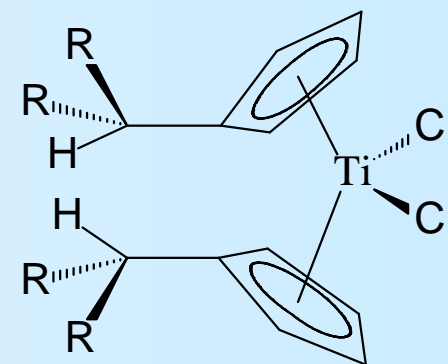


1. 2RLi

2. TiCl₄

CARBOLITHIATION

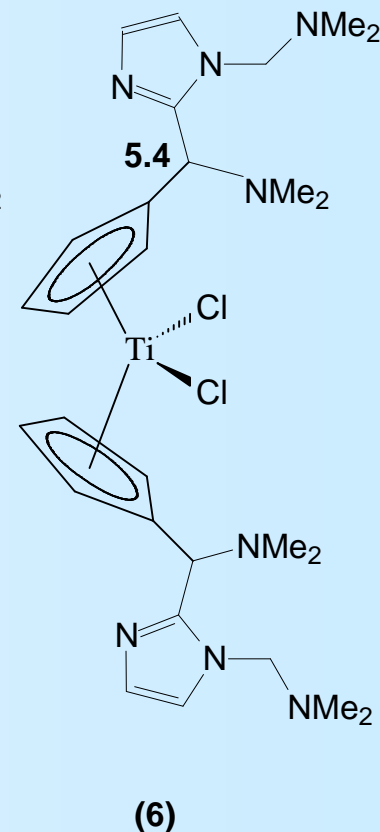
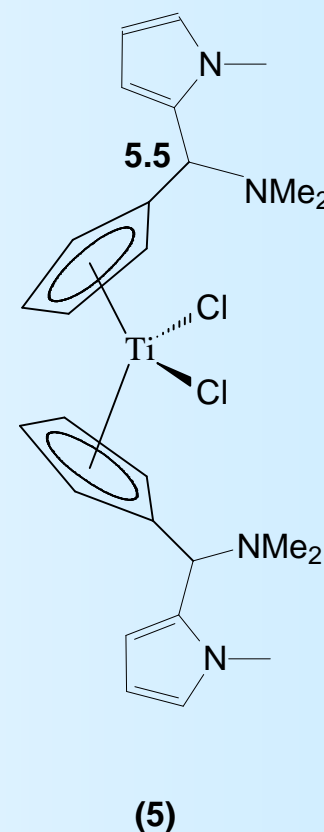
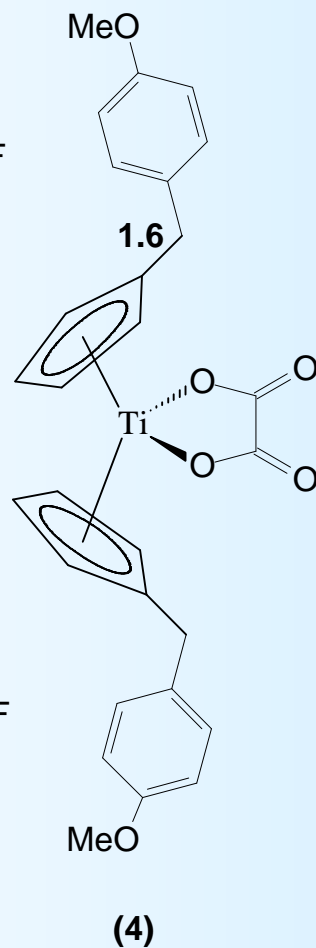
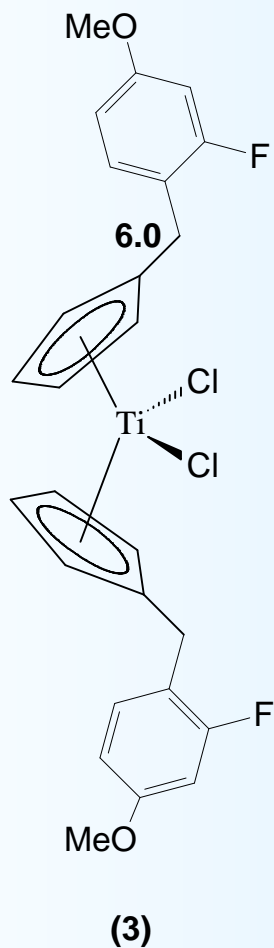
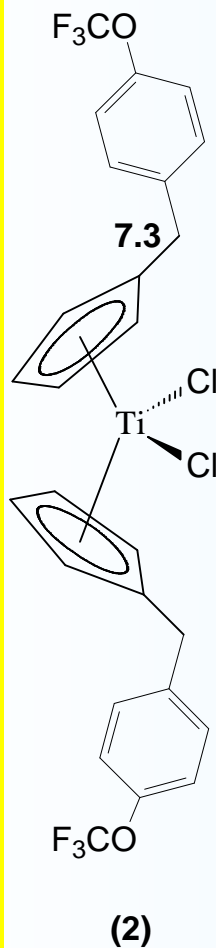
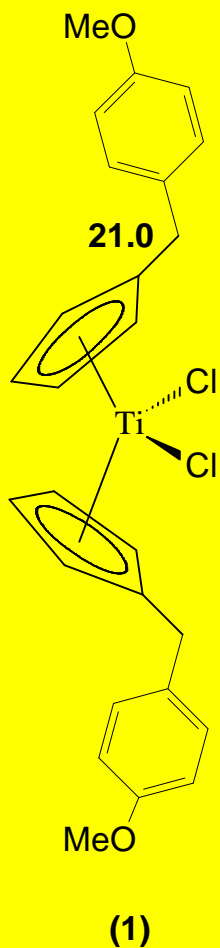
R = aryl



Hydridolithiation of Fulvenes

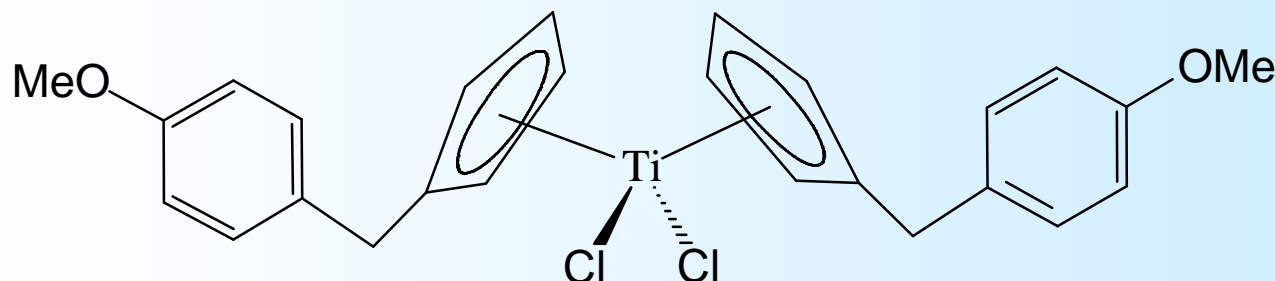
Pig kidney „carcinoma“ cell line (LLC-PK): IC50 [μM]

Titanocene Y



N. Sweeney, M. Tacke et al., *J. Organomet. Chem.* **2005**, 690, 4537.

Biological Results – Titanocene Y



- Titanocene Y induces apoptosis (G2/M arrest) in HeLa, A431 and PC3 cells in caspase-dependent and -independent pathways.
- Titanocene Y breaks Pt-resistance in human colon cancer cells, activates the immune system and does not induce myelosuppression.
- Titanocene Y is a cytotoxic and anti-angiogenic drug candidate targeting renal-cell cancer and other solid tumors.

M. Queiroz, M. Valadares, M. Tacke et al., Eur. J. Pharmacol., 2006, 534, 264.

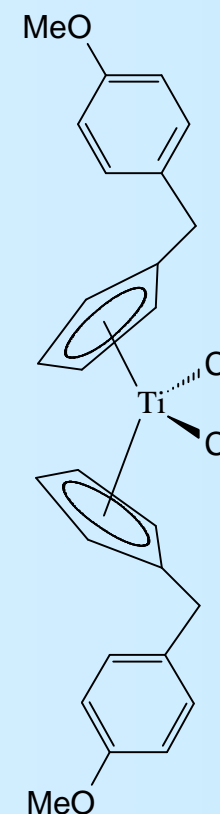
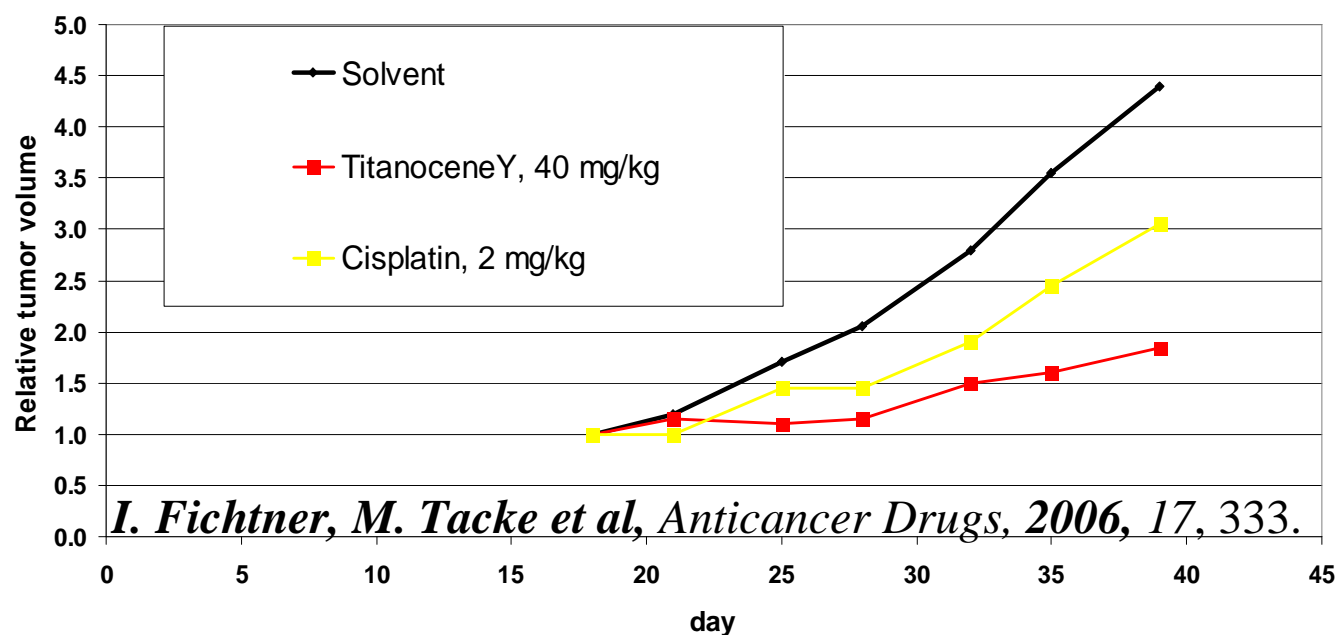
W. Watson, M. Tacke et al., Apoptosis, 2006, 11, 1205.

M. McGee, W. Watson, M. Tacke et al., Brit. J. Cancer, 2007, 97, 1234.

R. Hilger, M. Tacke et al., Toxicology in Vitro, 2009, in preparation.

Xenograft Mouse Models

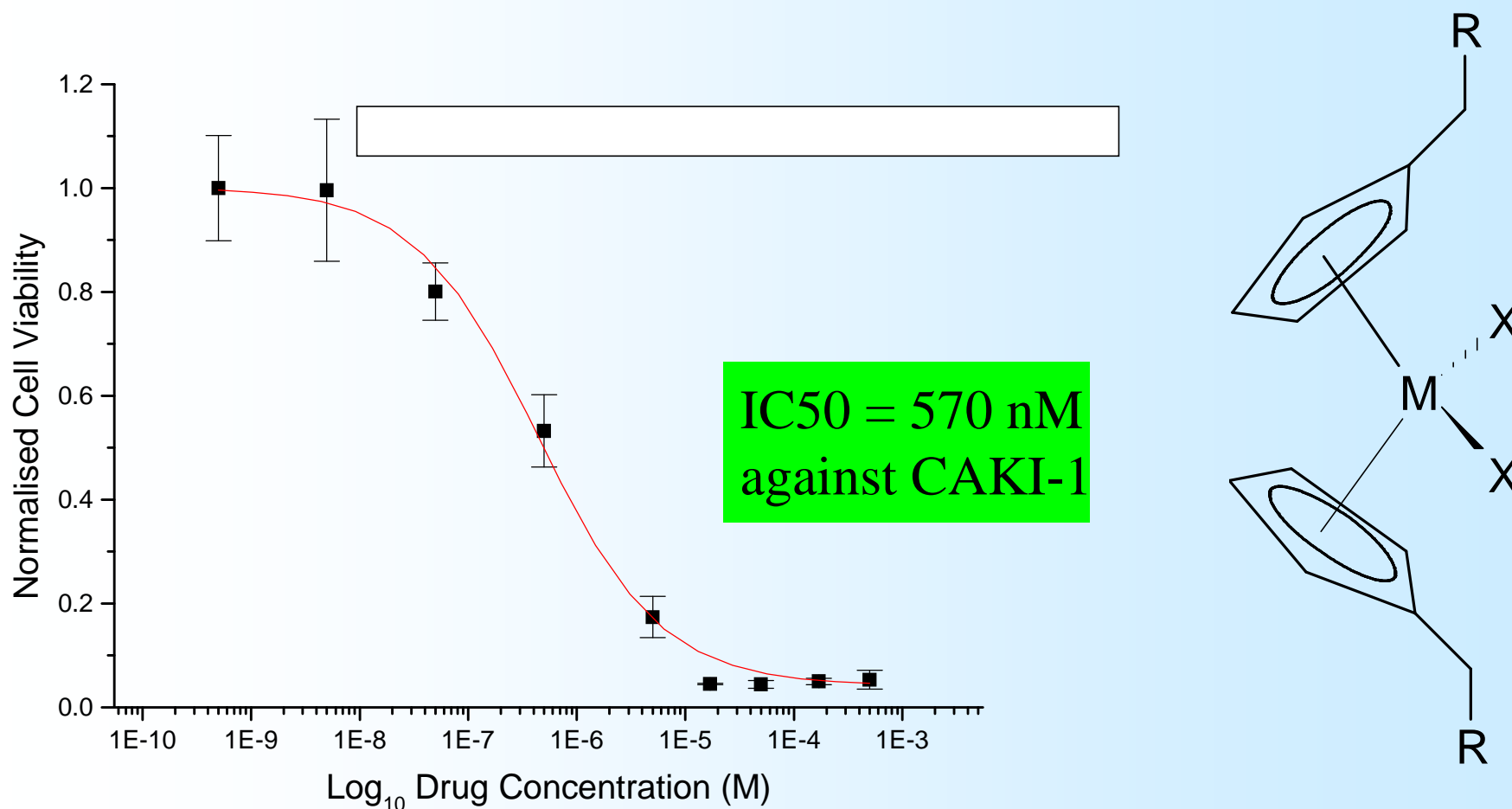
Activity of Titanocene Y Against Human Renal Clear Cell Carcinoma Caki-1



The animals were inoculated with the tumour (1×10^7 cells/animal) and treated for 5 consecutive days with doses of 40.0 mg/kg of Titanocene Y or 2 mg/kg of cis-platin.

Outlook - Quo Vadis Metallocenum?

The best metallocene shows now nanomolar activity!



Next Steps

- ⌘ Synthesis of one (or more) patentable metallocene aiming to deliver the first chemotherapy against renal-cell cancer.
- ⌘ Formulation of this final compound and its testing in xenograft mouse models to evaluate its efficacy, pharmacology and toxicity .
- ⌘ GMP synthesis and formulation; long-term toxicity testing against in two animal species.
- ⌘ Phase I clinical testing involving advanced renal-cell cancer patients.

We are searching for a small, medium or big pharma company, which helps us to take these next steps.

Please send inquiries to matthias.tacke@ucd.ie