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Design, Synthesis, and Biological Evaluation of Sila-Derivatives of Vitamin D with Application in Breast Cancer Therapy

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INTRODUCTION & AIM

Despite significant advancements in **breast cancer** therapeutic strategies, **current treatments**, particularly for triple-negative breast cancer (TNBC), a highly metastatic subtype associated with poor prognosis, remain **insufficient**. The vitamin D receptor (**VDR**) is increasingly recognised as a **promising** target for hyperproliferative diseases. However, the clinical use of its natural ligand, **calcitriol** (the active form of vitamin D_3, $1,25D_3$), is limited by **severe hypercalcaemic effects**. To overcome this limitation, the **first** reported **silicon-containing derivatives** of calcitriol were **designed**, in which a silicon atom replaces the carbon at the C25 side chain. This modification is intended to retain VDR-mediated **anticancer activity** while reducing the calcaemic effects. In this study, the six novel derivatives (**Sila-1** to **Sila-6**, Figure 1) were synthesised and evaluated for their anticancer and VDR-mediated activity in breast cancer models.

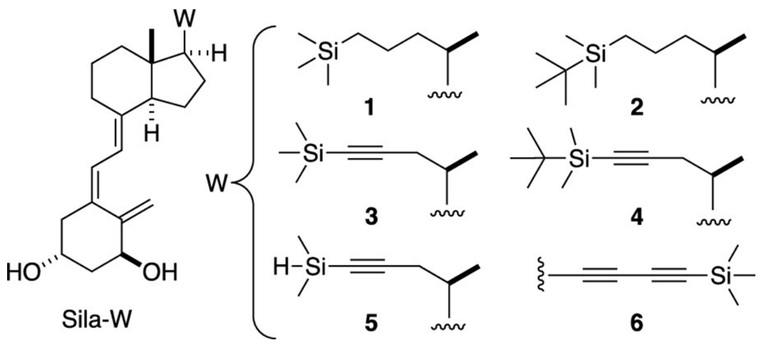
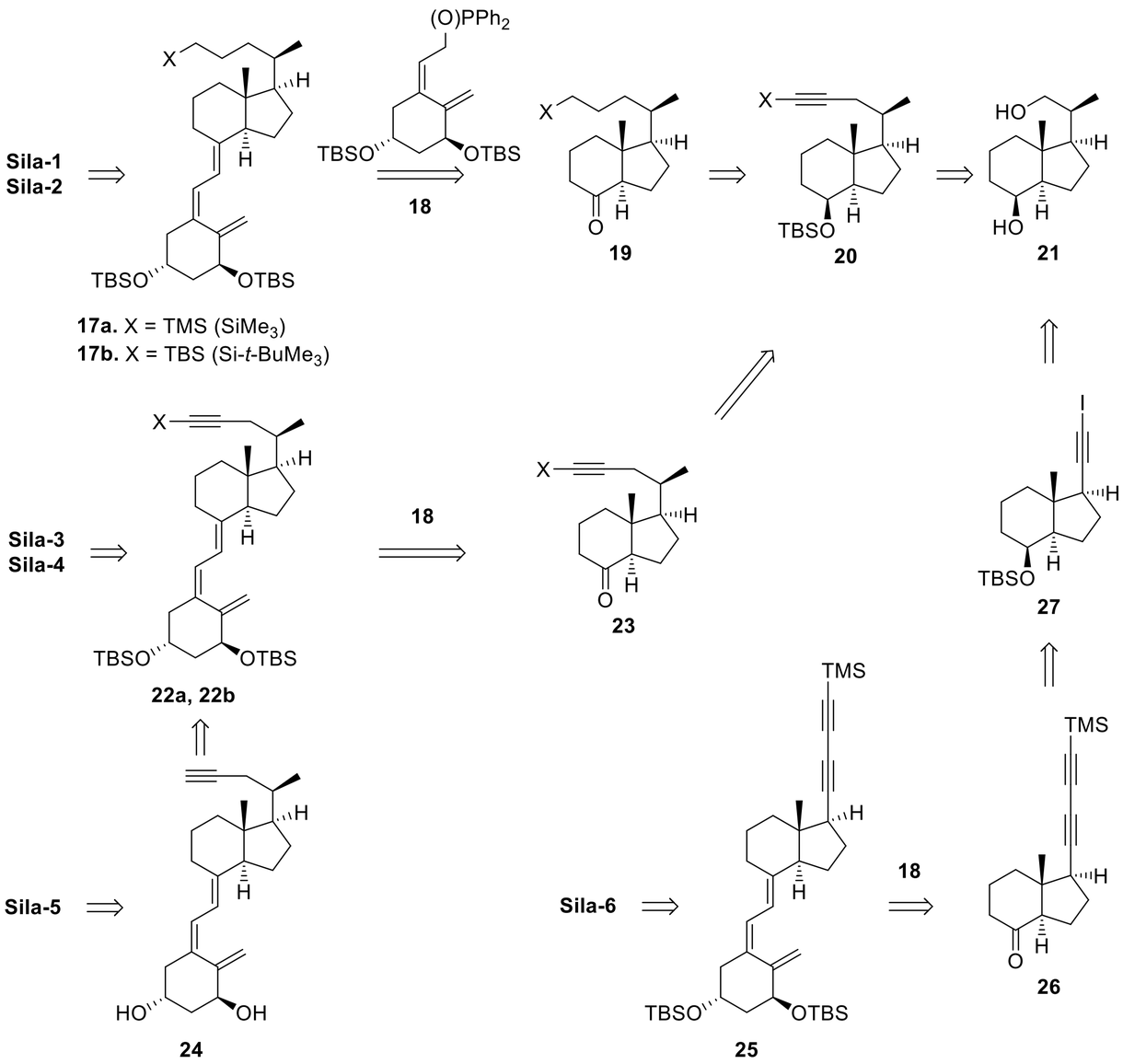


Figure 1. Structure of the six sila-vitamin D_3 derivatives **Sila-W**.

METHOD

The **Sila-W** derivatives (**Sila-1** to **Sila-6**) were designed by introducing a silicon atom at the C25 side chain and synthesised via a Wittig-Horner approach from the Inhoffen-Lythgoe diol, following the retrosynthetic route shown in Scheme 1.



Scheme 1. Retrosynthetic route for the six sila-vitamin D_3 derivatives **Sila-W**.

Their structures in complex with the VDR ligand-binding domain were determined by X-ray crystallography. Biological evaluation included VDR binding and transcriptional activity, evaluation of calcaemic effects *in vivo*, anticancer activity in MCF-7 and MDA-MB-231 breast cancer cells, and analysis of potential synergistic effects with paclitaxel.

RESULTS & DISCUSSION

A competitive binding assay demonstrated a similar affinity of the **Sila-W** derivatives and $1,25D_3$ to VDR (10^{-9} M), except **Sila-1** and **Sila-3** (Figure 2).

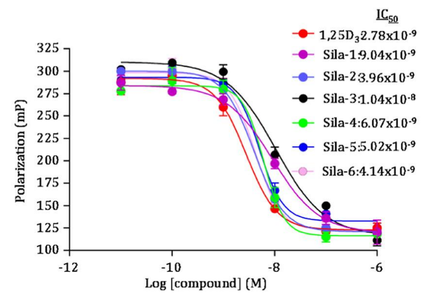


Figure 2. Competitive binding assay of $1,25D_3$ and **Sila-W** analogues to the human VDR. Dose response curves (10^{-11} to 10^{-6} M) were used to calculate the IC_{50} values.

$1,25D_3$ and **Sila-W** derivatives increased mRNA expression of the vitamin D target gene *CYP24A1* in MCF-7 cells, with **Sila-1** and **Sila-4** showing comparable results to $1,25D_3$ (Figure 3). Except for **Sila-2** and **Sila-6**, the derivatives also induced the expression of other vitamin D target genes, including *E-cadherin* in MCF-7 cells (Figure 3).

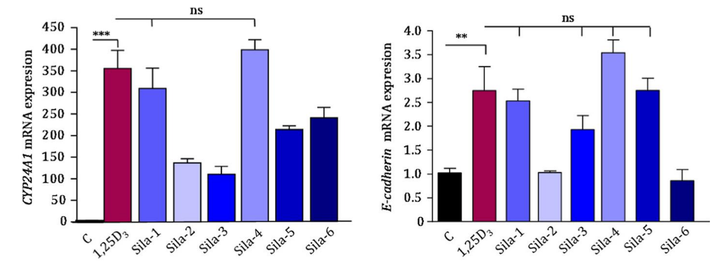


Figure 3. Evaluation of *CYP24A1* (left) and E-cadherin (right) mRNA levels by real-time PCR in MCF-7 cells treated for 48 h with $1,25D_3$ and the **Sila-W** derivatives at 10^{-7} M (ethanol was used as control, C).

In vivo, the **Sila-W** derivatives did not significantly raise serum calcium levels, in contrast to $1,25D_3$ (Figure 4).

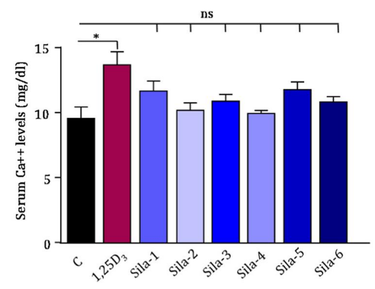


Figure 4. Serum calcium levels in mice treated every other day for 21 days with sesame oil (as control) and 0.5 µg/kg of $1,25D_3$ and **Sila-W** derivatives. Data are expressed as mean ± SD. ns = not significant, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

Lastly, except for **Sila-5**, all **Sila-W** derivatives significantly reduced MDA-MB-231 cell proliferation in both 2D cultures and spheroids. Additionally, co-treatment with **Sila 3-6** and paclitaxel (used in TNBC treatment) further decreased proliferation (Figure 5).

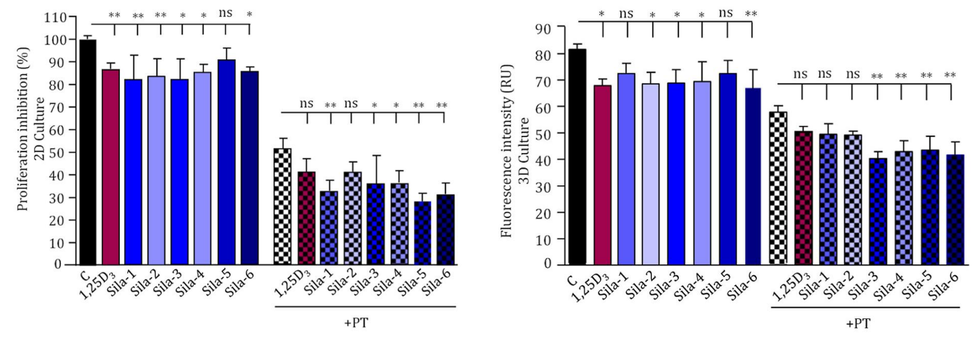


Figure 5. Effects of **Sila-W** derivatives (10^{-7} M) on breast cancer cell proliferation. MDA-MB-231 cells in 2D cultures (left) were treated with $1,25D_3$ or **Sila-W** derivatives, with or without paclitaxel (2 nM), for 2 days, and ethanol (as a control). MDA-MB-231 spheroids (right) were treated on days 6 and 8 under the same conditions. Data are expressed as mean ± SD. ns = not significant, $*p < 0.05$, $**p < 0.01$.

CONCLUSION

The results provide a framework for the development of silicon-modified secosteroidal VDR ligands with improved safety and therapeutic potential, highlighting new avenues for applications in both metabolic and cancer-related contexts.

REFERENCES

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