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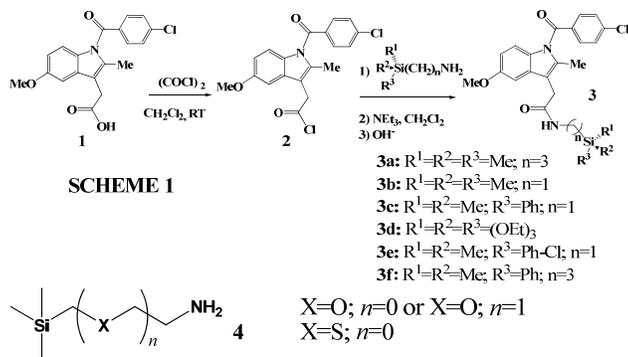
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## INTRODUCTION

Drug repurposing offers a rich alternative to diversifying the chemical scaffolds available to target cancer (1). A fundamental advantage of this approach is that the parent chemical agents that are derivatized are carefully selected from a library of compounds that have already been assessed for safety and use in complex stages of development. Moreover, many of these drugs have been modified to yield more bio-active compounds. Further introduction of silicon into these derivatives offers a new facet to drug repurposing that exploits the differences in atomic size, electronegativity, and lipophilicity between carbon and silicon to produce more efficient and selective analogs (2). Differences in atomic size change the bond lengths and angles in these sila drug derivatives, thus modifying their selectivity and the rate at which they are metabolized. The slightly different electronegativity of silicon in relation to carbon may affect bonding character (3). Lastly, silicon is more lipophilic than carbon which is anticipated to improve the half-life of these sila-derivatives and enhance tissue distribution as well as gastrointestinal absorption (1,2). Such advantages have been used to produce improved sila-indomethacin amide derivatives of type **3** that display increased carcinostatic selectivity and decreased toxicity (4). These results have been exploited to tune lipophilicity in these sila-indomethacin compounds.

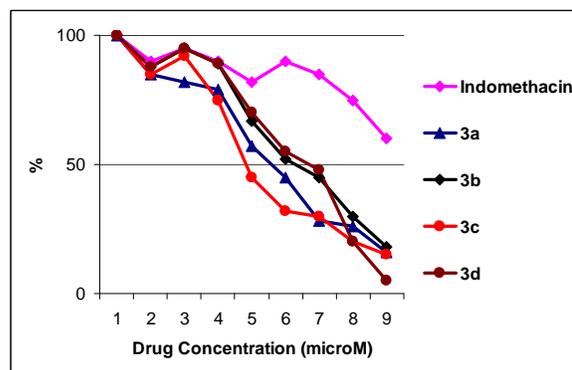
## EXPERIMENTAL

Details about the synthesis of silicon-containing indomethacin amide derivatives can be found in (4) and is briefly outlined in Scheme 1. In short, a two step protocol was adopted in which indomethacin acid chloride **2** was generated from the reaction of indomethacin, **1** with oxalyl chloride. The required aminosilane was then added to the acid chloride to produce variously substituted silicon-containing compounds **3**. Lipophilicity was tuned by introducing an oxygen moiety into the amino functional silanes to produce amino silanes of type **4**, which can then be reacted with **2**. The synthesis of further derivatives other than **4a** is in process.



## RESULTS

The synthesis and *in vitro* pharmacological and cancer cell growth inhibitory studies of a library of silicon-containing compounds based on the indomethacin scaffold are now reported. Amidation of the indomethacin carboxylate group using amino-functional silanes generates a series of novel lipophilic derivatives of indomethacin of type **3**. The pharmacological activity of these compounds tested against human recombinant cyclooxygenase-1 and 2 demonstrated that the silicon-containing amides of indomethacin demonstrated *in vitro* growth inhibitory activity against human MiaPaCa-2 pancreatic carcinoma cells at low  $\mu\text{M}$  concentrations, as shown in Fig 1. The **3a** and **3c** derivatives exhibited the most potent *in vitro* antiproliferative activity, with IC<sub>50</sub> 6.0  $\mu\text{M}$ , compared to unmodified indomethacin having an IC<sub>50</sub> > 100  $\mu\text{M}$ . However, these derivatives are rather lipophilic, as demonstrated by their compromised solubility in initial formulations. A synthetic methodology incorporating an oxygen moiety in the amino-functional silane has also been developed and used to generate a second generation of indomethacin sila-amide derivatives (5).



**Fig 1:** The inhibitory activity of sila amide indomethacin derivatives on human MiaPaCa-2 pancreatic cancer cell line.

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