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Design and synthesis of novel silicon-containing small molecule peptidomimetics with nanomolar anticancer activities

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Introduction

Cancer is a major health problem around the globe. Each year, tens of millions of people are diagnosed with cancer and more than half of the patients eventually die from it. In 2018, 1,735,350 new cancer cases and 609,640 cancer deaths are projected to occur in the United States. Though there has been a steady increase in survival for most cancers, the death rate remains unacceptable for certain cancers, e.g. lung (26%), prostate (9%), colon (8%), pancreas (7%) and breast (14%). In this study, we support the concept that the ideal drug should have a multi-targeted mechanism that affects several proteins or events that contribute to the etiology, pathogenesis and progression of disease. In addition, multi-pathway targeting is one of the strategies to overcome chemo-resistance.

Results and Discussion

To design our novel anticancer drugs with unique structural properties, we have taken an innovative and nontraditional approach where we combine pharmacophoric components to create new and highly potent small peptidomimetic molecules with a simple three component A-B-C structure where each pharmacophore is known to have anticancer properties on its own or when incorporated into a multicomponent small molecule drug. Recently, we developed a new generation of this simple 3-componentA-B-C structure, a highly potent anticancer compoundGH501 [1] (Figure 1). In our new compounds,GH1501 - GH1504, the A-component was further modified to contain a silicon atom [2] (Figure 1). Using silicon over carbon has many advantages: a) compounds are more lipophilic than their carbon equivalent b) silicon can improve compound permeability c) silicon can lower compound toxicity d) silicon can change receptor selectivity e) silicon can enhance anticancer activity of compounds f) silicon compounds can treat drug-resistant tumors. The "A"-component 4-[3-(trimethylsilyl)propoxy]benzoic acid (m.p.: 172-173 °C, crystallized from ACN) and 4-[butyl-dimethylsilyl)methoxy]benzoic acid (m.p.: 57-59 °C) were synthesized *via* a modified Hegyes method using 4-hydroxybenzoic acid methylester sodium salt. [3]. Interestingly, Zaltariov *et al.* [4] claimed that they synthesized 4-[3-(trimethylsilyl)propoxy]benzoic acid for the first time. Also, their synthetic method provided only the 3-(trimethylsilyl)propyl 4-hydroxybenzoate (m.p.: 114-117 °C) in our hands. The constituent at position A of our A-B-C structures is dependent on the composition of the B-component. When the B-component is 4-(2,6-dichloro-benzyloxy)-phenyl the best silyl-alk oxy-benzoyl derivative is GH1501 (compare GH1501 and GH1503, Table 1). When the B-component is biphenyl the best silyl-alkoxy-benzoyl derivative is GH1504 (compare GH1504 and GH1502, Table 1).

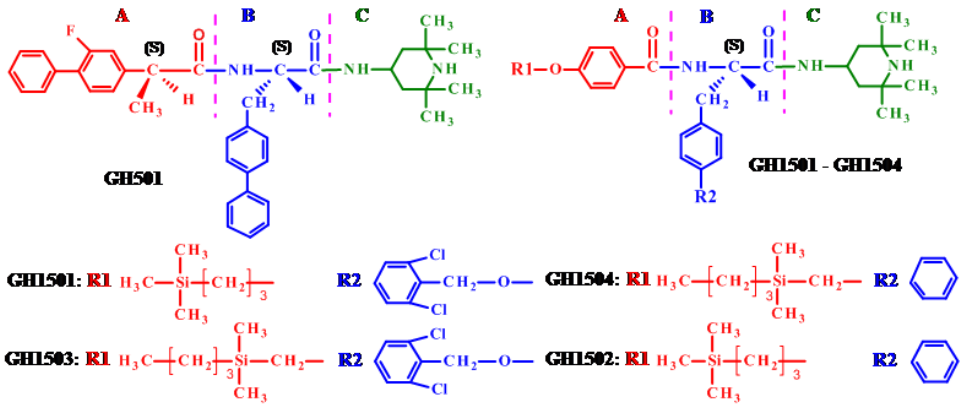

Figure 1: Structures of GH501 and GH1501 - GH1504

Table 1: Results of the NCI human colon cancer cell line. GI50: concentration in nanomolar that inhibits cancer growth by 50% Average: average of GI50 value for each compound Pink highlight is a GI50 value less than 500 nM Yellow highlight is the average GI50 value less than 500 nM

Cell Line	*GI_{50} (nanomolar) of selected anticancer compounds*				
Colon Cancer	GH501	GH1501	GH1503	GH1504	GH1502
COLO 205	184	216	342	215	392
HCC-2998	418	1050	1070	1110	1560
HCT-15	1440	357	323	309	437
HCT-116	145	206	319	218	297
HT29	178	263	342	315	430
KM12	461	363	382	376	413
SW-620	294	313	318	316	392
Average	446	395	442	408	560

GH501, GH1501-GH1504 were made using Boc-chemistry

GI50: concentration in nanomolar that inhibits cancer growth by 50% Average: average of GI50 value for each compound Pink highlight is a GI50 value less than 500 nM Yellow highlight is the average GI50 value less than 500 nM.

The diversity of the A-component can be Fluoro-biphenyl (GH501), silyl-alkoxy-benzoyl derivative (GH1501 or GH1504) depending on the "B"-component. The organo-silicon compounds showed cancer-type specific anticancer activity for colon cancer.

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