Rima D Alharthy et al., Organic Chem Curr Res 2017, 6:1(Suppl)
http://dx.doi.org/10.4172/2161-0401.C1.017

Synthesis and biological evaluation of hybrid acridine-HSP90 ligand conjugates as telomerase inhibitors

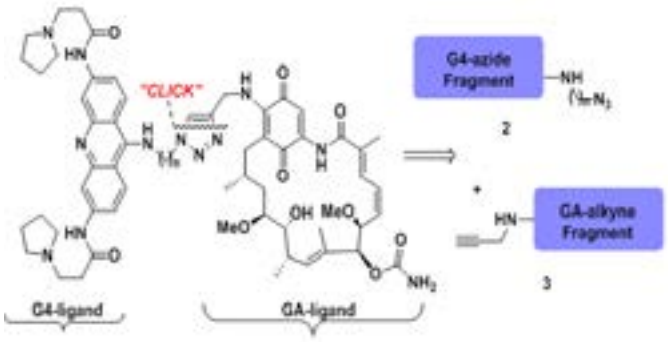
Rima D Alharthy[1], **S Roe**[2], **M Gunaratnam**[2], **C Spiteri**[2], **P Sharma**[2], **S Neidle**[3] and **J E Moses**[2]
[1]King Abdulaziz University, KSA
[2]University of Nottingham, UK
[3]University College London, UK

Statement of the Problem: Telomerase has emerged as a promising therapeutic target for novel anticancer therapy and several strategies have been formulated for down-regulating telomerase function. G-quadruplex DNA structures formed within the telomeric repeat sequence have been shown to inhibit telomerase activity, and ligands that stabilize these complexes are effective inhibitors of telomerase and exert growth inhibitory effects on tumor cells *in vitro* and *in vivo*. The bifunctional mode of this complex represents an intriguing example of ligand design and suggests new possibilities for achieving complementary biological activity in this area. We report here on the synthetic strategy and on preliminary biological evaluation of representative conjugates.

Methodology & Theoretical Orientation: Retrosynthetically, the bifunctional ligand type-1 could be achieved using the CuAAC 'click' reaction of the corresponding G4-azide type fragment 3 with the alkyne-GA derivative 2 (Scheme 1). We envisaged that this approach would allow the synthesis, for biological screening, of a selection of hybrid ligands of varying linker lengths.

Findings: The synthesis and biological evaluation of a series of bifunctional acridine-HSP90 inhibitor ligands as telomerase inhibitors is described. Four hybrid acridine-HSP90 inhibitor conjugates were prepared using a click-chemistry approach, and subsequently shown to display comparable results to the established telomerase inhibitor BRACO-19 in the TRAP-LIG telomerase assay. All four adducts are potent inhibitors of cell growth as measured by their IC_{50} values (the concentration required to produce 50% growth inhibition), with some conjugates showing sub-μM activity in several cell lines, notably the non-small cell lung cancer line A549. The conjugates also demonstrated significant cytotoxicity against a number of cancer cell lines, in the sub μM range.

Conclusion & Significance: Overall the results is supportive of the HSP90 inhibitor conjugates being stable in cells and active as conjugates, Further studies will be needed to determine details of their mode of action.



General Acridine-HSO90 ligand conjugate 1 (G4-GA)

Biography

Rima D Alharthy has her expertise as Organic Synthetic Chemist. During her Post-doctoral research, she was working on the synthesis of attractive bioactive compounds and consequently evaluating their activity. This includes the synthesis of heterocycles such as Pyrido[2,3-b]pyrazines, polyphenols, pyrazolo pyrimidine scaffolds and hybrid acridine-HSP90 ligand conjugates. She also focused on developing chemistry to design antisense therapies such as Morpholinos.

iaaalharte@kau.edu.sa