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BOOSTING THE ANTI-CANCER POTENTIAL OF COOH-BEARING PAK1-BLOCKERS BY INCREASING THEIR CELL-PERMEABILITY VIA CLICK CHEMITRY

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PAK1 is the major oncogenic/ageing Ser/Thr kinase that is activated by p21 (RAC/CDC42) and several other signal transducers such as PIX, three distinct Tyr-kinases (ETK, FYN and JAK2) and CK2 (casein kinase 2) in cells. PAK1 is essential for robust growth of almost all solid tumors which require PAK1-dependent angiogenesis. Besides this, kinase is required for many other diseases/disorders such as NF (neurofibromatosis), AD (Alzheimer's disease), PD (Parkinson's disease), depression, epilepsy, autism, schizophrenia, a variety of infectious and inflammatory diseases, diabetes (type 2), obesity, and even hyperpigmentation. Thus, the potential maket value of PAK1-blockers is enourmous. However, so far only a few PAK1-blockers are available on the maket, such as FK228, Gleevec, and the old antibiotic called minocycline (MC) but with a very limited FDA approval for cancer therapy. Thus, for a last decade, we have taken a great effort for identifying PAK1-blockers among natural or old (generic) products as well as the robust potentiation of their anti-cancer/anti-PAK1 activity mainly by increasing their cell-permeability. Here in this lecture, we shall introduce a few successful examples including 1,2,3-triazolyl esters of natural or generic COOH-bearing PAK1-blockers such as UA (ursolic acid), ARC (artepillin C), CA (caffeic acid), Ketorolac and MPA (mycophenolic acid), in which esterization by a simple reaction called CC (Click Chemistry) boosts their anti-cancer potential by 100-5000 times, depending on target cancer cell lines and the final chemical products. One of them called "15K" (ketorolac ester) has been proven to be among the most potent PAK1-blockers, suppressing the embryonic angiogenesis *in ovo* (fertilized chicken eggs) IC_{50} around 1 nmol/egg, and extending significantly the healthy lifespan of *C. elegans* by 30% at 50 nM, strongly suggesting that they could cure most of solid tumors without any severe side effect.

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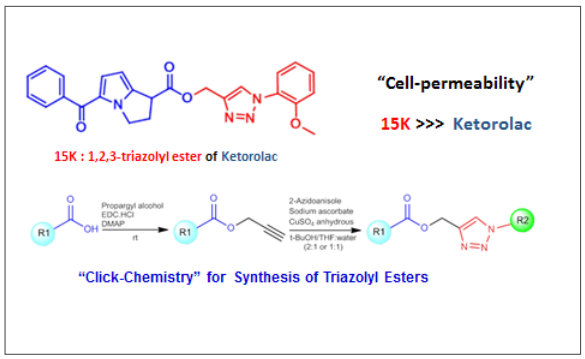

Figure: Click- Chemistry for Synthesis of Triazolyl Esters