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Development of Potent Inhibitors of the DNA-Dependent Protein Kinase

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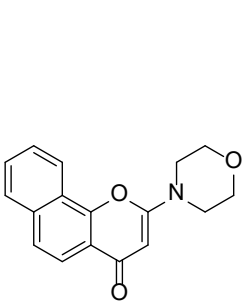
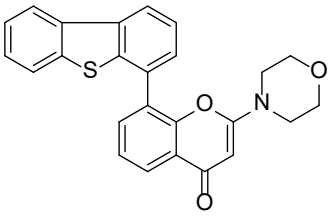
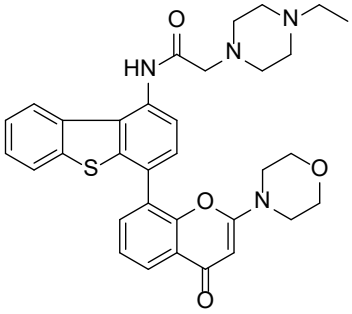
The cellular response to DNA double-strand break (DSB) formation is an essential component of normal cell survival following exposure to DNA-damaging chemicals and ionising radiation. The serine/threonine kinase DNA-dependent protein kinase (DNA-PK) plays an important role in DNA DSB repair *via* the non-homologous end-joining (NHEJ) pathway. DNA-PK inhibitors may therefore, be useful as agents to improve the activity of radio and chemo-therapy in the treatment of cancer. Identification of the lead benzo[*h*]chromen-4-one DNA-PK inhibitor NU7026 (IC_{50} = 0.23 uM), guided the subsequent development of the potent and selective ATP-competitive chromenone NU7441 (DNA-PK IC_{50} = 30 nm). Although proof of principle studies with NU7441 confirmed promising activity *in vitro* as a chemo and radio-potentiator in a range of human tumour cell lines, further biological studies with NU7441 were hampered by sub-optimal pharmaceutical properties.



NU7026



NU7441



KU-0060648

In collaboration with Astra Zeneca, structure activity relationship studies were conducted in conjunction with homology modelling. This approach predicted several positions on the pendant dibenzothiophen-4-yl substituent of NU7441 as tolerant to substitution without detriment to DNA-PK inhibitory activity. We will describe the rational design and syntheses of analogues that optimised the physicochemical and pharmacokinetic properties of NU7441. We identified compounds that combined potent DNA-PK inhibition with good solubility (20-40 mg/mL as acid salts), without compromising cellular activity. Prominent amongst these derivatives is KU-0060648 (DNA-PK IC_{50} = 8.6 nm), which exhibits 20-1000 fold selectivity for DNA-PK over related PIKK enzymes and PI3K family members. The discovery and further development of KU-0060648 will be described, including *in vivo* efficacy and combination studies.

Biography:

Celine Cano is Assistant Professor (Reader) in Medicinal Chemistry at Newcastle University. She graduated from the University of Poitiers, receiving her Ph.D. in 2004 for her work on the synthesis of biomolecules by 1,3-dipolar cyclo additions with carbohydrates. In 2004, she carried out post-doctoral work in the group of Professor John A. Joule at the University of Manchester working on the synthesis of analogues of cofactors of oxomolybdo enzymes. In 2005 she joined the Northern Institute for Cancer Research at Newcastle University as a research fellow, working on the synthesis of inhibitors of the DNA-dependent protein kinase (DNA-PK). She was appointed to a lectureship in Medicinal Chemistry at Newcastle University in 2008 and has since played a key role in helping to establish Newcastle as an internationally recognised centre for anti-cancer drug discovery. Celine was awarded the Elsevier Reaxys 2016 Prize for Medicinal Chemistry in recognition of her research into anticancer drug discovery. She is the academic lead for the Medicinal Chemistry and Chemical Biology Group within the School of Natural and Environmental Sciences.