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Development of potent inhibitors of the DNA-dependent protein kinase (DNA-PK)

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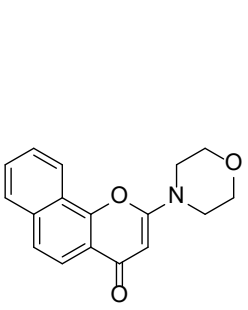
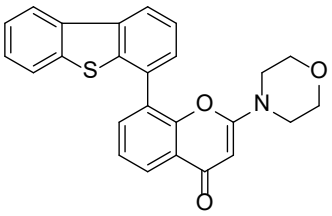
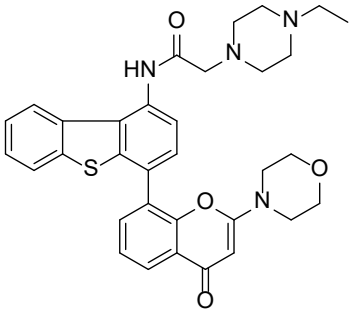
The cellular response to DNA double-strand break (DSB) formation is an essential component of normal cell survival, following exposure to DNA-damaging chemicals (*e.g.* cisplatin and doxorubicin) and ionising radiation.[1] The serine/threonine kinase DNA-dependent protein kinase (DNA-PK) is a member of the phosphatidylinositol (PI) 3-kinase related kinase (PIKK) family of enzymes, and plays an important role in DNA DSB repair *via* the non-homologous end-joining (NHEJ) pathway.[2] DNA-PK inhibitors may, therefore, be useful as agents to improve the activity of radio- and chemo-therapy in the treatment of cancer.[3] Identification of the lead benzo[*h*]chromen-4-one DNA-PK inhibitor NU7026 (IC_{50} = 0.23 μM), guided the subsequent development of the potent and selective ATP-competitive chromenone NU7441 (DNA-PK IC_{50} = 30 nM).[4] 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,[5] further biological studies with NU7441 were hampered by sub-optimal pharmaceutical properties.



NU7026



NU7441



KU-0060648

In collaboration with AstraZeneca Pharmaceuticals, structure-activity relationship studies for DNA-PK inhibition by chromenone-derivatives 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. These studies resulted in the identification of compounds that combined potent DNA-PK inhibition with excellent aqueous 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 and analogues will be described, including *in vivo* efficacy and combination studies.[6-8]

Biography:

Dr. Celine studied Organic Chemistry at the University of Poitiers (France) where she received her Ph.D. degree in 2004 for research on the synthesis of biomolecules by 1,3-dipolar cycloadditions with carbohydrates. From 2004-5, 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 oxomolybdoenzymes. In November 2005 she joined the Northern Institute for Cancer Research at Newcastle University as a research associate, working along Professors Roger Griffin and Bernard Golding on the synthesis of inhibitors of DNA-dependent protein kinase (DNA-PK). She was appointed to a lectureship at Newcastle in 2008, promoted to senior lectureship in 2013, and has since played a key role in helping to establish Newcastle as an internationally recognised centre for anti-cancer drug development.