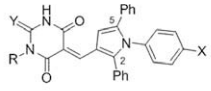
(also known as MDM4) was identified in 1996 and amplification (10%) or over-expression (17%) of MDMX has been found in many tumour types. Unlike MDM2, transcription of MDMX is not induced by DNA damage, and levels remain constant and the activity of the protein is regulated primarily by posttranslational modifications. MDM2 and MDMX appear to have different and complimentary activities, as both proteins inactivate p53. MDMX lacks a ubiquitin ligase function and acts by blocking the p53 transactivation domain. Importantly, over-expression of MDMX has been show to produce resistance to MDM2 inhibition with Nutlin-3.

Screening of commercially available compound libraries resulted in the discovery of novel and potent pyrrole inhibitors of the MDM2−p53 interaction exemplified by NU8324 (MDM2 IC_{50} = 168 nM). Structure–activity relationship (SAR) studies around the pyrrole scaffold have led to the identification of compounds with improved potency, e.g. NU8376 (MDM2 IC_{50} = 73 nM). Subsequently, the series was found to have potent MDMX−p53 activity. Regioselective syntheses of pyrroles bearing different 2- and 5- substituents have been developed and have generated further SARs. Key compounds with dual MDM2− and MDMX−p53 inhibitory activity have been investigated in cellular assays and the results will be reported.



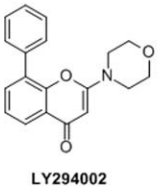
Compound	X	Y	R	MDM2 IC_{50} (nM)	MDMX IC_{50} (nM)
NU8324	NO_2	S	Me	168 ± 62	760 ± 140
NU8225	NO_2	O	H	153 ± 59	680 ± 180
NU8376	Br	S	Me	73 ± 2	-

443 POSTER

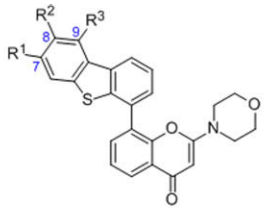
Development of potent inhibitors of DNA-dependent protein kinase (DNA-PK)

K.M. Clapham[1], T. Rennison[1], S. Rodriguez-Aristegui[1], J. Bardos[2], N.J. Curtin[3], B.T. Golding[1], I.R. Hardcastle[1], D.R. Newell[3], C. Cano[1], R.J. Griffin[1]. *[1]Newcastle Cancer Centre Northern Institute for Cancer Research, School of Chemistry Newcastle University, Newcastle-upon-Tyne, United Kingdom; [2]KuDOS Pharmaceuticals Ltd, 410 Cambridge Science Park Milton Rd, Cambridge, United Kingdom; [3]Newcastle Cancer Centre Northern Institute for Cancer Research, Paul O'Gorman Building Newcastle University, Newcastle-upon-Tyne, United Kingdom*

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. doxorubicin) and ionising radiation.[1] The serine/threonine kinase DNA-dependent protein kinase (DNA-PK) is a member of the phosphatidylinositol 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] ATP-competitive DNA-PK inhibitors may, therefore, be useful as agents to improve the activity of radio- and chemo-therapy in the treatment of cancer.[3]

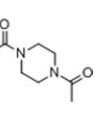


LY294002



NU7441; $R^1 = R^2 = R^3 = H$

NCL-00014518; $R^1 = R^2 = H$, R^3 =



In the absence of suitable structural biology information for DNA-PK, inhibitor design has been guided by a combination of structure–activity relationship (SAR) studies and homology modelling, based on the non-selective PIKK inhibitor LY294002. Identification of the lead dibenzothiophen-4-yl chromenone inhibitor NU7441 (DNA-PK; IC_{50} = 30 nM)[4] 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.

Subsequent substitution on the dibenzothiophen-4-yl moiety was investigated through the synthesis of novel analogues bearing a variety of groups at the 7-, 8- and 9-positions (e.g. R^1, R^2 or R^3 = Cl, OMe, OH, OR, NRR', SO_2Me, SO_2NMe_2). Interestingly, several of the newly synthesised compounds (e.g. NCL-00014518) showed high potency against the target enzyme (DNA-PK; IC_{50} = 0.29 nM). The synthesis and biological activity of these substituted dibenzothiophen-4-yl chromenone DNA-PK inhibitors will be discussed.

References

[1] J. H. J. Hoeijmakers, *Nature*, 2001, 411, 366.
[2] S. P. Jackson, J. Bartek, *Nature*, 2009, 461, 1071.
[3] S. Boulton *et al.*, *Carcinogenesis*, 1997, 17, 2285.
[4] I. R. Hardcastle *et al.*, *J. Med. Chem.,* 2005, 48, 7829.
[5] Y. Zhao *et al.*, *Cancer Res.*, 2006, 66, 5354.

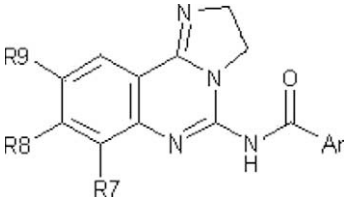
444 POSTER

Novel 2,3-dihydroimidazo[1,2-c]quinazolines PI3K inhibitors: Discovery and SAR

W.J. Scott[1], M. Hentemann[2], B. Rowley[3], C. Bull[3], A.M. Bullion[2], J. Johnson[2], A. Redman[2], N. Liu[1], R. Jones[3], E. Sibley[2]. *[1]Bayer Schering Pharma AG, Global Drug Discovery, Berlin, Germany; [2]Former Bayer Research Center, Medicinal Chemistry, West Haven CT, USA; [3]Former Bayer Research Center, Cancer Research, West Haven CT, USA*

Herein we report on BAY 80-6946, a highly selective and potent pan class I PI3K inhibitor currently in phase I clinical trials. Phosphatidylinositol-3-kinase (PI3K) has become an increasingly important target for oncology research due to the involvement of the PI3K/Akt/mTOR signaling cascade in a wide variety of cancers. PI3K involvement is often marked by amplifications or activating mutations in the PIK3CA gene, which encodes the p110 subunit of PI3Kα. In addition, PI3K signaling is negatively regulated by the dual phosphatase PTEN. However, loss of function or deletions in the gene which encodes PTEN is a common occurrence in human cancers. Moreover, signaling through the PI3K/Akt/mTOR pathway has been shown to be an important pathway in the development of resistance mechanisms to a variety of anti-tumor treatments.

A novel class of 2,3-dihydroimidazo[1,2]quinazolines has been discovered as potent and selective PI3K inhibitors. Beginning with initial lead compounds, activity against PI3Kα and β isoforms was optimized using traditional and structure-based approaches. Herein is presented the SAR for the 2,3-dihydroimidazo[1,2]quinazolines, leading to the selection of BAY 80-6946. BAY 80-6946 is currently in phase I clinical trials.



445 POSTER

Structure-based design of C8-substituted O6-alkylguanine CDK1 and 2 inhibitors

B. Carbain[1], C. Roche[1], J.A. Endicott[2], B.T. Golding[1], I.R. Hardcastle[1], C. Cano[1], L. Zhen-Wang[1], D.R. Newell[1], M.E.M. Noble[2], R.J. Griffin[1]. *[1]Newcastle Cancer Centre Northern Institute for Cancer Research, School of Chemistry, Newcastle-upon-Tyne, United Kingdom; [2]Laboratory of Molecular Biophysics, Department of Biochemistry, Oxford, United Kingdom*

Defects in the functioning of members of the cyclin-dependent kinase (CDK) family that regulate mitotic progression compromise the normal cell cycle, and are associated with the molecular pathology of cancer [1,2]. As a consequence, small-molecule ATP-competitive CDK inhibitors have potential therapeutic value as antitumor agents.[3] Employing structure-aided design we have previously identified a series of CDK1/2-selective O^6-cyclohexylmethylguanines derived from NU2058 (1) (CDK2, IC_{50} = 16 mM).[4] C-8 substitution within this series demonstrated that the potency of the compounds decreases with increasing size of an alkyl substituent.

Further structural analysis revealed that, to avoid unacceptable steric clashes with Phe80, the C-8 isopropyl derivative (2) adopts a 'reverse' binding mode in which the purine backbone has flipped 180º compared to the binding mode of NU2058. This binding mode provided a platform from which to investigate the design of more potent CDK inhibitors, using