were screened at multiple substitution points for every binding mode. The interaction between reagent and ensemble conformer was explored through simulated annealing optimisation of an empirical free-energy function.
Chemical synthesis and biological testing of the designed compounds showed that the protocol was successful in both improving the activity of the compounds and pinpointing the preferred binding mode. Further studies have resulted in the discovery of NU8231 (IC_{50} = 5 μM) which shows cellular activity.

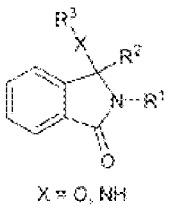

Figure 1. Isoindolinone scaffold.

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Chemical and structural studies on thioredoxin-inhibitory antitumour quinols

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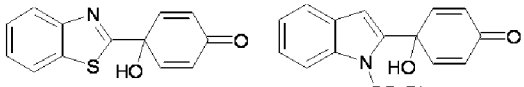
Quinols with a 6/5 heterobicyclic substituent, exemplified by the experimental antitumour agents AW 464 and BW 114, exhibit potent (low nanomolar GI_{50}) and selective activity in vitro and in vivo against certain colon and renal cell lines. Accumulated target evidence (NCI COMPARE, gene microarray, biochemical assay, mass spectrometry) strongly implicates the quinols as selective irreversible inhibitors of the 12kDa redox protein thioredoxin, a relevant anticancer drug target upregulated in certain tumours and with a multitude of intracellular functions relating to tumourigenesis (e.g. regulation of transcription factors NF-κ B, AP-1, and HIF-1α).
The lead quinol compounds are synthetically accessible, lipophilic small molecules. In the case of AW 464 (and related structures), syntheses of multigram quantities are available following a "one-pot" reaction between 2-lithiobenzothiazole and benzoquinone ketal followed by in situ deprotection. Members of the BW 114 family of compounds can be synthesised by an analogous synthetic route to the AW 464 series, or more efficiently via a palladium-catalysed Sonogashira coupling between an ortho-iodoarylsulfonylaniline and 4-ethynyl-4-hydroxycyclohexa-2,5-dienone. This latter route can be adapted towards the synthesis of more water-soluble BW 114 derivatives for potential preclinical development.
Crystal structures for the two antitumour quinols AW 464 and BW 114 have been determined. In both compounds the hydroxy group was found to interact intermolecularly with the ketone oxygen, via a water bridge in AW 464 and directly in BW 114. Michael adducts of 2× MeSH and various dithiols (including the ^{32}Cys-Gly-Pro-^{35}Cys fragment from thioredoxin) have been built computationally, leading to a thioredoxin adduct model that can accommodate both series of quinols. "Docking" studies have identified the most likely orientations of these quinols in the active site of human thioredoxin and the critical structural features contributing to recognition and potency



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Peptidomimetic inhibitors of Stat3: structure–activity relationships and cellular activity

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Signal transduction and activator of transcription 3 (Stat3) mediates signals from the IL-6 family of cytokines, EGF, Src etc., is constitutively activated in a variety of tumors (e.g breast, head and neck, prostate), and is a target for anti-cancer drug design [1]. Stat3 becomes activated by phosphorylation of Tyr705 and dimerizes by reciprocal interactions between SH2 domain of one molecule and the phosphotyrosine of the second. The dimer translocates to the nucleus and initiates transcription of anti-apoptotic genes resulting in cancer cell proliferation. To disrupt Stat3 activity we have embarked on the development of peptidomimetic inhibitors targeted to the SH2 domain. A lead peptide, acetyl-Y(p)LPQTV-amide (1), was found which exhibited an IC_{50} value of 150 nm [2]. SAR studies have revealed a number of important peptide-protein contacts, e.g. pY+1 backbone NH and the pY+3 Gln side chain NH_2 protons and the fact that the Leu-Pro peptide bond is *trans*. This work has lead to high affinity peptidomimetics with IC_{50} values of ca 100 nM in a fluorescence polarization assay. Pro-drug versions of one of the peptidomimetics as well as an analogue of peptide 1, when attached to the hydrophobic membrane transporting sequence AAVLLPVLLAAP, inhibit Stat3 activity in cells in culture. Stat3 translocation to the nucleus (measured by EMSA) and expression of a luciferase reporter gene were inhibited in IL-6 stimulated HepG2 and HepB3 hepatoma cells. Both inhibitors also inhibit the growth of breast carcinoma (MDA-MB231, MDA-MB468), epidermoid (A431) and multiple myeloma (MM-1) cells in culture. Thus our Stat3 inhibitors inhibit the growth of both EGFR and IL-6 pathway-dependant cells.

References

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125 POSTER

Synthesis, biological evaluation and structure activity relationships of a novel series of aromatic hydroxamic acids as potent HDAC inhibitors

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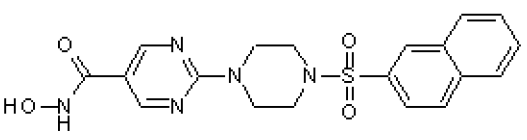
Histone deacetylases (HDACs) represent a family of enzymes that compete with histone acetyltranferases (HATs) for modification of the nucleosomal histone proteins. Histone acetylation status modulates chromatin structure and thereby regulates transcriptional activity of a subset of genes. Aberrant reduction in acetylation due to disruption of HDAC or HAT activity is associated with the development of cancer [1)]. Deregulated, sustained HDAC recruitment to the chromatin is observed in specific forms of leukaemia and lymphoma, such as APL and non Hodgkin's lymphoma [2)]. In agreement with a key role of HDAC activity in cancer, HDAC inhibitors from various structural families induce histone hyperacetylation, activate gene expression and consequently, inhibit the cell cycle, activate differentiation programmes or induce apoptosis. HDAC inhibitors have been described to exhibit potent anti-tumor activity in human xenograft animal models, suggesting that this class of compounds represents promising novel cancer therapeutic agents [3)]. We have recently described the discovery of R306465 (JNJ16241199) as a highly potent HDAC inhibitor, showing anti-proliferative activity in a wide panel of tumor cell lines of different origin and exhibiting anti-tumor activity when dosed orally in human xenograft-bearing nude mice [4)].
In order to fully explore the Structure Activity Relationship around the aryl hydroxamic acid core template, several compound libraries were generated. In this poster, the design and execution for representative libraries will be briefly described. The resulting chemical libraries were evaluated against an array of enzymatic and cellular assays, which generated a clear and consistent SAR. Representative data will be shown, complemented by ADME profiling results.



R306465 (JNJ16241199)

IC_{50} HDAC = 6 nM (HeLa nuclear extract)
IC_{50} A2780 = 30 nM (cell proliferation)