

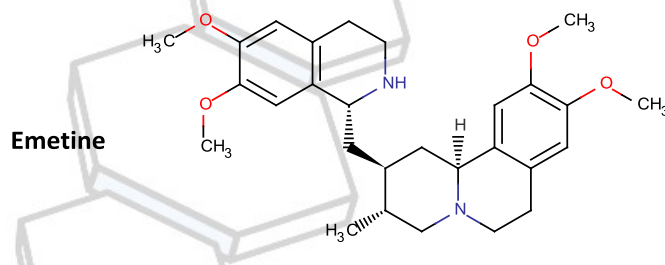
BIONET – Source of Unique and Active Compounds for Cancer Research

Novel Retinoblastoma-Binding Protein 9 (RBBP9) Inhibitors

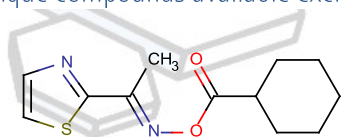
Pancreatic cancer is one of the most lethal malignancies. Alone in the UK, there are approximately 7,000 new cases each year. A recent report showed that the death rate is over 93%, with 8.6 out of 9.2 cases per 100,000 individuals. In the US, over 42,000 people are diagnosed with this condition each year and 85% of cases are fatal. The prognosis is relatively poor but has improved; the three-year survival rate is now about 30%, but for less than 5% of those diagnosed the life expectancy is up to five years after diagnosis. Complete remission is still rare.

Most recently, the retinoblastoma-binding protein 9 (RBBP9) has been identified as a tumour-associated serine hydrolase that displays elevated activity in pancreatic carcinomas.^[1] Whereas RBBP9 is expressed in normal and malignant tissues at similar levels, its elevated activity in tumour cells promotes anchorage-independent growth in vitro as well as pancreatic carcinogenesis in vivo. Although these data suggest that RBBP9 plays an important role in cancer, the biochemical function of this enzyme and identity of its endogenous substrate remain unknown.

In a recent report,^[2] Cravatts' group at Scripps has disclosed their results of adapting the chemical proteomic technology activity based protein profiling (ABPP) for HTS, focusing on the RBBP9. From an initial ~20,000 compounds fluopol-ABPP screen, the group identified the natural product Emetine as a reversible inhibitor of RBBP9 that selectively blocked FP-Rh labelling of this enzyme compared to other members of the serine hydrolase family.



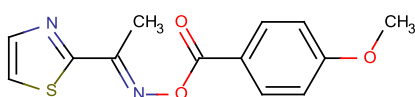
Emetine has also been shown to antagonize α_2 -adrenergic receptors and it has been concluded that these additional targets could complicate the use of emetine in biological studies of RBBP9. Therefore, additional classes of inhibitors for this enzyme are required. From a pool of over 200,000 compounds, Cravatts' group discovered an oxime-ester class of inhibitors of RBBP9 via a fluopol-ABPP screen.^[2] The most active compounds of this class of thiazole-containing ester-oximes were **9W-0837**, **6W-0841**, **9W-0835** and **6W-0842**, unique compounds available exclusively from Key Organics Bionet Screening collection.



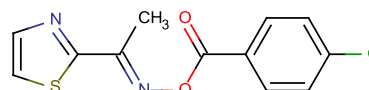
Bionet 9W-0837



Bionet 9W-0835



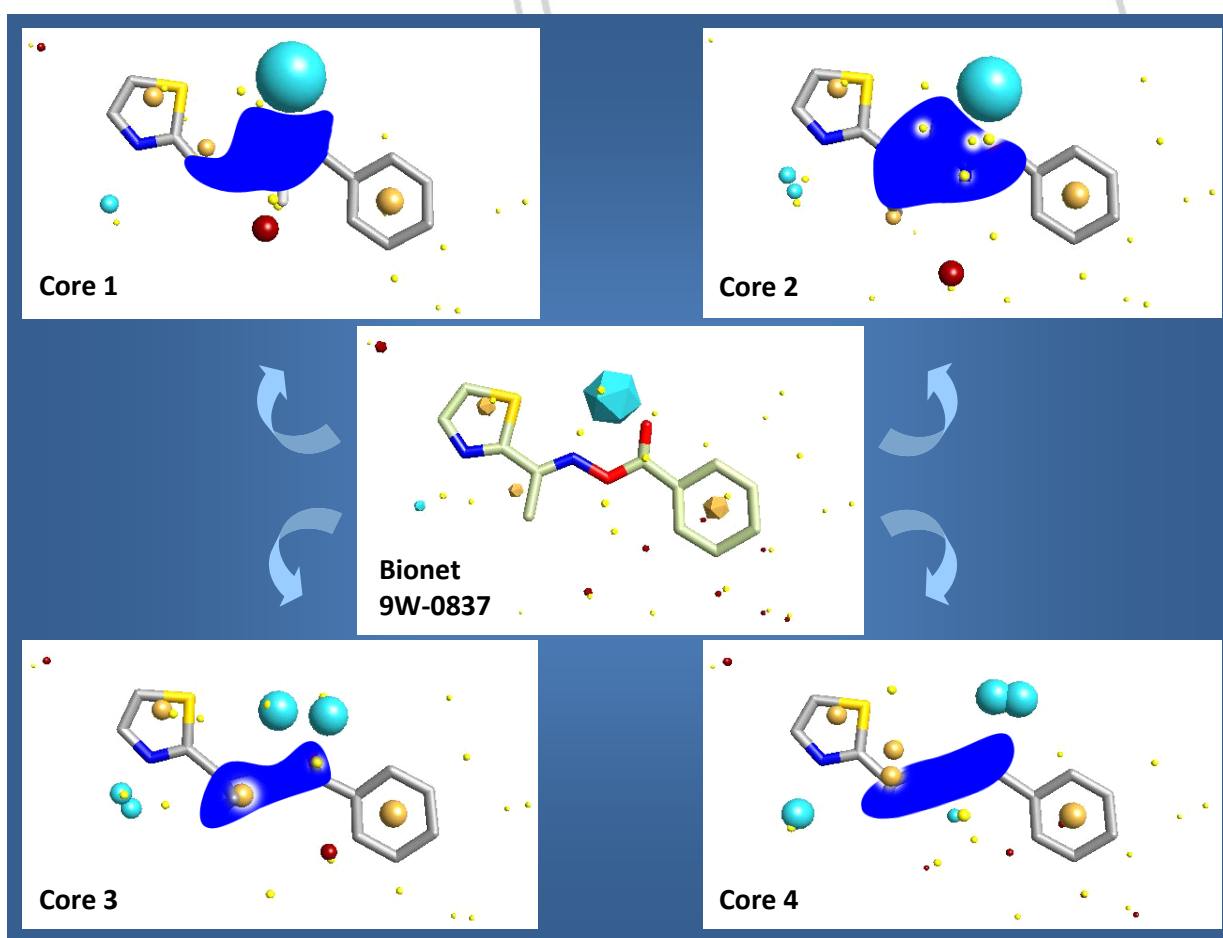
Bionet 6W-0841



Bionet 6W-0842

While Emetine inhibited RBBP9 in the initial fluopol-ABPP assay by 51% and inhibited this enzyme in the gel-based assay showing an IC_{50} of 7.8 μ M, the low-molecular weight compound **Bionet 9W-0837** inhibited 91% of the RBBP9 activity and gave a more potent IC_{50} value (0.64 μ M) in the gel-based assay. Moreover, this compound did not inhibit any other hydrolases, even at 200 μ M, in the mouse brain membrane proteome and was also selective for RBBP9 in HEK 293T cell proteomes. Further data demonstrated that the oxime-esters inhibit RBBP9 by covalently labelling the enzyme's serine nucleophile.^[2] Due to their nature, these compounds form transient covalent adducts that are eventually hydrolysed by water. However, the oxime-esters, as well as the natural product Emetine, can serve as useful scaffolds for future optimization of RBBP9 inhibitors. The authors suggested that further improvements in oxime-ester activity could derive from modifications that maintain binding interactions with RBBP9 while limiting the rate of hydrolysis of the parent compound and acyl-enzyme adduct.^[2]

Utilising unique computational technologies (molecular fields and quantum mechanics) combined with suitable X-ray and docking data, Key Organics is capable of designing and synthesizing novel focused libraries of compounds aimed at the RBBP9 or at other targets of choice.



Key Organics has always provided exceptional quality Bionet chemistry products and KOCAS chemistry services. Key Organics also offers the same reliability and competence in an integrated services format for all drug discovery needs. This integrated approach encompasses biological services and computational chemistry requirements necessary for a complete drug discovery platform.

1. Shields D.J. et al, "RBBP9: a tumor-associated serine hydrolase activity required for pancreatic neoplasia", Proc. Natl. Acad. Sci. USA, **2010** Feb 9, 107, 6, 2379-80.
2. Cravatt B.F. et al, "Oxime esters as selective, covalent inhibitors of the serine hydrolase retinoblastoma-binding protein 9 (RBBP9)", Bioorg. Med. Chem. Lett., in press, available online 6 February **2010**, doi: 10.1016/j.bmcl.2010.02.011.