

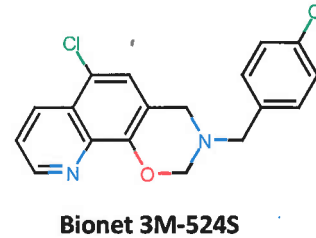
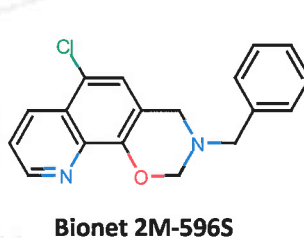
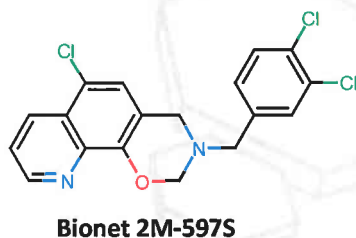
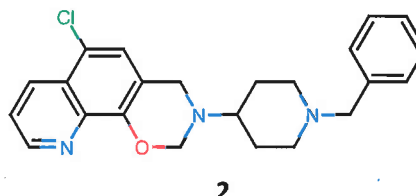
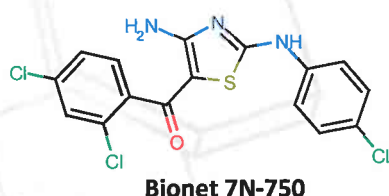
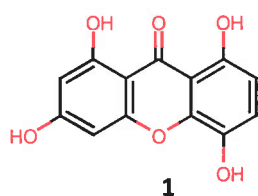
BIONET – Source of Unique and Active Compounds for CNS Research

Cdk5 Inhibitors

Cyclin-dependent kinase 5 (Cdk5) is a unique member of a family of proline-directed serine/threonine kinases that is primarily active in the nervous system^[1] and is essential for its development^[2]. A large body of data supports a role for this kinase in the pathogenesis of Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease, Niemann-Pick type C disease, and ischemia^[3]. Cdk5 has also been implicated in pathways known to modulate pain, published data has indicated important molecular roles for Cdk5 in pain signalling and opioid tolerance, which makes it a potential target for analgesic drug development^[4].

Several classes of chemical inhibitors for Cdk are known and have been reviewed^[5]. Generally, these small molecules compete with ATP and have IC₅₀ values in the micromolar range. Crystal structures of active Cdk5/p25 kinase complexed with three inhibitor moieties, (R)-roscovitine, aloisine-A, and indirubin-3'-oxime have been reported^[3]. These chemical species inhibit catalytic activity by binding to the conserved ATP binding pocket.

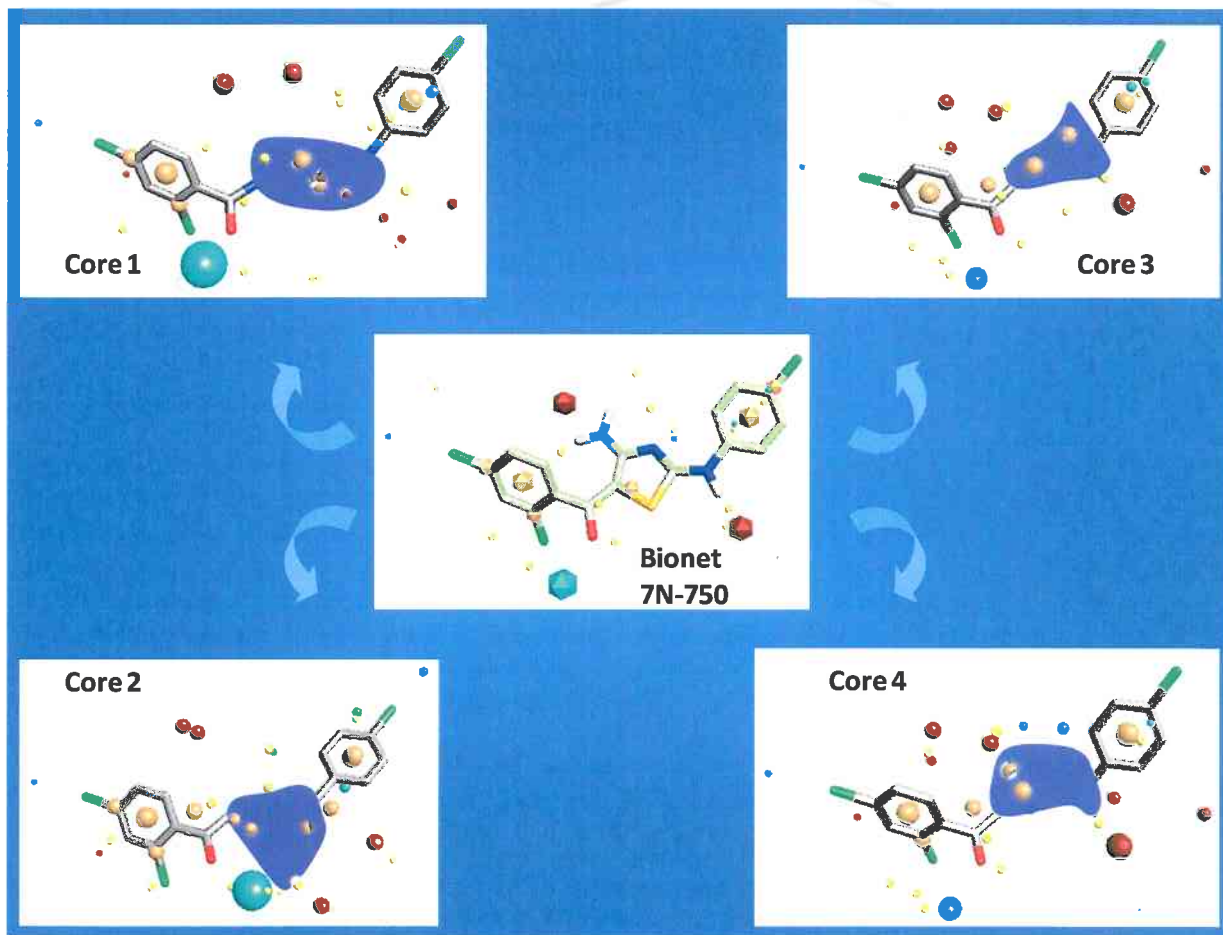
The continuous search for more potent and selective Cdk5 inhibitors has motivated an international group of collaborators from Harvard Medical School, MIT and European Institute of Oncology in Milan, to screen a library of 58,000 compounds acquired from various academic labs and 8 major vendors, including Key Organics' Bionet compound collection^[3]. The hit rate after confirmation was 0.5% and the top three, based on their structure and IC₅₀, represent three major classes: a xanthen-9-one natural product Bellidin (**1**), a 4-aminothiazole (**Bionet 7N-750**) and a 2,3-dihydro-1H-4-oxa-2,5-diazaphenanthrenes (**2**), a derivative based on a series of compounds unique to Bionet (2M-597S, 2M-596S, 3M-524S) according to the Symyx database of commercially available compounds.



Bionet 7N-750 showed competitive inhibition against ATP binding with a K_i of 0.6 μM under a saturated concentration of tau (20 μM). The compound also demonstrated non-competitive inhibition against tau binding under saturated ATP concentration (400 μM). Compound **2** showed a greater specificity for tau as a Cdk substrate, suggested by the IC₅₀ values of **2** for tau (17 μM) to FAK (272 μM), another well-characterized Cdk5 substrate^[3]. Further insight in to the Cdk5 ligand chemical space has been obtained by the same research group by the co-crystallisation **1** and **7N-750** with Cdk5/p25.

The conservation of the ATP pocket among Cdk5-related kinases represents a challenge to the discovery of more selective compounds. The three compounds reported inhibit Cdk5 by distinct mechanisms and each suggested strategies for future inhibitor optimization^[3].

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 Cdk5 or at other CNS targets of choice.



Key Organics has provided Bionet chemistry products and bespoke KOCAS chemistry services of exceptional quality and reliability, world-wide. With over 23 years of experience in early drug discovery research, Key Organics offers the same reliability and competence in an integrated services format for all drug discovery needs. This integrated approach encompasses biological services, computational chemistry requirements necessary for a complete drug discovery platform.

1. M. Mapelli and A. Musacchio, *The structural perspective on CDK5*, *Neurosignals* (2003) 12, 164–172.
2. J.C. Cruz and L.H. Tsai, *A Jekyll and Hyde kinase: roles for Cdk5 in brain development and disease*, *Curr. Opin. Neurobiol.* (2004) 14, 390–394.
3. J.S. Ahn et al., *Defining Cdk5 Ligand Chemical Space with Small Molecule Inhibitors of Tau Phosphorylation*, *Chemistry & Biology* (2005) 12, 811–823.
4. T.K. and Pareek and A.B. Kulkarni, *Cdk5: a new player in pain signalling*, *Cell Cycle* (2006), 5, 585–8.
5. P.M. Fischer, *Recent advances and new directions in the discovery and development of cyclin-dependent kinase inhibitors*, *Curr. Opin. Drug Discov. Devel.* (2001), 4, 623–634.