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Chicago Discovery Solutions

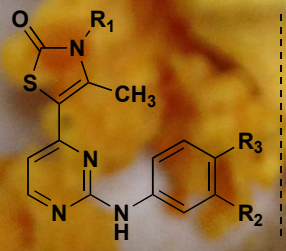
Cyclin Dependent Kinase (CDK) Inhibitors

A Library Collection of 2-Anilino-4-(thiazol-5-yl)pyrimidine Compounds

Cyclin dependent kinases are a family of protein kinases responsible for regulating the cell cycle. Certain kinases have regulatory functions in mRNA transcriptions at the level of RNA polymerase-II (RNAP-II) (1). The overabundance of cyclins is often observed in cancers, thus an area of focus in cancer therapy. Previous CDK candidates lacked specificity to a singular target preventing it from ever entering the market as anticancer agents. A movement of new CDK inhibitors is happening in the drug pipeline with Pfizer at its helm. Their CDK4/6 inhibitor palbociclib (PD-0332991), now a leading candidate for breast cancer, is in Phase 3 trial (2 and company communications). Pfizer's developments rekindled an interest in CDK4/6 inhibitors from other large pharma. A few examples are Eli Lilly's LY2835219, a target of mantle cell lymphoma, will soon enter Phase 2 while Novartis' LEE011, a cell proliferation blocker, is now in Phase 1. Dinaciclib , another CDK inhibitor from Merck is in clinical phase II.

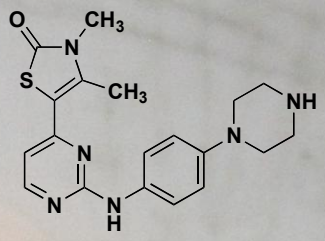
Deliberating which CDK inhibitor is the best reference compound for assays in clinical development can be an arduous process. A comparative table of available CDK inhibitors and its properties can be viewed:
http://www.selleckchem.com/pathways_CDK.html?gclid=CLD51M38trgCFcbm7AodYzUAnA
In addition to these CDK inhibitors, the staff at Chicago Discovery Solutions is now offering a unique family of 2-anilino-4-(thiazol-5-yl)pyrimidine compounds for research purposes.

CDK's 1, 2, 7, 8, 9 and 11 have all been implicated in the phosphorylation of the C- terminal domain (CTD) of the largest RNA polymerase II subunit (3) an area where transcription occurs. Of these cyclins, CDK7-H and CDK9-T are the most important for phosphorylation and an attractive target. A recent publication identified a library of 2-anilino-4-(thiazol-5-yl)pyrimidine analogues as inhibitors for CDK1, 2, 4, 7, and 9 (4). The four compounds below can be synthesized by CDS in 3-6 weeks for R&D purposes only (please refer to our Usage Statement).



$R_1 = CH_3$; $R_2 = H$; $R_3 = SO_2NH(CH_2)_2OCH_3$
$R_1 = CH_3$; $R_2 = CN$; $R_3 = H$
$R_1 = CH_3$; $R_2 = NO_2$; $R_3 = CH_3$
$R_1 = CH_3$; $R_2 = H$; $R_3 =$ Piperazine (CDS 1073)

From the family of thiazolone analogues above, the piperazine derivative emerged as a selective CDK7/9 inhibitor. The piperazine derivative, available as CDS 1073, has a unique biological profile that can be viewed in the table. CDS 1073, or 3,4-dimethyl-5-[2-(4-piperazin-1-yl-phenylamino)-pyrimidin-3-yl]-3H-thiazol-2-one, is in stock and available.



CDK	Kinase Inhibition (nM)	IC50 nM	IC50 nM
CDK1	449 ± 48	A2780*	MES-SA*
CDK2	149 ± 40	131 ± 9	150 ± 16
CDK4	68 ± 28		
CDK7	2.3 ± 0.2		
CDK9	0.38 ± 0.27	*cancer cell lines	

CDS 1073; CAS 85-1439-14 (in stock)

An alternative series, the 2-amino-substituted thiazole family (shown below) were active against a range of cyclin dependent kinases including CDK1, 2, 4, 7, and 9. They can be synthesized and delivered in approximately 6-8 weeks time for R&D purposes.

$R_1 = NH_2$; $R_2 = NO_2$; $R_3 = H$
$R_1 = NHEt$; $R_2 = SO_2NH_2$; $R_3 = H$
$R_1 = NHCH_3$; $R_2 = SO_2NH_2$; $R_3 = H$
$R_1 = NHCH_3$; $R_2 = SO_2NHCH_3$; $R_3 = H$
$R_1 = NH_2$; $R_2 = SO_2NHCH_3$; $R_3 = H$
$R_1 = NHCH_3$; $R_2 = SO_2CH_3$; $R_3 = H$
$R_1 = NHCH_2CH_3$; $R_2 = SO_2CH_3$; $R_3 = H$
$R_1 = NH_2$; $R_2 = H$; $R_3 = H$
$R_1 = NHCH_3$; $R_2 = SO_2$-morpholine; $R_3 = CH_3$
$R_1 = NH_2$; $R_2 = SO_2$-morpholine; $R_3 = CH_3$

The template that provided this active compound CDS-1073 is promising and there is need to develop more potent and selective compounds which can be considered suitable for further drug development as selective CDK inhibitors. We have designed several molecules using computational approaches that will provide novel, biologically active, drug-like chemicals. The Chemistry already developed by us will help us to synthesize previously untapped molecules that may aid in the search for innovative and selective CDK inhibitors.

Chicago Discovery Solutions provides high quality chemical synthesis of small molecular compounds and potential drug candidates. We can supplement your medicinal chemistry program from hit identification through lead optimization. Our medicinal chemists have extensive experience in developing drug candidates from screening hits. Please contact sales@chicagodiscoverysolutions.com for more information.

Usage Statement: Unless otherwise stated in our catalog or other company documentation accompanying the product(s), our products are intended for research use only and are not to be used for any other purpose, which includes but is not limited to, unauthorized commercial uses, in vitro diagnostic uses, ex vivo or in vivo therapeutic uses or any type of consumption or application to humans or animals.

References

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4. Wang, S., Griffiths, G., Midgley, C., Barnett, A., Cooper, M., Grabarek, J., Ingram, L., Jackson, W., Kontopidis, G., McClue, S., McInnes, C., McLachlan, J., Meades, C., Mezna, M., Stuart, I., Thomas, M., Zheleva, D., Lane, D., Jackson, R., Glover, D., Blake, G., Fischer. (2010) Chem. Biol. 17, 1111-1121.