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TARGET-FOCUSED LIBRARIES FROM OTAVA

more information, quotes and ordering, please send an e-mail to **north.america@otavachemicals.com** or **mol.design@otavachemicals.com**

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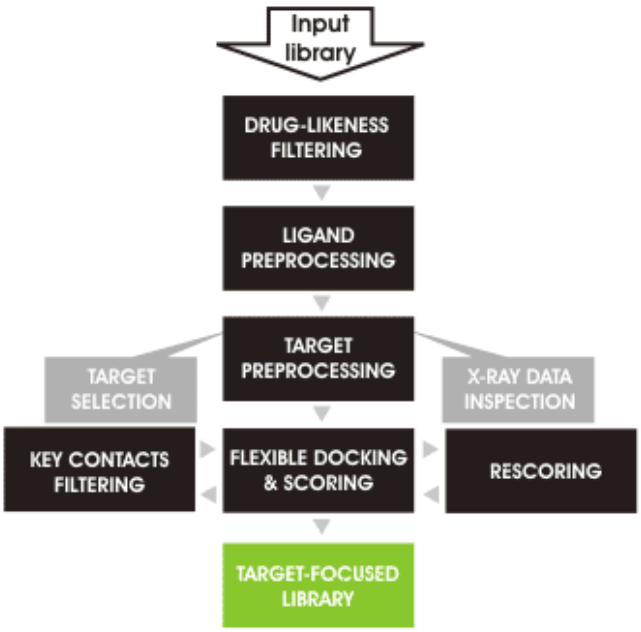
Table of Contents

Receptor-Based Target-Focused Libraries

For more information please send an e-mail to north.america@otavachemicals.com or, for quotes and ordering, to services@otavachemicals.com
OTAVA - North American Division: 15 Dundonald St., Suite 1902, Toronto, ON, M4Y 1K4, Canada;
Tel.: 1-416-305-9979, Fax: 1-866-881-9921 (Toll-free in US & Canada)

Building Receptor-Based Target-Focused Libraries



Design of Receptor-Based focused libraries.

This approach was employed for each of OTAVA's Receptor-Based Target-Focused libraries.

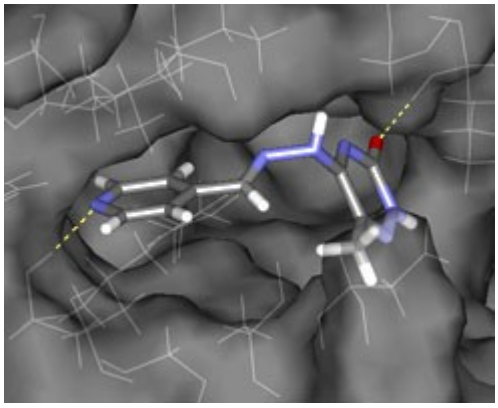
During the early stages of drug development, it is often necessary to perform *in silico* screening of large numbers of small molecules. The aim is to find the most active members from a stock collection that are to be subjected to *in vitro* evaluation. The result is a library of molecules that possesses significant activity. The quality of the library, however, can only be as good as the screening method used.

It is quality that OTAVA wants to bring to its customers. Our Receptor-Based Target-Focused libraries are created from an extensive stock collection, and a rigorous process of refinement that involves harnessing the most current methods of theoretical medicinal chemistry.

OTAVA's Receptor-Based Target-Focused libraries are generated through a unique approach. First, the stock collection is filtered according to the Lipinski and Veber rules:

- CLogP from 0 to 5
- MW from 160 to 500
- number of H-donors from 0 to 5
- number of H-acceptors from 0 to 9
- number of NO_2 groups from 0 to 2
- number of rotatable bonds from 0 to 10

Building Receptor-Based Target-Focused Libraries, *continued*



Ligand in Aurora B active site.

Docking example from the OTAVA Aurora B Kinase Receptor-Based Target-Focused library.

The detection of H-bonds between the ligand and a key Aurora B residue (Ala173) was used in preparation of the library.

OTAVA's approach uses Sharp Focusing: each molecule's interaction is measured with only a single target in a protein family. The target's X-ray crystallography data is thus incorporated. Next, after preprocessing, the molecules are individually docked. Flexible molecular docking is the core of OTAVA's approach.

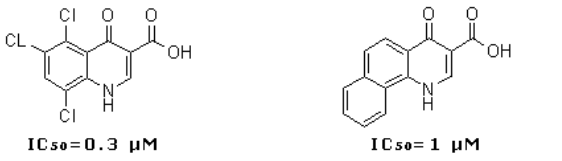
After docking the ligand, a *re-scoring* algorithm is applied. This re-scoring procedure involves correcting the final summation of interaction energies (the score) according to the ligand's structural features.

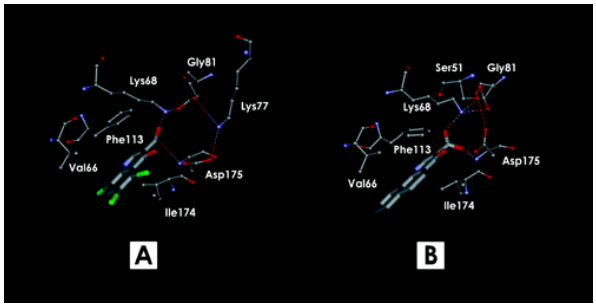
Finally, each docking complex is scanned for key contacts: H-bonds formed between the ligand and critical amino acid residues in the protein's active site. This detailed analysis of each docked protein-ligand complex is critical to OTAVA's approach.

Our libraries, created this way, are expected to have a higher probability of interacting with potential drug targets.

All of the Receptor-Based Target-Focused libraries in this catalogue are available upon request, and come with docking scores and values for drug-like properties.

Human Protein Kinase CK2 Inhibitors: OTAVA's Approach in Action





*3D representation of the structural model that characterizes binding features of the inhibitors (**A**) and (**B**).*

The most important intermolecular and intramolecular hydrogen bonds are represented as dashed lines. The CK2 amino acid residues involved in key hydrophobic interactions with the ligand are indicated as well.

Ref.: Evaluation of 3-Carboxy-4(1*H*)-quinolones as Inhibitors of Human Protein Kinase CK2. Golub, A.G., Yakovenko, O.Ya., Bdzhola, V.G., Sapelkin, V.M., Zien, P., and Yarmoluk, S.M. *J. Med. Chem.*, 2006, 10.1021/jm050048t
http://dx.doi.org/10.1021/jm050048t

Protein kinase CK2 is a molecule that participates in the development of some cancers, viral infections and inflammatory failures. As such, small organic inhibitors of CK2, besides application in scientific research, may have therapeutic significance.

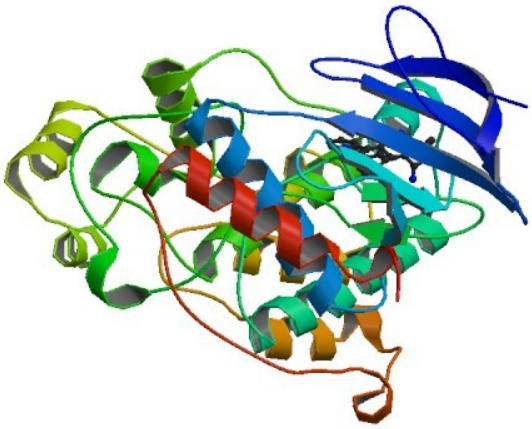
In our recent *Journal of Medicinal Chemistry* paper (see ref. below) we presented a new class of CK2 inhibitors: 3-carboxy-4(1*H*)-quinolones. This class of inhibitors was discovered through *receptor-based virtual screening of the OTAVA 70,000-compound library*.

According to theoretical calculations and experimental data, a structural model describing the key features of 3-carboxy-4(1*H*)-quinolones responsible for tight binding to the CK2 active site was developed. Docking and molecular dynamics studies allowed us to propose a binding mode in which the key interactions were hydrogen bonds between the ligand's 3-carboxy group and the two residues (Lys68 and Asp175) in the CK2 ATP-binding cleft, as well as hydrophobic contacts with Val66, Ile174, and Phe113. The resulting model correlated well with X-ray data for the complex CK2-IQA.

It was revealed that the most active compounds — 5,6,8-trichloro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**A**) (IC_{50} = 0.3 μM) and 4-oxo-1,4-dihydrobenzo[*h*]quinoline-3-carboxylic acid (**B**) (IC_{50} = 1 μM) — were ATP competitive (K_i values were 0.06 and 0.28 μM, respectively). *In vitro* evaluation of the inhibitors on seven protein kinases demonstrated considerable selectivity toward CK2.

Extracellular Signal-Regulated Kinase 2

NEW!

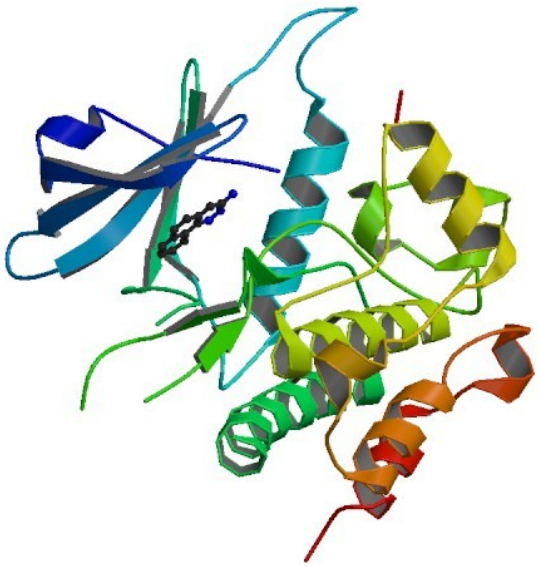


Extracellular signal-regulated kinase 2 (ERK2) has become an attractive target for the development of therapeutics for the treatment of cancer. Eight new inhibitors of ERK2 by means of a drug design protocol involving the virtual screening with docking simulations and in vitro enzyme assay were recently identified. The newly discovered inhibitors can be categorized into three structural classes and reveal a significant potency with IC50 values ranging from 1 to 30 μM.

Ref.: Park H, Bahn YJ, Jeong DG, Woo EJ, Kwon JS, Ryu SE. Identification of novel inhibitors of extracellular signal-regulated kinase 2 based on the structure-based virtual screening. Bioorg Med Chem Lett. 2008 Oct 15;18(20):5372-6.

Product Description	Number of Compounds	Target	Source	Input Libraries
Extracellular Signal-Regulated Kinase 2 focused library	**2053**	Extracellular Signal-Regulated Kinase 2	*Homo sapiens*	OTAVA Stock Collection + Life Chemicals Stock Collection **500,000 compounds**

Death-Associated Protein Kinase 2

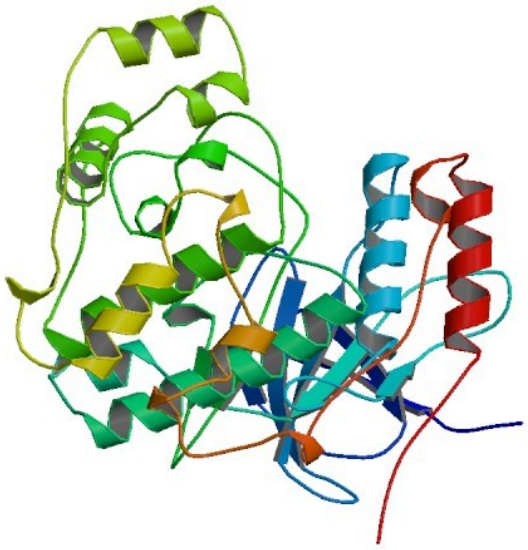


Death associated protein kinase (DAPK) is a calmodulin (CaM)-regulated serine/threonine protein kinase implicated in diverse apoptosis pathways, including those involved in neuronal cell death and tumour suppression. The requirement of DAPK catalytic activity for its proposed cell functions and the validation of protein kinases as therapeutic targets demand that DAPK be examined as a potential therapeutic target in human disease. The current body of knowledge raises the possibility of DAPK as a therapeutic target for diseases characterised by rapid neurodegeneration, such as stroke or traumatic brain injury. The unmet need in these diseases is for an acute treatment schedule that might reduce neuronal loss. Bioavailable inhibitors of DAPK catalytic activity that target the central nervous system have a potential to fill this need.

Ref.: Schumacher AM, Velentza AV, Watterson DM.
Death associated protein kinase as a potential therapeutic target.
Expert Opinion on Therapeutic Targets. 2002 August; 6 (4):497-506.

Product Description	Number of Compounds	Target	Source	Input Libraries
Death-Associated Protein Kinase 2 focused library	**2012**	Death-Associated Protein Kinase 2	*Homo sapiens*	OTAVA Stock Collection + Life Chemicals Stock Collection **500,000 compounds**

p38 MAP Kinase Alpha



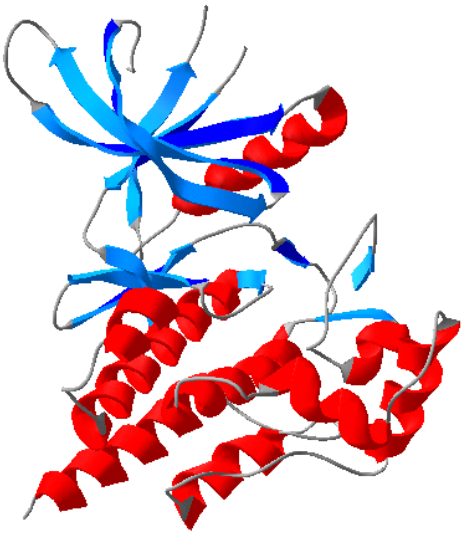
It is now known that there are four members of the p38 MAP kinase family. They differ in their tissue distribution, regulation of kinase activation and subsequent phosphorylation of downstream substrates. They also differ in terms of their sensitivities toward the p38 MAP kinase inhibitors.

The p38 MAP kinase inhibitors are efficacious in several disease models, including inflammation, arthritis and other joint diseases, septic shock, and myocardial injury. In all cases, p38 activation in key cell types correlated with disease initiation and progression. Treatment with p38 MAP kinase inhibitors attenuated both p38 activation and disease severity. Structurally diverse p38 MAP kinase inhibitors have been tested extensively in preclinical studies.

Ref.: Lee JC, Kumar S, Griswold DE, Underwood DC, Votta BJ, Adams JL. Inhibition of p38 MAP kinase as a therapeutic strategy. Immunopharmacology. 2000 May;47(2-3):185-201. Review.

Product Description	Number of Compounds	Target	Source	Input Libraries
p38 MAP Kinase Alpha focused library	**2221**	p38 MAP Kinase Alpha	*Homo sapiens*	OTAVA Stock Collection + Life Chemicals Stock Collection **400,000 compounds**

Janus Kinase 2

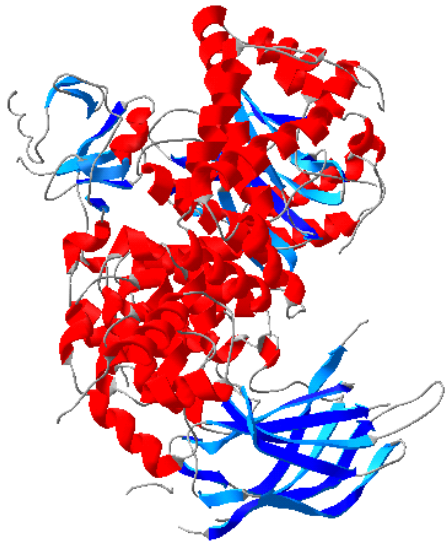


In humans, the Janus protein tyrosine kinase family (JAK) consists of four members: JAK1, JAK2, JAK3 and TYK2. Their purpose is to phosphorylate STATs (signal transducers and activators of transcription). Since there are several cellular mechanisms in place to inhibit JAK/STAT signaling, it may, in principle, be possible to produce a positive therapeutic effect by modulating specific JAK/STAT-mediated cellular signals through the inhibition of JAK kinase activity. It is an exciting prospect, as yet unrealized. While current data suggest no therapeutic use for JAK1 or TYK2 inhibition, JAK2 inhibition seems to be a promising mechanism for the treatment of leukemia.

Ref.: Thompson JE. JAK protein kinase inhibitors. *Drug News Perspect.* 2005 Jun; 18(5): 305-310.

Product Description	Number of Compounds	Target	Source	Input Libraries
Janus Kinase 2 focused library	**2190**	Janus Kinase 2 (JAK2)	*Homo sapiens*	OTAVA Stock Collection **70,000 compounds** + Life Chemicals Stock Collection **300,000 compounds**

Phosphatidylinositol 3-Kinase

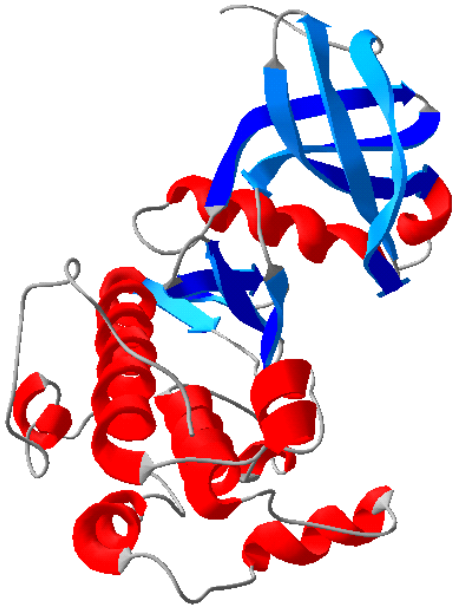


The phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B, PKB) signaling pathway plays a critical role in cell growth and survival. Dysregulation of this pathway has been found in a variety of cancer cells. Recently, constitutively active PI3K/Akt signaling has been firmly established as a major determinant for cell growth and survival in an array of cancers. Blocking the constitutively active PI3K/Akt signaling pathway provides a new strategy for targeted cancer therapy. Thus, inhibitors of this signaling pathway would be potential anticancer agents, particularly for cancer cells whose survival and growth are dominated by constitutively active PI3K/Akt signaling.

Ref.: Chen, Y. L.; Law, P.- Y.; Loh, H. H. Inhibition of PI3K/Akt Signaling: An Emerging Paradigm for Targeted Cancer. *Curr Med Chem Anticancer Agents.* 2005 Nov; 5(6): 575-589.

Product Description	Number of Compounds	Target	Source	Input Libraries
Phosphatidylinositol 3-Kinase focused library	**2040**	Phosphatidyl-inositol 3-Kinase (PI3K)	*Homo sapiens*	OTAVA Stock Collection **70,000 compounds** + Life Chemicals Stock Collection **300,000 compounds**

3-Phosphoinositide-Dependent Kinase-1

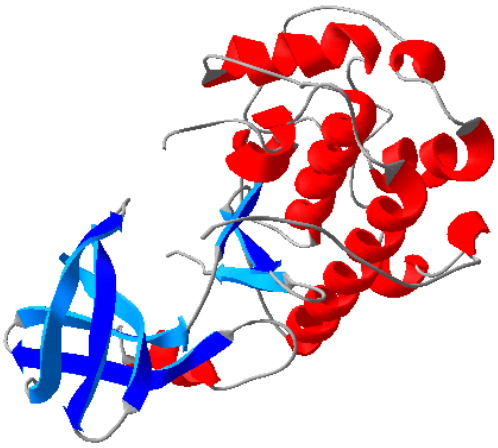


The PI3K/PDK-1/Akt signaling cascade is a convergence point for a plethora of receptor tyrosine kinase and cytokine-mediated pathways. By regulating cell proliferation and survival, it provides a framework for understanding the role of various extracellular trophic factors in cell survival. Dysregulation of this signaling cascade, through PTEN mutations and/or constitutive growth factor-receptor activation, results in Akt up-regulation, which consequently promotes tumor invasiveness, angiogenesis, and progression. Thus, PDK-1/Akt signaling inhibitors are of growing importance, recognized for their potential to be developed into useful chemotherapeutic or chemopreventative agents.

Ref.: Zhu J, Huang JW, Tseng PH, Yang YT, Fowble J, Shiau CW, Shaw YJ, Kulp SK, Chen CS. From the cyclooxygenase-2 inhibitor celecoxib to a novel class of 3-phosphoinositide-dependent protein kinase-1 inhibitors. *Cancer Res*. 2004 Jun 15; 64(12): 4309-4318.

Product Description	Number of Compounds	Target	Source	Input Libraries
3-Phosphoinositide-Dependent Kinase-1 focused library	**1975**	3-Phosphoinositide-Dependent Kinase-1 (PDK-1)	*Homo sapiens*	OTAVA Stock Collection **70,000 compounds** + Life Chemicals Stock Collection **300,000 compounds**

Cyclin-Dependent Kinase 2



The cell division cycle is controlled by cyclin-dependent kinases (cdk), which consist of a catalytic subunit (cdk1-cdk8) and a regulatory subunit (cyclin A-cyclin H). Cyclin-dependent kinase 2 (CDK2) plays a critical role in the G1- to S-phase checkpoint of the cell cycle.

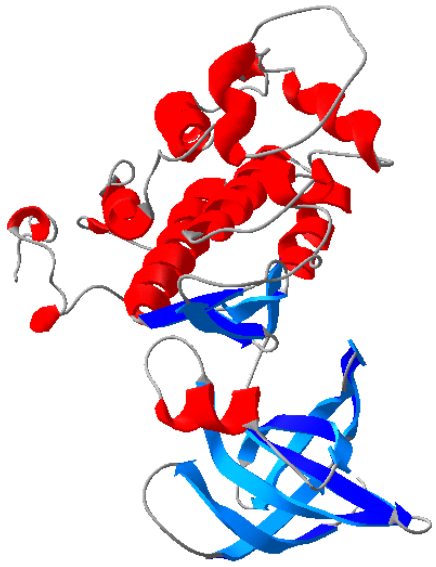
Like several other protein kinases, CDK2 consists of a relatively small N-terminal domain that is rich in B-sheet structure, and a larger C-terminal domain which is predominantly A-helical. The ATP-binding site is located in a pocket between the two domains.

Inhibition of cyclin-dependent kinases is a theme of major interest in current anti-cancer agents research. Different classes of chemical inhibitors of these enzymes have been identified during the past decade. Furthermore, the structural basis of inhibition has been elucidated by X-ray crystallography studies of CDK2. Several types of cdk inhibitors have been described so far: staurosporine, flavopiridole, butyrolactone purine derivatives, indirubin, paullones, amongst others.

Ref.: Morgan, D.O. Cyclin-dependent kinases: engines, clocks, and microprocessors. *Annu. Rev. Cell. Dev. Biol.*, 1997, 13: 261-291.

Product Description	Number of Compounds	Target	Source	Input Library
Cyclin-Dependent Kinase 2 focused library	**1281**	Cyclin-Dependent Kinase 2 (CDK2)	*Homo sapiens*	OTAVA Stock Collection **70,000 compounds**

Glycogen Synthase Kinase-3



Glycogen synthase kinase-3 (GSK3) was initially identified more than two decades ago as an enzyme involved in the control of glycogen metabolism. In recent years it has been shown to have key roles in regulating a diverse range of cellular functions, which have prompted efforts to develop GSK3 inhibitors as therapeutics.

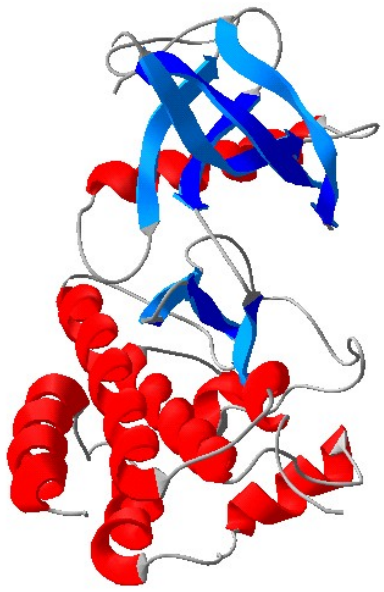
GSK3 inhibitors have now been shown to be effective in normalizing blood glucose levels in animal models of type 2 diabetes. Their effects appear to result primarily from an increase in hepatic glycogen synthesis and a decrease in hepatic gluconeogenesis.

GSK3 inhibitors might also have the potential to treat neurodegenerative disorders, such as Alzheimer's disease. For example, there is recent evidence that GSK3 increases the production of ß -amyloid, which has a key role in the pathogenesis of Alzheimer's disease. Inhibition of GSK3 might reduce ß-amyloid levels.

Ref.: Philip Cohen & Michel Goedert. GSK3 inhibitors: development and therapeutic potential. *Nat Rev Drug Discov.* 2004 Jun; 3(6): 479-487.

Product Description	Number of Compounds	Target	Source	Input Library
Glycogen Synthase Kinase-3 focused library	**980**	Glycogen Synthase Kinase-3 (GSK-3)	*Homo sapiens*	OTAVA Stock Collection **70,000 compounds**

Fibroblast Growth Factor Receptor 1 Tyrosine Kinase

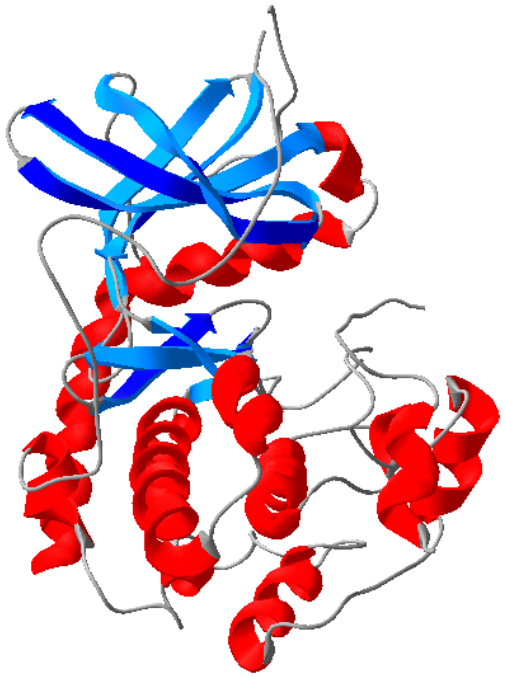


Fibroblast growth factor receptors (FGFR) are members of a family of polypeptides synthesized by a variety of cell types during the processes of embryonic development. FGFRs have been detected in normal and malignant cells, and are involved in biological events that include mitogenic and angiogenic activity. Consequently, they play a crucial role in cell differentiation and development. To activate signal transduction pathways, FGFRs are coupled to fibroblast growth factors (FGF) and heparan sulfate (HS) proteoglycans to form a biologically fundamental ternary complex. Based on these considerations, a variety of inhibitors able to block the signaling cascade through a direct interaction with FGFRs have been designed and investigated for their biological properties related to antiangiogenesis and antitumor activity.

Ref.: Manetti F, Botta M. Small-molecule inhibitors of fibroblast growth factor receptor (FGFR) tyrosine kinases (TK) *Curr Pharm Des.* 2003; 9(7): 567-581.

Product Description	Number of Compounds	Target	Source	Input Libraries
Fibroblast Growth Factor Receptor 1 Tyrosine Kinase focused library	**1761**	Fibroblast Growth Factor Receptor 1 Tyrosine Kinase (FGFR1K)	*Homo sapiens*	OTAVA Stock Collection **70,000 compounds** + Life Chemicals Stock Collection **300,000 compounds**

cAMP-Dependent Protein Kinase

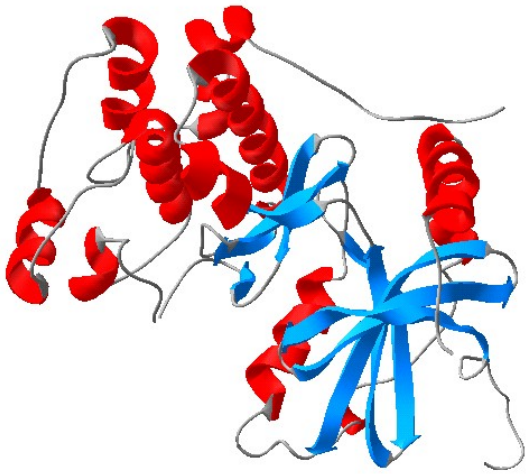


In mammalian cells a ubiquitous enzyme known as protein kinase A (or PKA) regulates a large number of processes, including growth, development, memory, metabolism, and gene expression. Failure to keep PKA under control can have disastrous consequences, such as development of cancer. The task of keeping PKA in check falls to cyclic adenosine monophosphate (*c*AMP), a messenger molecule involved in transmitting signals within the cell. Drugs based on inhibiting PKA activity are under development with the aim of treating disease. Thus, understanding how *c*AMP accomplishes this task is of interest to life scientists.

Ref.: C. Kim, N.-H. Xuong, and S.S. Taylor. Crystal structure of a complex between catalytic and regulatory (RI?) subunits of PKA. *Science,* 307, 690 (2005).

Product Description	Number of Compounds	Target	Source	Input Libraries
cAMP-Dependent Protein Kinase focused library	**1877**	cAMP-Dependent Protein Kinase (PKA)	*Mus musculus*	OTAVA Stock Collection **70,000 compounds** + Life Chemicals Stock Collection **300,000 compounds**

Aurora B Kinase



The serine/threonine protein kinases of the aurora family of genes play a critical role in the regulation of key cell cycle processes. One such kinase, Aurora B, mediates chromosome segregation by ensuring orientation of sister chromatids. Over-expression of Aurora B in diploid human cells induces multinuclearity.

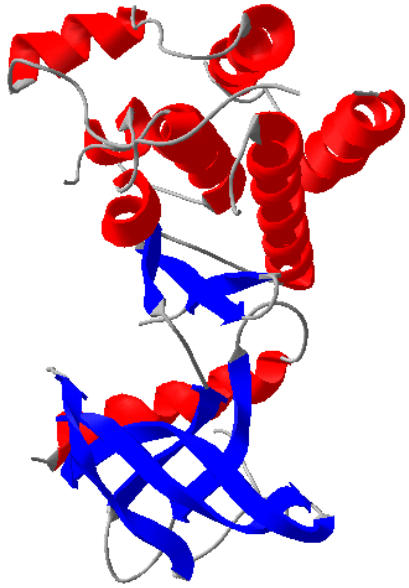
In human thyroid carcinomas, cell lines originating from different histotypes displayed an increase in Aurora B expression. Immunohistochemical analysis of archived samples revealed a high expression of Aurora B in anaplastic thyroid carcinomas; conversely, Aurora B expression was not detectable in normal thyroid tissue. Real-time PCR analysis confirmed a strong expression of Aurora B in anaplastic thyroid carcinomas.

The inhibition of Aurora B expression induced by RNA interference, or by using an inhibitor of Aurora kinase activity, significantly reduced the growth of thyroid anaplastic carcinoma cells. Therefore, developing Aurora B kinase inhibitors could lead to the discovery of potent anti-cancer drugs.

Ref.: Sorrentino et al. Aurora B overexpression associates with the thyroid carcinoma undifferentiated phenotype and is required for thyroid carcinoma cell proliferation. *J Clin Endocrinol Metab.* 2005 Feb; 90(2): 928-935.

Product Description	Number of Compounds	Target	Source	Input Libraries
Aurora B Kinase focused library	**2069**	Aurora B Kinase (AURKB)	*Xenopus laevis*	OTAVA Stock Collection **70,000 compounds** + Life Chemicals Stock Collection **300,000 compounds**

Vascular Endothelial Growth Factor Receptor-2 Kinase



Tumor-induced angiogenesis is a requirement for solid tumor growth and metastates. Vascular endothelial growth factor (VEGF) is a stimulator of tumor angiogenesis, and a promoter of endothelial cell proliferation and migration. To initiate this activity, VEGF binds to VEGF-specific tyrosine kinase receptors expressed on the cell surface. Among these receptors, vascular endothelial growth factor receptor-2 (VEGFR2) is the principal one through which VEGFs exert their effects.

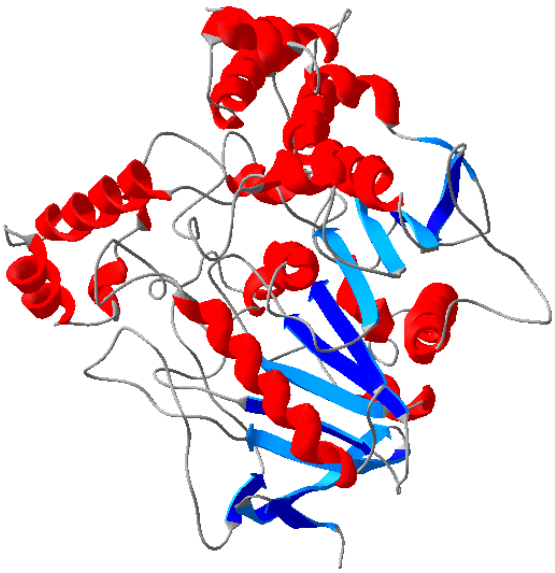
Consequently, the VEGF signaling pathway has long been the target of research aimed at discovering therapies that limit the tumor angiogenesis process. Recently, Genentech's anti-VEGF monoclonal antibody bevacizumab was approved, while some small molecule inhibitors of VEGFR2 have advanced to the clinical stages of drug development.

Ref.: Borzilleri, R. M. *et al*. Discovery and Evaluation of BMS-605541, a Selective and Orally Efficacious Inhibitor of Vascular Endothelial Growth Factor Receptor-2. *Journal of Medicinal Chemistry* (2006), 49(13), 3766-3769.

Ref.: Underiner T.L.; Ruggeri B.; Gingrich D.E. Development of vascular endothelial growth factor receptor (VEGFR) kinase inhibitors as anti-angiogenic agents in cancer therapy. *Curr Med Chem.* 2004 Mar; 11(6): 731-45.

Product Description	Number of Compounds	Target	Source	Input Library
Vascular Endothelial Growth Factor Receptor-2 Kinase focused library	**2235**	Vascular Endothelial Growth Factor Receptor-2 Kinase (VEGFR2)	*Homo sapiens*	OTAVA Stock Collection **70,000 compounds** + Life Chemicals Stock Collection **300,000 compounds**

Acetylcholinesterase



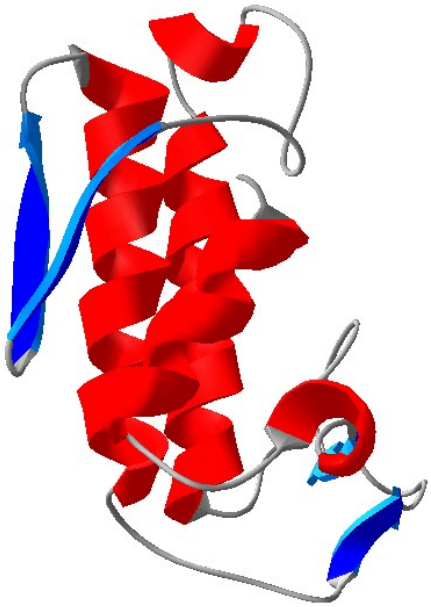
Over the last decade, acetylcholinesterase inhibitors (AChEIs) have been the mainstays of Alzheimer's Disease (AD) therapy. They work by increasing acetylcholine concentrations,thus increasing their availability for synaptic transmission as well. In the U.S. and Europe, previously marketed agents in this class include tacrine (Cognex, Parke Davis), donepezil (Aricept, Pfizer), and rivastigmine (Exelon, Novartis). In clinical trials, most of these products were shown to improve cognitive function modestly, and to have acceptable tolerability profiles. The exception is tacrine, which is rarely used because of its potential to induce severe hepatic complications.

Unfortunately, the current therapies for AD treat only the symptoms and do not halt the progression of the disease. Nonetheless, these agents are the only compounds approved for the treatment of AD. Therefore, the development of newer agents that are designed to be more effective and have fewer side effects is a high priority.

Ref.: Martin S. Maltz and Harold L. Kirschenbaum. Galantamine: A New Acetylcholinesterase Inhibitor for the Treatment of Alzheimer's Disease. *P&T*, 2002, Vol. 27 No. 3, 135-138.

Product Description	Number of Compounds	Target	Source	Input Library
Acetylcholinesterase focused library	**828**	Acetylcholinesterase (AChE)	*Homo sapiens*	OTAVA Stock Collection **70,000 compounds**

Phospholipase A2



Ref.: Meyer MC, Rastogi P, Beckett CS, McHowat J. *Curr Pharm Des.* 2005;11(10):1301-1312.

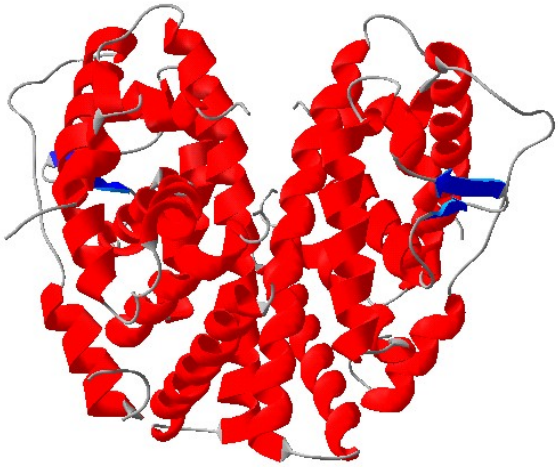
Phospholipase A(2)-catalyzed hydrolysis of membrane phospholipids results in the stoichiometric production of a free fatty acid (most importantly arachidonic acid) and a lysophospholipid. Both of these phospholipid metabolites serve as precursors for inflammatory mediators such as eicosanoids or platelet-activating factor (PAF).

Since the initial discovery that non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis, a vast amount of drug development has been geared towards the selective inhibition of the production of the inflammatory metabolites of arachidonic acid. This research has culminated in the development of selective cyclooxygenase-2 (COX-2) inhibitors that act on the inducible, inflammatory COX enzyme, but do not affect the constitutive prostaglandin synthesis in cells being mediated through COX-1.

The development of PLA(2) inhibitors as potential anti-inflammatory agents has also been extensively pursued, as the release of arachidonic acid from membrane phospholipids by PLA(3) is one of the rate-limiting factors for eicosanoid production. In addition to the production of eicosanoids, PLA(2)-catalyzed membrane phospholipid hydrolysis is also the initiating step in the generation of PAF, a potent inflammatory agent. Thus, inhibition of PLA(2) activity should, in theory, be a more effective anti-inflammatory approach.

Product Description	Number of Compounds	Target	Source	Input Library
Phospholipase A2 focused library	**1018**	Phospholipase A2 (PLA(2))	*Homo sapiens*	OTAVA Stock Collection **70,000 compounds**

Estrogen Receptor (Alpha)



Ref.: Namba, R.; Young, L.J.T.; Maglione, J.E.; McGoldrick, E.T.; Liu, S.; Wurz, G.T.; DeGregorio, M.W.; Borowsky, A.D.; MacLeod, C.L.; Cardiff, R.D.; Gregg, J.P. Selective estrogen receptor modulators inhibit growth and progression of premalignant lesions in a mouse model of ductal carcinoma in situ. *Breast Cancer Research* 2005, 7: R881-R889.

The sex steroid hormone estrogen is important in both men and women for a variety of physiologic processes. Nearly all of the effects of estrogens are mediated through their binding to nuclear proteins called estrogen receptors (ER): transcription factors that regulate expression of estrogen-responsive genes. Other natural compounds and synthetic drugs are also capable of binding to the ER. Some of these compounds mimic the effects of estrogen; others have more antiestrogenic activity.

The recognition that certain ligands can modulate the ER in different ways has led to an explosion in the development of new drugs tailored to have specific and selective effects on ER function. These drugs, of which tamoxifen is the prototype, are now collectively known as selective estrogen receptor modulators (SERMs). SERMs can be conveniently divided into three major categories: (1) triphenyl-ethylene derivatives like tamoxifen, (2) other nonsteroidal compounds, and (3) steroidal compounds that have more complete antiestrogenic activity.

It is now clear that SERMs with activities ranging from nearly full estrogenic activity to almost pure antiestrogenic activity can be developed for specific therapeutic uses, ranging from treatment and prevention of osteoporosis to the prevention and/or treatment of breast cancer.

Product Description	Number of Compounds	Target	Source	Input Library
Estrogen Receptor (Alpha) focused library	**935**	Estrogen Receptor (Alpha)	*Homo sapiens*	OTAVA Stock Collection **70,000 compounds**

Receptor-Based Target-Focused Libraries: preparation on request

On your request, 114 protein kinase receptor-based focused libraries could be prepared by our specialists.

How can you to get your focused library?

STEP1 Choose your Kinase target from the list below.

STEP2 Send an email to mol.design@otavachemicals.com or north.america@otavachemicals.com. Our experts will contact you shortly.

STEP3 Cherry-pick from your kinase focused library and order compounds of your choice.

The term of focused library preparation is **1 MONTH.**

The typical focused library contain from **1,000 to 2,000 cmpds.**

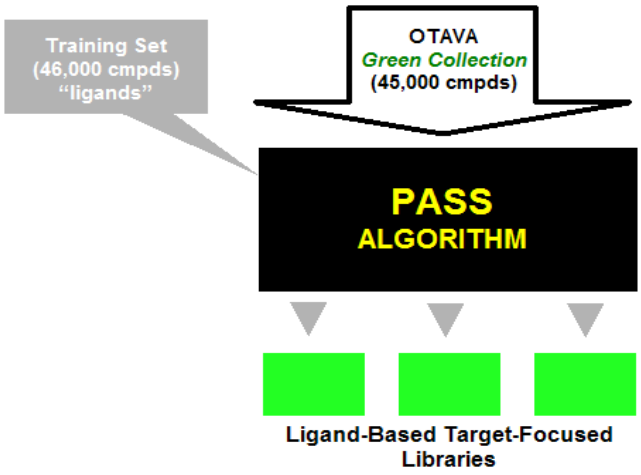
INTERESTING?
Fell free to contact us for detailed information.

List of OTAVA's Receptor--Based Target-Focused libraries you may request for:

ABL1
ACVR2B
AKT1
AKT2
AURKA
BRAF
CAMK1D
CAMK1G
CAMK2B
CAMK2D
CAMK2G
CASK
CDK2
CDK5
CDK6
CDK7
CDK9
CHEK1
CHEK2
CLK1
CLK3
CSF1R
CSK
CSNK1G1
CSNK2A1
DAPK1
DAPK2
DAPK3
DMPK
EGFR
EPHA2
EPHA3
EPHA5
EPHA7
EPHB2
EPHB4
ERBB4
FES
FGFR1
FGFR2
FLT3
FYN
GRK6
GSK3B
HCK
IGF1R
INSR
IRAK4
ITK
JAK3
KDR
KIT
LCK
MAP2K1
MAP2K2
MAP3K5
MAPK1
MAPK10
MAPK12
MAPK13
MAPK14
MAPK6
MAPK8
MAPKAPK2
MARK1
MARK3
MERTK
MET
MKNK1
MKNK2
NEK2
OXSR1
PAK1
PAK4
PAK6
PAK7
PDK1
PDK2
PDK3
PDK4
PDPK1
PIK3CA
PIK3CG
PIM1
PIM2
PLK1
PLK4
PRKAA2
PRKCB1
PRKCI
PRKCQ
PTK2
PTK2B
RET
ROCK1
RPS6KA2
RPS6KA5
SLK
SRC
SRPK1
STK10
STK16
STK24
STK4
SYK
TEK
TGFBR1
TNK2
TTK
TTN
VRK2
VRK3
WEE1
ZAP70

Ligand-Based Target-Focused Libraries

Building Ligand-Based Target-Focused Libraries



Design of Ligand-Based focused libraries.

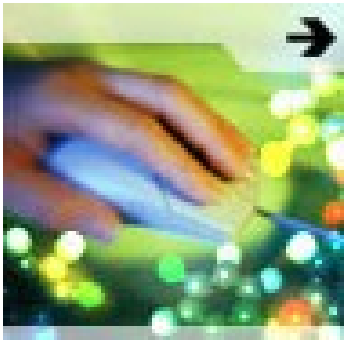
This approach was employed for OTAVA's Ligand-Based Target-Focused libraries.

Not every biological target has a structure characterized well enough for a Receptor-Based approach to library design. Nevertheless, it is still possible to generate libraries of compounds predicted to interact with that target using a Ligand-Based approach.

In the Ligand-Based approach, it is sufficient to have a number of compounds (ligands) with known biological activity against the target. A collection of in-house chemicals is then screened *in silico* against desired features related to those ligands.

To do this, OTAVA employs the PASS (Prediction of Activity Spectra for Substances) algorithm. A set of well characterized biologically active compounds, known as a *training set*, is used in the algorithm, and supplies the ligands of known activity. The PASS algorithm, using the training set, makes predictions of 4535 different kinds of biological activities for the compounds of the in-house collection. These activities fall under the categories of pharmacological effects, molecular mechanisms, and side effects and toxicities. The compounds of the in-house collection that meet the probability threshold for possessing a particular biological activity become members of that library.

Building Ligand-Based Target-Focused Libraries, *continued*



The quality of a target-focused library generated this way relies heavily on the size and quality of the training set. The training set is comprised of 46,000 biologically active compounds: 30,000 are drug candidates under current clinical or advanced pre-clinical testing, and 16,000 are previously launched drugs. This set has been compiled since 1972, from a variety of sources, including publications, patents, and databases.

OTAVA's Ligand-Based Target-Focused libraries were all created using its drug-like in-house *Green Collection* of compounds. The *Green Collection* library consists of more than 45,000 compounds, and was prepared by applying the Lipinsky rules to the OTAVA Stock Collection + Life Chemicals Stock Collection (500,000 compounds).

247 Ligand-Based Target-Focused libraries are available

List of OTAVA's Ligand-Based Target-Focused libraries

2,3 Oxidosqualene lanosterol cyclase inhibitor
5 Hydroxytryptamine 1 antagonist
5 Hydroxytryptamine 1A agonist
5 Hydroxytryptamine 1D antagonist
5 Hydroxytryptamine 2 agonist
5 Hydroxytryptamine 2A antagonist
5 Hydroxytryptamine 2C antagonist
5 Hydroxytryptamine 3 agonist
5 Hydroxytryptamine antagonist
5 Hydroxytryptamine uptake inhibitor
Acaricide
Acetyl CoA transferase inhibitor
Acetylcholine M2 receptor antagonist
Acetylcholine M3 receptor antagonist
Acetylcholine muscarinic antagonist
Acetylcholine nicotinic agonist
Acetylcholine nicotinic antagonist
Acetylcholinesterase inhibitor
Acute neurologic disorders treatment
ADP ribose polymerase inhibitor
Adrenaline antagonist
Adrenaline uptake inhibitor
Adrenergic
Adrenergic, ophthalmic
Aldose reductase inhibitor
Alpha 1 adrenoreceptor agonist
Alpha 1 adrenoreceptor antagonist
Alpha 1a adrenoreceptor antagonist
Alpha 2 adrenoreceptor agonist
Alpha adrenoreceptor agonist
Alpha adrenoreceptor antagonist
Analeptic
Analgesic

List of OTAVA's Ligand-Based Target-Focused libraries, *continued*

Analgesic, non-opioid
Anesthetic
Anesthetic general
Anesthetic inhalation
Anesthetic local
Anorexic
Antiadrenergic
Antiallergic
Antiamebic
Antianginal
Antiarrhythmic
Antibacterial
Anticataract
Anticoagulant
Anticonvulsant
Antidepressant
Antidiabetic
Antidiabetic symptomatic
Antifungal
Antiglaucomic
Anti-Helicobacter pylori
Antihelmintic
Antihistaminic
Antihypercholesterolemic
Antihypertensive
Antiinfective
Antiinflammatory
Antiinflammatory, intestinal
Antiischemic, cerebral
Antimigraine
Antimycobacterial
Antineoplastic
Antineoplastic enhancer
Antiobesity

List of OTAVA's Ligand-Based Target-Focused libraries, *continued*

Antiosteoporotic
Antioxidant
Antiparasitic
Antiparkinsonian
Antiprotozoal
Antiprotozoal (Coccidial)
Antipsoriatic
Antipsychotic
Antipyretic
Antischistosomal
Antisecretoric
Antiseptic
Antithrombotic
Antitreponemal
Antitrypanosomal
Antituberculosic
Antitussive
Antiulcerative
Antiuremic
Antiviral
Antiviral (hepatitis C)
Antiviral (hepatitis)
Antiviral (poxvirus)
Antiviral (trachoma)
Anxiolytic
Benzodiazepine agonist
Benzodiazepine agonist partial
Bone diseases treatment
Bone formation stimulant
Bronchodilator
Calcium channel antagonist
Capillary fragility treatment
Carcinogenic

List of OTAVA's Ligand-Based Target-Focused libraries, *continued*

Cardiodepressant
Cardiotonic
Cathepsin B inhibitor
Cathepsin L inhibitor
Choleretic
Cholesterol synthesis inhibitor
Cholinergic
Cholinergic antagonist
CNS active muscle relaxant
Coagulant
Cognition disorders treatment
Corticotropin releasing factor 1 receptor antagonist
Cyclic GMP phosphodiesterase inhibitor
Cyclin-dependent kinase inhibitor
Cyclooxygenase inhibitor
Cytostatic
Dermatologic
Dihydroorotate dehydrogenase inhibitor
Dihydropteroate synthase inhibitor
Diuretic
Diuretic inhibitor
DNA synthesis inhibitor
DNA topoisomerase inhibitor
Dopamine autoreceptor agonist
Dopamine D3 agonist
Dopamine D3 antagonist
Dopamine D4 antagonist
Embryotoxic
Endothelial growth factor antagonist
Endothelin A receptor antagonist
Endothelin B receptor antagonist
Endothelin receptor antagonist

List of OTAVA's Ligand-Based Target-Focused libraries, *continued*

Epidermal growth factor receptor kinase inhibitor
Excitatory amino acid antagonist
Expectorant
Factor VIIa inhibitor
Factor Xa inhibitor
Free radical scavenger
GABA A receptor agonist
Gastrin inhibitor
Glucagon receptor antagonist
Growth hormone agonist
Growth stimulant
HCV serine protease inhibitor
Hemostatic
Hepatic disorders treatment
Hepatoprotectant
Histamine antagonist
Histamine release inhibitor
Hypertensive
Hypoglycemic
Hypolipemic
Hypotermic
Insecticide
Insulin secretagoues
Interleukin 8 antagonist
Irritable Bowel syndrome treatment
Kallikrein inhibitor
Keratolytic
Lactamase C inhibitor
Leukotriene B4 antagonist
Leukotriene E4 antagonist
Lipase inhibitor
Lipid peroxidase inhibitor
Lipoxygenase inhibitor

List of OTAVA's Ligand-Based Target-Focused libraries, *continued*

Liver fibrosis treatment
Maillard reaction inhibitor
MAO inhibitor
MAP kinase inhibitor
Matrix metalloproteinase 1 inhibitor
Matrix metalloproteinase inhibitor
Mediator release inhibitor
Metalloproteinase inhibitor
Metalloproteinase-9 inhibitor
Miotic
Muscle relaxant
Mutagenic
Narcotic
Neurokinin 1 antagonist
Neurokinin 3 antagonist
Neuropeptide antagonist
Neuropeptide Y antagonist
Non-steroidal antiinflammatory agent
Oxytocic
Oxytocin antagonist
P38 kinase inhibitor
P38 MAP kinase inhibitor
Para amino benzoic acid antagonist
Peroxisome proliferator-activated receptor agonist
Peroxisome proliferator-activated receptor gamma agonist
Phosphodiesterase inhibitor
Phosphodiesterase V inhibitor
Phospholipase A2 inhibitor
Phospholipase inhibitor
Platelet aggregation inhibitor
Polarisation inhibitor
Potassium channel antagonist
Prostaglandin antagonist
Prostaglandin synthase inhibitor

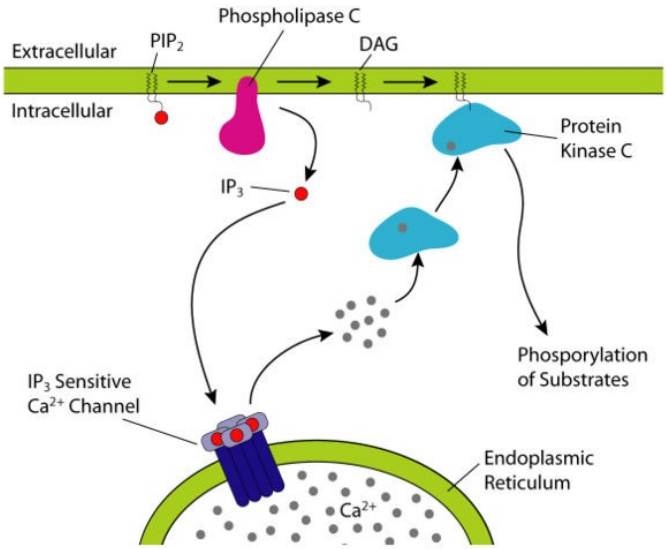
List of OTAVA's Ligand-Based Target-Focused libraries, *continued*

Protease inhibitor
Protein synthesis inhibitor
Psychotropic
Radioprotector
Radiosensitizer
Reductant
Renal disease treatment
Respiratory analeptic
Restenosis treatment
Reverse transcriptase inhibitor
Ribonucleoside diphosphate reductase inhibitor
Ribonucleoside triphosphate reductase inhibitor
Ribonucleotide reductase inhibitor
S-adenosyl-L-methionine decarboxylase inhibitor
Saluretic
Sedative
Sigma receptor antagonist
Skeletal muscle relaxant
Skin irritative effect
Sleep disorders treatment
Sodium channel blocker
Sodium channel blocker class Ib
Spasmogenic
Spasmolytic
Spasmolytic, Papaverin-like
Spasmolytic, urinary
Stromelysin inhibitor
Substance P antagonist
Sweetener
Teratogen
Thromboxane A2 antagonist
Thromboxane antagonist
Thromboxane synthase inhibitor

List of OTAVA's Ligand-Based Target-Focused libraries, *continued*

TNF convertase inhibitor
Topoisomerase inhibitor
Trypsin inhibitor
Tryptase inhibitor
Tyrosine kinase inhibitor
Ulcerogenic
Uric acid diuretic
Uricosuric
Urinary incontinence treatment
Uterine relaxant
Vanilloid antagonist
Vasodilator
Vasodilator, coronary
VLA antagonist
Xanthine oxidase inhibitor

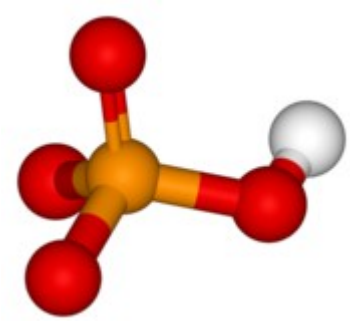
Lipid Signaling Inhibitors



Lipids of the cell membrane are often used as second messengers in cellular signaling. These messengers are activated by various extracellular signals, including inflammatory cytokines and growth factors. Once activated, they participate in a variety of cell activities, of which proliferation, differentiation, and apoptosis are examples. Lipid signaling is thought to play a critical role in carcinogenesis.

Product Description
2,3-Oxidosqualene lanosterol cyclase inhibitor library
5-Lipoxygenase inhibitor library
Cyclooxygenase inhibitor library
Lipid peroxidase inhibitor library

Phosphorylation/Dephosphorylation Inhibitors

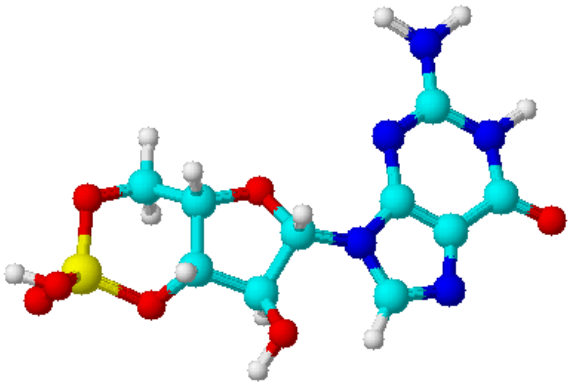


Phosphorylation refers to the incorporation of an inorganic phosphate group into a molecule. In animal cells, the phosphorylation event plays a critical role, as various enzymes and receptors are activated or deactivated by the addition or the removal of a phosphate group. Indeed, phosphorylation can dramatically alter the physical properties of a biomolecule.

The agents responsible for phosphorylation are protein kinases, whereas protein phosphatases (of which ATPase is an example) are responsible for dephosphorylation. Kinases and phosphatases are found ubiquitously in many different cell signaling processes.

Product Description
Epidermal growth factor receptor kinase inhibitor library
Tyrosine kinase inhibitor library
ATPase inhibitor library
Adenylate cyclase inhibitor library
Sodium channel blocker library

Phosphodiesterase Inhibitors



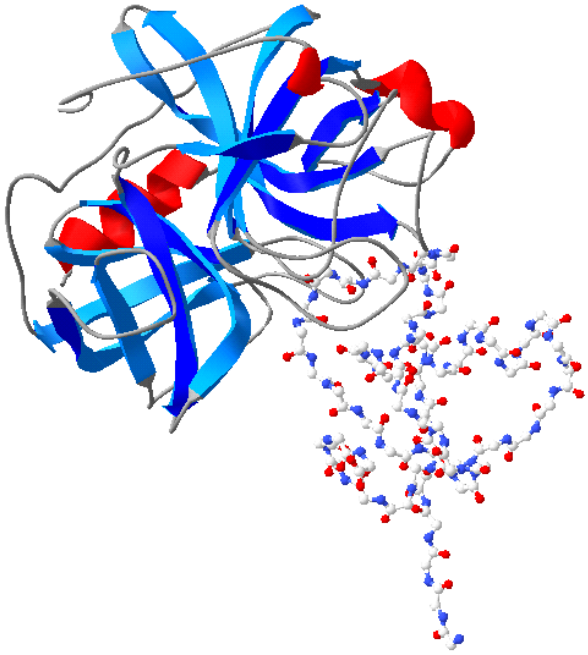
Phosphodiesterases are a group of enzymes that catalyze the hydrolysis of the second messenger molecules cAMP and cGMP. As such, phosphodiesterases play an important role in signal transduction events.

Phosphodiesterases have been the target of pharmacological therapies in the past. The classic example is that of sildenafil (Viagra). Sildenafil inhibits the cGMP-specific phosphodiesterase type 5, and thereby increases the vasodilatory effects of cGMP. This approach has been successful in the treatment of erectile dysfunction.

It has been speculated that phosphodiesterase inhibitors may one day be developed into anti-hypertensives, anti-depressants, and anti-psychotics.

Product Description
Cyclic AMP phosphodiesterase inhibitor library
Cyclic GMP phosphodiesterase inhibitor library
Phosphodiesterase V inhibitor library

Protease Inhibitors

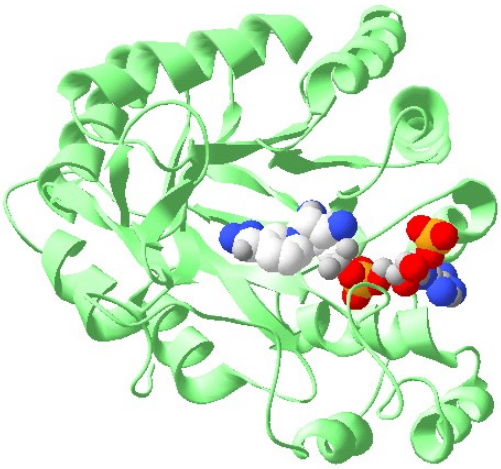


Proteases are enzymes that hydrolyze the peptide bond between two amino acids. These enzymes are involved in a variety of processes, from food digestion to signaling cascades. Indeed, the proteolytic action can deactivate a protein, by reducing it down to its building blocks, or activate it, by modifying its overall structure.

Examples of proteases include the HCV serine protease and cathepsin B. The hepatitis virus makes use of a serine protease for cleavage of its polypeptides during replication. Cathepsin B is a protease that occurs in cells found in all animals, and is thought to be implicated in cancer, Alzheimer's disease, arthritis, and stroke. Finding inhibitors of these targets may thus prove to be beneficial.

Product Description
HCV serine protease inhibitor library
Cathepsin B inhibitor library

Reductase Inhibitors



A reductase is simply an enzyme that catalyzes the reduction of a biochemical substrate. Reductases are involved in many different cellular processes, from participating in the building of nucleotides to the processing of carbohydrates.

Ribonucleoside di- and tri-phosphate reductases participate in the building of deoxyribonucleotides for DNA synthesis. Increased activity of these enzymes has been associated with malignancies and tumor growth. Inhibitors of these enzymes may slow the advance of cancerous growth.

Aldose reductase is an enzyme that is present all over the body. It is partly involved in converting glucose into fructose. When the glucose level rises in a diabetic, so does aldose reductase activity. Inhibitors of aldose reductase might prevent the associated damage to the nerves and eyes in a diabetic.

Product Description
Aldose reductase inhibitor library
Ribonucleoside diphosphate reductase inhibitor library (and) Ribonucleoside triphosphate reductase inhibitor library