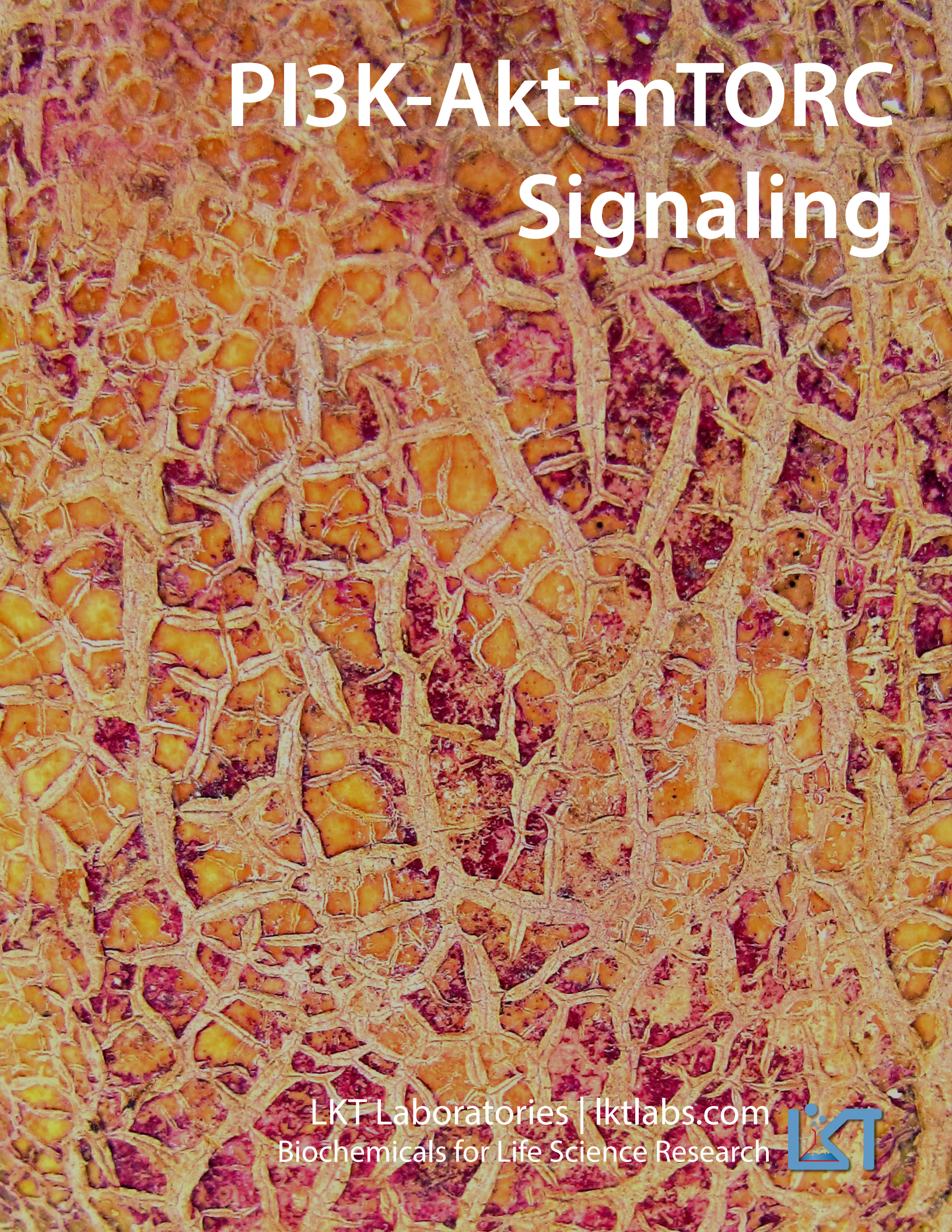
PI3K-Akt-mTORC Signaling



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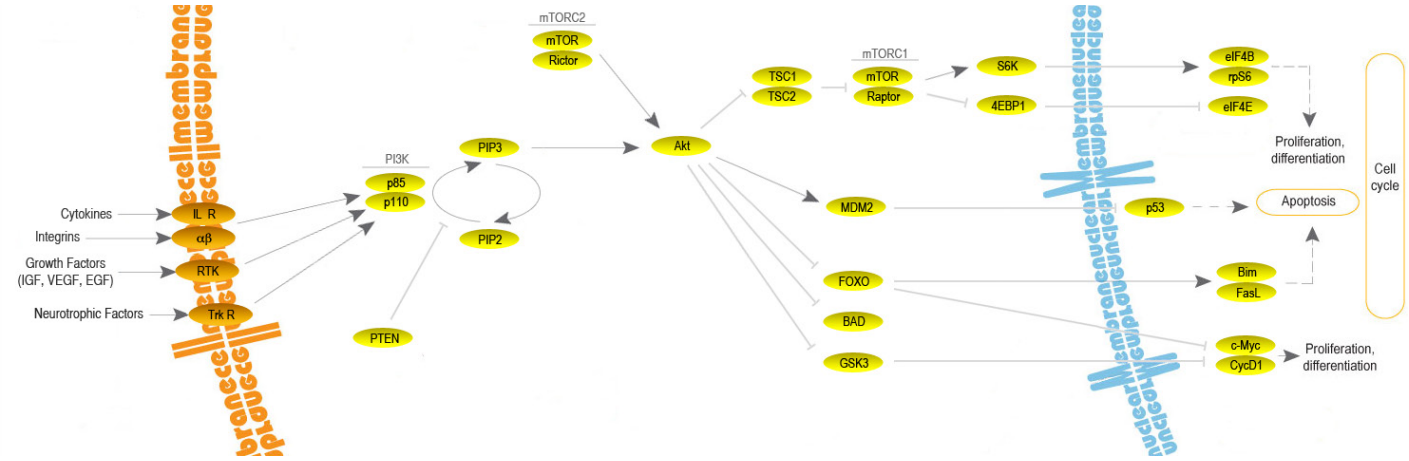
Biochemicals for Life Science Research

Introduction to the PI3K-Akt-mTORC signaling pathway



The PI3K-Akt-mTORC signaling pathway plays a significant role in cell survival. It transduces extracellular signaling from ligands of receptor tyrosine kinases in the cell membrane to nuclear transcription factors that regulate gene product synthesis. Activation of this pathway, Akt in particular, enhances the survival of cells by inhibiting pro-apoptotic proteins, allowing for continual cell proliferation. Overactive signaling by this pathway is found in many cancers, where it has enabled unchecked cell growth that leads to tumor initiation or progression. As a result, its proteins and receptors make excellent targets for anticancer chemotherapeutic compounds. In stem cell research, this pathway can be used to alter the balance between stem cell proliferation and differentiation. Akt promotes cell growth in part by indirect activation of mTORC1, an important regulator of translation initiation. Modulation of the PI3K-Akt-mTORC to maintain pluripotency or promote differentiation further increases the utility of small molecules targeting this pathway.

mTOR

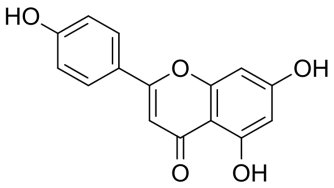
ID	Product Name	Description	Purity
A4617	Aloe-emodin	Inhibits mTORC2	≥98%
A9710	AZD2014	Inhibits mTORC1/2	≥98%
A9914	AZD-8055	Inhibits mTORC1/2	≥98%
B1996	BEZ235	Inhibits mTORC1/2 and PI3K	≥98%
C8069	Curcumin	Inhibits mTORC2's phosphorylation activity	≥98%
E5057	Emodin	Inhibits mTORC2	≥95%
E8419	Everolimus	Inhibits mTORC1	≥98%
G1209	GDC-0980	Inhibits mTORC1/2 and PI3K	≥98%
G7342	GSK2126458	Inhibits mTORC1/2 and PI3K	≥99%
I5440	INK128	Inhibits mTORC1/2	≥99%
M3196	MHY-1485	Activates mTORC1/2	≥98%
N8604	NVP-BGT226	Inhibits mTORC1/2 and PI3K	≥98%
O7332	OSI-027	Inhibits mTORC1/2	≥98%
P2002	PF-04691502	Inhibits mTORC1/2 and PI3K	≥98%
P4132	PKI-402	Inhibits mTORC1/2 and p110α PI3K	≥98%
P6004	PP-242	Inhibits mTORC1/2	≥98%
R0161	Rapamycin	Inhibits mTORC1/2	≥98%
S8253	Sunitinib Malate	Inhibits mTORC1	≥98%
T176503	Temsirolimus	Inhibits mTORC1/2	≥98%
T5870	Torin 1	Inhibits mTORC1/2	≥98%
T5871	Torin 2	Inhibits mTORC1/2	≥98%
T6833	Triacetyl Aloe-emodin	Inhibits mTORC2	≥98%

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that is the catalytic subunit of complexes mTORC1 and mTORC2. mTORC1 includes mTOR, Raptor, MLST8, PRAS40, and DEPTOR and is involved in energy homeostasis signaling. Akt phosphorylates regulatory protein TSC2, inactivating the TSC1/TSC2 heterodimer and limiting its ability to inhibit mTORC1; this results in continual activation of mTORC1. mTORC2 is composed of mTOR, Rictor, MLST8, and mSin1 and plays a role in cell survival. mTORC2 is responsible for phosphorylating Akt, leading to its full activation and downstream anti-apoptotic effects.

Inhibitors of mTOR and mTORC1/2 exhibit chemotherapeutic benefit in the treatment of many cancers; compounds that inhibit this kinase and its complex include sunitinib maleate, everolimus, INK128, and curcumin.

PI3K

Phosphoinositide 3-kinases (PI3Ks) compose a category of enzymes that are responsible for the formation of phosphatidylinositol-3-phosphate (PIP) products such as PIP, PIP2, and PIP3. PI3Ks are subdivided into three classes; class I PI3Ks are responsible for cell survival signaling. Class I PI3Ks are primarily composed of a p85 regulatory subunit and a p110 catalytic subunit. Activation of PI3Ks by growth factor and survival factor receptor tyrosine kinases induces production of PIP3, which together with mTOR, activates Akt. Specific isoforms of the p110 subunit of class I PI3Ks are being studied as targets in the development of new anticancer compounds, such as BYL719, GSK2636771, and CAL101.



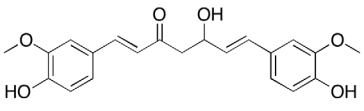
A6234 Apigenin

ID	Name	Description	Purity
A0002	A66	Inhibits p110α	≥98%
A6234	Apigenin	Inhibits PI3K (non-selective) and Akt	≥98%
A7200	AS-252424	Inhibits p110α PI3K	≥98%
B0396	BAY80-6946	Inhibits p110α	≥98%
B1996	BEZ235	Inhibits PI3K (non-selective) and mTORC1/2	≥98%
B4248	BKM120	Inhibits PI3K (non-selective)	≥98%
B9700	BYL719	Inhibits p110α PI3K	≥99%
C0044	CAL101	Inhibits p110δ PI3K	≥98%
C8112	CUDC-907	Inhibits PI3K and HDACs (class, I/II)	≥98%
G1308	GDC-0032	Inhibits p110α/δ/γ PI3K	≥98%
G1209	GDC-0980	Inhibits PI3K (non-selective) and mTORC1/2	≥98%
G7342	GSK2126458	Inhibits p110α PI3K and mTORC1/2	≥99%
G7346	GSK2636771	Inhibits p110β PI3K	≥98%
L4796	LY294002	Inhibits PI3K (non-selective)	≥99%
M1874	3-Methyladenine	Inhibits Vps34 PI3K	≥98%
P2002	PF-04691502	Inhibits PI3K (non-selective) and mTORC1/2	≥98%
P3209	Piceatannol	Inhibits PI3K (non-selective)	≥98%
P4132	PKI-402	Inhibits p110α and mTORC1/2	≥98%
P6002	PP-121	Inhibits p110α, mTORC1/2, Abl, Hck, Src, VEGFR2, PDGFR	≥98%
P9200	PX-866	Inhibits PI3K (non-selective)	≥98%
W5726	Wogonin	Inhibits PI3K (non-selective) and Akt	≥98%
W5769	Wortmannin	Inhibits PI3K (non-selective)	≥97%
Z7477	ZSTK474	Inhibits PI3K (non-selective)	≥98%

AKT

ID	Name	Description	Purity
A9601	AZD5363	Inhibits Akt	≥99%
C0252	Canertinib 2HCl	Indirectly inhibits Akt (via VEGFR)	≥98%
C1176	CCT-128930	Inhibits Akt	≥98%
C8069	Curcumin	Inhibits phosphorylation of Akt and indirectly inhibits Akt (via Notch-1)	≥97 %
D0006	Dacomitinib	Indirectly inhibits Akt (via EGFR)	≥99%
G0104	Gabexate Mesylate	Indirectly inhibits Akt (via PTEN)	≥98%
G0248	Gambogic Acid	Indirectly inhibits Akt (via EGFR)	≥98%
G1200	GDC-0068	Inhibits Akt	≥99%
G5772	Goserelin	Indirectly inhibits Akt	≥98%
G7242	GSK-690693	Inhibits Akt	≥98%
M4000	MK2206	Inhibits Akt	≥99%
N3577	Nitidine Chloride	Indirectly inhibits Akt	≥98%
P1845	Pelitinib	Indirectly inhibits Akt (via EGFR)	≥98%
P1969	Perifosine	Inhibits Akt	≥98%
P3076	PHT-427	Inhibits Akt and PDK1	≥98%
P3209	Piceatannol	Indirectly inhibits Akt (via PI3K, insulin receptor)	≥98%
S8098	SU-1498	Indirectly inhibits Akt (via VEGFR2)	≥98%
T0152	Tandutinib	Indirectly inhibits Akt (via c-Kit)	≥98%
T2936	Thioridazine HCl	Indirectly inhibits Akt (via FAK, αvβ3 integrin)	≥98%
W3576	Withaferin A	Indirectly inhibits Akt (via Notch-1, HSP90)	≥98%

Akt, also known as protein kinase B, is a serine/threonine protein kinase involved in anti-apoptotic signaling. Akt phosphorylates and inactivates pro-apoptotic protein Bad and alters IkB kinase activity to allow NF-kB activation and subsequent expression of anti-apoptotic gene products. Akt activation can be prevented by tumor suppressor PTEN's dephosphorylation of PIP3. Activity of Akt is associated with cancer progression and tumor development. Inhibitors of Akt include MK2206, GDC-0068, and AZD5363.

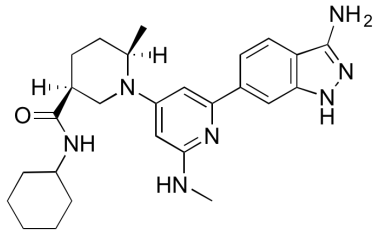


C8069 Curcumin

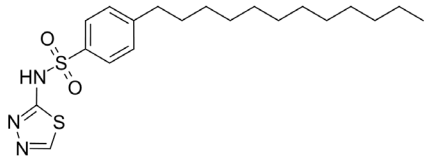
PDK1

3-phosphoinositide-dependent protein kinase-1 (PDK1) is an enzyme that is critical to the PI3K-Akt signaling pathway, regulating the activity of most other AGC protein kinases like PKC and SGK. It plays a key role in cell survival, metabolism, and tumorigenesis. It is notably overexpressed in melanomas, especially metastatic melanomas. Dysregulation of PDK1 has also been shown to be a key component of oncogenic PI3K signaling in breast cancer. Targeting PDK1 with small molecule inhibitors delays tumor initiation, growth, and metastasis in in vitro models. Combination therapies using PDK1 inhibitors and other small molecules have also increased efficacy and overcome drug resistance in recent treatment studies.

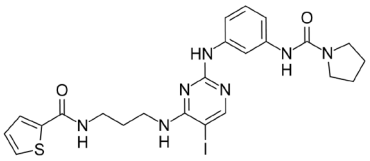
ID	Name	Description	Purity
B9200	BX-795	Potent inhibitor of PDK1, IKKe, and TBK1.	≥98%
B9202	BX-912	Inhibitor of PDK1. Slows growth in mutiple cancer lines.	≥98%
G7344	GSK-2334470	Selectively inhibits PDK1 without effecting activity of other AGC enzymes.	≥99%
O7400	OSU-03012	Inhibits growth of squamous cell carcinoma cells and slows growth of tumors in animal models of meningioma.	≥98%
P3076	PHT-427	Inhibitor of PDK1 and Akt, slowing tumor growth in animal models of breast cancer.	≥98%



G7344 GSK-2334470



P3076 PHT-427



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