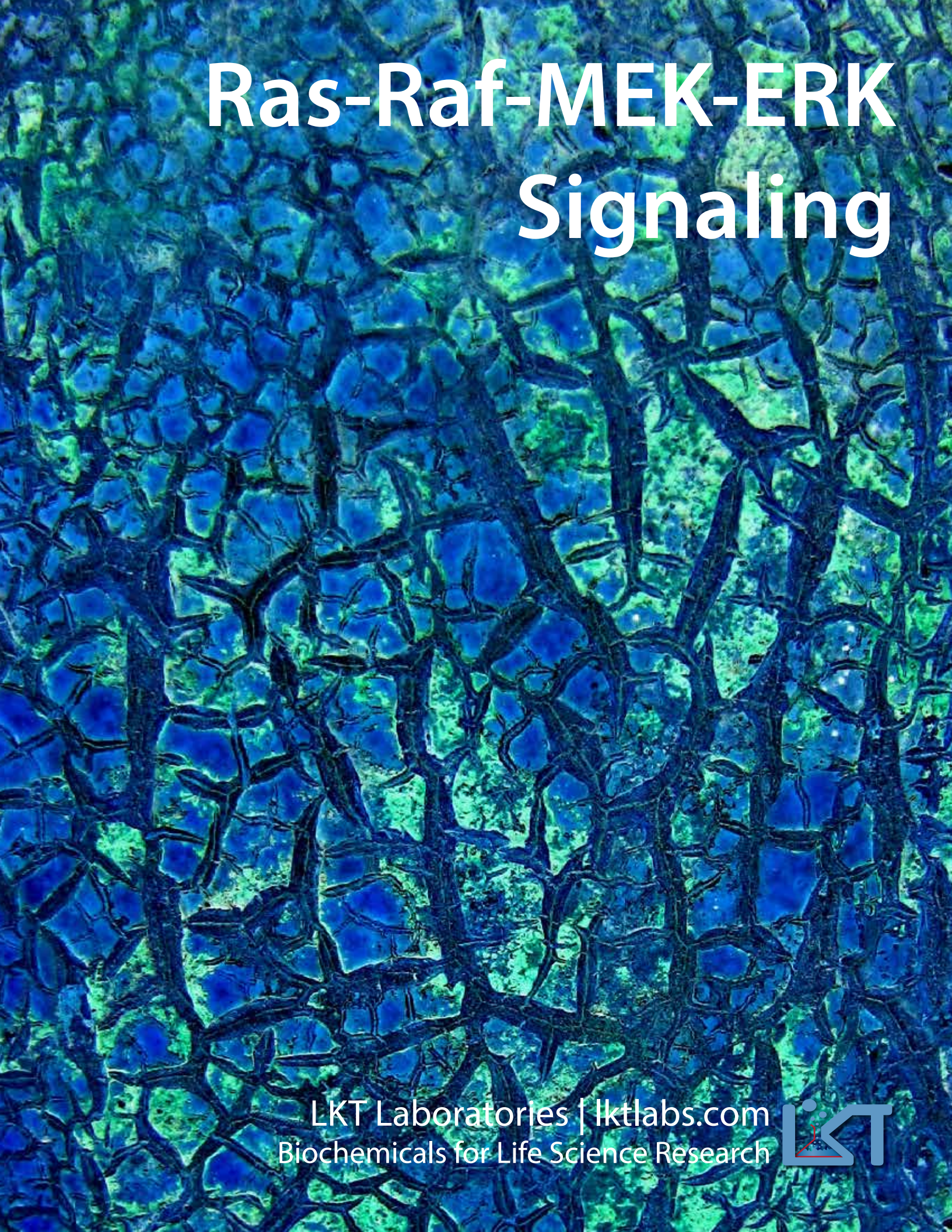
Ras-Raf-MEK-ERK Signaling



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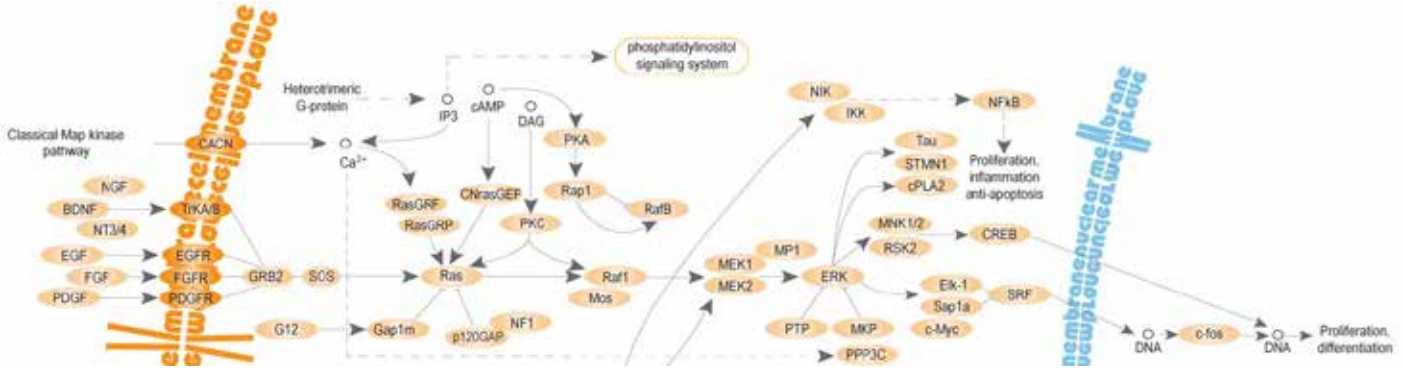
Biochemicals for Life Science Research

Introduction to the Ras-Raf-MEK-ERK signaling pathway



The Ras-Raf-MEK-MAPK-ERK signaling pathway plays a significant role in cell differentiation, proliferation, and survival. This pathway transduces extracellular signaling from ligands of receptor tyrosine kinases in the cell membrane to nuclear transcription factors that regulate gene product synthesis. Mutations in proteins of this pathway are found in many cancers, resulting in overactive signaling and unchecked cell growth. As a result, its proteins and receptors make excellent targets for anticancer chemotherapeutic compounds. The Ras signaling cascade also influences aging and metabolism, and small molecules targeting it are of interest in neuroscience and the study of neurodegenerative disease. For example, Ras/ERK is activated by amyloid precursor protein, which then enhances neurodegeneration through the creation of neuritic plaques. Further study on the effects of this critical pathway using small molecules will continue to unlock new therapies for a variety of diseases.

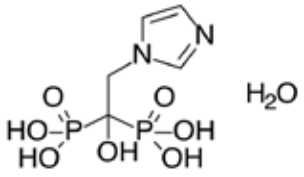
MEK

MEK, or mitogen-activated protein kinase kinase (MAP2K), is a family of tyrosine/threonine kinases activated by Raf responsible for phosphorylating ERK and other MAPK proteins. MEK enzymes have two primary isoforms, MEK1 and MEK2. These kinases may also be mutated in some forms of cancer, allowing continual and unregulated activation. Compounds that target MEK1/2 include RDEA119, ARRY-1662, selumetinib, and PD-325901.

ID	Name	Description	Purity
A6971	ARRY-162	Inhibits MEK1/2	≥99%
A7203	AS-703026	Inhibits MEK1/2	≥98%
A9715	AZD8330	Inhibits MEK1/2	≥98%
G1210	GDC-0623	Inhibits MEK1/2	≥98%
G7440	GSK1120212	Inhibits MEK1/2	≥98%
P1200	PD184352	Inhibits MEK1/2	≥98%
P1202	PD325901	Inhibits MEK1/2	≥98%
R1217	RDEA119	Inhibits MEK1/2	≥98%
S1846	Selumetinib	Inhibits MEK1/2	≥98%

Ras

ID	Name	Description	Purity
D1746	Deltarasin Hydrochloride	High affinity PDEδ-KRas interaction inhibitor	≥99%
H9716	(E,Z)-4-Hydroxytamoxifen	Increases degradation of K-Ras	≥97%
K5604	Kobe 0065	Inhibits Ras	≥98%
K5606	Kobe 2602	Inhibits Ras	≥98%
M017545	Manumycin A	Inhibits Ras	≥97%
N5605	Nobiletin	Indirectly inhibits Ras (via PKC)	≥97%
Z5744	Zoledronic Acid Hydrate	Inhibits prenylation of Ras	≥98%



Z5744 Zoledronic Acid Hydrate

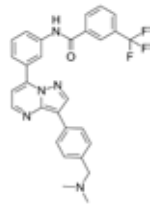
Ras family proteins are small GTPases, much like Rho, Ran, and Arf, which control other cellular processes like nuclear and vesicular transport signaling. Ras proteins are typically activated by receptor tyrosine kinases such as growth factor receptors, and ephrin receptors. K-Ras, H-Ras, and N-Ras are specific proteins within the Ras family that propagate growth factor signaling through activation of downstream targets such as Raf and PI3K. Overactive mutant isoforms of K-Ras have been implicated in the development of colorectal and pancreatic cancers. Activating mutations in H-Ras have been associated with the progression of bladder cancer. Similarly, N-Ras mutations are often found in melanomas and in thyroid cancer. Ras family proteins are targeted by treatments such as zoledronic acid and nobiletin.

RAF

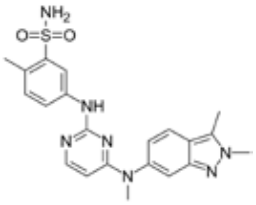
Raf proteins are serine/threonine kinases that transduce signals from Ras proteins and amplify them using the MAPK signaling cascade. The three primary Raf proteins include A-Raf, B-Raf, and C-Raf (Raf-1).

Mutations occasionally occur in A-Raf and C-Raf kinases, but mutant forms of B-Raf play a significant role in the development of many cancers. In B-Raf, V599 and V600 compose part of the activation loop. Typically these residues are responsible for keeping B-Raf in an inactive conformation until the enzyme is phosphorylated, but mutations such as V599K or V600E destabilize these interactions, inducing activation and resulting in potentially uncontrolled downstream signaling and cell growth. In recent research, Raf proteins are under exploration as targets for new chemotherapeutics such as dabrafenib and vemurafenib.

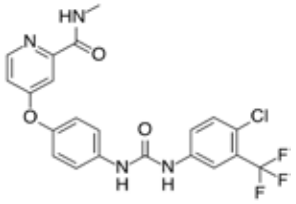
ID	Name	Description	Purity
A9662	AZ628	Inhibits V600E B-Raf, C-Raf (Raf-1)	≥96%
B6902	B-Raf IN 1	Inhibits B-Raf, C-Raf (Raf-1)	≥98%
C1660	CEP-32496	Inhibits V600E B-Raf	≥98%
D0004	Dabrafenib	Inhibits WT B-Raf, V600E/K/D B-Raf, C-Raf (Raf-1)	≥98%
D0005	Dabrafenib Mesylate	Inhibits WT B-Raf, V600E/K/D B-Raf, C-Raf (Raf-1)	≥98%
G1208	GDC-0879	Inhibits V600E B-Raf	≥96%
G8850	GW5074	Inhibits C-Raf (Raf-1)	≥98%
M4452	MLN2480	Inhibits B-Raf	≥98%
P0397	Pazopanib	Inhibits WT B-Raf	≥97%
P1200	PD184352	Inhibits V600E B-Raf	≥98%
P1202	PD325901	Inhibits V600E B-Raf	≥98%
P4492	PLX4720	Inhibits V600E B-Raf	≥98%
R0020	RAF265	Inhibits WT B-Raf, V600E B-Raf, C-Raf (Raf-1)	≥98%
R1626	Regorafenib Monohydrate	Inhibits B-Raf	>99%
S0459	SB-590885	Inhibits B-Raf	≥98%
S5868	Sorafenib	Inhibits WT B-Raf, mutant B-Raf, C-Raf (Raf-1)	≥98%
T0140	TAK-632	Inhibits all Raf isoforms	≥98%
V1668	Vemurafenib (PLX4032)	Inhibits V600E B-Raf	≥98%
Z4833	ZM-336372	Activates C-Raf (Raf-1)	≥98%



B6902 B-Raf IN 1



P0397 Pazopanib



S5868 Sorafenib

ERK

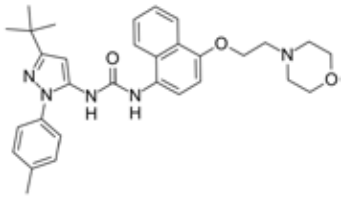
ID	Name	Description	Purity
A6234	Apigenin	Indirectly inhibits ERK1/2	≥98%
B3573	Bisdemethoxycurcumin	Indirectly inhibits ERK1/2	≥98 %
C0252	Canertinib 2HCl	Indirectly inhibits ERK1/2 (via VEGFR)	≥98%
C8500	CV-65	Indirectly inhibits ERK5, JNK, p38 MAPK	≥60%
C8501	CV-66	Indirectly inhibits ERK5, JNK, p38 MAPK	≥95%
D1850	Demethoxycurcumin	Indirectly inhibits ERK1/2	≥98%
E537333	Enniatin A1	Indirectly inhibits ERK1/2	≥96%
E537335	Enniatin B1	Indirectly inhibits ERK1/2	≥99%
M184770	4-O-Methylhonokiol	Indirectly inhibits ERK1/2	≥98%
N3577	Nitidine Chloride	Indirectly inhibits ERK1/2	≥98%
N5605	Nobiletin	Indirectly inhibits ERK1/2 (via PKC, Ras)	≥97%
O4556	Olomoucine	Indirectly inhibits ERK1/2	≥98%
P1845	Pelitinib	Indirectly inhibits ERK1/2 (via EGFR)	≥98%
S8098	SU-1498	Inhibits pERK1/2 (directly and via VEGFR2)	≥98%
T0253	Tangeretin	Indirectly inhibits ERK1/2	≥98%
U451349	Ulixertinib	Inhibits ERK1/2	≥98%
V9201	VX-11e	Inhibits ERK2	≥98%

ERKs, or extracellular signal-related kinases, are classical MAP kinases that receive signals from MEK and other proteins involved in the MAPK cascade, causing dowstream activation of transcription factors such as c-Fos, c-Myc, and ELK1. These transcription factors regulate the production of gene products involved in meiosis, mitosis, and cell differentiation. Signaling involving ERK1 or ERK2 plays a major role not just in the development and progression of cancers, but also in migraines and mood disorders such as schizophrenia and bipolar disorder. Inhibitors of ERK enzymes include CV65, VX-11e, SU-1498, nobiletin, and olomoucine.

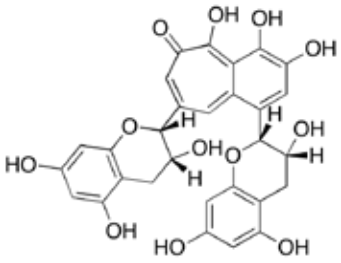
p38 MAPK

The p38 mitogen-activated protein kinases (MAPKs) are protein kinases associated with cell differentiation, apoptosis, and autophagy. p38 MAPKs participate in a signaling cascade that controls responses to environmental stress and inflamed cytokines in the cell. There are four known p38 MAPKs: p38-α (MAPK14), p38-β (MAPK11), p38-γ (NAPK12 or ERK6), and p38-δ (MAPK13 or SAPK4). Activation of the p38 pathway can initiate the production of pro-apoptotic transcription factors. As a modulator of cell survival, dysregulation of the p38 pathway is a critical factor in some cancers, giving p38 MAPK modulating compounds the potential to be used as cancer therapeutics. Targeting this pathway with small molecules has also shown potential in the treatment of autoimmune disease and inflammatory processes.

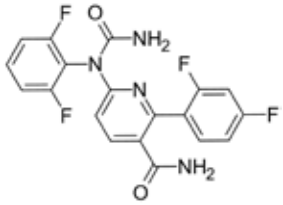
ID	Name	Description	Purity
D5868	Doramapimod	Inhibits p38 MAPK, JNK	≥98%
E537334	Enniatin B	Activates p38 MAPK	≥99%
H9862	Hypothemycin	Inhibits p38 MAPK, ERK	≥96%
S041001	SB-202190	Inhibits p38 MAPK	≥99%
S0500	SB-203580	Inhibits p38 MAPK	≥98%
T286161	Theaflavin	Inhibits p38 MAPK	≥98%
V9202	VX-702	Inhibits p38 MAPK	≥98%



D5868 Doramapimod



T286161 Theaflavin



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