Protein serine/threonine kinases (E.C. 2.7.1.-)

Overview: Protein serine/threonine kinases use the co-substrate ATP to phosphorylate serine and/or threonine residues on target proteins. Most inhibitors of these enzymes have been assessed in cell-free investigations and so may appear to 'lose' potency and selectivity in intact cell assays. In particular, ambient ATP concentrations may be influential in responses to inhibitors, since the majority are directed at the ATP binding site (Davies *et al.*, 2000).

It is beyond the scope of the Guide to list all protein kinase activities; this summary focusses on protein kinases involved in signalling from 7-transmembrane receptors.

Nomenclature	Protein kinase A	Protein kinase B	Protein kinase G	Rho kinase
Preferred abbreviation	PKA	PKB	PKG	–
Other names	Cyclic AMP-dependent protein kinase	Akt	Cyclic GMP-dependent protein kinase	P160ROCK, Rho-activated kinase
Ensembl ID	*Regulatory subunits*: PRKAR1A (ENSG00000108946); PRKAR1B (ENSG00000188191); PRKAR2A (ENSG00000114302); PRKAR2B (ENSG00000005249); *Catalytic subunits*: PRKACA (ENSG00000072062); PRKACB (ENSG00000142875); PRKACG (ENSG00000165059)	AKT1 (ENSG00000142208); AKT2 (ENSG00000105221); AKT3 (ENSG00000117020)	PRKG1 (ENSG00000185532); PRKG2 (ENSG00000138669)	ROCK1 (ENSG00000067900); ROCK2 (ENSG00000134318)
Endogenous activator	cAMP	PDK1 (Alessi *et al.*, 1997)	cGMP	Rho
Selective activators	N^6-Benzyl-cAMP (Christensen *et al.*, 2003)	–	–	–
Selective inhibitors	Rp-cAMPS	–	Rp-8-CPT-cGMPS (Butt *et al.*, 1994)	Y27362 (Uehata *et al.*, 1997), fasudil (Asano *et al.*, 1989)
Probes	[^{3}H]-cAMP	–	–	–

PKA is a heterotetrameric enzyme composed of two regulatory and two catalytic subunits, which can be distinguished from Epac (exchange protein directly activated by cAMP, de Rooij *et al.*, 1998) by differential activation by N^6-benzyl-cAMP and CPT-2′*O*Me-cAMP, respectively (Kang *et al.*, 2005). AKT1 and AKT2 can be selectively inhibited by AKT 1/2 inhibitor with pIC_{50} values of 7.3 and 6.8, respectively (Zhao *et al.*, 2005), while deguelin API2 (Yang *et al.*, 2004), SH5 (Kozikowski *et al.*, 2003) and Akt inhibitor IV (Kau *et al.*, 2003) can inhibit PKB activity by inhibiting activation by upstream kinases.

Protein kinase C

Protein kinase C is the target for the tumour-promoting phorbol esters, such as tetradecanoyl-β-phorbol acetate (TPA).

Classical protein kinase C isoforms: Members of the classical protein kinase C family are activated by Ca^{2+} and diacylglycerol, and may be inhibited by GF109203X, calphostin C, Gö6983, chelerythrine and Ro318220.

Nomenclature	PKCα	PKCβ1	PKCβ2	PKCγ
Other names	PRKCA	PRKCB1	PRKCB2	PRKCG
Ensembl ID	ENSG00000154229	ENSG00000166501	ENSG00	ENSG00000126583
Selective inhibitors	–	Ruboxistaurin (8.3, Jirousek *et al.*, 1996), CGP53353 (6.4, Chalfant *et al.*, 1996)	Ruboxistaurin (8.2, Jirousek *et al.*, 1996)	–

Novel protein kinase C isoforms: Members of the classical protein kinase C family are activated by diacylglycerol and may be inhibited by calphostin C, Gö6983 and chelerythrine.

Nomenclature	PKCδ	PKCε	PKCη	PKCθ	PKCμ
Other names	PRKCD	PRKCE	PRKCH	PRKCQ	KPCD1, nPKC-D1, protein kinase D
Ensembl ID	ENSG00000163932	ENSG00000171132	ENSG00000027075	ENSG00000065675	ENSG00000184304

Atypical protein kinase C isoforms

Nomenclature	PKCζ	PKCι	PKN
Other names	PRKCZ	PRKCI (PKCλ in rodents)	PRK, Protein kinase N1, protein kinase C-related kinase 1
Ensembl ID	ENSG00000067606	ENSG00000163558	ENSG00000123143
Endogenous activator	Arachidonic acid	–	Rho, PIP_3

Mitogen-activated protein kinases (MAP kinases)

MAP kinases (CMGC kinases, ENSF00000000137) may be divided into three major families: ERK1/2, JNK and p38 MAP kinases.

Nomenclature	ERK1	ERK2	JNK1	JNK2	JNK3
HUGO Nomenclature	MAPK3	MAPK1	MAPK8	MAPK9	MAPK10
Other names	Insulin-stimulated MAP2 kinase, ERT2, p44-MAPK, Microtubule-associated protein-2 kinase	Mitogen-activated protein kinase 2, p42-MAPK, ERT1	SAPK1, c-Jun N-terminal kinase 1, JNK-46	c-Jun N-terminal kinase 2, JNK-55	c-Jun N-terminal kinase 3, MAP kinase p49 3F12
Ensembl ID	ENSG00000102882	ENSG00000100030	ENSG00000107643	ENSG00000050748	ENSG00000109339
Endogenous activator	MAP2K1, MAP2K2	MAP2K1, MAP2K2	MAP2K4, MAP2K7	MAP2K4, MAP2K7	MAP2K4, MAP2K7
Selective inhibitors			SP600125 (6.7, Bennett *et al.*, 2001)	SP600125 (6.7, Bennett *et al.*, 2001)	SP600125 (6.7, Bennett *et al.*, 2001)

The inhibitors PD98059 (Alessi *et al.*, 1995; Dudley *et al.*, 1995) and U0126 (Duncia *et al.*, 1998; Favata *et al.*, 1998) are used as selective inhibitors of ERK1 and ERK2, but have been shown rather to target the upstream kinase cascade (Davies *et al.*, 2000).

Nomenclature	p38α	p38β	p38γ	p38δ
HUGO Nomenclature	MAPK14	MAPK11	MAPK12	MAPK13
Other names	Cytokine suppressive anti-inflammatory drug binding protein, MAX-interacting protein 2	p38-2, SAPK2	ERK-6, ERK5, SAPK3	SAPK4
Ensembl ID	ENSG00000112062	ENSG00000185386	ENSG00000188130	ENSG00000156711
Endogenous activator	MAP2K3, MAP2K6	MAP2K3, MAP2K6	MAP2K3, MAP2K6	MAP2K3, MAP2K6
Selective inhibitors	SB203580 (8.0, Eyers *et al.*, 1998)	SB202190 (Lee *et al.*, 1994), SB203580 (7.0, Eyers *et al.*, 1998)	–	–

Selected other protein kinase activities

Nomenclature	AMP kinase	Casein kinase 2	Myosin light chain kinase	Calmodulin-dependent kinase II
Preferred abbreviation	AMPK	CK2	MLCK1 (smooth muscle and non-muscle isoform), MLCK2 (skeletal muscle isoform)	CaMKII
Other names	–	EC 2.7.11.1	MYLK	–
Ensembl ID	α1 (ENSG00000132356); α2 (ENSG00000162409); β1 (ENSG00000111725); β2 (ENSG00000131791); γ1 (ENSG00000181929), γ2 (ENSG00000106617); γ3 (ENSG00000115592)	α ENSG00000101266; α′ ENSG00000070770; β ENSG00000204435	MLCK1 ENSG00000065534; MLCK2 ENSG00000101306	α (ENSG00000070808); β (ENSG00000058404); γ (ENSG00000148660); δ (ENSG00000145349)
Endogenous activator	AMP	–	Ca^{2+}-calmodulin	Ca^{2+}-calmodulin
Selective activators	AICA-riboside (Corton *et al.*, 1995)	–	–	–
Selective inhibitors	–	DRB (Zandomeni *et al.*, 1986)	–	K252a (Hashimoto *et al.*, 1991)

AMP-activated protein kinase is a heterotrimeric protein kinase, made up of α, β and γ subunits, while casein kinase 2 is a heterotetrameric protein kinase, made up of 2 β subunits with two other subunits of α and/or α′ composition. STO609 is an inhibitor of calmodulin kinase kinase (Tokumitsu *et al*., 2002), an upstream activator of calmodulin-dependent kinase.

Abbreviations: **AICA-riboside,** 5-aminoimidazole-4-carboxamide-1-*β*-riboside, also known as acadesine; **AKT1/2**, 1,3-dihydro-1-(1-[[4-(6-phenyl-1*H*-imidazo[4,5-g]quinoxalin-7-yl)phenyl]methyl]-4-piperidinyl)-2H-benzimidazol-2-one trifluoroacetate salt hydrate; **Akt inhibitor IV**, 5-(2-benzothiazolyl)-3-ethyl-2-(2-[methylphenylamino]ethenyl)-1-phenyl-1*H*-benzimidazolium iodide; **API2**, 1,5-dihydro-5-methyl-1-β-D-ribofuranosyl-1,4,5,6,8-pentaazaacennaphthylen-3-amine, also known as triciribine; **CGP53353**, 5,6-bis([4-fluorophenyl]amino)-2*H*-isoindole-1,3-dione; **CPT-2′-OMe-cAMP**, 8-(4-chlorophenylthio)-2′-O-methyladenosine 3′,5′-cyclic monophosphate monosodium hydrate; **DRB**, 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole; **fasudil**, 1-(5-isoquinolinylsulfonyl)homopiperazine dihydrochloride, also known as HA1077; **PD98059**, 2-(2-amino-3-methoxy-phenyl)chromen-4-one; **PDK1**, phosphoinoisitide-dependent protein kinase 1 (ENSG00000152256); **Rp-8-CPT-cGMPS**, Rp-8-[(4-chlorophenyl)thio]-guanosine-cyclic 3′,5′-hydrogen phosphorothioate; **ruboxistaurin**, (S)-13-[(dimethylamino)methyl]-10,11,14,15-tetrahydro-4,9:16,21-dimetheno-1*H*,13*H*-dibenzo[*e*,*k*]pyrrolo[3,4-*h*][1,4,13]oxadiazacyclohexadecene-1,3(2*H*)-dione, also known as LY333531; **SB203580**, 4-(5-[4-fluorophenyl]-2-[4-methylsulfinylphenyl]-3*H*-imidazol-4-yl)pyridine; **SP600125**, anthra[1,9-*cd*]pyrazol-6(2*H*)-one; **SH5**, **STO609**, trans-4-[(1R)-1-aminoethyl]-N-4-pyridinyl-cyclohexane carboxamide (Y-27632), and 7-oxo-7H-benzimidazo (2,1a) benz (de) isoquinoline-3-carboxy acid acetate

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