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DYRK Inhibitors

DYRK (dual-specificity tyrosine-regulated kinase) family members constitute an evolutionarily conserved family of protein kinases that have been identified in different organisms such as yeast, Drosophila and human.

Seven mammalian DYRK-related kinases have been identified: DYRK1A, DYRK1B, DYRK1C, DYRK2, DYRK3, DYRK4A and DYRK4B. The DYRK proteins are dual-specificity protein kinases that autophosphorylate a conserved tyrosine (Y) residue in their own activation loop but phosphorylate their substrates at serine (S) or threonine (T) residues. The Y autophosphorylation occurs during translation and induces kinase activation; however, once the protein is fully translated, kinase activity becomes restricted to S and T residues and no longer depends on Y phosphorylation.

An increasing number of substrates involved in signal transduction pathways is being reported for DYRKs. These substrates of DYRKs have diverse effects such as enhancement of transcription factor activity, modulation of subcellular protein distribution and regulation of enzyme activity. Some DYRKs also control protein stability by inducing the proteasome system or by stabilizing short-lived proteins. One characteristic feature of several DYRK kinases is their function as priming kinases, meaning that the phosphorylation of a given residue by a DYRK is prerequisite for the subsequent phosphorylation of a different residue by another protein kinase (GSK3 or PLK). Phosphorylation by protein kinases is the most universally used mechanism by cells to control their structural proteins and enzymes. All major physiological phenomena are regulated by phosphorylation and many diseases are associated with abnormal phosphorylation. Therefore, the search for pharmacological inhibitors has become a major area of research for the discovery and development of new therapies.

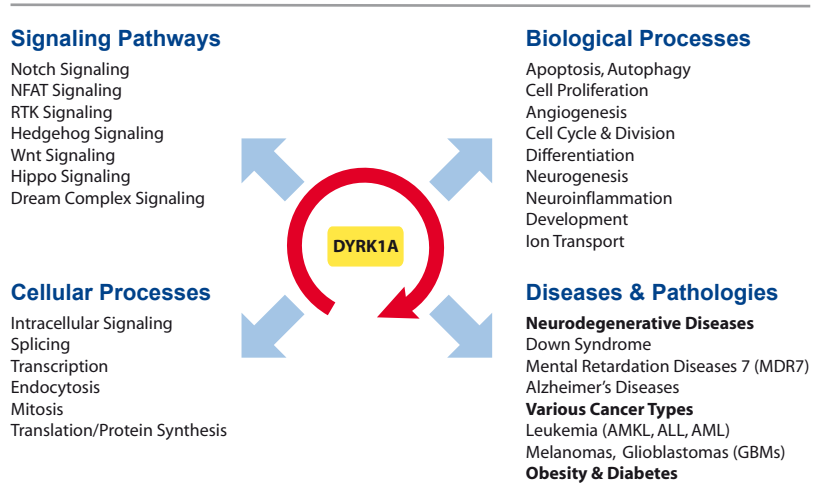


FIGURE 1: DYRK1A - Regulator of a myriad of processes and signaling pathways.

SELECTED REVIEW ARTICLES

Activation, regulation, and inhibition of DYRK1A: W. Becker & W. Sippl; FEBS J. **278,** 246 (2011) • DYRK1A kinase inhibitors with emphasis on cancer: A. Ionescu, et al.; Mini Rev. Med. Chem. **12,** 1315 (2012) • DYRK1A: the double-edged kinase as a protagonist in cell growth and tumorigenesis: P Fernandez-Martinez, et al.; Mol. Cell Oncol. **2,** e970048 (2015) • DYRK1A, a dosage-sensitive gene involved in neurodevelopmental disorders, is a target for drug development in Down Syndrome: A. Duchon & Y. Herault; Front. Behav. Neurosci. 10, **104** (2016) • Novel factors modulating human β-cell proliferation: J. Shirakawa & R.N. Kulkarni; Diabetes Obes. Metab. **18,** 71 (2016)

DYRK1A ('dual specificity, tyrosine phosphorylation regulated kinase 1A') is the most extensively studied among this family of kinases because its gene maps to human chromosome 21 within the Down syndrome critical region (DSCR) and may play a significant role in developmental brain defects, early neurodegeneration and cancer susceptibility of individuals with this syndrome. Recent studies have shown that abnormalities in DYRK1A dosage are associated with cognitive disorders observed in Down syndrome, Mental Retardation Disease 7 (MRD7) and Alzheimer's disease. Moreover, DYRK1A plays key functions in different cancer types, such as AMKL, AML, ALL, melanomas and glioblastomas.

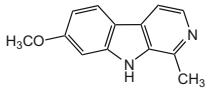
DYRK1A targets a multitude of exogenous protein substrates, including transcription factors (CREB, NFAT, STAT3, FOXO1, GLI1, RNApol2), splicing factors (Cyclin L2, SF2, SF3), translation factor (eIF2Bε) or cytoskeletal targets (TAU and MAP1B) and synaptic proteins (dynamin I, amphiphysin I, synaptojanin I). DYRK1A phosphorylates the intracellular domain of the Notch receptor, attenuating the transcriptional effect and regulating Notch-dependent biological processes such as angiogenesis, differentiation or transcription. By phosphorylating APP, Tau, presenilin 1, Asf and septin-4; all proteins involved in either neurofibrillary degeneration or β-Amyloidosis, DYRK1A consequently is an important factor in neuronal cell death and reduced cognitive functioning.

β-Carboline Class DYRK1A Inhibitors

Harmine

AG-CN2-0510

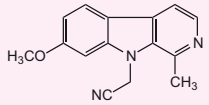
Formula: $C_{13}H_{12}N_2O$ | **MW:** 212.3 | **CAS:** 442-51-3
DYRK Activity: DYRK1A | DYRK2 | DYRK3 (IC_{50}=0.08 | 0.9 | 0.8µM)
Other Kinase Activity: CLK2, PIM3, CK1, MAO-A
LIT: T. Adayev, et al.; Arch. Biochem. Biophys. **507,** 212 (2011)



NEW DYRK1A/B Inhibitor AnnH31

AG-CR1-3650

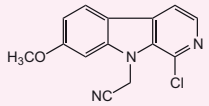
Formula: $C_{15}H_{13}N_3O$ | **MW:** 251.3 | **CAS:** 241809-12-1
DYRK Activity: DYRK1A (IC_{50}=81nM) | DYRK1B
Other Kinase Activity: CLK1, DYRK2, HIPK2, MAO-A (minimal)
LIT: K. Ruben, et al.; Plos One **10,** e0132453 (2015)



NEW DYRK1A/B Inhibitor AnnH75

AG-CR1-3651

Formula: $C_{14}H_{10}ClN_2O$ | **MW:** 271.7
DYRK Activity: DYRK1A (IC_{50}=181nM) | DYRK1B
Other Kinase Activity: CLK1, CLK4, Haspin/GSG2
LIT: K. Ruben, et al.; Plos One **10,** e0132453 (2015)



Control Compound:

DYRK1 Inhibitor Negative Control AnnH79

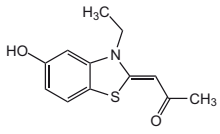
AG-CR1-3652

INDY Class DYRK Inhibitors

INDY

AG-CR1-3665

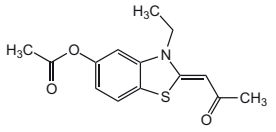
Formula: $C_{12}H_{13}NO_2S$ | **MW:** 235.3 | **CAS:** 1169755-45-6
DYRK Activity: DYRK1A (IC_{50}=240nM) | DYRK1B (IC_{50}=230nM) | DYRK2 | DYRK3
Other Kinase Activity: CLK1, CLK4, CSNK1D, PIM1
LIT: Y. Ogawa, et al.; Nat. Commun. **1,** 86 (2010)



TG007 [ProINDY]

AG-CR1-3666

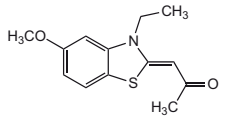
Formula: $C_{14}H_{15}NO_3S$ | **MW:** 277.3 | **CAS:** 719277-30-2
DYRK Activity: DYRK1A | DYRK1B
LIT: Y. Ogawa, et al.; Nat. Commun. **1,** 86 (2010)



TG003

AG-CR1-3656

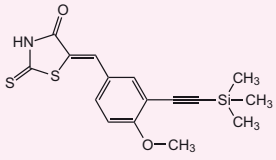
Formula: $C_{13}H_{15}NO_2S$ | **MW:** 249.3 | **CAS:** 300801-52-9
DYRK Activity: DYRK1A | DYRK1B
Other Kinase Activity: CLK1, CLK2, CLK4
LIT: M. Muraki, et al.; J. Biol. Chem. **279,** 24246 (2004)



NEW FINDY

AG-CR1-3662

Formula: $C_{16}H_{17}NO_2S_2Si$ | **MW:** 347.5 | **CAS:** 1507367-37-4
DYRK Activity: Suppressor of DYKR1A intramolecular Ser^{97}-autophosphorylation.
Other Kinase Activity: GSK3β, MARK4, PIM1, PIM3, PLK3
LIT: I. Kii, et al.; Nat. Commun. **7,** 11391 (2016)



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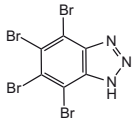
Note: *All indicated IC_{50}-Values are from Literature References.*

TBI (Tetrabromo-benzimidazole) Derivatives & Analogs

TBB

AG-CR1-3660

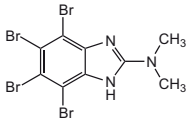


Formula: $C_6HBr_4N_3$ | **MW:** 434.7 | **CAS:** 17374-26-4
DYRK Activity: DYRK1A (IC_{50}=4.4μM)
Other Kinase Activity: CK2, CCK2/cyclin A, GSK3β

LIT: M.A. Pagano, et al.; Biochem. J. **415,** 353 (2008)

DMAT

AG-CR1-3654



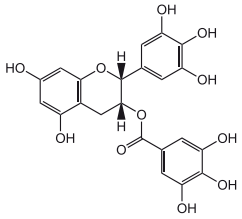
Formula: $C_9H_7Br_4N_3$ | **MW:** 476.8 | **CAS:** 749234-11-5
DYRK Activity: DYRK1A (IC_{50}=0.4μM) | DYRK2 (IC_{50}= 0.4μM)
Other Kinase Activity: CK2, PIM1, PIM3, HIPK2, HIPK3, PKD1, CDK2

LIT: M.A. Pagano, et al.; Biochem. J. **415,** 353 (2008)

Other DYRK1A Inhibitors

(-)-Epigallocatechin gallate [EGCG]

AG-CN2-0063

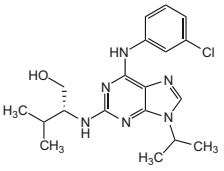


Formula: $C_{22}H_{18}O_{11}$ | **MW:** 458.4 | **CAS:** 989-51-5
DYRK Activity: DYRK1A (IC_{50}=330nM)
Other Kinase Activity: PRAK

LIT: J. Bain, et al.; Biochem. J. **371,** 199 (2003) • R. De la Torre, et al.; Mol. Nutr. Food Res. **58,** 278 (2014)

Purvalanol A

AG-CR1-2903



Formula: $C_{19}H_{25}ClN_6O$ | **MW:** 388.9 | **CAS:** 212844-53-6
DYRK Activity: DYRK1A (IC_{50}=300nM)
Other Kinase Activity: CDK1, CDK2/cyclin A, Cdc2/cyclin B, CDK2/cyclin E, CDK4/cyclin D1, CDK5/p35

LIT: J. Bain, et al.; Biochem. J. **371,** 199 (2003)

(S)-CR8

AG-MR-C0004

Formula: $C_{24}H_{29}N_7O$ | **MW:** 431.5 | **CAS:** 1084893-56-0
DYRK Activity: DYRK1A (IC_{50}=0.9 μM)
Other Kinase Activity: CDK1, CDK2, CDK5, CDK9, CK1δ/ε

LIT: K. Bettayeb, et al.; Oncogene **27,** 5797 (2008)

UNIQUE (S)-Perharidine 1

AG-MR-C0012

Formula: $C_{25}H_{30}N_6O$ | **MW:** 430.6 | **CAS:** 1133437-81-6
DYRK Activity: DYRK1A (IC_{50}=2.8 μM)
Other Kinase Activity: CDK1, CDK2, CDK5, CDK9, CK1δ/ε

LIT: L. Meijer, et al.; Patent WO2009034475A2 (2009)

NU6102

AG-CR1-0020

Formula: $C_{18}H_{22}N_6O_3S$ | **MW:** 402.5 | **CAS:** 444722-95-6
DYRK Activity: DYRK1A (IC_{50}=0.9 μM)
Other Kinase Activity: CDK1, CDK2, CDK4, PDK1, ROCK-II

LIT: T.G. Davies, et al.; Nat. Struct. Biol. **9,** 745 (2002)

SMI-16a

CDX-P0110

Formula: $C_{13}H_{13}NO_3S$ | **MW:** 263.3 | **CAS:** 587852-28-6
DYRK Activity: DYRK1A
Other Kinase Activity: Pim-1, Pim-2

LIT: Z. Xia, et al.; J. Med. Chem. **52,** 74 (2009)

SB216763

AG-CR1-3659

Formula: $C_{19}H_{12}Cl_2N_2O_2$ | **MW:** 371.2 | **CAS:** 280744-09-4
DYRK Activity: DYRK1A (IC_{50}=0.8μM)
Other Kinase Activity: GSK3α, GSK3β

LIT: J. Bain, et al.; Biochem. J. **408,** 297 (2007)

SB415286

AG-CR1-3658

Formula: $C_{16}H_{10}ClN_3O_5$ | **MW:** 359.7 | **CAS:** 264218-23-7
DYRK Activity: DYRK1A (IC_{50}=0.9μM)
Other Kinase Activity: GSK3α, GSK3β

LIT: J. Bain, et al.; Biochem. J. **408,** 297 (2007)

Staurosporine

AG-CN2-0022

Formula: $C_{28}H_{26}N_4O_3$ | **MW:** 466.5 | **CAS:** 62996-74-1
DYRK Activity: DYRK1A (IC_{50}=20nM)
Other Kinase Activity: PKA, CaMK, MLCK, PKC, PKG, CDK1/cyclin B, CDK2/cyclin A, CDK4/cyclin D, CDK5/p25, GSK-3β, Pim-1

LIT: C. Sanchez, et al.; Chem. Commun. **2009,** 4118 (2009)

Note: *All indicated IC_{50}-Values are from Literature References.*

UNIQUE

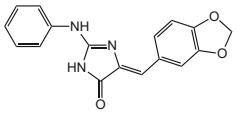
Leucettamine DYRK1A Inhibitor

Leucettine L41

AG-MR-C0023

Formula: $C_{17}H_{13}N_3O_3$ | **MW:** 307.3 | **CAS:** 1112978-84-3
DYRK Activity: DYRK1A (IC_{50}=40nM) | DYRK2 (IC_{50}=35nM)
Other Kinase Activity: CLK1, CLK3, GSK-3α/β, PIM1

LIT: M. Debdab, et al.; J. Med. Chem. **54,** 4172 (2011)



NEW

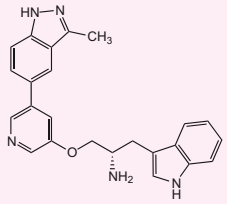
Potent DYRK1A Inhibitors

A-443654

AG-CR1-3663

Formula: $C_{24}H_{23}N_5O$ | **MW:** 397.5 | **CAS:** 552325-16-3
DYRK Activity: DYRK1A (IC_{50}=10nM) | DYRK3 (low nM range)
Other Kinase Activity: PKBα, PKBβ, PKBγ, PRK2, MSK1

LIT: B. Smith, et al.; ACS Chem. Neurosci. **3,** 857 (2012)

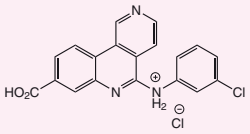


CX-4945 . HCl

AG-CR1-3629

Formula: $C_{19}H_{12}ClN_3O_2$. HCl | **MW:** 349.8 . 36.5 | **CAS:** 1009820-21-6 (free acid)
DYRK Activity: DYRK1A (IC_{50}=6.8nM) | DYRK1B (IC_{50}=6.4nM) | DYRK3 (IC_{50}=18nM)
Other Kinase Activity: CK2, CLKs

LIT: A. Siddiqui-Jain, et al.; Cancer Res. **70,** 10288 (2010) | H. Kim, et al.; Dis. Model Mech. **9,** 839 (2016)



DYRK1B/DYRK2-4 Inhibitors

Note: *All indicated IC_{50}-Values are from Literature References.*

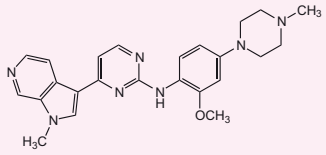
NEW

AZ191

AG-CR1-3657

Formula: $C_{24}H_{27}N_7O$ | **MW:** 429.5 | **CAS:** 1594092-37-1
DYRK Activity: DYRK1B (IC_{50}=17nM)
Other Kinase Activity: DYRK1A, DYRK2

LIT: A.L. Ashford, et al.; Biochem. J. **457,** 43 (2014)



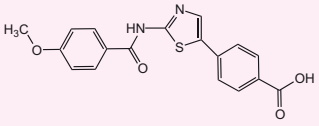
NEW

CK2 Inhibitor 10

AG-CR1-3626

Formula: $C_{18}H_{14}N_2O_4S$. $0.5H_2O$ | **MW:** 354.4 . 9.0 | **CAS:** 1361229-76-6
DYRK Activity: DYRK1B
Other Kinase Activity: CK2α, Flt3

LIT: Z. Hou, et al.; J. Med. Chem. **55,** 2899 (2012)

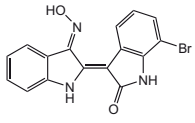


7BIO

AG-MR-C0020

Formula: $C_{16}H_{10}BrN_3O_2$ | **MW:** 356.2 | **CAS:** 916440-85-2
DYRK Activity: DYRK1A (IC_{50}=1.9 µM) | DYRK2 (IC_{50}=1.3 µM)
Other Kinase Activity: Aurora B Kinase, Aurora C Kinase, Flt3

LIT: V. Myrianthopoulos, et al.; ACS Med. Chem. Lett. **4,** 22 (2013)

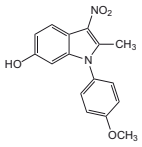


ID-8

AG-CR1-3655

Formula: $C_{16}H_{14}N_2O_4$ | **MW:** 298.3 | **CAS:** 147591-46-6
DYRK Activity: DYRK2 | DYRK4

LIT: K. Hasegawa, et al.; Stem Cells Transl. Med. **1,** 18 (2012)



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