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DYRK1A Kinase Inhibitors with Emphasis on Cancer

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Abstract: Various types of cancers (including gliomas, melanomas, and esophageal, pancreas and non-small-cell lung cancers) display intrinsic resistance to pro-apoptotic stimuli, such as conventional chemotherapy and radiotherapy, and/or the activation of a multidrug resistance phenotype, which are major barriers to effective treatment and lead to poor patient prognosis. The DYRK1A kinase is directly implicated in the resistance of cancer cells to pro-apoptotic stimuli and drives several pathways that enhance proliferation, migration, and the reduction of cell death, leading to very aggressive biological behavior in cancer cell populations. The DYRK1A kinase is also implicated in neurological diseases and in neoangiogenic processes. Thus, the DYRK1A kinase is of great interest for both cancer and neuroscience research. During the last decade, numerous compounds that inhibit DYRK1A have been synthesized. The present review discusses the available molecules known to interfere with DYRK1A activity and the implications of DYRK1A in cancer and other diseases and serves as a rational analysis for researchers who aim to improve the anti-DYRK1A activity of currently available compounds.

Keywords: DYRK1A kinase, cancer, neurological diseases, anti-DYRK1A compounds.

INTRODUCTION

DYRK1A Kinase

Dual-specificity tyrosine-regulated kinases (DYRKs) belong to the CGMC kinome group that includes cyclin-dependent kinases (**C**DKs), glycogen synthase kinases (**G**SKs), mitogen-activated protein kinase (**M**APKs), and CDK-like kinases (**C**LKs). The DYRK family includes DYRK1A, DYRK1B, DYRK2, DYRK3 and DYRK4 [1]. DYRK family kinases are evolutionarily conserved from yeast to humans and have recently been reviewed [2]. Among the members of this family, research has focused primarily on DYRK1A because of its localization on chromosome 21 and its association with Down's syndrome [3,4]. DYRK1A is expressed ubiquitously in mammalian tissues [5] with high expression levels in the brain during development [6].

As its name implies, DYRK1A has dual substrate specificity. During protein synthesis, DYRK1A undergoes autophosphorylation at a conserved tyrosine residue (Tyr321) in the activation loop of the catalytic domain [7] by the intramolecular formation of a transitory intermediate, which produces a constitutively active form of DYRK1A [7]. Once matured, DYRK1A only targets substrates at serine or threonine residues [7]. The DYRK1A domain structure includes an N-terminal nuclear localization signal, a kinase domain, a PEST domain for protein degradation, a 13-consecutive-histidine repeat for nuclear targeting and an S/T rich region [8].

DYRK1A substrates comprise both nuclear and cytosolic proteins, including transcription factors (CREB, NFAT, STAT3, KFHR, Gli1), splicing factors (cyclin L2, SF2, SF3), a translation factor (eIF2Bε), synaptic proteins (dynamin I, amphiphysin I, synaptojanin I), and miscellaneous proteins (glycogen synthase, caspase-9, Notch) [4,9-11]. DYRK1A activity is mediated by a second autophosphorylation at a C-terminal serine (Ser520) [13], which can be increased through its binding to 14-3-3 proteins [12].

DYRK1A plays a major role in cell proliferation and cell death, which is further emphasized below.

It is well established that DYRK1A is associated with some Down's syndrome phenotypes, mental retardation, motor defects [14-16] and neurodegenerative diseases, such as Alzheimer's [17-19], Parkinson's and Huntingon's diseases [20-22]. Park and colleagues [4] recently reviewed the molecular mechanisms implicating DYRK1A in Down's syndrome.

The current review focuses on the implications of DYRK1A in cancer development, aggressiveness and resistance to conventional chemotherapy and radiotherapy. Thus, particular attention is paid to compounds that display anticancer activity through the targeting of DYRK1A.

The DYRK1A Kinase and Its Implication in Cancer Biology

Epidemiological studies suggest that although individuals with Down's syndrome have an increased risk of leukemia,

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they have a considerably reduced incidence of most solid tumors [23-27]. Cancer protection in the Down's syndrome population may, in part, be due to suppression of angiogenesis. Indeed, increased levels of DYRK1A seem to act in concert with RCAN1 (regulator of calcineurin 1) to suppress tumor angiogenesis by attenuating VEGF-calcineurin-NFAT signaling in endothelial cells [27]. By disrupting NFAT phosphorylation, DYRK1A blocks transactivation of NFAT-dependent target genes [28,29]. Moreover, Down's syndrome individuals have a reduced incidence of other angiogenesis-related diseases, such as diabetic retinopathy [30] and atherosclerosis [31].

DYRK1A belongs to the family of NFAT1 upstream kinases that affect the cellular localization and transcriptional activity of NFAT1 [29,32]. In addition to promoting angiogenesis in endothelial cells, NFAT1 has also been reported to increase the migration and invasion of breast cancer [33,34].

Various studies have identified a number of potential DYRK1A family substrates that directly implicate this kinase in cancer development and aggression. DYRK1A potentiates the transcriptional activity of one such substrate, Gli1 (glioma-associated oncogene homologue 1), a transcription factor that acts as a terminal effector of hedgehog signaling, which is a key pathway for embryogenesis, stem cell maintenance and tumorigenesis [35]. The implications of the hedgehog pathway in cancer biology have been assessed by Peukert and Miller-Moslin [36]. STAT3 (signal transducers and activators of transcription 3) is another transcription factor that can be activated by DYRK1A and is known to play critical roles in the development and progression of a variety of tumors by regulating cell proliferation, cell cycle progression, apoptosis, angiogenesis, immune evasion, epithelial-mesenchymal transition (EMT) and by other effects in cancer stem cells [37]. STAT3 is over-expressed in various cancers and represents an interesting target to impede cancer progression [38,39].

In addition, DYRK1A is demonstrated to attenuate Notch1 signaling in neuroblastomas [11]. Notch1 signaling is associated with angiogenesis, down-regulation of caspase-3 [42] and Notch1 oncogenic activity has been demonstrated in gliomas [40] and other malignancies [41]. Interestingly, DYRK1A acts as a negative regulator of apoptosis by phosphorylating Thr125 of caspase-9 [43,44]. Subsequently, inhibition of DYRK1A by harmine leads to the activation of caspase-9 and causes massive apoptosis in various human cell types [43, 10]. Thus, inhibiting DYRK1A activity in cancer cells could offer a new strategy to combat the dismal prognosis associated with cancers that display resistance to pro-apoptotic stimuli. Indeed, approximately 90% of cancer patients die from their metastases, which is largely due to the intrinsic resistance of metastatic cancer cells to pro-apoptotic stimuli because of their inherent resistance to the anoïkis process [45,46]. In addition, approximately one-third of solid tumors in adult patients are intrinsically resistant to pro-apoptotic stimuli, and thus to conventional chemotherapy and radiotherapy, before metastasizing, which is the case for non-small-cell lung cancers [47], melanomas [48,49], esophageal cancers [50], pancreatic cancers [51] and gliomas [52]. Thus, an elegant strategy for overcoming the intrinsic resistance of various cancer types to pro-apoptotic stimuli would be to combine DYRK1A inhibitors with conventional radiotherapy and/or chemotherapy.

STRUCTURE-ACTIVITY RELATIONSHIP (SAR) ANALYSES WITH RESPECT TO DYRK1A INHIBITORS

How DYRK1A Inhibitors Interact with their Target?

Regarding all compounds that have been described as DYRK1A inhibitors, it is difficult to draw clear-cut SAR analyses to direct further chemical syntheses. However, docking experiments and co-crystallization performed with ATP competitive inhibitors could highlight amino acids residues within DYRK1A that are important for interactions with DYRK1A inhibitors [8] (Fig. **1**). Most DYRK1A inhibitors are ATP-competitor and act by binding within the DYRK1A kinase domain [8]. Inhibitors could also bind to other regions of DYRK1A to prevent the functionality of the ATP-binding site and, thus, act as an indirect ATP-competitor [8]. Furthermore, compounds could interact directly or indirectly with the DYRK1A activation loop to prevent autophosphorylation and to inhibit kinase activity [8].

The X-ray structure of DYRK1A has been solved recently by complexing the protein with the indazole compound, D15 (N-(5-{[(2S)-4-amino-2-(3-chlorophenyl)butanoyl]amino}-1H-indazol-3-yl)benzamide) (PDB: 2WO6) [53]. D15 interacts with the ATP-binding site, forming hydrogen bonds with Asp307, Glu239, Asn292 and Leu241. D15 could also interact with Val306 and Val173, given their close proximity [53] (Fig. **1A**).

Harmine has also been co-crystallized with the DYRK1A kinase domain (PDB: 3ANR) [54], which confirms that harmine acts as an ATP-competitor. Harmine (**48**) (Table **3**) forms hydrogen bonds with Leu241 and Lys188 and could interact with Leu294, Val222, Val306, Phe238, Glu203, Glu239 and Asp307 [55] (Fig. **1B**).

The third molecule that has been co-crystallized with DYRK1A is the benzothiazole INDY (**13**), which forms hydrogen bonds with Lys188 and Leu241 within the ATP binding-pocket and could possibly interact with Ala186 and Val173 (PDB: 3ANQ) [54] (Fig. **1C**).

Before the X-ray structure of DYRK1A was determined, several docking experiments were performed to design specific inhibitors. Initial DYRK1A *in silico* models were based on either the crystal structure of GSK-3β [20] or the homology model of the phosphorylated MAP kinase extracellular signal-regulated kinase-2 (ERK2) [56]. These templates were chosen due to their similarity with the kinase domain of DYRK1A, although they only share ~30% of the overall sequence identity. Compounds **1**-**3** (Table **1**) were designed from these docking experiments [20,57].

The means by which other DYRK1A inhibitors interact with their target remain poorly understood. Most directly compete with ATP, although docking experiments and co-crystallization have not been performed on DYRK1A in all cases. Quinazolinone IQA (**53**) (Table **3**) and quinolone derivatives (**18** and **19**) (Table **2**) are known to bind to the

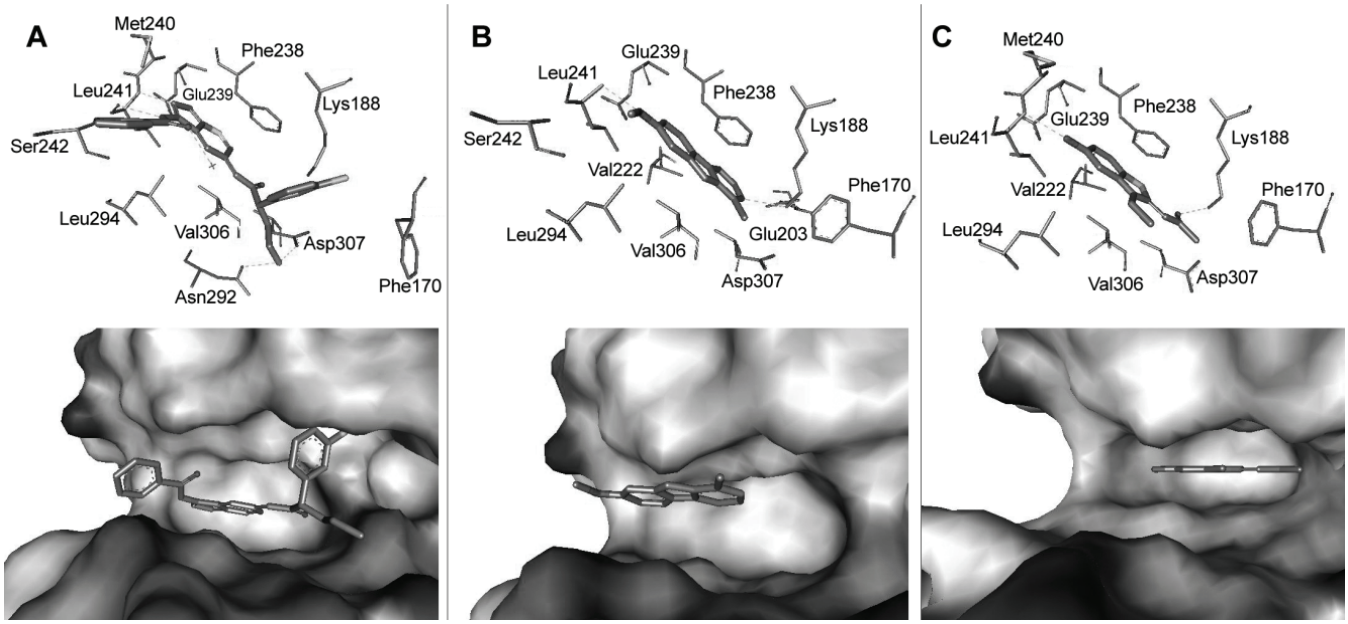


Fig. (1). Crystal structure of the DYRK1A/D15 (**A**), DYRK1A/harmine (**B**) and Dyrk1A/INDY (**C**) complexes. Up: stereo views of the ligand-binding site of the Dyrk1A/ligand complex. The dotted lines indicate hydrogen bonds. Down: surface representation of the ATP-binding site of DYRK1A in complex with each ligand. The following interactions are visible: D15 interacts with Asp307, Asn292 and Leu241. D15 could also interact with Val306 and Phe238. Harmine interacts with Leu241 and Lys188. It could also interact with Val222 and Phe238. INDY interacts with Lys188 and Leu241.

kinase domain of CK2 [58,59]. Meriolin derivatives (**29**, **31**) and variolin (**39**) (Table **2**) have been co-crystallized with CDK2 and bind the protein kinase domain (PDB: 3BHT / 3BHU) [60].

Interestingly, one of the most potent DYRK1A inhibitors, epigallocatechin gallate (EGCG; **66**) (Table **5**), does not compete with ATP when inhibiting DYRK1A activity [61], and its mechanism of action still remains unknown.

HOW DID WE CLASSIFY DYRK1A INHIBITORS?

Numerous DYRK1A inhibitors have been described in the literature over the past decade. To inhibit DYRK1A activity, compounds prevent protein autophosphorylation or bind to the mature protein, most frequently at the ATP binding site. All of the DYRK1A inhibitors described in the literature are either nitrogenous heterocycles or polyphenols. For this review, we categorized the nitrogenous heterocyclic derivatives into six different compound families according to the number of fused cycles in their scaffold, from monocyclic to octacyclic scaffold derivatives. We dedicated the last class to polyphenolic compounds. Tables **1-5** describe the most active DYRK1A inhibitors belonging to the seven distinct chemical classes mentioned above.

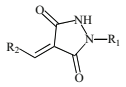
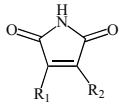
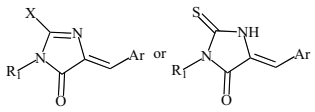
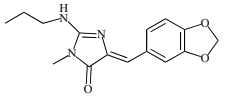
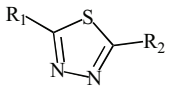
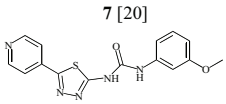
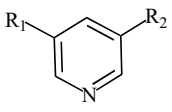
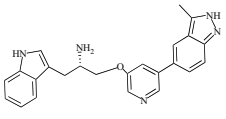
The Various Classes of DYRK1A Inhibitors

The first family of nitrogenous heterocyclies possesses a monocyclic core (Table **1**). Compound **1**, with a pyrazolidine-3,5-diones core, was identified in the field of learning and memory by Kim and colleagues [20] as a DYRK1A inhibitor in a patient with neurological deficits, by utilizing a combination of *in silico*, *in vitro* and cell-based screening. Later, the same team developed two series of pyrazolidine-3,5-diones derivatives to perform SARs between DYRK1A and different substitutes.

Compounds **2** and **3** emerged as hits and also showed inhibitory activity against DYRK1A autophosphorylation (Table **1**) [57].

Small molecules, such as SB216763 (**4**) and SB415286 (**5**) pyrrole-2,5-dione derivatives, were first identified as GSK-selective, ATP-competitive inhibitors (IC_{50} concentrations ranging between 100 and 200 nM) and were later reported to inhibit DYRK1A activity *in vitro* at slightly higher concentrations (IC_{50} from 0.8 to 2 μM) (Table **1**) [62,63]. The specificity of **4** has been examined against a panel of 71 protein kinases, which revealed that the compound only interacts with four protein kinases (extracellular signal-regulated kinase 8 (ERK8), GSK3β, inositol phosphate kinase 2 (IPK2) and serine-rich protein kinase 1 (SRPK1)) in addition to DYRK1A [63]. Interestingly, within the DYRK1A family, this compound is specific for DYRK1A [63]. Within the framework of drug discovery for the learning and memory deficits in Down's syndrome, thia-3,4-diazole derivative **7** emerges as a potent DYRK1A inhibitor [20] and inhibits both autophosphorylation and mature protein activity [20]. The specificity of compound **7** for DYRK1A was confirmed by screening 15 other protein kinases that were structurally close to DYRK1A (Table **1**). MADE 44 (**6**) is the lead compound from a series of alkaloid leucettamine B derivatives that were developed and patented as DYRK1A inhibitors [64].

Table 1. DYRK1A Inhibitors Displaying Monocyclic Scaffolds (Class I)

Chemical Structures[i]		Inhibits Mature Protein (IC_{50}[ii]; μM)		Inhibits Auto-phosphorylation (IC_{50}[ii]; μM)	Specificity[iii] (IC_{50} in μM)	Inhibition Mechanism	Clinical Indications
Pyrazolidine-3,5-dione derivatives 	**1** (R_1=3,4-dichlorophenyl, R_2=3-methoxy-4-hydroxyphenyl) [20]	< 10		2.5	CLK3 < 10 (tested on 15 kinases)	Docking in model DYRK1A ATP binding site	-
	2 (R_1=3,4-dichlorophenyl, R_2=3-nitro-4-hydroxyphenyl) [57]	1.3		0.6	Dyrk2 < 15	Docking in the ATP binding site	-
	3 (R_1=4-cyanophenyl, R_2=3 methoxy-4-hydroxyphenyl) [57]	6		0.6	-	Unknown	-
Pyrrole-2,5-dione derivatives 	**4** (SB 216763): (R_1=3-(N-methyl)indolyl, R_2=2,4-dichlorophenyl)	0.8 [62]		~ 50 (Ser720 Auto-phosphorylation) [13]	[63]: ERK8, GSK3β, CDK2-Cyclin A, RSK1, PIM3, SRPK1, HIPK2, HIPK2 < 2 [62]: GSK3β: 0.10 CDK2-cyclin A: 0.95 CHK1, RSK1, PKC < 10	Unknown	Type II diabetes [94]
	5 (SB 415286): (R_1=2-nitrophenyl, R_2=amino(3-chloro-4-hydroxy)phenyl)	0.9 [62]		-	[62]: GSK3β: 0.20 CDK2-Cyclin A: 0.80 [63]: MKK, ERK8, RSK1, RSK2, PRK2, PKCα, CaMKKβ, AMPK, MARK3, BRSK2, PIM1, PIM2, PIM3, MST2 < 10	Unknown	Type II diabetes [94]
Imidazolone (Leucettamine) derivatives  X=-NHR_2, -SR_2, -$NHCOR_2$	**6** (MADE 44) [64] 	34 compounds with IC_{50} < 1 **6**: 0.07		-	No selectivity assay reported.	Unknown	-
Thia-3,4-diazole derivatives 	**7** [20] 	< 10		5	CLK3, GSK3β, Dyrk2 < 10	Unknown	-
Pyridine derivatives 	**8** (A-443654) [65] 	< 0.01		-	ERK8, RSK1, RSK2 PKBα, PKBβ, S6K1 PKA, ROCK2, PRK2, PKCα, PKD1, MSK1, SmMLCK, GSK3β, CDK2-Cyclin A, DYRK2, DYRK3, PIM1, PIM2, PIM3, MST2, HIPK2 < 0.10	Unknown	-

i) the activity of the most efficient DYRK1A inhibitors are presented at the levels of phosphorylation or autophosphorylation with IC_{50}< 10μM.

ii) the assays were carried out with variable reaction conditions.

iii) other kinases that are inhibited at a concentration close to DYRK1A's IC_{50} are listed.

Pyridine derivative **8** (from Abbott labs, referenced as A-443654) was initially identified as a potent Akt inhibitor for use in the anticancer research field [65]. However, **8** also inhibits other members of the AGC subfamily of protein kinases as well as DYRK1A at slightly lower potency (Table **1**). Its anticancer properties have been reported in the literature [65,66] and could be related to its pan-anti-kinase effects.

Table **2** details bicyclic scaffold-related compounds that efficiently inhibit DYRK1A kinase.

Among the purine derivatives and analogs, purvalanol A (**9**) and roscovitine (**10**) are several-fold more potent inhibitors of cyclin dependent kinases (CDKs) compared to DYRK1A. (Table **2**) Thus, their use for neurodegenerative diseases may be limited due to their effects on the cell cycle [67]. The (*R*)-roscovitine (Siliciclib) has already entered clinical trials as an anticancer drug for solid and non-solid cancers. In an effort to identify new roscovitine analogs with increased antitumor potency, two compounds closely related to roscovitine, N-&-N1 and N-&-N2 (**11** and **12**), were synthesized and studied by Laurent Meijer's team, who previously discovered roscovitine (Table **2**). Similar to roscovitine, these two compounds are more potent inhibitors of CDKs compared to DYRK1A [68].

The benzothiazole derivative **13,** referred to as INDY (INhibitor of DYrk1A) by Ogawa and colleagues [54], displays potent and selective inhibition of DYRK1A (Table **2**). Its selectivity has been tested against a panel of 66 kinases, and it only inhibited other members of the DYRK family, including DYRK1B, DYRK2, DYRK3 and DYRK4, as well as Clk family kinase [54]. The potential antitumor activity and/or neural benefits of INDY have not yet been reported. The related TG003 compound **14** was profiled against a panel of 402 protein kinases and was found to bind to DYRK1A, Clk1, Clk2 and Clk4 selectively (Table **2**) [69].

The tetrabromobenzimidazole derivatives, TBB, TBI and DMAT (**15 -17**) (Table **2**), were first investigated to specifically inhibit casein kinase 2 (CK2) but also display marked activity on kinases that belong to the DYRK family as well as three other kinase groups [70].

Quinolone derivatives **18** and **19** (Table **2**) show higher activity against CK2 than DYRK1A but remain selective for both kinases compared to a panel of five serine/threonine kinases and two tyrosine kinases [71]. The quinazoline derivative **20** (Table **2**) was profiled against a panel of 402 kinases and was found to be remarkably selective for DYRK1A, Clk1 and Clk4, which all belong to the CGMC kinase group [69]. Quinazoline derivative **23** (Table **2**) inhibits the autophosphorylation of DYRK1A at 5 μM but does not display significant anti-DYRK1A effects at this concentration [20]. In the cancer research field, hydroxy-quinoline-carboxylic acids were designed to interact with the CGMC threonine/serine Pim-1 kinase, which has been labeled as an oncogene [72]. Compounds **24** and **25** (Table **2**) display significant anti-kinase activity against DYRK1A [73]. Compound **26** (Table **2**) inhibits autophosphorylation and kinase activity at a concentration of 10 μM [20].

Meriolin derivatives (**27**–**38**; Table **2**), which we included in the pyrimidinyl azaindole chemical subgroup, are chemical hybrids between the marine alkaloids, meridianin and variolin (**39**) (Table **2**). Meriolins display anti-DYRK1A activity and marked antiproliferative and pro-apoptotic effects in tumor cells [60].

Synthetic analogues of meridianins, with diverse substitutions at the C-5 position of the pyrimidine ring and both unmethylated and methylated forms of the indole nitrogen (compounds **40** - **44**), displayed sub-micromolar inhibition of DYRK1A (Table **2**). However, none of these compounds displayed significant cytotoxic effects on primary cultured fibroblasts or two human solid-tumor cell lines (MCF7 and PA1) [74].

The two amino-imidazopyridine-oxadiazole derivatives (compounds **45** and **46**; Table **2**) have been synthesized to selectively inhibit mitogen- and stress-activated protein kinase 1 (MSK1); they also display inhibitory effects toward DYRK1A but at concentrations of approximately one thousand times higher than for MSK-1 [75].

Compound **47** (Table **2**) and its analogs have been patented for leukemia treatment and display anti-DYRK1A activity [76].

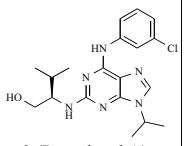
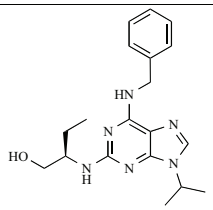
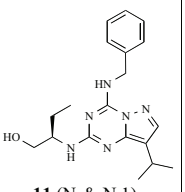
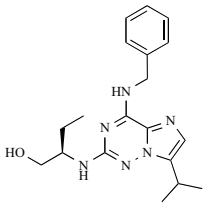
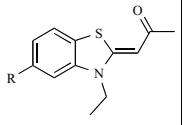
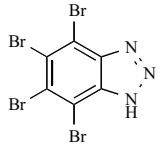
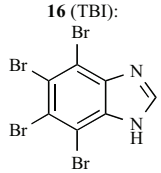
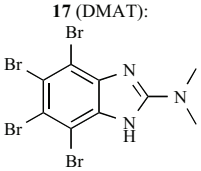
The alkaloid compound harmine (**48**) (Table **3**) has been identified as a potent and selective inhibitor of DYRK1A [63] and has primarily been used to identify the role of DYRK1A substrates *in vivo* and as a negative control for the pathological effects of DYRK1A overexpression [44]. Additionally, harmine (**48**) has been commonly used as a chemotherapeutic drug for a number of diseases [43,77,78]. In a study unrelated to DYRK1A, harmine and related β-carbolines (**49**-**52**) display cytotoxic activity toward human tumor cell lines in culture (Table **3**) [79], which suggests their potential use in anticancer therapeutics [80].

However, in addition to being an effective DYRK1A inhibitor, harmine is an even more potent inhibitor of monoamine oxidase A (MAOA) [81]. Harmine could inhibit the resistance of cancer cells to apoptotic stimuli by inhibiting DYRK1A, thus preventing the autoprocessing of caspase-9 [43]. A study performed on breast cancer cell lines that overexpress BCRP (breast cancer resistance protein), a protein that leads to DNA topoisomerase I inhibitor resistance, showed that co-treatment with a non-toxic dose of harmine with camptothecin reversed BCRP-mediated resistance [82].

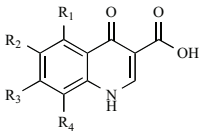
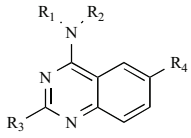
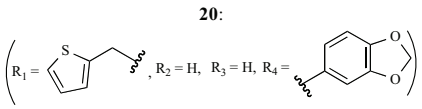
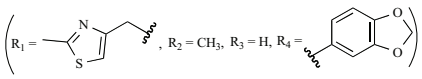
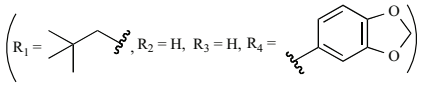
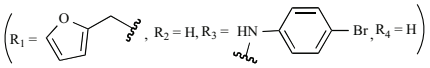
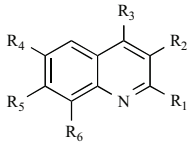
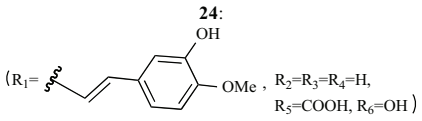
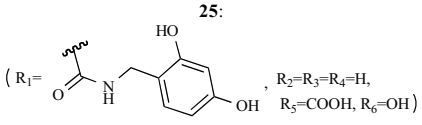
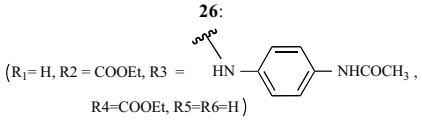
The quinazolinone IQA (**53**; Table **3**) was developed to specifically target CK2 (casein kinase) for use as an anticancer therapeutic. It also targets DYRK1A, with an IC_{50} that is twenty-fold weaker than its IC_{50} on CK2 [59].

The DYRK1A inhibitors that displayed five fused cycles (**54**-**62**; Table **4**) were derived from marine invertebrates and were termed lamellarins. These compounds are potent inducers of apoptosis and have been shown to revert to the multidrug resistance phenotype [83-85]. The kinases selectively targeted by these compounds include DYRK1A, CDK1, GSK and CK1 [83].

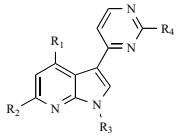
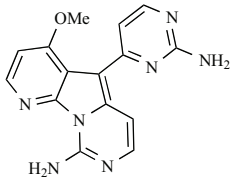
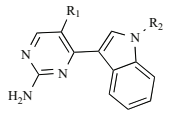
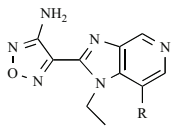
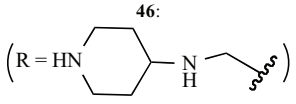
Table 2. DYRK1A Inhibitors Displaying Bicyclic Scaffolds (Class II)

Chemical Structures[i]		Inhibits mature protein (IC_{50}[ii], μM)	Inhibits Auto-phosphorylation (IC_{50}[ii], μM)	Specificity[iii] (IC_{50} in μM)		Inhibition mechanism	Clinical indication
Purine derivatives and analogs							
 **9** (Purvalanol A)	 **10** (Roscovitine)	**9**: 0.3 [67] **10**: 3.1 [67, 68] **11**: 1.3 [68] **12**: 2.0 [68]	**10**: 5 [62]	**9** [63]: CDK2: 0.03 PAK4: 0.1 Src < 0.1 μM MAPK/ERK2, MAPKAP-K1a, PHK, LCK, CSK : < 10 [67]: CDK2/cyclin A: 0.1 RSK1: 1.5 **10** ERK8 < 1 CDK2: 0.1 PAK4: 7 [63] CDK2/cyclin A: 0.25 CK1δ: 17 [67] **11** CDK1/cyclin B, CDK2/cyclin A, CDK2/cyclin E, CDK5/p25, CDK7/cyclin H, CDK9/cyclin T, CK1, Erk2 < 4 [68] **12** CDK1/cyclin B, CDK2/cyclin A, CDK2/cyclin E, CDK5/p25, CDK7/cyclin H, CDK9/cyclin T, CK1 < 1.3 [68]		**10** & **11**: Crystallization with CDK2/cyclinA shows that they dock in the ATP binding site. [68]	**10**: Phase 2 clinical trials for B-cell malignancies, lung and breast cancer Phase 1 trials for glomerulo-nephritis, and Phase 2 trials in IgA nephropathy. [96]
 **11** (N-&-N 1)	 **12** (N-&-N 2)						
Benzothiazole derivatives							
Benzothiazole derivatives 	**13** (INDY: R=OH) **14** (TG003: R=CH_3O)	**13**: 0.2 [54] **14**: 0.9 [54] K_d[iii]: 0.01 [69]	-	**13** [54]: DYRK1B : 0.24 CDK1/cyclin B, CDK2/cyclin A, CDK5/p25, CLK1, CLK2, CLK3, CLK4, CSNK1A1 (CK1α1), CSNK1D (CK1δ), CSNK1G2 (CK1γ2), PIM1, MET, DYRK2, DYRK3, DYRK4, FLT3, GSK3α, GSK3β, LRPK2 ≤ 10	**14** [95]: DYRK 1B : 2 mClk1 : 0.02 mClk2 : 0.2 Dyrk1B: 0.1 Kd [69] versus: Clk3: 3 CSNK1D: 0.2 CSNK1E: 0.3 Dyrk1B: 0.1 PIM1: 0.1 PIM3: 0. 3 Ysk4: 0.3 CSNK1G2: 0.3 CSNK1G3: 0.3 Ysk4: 0.3	Unknown	-
4,5,6,7-Tetrabromobenzimidazole (TBI) derivatives and analogs							
15 (TBB):  **16** (TBI):  **17** (DMAT): 		**15**: 4.4 [70] 1.1 [55] **16**: 2.1 [70] **17**: 0.1 [93] 0.4 [70]	-	**15** [70]: CK2: 0.2 PIM1: 1 PIM2: 4 PIM3: 1 HIPK2: 5 HIPK3: 5 DYRK2: 1 DYRK3: 5 PKD1: 6 CDK2: 14 CDK2: 0.5 [59] **16** [70]: CK2: 0.6 PIM1: 0.1 PIM2: 0.2 PIM3: 0.07 HIPK2: 0.7 HIPK3: 1.2 DYRK2: 0.3 DYRK3: 4 PKD1: 0.3 CDK2: 0.6	**17** [70]: PIM1: 0.2 PIM2: 2 PIM3: 0.1 HIPK2: 0.4 HIPK3: 0.6 DYRK2: 35 DYRK3: 2 PKD1: 0.2 CDK2: 0.6 [93]: CK2 : 0.1 MKK: 11 MAPKAP-K1a: 10 SGK: 4 Phosphorylase kinase: 7 CDK2/cyclin A: 2	Unknown	-

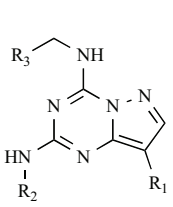
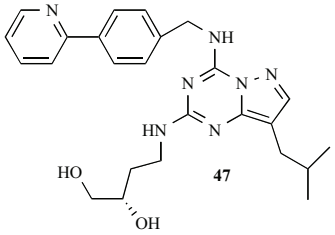
(Table 2) contd….

Chemical Structures[i]	Inhibits mature protein (IC_{50}[ii], µM)	Inhibits Auto-phosphorylation (IC_{50}[ii], µM)		Specificity[iii] (IC_{50} in µM)	Inhibition mechanism	Clinical Indication
Quinolones/ Quinazolines/ Quinolines						
3-Carboxy-4(1*H*)-quinolone derivatives  [71]	**18**: (R_1=R_2=R_4=Cl, R_3=H) **19**: (R_1=R_2=H, R_3–R_4=phenyl)	**18**: < 10 **19**: > 10	-	CK2 C7: 0.3 C9: 1	In inhibiting CK2, **18** & **19** are ATP competitive	-
4-amino-6-arylquinazolin derivatives 	**20**:  **21** :  **22** :  **23**: 	**20**: K_d[iv]: 0.03 [69] 0.07 [92] **21**: 0.01 [92] **22**: 0.02 [92] 28 compounds with 10 > IC_{50} > 0.1 and 17 compounds with 0.1 > IC_{50} > 0.01 [92] **23**: >10 [20]	**21**: 5 [62] **23**: 5 [20]	**20** [92]: Clk1: 0.06 Clk2: 2 Clk3: 7 Clk4: 0.04 [Dyrk1B: 0.7 Clk4 : 0.06 [69] Kd [69]: Clk1: 0.04 Clk4: 50 EGFR: 230 Clk2: 680 Clk3: 470 Dyrk1B: 430 **21** [92]: Clk1: 0.02 Clk2: 0.2 Clk3: 2 Clk4: 0.01 Dyrk1B: 0.03 **22** [92]: Clk1: 0.2 Clk2: 584 Clk3: 0.4 Clk4: 0.07 Dyrk1B: 0.08	Unknown	-
Quinoline derivatives: 	**24**:  **25**:  **26**: 	**24**: 1.3 [73] **25**: 4.5 [73] **26**: 10 [20]	**26**: 10 [20]	**24** [73]: Pim-1: 0.5 DYRK2: 1 CLK: 8 **25** [73]: Pim-1: 0.4 DYRK2: 6	Unknown	-

(Table 2) contd….

Chemical Structures[i]		Inhibits mature protein (IC_{50}[ii], µM)	Inhibits Auto-phosphorylation (IC_{50}[ii], µM)	Specificity[iii] (IC_{50} in µM)		Inhibition mechanism	Clinical indication
Pyrimidinylindol/azaindole derivatives							
Meriolins (3-(4-pyrimidinyl)-7-azaindole) [60] 	**27**: (R_1=H, R_2=H, R_3=H, R_4=NH_2) **28**: (R_1=OH, R_2=H, R_3=H, R_4=NH_2) **29**: (R_1=OMe, R_2=H, R_3=H, R_4=NH_2) **30**: (R_1=OEt, R_2=H, R_3=H, R_4=NH_2) **31**: (R_1=OPr, R_2=H, R_3=H, R_4=NH_2) **32**: (R_1=OiPr, R_2=H, R_3=H, R_4=NH_2) **33**: (R_1=OH, R_2=H, R_3=Me, R_4=NH_2) **34**: (R_1=Cl, R_2=H, R_3=H, R_4=NH_2) **35**: (R_1=H, R_2=Br, R_3=H, R_4=NH_2	**36**: (R_1=OMe, R_2=H, R_3=H, R_4=SMe) **37**: (R_1=OH, R_2=H, R_3=H, R_4=H) **38**: (R_1=OMe, R_2=H, R_3=H, R_4=H) **39** (Variolin B): 	**27**: 0.1 **28-32**: ≤ 0.04 **33**: 1.2 **34-38**: ≤ 1 **39**: 0.08	-	Variolin B and Meriolins **27-32**: CDK1/ cyclin B, CDK2/ cyclin A, CDK5/p25, CDK9/cyclinT, GSK-3 α/β, CK1 < 0.8 Meriolin **33**: CDK1/ cyclin B, CDK2/ cyclin A, CDK5/p25, CDK9/cyclinT, GSK-3 α/β, CK1 < 6 Meriolins **34-38** : CDK1/ cyclin B, CDK2/ cyclin A, CDK5/p25, CDK9/cyclinT, GSK-3 α/β, CK1 < 30	X-ray Crystallog ra-phic structure of meriolin 5 and variolin B in complex with CDK2/cy clin A show that they fit inside the ATP-binding site.	-
Aminopyrimidinyl-indole Derivatives [74] 	**40**: (R_1=(3-methoxy)phenyl, R_2=H) **41**: (R_1=(3-amino)phenyl, R_2=H) **42**: (R_1=(4-amido)phenyl, R_2=H) **43**: (R_1=(4-carboxy)phenyl, R_2=CH_3) **44**: (R_1=I, R_2=CH_3)		**40**: 0.6 **41**: 0.6 **42**: 0.6 **43**: 0.9 **44**: 0.4	-	**40**: CK1δ/ε GSK3α/β Erk2 < 4 **41**: CK1δ/ε GSK3α/β Erk2 < 7 **42**: CK1δ/ε GSK3α/β Erk2 < 4 **44**: CDK5/p25 CK1δ/ε GSK3α/β Erk2 < 5	Unknown	-
1*H*-Imidazo[4,5-c]pyridin-2-yl)-3-amino-1,2,5-oxadiazole derivatives							
	**45**: (R=H) **46**: 		**45**: 0.1 **46**: 4.9 [75]	-	**45**: GSK3b: 0.005 MSK-1 : 0.03 RSK-1: 0.02 P70S6K : 0.07 ROCK : 0.01 CDK2 : 0.2 AMPK, DYRK1a, MAPKAP-K1a, PKA, PKCa, SGK < 10 **46**: MSK-1 : 0.0005 GSK3b : 2 RSK-1: 0.2 P70S6K : 0.3 ROCK : 0.1	Unknown	-

(Table 2) contd….

Chemical Structures[i]		Inhibits mature protein (IC_{50}[ii], µM)	Inhibits Auto-phosphorylation (IC_{50}[ii], µM)	Specificity[iii] (IC_{50} in µM)	Inhibition mechanism	Clinical indication
Pyrazolo[1,5-a]-1,3,5-triazine derivatives						
	**47** [76]:  **47**	18 Compounds with IC_{50} between 0.3 - 3 **47**: 0.3	-	18 Compounds tested on 7 kinases **47**: CDK1/cyclin B : 0.02 CDK2/cyclin: 0.01 CDK5/p25: 0.01 CDK9/cyclin T: 0.04 CK1: 0.06	Unknown	-

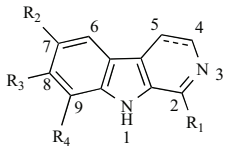
i) the activity of the most efficient DYRK1A inhibitors are presented at the levels of phosphorylation or autophosphorylation with IC_{50}< 10µM.

ii) the assays were carried out with variable reaction conditions.

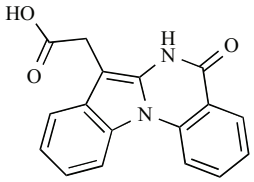
iii) other kinases that are inhibited at a concentration close to DYRK1A's IC_{50} are listed.

iv) K_d = kinase binding: % of kinase bound to an immobilized ligand in the presence and absence of the test reagent as compared to DMSO.

Table 3. DYRK1A Inhibitors Displaying tri- (Class III) and Tretracyclic (Class IV) Scaffolds

Chemical Structures[i]		Inhibits Mature Protein (IC_{50}[ii]; µM)	Inhibits Auto-phosphorylation (IC_{50}[ii]; µM)	Specificity[iii] (IC_{50} in µM)	Inhibition Mechanism	Clinical Indications
Class III: Tricyclic Scaffold						
β-Carbolines 	**48** (Harmine): (R_1=Me, R_2=H, R_3=OMe, R_4=H, 4-5: =) **49** (Harmane): (R_1=Me, R_2=H, R_3=H, R_4=H, 4-5: =) **50** (Harmalol): (R_1=Me, R_2=H, R_3=OH, R_4=H, 4-5: -) **51** (Harmaline): (R_1=Me, R_2=H, R_3=OMe, R_4=H, 4-5: -) **52** (PS-1145): (R_1=H, R_2=Cl, R_3=H, R_4=3-pyridinecarboxamide, 4-5: =)	**48**: 0.03 [91] 0.08 [63] 0.4 [54] 0.08 [55]	**48**: Tyr321: 2 [91] Ser520: 5 [10]	DYRK 1B : 0.2 (85% sequence identity in catalytic domain) [91] [54]: DYRK1B : 0.3 CLK1, CLK2, CLK3 < 10 [91]: DYRK2 :2 DYRK4 : 80 MNB: 0.2 [4]: CK1: 2 [63]: DYRK2 : 1 DYRK3 : 1 PIM3: 4 K_i [81]: MAO: 0.005	Crystallographic structure of Dyrk1A in complex with harmine shows that the inhibitor binds in the ATP site. [54]	-
		49: 2 [55] < 1 [63]		Inhibits other kinases at concentrations > 1 [63, 55]	Unknown	-
		50: > 1 [63]		Inhibits other kinases at concentrations > 1 [63]	Unknown	-
		51: 5 [55] < 1 [63]		ERK8, DYRK3 < 1 DYRK2 > 1 [63, 55]	Unknown	-
		52: < 10 [63]		ERK8, MNK1, DYRK3, IKKβ, PIM1, PIM2, PIM3 < 10 [63]	Unknown	-

(Table 3) contd….

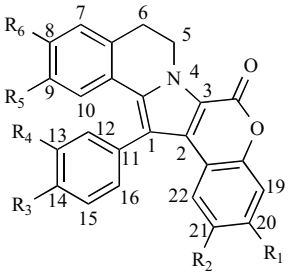
Chemical Structures[i]	Inhibits mature protein (IC_{50}[ii]; µM)	Inhibits Auto-phosphorylation (IC_{50}[ii]; µM)	Specificity[iii] (IC_{50} in µM)	Inhibition mechanism	Clinical indications
Class IV: Tetracyclic Scaffold					
Quinazolinone **53**: (IQA, CGP029482) [59] 	**53:** 8	-	CK2: 0.4 PKA: 16 GSK3β: 14 Lck: 11	X-ray crystallography of CK2/IQA shows that IQA binds to CK2 at the ATP-binding site.	-

i) the activity of the most efficient DYRK1A inhibitors are presented at the levels of phosphorylation or autophosphorylation with IC_{50}< 10µM.

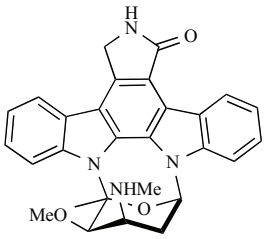
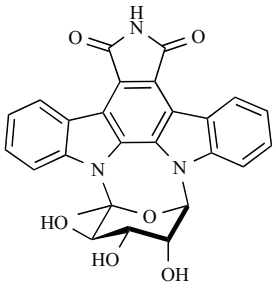
ii) the assays were carried out with variable reaction conditions.

iii) other kinases that are inhibited at a concentration close to DYRK1A's IC_{50} are listed.

Table 4. DYRK1A Inhibitors Displaying Penta- (Class V) and Octacyclic (Class VI) Scaffolds

Chemical Structures[i]			Inhibits Mature Protein (IC_{50}[ii]; µM)	Specificity[iii] (IC_{50} in µM)		Inhibition mechanism	Clinical Indications
Class V: Pentacyclic Scaffold							
Lamellarins  [83]	**54** (Lam. D): (R_1=OH, R_2=OMe, R_3=OH, R_4=OMe, R_5=OMe, R_6=OH, 5-6: =) **55** (Lam. α): (R_1=OH, R_2=OMe, R_3=OH, R_4=OMe, R_5=OMe, R_6=OMe, 5-6: =) **56** (di-H-Lam.D): (R_1=OH, R_2=OMe, R_3=OH, R_4=OMe, R_5=OMe, R_6=OH, 5-6: -) **57** (Lam. N): (R_1=OH, R_2=OMe, R_3=OMe, R_4=OH, R_5=OMe, R_6=OH, 5-6: =) **58** (Lam. L): (R_1=OH, R_2=OMe, R_3=OMe, R_4=OH, R_5=OMe, R_6=OH, 5-6: -)	**59** (Lam. 3): (R_1=OH, R_2=H, R_3=OH, R_4=OMe, R_5=OMe, R_6=OH, 5-6: =) **60** (Lam. 4): (R_1=H, R_2=OMe, R_3=OH, R_4=OMe, R_5=OMe, R_6=OH, 5-6: =) **61** (Lam. 6): (R_1=OH, R_2=OMe, R_3=OH, R_4=H, R_5=OMe, R_6=OH, 5-6: =) **62** (Lam. 8): (R_1=H, R_2=H, R_3=OH, R_4=OMe, R_5=OMe, R_6=OH, 5-6: =)	**54**: 0.5 **55**: 5 **56**: 0.5 **57**: 0.04 **58**: 0.1 **59**: 0.06 **60**: 0.08 **61**: 0.09 **62**: 1	**54**: CDK1/cyclin B CDK5/p25 GSK-3α/ß PIM1 < 0.6 **55**: CDK1/cyclin B GSK-3α/ß PIM1 CK1< 8 **56**: CDK1/cyclin B CDK5/p25 GSK-3α/ß PIM1, CK1 < 6 **57**: CDK1/cyclin B CDK5/p25 GSK-3α/ß PIM1 < 0.07 AMPKα, CaMK2α, CHK2, CSK, FGFR2, FLT-1, FLT-3, Fyn, JNK 2, KDR, Lck, Lyn, PDGFRβ, Ret, RSK2, TRKA < 10	**58**: CDK1/cyclin B CDK5/p25 GSK-3α/ß PIM1 < 0.04 **59**: CDK1/cyclin B CDK5/p25 GSK-3α/ß PIM1 CK1 < 0.6 **60**: CDK1/cyclin B CDK5/p25 GSK-3α/ß PIM1 CK1 < 2 **61**: CDK1/cyclin B CDK5/p25 GSK-3α/ß PIM1, CK1 < 0.2 **62**: CDK1/cyclin B CDK5/p25 GSK-3α/ß PIM1 < 5	Unknown	-

(Table 4) contd….

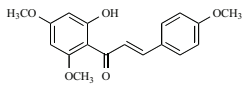
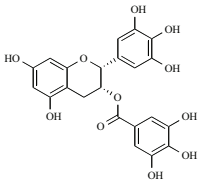
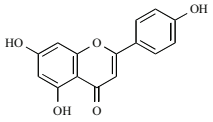
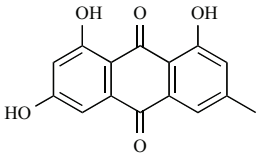
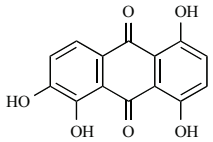
Chemical Structures[i]		Inhibits Mature Protein (IC_{50}[ii]; μM)	Specificity[iii] (IC_{50} in μM)		Inhibition mechanism	Clinical Indications
Class VI: Octacyclic Scaffold						
Glycosylated indolocarbazole derivatives						
63 (Staurosporine) [86]: 	**64** [86]: 	**63**: 0.02 **64**: 0.004	**63**: Aurora A: 0.0072 Aurora B: 0.02 Chk1: 0.001 Ftl3 : 0.003 HGK: 0.001 Ikkb: 0.0005 Jak2: 0.001 KDR: 0.01 SYK: 0.004	**64**: Chk1: 0.001 Ftl3: 0.0006 FGFR1: 0.009 HGK: 0.0008 Ikkb: 0.002 Jak2: 0.0005 KDR: 0.004 SYK: 0.001	X-ray crystallographic structures of PI3K-γ with staurosporine shows this compound binds into the ATP site. [97]	-

i) the activity of the most efficient DYRK1A inhibitors are presented at the levels of phosphorylation or auto-phosphorylation with IC_{50}< 10μM.

ii) the assays were carried out with variable reaction conditions.

iii) other kinases that are inhibited at a concentration close to DYRK1A's IC_{50} are listed.

Table 5. DYRK1A Inhibitors with Polyphenolic Structures (Class VII)

Chemical Structures[i]			Inhibits mature protein (IC_{50}[ii], μM)	Specificity[iii] (IC_{50} in μM)	Inhibition mechanism	Clinical indications
Class VII: Polyphenols						
65 (Flavokavain A):  *Piper methysticum* (Kava) derivatives	**66** (EGCG): 	**67** (Apigenin): 	**65**: < 10 [88] **66**: 0.3 [67] 0.04 [61] **67**: < 10 [59] **68**: < 10 [59] 0.7 [55] **69**: K_i[iv] =5.9 [58]	**65** [88]: Aurora B < 10 μM (Tested on 52 protein kinases) **66** [67]: PRAK: 1 μM PDK: 10 μM **67** [59]: CK2: 1 μM SGK, CDK2/cyclinA, Lck, c-Fgr < 10 μM **68** [58]: PIM3: 0.08μM CK2: 2.5 μM CK2: 0.9 μM [59] **69** [58]: K_i CK2: 0.05 μM (IC50 = 0.1 μM) PIM1: 1 μM PIM3: 1 μM (IC50 = 2 μM) HIPK2: 2 μM (Specific inhibitor of CK2)	**66**: Not competitive with ATP [61] **69**: CK2 inhibition is competitive with ATP. [58]	**66**: 28 clinical trials on cancer, one clinical trial on down syndrome, 63 clinical trials in total (Administered as drug or as tea/ tea extracts dietary supplements) [clinicaltrials.gov] **67**: Phase II - suspended clinical trial on prevention of neoplasia recurrence [clinicaltrials.gov]
68 (Emodin): 		**69** (Quinalizarin): 				

i) the activity of the most efficient DYRK1A inhibitors are presented at the levels of phosphorylation or auto-phosphorylation with IC_{50}< 10μM.

ii) the assays were carried out with variable reaction conditions.

iii) other kinases that are inhibited at a concentration close to DYRK1A's IC_{50} are listed.

iv) K_d = kinase binding: % of kinase bound to an immobilized ligand in the presence and absence of the test reagent as compared to DMSO.

The octacyclic core compounds that have been reported to display anti-DYRK1A properties include the glycosylated indocarbazole derivative staurosporine (**63**) and the close analogue **64** (Table **4**), which inhibits 11 out of a panel of 57 kinases tested, including DYRK1A, at or below single-digit nanomolar concentrations, [86]. When compared to **63**, **64** displays slightly higher selectivity [86].

The last class of DYRK1A protein kinase inhibitors includes polyphenolic compounds (Table **5**). Polyphenols are known to display antioxidant, anti-inflammatory and anti-tumor properties [87]. We recently reviewed the general topic of natural polyphenols that display anticancer properties through anti-kinase activity [87]. Among them, flavokavain A (**65**), EGCG (**66**), apigenin (**67**), emodin (**68**) and quinalizarin (**69**) show anti-DYRK1A properties with IC_{50} values in the low and sub-micromolar range.

Marc Diederich's team reports that flavokavain A (**65**) substantially decreases the activity of DYRK1A and that of two other kinases, Aurora B and PRAK, and it does not interact with the remaining subset of 49 kinases that were also tested [88]. Furthermore, **65** is reported to possess anticancer activity that is associated with its ability to induce a loss of mitochondrial potential and cytochrome C release [89].

The green tea polyphenol extract EGCG (**66**) emerges as an effective and specific DYRK1A inhibitor (Table **5**) [67,90]. However, EGCG is not a selective inhibitor of DYRK1A [87].

The apigenin (**67**) (Table **5**) is a flavonoid, which is found at high concentrations in several herbs, including parsley, thyme and peppermint, and its anti-DYRK1A properties have already been highlighted [59]. Similar to emodin (**68**) and quinalizarin (**69**) (Table **5**), numerous ATP-competitive inhibitors developed against CK2 are also effective against DYRK1A [55].

The phenolic compound emodin (**68**), obtained from rhubarb or frangula bark, (Table **5**) has also been studied for its DYRK1A inhibitory properties [55,59]. Emodin (**68**) inhibits DYRK1A and CK2 with comparable efficacy and remained selective for those two kinases when used at 10 μM among a panel of 33 protein kinases [55,59]. Interestingly, another anthraquinone derivative, quinalizarin (**69**), (Table **5**) has been identified as a potent CK2 inhibitor, but it displays ten-fold weaker inhibition toward DYRK1A compared to CK2 and to the inhibition of DYRK1A induced by emodin [55,58].

CONCLUSION

The protein kinase DYRK1A has mostly been investigated within the framework of neurodegenerative diseases, in which it must be as selective as possible in order to not disturb the cell cycle and general cell metabolism. In contrast, in cancer treatment, absolute selectivity may not be essential for a kinase inhibitor to be a drug candidate, and some promiscuity may actually be an advantage in terms of clinical efficiency, as it is the case with roscovitine (**10**).

There are dozens of currently available compounds that inhibit DYRK1A activity with differential selectivity. The majority of DYRK1A inhibitors reviewed here were initially designed to target the active site of some other kinases such as quinazolinone and quinolone derivatives (**53**, **58**, **59**) for CK2 inhibition, or pyrrole-2,5-dione derivatives for GSK inhibition (**4**, **5**). Because its X-ray structure has only been solved quite recently, too few studies of the actual selective inhibition of DYRK1A have yet been carried out in order to draw any general conclusions about its structure-activity relationship (SAR).

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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