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REVIEW ARTICLE

A Comprehensive Investigation on the Role of Bioactives on DYRK1A to Avert Alzheimer's Disease

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Abstract

DYRK1A belongs to the CMGC kinase group, which is an evolutionarily conserved family. A particular kind of gene situated in the 21q22.2 of the chromosome in the human domain encodes DYRK1A, which has garnered focus because it has been linked to neuropathological traits of people who have Down Syndrome (DS). Both DS and Alzheimer's Disease (AD) cognitive dysfunctions are lessened in animal models when DYRK1A is inhibited. There are, at present, very few therapy options available for the cognitive deficits linked to AD as well as DS, which represents a significant unfulfilled therapeutic necessity. Pharmacological treatment for cognitive deficits connected to AD, along with various neurological disorders, might be attainable by inhibiting brain DYRK1A activity with small molecules. Here, we provide a comprehensive summary of DYRK1A's role in the pathophysiology of AD along with details on its structure, function, and regulation. We also include a brief analysis of DYRK1A's natural inhibitors, such as Aristolactam BIII, Epigallocatechin Gallate (EGCG), Harmine, along with marine compounds such as Meridianins, Leucettines that have a particular interaction with the ATP binding domain of DYRK1A, and their Structure-Activity Relationship (SAR) investigations.

Major Findings: Natural DYRK1A inhibitors help reduce the cognitive dysfunctions observed in animal models by inhibiting DYRK1A. With an IC_{50} analogs of 580 nM, compound-7 i.e. 3-(2-amino-4-(3H-indol-3-yl) pyrimidin-5-yl) benzamide, showed the greatest inhibitory activity against DYRK1A of all the DYRK1A inhibitors discussed.

Keywords: Amyloid Hypothesis, DYRK1A, DYRK1A's Structure, Aristolactam BIII, Epigallocatechin Gallate (EGCG)

1. Introduction

Alzheimer's is one of the frequently observed kinds of progressive loss of memory and other thinking abilities. Numerous symptoms, including deteriorating language skills, increased memory loss, behavioural abnormalities, and other cognitive impairments, are indicative of AD[1]. Senile plaques (which cause amyloid materials to be deposited), neurofibrillary tangles, genetic factors like mutations in genes that code such as Apolipoprotein (APOE) genes and presenilin 1 and 2 gene, aging, metals like aluminum, neuroinflammation, synaptoxicity, neuropil, loss of calcium control, and oxidative stress[2] are some of the factors that contribute to the ailment's progression. The genesis and course of AD can be better understood in DS, a genetic abnormality characterised by an additional copy of chromosome 21 (trisomy 21). This is mostly because the two conditions share many genes and molecules. The individuals with DS have sooner cerebral Aβ accumulation, DS is frequently emphasised as a model condition leading to AD[3].

Non-communicable illnesses accounted for 7 out of 10 main causes of mortality globally in 2021, accounting for 38% of all deaths, or 68% of the top 10 causes, according to WHO data. AD and associated kinds of dementia killed 1.8 million individuals in 2021, making them the seventh most common cause of death. Compared to men, women are significantly impacted. Women are 68% more likely than males to die with Alzheimer's, along with associated dementias, worldwide. In upper-middle-income countries, Alzheimer's and all kinds of

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dementia became the sixth most common cause of mortality, and in high-income countries, they rank as the fourth[4].

Dual-specificity tyrosine phosphorylation-regulated kinases (DYRK1A) belong to the DYRK family. These threonine kinases are closely associated with the CMGC group and include kinases that depend on Cyclin (CDKs), Mitogen-Activated Protein (MAPs), Glycogen Synthase Kinases (GSKs), CDK-like kinases, or CLKs[5]. Due to its location in the crucial area of mammalian chromosomal 21 associated with DS, the DYRK1A gene is identified as a putative gene for DS[6]. Organisms like Drosophila (minibrain, mnb), fission yeast (POM1), and baker's yeast (YAK1) have been found to contain DYRKs[7]. The two groups of DYRKs, which include DYRKs (1A,1B), and the second group of DYRKs, which include DYRKs (2, 3, and 4), are separated by sequence homology from the five known DYRK subtypes (1A,1B,2,3, and 4) identified in creatures such as mammals (Figure 1)[8]. Auto-phosphorylating a residue of tyrosine (Tyr-Y321) in the loop of activation self-activates DYRK1A, which is considered a dual-specificity protein kinase that promotes the process of phosphorylation of both serine as well as threonine remains of the substrates[9,10].

In addition to its crucial functions in transmission of signals, splicing, cell cycle control, and cell death, DYRK1A has also been linked to brain development,[9] development of neurons[11], synaptic transmission[12]. DYRK1A excessive activity has been linked to early-onset AD, malignancy, neurodegeneration, aberrant brain development, and cognitive impairments in people with DS[13-16]. Because of this, the demand for DYRK1A inhibitors with the approach of using bioactives has grown significantly, which has spurred researchers to create possible pharmacological inhibitors for use in DS[17] as well as in AD[18,19]. The bioactives such as Harmine, Aristolactam BIII, Epigallocatechin Gallate (EGCG), and marine compounds such as Meridianins, Leucettines, alleviate various DS-associated traits linked to AD by inhibiting DYRK1A.

2. Detailed Structural Study of DYRK1A

The molecular domain of DYRK1A kinase consists of a larger C-terminal lobe along with the N-terminal lobe[20]. Five antiparallel β-strands make up the N-terminal lobe, while a conserved regulatory α lobe is made up of C-terminal helices and a sort of α C-helix. DYRK1A's C-terminal lobe has the CMGC insert, just like other CMGC kinases. At the base of the C-lobe, the CMGC-insert directly touches the G- and αH-helices of the kinase domain. The N-terminus portion of the CMGC-insert produces two short helices, α near the α L and α L', prior to the G helix diverging[21]. Additionally, DYRKs have a longer MAP kinase insertion in the C-lobe than other CMGC family members like GSK3β, CLK1, CLK2, or MAPKs. This insert creates a 40-residue complicated substructural domain. In addition, the hinge region—which joins the C-terminus and the N-terminal lobes—is an essential component of the ATP pocket. Furthermore, DYRK1A's ATP pocket has an essential "gatekeeper" residue (F238) that controls inhibitor selection[20]. The general composition of DYRK1A is seen in Figure 2. As shown in Figure 1, DYRK1A may also be separated into three parts: the C-terminus, the conserved catalytic domain, and the N-terminus. The N-terminus contains a functioning dichotomous Nuclear Localisation Signal (NLS) and a conserved DYRK homology box (DH box). The DH box, which is situated above the kinase domain's N-terminus lobe, engages in extensive network interactions with each of the five N lobe β-sheet strands[18]. Its primary goal is to preserve the N-terminus's tertiary integrity at DYRK1A. The DH box's two core tyrosines (Tyr140 and Tyr147) stabilise the independent folding unit that includes the DH box and the catalytic conformational region of the enzyme. DYRK1A's catalytic capabilities will decrease if the DH box region is removed[22]. The second component, the conserved catalytic domain, is in charge of kinase action. The self-phosphorylation of the tyrosine 321 residue (Tyr321, the second tyrosine residue on the YxY sequence) in this domain is the key to DYRK1A's self-activation. Following this, Ser/Thr residues on substrates may be identified and phosphorylated by DYRK1A with specificity[23]. Tyr321 mutations will significantly reduce DYRK1A's catalytic functioning and affect the overall function of its orthologs[22,24,25]. The C-terminus contains a serine/threonine repeat region, a polyhistidine band, and a PEST motif[26,27]. With a high concentration of proline (P), glutamic acid (E), serine (S), and threonine (T), the PEST motif promotes the depletion of DYRK1A. It has been proposed that Ser-520 self-phosphorylation

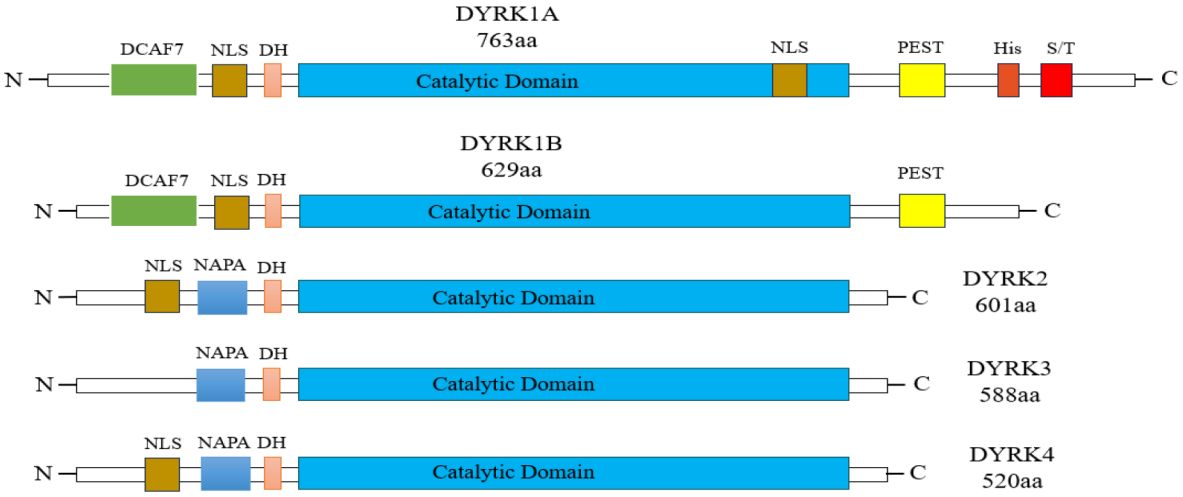


Figure 1. The arrangement of DYRK protein domains**.** The DYRK proteins' design constraints are shown. The DYRK1 protein has an NLS at the N-terminus, a DCAF7 binding domain, a DYRK homology box (DH) and Proline (P), glutamic acid (E), serine (S), and threonine (T) are all prominent in the PEST region at the C-terminus. DYRK1A's catalytic domain consists of an NLS, a histidine-rich (His) region, and a serine/threonine-rich (S/T) region. DYRK (2,3, and 4) all contain the catalytic domain, DH, and the N-terminus self-phosphorylation accessory (NAPA) domain. Moreover, an NLS is present in DYRK (2 and 4).

in this area controls DYRK1A's catalytic activity and facilitates the complex formation with the 14-3-3β protein[28]. The polyhistidine band-aids in proteins are localised to nuclear regions and provide an organic Histag to help in the clarification and improvement of DYRKs, generating DYRK1A using immobilised metal affinity chromatography[29]. The area of serine/threonine repeats controls catalytic activity[27].

3. Activation, Regulation of DYRK1A

Most protein kinases function as molecular switches that can adopt distinct active and inactive conformations. Conversion between these states is in many cases regulated by reversible phosphorylation of discrete serine, threonine, or tyrosine residues in the centrally located so-called 'activation loop'. Phosphorylation of the activation loop stabilises a conformation with an appropriately positioned substrate binding site[30]. Typically, this conformational change is driven by the electrostatic interactions between the phosphoresidue and a positively charged binding site named the RD pocket. Main contributors to the basic nature of this pocket are a conserved arginine (R) immediately preceding the invariant aspartate (D) in the catalytic loop and a basic residue in the β9 strand[31]. Kinases of the DYRK family depend on the phosphorylation

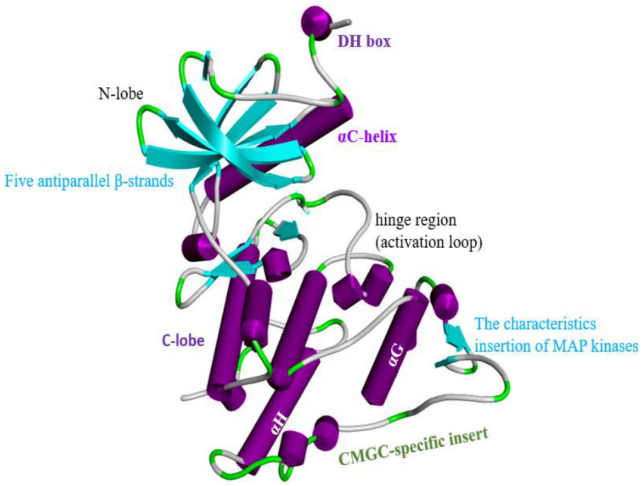


Figure 2. PDB 2VX3: General structure of DYRK1A. The CMGC-specific insert was represented by White-green colour, whereas sky-blue colour represents the distinctive insertion of MAP kinases, the five antiparallel β-strands represented in sky blue colour, purple represents the conserved regulatory α C-helix, DH box, G and H helices, and grey represents the hinge region.

of a conserved tyrosine residue in the activation loop to achieve full activity[24,25]. This tyrosine (Y321 in DYRK1A) corresponds to Y185 in the doubly phosphorylated TEY motif of ERK2, a residue classified as a 'secondary activation loop phosphorylation site' because it does not interact with the RD pocket[30].

Instead, the phosphorylated tyrosine forms salt bridges with two arginines in the P + 1 loop (R189 and R192 in ERK2). Many kinases of the CMGC group contain a tyrosine at the same position, either in combination with a threonine as the 'primary phosphorylation site' in a TxY motif, as in the MAP Ks, or the absence of a primary site, as in the DYRKs and GSK3a/b. In DYRK1A, pY321 is engaged in the same interactions with the two arginines as pY185 in ERK2 (R325andR328in DYRK1A). Tyrosine phosphorylation of DYRKs and GSK3occurs by autophosphorylation and appears to be constitutive[25,32]. This one-off autoactivation takes place during or immediately after translation by an intramolecular reaction[33,34]. In Drosophila DYRK2 (dDYRK2), tyrosine autophosphorylation depends on the presence of an N-terminal autophosphorylation accessory region. The N-terminal autophosphorylation accessory region is conserved in a subgroup of the DYRK family (class 2 DYRKs) but is not required for tyrosine autophosphorylation of MNB[35]. We have shown for mammalian DYRK1A that tyrosine autophosphorylation is an intrinsic capacity of the catalytic domain and does not depend on other domains or any cofactor[36]. However, so far, there is no evidence that the catalytic activity of any member of the DYRK family is reversibly regulated by phosphorylation /dephosphorylation of the activation loop tyrosine. Mature DYRKs phosphorylate their substrates only on serine or threonine residues and cannot rephosphorylate on tyrosine after phosphatase treatment[33,37].

There are several open questions concerning the activation mechanism of DYRK1A. The substitution of the activation loop tyrosine with biphenyl alanine markedly reduces (>80%) the catalytic activity of DYRK1A[24,25,38]. Surprisingly, dephosphorylation does not inactivate mature DYRK1A[37] and reduces the activity of Drosophila dDYRK2 and MNB by only 50%[33]. It is conceivable that tyrosine phosphorylation is only required for the switch into the active conformation but not for maintaining this state. Alternatively, the stabilising effect of the salt bridges between the phosphotyrosine with the two arginines in the P + 1 may be critical in living cells, but less so *in vitro* assays. For comparison, it is interesting to consider the role of the phosphotyrosine (pY216) in GSK3b, which resembles the DYRKs in its autoactivation mechanism[32,34]. Analysis of crystal structures revealed that unphosphorylated GSK3b, in stark contrast to unphosphorylated ERK2, can acquire a catalytically active conformation[39,40]. However, dephosphorylation destabilises the active conformation and leads to a loss of activity over time[32].

3.1 Regulation

The available evidence suggests that DYRK1A is always catalytically active when isolated from tissues or cells. However, the role of protein kinases as cellular regulators implies that their activity is somehow regulated. DYRK1A has severe phenotypic consequences, as exemplified by patients with homozygous deficiency of DYRK1A[41] and transgenic animal models[42]. Thus, the function of DYRK1A may be controlled by more subtle changes in activity than the paradigmatic on / off switches as known from MAPKs, cAMP-dependent protein kinase, receptor tyrosine kinases, and many other kinases[31]. In the neuroblastoma cell line SH-SY5Y, an increase in DYRK1A mRNA was induced by the b-amyloid peptide, but nothing is known about the potential mechanism of regulation[43]. The transcription factor E2F1 increases DYRK1A mRNA levels by enhancing promoter activity[44]. In a recent report, the nuclear factor of activated T-cells (NFATc1) was shown to upregulate DYRK1A levels in bone marrow macrophages[45]. Recently, SPRED1 and SPRED2 (sprouty-related protein with an EVH1 domain) were found to directly interact with the catalytic domain of DYRK1A and to inhibit the phosphorylation of the substrate proteins, Tau and STAT3[46]. Interestingly, the inhibitory effect of the SPRED proteins appears to be due to competition with the substrate proteins and not due to a general inhibition of catalytic activity. DYRK1A harbours a functional nuclear localisation sequence in its N-terminal domain and has been found in both the nucleus and in the cytoplasm, possibly depending on the cell type. Furthermore, DYRK1A phosphorylates both nuclear and cytoplasmic proteins[26,47]. DYRK1A controls nuclear import (GLI1) or export (FOXO1, NFAT) of several transcription factors[48-50], but the question of whether DYRK1A itself undergoes cytoplasmic nuclear shuttling has not yet been directly addressed.

4. Mechanistic Pathway Associated with DYRK1A in AD Progression

The DYRK1A gene is situated in the Down Syndrome Critical Region (DSCR) located on human chromosomal locus 21, which causes the overexpression of DYRK1A to be 1.5 times more than normal when trisomy occurs. In individuals with DS as well as neurodegenerative ailments such as Huntington's chorea, Parkinsonism, and frontotemporal dementia, as well as intermittent and well-known AD, although increased DYRK1A function has been noted in several regions of the brain, little is understood about how DYRK1A functions in each of these three ailments. Specifically, DYRK1A-positive nuclei make up over 10% of the frontal cortex of AD brains, whereas normal brains have 0.5% of these nuclei[51,52].

4.1 Amyloid-β pathway: APP Phosphorylation Causes Aβ Plaques

A cytosolic protein called DYRK1A phosphorylates APP (Amyloid precursor protein) at Thr668. Phospho-APP is found to be elevated in AD, especially in the hippocampus[53]. Three types of proteolytic enzymes (a/γ/β secretases) typically break down APP. Transmembrane glycoprotein (APP) is phosphorylated by DYRK1A through both amyloidogenic as well as non-amyloidogenic routes. 90% to 95% of the non-amyloidogenic pathway is chosen by α-secretase, which then cleaves the APP's Aβ region to liberate αAPPs or non-amyloidogenic sections[5]. The enzyme α-secretase splits APP into a soluble N-terminus fragment (sAPPα) along with the C-terminus fragment (C-83) in the first pathway. The enzyme γ-secretase further separates the C-83 fragment, creating a smaller C-terminus fragment (C3) of 3 kDa in size and AICD, which attaches with genetic material to trigger proteins to develop distinct physiological features. APP splitting is controlled by a protein breakdown enzyme that is bound to the cell membrane and is a member of the ADAM (a disintegrin and metalloproteinase) family. ADAM-10 as well as ADAM-17 contribute to the proteolytic function of α-secretase[54,55]. APP's α-secretase splitting prevents the synthesis of amyloid peptides inside the chain of amino acids that corresponds to the Aβ peptide[56]. The enzyme β-secretase breaks down APP in the second pathway into two parts: the lengthy C-terminal fragment (C99), which contains the whole amyloidogenic amino acid sequence, and the smaller N-terminal fragment (sAPPβ). Amyloid-β peptides (Aβ) are produced when an enzyme called γ-secretase further splits C99. Single peptides of Aβ are produced, which assemble in the form of two, three, or many peptides to form protofibrils and fibrils, and at last accumulate and generate amyloid plaques. The most neurotoxic Aβ peptide is Aβ42, which is also the most vulnerable and has a higher propensity to aggregate and fibrilise[57]. Recent studies provide strong evidence that soluble oligomers of Aβ play a part in AD dementia[58]. Aβ-induced *in vitro* activation of DYRK1A mRNA level in neuroblastoma cell lines and elevated DYRK1A mRNA expression in AD patients' hippocampal regions[43] suggest that DYRK1A and Aβ may positively feedback and speed up the generation of Aβ. Additionally, DYRK1A phosphorylates γ-secretase subunit presenilin 1 (PS1), which raises γ-secretase protease activity and further enhances the synthesis of Aβ peptide[59]. Furthermore, research indicates favourable remarks in which Aβ accelerates the synthesis of neurologically hazardous peptides made from Aβ by promoting DYRK1A expression[43].

Additionally, DYRK1A catalyses the gene that codes for the DSCR's regulator of calcineurin-1 (RCAN1). When DYRK1A phosphorylates RCAN1 at Thr192, it increases the strength of the bond between calcineurin (Caln) and RCAN1, lowers its breakdown. This enhances RCAN1's ability to block Caln phosphatase activity, increasing phosphorylated tau protein concentrations while decreasing Caln/NFAT gene expression. DYRK1A Tg mice's brains indeed exhibit elevated expression of pThr192 RCAN1. Additionally, GSK-3β-regulated phosphorylation at Ser108 is preceded by DYRK1A catalysing RCAN1 at Ser112The downstream consequences of this process are yet unclear; however, DYRK1A's promotion of GSK-3β activity has been linked to the development of AD[60] (Figure 3A, B).

4.2 Tau Proteins

Tau is essential for both axonal transit and the development of the neurological cellular structure[61]. Another important characteristic of AD is the formation of Neurofibrillary Tangled Structures (NFTs), which are caused by DYRK1A's excessive phosphorylation of the

protein tau. The phosphorylated Tau protein (PHF-tau proteins) associated with the microtubules, aggregates to generate NFT, the second main pathogenic finding in AD. NFT is made up of aberrant filament bundles that accumulate in the axons, dendrites, and perikarya of neurons[62,63]. Initially, tau proteins were found to co-polymerise with microtubules and promote their formation[64]. In addition to being essential for maintaining the structure of neurons, microtubules are also involved in the axoplasmic transport of different chemicals and organelles. Microtubule stability and propagation are less effectively promoted by tau proteins that are over phosphorylated. Tau's excessive phosphorylation and accumulation in AD is a complicated process initiated by several enzymes, with DYRK1A appearing to play a key role.

DYRK1A appears to be a major player in the complicated procedure of tau's excessive phosphorylation and accumulation in AD, which is initiated by multiple enzymes. First, studies have shown that at least 11 threonine and serine residues in tau protein, including the amino acids Ser-396, Ser-400, Ser-404, Ser-422, Thr-181, Ser-199, Ser-202, Thr-205, Thr-212, Thr-217, and Thr-231, are directly phosphorylated by DYRK1A[65]. In people's brains with DS-associated AD as well as late onset AD, some of these residues have also been discovered to be phosphorylated in tau accumulates of neurofibrillary tangled structure[66-68]. Tau phosphorylation is also linked to overexpression of DYRK1A in mice with DS trisomy, or Ts65Dn mice, which have an extra copy of the distal region of the rodent sixteenth chromosome, which contains the DYRK1A gene[69]. These animals exhibit elevated tau protein phosphorylation and 1.5-fold higher DYRK1A expression and activity[65]. According to neuropathological as well as molecular research, excessively expressed nuclear DYRK1A has a role in neurofibrillary breakdown and tau alternative splicing modifications. At Ser-227, Ser-234, and Ser-238, DYRK1A phosphorylates the alternative splicing factor (ASF). The phosphorylation of these three sites is not catalysed or impacted by DNA topoisomerase I[71] or all three previously identified ASF kinases (SRPK1, SRPK2, along with Clk/Sty)[70]. The phosphorylation of

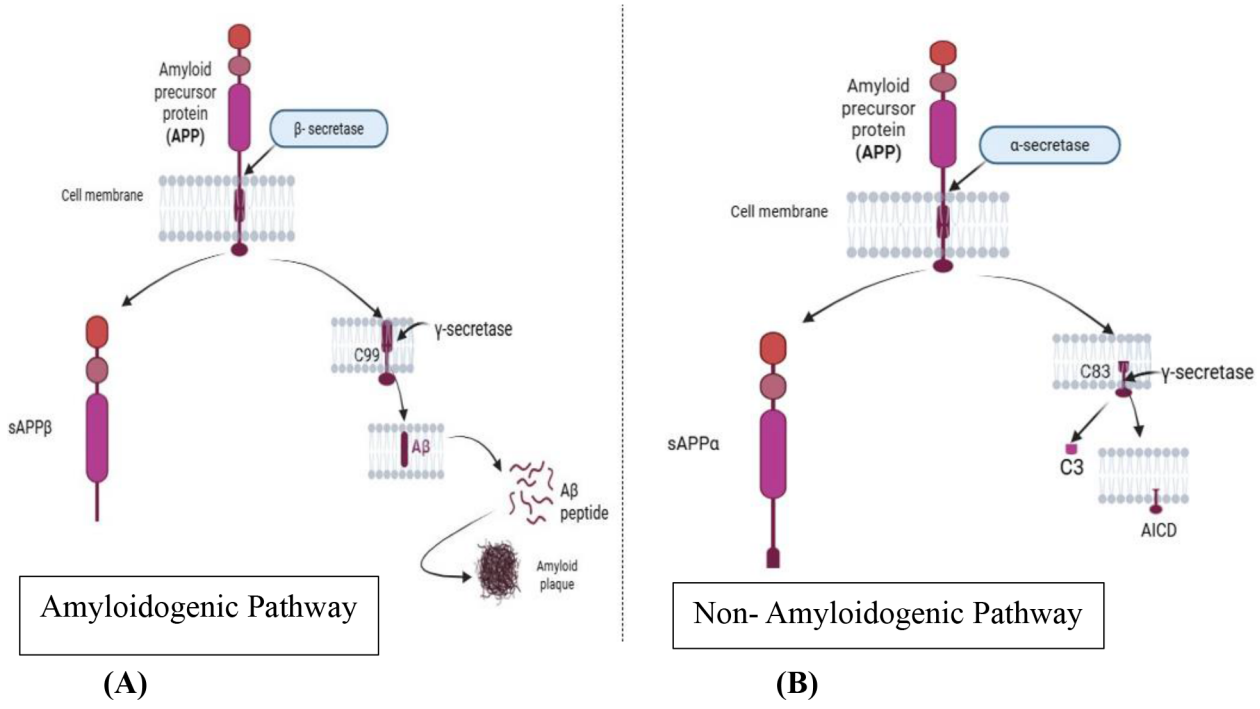


Figure 3. (A) Amyloidogenic Pathway - APP cleavage by BACE (β-secretase) releases soluble βAPPs along with C99 fragments that adhere to the cell membrane and are then broken down by γ-secretase into Aβ 40 (soluble) and 42 (insoluble-form plaque). (B) Non-Amyloidogenic Pathway – APP cleavage by α-secretase into soluble αAPPs and more hazardous C83 and C3 fragments, of which C83 is subsequently converted into AICD.

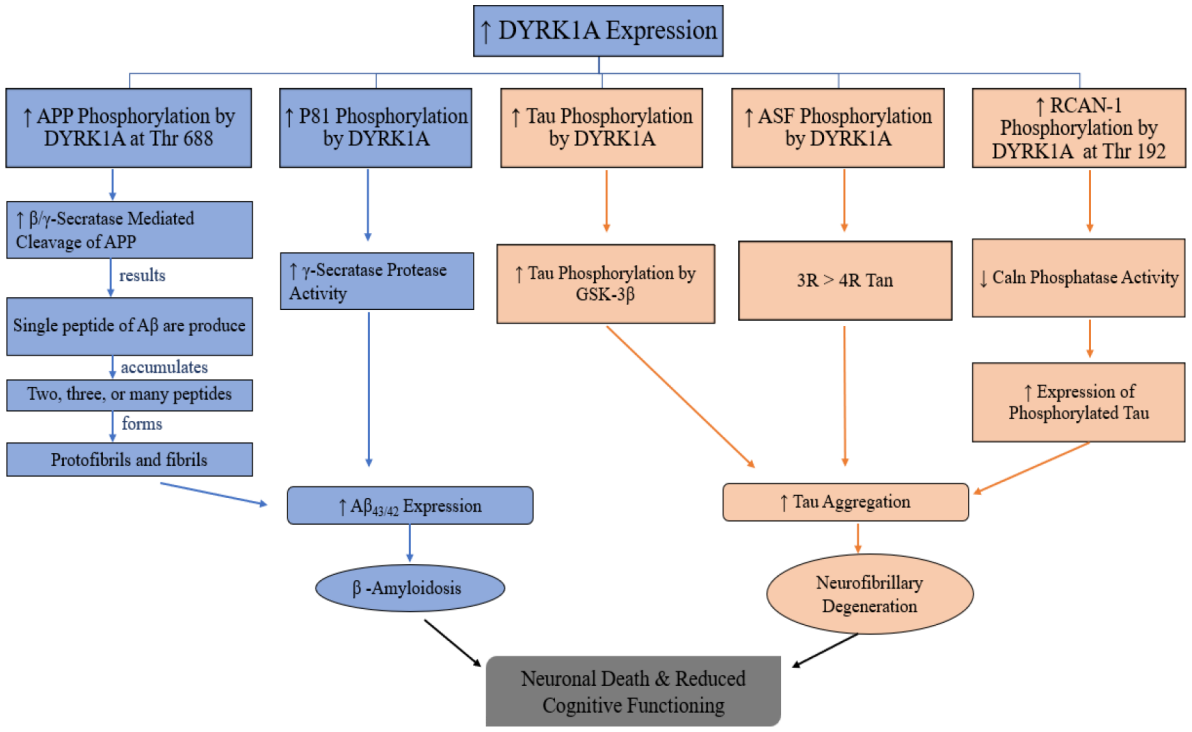


Figure 4. A diagram illustrating the several mechanisms by which DYRK1A causes neuronal degeneration and cognitive impairment.

ASF by highly expressed DYRK1A is assumed to cause an approximately fourfold increase in 3R-tau in DS. The rise in the quantity of unbound 3R tau available for aberrant excessive phosphorylation in DS results in alterations to the cell cytoskeleton and neurofibrillary degeneration[70] (Figure 4).

5. Classification of DYRK1A Inhibitory Compounds

Initially, it was thought that a number of DYRK1A inhibitors would selectively inhibit various protein kinases. However, throughout time, several DYRK1A inhibitor classes have been identified, some of which are employed as pharmaceutical agents. Kinase inhibitors can generally be classified as the following: class I, class II, and class III. ATP competitors, also referred to as class I inhibitors, attach to the kinase domain's ATP binding site upon phosphorylation of the activation loop. But class II and III do not compete with ATP. Class III inhibitors bind to an allosteric pocket directly, whereas type II inhibitors attach to the ATP binding region and a limited extent, bind to an allosteric pocket only. Inhibitors of classes II as well as III alter the specific enzyme's structure, which lowers kinase activity. The typical DYRK1A inhibitor is harmine, an ATP competitor alkaloid molecule[72]. In this article, we have concentrated on the naturally occurring DYRK1A inhibitor and its variants.

5.1 Aristolactam BIII

Herbal plants belonging to the Aristolochiaceae, Annonaceae, Monimimaceae, Menispermaceae, and Piperaceae families are the primary source of aristolactams, a small category of aporphine alkaloids with a phenanthrene chromophore. There are currently just a few documented biological actions of Aristolactam BIII[73]. Aristolactam BIII was reported to substantially prevent the accumulation of cleaned bunny thrombocytes induced by collagen, thrombin, and platelet-activating factors[74]. To investigate if Aristolactam BIII (Figure 5) and its analogs inhibit DYRK1A, a structure-based computational screening (SBCS) of the ATP-binding region was performed. The selected respondents were then evaluated using an NFAT-RE promoter assay based on mammalian cells. Aristolactam BIII was discovered to efficiently reduce DYRK1A-mediated excessive phosphorylation

of Tau in cells of mammals and to significantly inhibit DYRK1A activity *in vitro*. Oral therapy with aristolactam BIII significantly decreased tau excessive phosphorylation in the brains of DYRK1A Transgenic mice. Aristolactam BIII corrected cognitive and behavioural abnormalities in DYRK1A Transgenic mice and DS-like Drosophila mutants. The results demonstrated that aristolactam BIII is a new DYRK1A inhibitor that restores DS characteristics in cells and living tissue, and they suggested that it has medicinal potential for the management of DYRK1A-related illnesses. Aristolactam BIII significantly reduced the kinase activity of DYRK1A with an IC50 kinases (IC50 of 9.67 nM, the most potent of all examined = 50.28, 404.8,849.8, 1184, and 240.3 nM for CDK1/cyclin B, DYRK4, CLK1, GSK-3β, and CK2 α 1, accordingly Dibenzo[c,d,f]indol-4(5H)-one rings, or aristolactam BIII, have a lot of interactions with DYRK1A's active site and fit nicely into its ATP-binding region. While the isoindolin-1-one group creates hydrogen bonds with the amide group of Leu241 in the hinge domain and the core carbonyl of Glu239, the indolin-4(5H)-one rings form hydrophobic associations with Ala186, Val173, Val306, Leu241, and Leu294 in the vicinity of the attachment region. The 9-methoxy-substitute, in particular, forms additional bonds of hydrogen with the side chain of Lys188, which appears to be essential for this binding. Tau protein was used as a model protein to further examine the DYRK1A inhibitory effects of aristolactam BIII in mammalian cells. In these conditions, dose-sensitive administration of aristo lactam BIII resulted in a considerable reduction in phosphorylation of Tau protein with an IC50 value of around 50 nM. At 1,000 nM, there was almost complete suppression. Moreover, harmine was less effective than aristolactam BIII at inhibiting DYRK1A[75].

5.2 Acridone Alkaloids

The studies on tropical botanical extracts have grown recently. Beniddir and his colleagues discovered that the greatest inhibitory action against DYRK1A was shown by the EtOAc bark extract of G. chlorosperma (IC 50 = 0.66 μg/mL). The docking results are in agreement with the activity data and explain the good inhibitory effect. This is the first report of a natural acridone with a strong DYRK1A inhibitory action that offers an active scaffold for DYRK1A inhibitors[76].

4.3 Epigallocatechin Gallate (EGCG)

Green tea extract's main ingredient, EGCG, is a strong DYRK1A inhibitor[77]. EGCG is a unique family of phytochemicals with anti-inflammatory, anti-cancer, and antioxidant qualities. It was an initial DYRK inhibitor in both people and animals[78]. A variety of catechins, including epicatechin gallate, epigallocatechin, epigallate, and epicatechin, are found in green tea. Trans-catechin derivatives have higher inhibitory efficacy than cis-catechin derivatives, according to the research carried out by Araldi *et al.* that looked at the inhibiting activity of EGCG using ELISA. Additionally, the B- or D-ring's hydroxyl group is necessary for EGCG's action. When methoxy is used in place of the hydroxyl group, the activity is decreased, and by adding the element fluorine to the B or both D rings of EGCG, these compounds' structural changes can also significantly boost their activity[79]. Although EGCG is strong and has a generally favourable safety record[80], its pharmacokinetic characteristics are subpar[81,82]. EGCG has limited bioavailability due to reduced permeability, molecular unpredictability, and metabolic processes such as biological transformation, especially at the gut (GI) and liver sites when administered directly through the mouth. The bioavailability when taken by mouth (F) of EGCG, a BCS pharmaceutical class 3 medication, has been shown to be incredibly low in experimental animals; in mice, F can reach as high as twelve percent[83], whilst in rats, it can attain as high as five percent[84,85]. EGCG significantly inhibited DYRK1A with an IC_{50} = 330 nM, according to Bain and colleagues' analysis of 29 protein kinases that were both physically and biologically associated with DYRK1A[77]. The mutant mice with DYRK1A excessive expression that were administered a diet high in antioxidant-rich green tea from infancy to maturity had improvements in both short- and long-term memory as well as brain structural development (measured by weight of the brain and thalamus-hypothalamus volume)[86]. EGCG has been shown in several preclinical and clinical trials to alleviate various DS-associated traits by decreasing DYRK1A[87] (Figure 6).

5.4 Harmine

Harmine, an indole β-carboline from the Nitrariaceae family, has been isolated from the plant *Peganum harmala*. In the southern American creeper

Banisteriopsis caapi, its pyrido[3,4-b] indole ring has been identified[88]. Antioxidants, anti-inflammatory, anti-bacterial, and neuroprotective actions are among its many medicinal effects[89]. It exhibits neuroprotective effectiveness via inhibiting AChE, MAO-A, MAO-B[90], and DYRK1A[91]. A laboratory study found that harmine at a dosage of 20 mg/kg might proficiently improve spatial thinking and memory impairment via cholinergic neurotransmission improvement[92]. The accumulation of tau proteins and an increased amount of the brain growth factor DYRK1A are hallmarks of AD[93]. Harmine promotes brain development and growth by inhibiting DYRK1A[91]. It also greatly reduces tau protein phosphorylation by inhibiting DYRK1A-catalysed tau phosphorylation. These outcomes indicated that harmine could provide beneficial and pleasant aid in the management of AD[88]. Jarhad and his colleagues found in 2007 that harmine with an IC_{50} = 80 nM was a powerful and selective inhibitor of DYRK1A among 69 protein kinases *in vitro*[94] with the DYRK1A kinase region indicates that it binds to the ATP binding region of DYRK1A and, through direct competition with ATP, suppresses the serine/threonine phosphorylation activity[72,95]. At an IC_{50} of 48 nM, it substantially suppresses endogenous DYRK1A in HeLa cells[36]. Harmine has been thought to be a powerful and orally easily absorbable DYRK1A inhibitor, but it also showed a much higher inhibition of monoamine oxidase (MAO)-A, which resulted in adverse effects that severely limited its potential therapeutic use[96]. Several harmine and β-carboline analogs, compounds 2–6, have been created as strong DYRK1A inhibitors to counteract the poisonous and hallucinatory effects of compound 1. Harmol (2), which was produced by demethylating a methoxy group, had minimal inhibition of MAO-A but only a minor impact on DYRK1A inhibition[97]. Compound 2 was more potent than Compound 1 (IC_{50} = 700 nM) at inhibiting Tau phosphorylation facilitated by DYRK1A (IC_{50} = 90 nM). With an IC_{50} value of 400 nM, 9-ethylamine (3) demonstrated a comparable inhibition[98]. Drung and colleagues (2014) produced several β-carboline derivatives, examined their DYRK1A functionality, and found that compound 4 was more efficient than compound 1[99]. At 10 μM, compound 4 (IC_{50} = 130 nM) showed 97% inhibition of DYRK1A and only 34% inhibition of MAO-A, while compound 1 demonstrated full inhibition of MAO-A (103% inhibition at 1 μM). The core ring amine is required for MAO- The core ring amine is required for MAO-A interaction, but not for DYRK1A binding, as demonstrated by the increased inhibition of MAO-A in compound 1[97]. Remarkably, compound 4 inhibited DYRK1A more than different cyclin-like kinases and DYRKs (eighty-five inhibition at 1 μM)[99]. Their activities were compared with

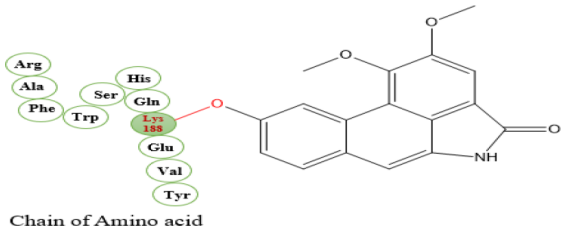


Figure 5. Aristolactam BIII binds to DYRK1A -The side chain of Lys188 of DYRK1A is where the 9-methoxy-substitute makes extra hydrogen bonds, which appear to be essential for this binding.

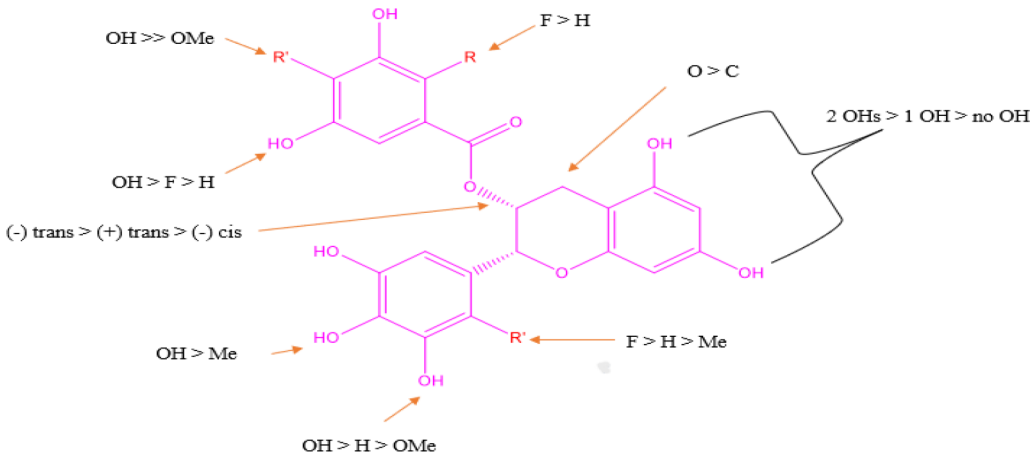
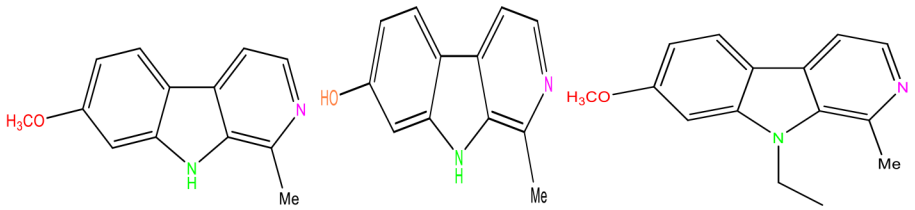


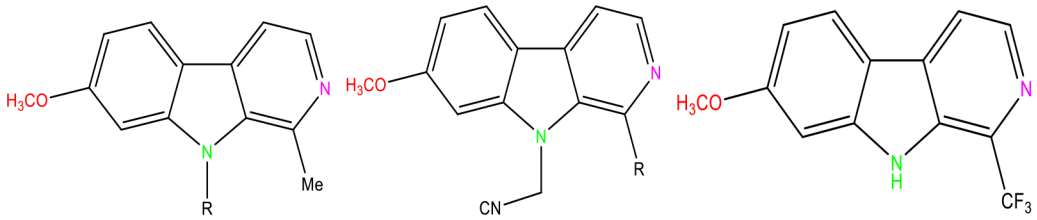
Figure 6. SAR of EGCG as DYRK1A Kinase inhibitor.

1 using the kinase-GLO test Their activities were compared with 1 using the kinase-GLO test Harmine analogs 5a and 5b were developed to enhance the effectiveness against DYRK1A while lowering the enzyme activity against MAO-A. Their activities were compared with 1 using the kinase-GLO test. In order to increase the activity against DYRK1A while decreasing the activity of MAO-A, harmine analogs 5a and 5b were created, and a kinase-GLO assay was used to compare their activities with 1[100]. Unlike 5a with an IC_{50} = 81 nM and 5b with an IC_{50} = 181 nM, which showed superior inhibition (eight per cent and ten per cent unconstrained control, respectively), nevertheless, the data showed that inhibitor 1 at 1 µM reduced DYRK1A by more than 60%. The MAO-A inhibition was significantly reduced by compound 5b (IC50 > 10 µM), while compound 5a inhibited MAO-A to a much lesser degree (IC_{50} = 3.24 µM). The same phenomenon was displayed by compound 6. The activity against DYRK1A was retained when the methyl group at position 1 was substituted with a trifluoromethyl or chloro group, indicating that the 1 position of the β-carboline is crucial for differentiating between the inhibition of DYRK1A and MAO-A[97]. In an interconnected *in vitro* transcription-translation process, 5b's impact on tyrosine self-phosphorylation during DYRK1A translation and threonine (Thr434) phosphorylation in substrate protein splicing factor 3b1 (SF3B1) was assessed. At doses >1 µM, compound 5b inhibited DYRK1A's tyrosine self-phosphorylation, but SF3B required greater concentrations of 5b to decrease threonine phosphorylation[100].

Drung and colleagues carried out research whereby they used MOE software to compare structure-based and ligand-based computational approaches to create many molecules computationally. They then verified



Harmine Harmol 9- Ethylharmine
(Compound 1) (Compound 2) (Compound 3)



(Compound 4) (Compound 5) (Compound 6)
5a (R = Me) and 5b (R= Cl)

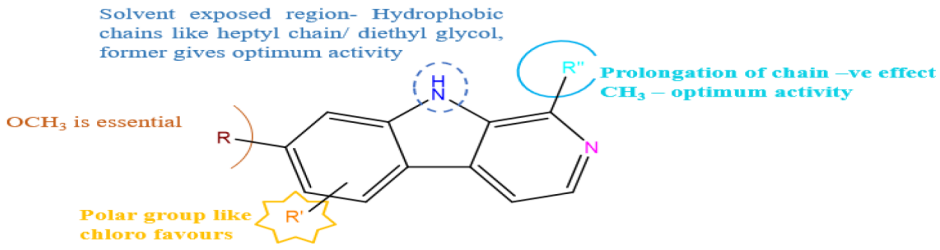
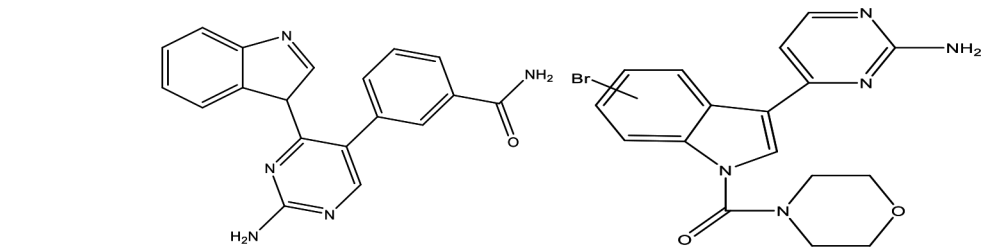


Figure 7. SAR of Harmine.

their designs through *in vitro* experiments. The majority of them lacked MAO selectivity. To create models, they employed 127 structurally varied compounds with active and inactive properties ranging from (IC_{50}>10mM to <250nM). Harmine was determined to be the most appropriate of all the pharmacophore models they found, and it was used as a guide for future chemical creation. The ligand harmine's pyridyl nitrogen provided the h-bond acceptor projection, while the methyl and methoxy substituents at the ligand's exterior provided the two hydrophobic centres F3 and F4, and the two aromatic features F1 and F2 fitted by the indole scaffold. Its interaction with the receptor DYRK1A to provide the best fit validated the pose. Lastly, they constructed SAR (Figure 7) following the properties specified by the theory and synthesised several compounds by derivatisation. They discovered that methoxy replacements on the indole's aromatic ring promote replacement, but reduction and elongation reduce activity. Likewise, the inhibitory action was hindered by chlorination in its ortho location. Additionally, as the model anticipated, the best discovered molecule is the one that favours activity by around 97% when hydrophobic groups, such as the heptyl chain at the nitrogen of the indole ring, are prolonged[99].

5.5 Meridianins

3-(pyrimidine-4-yl)-1H-indole is the building block of meridins, which are organically produced substances. They appeared from the South Atlantic tunicate *Aplidium meridianum*, a marine origin[101]. A number of artificial meridin analogs have been shown to efficiently and specifically inhibit DYRK1A. For example, by adding a methyl group to the compound, either in conjunction with or without the indole nitrogen, and various aryl substitutions at the fifth carbon of the 2-aminopyrimidine ring, Akué-Gédu *et al.*[102] produced 10 new Meridianin compounds. They assessed the inhibitory efficacy of these compounds in opposition to a total of five distinct protein kinases and found that the non-methyl compounds inhibited DYRK1A more effectively in comparison to their NCH3 counterparts. Compound 7 (with an IC_{50} analogs = 580 nM) had the strongest inhibitory effect on PA 1 cell growth and the strongest inhibitory efficacy towards DYRK1A among all[102]. Yadav *et al.*[103] created several. Meridianin compounds by substituted at the N position and examined for their capacity to inhibit DYRK1A as an additional example. Additionally, they screened all compounds for cytotoxicity at a therapeutic dose of 30 μM in the cells of SH-SY5Y. They selected the two compounds based on the IC_{50} value of inhibitory action against DYRK1A. However, compound 8 is a little more selective with an IC_{50} = 500 nM; both of these compounds significantly protected SH-SY5Y cells from glutamate-induced toxicity in neurons. Compound 8 did not substantially inhibit 15 kinases, including the protein PKB α 3β, the transcription factor CDK-2, and others, at a dosage of 0.5 μM (Figure 8A, B). The most crucial property is its selectiveness for DYRK1A, which is 2.8 or four times stronger compared to that of DYRK2 and DYRK3, respectively, while inhibiting both of these



(Compound 7) (Compound 8)

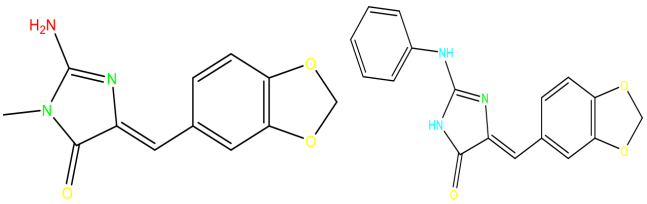
(A) **(B)**

Figure 8. **(A)** 3-(2-amino-4-(3H-indol-3-yl) pyrimidin-5-yl) benzamide (Compound-7) with an (IC_{50} analogs = 580 nM) had the strongest inhibitory efficacy towards DYRK1A among 10 new Meridianin compounds. **(B)** (3-(2-aminopyrimidine-4-yl)-1H-indol-1-yl) (morpholino) methanone compound with bromomethane (1:1) (Compound 8) with its highest selectivity towards DYRK1A, which is 2.8 or four times stronger than when compared to DYRK2 and DYRK3.

proteins[103]. The associated structure–activity link is being investigated by several researchers. Meridianins' indole structure might be replaced with a 6-azaindole structure, which would let the inhibitor to bind to DYRK1A more efficiently and prolong the duration of NFAT's presence in the nucleus More precisely, increased NFAT is kept in the nucleus due to a binding contact among the amino acid Lys-188 in the DYRK1A back envelope and the nitrogen at 6th position in this structure[104].

5.6 Leucettines

They come from a naturally occurring source chemical called leucetamine B, which was initially discovered in the marine calcium-rich sponge Leucetta Micrographs[105]. Tahtouh and colleagues were motivated by leucettamine-B (compound 6, the IC_{50} = 420 nM) and developed several variations and analogs of the 2-amino imidazoline structure (L_1-L_{41})[106,107]. When researchers looked at the preparation of sixty-eight leucettines and their corresponding structural connections, they discovered that benzo dioxane had the greatest kinase inhibition and that leucettamine-B (compound 6, IC_{50} = 420 nM) had methoxy in the para-ring position instead of the in-between aromatic ring. Additionally, they demonstrated that carbonyl groups were essential to the action and that the inhibitory activity was greatly influenced by N-1 and N-3 replacements as well as exocyclic amines (N-1′) configurations[108]. The most prominent member of the Leucettine B kinase inhibitor family is Compound 10 (leucettine L_{41}). Compound 10 is associated with several stages of AD and targets multiple proteins, such as DYRK1A (IC_{50} = 320 nM), DYRK1B (IC_{50} = 490 nM), CLK-1 (IC_{50} = 100 nM), the transcription factor GSK (IC_{50} = 410 nM), and others. Despite having poor selectivity, compound 7 is nevertheless a rather potent inhibitor. *In vitro*, L_{41} showed neuroprotective properties[107]. Using spontaneous alternation in the Y-maze, Naert *et al.*[109] administered Leucettine L_{41} to mice treated with $A\beta_{25-35}$ to evaluate the mice's spatial working memory capacity. Compound 10 may shield mice against *in vivo* $A\beta_{25-35}$-provoked hippocampal loss of memory and degeneration of neurons, as it was found that the deficits were considerably averted in mice[109]. To sum up, leucettines show promise in clinical settings.



Leucettamine B (Compound 9) Leucettine L41 (Compound 10)

6. Conclusion

DYRK1A inhibition is a very new area of research that is quickly attracting attention as more and more research confirms DYRK1A as an attractive candidate for modifying the disease therapy of certain neurological disorders, including AD and DS. A growing field of research is the inhibition of DYRK1A, and many DYRK1A inhibitors have been found, primarily by focusing on the ATP competitive binding site. Although there are many other mechanisms and targets involved in the pathogenesis of AD. The most effective pharmacological target for inhibiting the growth of NFT production and amyloid plaque deposition is DYRK1A. Inhibiting DYRK1A may be a viable strategy to tackle the fundamental aetiology of AD pathogenesis. Due to this, scientists are now interested in designing and discovering DYRK1A inhibitors to treat AD. Increased interest is being shown in finding substitute targets of therapy for β-secretase, which have not yet shown promise in clinical studies. This trend implies that organic compounds with high efficacy and selectivity for DYRK1A, such as the compound harmine or EGCG and aristolactam BIII, as well as marine substances like Meridianins, Leucettines, may still be worthwhile research subjects. Although harmine and Aristolactam BIII continue to be the most effective and orally accessible inhibitors found to date, their therapeutic application is now limited by a number of pharmacological adverse effects. However, even though most polyphenolic compounds are nonselective, the potency of EGCG and its beneficial effects on thinking ability seen in *in vivo* investigations make it worthy of further investigation. Meridianins, leucettines, and their derivatives are marine compounds that have been shown to efficiently and specifically block DYRK1A. This review is one of many that have offered a thorough examination of practically all of the SAR research and processes behind DYRK1A-mediated AD in humans.

We believe that the diagnosis and treatment of many neurodegenerative diseases, especially AD, may undergo significant modifications in the future.

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8. Author Contribution

Manu Sharma: Wrote the main manuscript; Rupa Mazumder and Swarupanjali Padhi: Conceptualised the review; Km Shivangi: Prepared Figures 1-7. All authors have read and agreed to the published version of the manuscript.

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