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REVIEW



# Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) inhibitors: a survey of recent patent literature

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**ABSTRACT**

**Introduction**: Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) is a eukaryotic serine-threonine protein kinase belonging to the CMGC group. DYRK1A hyperactivity appears to contribute to the development of a number of human malignancies and to cognitive deficits observed in Down syndrome and Alzheimer's disease. As a result, the DYRK1A kinase represents an attractive target for the synthesis and optimization of pharmacological inhibitors of potential therapeutic interest.

Like most tyrosine kinase inhibitors developed up to the market, DYRK1A inhibitors are essentially acting by competing with ATP for binding at the catalytic site of the kinase.

**Areas covered**: This paper reviews patent activity associated with the discovery of synthetic novel heterocyclic molecules inhibiting the catalytic activity of DYRK1A.

**Expert opinion**: Despite the important role of DYRK1A in biological processes and the growing interest in the design of new therapeutic drugs, there are only few patented synthetic DYRK1A inhibitors and most of them were and are still developed by academic research groups, sometimes with industrial partners.

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**KEYWORDS**
DYRK1A; DYRK kinases; heterocyclic compounds; patents; microwave chemistry; kinase inhibitor; down syndrome; Alzheimer's disease



## 1. Introduction

Protein phosphorylation, catalyzed by protein kinases, is one of the major intracellular mechanisms which cells use to regulate their structural and enzymatic proteins. Reversible phosphorylation/dephosphorylation is involved in essentially all physiological events. Abnormal phosphorylations and kinase activities have been observed under many pathological situations. Consequently, the search for pharmacological inhibitors of specific kinases has developed in the last three decades as a major approach to discover new therapeutic drugs (reviews in [1–4]). Initially focused on tyrosine kinase inhibitors and on cancer indications, the field is now rapidly expanding toward serine/threonine kinases and essentially all other therapeutic indications.

Among the 518 human kinases, dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) is a conserved eukaryotic serine/threonine protein kinase that belongs to the DYRKs family including also DYRK1B, DYRK2, DYRK3, and DYRK4 (Figure 1) (reviews in [5–7]). DYRK kinases belong to the CMGC group which includes cyclin-dependent kinases (**C**DKs), mitogen-activated protein kinases (**M**AP kinases), glycogen synthase kinases (**G**SK) and Ccd2-like kinases (**C**LKs) (Figure 1).

Like many members of the CMGC group, the phosphorylation/dephosphorylation of a conserved tyrosine regulates the catalytic activity of the kinase. In DYRK1A, the Tyr321 residue has been described to be autophosphorylated in the activation loop allowing stabilization of the active conformation of DYRK1A [8]. In its mature form, DYRK1A is then able to phosphorylate a plethora of protein targets on their serine or threonine residues, reflecting its role in multiple biological functions. Indeed, DYRK1A is involved in cell cycle and differentiation regulation [9,10], T cell regulation [11], cytoskeleton stabilization [12], brain neurodevelopment [13] and, last but not least, synaptic activities [14].

These processes are perturbed when the activity of DYRK1A is increased as seen in a number of human pathologies such as glioblastoma or pancreatic cancer [15,16]. Moreover, as the DYRK1A gene is located on the human chromosome 21q22.2 'Down syndrome (DS) critical region,' DYRK1A hyperactivity has been shown to be correlated with neuropathology and cognitive deficits observed in DS as well as in Alzheimer's disease (AD) [17–19]. DYRK1A thus represents an attractive target for the design of pharmacological inhibitors with potential therapeutic applications in DS [20–22], AD [21], diabetes [23–25], cancer [26], and inflammation [27]. Furthermore, since unicellular organisms such as *Plasmodium, Leishmania, Toxoplasma, Trypanosoma*, all express DYRK1A orthologues [28,29], inhibitors to these kinases may find applications in diseases originating from these parasitic protozoa.

Several chemical products that inhibit the DYRK1A catalytic activity have already been identified and characterized (reviews in [30,31]), they differ by their structure, selectivity, and potency. The most frequently used

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**Article highlights**

- DYRK1A inhibitors have potential applications in various medical indications: Down syndrome, Alzheimer's disease, several cancers, inflammation, diabetes.
- Numerous synthetic DYRK1A inhibitors have been described, some of which were inspired by natural alkaloids.
- Synthetic routes to heterocyclic inhibitors of DYRK1A are briefly presented.
- Most of the developed DYRK1A inhibitors are nitrogen-containing heterocycles.
- Academic research groups are very productive in this research area.

This box summarizes key points contained in the article.

DYRK1A inhibitors (as pharmacological tools) encompass the plant natural products harmine [32,33] and EGCG [34], Leucettine 41 [35,36], derived from a marine sponge natural product, INDY [37] and EHT 1610 [38]. Their structure is presented in Figure 2.

Most DYRK1A inhibitors inhibit the kinase catalytic activity by competing with ATP at the ATP-binding site of the kinase as illustrated by co-crystal structures of DYRK1A in complex with various inhibitors (Figure 3).

Here, we report patent activity associated with the discovery/optimization/characterization of synthetic, low-molecular-weight heterocyclic products displaying DYRK1A inhibitory activity and potential therapeutic applications.

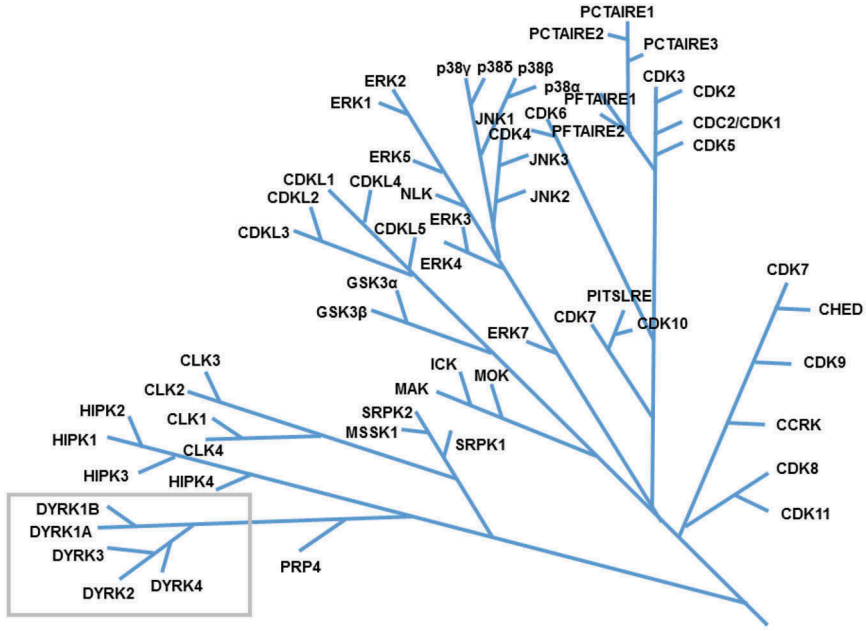



Figure 1. Phylogenetic tree of the CMGC class of kinases with a zoom on the DYRK kinases family.

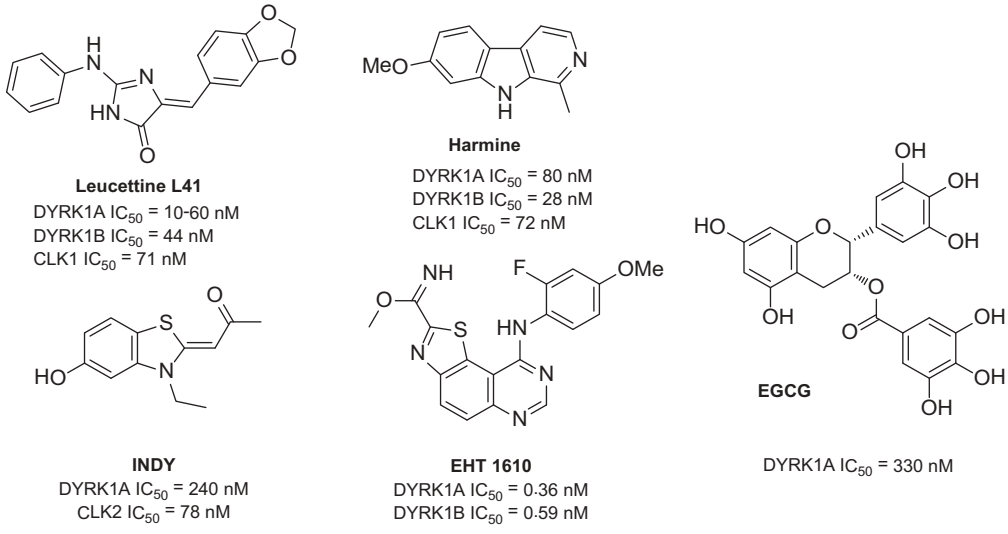



Figure 2. Structures of the five most commonly used pharmacological inhibitors of DYRK1A: Leucettine L41, Harmine, EHT 1610, INDY and EGCG.

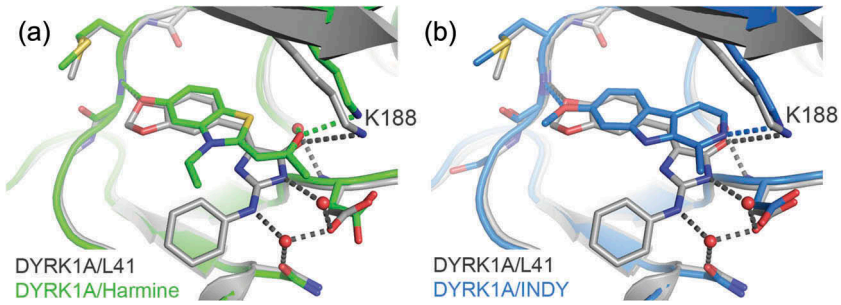



Figure 3. Superimposition of the DYRK1A/Leucettine L41 co-crystal structure with other DYRK1A/inhibitor co-crystal structures. The DYRK1A crystal structure was modeled with the active site water molecules that are visible in the higher resolution DYRK2 crystal structure, to allow comparison of ligand hydrogen bonding. DYRK1A/Leucettine L41 co-crystal structure (grey) (PDB: 4AZE) with co-crystal structures of (**a**) DYRK1A with harmine (green) (PDB: 3ANR), (**b**) DYRK1A with INDY (blue) (PDB: 3ANQ). Figures were prepared with Pymol (www.pymol.org). From Suppl. Data in [36]. Full color available online.

## 2. Patent evaluation

This review highlights patents describing an intended inhibition of DYRK1A. Nevertheless, this protein kinase is not always the main target of the compounds tested and it is frequently inserted in kinase selectivity panels. For this review, we decided to briefly describe the chemical syntheses developed and to comment on the data found in the various patents and relevant articles.

### 2.1. Pyrimidine derivatives

#### 2.1.1. Pyrido[3,2-d]pyrimidines

An array of pyrido[3,2-*d*]pyrimidines was prepared and claimed to inhibit DYRK1A. The patent assigned to CNRS [39] describes mainly the synthesis and biological evaluation of a V-shaped family of original 2,4 or 2,7-disubstituted pyrido[3,2-*d*]pyrimidines. The main part of the target molecules were prepared from a single 2,7-dichloropyrido[3,2-*d*]pyrimidine, using sequential cross-coupling reactions. The C2 position was functionalized via a selective Suzuki-Miyaura type reaction, whilst position C7 was selectively substituted via a Suzuki or a Buchwald-type reaction using available boron derivatives. The synthetic strategy was also extended in an academic paper [40] describing more examples. The V-shaped structure of these novel pyrido[3,2-*d*]pyrimidines was in fact inspired by previous works on V-shaped pyridines or pyrazines which exhibited interesting DYRK1A inhibitory activities ($IC_{50}$ = 60 nM for the lead compounds, see Scheme 1) [41] (not patented).

#### 2.1.2. Pyrido[2,3-d]pyrimidines

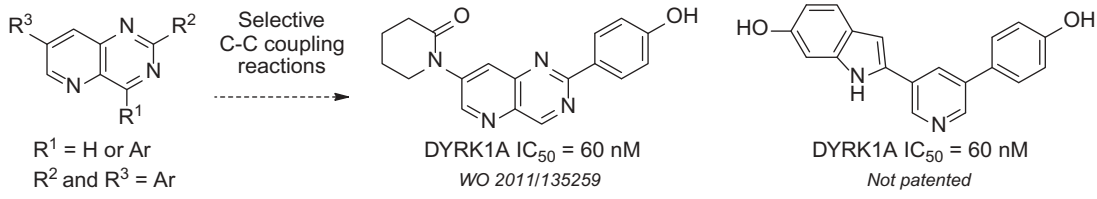
Hoffman-La Roche AG reported the synthesis and structure/activity relationship (SAR) of pyrido[2,3-*d*]pyrimidines acting as inhibitors of DYRK1A/1B [42,43]. It was claimed that these products might be useful for the treatment of cancers as well as in the control of DS or early phases of AD. Inspired by previous work [44], the quinolone ring was replaced by a pyrido[2,3-*d*]pyrimidine. Through this change, the lipophilicity of the target molecules was reduced while the synthesis of extended fragments in position C2 of the pyrimidine ring was easier. Various chemical routes inspired by a seminal paper were described [45]. The best products exhibited nanomolar $IC_{50}$ values for DYRK1A but also for DYRK1B. Selectivity DYRK1A vs. DYRK1B was difficult to obtain in this series (Scheme 2).

The synthesis strategy involved the base-catalyzed condensation of an appropriately functionalized 4-amino-5-formylpyrimidine with dimethylmalonate or its amide derivatives (Scheme 3).

A second patent dealing with 1,6- and 1,8-naphthyridine analogs of the previous pyrido[2,3-*d*]pyrimidines is assigned to F. Hoffman-La Roche AG targeting DYRK1A/1B inhibitors for the treatment or control of cancer (especially solid tumors) along with the amelioration, treatment or control in neurodegenerative diseases such as AD and DS (Scheme 4) [46]. Despite nanomolar-range $IC_{50}$ values for DYRK1A and DYRK1B, none of these de-aza analogs of the pyrimidines described above were as good as their pyrido[2,3-*d*] congeners.

#### 2.1.3. Pyrazolopyrimidines

Pursuing its efforts Hoffman-La Roche AG reported the synthesis and SAR studies of pyrazolo[3,4-*d*]pyrimidines aiming at novel DYRK1A/1B inhibitors [47,48]. In accordance with strategies described in the preceding examples, the chemical work was focused on methods able to add aromatic groups or more lipophilic alkyl chains in position C3 and C6 of the 1*H*-pyrazolo[3,4-*d*]pyrimidine scaffold. The syntheses started with a simple

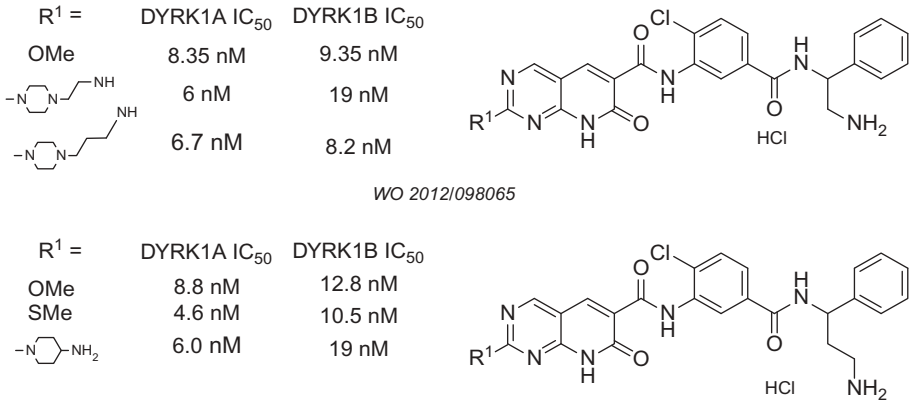



$R^1$ = H or Ar
$R^2$ and $R^3$ = Ar

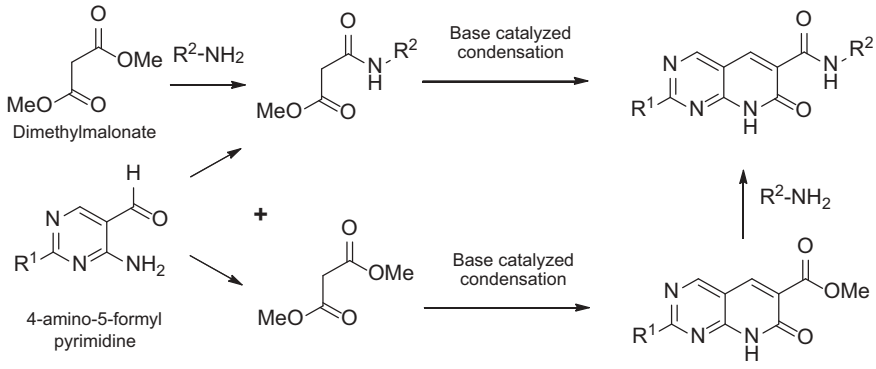
DYRK1A $IC_{50}$ = 60 nM
*WO 2011/135259*

DYRK1A $IC_{50}$ = 60 nM
*Not patented*

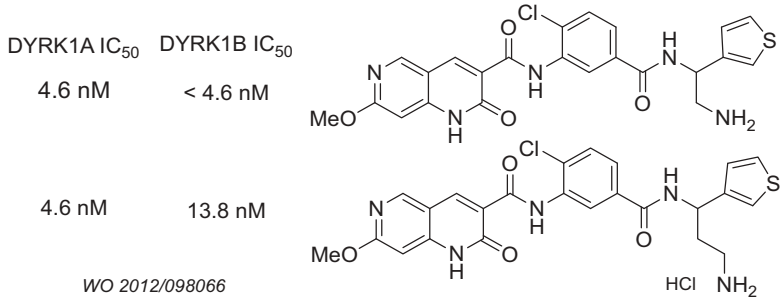
Scheme 1. The most active V-shaped pyrido[3,2-*d*]pyrimidine derivative and its pyridine analogue (right).




Scheme 2. Selected pyrido[2,3-*d*]pyrimidines described by Hoffman-La Roche AG as DYRK1A/1B inhibitors.




Scheme 3. Brief description of synthetic routes leading to the most potent pyrido[2,3-*d*]pyrimidines [43–45].

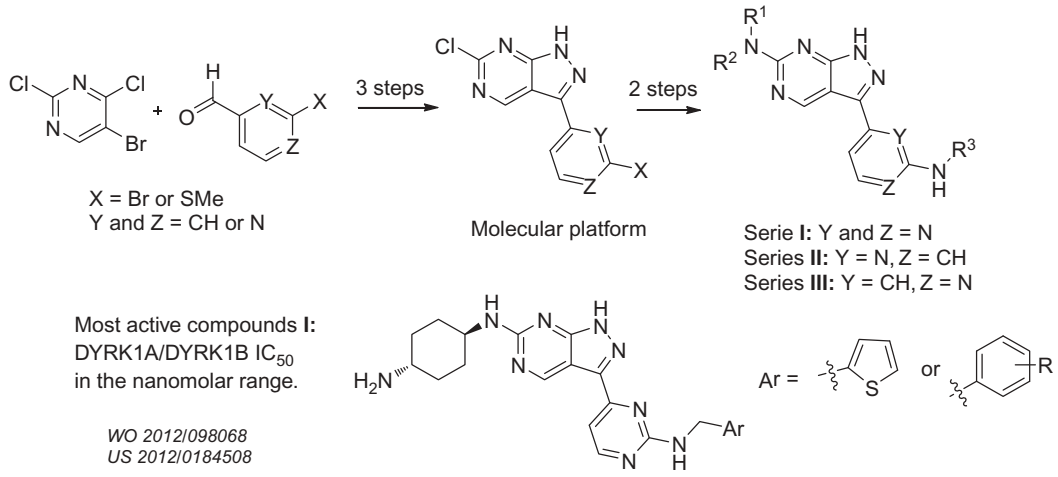



Scheme 4. The two most active 1,6-naphthyridine analogues derived from previous pyrido[2,3-*d*]pyrimidines by Hoffman-La Roche AG.

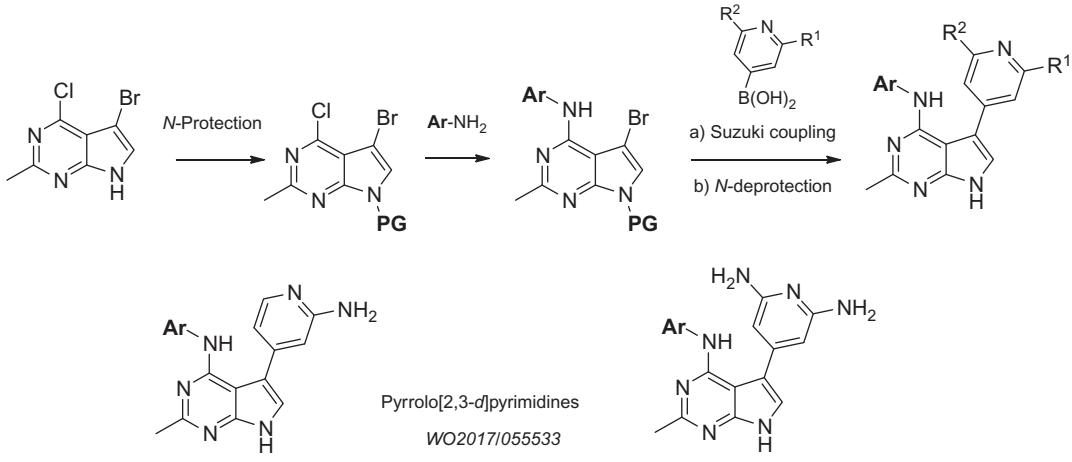
5-bromo-2,4-dichloropyrimidine which reacted with an appropriate aldehyde to give intermediate alcohols which were successively oxidized and condensed with hydrazine to afford the corresponding 6-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine as a versatile molecular platform. Nucleophilic addition of appropriate amines was performed in position C6 and the bromide or SMe groups were then removed under Buchwald conditions (Scheme 5). The exemplified compounds **I** were tested for both DYRK1A/1B inhibitory activity, and for antitumor activity (data given). The best results are depicted in Scheme 5.

### 2.1.4. Pyrrolo[2,3-d]pyrimidines

Servier (FR) in association with Vernalis R&D Ltd. (UK) described novel pyrrolo[2,3-*d*]pyrimidine [49] derivatives as dual DYRK1A/CLK1 inhibitors for the treatment of cancer, neurodegenerative disorders and metabolic disorders. More than 200 molecules were prepared in this patent. Biological data provided in this patent showed molecules displaying a relative homology with the V-shaped pyrido[3,2-*d*]pyrimidines described above. Nanomolar inhibitory values (DYRK1A $IC_{50}$ = 2–9 nM) were obtained for approximately 15 molecules. Structures presented in Scheme 6 are representative of the most active derivatives.




Scheme 5. Synthetic route of pyrazolo[3,4-*d*]pyrimidines developed by Hoffman-La Roche AG.




Scheme 6. Synthetic route and general structures of the most active DYRK1A inhibitors developed by Servier [49].

The synthetic route started from a versatile platform allowing sequential and regioselective functionalization.

## 2.2. Quinolines and quinazolines

### 2.2.1. Quinolines

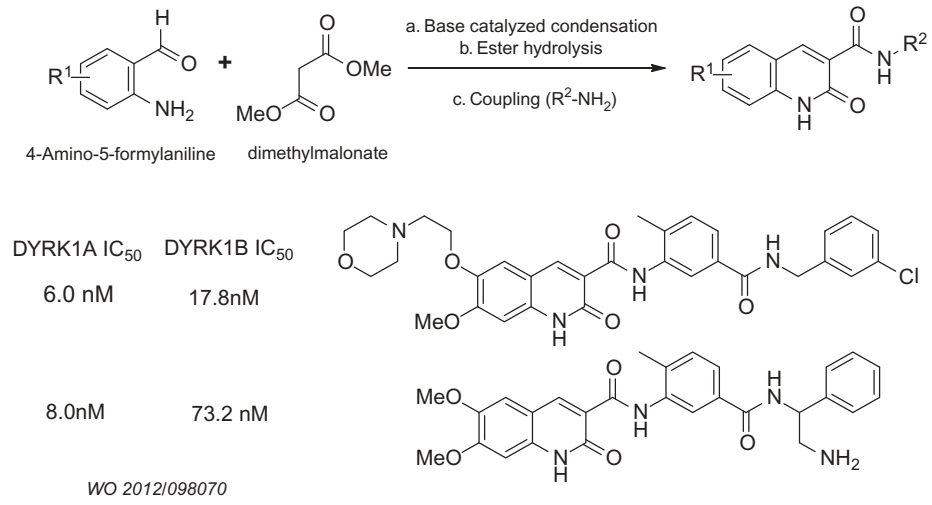
In addition to the aforementioned aza-heterocycles, Hoffman-La Roche AG patented a series of quinoline derivatives and analogs which inhibited DYRK1A/1B and which were claimed useful for the treatment or control of cancer (especially solid tumors) as well as in the amelioration, treatment or control in neurodegenerative diseases such as AD and DS [50]. The chemistry methods and strategies involved were similar to those described in the preceding heterocyclic systems. The most active molecules shared structural analogies with the nitrogen-containing analogs, exhibiting nanomolar-range $IC_{50}$ values for DYRK1A and DYRK1B (Scheme 7).

### 2.2.2. Quinazolines

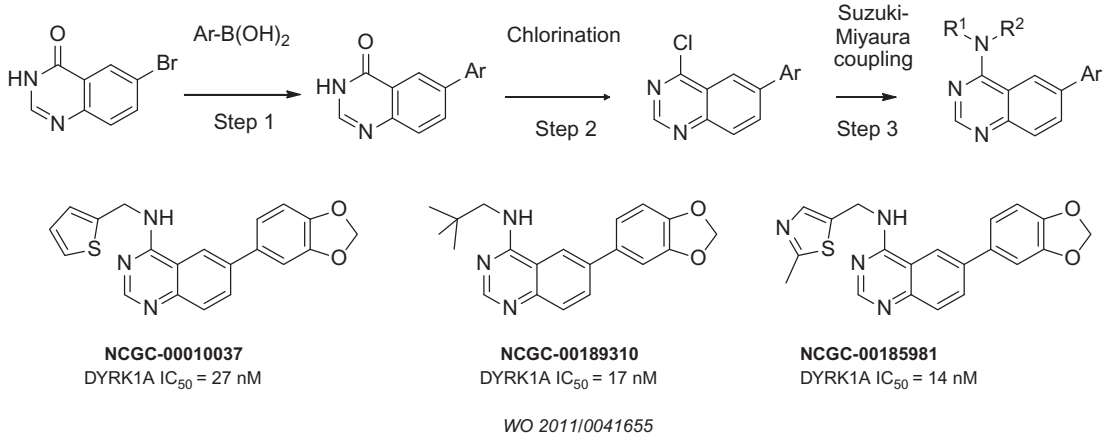
Quinazolines, sometimes named 5,6-benzopyrimidines, are aza analogs of naphtalene and isomers of cinnolines and quinoxalines. The quinazoline moiety is a building block for numerous recent FDA-approved drugs as small-molecules tyrosine kinase inhibitors [1–3].

**2.2.2.1. *N*-Aryl –6-arylquinazolin-4-amines.** The National Institute of Health (NIH) in Bethesda (USA) patented quite selective inhibitors of DYRK1A and CLK1 [51]. These 6-arylquinazolin-4-amines were synthesized in three steps from the commercially available 6-bromoquinazolin-4-one (Scheme 8). SAR studies highlighted the importance of retaining a benzo [1,3]dioxole ring on position C6. In the same study, analogs of the lead compound NCGC00010037 (Scheme 8) were prepared by varying the alkyl and aromatic groups linked to the amine in position C4 of the pyrimidine moiety. Some of these molecules were very good inhibitors of CLK1, CLK4, and DYRK1A ($IC_{50}$ values <100 nM) and highly selective for these kinases compared to CLK2, CLK3, and DYRK1B. Modeling studies suggest that these compounds inhibit DYRK1A by competition with ATP [52,53].

**2.2.2.2. Thiazolo[5,4-*f*]quinazoline.** Exonhit SA (now Diaxonhit) reported the design and synthesis of novel thiazolo[5,4-f]quinazoline compounds that are expected to be




Scheme 7. Brief synthetic route and description of two of the most active quinolones described by Hoffman-La Roche AG.




Scheme 8. Synthetic route and structures of the most potent 6-arylquinazolin-4-amines developed by NIH as DYRK1A inhibitors.



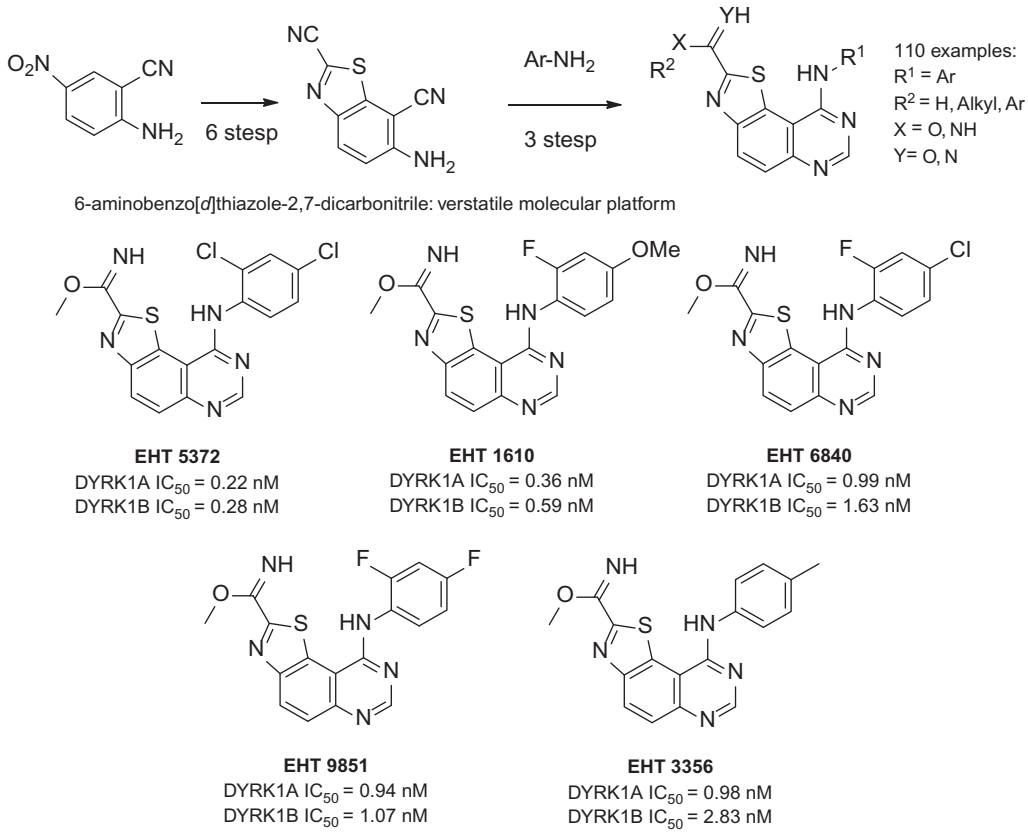
useful in the amelioration, treatment or control of DS, early AD or in cancers, especially solid tumors [38,54–56]. More specifically, the invention relates to DYRK1A and/or DYRK1B inhibitors and to methods for preparing such compounds. Inspired by natural marine alkaloids (e.g. dercitines and kuanoniamines) bearing a thiazole ring, these tricyclic pyrimidines derivatives were synthesized from 6-aminobenzo[d]thiazole-2,7-dicarbonitrile, a very versatile molecular platform, precursor of over a 100 derivatives (Scheme 9). Compounds were evaluated on DYRK1A and DYRK1B, along with some known reference DYRK1A/1B inhibitors (harmine, TG003, NCGC-00189310, and Leucettine L41). Five of the novel thiazolo[5,4-f]quinazoline derivatives, EHT 5372, EHT 1610, EHT 6840, EHT 9851, and EHT 3356 (Scheme 9) displayed single-digit nanomolar or subnanomolar $IC_{50}$ values and are among the most potent DYRK1A/1B inhibitors disclosed to date [31,57].

Around the same time, a University of Rouen academic research group collaborating with Exonhit SA developed synthetic routes for an access to novel $N^8$-aminothiazolo[5,4-*f*]quinazolin-9-one derivatives [58,59] (not patented) which were evaluated for their ability to inhibit DYRK1A and CLK1 using *in vitro* kinase functional assays. Inhibitory activities obtained with the $N^8$-aminoquinazolin-9-ones (Scheme 10, left) were poor compared to those obtained with the C9-aminosubstituted quinazolines described in the Exonhit's patent. Another academic collaborative work led to the synthesis of pyrazolo[4,3-*f*]quinazolin-9-ones (Scheme 10, right) as a novel family of DYRK1A inhibitors but with lower $IC_{50}$ values (not patented) [60].

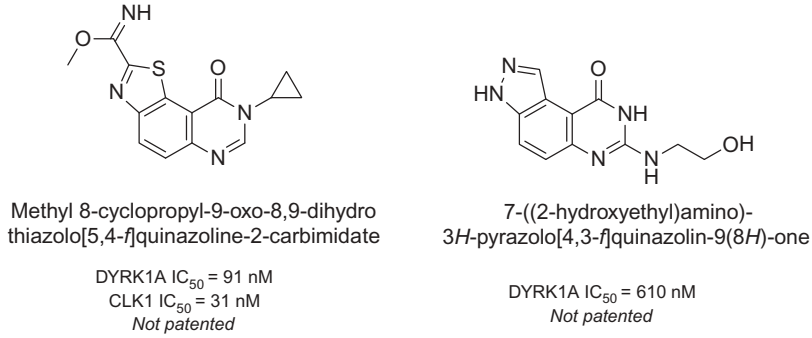
## 2.3. Indole derivatives

### 2.3.1. 7-Azaindoles (DANDYs)

An academic consortium (CNRS, University of Reims Champagne-Ardennes and University of Paris Diderot/Paris 7) described a series of diaryl-azaindole inhibitors of DYRK1A (DANDYs) [61–63]. These 3,5-diaryl-1*H*-pyrrolo[2,3-*b*]pyridines exhibited strong DYRK1A kinase inhibition, *in vitro*. Derivatives having hydroxyl groups on the aryl moieties were the most potent with 3–20 nM $IC_{50}$ values [61]. Complementary studies demonstrated that these 7-azaindole derivatives were noncytotoxic and relatively selective in a selectivity panel of 13 kinases [62]. The synthetic route to the DANDYs molecular family was established applying standard procedures from




Scheme 9. Global chemistry strategy and structures of the five best DYRK1A/1B inhibitors described by Exonhit SA.



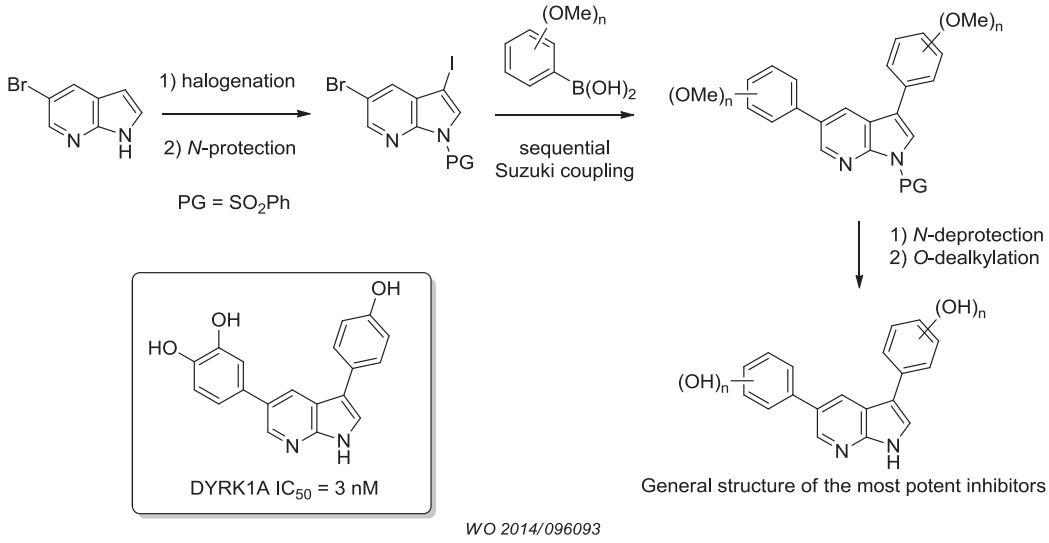

Scheme 10. Unpatented analogues of the EHT derivatives [58–60].

the commercially available 5-bromo-7-azaindole [63]. As often observed for DYRK1A inhibitors, the most potent DANDY analog (DYRK1A $IC_{50}$ = 3 nM) inhibited CLK1 with equipotency (Scheme 11).

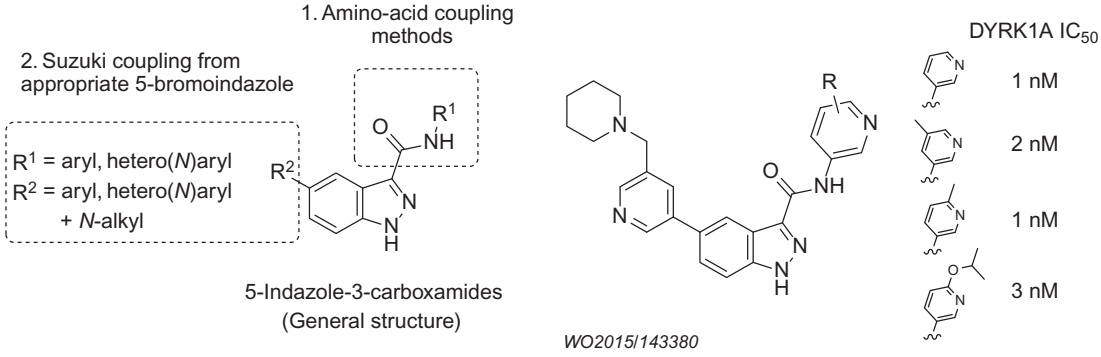
3-Substituted 7-azaindoles derivatives had been prepared and described earlier by academic groups [64–66]. These molecules named meriolines consisted of a structural hybrid between two marine natural products, variolin B [64] and meridianin A [67]. These compounds exhibited DYRK1A $IC_{50}$ values in the nanomolar range but their lack of selectivity most probably contributed of their cytotoxicity. Recently, novel 7-azaindoles were described but not patented by academic research groups as DYRKs/CLKs inhibitors for the potential treatment of glioblastoma [31].

### 2.3.2. 5-Indazole-3-carboxamides

Samumed, LLC (USA) recently patented 5-indazole derivatives for treating disorders characterized by modulation of cellular events (*e.g.* cancer) or neurodegenerative diseases (*e.g.* AD) where some signaling pathways are impacted by abnormal DYRK1A expression. Two hundred 5-substituted indazole-3-carboxamide compounds were designed and prepared applying usual chemical strategies (Scheme 12). Their affinity for DYRK1A was evaluated and results showed that about 30




Scheme 11. Synthetic route for the 7-azaindoles inhibitors and structure of the most potent analogue.

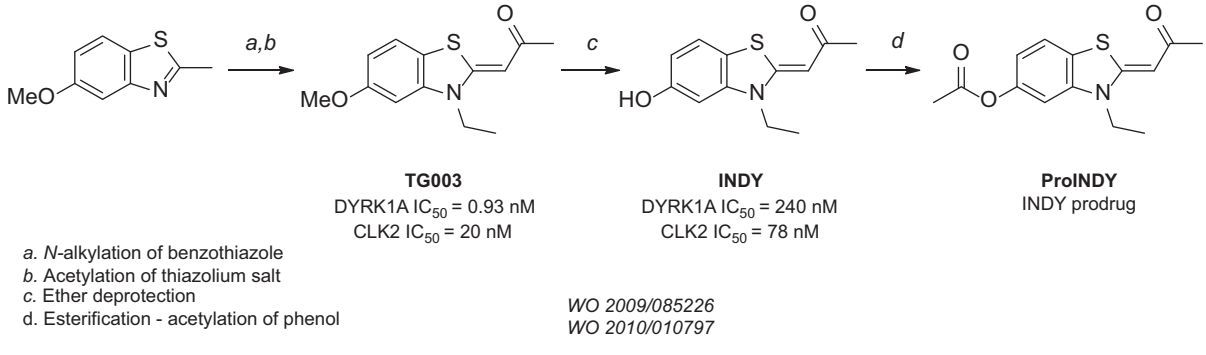



Scheme 12. General structure of the 5-indazoles DYRK1A inhibitors and structure of the most active compounds.

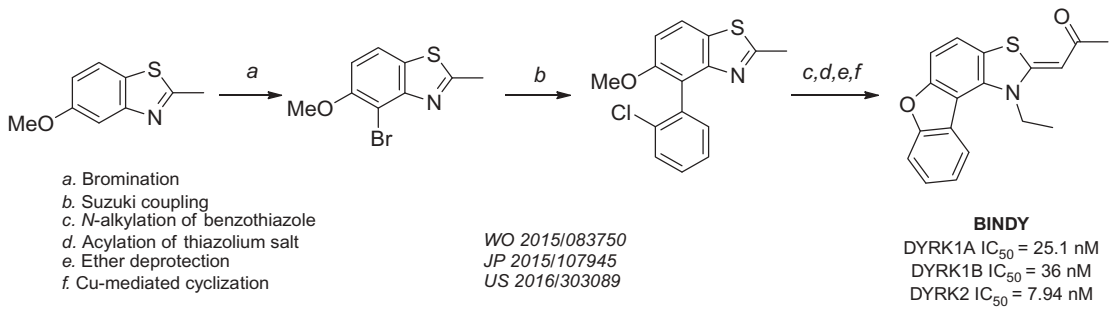
derivatives were very powerful DYRK1A inhibitors with $IC_{50}$ values in the 1–6 nM range [68].

## 2.4. Benzothiazole derivatives (TGOO3, INDY and BINDY)

The benzothiazole ring is present in many natural and synthetic compounds. INDY (inhibitor of DYRK1A) is one of the most potent benzothiazole described in literature. INDY [(*Z*)-1-(3-Ethyl-5-hydroxy-2(3*H*)-benzothiazolylidene)-2-propanone)] is a structural analog of TG003. The two molecules were first reported and patented as CLK inhibitors (CLK2 $IC_{50}$ = 20 and 78 nM for TG003 and INDY, respectively) [37,69,70]. In 2010, Sirtris Pharmaceuticals, Inc. (USA) and Kinopharma S.L. (Japan) published a study describing the development of INDY as a novel selective inhibitor of DYRK1A ($IC_{50}$ = 240 nM). INDY interacted with the target kinase in an ATP-competitive manner and it inhibited DYRK1B ($IC_{50}$ = 220 nM) but, in contrast with the natural product Harmine, it did not target monoamine oxidase [71]. In this work, INDY and its prodrug ProINDY (an acetylated derivative of INDY used for *in vivo* tests, Scheme




Scheme 13. Synthetic route of INDY and its derivatives.




Scheme 14. Brief description of the synthetic route of BINDY.

13) were used as selective inhibitors of DYRK1A to investigate molecular mechanisms involved in DS.

In terms of chemistry, TG003 is the precursor of INDY, itself being the precursor of proINDY. These products were prepared according to reported methods [72] from commercially available 5-methoxy-2-methylbenzothiazole (Scheme 13).

The same group of researchers next patented a tetracyclic analog of INDY. This work was inspired by the crystal structure of the DYRK1A/INDY complex [73,74]. The newly designed benzofuro-fused INDY (BINDY) was prepared in six steps from 5-methoxy-2-methylbenzothiazole (Scheme 14). Kinase assays performed on a panel of 304 kinases showed that BINDY was a selective inhibitor of DYRKs/CLKs with DYRK1A, DYRK1B, and DYRK2 $IC_{50}$ values of 25.1, 36, and 7.94 nM, respectively.

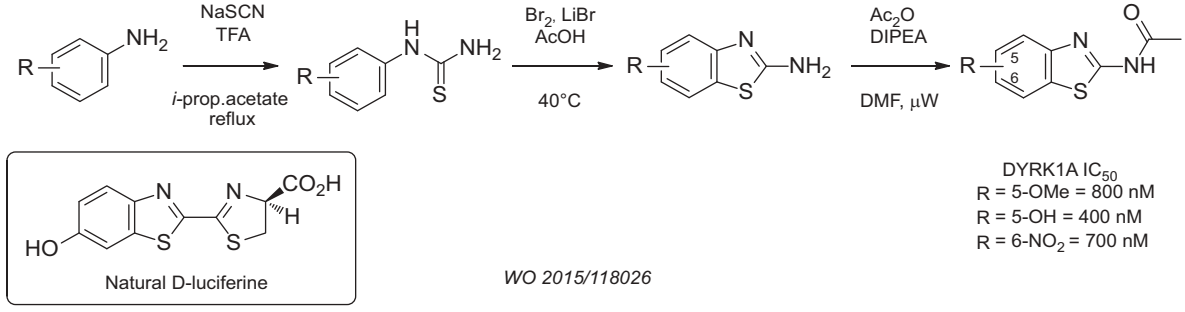
More recently, a patent assigned to Lytix Biopharma AS and its academic associates (UiT The Artic University of Norway) described novel benzothiazoles as DYRK1A inhibitors for neurodegenerative therapies [75]. The compounds described were structurally inspired from luciferine, a natural product used in substrate-catalyzed bioluminescence (Scheme 15). Lytix Biopharma and its partners have previously described luciferine and analogs as potent inhibitors of several protein kinases including DYRKs [76,77]. The design of a novel benzothiazoles library led to introduction of an acetamido group in position 2 of the thiazole nucleus and an enlarged panel of substituents on the benzenic part of the molecule. Various groups were chosen according to their ability to donate or accept hydrogen bonds and to affect the aromatic system$\pi$-electron enrichment. The most effective inhibitors exhibited quite modest affinity for DYRK1A ($IC_{50}$ = 400–800 nM) compared to the aforementioned thiazole derivatives. The array of target molecules was obtained by acetylation of the corresponding 2-aminobenzothiazole, either commercially available or synthesized via a modified Stuckwisch procedure (Scheme 15).

## 2.5. Imidazoles

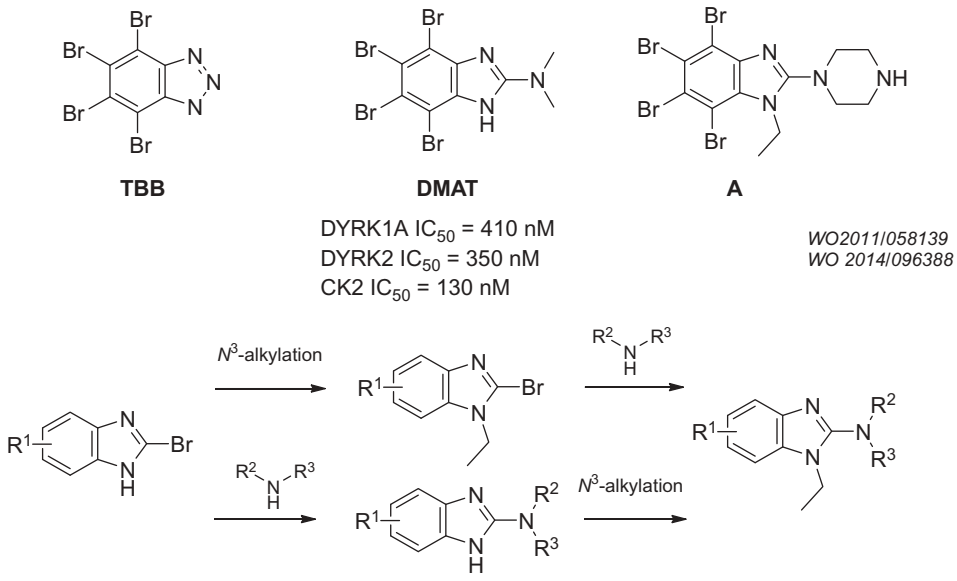
### 2.5.1. Benzimidazoles (TBBi)

A patent assigned to Selvita SA (Poland) described novel benzimidazole series with promising kinase inhibitory activities [78,79]. More precisely the new tetra-halogenated derivatives are potent inhibitors of certain serine/threonine kinases and were claimed to be useful for the treatment of DYRK1A-related biological disorders such as cancer and neurodegenerative diseases [77,78]. The patented benzimidazoles appear to be inspired by previous work initiated by Pagano *et al.* [80,81]. In an attempt to obtain specific CK2 inhibitors, the $N^2$ of a bioactive benzotriazole scaffold (TBB: 4.5.6.7-tetrabromo-1*H*-benzotriazole) was replaced by a carbon atom linked to different polar groups. The most effective inhibitor DMAT (2-dimethylamino-4,5,6,7-tetrabromo-1H-benzoimidazole), inhibited DYRK1A and DYRK2 to a similar level as CK2 ($IC_{50}$ values of 410, 350, and 130 nM, respectively) (Scheme 16). The benzimidazoles described in the Selvita's invention were screened against human cancer cell lines [79]. Compound A (Scheme 16) was one of the most active derivatives. It displayed some affinity for Pim kinases as well as other kinases (including DYRKs) in kinase-binding experiments.

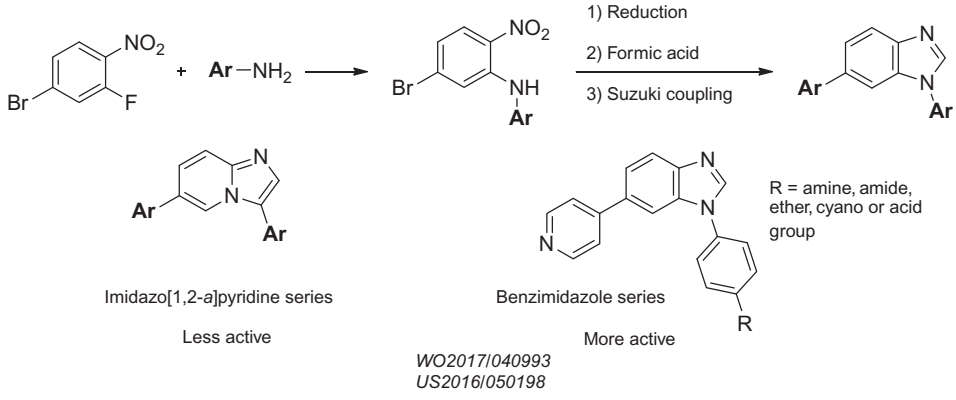
In a recent study, the Arizona Board of Regents, on behalf the University of Arizona (USA), patented a large set of benzimidazoles and imidazo[1,2-*a*]pyridines as DYRK1A inhibitors for an expected use as therapeutics in the treatment of AD, DS, glioblastoma, autoimmune diseases, inflammatory




Scheme 15. Synthetic route of recent luciferine-inspired benzothiazoles as potent DYRK1A inhibitors.




Scheme 16. Synthetic routes of the benzimidazoles described by Selvita [79]. Structures of the seminal TBB and DMAT accompanied by one of the most active analogue **A.**

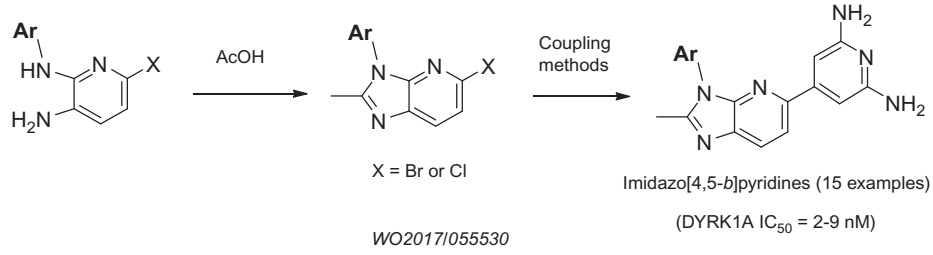



Scheme 17. Synthetic route of the active benzimidazoles described by the University of Arizona Board of Regents [82].

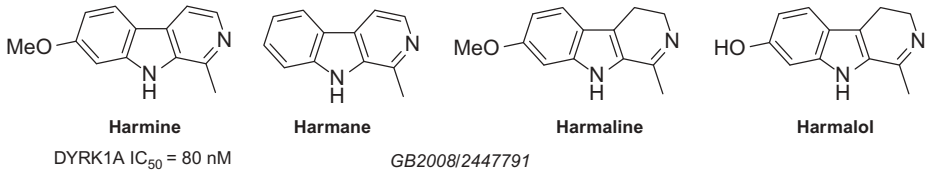
disorders, and other diseases [82]. The most active compounds were the benzimidazole analogs which exhibited 60–100% inhibition of DYRK1A kinase at 10 µM (Scheme 17).

### 2.5.2. Imidazo[4.5-b]pyridines

Servier (FR) and Vernalis R&D Ltd. (UK) patented novel imidazo [4.5-*b*]pyridines [83] derivatives as dual DYRK1A/CLK1 inhibitors for the treatment of cancer, neurodegenerative disorders, and metabolic disorders. Almost 200 molecules were described and 20 analogs showed interesting biological data. The potent DYRK1A inhibitors were structurally close to the V-shaped 3,5-diaryl-1*H*-pyrrolo[2,3-*b*]pyridines (DANDY's family) described above. The general structure of the most active compounds is depicted in Scheme 18. Synthesis of these compounds started from a versatile bicyclic platform which allowed sequential reactions (Scheme 18).




Scheme 18. General structures of the most active imidazo[4.5-*b*]pyridines patented by Servier as DYRK1A inhibitors [83].




Scheme 19. Structure of the four natural β-carboline alkaloids described as DYRKs inhibitors.

### 2.6. Harmine derivatives

In 2007, a patent issued to the University of Dundee (UK) claimed a series of four natural β-carboline alkaloids (harmine, harmaline, harmane, and harmalol). The potency of these attractive compounds as DYRK kinases inhibitors suggested the development toward a treatment of learning deficiencies associated with DS [83]. Harmine (7-methoxy-1-methyl-*β*-carboline) was highlighted as the most potent selective inhibitor of DYRK1A ($IC_{50}$ = 80 nM) [83], while other members of the DYRK family were inhibited to a lesser extent ($IC_{50}$ = 900 and 800 nM for DYRK2 and DYRK3, respectively) (Scheme 19).

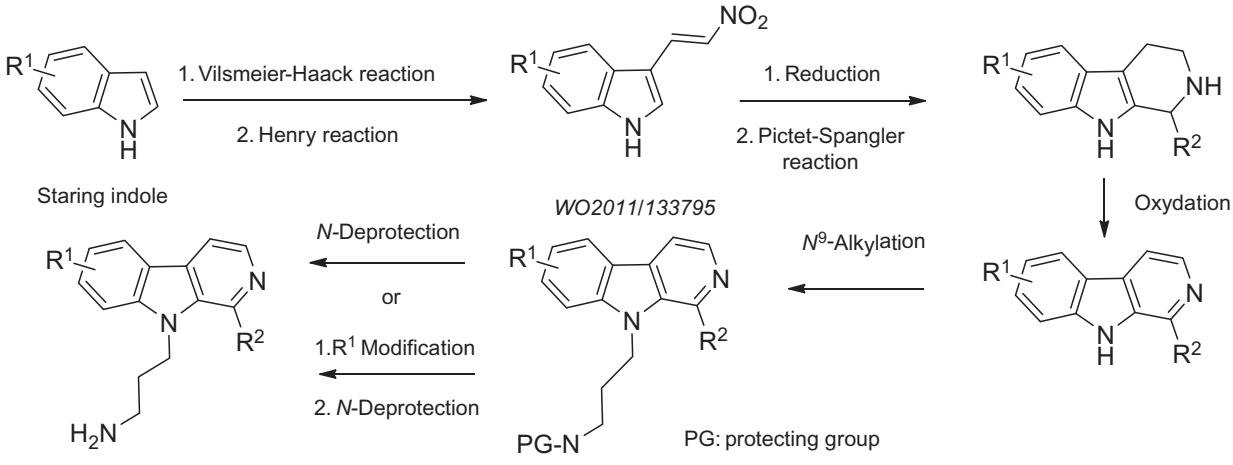
With the aim of suppressing the psychoactive and toxic effects observed with harmine and β-carboline analogs [20], numerous academic and research groups have focused their efforts on synthetic routes allowing the generation of various 6,5,6-fused tricyclic scaffolds structurally related to harmine. The most recently patented harmine-inspired molecules are presented in the following paragraphs.

#### 2.6.1 β-Carboline and acridine derivatives

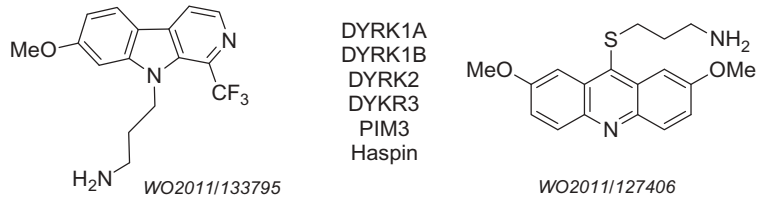
*2.6.1.1. Brigham and women's hospital, Inc. (Boston, USA).* Brigham and Women's Hospital, Inc. (Boston, USA) patented a library of β-carbolines directly inspired by harmine and harmol (7-hydroxy)-1-methyl-*β*-carboline) [84,85]. Several β-carbolines were prepared by *N*-alkylation of harmine or harmol, themselves obtained in four steps from 6-methoxyindole (Scheme 20). The aliphatic chains added to the natural structures were terminated by primary or secondary amines. Removal of the methyl in position 1 or replacement with alkyl groups (ethyl, isopropyl) was performed. Either detrimental or equivalent in terms of biological activity, changes in position C1 and C7 seriously impacted the kinase inhibitory profile of these compounds. The most potent derivative was assessed against a panel of 292 kinases at 10 µM. At this high concentration, it inhibited 13 kinases, including haspin for which its activity was the strongest. DYRK1A, 1B, 2 and 3 were among the 13 inhibited kinases.

Around the same time, Brigham and Women's Hospital, Inc. associated with academic partners (Harvard College, USA and University of Aix-Marseille III, France) in the patenting of acridine derivatives as inhibitors of haspin and DYRK kinases [86]. The structure of the novel acridines described in this work was directly inspired by the preceding β-carbolines, according to 'scaffold-hopping' strategies. The most powerful inhibitor derived from acridines was analyzed with its β-carboline congener and comparison of their selectivity profiles suggested that only six kinases were inhibited by both compounds: DYRK1A, 1B and 3, Haspin, CLK1 and PIM3) (Scheme 21) [86].

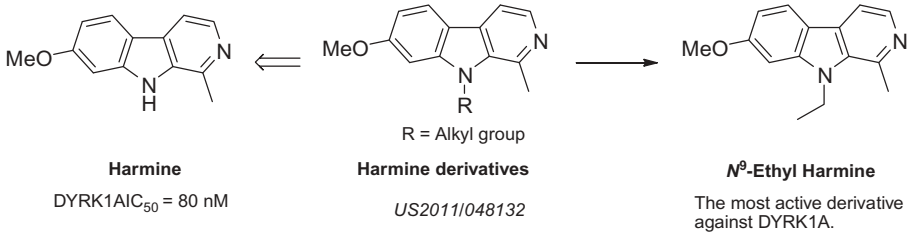
*2.6.1.2. Translational genomic research institute (USA).* The neurogenomic division of the Translational Genomic Research Institute (Phoenix, USA) patented in 2012 [87] a series of β-carbolines directly prepared from harmine which can inhibit tau phosphorylation on multiple sites. In this study, harmine or its derivatives were alkylated on $N^9$ via usual methods. The $N^9$-ethyl substituted harmine analog was found to be the most potent at reducing total and phospho-Tau levels beyond 50% of control levels. This work confirmed that modification of structural components of the β-carboline skeleton significantly affected the ability of these compounds to inhibit tau phosphorylation (Scheme 22).




Scheme 20. Synthetic route for the preparation of β-carboline libraries.




Scheme 21. Structure of the two most potent acridine-derived inhibitors described [84–86] and set of kinases inhibited by both molecules.




Scheme 22. Structures of the $N^9$-substituted β-carboline alkaloids described by the translational genomic research institute.



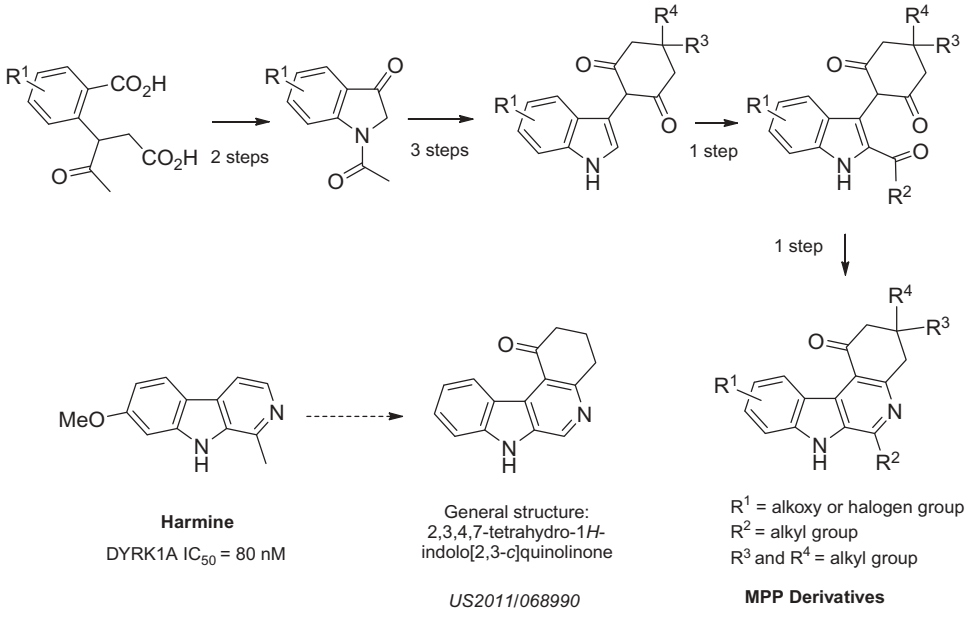
*2.6.1.3. MediPropharma (USA).* Pursuing similar strategies MediProPharma (USA) investigated the possibility of modifying the pyrido ring of harmine [88]. The new 2,3,4,7-tetrahydro-1*H*-indolo[2,3-c]quinolinones obtained (also named MPP derivatives) were studied for their ability to inhibit DYRK1A to modulate Tau phosphorylation and to influence the effect of Tau pathology in DS and AD. Seven steps were needed for the synthesis of 2,3,4,7-tetrahydro-1*H*-indolo[2,3-*c*]quinolinone derivatives, starting from the appropriate anthranilic acid (2-aminobenzoic acid) as briefly described in Scheme 23.

The Translational Genomic Research Institute and MediProPharma joined their efforts in a research consortium and published together the highlights of their results on the benefits of inhibiting DYRK1A to control Tau phosphorylation [89]. Comparison of the results obtained for the $N^9$-ethyl harmine and some MPP derivatives showed a more potent activity for the harmine congener.

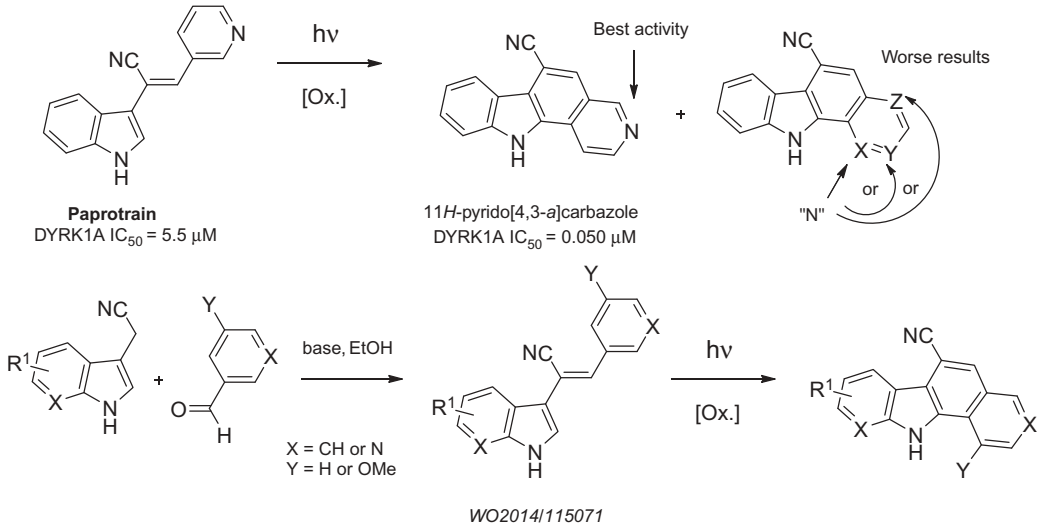
### 2.6.2. Harmine-inspired heterocycles

Compounds described in this paragraph have a structural analogy with the natural β-carboline and indole.

*2.6.2.1. 11h-pyrido- and 11h-benzocarbazoles.* The CNRS recently patented submicromolar to nanomolar inhibitors of the kinase DYRK1A [90,91]. Although the initial study of this work started from a natural indole derivative (paprotrain), the final chemical structures displayed some analogy with harmine (skeleton similarity and planarity) and could be considered as phenylogues. The authors observed that paprotrain and analogs afforded two types of cyclized pyridocarbazoles, under




Scheme 23. Structure and synthetic route of novel 2,3,4,7-tetrahydro-1*H*-indolo[2,3-*c*]quinolinones as harmine derivatives described by MediProPharma.




Scheme 24. General synthesis of the 11*H*-pyrido[4,3-*a*]carbazole library [90,91].



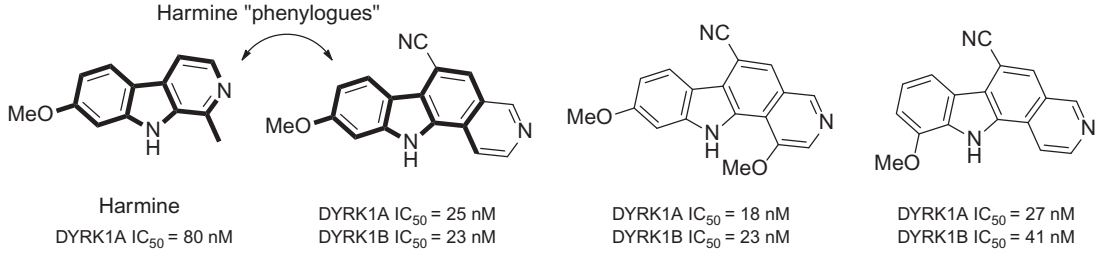
photoactivated conditions in the presence of air (Scheme 24). Tested on a panel of relevant central nervous system (CNS) kinases, paprotrain itself showed a moderate activity on DYRK1A ($IC_{50}$ = 5.5 µM) whereas its cyclization to a 11*H*-pyrido [4,3-*a*]carbazole derivative provided nanomolar inhibitor ($IC_{50}$ = 50 nM), with submicromolar values for CDK5 and GSK3.

SAR studies were performed changing the position of the nitrogen atom in the pyrido part or/and changing the position of the methoxy groups present on the benzenic part. The three most active pyrido[4,3-*a*]carbazoles are described in Scheme 25, they exhibited potent activities on DYRK1A/DYRK1B with $IC_{50}$ values in the nanomolar range. Only one noncyclized paprotrain analogue exhibited a selective nanomolar inhibitory activity for DYRK1A ($IC_{50}$ = 21 nM).

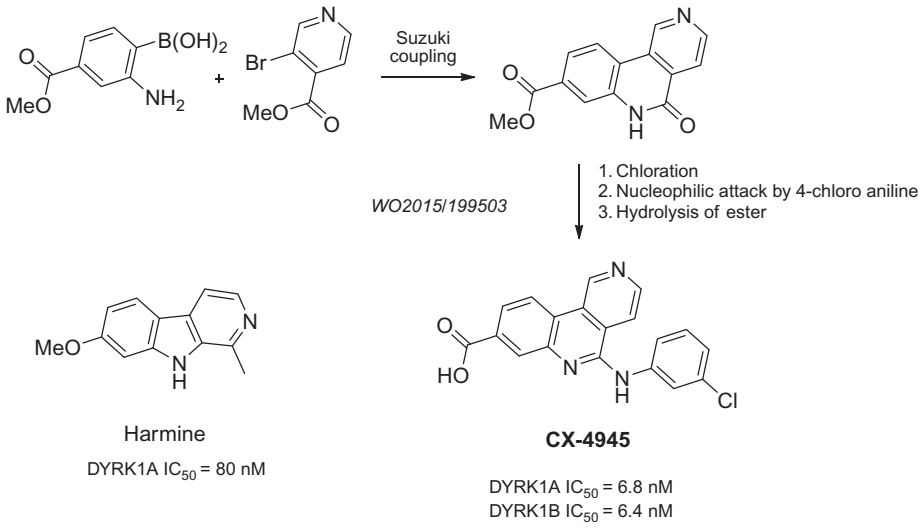
**2.6.2.2. CX-4549: a benzo[*c*][2,6]naphthyridine-8-carboxylic acid derivative.** CX-4945 (5-[(3-chlorophenyl)amino] benzo[*c*][2,6]naphthyridine-8-carboxylic acid), a drug candidate for cancer treatment, is known as a strong inhibitor of CK2 and CLKs [92,93]. The Korea Research Institute of Bioscience and Technology (Daejeon, South Korea) also described and patented CX-4945 as a potent ATP-competitive inhibitor of DYRK1A/1B with nanomolar $IC_{50}$ values [94] (Scheme 26). CX-4549 showed a better inhibitory potency compared with harmine, INDY and proINDY, which are usually cited as well-known inhibitors of DYRK1A. CX-4945 has undergone clinical phase I safety trials and a phase II trial for cancer for or its CK2 inhibitory effects. These clinical results now allow CX-4945 to be repurposed as a disease-modifying treatment of DS and AD [95].

## 2.7. Imidazolones (Leucettines)

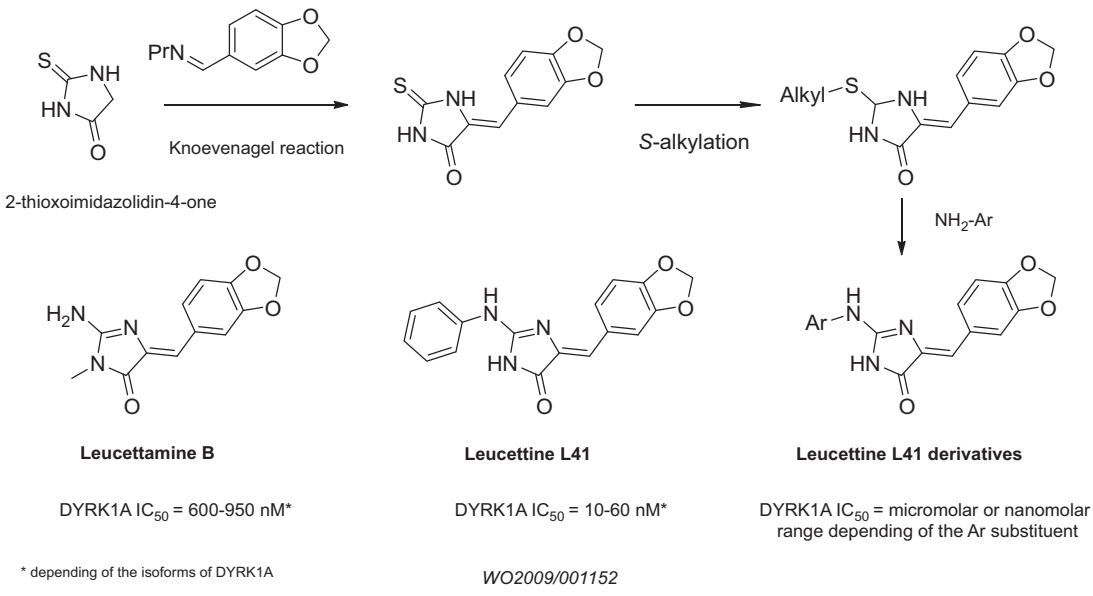
The University of Rennes I (France) and CNRS (France) reported the patented synthesis of imidazolones as derivatives of Leucettamine B, a marine alkaloid isolated from marine sponges [96]. In this work, a SAR study was performed and, along with the resolution of DYRK1A/Leucettine L41 and DYRK2/Leucettine L41 co-crystal structures [35,36], provided key information for structure-based optimization. Among the numerous compounds described, Leucettine L41 was a potent inhibitor of DYRK and CLK kinases and it was extensively characterized in terms of biological effects [35,36,97]. L41 inhibits DYRK1A, DYRK1B, DYRK2, and CLK1 with $IC_{50}$ values of 10–60, 44, 73, and 71 nM, respectively [36]. Leucettines constitute a very promising scaffold for the design and optimization of more selective kinase inhibitors, with potential applications to the treatment of AD and DS associated cognitive deficits. Because of its extensive characterization, Leucettine L41 is frequently used as a pharmacological tool and a reference molecule in investigations on the function of DYRK1A [35,36,96,97]. To access derivatives of Leucettamine B, a number of synthetic routes have been developed which can be adapted in function




Scheme 25. Structure of the most active harmine 'phenylogues' [91].




Scheme 26. CX-4945 structure and brief description of its synthesis [94,95].




Scheme 27. General procedure for the synthesis of Leucettine L41 and its derivatives.

of the substituents to be added to (or taken off from) the main skeleton [96]). Leucettine L41 was prepared in three steps from 2-thioxoimidazolidin-4-one (Scheme 27).

## 3. Expert opinion

Research on the DYRK1A kinase (much more than on other members of the DYRK family) has been expanding considerably over the last few years. Indeed DYRK1A is a regulator of various key molecular processes underlying numerous neuronal and non-neuronal physiological functions. There has been a long-standing interest in the CNS functions of DYRK1A and its key role in cognitive dysfunctions in DS and AD (reviews in [7,21]). More recently, this interest in DYRK1A functions and regulation has started to expand to other organs, functions, and human pathologies. Finally, the research interest is now spreading to the related DYRK1B, DYRK2-4, and CLKs.

It is therefore no wonder that the design and optimization of physiological inhibitors of DYRK1A has grown considerably in recent years, especially those aiming at the treatment of cognitive deficits associated with various neurodegenerative diseases. Medicinal chemistry has greatly benefited from the resolution of numerous three-dimensional structures of DYRK1A in complex with various ATP-competitive inhibitors. Although its targets are still debated, EGCG has reached clinical trial to improve cognitive functions in DS patients [98,99]. Its potential in the treatment of AD was recently reviewed [100]. These first results call for more selective and potent, synthetic drugs. We expect to see such DYRK1A drug candidates to reach clinical trials in the near future. Besides therapeutic aims, potent and selective inhibitors of DYRK1A provide the Academic research community with essential pharmacological tools to investigate the functions and regulations of DYRK1A and related kinases.

Molecular tools allowing fast and precise monitoring of the effects of DYRK1A inhibitors in cells, animals, and patients are now urgently needed. Such biomarkers will be essential to demonstrate target engagement following treatment of animal models and patients with DYRK1A drug candidates. In this context, investigating the scope of DYRK1A substrates and interacting proteins will be of major importance.

As seen by the number of patents presented in this review, the question no longer arises whether DYRK1A is a relevant target for the development of future drugs. Until now, and in connection with biologists' queries, the design of DYRK1A inhibitors has been carried out mostly by academic laboratories, with occasional collaborations with the pharmaceutical industry which is becoming increasingly aware of the therapeutic interest in developing inhibitors of this key kinase.

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## Declaration of interest

TB and CF are members of University of Rouen (FR) and declare no conflict of interest. TLN and YH are members of University of Strasbourg (FR) and declare no conflict of interest. LM is CEO and CSO of the ManRos Therapeutics start-up company and co-inventor on the Leucettines patent. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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