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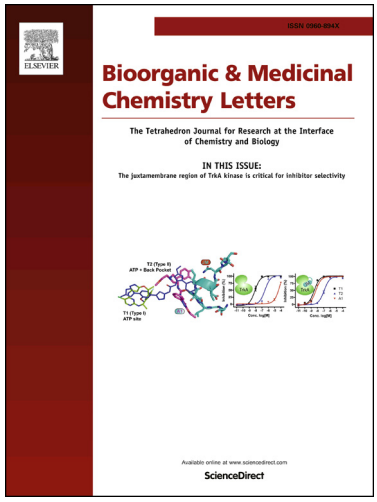

Developing DYRK inhibitors derived from the meridianins as a means of increasing levels of NFAT in the nucleus

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Graphical Abstract

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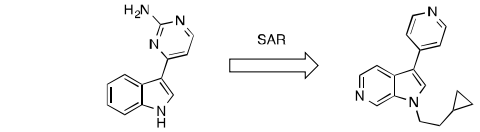

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ABSTRACT

A structure-activity relationship has been developed around the meridianin scaffold for inhibition of Dyrk1a. The compounds have been focussed on the the inhibition of kinase Dyrk1a, as a means to retain the transcription factor NFAT in the nucleus. NFAT is responsible for up-regulation of genes responsible for the induction of a slow, oxidative skeletal muscle phenotype, which may be an effective treatment for diseases where exercise capacity is compromised. The SAR showed that while strong Dyrk1a binding was possible with the meridianin scaffold the compounds have no effect on NFAT localisation, however, by moving from the indole to a 6-azaindole scaffold both potent Dyrk1a binding and increased NFAT residence time in the nucleus were obtained - properties not observed with the reported Dyrk1a inhibitors. One compound was shown to be effective in an ex vivo muscle fiber assay. The increased biological activity is thought to arise from the added interaction between the azaindole nitrogen and the lysine residue in the back pocket.

Dual-specificity Tyrosine-regulated Kinase (Dyrk) belongs to the CMGC family of kinases, which includes the Glycogen Synthase Kinase 3β (GSK3β), Casein Kinase 2 (CK2), Cyclin Dependent Kinases (CDKs) and Mitogen-Activated Protein Kinase (MAPK). The Dyrk family consists of five members in two classes – class 1 (1a and 1b) and class 2 (2, 3 and 4). Dyrk1a is found on chromosome 21, and is responsible for some of the phenotypes found in Down's Syndrome patients, including growth abnormalities.[1-3] Further, Dyrk1a has been shown to phosphorylate Tau and has been implicated in Alzheimer's disease,[4-6] indeed symptoms of Alzheimer's occur earlier in patients with Down's Syndrome than the general population. While there is a clear need for intervention in these situations we were intrigued by an additional role of Dyrk1a – as a priming kinase for the inactivation of nuclear factor of activated T-cells (NFAT).[7]

NFAT is a transcription factor with several roles including the switch from fast twitch to slow twitch muscle fibre[8] and the up-regulation of utrophin through interaction with the utrophin A promoter.[9] After phosphorylation by Dyrk1a, NFAT is further phosphorylated by GSK3β and CK1, resulting in its removal from the nucleus and thus inactivation.

Increasing levels of utrophin has been proposed as a possible therapeutic in muscular dystrophy, since it has been shown that utrophin can serve as a functional replacement for dystrophin. Indeed this approach has shown to be successful in animal models with the compound SMT C1100, a utrophin up-regulator, in clinical trials for Duchenne muscular dystrophy.[10] We believed that inhibition of Dyrk1a would increase the residence of NFAT in the nucleus resulting in increased transcription of utrophin A.

Harmine **1** (Figure 1) is often used as the archetypical Dyrk1a inhibitor. However, in recent years, several classes of Dyrk1a inhibitors have been reported (INDY,[11] V-shaped molecules,[12] leucettines,[13] lamellarin D analogues,[14] a series of pyrimidines,[15] and azaindoles[16]), including a series derived from the meridianin natural products.[17, 18] The meridianins, isolated from the tunicate *Aplidium meridianum*, are marine alkaloids characterized by an indole ring connected to a pyrimidine at the three position e.g. meridianin G, **2**. Meridianins bind in the ATP binding pocket through a hinge contact between the pyrimidine *N*-1 and the 2-amino group of the pyrimidine, while the indole sits in the back pocket, with the potential to form a π-π interaction with the phenylalanine gatekeeper. Derived from meridianins there have been *N*-1-substituted derivatives[19] reported as well as the analogous 6-azaindole scaffold reported by Kettle et al,[20] which resulted in **3**, a compound designed for selective Dyrk1b inhibition. These results have prompted us to report our own initial efforts to investigate meridianin derivatives as Dyrk1a inhibitors, which were able to increase residence time of NFAT in the nucleus as an initial step in increasing utrophin A levels.

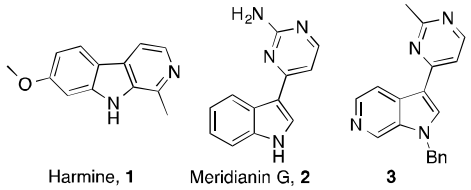
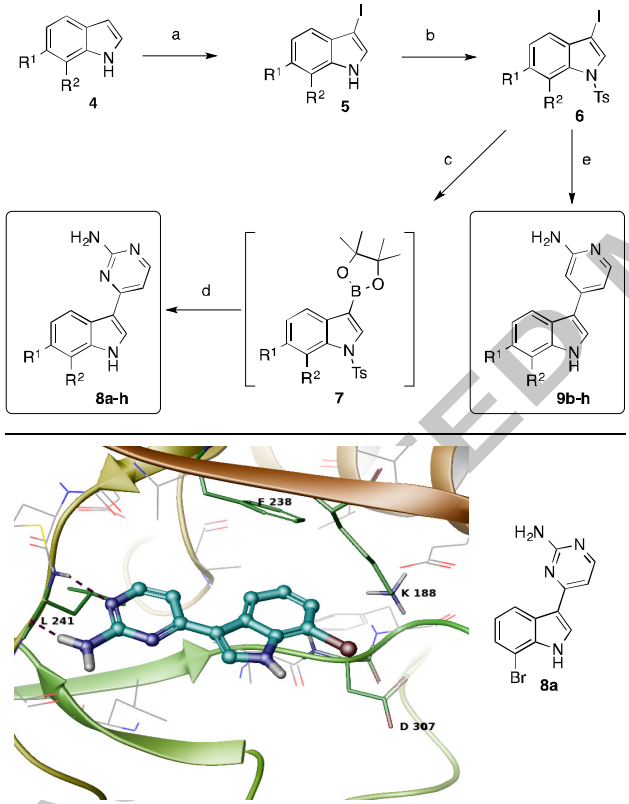


Figure 1. Structures of Dyrk inhibitors.

We began our studies by investigating the meridianin indole scaffold. In particular, analysis of the docking suggested that the hinge binding was effected by the pyrimidine *N*-1 and the amino group at the 2-position with no contribution from the pyrimidine *N*-3.[21] To investigate this hypothesis, a series of compounds were generated with the 2-aminopyrimidine and the corresponding 2-aminopyridine at the 3-position of the indole ring (Scheme 1, Table 1). Compounds were synthesized by iodination of the indole to generate **5** followed by *N*-tosylation to **6**. A one-pot two-step protocol developed by Müller[22] (Masuda borylation followed by Suzuki coupling **6** to **7** to **8**) followed by removal of the tosyl group resulted in the pyrimidine derivatives **8a**-**h**. The pyridine derivatives **9b**-**h** were generated through Suzuki coupling between the 3-iodoindole **6** and 2-aminopyrine-4-boronic acid, with in situ deprotection of the tosyl group.



Scheme 1. Upper - Synthesis of meridianin and pyridine analogues. Reagents and conditions (a) NIS, CH_3CN, rt, 2h (b) NaH, DMF, 0°C, 1h, TsCl, 0°C, 3h (c) pinacol borane, $Pd(PPh_3)_4$, dioxane, 80°C, 3h, cool to rt, (d) MeOH, 4-chloro-2-aminopyrimidine, Cs_2CO_3, 100°C, 14h (e) 2-aminopyridine-4-boronic acid, K_3PO_4, $Pd(PPh_3)_4$, *n*-butanol, H_2O, 140°C, 1h. Lower - A pose of compound **8a** docked to DYRK1a.

Table 1. Meridianin derivatives synthesized and their binding activities and ability to translocate NFAT

Compound	R^1	R^2	Binding IC_{50} (μM)[a]		NFAT (μM)
			Dyrk1a	GSK3β	
1, Harmine			0.041	IA[c]	ND[c]
2, Meridianin G			0.588 (0.700)[b]	14.81	ND
3			0.019	IA	IA
8a	H	Br	0.079 (0.068)[b]	22.45	ND
8b	H	NO_2	(0.085)[b]	9.95	ND
9b	H	NO_2	0.285	IA	IA
8c	H	Cl	0.046	IA	IA
9c	H	Cl	0.094	IA	IA
8d	Cl	H	0.406	10.69	ND
9d	Cl	H	2.939	IA	ND
8e	H	OMe	0.242	15.84	9.8
9e	H	OMe	2.142	IA	ND
8f	OMe	H	0.443	7.96	ND
9f	OMe	H	2.904	12.70	ND
8g	H	CN	0.138	5.16	21.7
9g	H	CN	0.790	13.86	IA
8h	CF_3	H	0.062	15.29	ND
9h	CF_3	H	4.335	IA	ND

[a] Invitrogen LanthaScreen™ Eu Kinase Binding Assay (www.thermofisher.com); [b] from reference 15; [c] IA –inactive, ND – not determined

Our binding data for the literature compounds (**1**-**3**) are consistent with that reported (compound **3** IC_{50} for Dyrk1b 0.007 μM). However, although the 3-position nitrogen in the pyrimidine ring does not appear to be necessary for binding to Dyrk1a in the docking studies, the aminopyridine compounds **9b**-**h** are consistently significantly weaker in the binding assay than the analogous aminopyrimidines **8a**-**h** (Table 1). The exception is the 7-chloroindole **9c**, which does show good binding although weaker than the corresponding aminopyrimidine **8c** (0.094 μM vs. 0.046 μM). Further comparison of the 6-substituted compounds relative to the corresponding 7-substituted analogues (e.g. **8c** vs **8d** and **8e** vs **8f**) shows the 7-substitution to be superior. All the compounds show good selectivity for Dyrk1a over GSK3β (**8f** being the lowest at 18-fold). The most potent Dyrk1a binders (**8c**, **9c**, **7h**) did not show any activity in our translocation assay.

In the translocation assay itself we transfected cells with green fluorescent protein (GFP) tagged NFAT and analyzed for GFP in the nucleus. The NFAT number refers to the concentration required to maintain 50% of the GFP-tagged NFAT in the nucleus after a three-hour treatment. It was shown that electrical stimulation of the cells resulted in GFP-tagged NFAT going into the nucleus and subsequently dissipating over approximately 30 minutes. However, for the experiments described in this manuscript there was no stimulation used apart from the compound itself. Ionomycin is used as a positive control for the assay, which is described more fully in the Supplementary Material.

It was considered that the compounds might show improved potency in the NFAT translocation assay if we could increase the number of binding interactions of the molecules in the binding pocket. Moving from the indole to the 6-azaindole scaffold was

considered to be one method of effecting such an increase in binding by allowing for an interaction between the 6-nitrogen of the azaindole with the back-pocket lysine-188 of the Dyrk1a protein.

Synthesis of the 6-azaindole meridianin analogue **10** was carried out from 6-azaindole **11** using a route reported in the patent literature,[23] that is to say iodination and *N*-1 protection to form **12**. A Sonogashira reaction was used to introduce a hydroxymethylacetylene, which was oxidized to the ynal **13**. Reaction of ynal **13** with guanidine hydrochloride resulted in the aminopyrimidine **10**. The pyridine analogues **14**-**21** could be obtained from **12** through Suzuki reaction (Scheme 2).

A further series of *N*-alkyl compounds **22**-**27** of 3-(4-pyridyl)-6-azaindole **14** were synthesized through a Mitsunobu protocol. In carrying out this reaction a more polar compound was also obtained, which was believed to be the regioisomer in which the alkyl group was located at the 6-position of the azaindole (Scheme 2). These regioisomeric compounds were not able to bind Dyrk1a and as such were not active in the NFAT translocation assay. The result is consistent with the docking pose for **14**, which shows that the nitrogen in the 6-position of the azaindole makes an interaction with the lysine-188 in the back pocket of the ATP binding site. It is noteworthy that the docking suggests that there is little space for substitution around the pyridine ring of the azaindole (Figure 2).

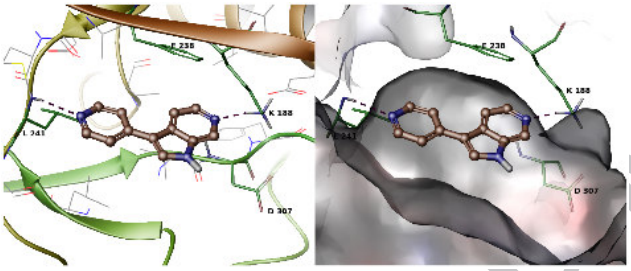
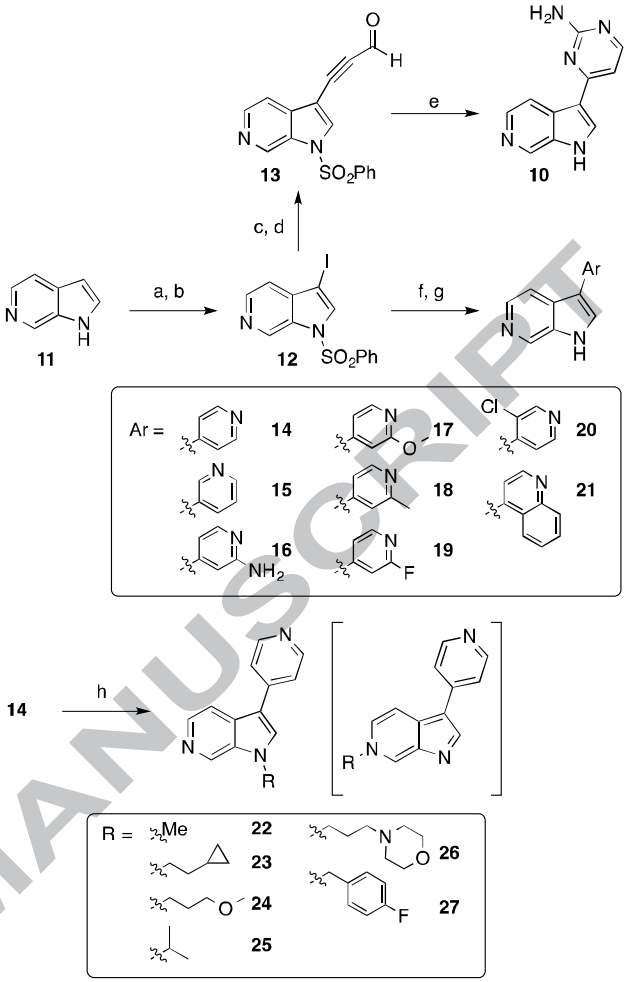


Figure 2. Docking of compound **14** into the Dyrk1a ATP binding site.



Scheme 2. Synthesis of 6-azaindole meridianin analogues. Reagents and conditions (a) NIS, CH_3CN, rt 1.5h (b) NaH, DMF, 0°C, 30 min, $PhSO_2Cl$, 0°C, 3h (c) $HCCCH_2OH$, $Pd(PPh_3)_4$, CuI, dioxane, 100°C, 14h (d) Dess-Martin periodane, CH_2Cl_2, rt, 20 min (e) guanidine.HCl, $MeOCH_2CH_2OH$, 80°C, 10h (f) $ArB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, dioxane, H_2O, 130°C, 1h, μwave (g) NaOMe, MeOH, 100°C, 45 min (h) ROH, PPh_3, DIAD, THF, 0°C, 2h then rt, 14h

The 6-azaindole compounds were screened for their ability to bind both Dyrk1a and GSK3β along with their ability to translocate NFAT into the nucleus in human primary myotubes (Table 2). The results showed that the introduction of a binding interaction in the back pocket of the ATP binding site does increase the binding potency without impact on the selectivity relative to GSK3β. Further, the more potent Dyrk1a inhibitors were able to effect translocation of NFAT into the nucleus. For example, the 2-aminopyrimidin-4-yl compound **10** shows 1 nM binding potency to Dyrk1a and the increase in binding results in an improvement in NFAT translocation. More strikingly, the 4-pyridyl compound **14** shows similar 1 nM binding to Dyrk1a. Again the compound is able to translocate NFAT in cells. Moving from a 4-pyridyl to the 3-pyridyl (**14** vs. **15**) results in a significant drop in binding which is assumed to be due to the ineffective interaction with the hinge in the case of **15**, showing that both the hinge interaction and the lysine back-pocket interaction are important for effective binding. Substitution of the pyridine ring *ortho* to the pyridine nitrogen ring results in a reduction in binding potency (e.g. **14** vs. **16**, **17**, **21**). The 2-methylpyridine **18** and 2-fluoropyridine **19** binding to Dyrk1a in the 70 nM range, with **19** able to translocate NFAT in cells. The

synthetically more challenging Suzuki coupling with substitution of the pyridine at the *meta* position as in the 3-chloropyridyl compound **20** also results in reasonable potency.

Table 2. Biological data for 6-azaindole compounds.

Compound	Binding IC_{50} (μM)		NFAT (μM)
	Dyrk1a	GSK3β	
10	0.001	12.30	4.80
14	0.001	9.23	2.98
15	7.957	31.01	IA
16	2.024	IA	IA
17	0.351	IA	IA
18	0.075	IA	20.82
19	0.069	IA	4.85
20	0.061	9.61	5.31
21	0.277	IA	42.98
22	0.089	4.78	2.21
23	0.008	1.14	1.59
24	0.010	3.00	6.90
25	0.008	0.66	0.31
26	0.109	7.58	6.96
27	0.012	1.01	7.58

The addition of an *N*-1 substituent does not improve Dyrk1a binding; however an improvement in NFAT translocation is observed in several cases (compounds **22**, **23** and **25**), with the *N*-isopropyl compound **25** showing submicromolar potency. The more polar *N*-morpholinoethyl **26** shows weaker binding and poor NFAT translocation suggesting a preference for hydrophobic groups. While **25** and **27** show reduced binding selectivity for Dyrk1a over GSK3β, both maintain a selectivity ratio of greater than 10-fold. We believe that for these compounds Dyrk1a inhibition is the main driver of potency in the NFAT translocation assay. It is interesting to note that compound **3** was inactive in the NFAT translocation assay despite having the same 6-azaindole as the compounds presented in Table 2 and binding to Dyrk1a in a similar range, however, the result is consistent with **27**. Both compounds contain a benzylic N-1 substituent and show poor potency in the NFAT translocation assay.

The 3-(4-pyridyl)-6-azaindole **14** was screened in a kinase panel at 10 μM. The compound inhibited both Dyrk1a and Dyrk1b as expected; however, the compound showed no significant inhibition (less than 30% inhibition) against any of the remaining kinases in the panel, including members of the CMGC kinase family, GSK3β, the CDK's, casein kinases (CK's) and MAP kinases (see Supplementary Material for full details).

Finally an ex vivo experiment was carried out in which muscle fibers were dissociated from the paw of a mouse and transfected with GFP-NFAT. The most potent compound in the cellular assay, the 1-isopropyl-3-(4-pyridyl)-6-azaindole **25**, clearly showed the ability to retain NFAT in the nucleus relative to the DMSO control - compound treated muscle strips show more of the GFP concentrated in spots, which correlate to the nucleus, while in the DMSO treated muscle strip the GFP is more diffuse (Figure 3 and Supplementary Material). The compound was determined to have an EC_{50} of 2.8 μM in this assay.

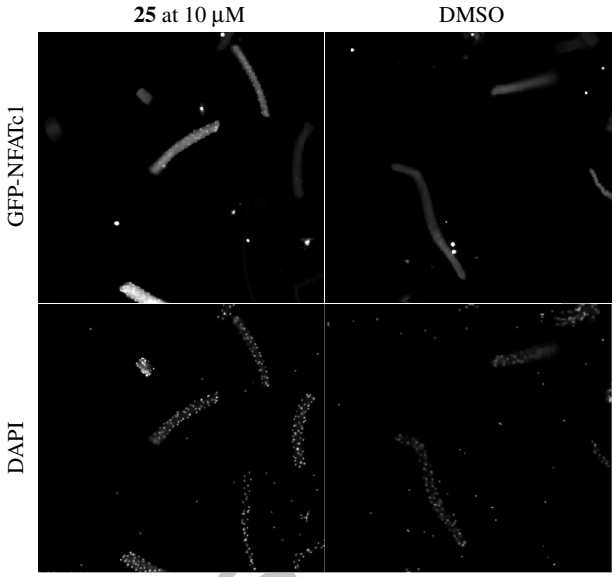


Figure 3. The image shows the comparison of dosing of compound **25** at 10 μM to DMSO for the location of GFP-NFAT in the top pane and DAPI staining for the nucleus in the lower pane.

In summary we have described a series of meridianin derived 6-azaindole inhibitors of Dyrk1a, which are able to increase the residence time of the transcription factor NFAT within the nucleus. Key to the NFAT activity in cells was the use of the 6-azaindole scaffold, which allows for a binding interaction in the back pocket of the kinase between the 6-position nitrogen and Lys-188 of Dyrk1a. The compounds have demonstrated greater than 10-fold selectivity for Dyrk1a over GSK3β a fellow GMCG family member. In addition the most potent compound was shown to be active in an ex vivo muscle fiber assay. The effect on NFAT has not been reported previously for Dyrk inhibitors, and is an effect we observe only weakly with the reported meridianin-derived compounds. While the translocation assay tracks with the binding assay in terms of the order of potency reasonably well, there remains a difference in sensitivity between the two assays - the most potent nanomolar binders of Dyrk1a show micromolar potency in the translocation assay. In addition to the limitations of isolated kinase assays to mimic the cell environment, we note that the translocation of NFAT into the nucleus is a complex dynamic process. It involves the action of kinases and phosphatases as well as proteins required for the import and export of NFAT into and from the nucleus, which may be responsible for the differences between the two assays. Current studies are aimed at identifying compounds with suitable PK properties for animal models, which may be able to switch muscle fibers from fast- to slow-twitch and potentially have an effect on utrophin levels.

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Supplementary Material

Experimental procedures for the translocation assay, synthesis of the compounds and spectral characterization is provided along with a complete list of kinases screened for compound **14** and a larger version of Figure 3.