Synthesis and biological evaluation of new thiazolo [5,4-f]quinazolines as serine/threonine kinases inhibitors

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Synthesis and biological evaluation of new thiazolo [5,4-f]quinazolines as serine/threonine kinases inhibitors

Graphical Abstract

EHT 5372 (8c)  
DYRK1A IC₅₀ = 0.22 nM  
DYRK1B IC₅₀ = 0.28 nM

EHT 6840 (8h)  
DYRK1A IC₅₀ = 0.99 nM  
DYRK1B IC₅₀ = 1.63 nM

EHT 1610 (8i)  
DYRK1A IC₅₀ = 0.36 nM  
DYRK1B IC₅₀ = 0.59 nM

EHT 9851 (8k)  
DYRK1A IC₅₀ = 0.94 nM  
DYRK1B IC₅₀ = 1.07 nM

EHT 3356 (9b)  
DYRK1A IC₅₀ = 0.98 nM  
DYRK1B IC₅₀ = 2.83 nM
Abstract: In our continuous effort aiming at preparing novel heterocyclic scaffolds able to modulate the activity of kinases in signal transduction, thiazolo[5,4-f]quinazolines were particularly studied. This presentation describes a novel strategy for a convenient structure-activity-relationship study towards five serine/threonine kinases (CDK1/cyclin B, CDK5/p25, DYRK1A, CK1, and GSK-3α/β) involved in Alzheimer’s disease. The chemical highlight of this work was the use of Appel salt (4,5-dichloro-1,2,3-dithiazolium chloride) for the conception of 6-amino-2-cyanobenzo[d]thiazole-7-carboxylate derivatives as a versatile molecular platform from the 5-nitroanthranilic acid. Thus, introduction of various aliphatic, aromatic or amino substituents at position 8 was best achieved by one-pot DMFDMA-mediated cyclisation. Transformation of carbonitrile group into various chemical functions (e.g. imidate, ester, amidine...) allowed the efficient preparation of a library of novel thiazoloquinazoline derivatives. The first biological results have identified great and selective inhibition against DYRK1A and DYRK1B. The more active compounds are imidate derivatives exhibiting inhibitory activity in a subnanomolar range against DYRK1A.

Keywords: thiazolo[5,4-f]quinazolines; serine/threonine kinases; Appel salt; DMFDMA-mediated cyclisation
Introduction

Kinases are one of the largest enzyme families of the genome. More than 500 kinases play an important role in the regulation of most cellular processes. These enzymes are involved in all major diseases, including cancer, neurodegenerative disorders and cardiovascular diseases. Our research groups are mainly invested in the synthesis of C,N,S- or C,N,O-containing heterocyclic precursors of bioactive molecules able to modulate the activity of kinases in signal transduction, and especially Ser/Thr kinases (CDK5, GSK3, CLK1 and CK1) and dual-specificity kinases (DYRK family), selected for their strong implication in various human pathologies, especially in Alzheimer disease and cancer.

Among the DYRK kinases family, DYRK1A is certainly the most studied and is a novel, high-potential therapeutic target for pharmacological interventions seeking to modify the course of AD.

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2. Flajolet, M.; He, G.; Heiman, M.; Lin, A.; Nairn, A.C.; Greengard, P. Proc. Nat. Acad. Sci. USA 2007, 104, 4159–4164.
3. Weinmann, H.; Metternich, R. ChemBioChem 2005, 6, 455–459.
Introduction

In the course of our work, we described ten years ago the synthesis of the 8H-thiazolo[5,4-f]quinazolin-9-ones (A). Brief studies of their structure-activity relationships as dual CDK1/GSK-3 kinases inhibitors were described. More recently, the synthesis and the kinase inhibitory potency of various benzo-, pyrido- and pyrazinothieno[3,2-d]pyrimidines derivatives (B), have been published. Kinase inhibition of the compounds was evaluated on Ser/Thr kinases (CDK5, GSK3, DYRK1A, CLK1 and CK1) selected for their strong implications in various human pathologies, especially in AD.

Previous works

Eur. J. Med. Chem. 2008, 43, 1469.  
Bioorg. Med. Chem. Lett. 2006, 16, 3419.  
Tetrahedron Lett. 2003, 44, 4455.

Eur. J. Med. Chem. 2015, 92, 124-134. 
Bioorg. Med. Chem. Lett. 2013, 23, 6784-6788. 
Eur. J. Med. Chem. 2013, 59, 283-295. 
Eur. J. Med. Chem. 2012, 58, 171-183.
Introduction

Pursuing our studies, we conceived new series of thiazolo[5,4-f]quinazolines substituted in position 4 of the pyrimidine ring by an aromatic amine and by carboximidamide groups in position 2 of the thiazole moiety (see general formula C).

The aromatic amine groups linked to the main thiazoloquinazoline structure were selected because of their frequent presence in drugs or drug candidates.

For a complete review see: Harris, C.S.; Hennequin, L.; Morgentin, R.; Pasquet, G. Synthesis and functionnalization of 4-substituted quinazolines as kinases templates. In Targets in Heterocyclic Systems—Chemistry and Properties; Attanasi, O.A., Spinelli, D., Eds.; Italian Society of Chemistry: Roma, Italia, 2010; Volume 14, pp. 315–350.
Results and discussion

General retrosynthetic pathways envisioned for this work.

First route

Second route

Dimroth rearrangement

Cu(I)-mediated cyclization

Appel salt chemistry

Molecules 2014, 19, 15411-15439 & Molecules 2014, 19, 15546-15571
First Synthetic route experimented for the access to the target compounds (series 7–10).

**Scheme 1:**

1. **1:** 
   - Reagents: DMFDMA, DMF, 70°C (µw), 2 min, 94%.
   - Reaction: 
     - **2:** 
       - Reagents: aniline (1.5 eq.), AcOH, 118°C (µw), 2-45 min, 77-99%

2. **1b:** 
   - Reagents: Br₂, AcOH, CH₂Cl₂, r.t., 3.5 h, quant.

3. **2b:** 
   - Reaction: 
     - **3a-d:** 
       - Reagents: HCO₂NH₄, Pd.C, EtOH, 78°C (µw), 30 min, 93-99%

4. **4a-d:** 
   - Reaction: 
     - **5a-d + 5e:** 
       - Reagents: Br₂, AcOH, CH₂Cl₂, r.t., 3.5 h, quant.

5. **6a-d:** 
   - Reaction: 
     - **7-10 (24-49%):** 
       - Compounds: 3a-6a, 7, 3b-6b, 8, 3c-6c, 9, 3d-6d, 10, 5e

**Due to the nature of the compounds, alternative and unsuccessful route for 5b is indicated.**

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Multistep synthesis of polyfunctionalized benzothiazole 16.

Despite its effectiveness, the synthesis presented above has some limitations.

A) Each modification of the substituent in \( N^3 \) of the pyrimidine ring generates three intermediates for which biological significance is not established.

B) Reduction and bromination steps require being adapted to the aromatic substituent of the intracyclic \( N^3 \)-nitrogen atom.

C) It implied synthesis of a versatile platform:

\[
\begin{align*}
\text{O}_2\text{N-CN} & \quad \xrightarrow{a} \quad \text{O}_2\text{N-CN} \quad \xrightarrow{b} \quad \text{H}_2\text{N-CN} \quad \xrightarrow{c} \quad \text{H}_2\text{N-CN} \\
\text{1} & \quad \quad \text{11} & \quad \quad \text{12} & \quad \quad \text{13} \\
\text{NC} & \quad \quad \text{NC} & \quad \quad \text{NC} & \quad \quad \text{NC} \\
\text{16} & \quad \quad \text{15} & \quad \quad \text{14} \\
\end{align*}
\]

Reagents and conditions: (a) Boc\(_2\)O, DMAP, Et\(_3\)N, CH\(_2\)Cl\(_2\), r.t., 4 h; (b), HCO\(_2\)NH\(_4\), Pd.C, EtOH, 78 °C (μw), 30 min; (c) Br\(_2\), AcOH, CH\(_2\)Cl\(_2\), r.t., 2.5 h; (d) Appel salt, Py. (2 eq), CH\(_2\)Cl\(_2\), r.t., 4 h; (e) AcOH, 118 °C (μw), 2 h; (f) Cul, Py., 130 °C (μw), 20 min.
This molecular system was designed as an efficient precursor of various target molecules.

Possible transformations of benzothiazole 16 as a versatile molecular platform.

\[ X = \text{NH, O} \]

*Dimroth rearrangement*

*Molecules 2014, 19, 15411-15439 & Molecules 2014, 19, 15546-15571*
Synthesis of thiazolo[5,4-f]quinazoline-2-carbonitriles (7–10) and their derivatives via transformation of the carbonitrile functions in carboxamidines (a–g), amides (h) or imidates (i).

Reagents and conditions: (a) DMFDMA, DMF, 70 °C (μw), 2 min, 86%; (b) aniline (1.5 eq), AcOH, 118 °C (μw), 2 min, 99% (7)/45 min, 95% (8)/30 min, 70% (9)/10 min, 77% (10); (c) amines, THF, r.t., 12 h, for yields see Table 1; (d) NaOHaq (2.5 N), butanol, 117 °C (μw), 30 min, 98% (7h)/91% (8h)/71% (9h)/98% (10h); (e) NaOMe (0.5M in MeOH), MeOH, 65 °C (μw), 30 min, 82% (7i)/92% (8i)/94% (9i)/98% (10i).
Chemical structures and yields obtained for the synthesis of the four series (7a–g–10a–g)

| R1 | R2 | Compound | Yield a (%) | R1 | R2 | Compound | Yield a (%) |
|----|----|----------|------------|----|----|----------|------------|
|    |    | 7a       | 41         |    |    | 9a       | 85         |
|    |    | 7b       | 43         |    |    | 9b       | 72         |
|    |    | 7c       | 47         |    |    | 9c       | 68         |
|    |    | 7d       | 53         |    |    | 9d       | 64         |
|    |    | 7e       | 50         |    |    | 9e       | 86         |
|    |    | 7f       | 28         |    |    | 9f       | 68         |
|    |    | 7g       | 67         |    |    | 9g       | 40         |
|    |    | 8a       | 41         |    |    | 10a      | 71         |
|    |    | 8b       | 34         |    |    | 10b      | 82         |
|    |    | 8c       | 48         |    |    | 10c      | 69         |
|    |    | 8d       | 30         |    |    | 10d      | 50         |
|    |    | 8e       | 66         |    |    | 10e      | 50         |
|    |    | 8f       | 21         |    |    | 10f      | 69         |
|    |    | 8g       | -b         |    |    | 10g      | 43         |

\[^a\] Isolated yield; \[^b\] Not prepared.
Kinase inhibitory activity of the four thiazolo[5,4-f]quinazoline series (7a–i–10a–i)

Compounds of series 7 (7, 7a–i), series 8 (8, 8a–i), series 9 (9, 9a–i) and series 10 (10, 10a–i) were tested on four different in vitro kinase assays (CDK5/p25 (cyclin-dependent kinase), CK1δ/ε(casein kinase 1), GSK3α/β(Glycogen Synthase Kinase 3) and DYRK1A (dual-specificity, tyrosine phosphorylation regulated kinase) to evaluate their inhibition potency [19–23]. These four kinases are all involved in Alzheimer’s disease (AD), a multi-kinase inhibitor able to target two or three of them could be quite desirable. This is linked to the fact that it is still not known whether any of these four kinases plays a more prominent role in Alzheimer’s disease than the others and, consequently, which one should therefore preferably be targeted. In pathological situations such kinases are overexpressed and-activated, this fact justify the interest of multi-target-directed ligands (MTDLs) while complete inhibition is likely to be detrimental.

Molecules 2014, 19, 15411-15439 & Molecules 2014, 19, 15546-15571
Kinase inhibitory activity \(^{a,b,c}\) of the four thiazolo[5,4-\(f\)]quinazoline series (7a–i–10a–i)

| Compound | DYRK1A | CK1 | CDK5 | GSK3 | Compound | DYRK1A | CK1 | CDK5 | GSK3 |
|----------|--------|-----|------|------|----------|--------|-----|------|------|
| 7        | >10    | >10 | >10  | ≥10  | 9        | >10    | >10 | >10  | >10  |
| 7a       | >10    | >10 | >10  | 1.10 | 9a       | >10    | >10 | >10  | 1.8  |
| 7b       | >10    | >10 | >10  | 2.50 | 9b       | >10    | >10 | >10  | 0.53 |
| 7c       | >10    | >10 | >10  | 2.00 | 9c       | >10    | >10 | >10  | 2.20 |
| 7d       | >10    | >10 | >10  | >10  | 9d       | >10    | >10 | >10  | 0.95 |
| 7e       | 4.00   | >10 | >10  | 1.30 | 9e       | >10    | >10 | >10  | 2.10 |
| 7f       | 8.00   | >10 | >10  | 2.00 | 9f       | >10    | >10 | >10  | 1.80 |
| 7g       | 0.70   | >10 | >10  | 1.10 | 9g       | 0.27   | >10 | >10  | 0.60 |
| 7h       | 0.50   | >10 | >10  | 0.30 | 9h       | 0.67   | >10 | >10  | 0.13 |
| 7i       | 0.040  | >10 | >10  | 0.20 | 9i       | 0.050  | >10 | >10  | 0.16 |
| 8        | >10    | >10 | >10  | ≥10  | 10       | >10    | >10 | >10  | >10  |
| 8a       | 2.20   | >10 | >10  | 0.97 | 10a      | >10    | >10 | >10  | 3.50 |
| 8b       | 2.00   | >10 | >10  | 1.10 | 10b      | >10    | >10 | >10  | 1.40 |
| 8c       | 1.10   | >10 | >10  | 0.36 | 10c      | >10    | >10 | >10  | 2.50 |
| 8d       | 1.05   | >10 | >10  | 0.25 | 10d      | >10    | >10 | >10  | 3.00 |
| 8e       | 6.50   | >10 | >10  | 0.80 | 10e      | >10    | >10 | >10  | 7.00 |
| 8f       | >10    | >10 | >10  | 2.00 | 10f      | >10    | >10 | >10  | >10  |
| 8g       | -      | -   | -    | -    | 10g      | 6.50   | >10 | >10  | 7.20 |
| 8h       | 0.80   | >10 | >10  | 0.77 | 10h      | 1.60   | >10 | >10  | 0.66 |
| 8i       | 0.047  | >10 | >10  | 0.66 | 10i      | 0.25   | >10 | >10  | 0.69 |

\(^a\) IC\(_{50}\) values are reported in \(\mu\)M. The most significant results are presented in bold; \(^b\) Kinases activities were assayed in triplicate. Typically, the standard deviation of single data points was below 10\%; \(^c\) Harmine (IC\(_{50}\) in \(\mu\)M): DYRK1A: 0.029; CK1: 1.50; CDK5 and GSK3α/β: > 10 [27]; Leucettine L41 (IC\(_{50}\) in \(\mu\)M): DYRK1A: 0.040; CK1: > 10; CDK5: > 10 and GSK3α/β: 0.040 [27]; \(^d\) Not determined.

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The two most interesting series are 8 and 9

Series 8 is really promising with micromolar range activities against DYRK1A (6.5 μM < IC$_{50}$ < 1.05 μM) and submicromolar IC$_{50}$ values against GSK3α/β (0.25 μM < IC$_{50}$ < 0.97 μM).

The most active molecules prepared in this study were series g–i of the four family of thiazolo[5,4-f]quinazolines (7–10) with spectacular submicromolar activities against DYRK1A (0.04 μM < IC$_{50}$ < 0.70 μM) and GSK3α/β kinases (0.16 μM < IC$_{50}$ < 0.77 μM) with a marked preference for the first one, respectively.

The DYRK1A IC$_{50}$ values obtained for 7i, 8i and 9i are situated in the double-digit nanomolar range (40, 47 and 50 nM, respectively) demonstrating that small-sized groups linked to the thiazole ring were able to induce a dramatic enhancement of the inhibitory activity against DYRK1A.

*Molecules* 2014, 19, 15411-15439 & *Molecules* 2014, 19, 15546-15571
A methyl 9-(arylamino)thiazolo[5,4-f]quinazoline-2-carbimidate derivative library with highly potent DYRK1A/1B kinase inhibitory activities

The previous part of this showed that lead compounds possess a methylcarbimidate function in position 2 of the thiazole ring, associated with an N-aryl substituent on position 9 of the thiazolo[5,4-f]quinazoline scaffold (compounds C).

Methyl carbimidate function: best affinity for DYRK1A

The overall potential therapeutic interest of these compounds encouraged us to extend this series of thiazolo[5,4-f]quinazolines by substituting the position 4 of the pyrimidine ring with various aromatic amines and by leaving a methyl carbimidate group in position 2 of the thiazole moiety.

Molecules 2014, 19, 15411-15439 & Molecules 2014, 19, 15546-15571
Synthesis of 7, 8 and 9 series (C) via transformation of 4, 5 and 6 series

**Reagents and conditions:** (a) DMF/DMA, DMF, 70 °C (μw), 2 min, 86%; (b) aniline (1.5 equiv.), AcOH, 118 °C (μw), for time and yields see Table 1; (c) NaOMe (0.5 M in MeOH), MeOH, 65 °C (μw), 30 min, for yields see Table.
Synthesis of $^9N$-methylated derivatives of 7a, 7c and 7e.

Reagents and conditions: (a) ICH$_3$, NaH, DMF, 0 °C then r.t., 2 h, 60% (10a); 74% (10b); 30% (10c); (b) NaOMe (0.5 M in MeOH), MeOH, 65 °C (μw), 30 min, 93% (11a); 73% (11b); 66% (11c).

| Series | R        | 10a-c            | 11a-c            |
|--------|----------|------------------|------------------|
| 4a     | ![4a](image) | ![NC=S]([N-R][N-R])_10a-c (30-74%) | ![NC=S]([N-R][N-R])_11a-c (66-93%) |
| 4e     | ![4e](image) | | |
| 4c     | ![4c](image) | | |

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Synthesis of ethyl, isopropyl and benzyl carbimidates 12a–c and methyl carboxylate 13 from carbonitrile 7b.

| Compound | R  | Yield (%) |
|----------|----|-----------|
| 12a      | Et | 79        |
| 12b      | i-Pr | 27      |
| 12c      | Bn | 28        |

Reagents and conditions: (a) RONa (0.5–1.0 M in ROH), ROH, 80–100 °C (μw), 30 min–2 h, R = Et (12a), i-Pr (12b) and Bn (12c); (b) MeOH-H2O/TFA (0.1%) (6:4, v/v), r.t., 12 h.

Molecules 2014, 19, 15411-15439 & Molecules 2014, 19, 15546-15571
Note concerning microwave-assisted methods used in this work

Microwave heating in this work was mainly performed at atmospheric pressure in a controlled multimode cavity with a microwave power delivery system ranging from 0 to 1200 W (Milestone). Open vessel microwave experiments have some advantages, such as the possibility of easier scale-up and the possibility to use current laboratory glassware.

Our choice was also guided by the tendency of pressure to accumulate when a product as DMF/DMA was heated into pressurized vials, especially under microwaves.

In the main part of reactions studied, 600–800 W irradiation was enough to efficiently reach the programmed temperature. This parameter was mainly monitored via a contactless-infrared pyrometer, which was calibrated in control experiments with a fiber-optic contact thermometer.
DYRK1A and DYRK1B kinase inhibitory activity of the four methyl thiazolo[5,4-$f$]quinazoline carboximidae series (7, 8, 9, and 11); ethyl, isopropyl and benzyl carboximidaes (12a–c) and methyl carboxylate (13).

| Amine in Position 9 (R-NH$_2$) | Compound | DYRK1A IC$_{50}$ (nM) | DYRK1B IC$_{50}$ (nM) |
|---------------------------------|----------|------------------------|------------------------|
| 4-methoxylaniline                | 7a       | 13.08                  | 19.22                  |
| 3,4-(methyleneoxy)aniline       | 7b       | 1.65                   | 4.20                   |
| 1,4-benzodioxan-6-amine         | 7c       | 8.00                   | 17.60                  |
| 2,3-dihydro-1-benzofuran-5-amine| 7d       | 1 < IC$_{50}$ < 1000   | 7 < IC$_{50}$ < 1000   |
| 3,4-dimethoxylaniline           | 7e       | 128.80                 | 160.6                  |
| 2,4-dimethoxylaniline           | 7f       | 9.53                   | 11.13                  |
| 3,5-dimethoxylaniline           | 7g       | 298.90                 | 530.90                 |
| 3-nitro-4-methoxylaniline       | 7h       | 123.50                 | 599.80                 |
| 4-aminophenol                   | 7i       | 1 < IC$_{50}$ < 1000   | 7 < IC$_{50}$ < 1000   |
| 5-aminobenzophenol              | 7j       | 1 < IC$_{50}$ < 1000   | 7 < IC$_{50}$ < 1000   |
| 4-aminobenzonitrile             | 8a       | 4.91                   | 5.68                   |
| 4,5-trimethoxylaniline          | 8b       | 436.10                 | 485.80                 |
| 4-chloroaniline                 | 8c (EHT 5372) | 0.22               | 0.28                   |
| 2,3-dichloroaniline             | 8d       | 66.82                  | 99.34                  |
| 4-fluoroaniline                 | 8e       | 6.06                   | 9.64                   |
| 4-bromo-2-fluoroaniline         | 8f       | 3.6                    | 6.55                   |
| 3-chloro-4-fluoroaniline        | 8g       | 1 < IC$_{50}$ < 1000   | 7 < IC$_{50}$ < 1000   |
| 4-chloro-2-fluoroaniline        | 8h (EHT 6840) | 0.99               | 1.63                   |
| 2-fluoro-4-methoxylaniline      | 8i (EHT 1610) | 0.36              | 0.59                   |
| 4-aminobenzoic fluoride         | 8j       | 8.63                   | 11.00                  |
| 4-aminobenzonitrile             | 8k (EHT 9851) | 0.94             | 1.07                   |
| 4-aminobenzyl fluoride           | 8l       | 54.84                  | 186.40                 |
| aminopiperidine                 | 9a       | 1.81                   | 3.48                   |
| 4-aminophenol                   | 9b (EHT 3355) | 0.98              | 2.83                   |
| 4-aminobenzonitrile             | 9c       | 39.03                  | 93.84                  |
| 3-aminobenzonitrile             | 9d       | 40.76                  | 46.29                  |
| 4-aminobenzonitrile             | 9e       | 3.89                   | 7.69                   |
| 3-aminobenzonitrile             | 9f       | 42.70                  | 71.98                  |
| 6-aminobenzimidazole            | 9g       | 4.44                   | 4.65                   |
| N,N-dimethyl-p-phenylene-diamine| 9h       | 35.64                  | 64.28                  |
| 4-(pyrrolidin-1-y1)aniline      | 9i       | n.t.$^c$               | n.t.$^c$               |
| 4-methoxylaniline               | 11a      | 79.85                  | 84.94                  |
| 3,4-dimethoxylaniline           | 11b      | 3768.00                | 4458.00                |
| 1,4-benzodioxan-6-amine         | 11c      | 1 < IC$_{50}$ < 1000   | 7 < IC$_{50}$ < 1000   |
| 3,4-(methyleneoxy)aniline       | 12a      | 6.02                   | 7.72                   |
| 3,4-(methyleneoxy)aniline       | 12b      | 124.7                  | 217.80                 |
| 3,4-(methyleneoxy)aniline       | 12c      | 33.93                  | 37.34                  |
| 3,4-(methyleneoxy)aniline       | 13       | 1 < IC$_{50}$ < 1000   | 7 < IC$_{50}$ < 1000   |

*Molecules 2014, 19, 15411-15439 & Molecules 2014, 19, 15546-15571*

Structure of the DYRK1A/1B reference compounds used in this study.

Harmine

![Image of Harmine]

TG003

![Image of TG003]

NCGC-00189310

![Image of NCGC-00189310]

Leucettine L41

![Image of Leucettine L41]
Structures and DYRK1A/1B IC$_{50}$ values of the five lead compounds identified in this study.

![Compound Structures](image)

| Compound | Structure | CLogP | DYRK1A IC$_{50}$ | DYRK1B IC$_{50}$ |
|----------|-----------|-------|------------------|------------------|
| EHT 5372 (8c) | ![Structure](image) | 4.56 | 0.22 nM | 0.28 nM |
| EHT 6840 (8h) | ![Structure](image) | 3.99 | 0.99 nM | 1.63 nM |
| EHT 1610 (8i) | ![Structure](image) | 3.24 | 0.36 nM | 0.59 nM |
| EHT 9851 (8k) | ![Structure](image) | 3.42 | 0.94 nM | 1.07 nM |
| EHT 3356 (9b) | ![Structure](image) | 3.62 | 0.98 nM | 2.83 nM |

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*Molecules* 2014, 19, 15411-15439 & *Molecules* 2014, 19, 15546-15571

Design and Synthesis of Thiazolo[5,4-f]quinazolines as DYRK1A Inhibitors, Part I and II.

ClogP were calculated with Chemdraw V12.0.
IC_{50} of EHT 5372 on the hits of a selectivity profile performed on a total of 339 kinases.

| IC_{50} (nM) | DYRK1A | DYRK1B | DYRK2 | DYRK3 | DYRK4 | GSK3α | CLK1 | CLK2 | CLK3 | CLK4 | GSK3β |
|--------------|--------|--------|-------|-------|-------|-------|------|------|------|------|-------|
| EHT 5372    | 0.22   | 0.28   | 10.8  | 93.2  | n.i.  | 7.44  | 22.8 | 88.8 | >10000 | 59  | 221   |
| Selectivity ratio | 1 | 1.28 | 49.1 | 423.6 | nd | 33.8 | 103.6 | 403.6 | nd | 268.1 | 1004.5 |

Selectivity ratio

| IC_{50} (nM) | DYRK1A | DYRK1B |
|--------------|--------|--------|
| Harmine      | 21.8   | 27.8   |
| TG003        | 24.01  | 34.39  |
| L41          | 7.60   | 37     |
| EGCG         | 11130  | 1244   |

EHT 5372 inhibits DYRK1A-induced Tau phosphorylation at multiple AD-relevant sites in biochemical and cellular assays. EHT 5372 also normalizes both Aβ-induced Tau phosphorylation and DYRK1A-stimulated Aβ production.

A Novel DYRK1A (Dual Specificity Tyrosine Phosphorylation-Regulated Kinase 1A) Inhibitor for the Treatment of Alzheimer’s Disease: Effect on Tau and Amyloid Pathologies in Vitro.
Courtadeur, S.; Benyamine, H.; Delalonde, L.; de Oliveira, C.; Leblond, B.; Foucourt, A.; Besson, T.; Casagrande, A.-S.; Taverne, T.; Girard, A.; Pando, M.P.; Désiré, L. J. Neurochem. 2015, 133, 440-451.
Results concerning EHT 5372 and other derivatives on the inhibition of DYR1B/Mirk and quiescence of cancer cells:

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Results concerning EHT 1610 and DYRK1A:

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DYRK1A controls the transition from proliferation to quiescence during lymphoid development by destabilizing Cyclin D3. Thompson, B.; Bhansali, R.; Diebold, L.; Cook, D. E.; Stolzenburg, L.; Casagrande, A. –S.; Besson, T.; Leblond, B.; Desire, L.; Malinge, S.; Crispino, J. D. *J. Exp. Med. 2015, 212, 723*
Conclusion

These results confirm that the thiazolo[5,4-f]quinazoline scaffold has a great potential in the development of novel and highly potent dual inhibitors of DYRK1A and DYRK1B kinases that are involved in many neurodegenerative diseases (AD and other tauopathies), in genetic disease (DS), in oncology, and in diseases involving abnormal pre-mRNA splicing.
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