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

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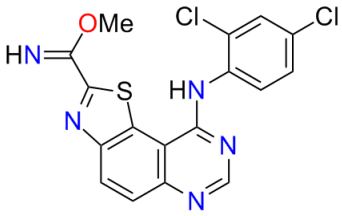
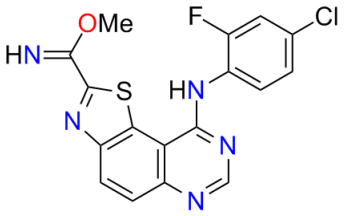
Synthesis and biological evaluation of new thiazolo [5,4-*f*]quinazolines as serine/threonine kinases inhibitors

Graphical Abstract



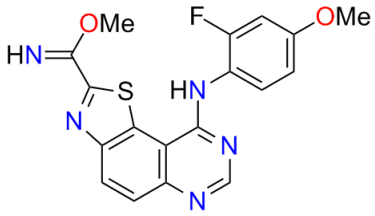
EHT 5372 (**8c**)

DYRK1A IC_{50} = 0.22 nM
DYRK1B IC_{50} = 0.28 nM



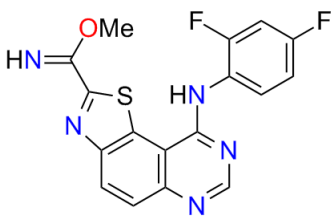
EHT 6840 (**8h**)

DYRK1A IC_{50} = 0.99 nM
DYRK1B IC_{50} = 1.63 nM



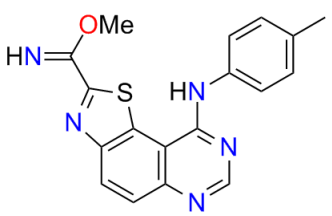
EHT 1610 (**8i**)

DYRK1A IC_{50} = 0.36 nM
DYRK1B IC_{50} = 0.59 nM



EHT 9851 (**8k**)

DYRK1A IC_{50} = 0.94 nM
DYRK1B IC_{50} = 1.07 nM



EHT 3356 (**9b**)

DYRK1A IC_{50} = 0.98 nM
DYRK1B IC_{50} = 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

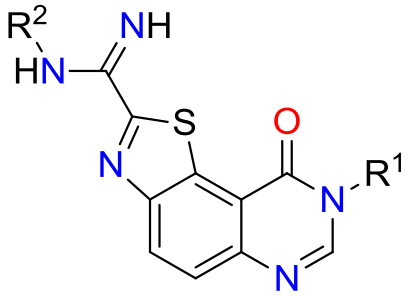
Kinases are one of the largest enzyme families of the genome. More than 500 kinases play an important role in the regulation of most cellular processes. These enzymes are involved in all major diseases, including cancer, neurodegenerative disorders and cardiovascular diseases. Our research groups are 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.

1. Martin, L.; Latypova, X.; Wilson, C.M.; Magnaudeix, A.; Perrin, M.-L.; Terro, F. *Ageing Res. Rev.* **2013**, *12*, 289–309.
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

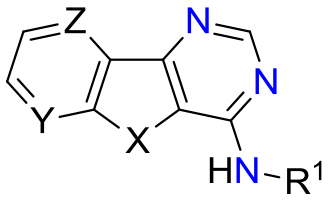
In the course of our work, we described ten years ago the synthesis of the 8*H*-thiazolo[5,4-*f*]quinazolin-9-ones (**A**). Brief studies of their structure-activity relationships as dual CDK1/GSK-3 kinases inhibitors were described. More recently, the synthesis and the kinase inhibitory potency of various 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.



A

X = NH or O
Y = CH or NH
Z = CH or NH

R^1 = Alkyl or aryl
R^2 = Alkyl or aryl



B

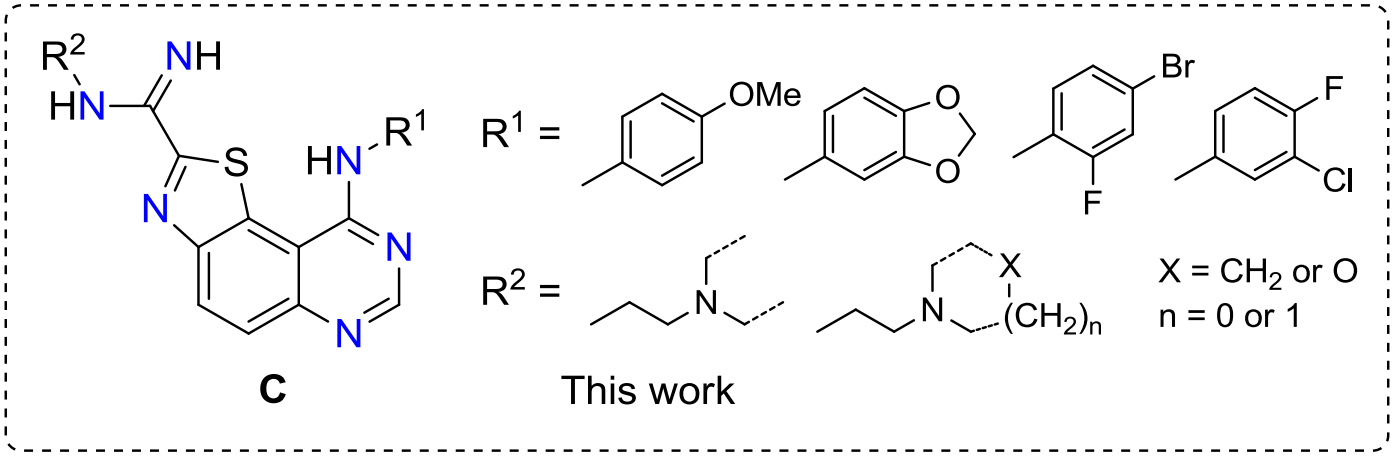
Previous works

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**).

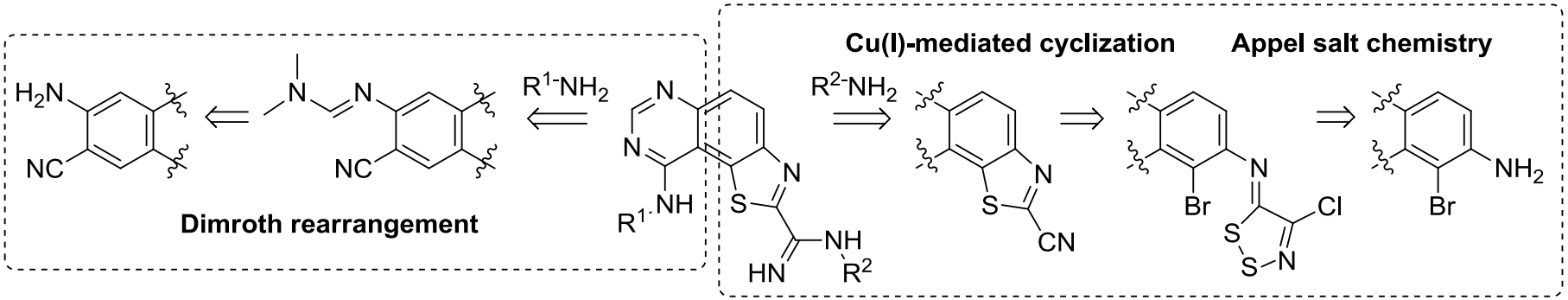


The aromatic amine groups linked to the main thiazoloquinazoline structure were selected because of their frequent presence in drugs or drug candidates.

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.

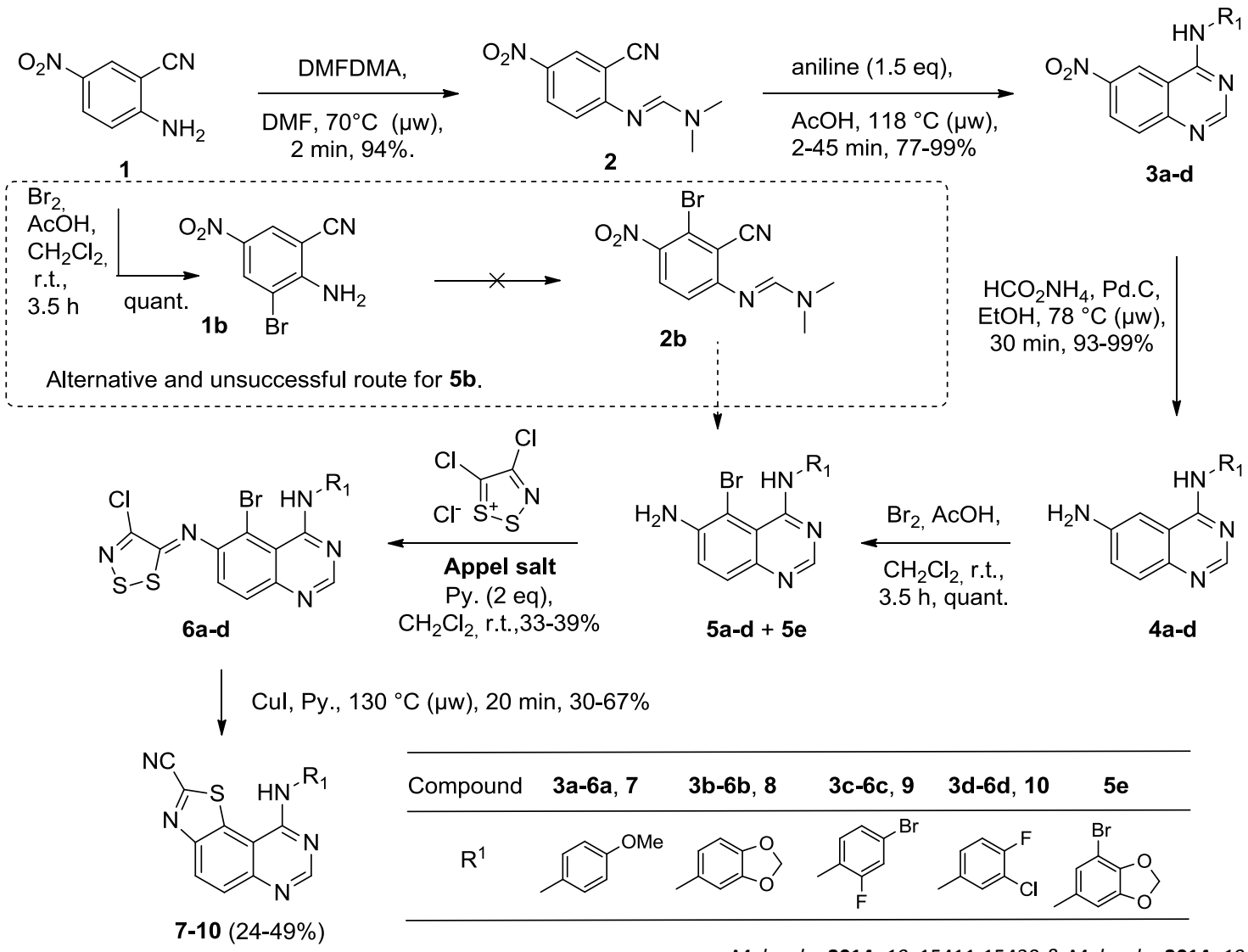


First route

Second route

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

First Synthetic route experimented for the access to the target compounds (series 7–10).



Compound	3a-6a, 7	3b-6b, 8	3c-6c, 9	3d-6d, 10	5e
R^1					

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

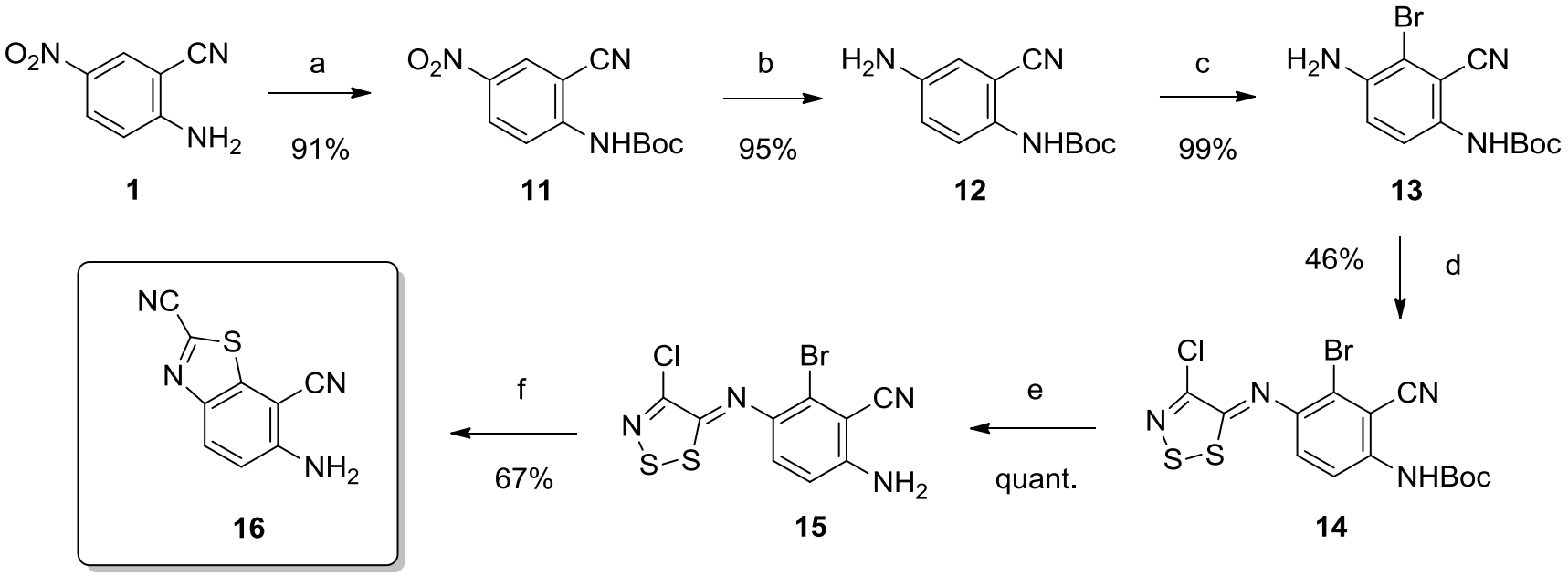
Multistep synthesis of polyfunctionalized benzothiazole 16.

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.

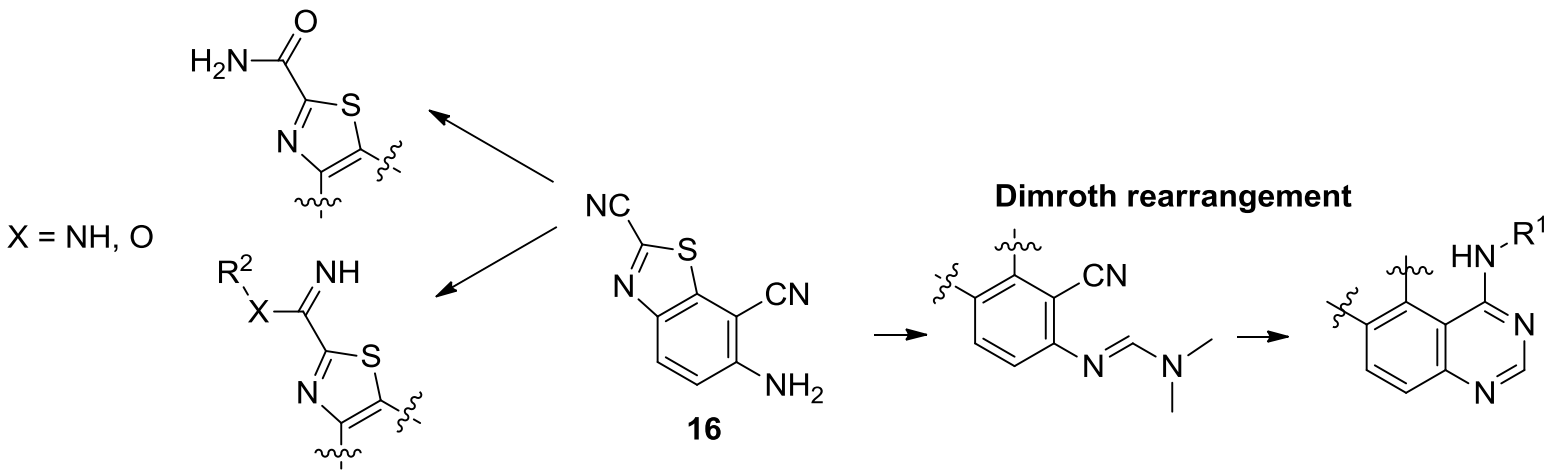
C) It implied synthesis of a versatile platform:



Reagents and conditions: (a) Boc_2O, DMAP, Et_3N, CH_2Cl_2, r.t., 4 h; (b), HCO_2NH_4, Pd.C, EtOH, 78 °C (μw), 30 min; (c) Br_2, AcOH, CH_2Cl_2, r.t., 2.5 h; (d) Appel salt, Py. (2 eq), CH_2Cl_2, r.t., 4 h; (e) AcOH, 118 °C (μw), 2 h; (f) CuI, Py., 130 °C (μw), 20 min.

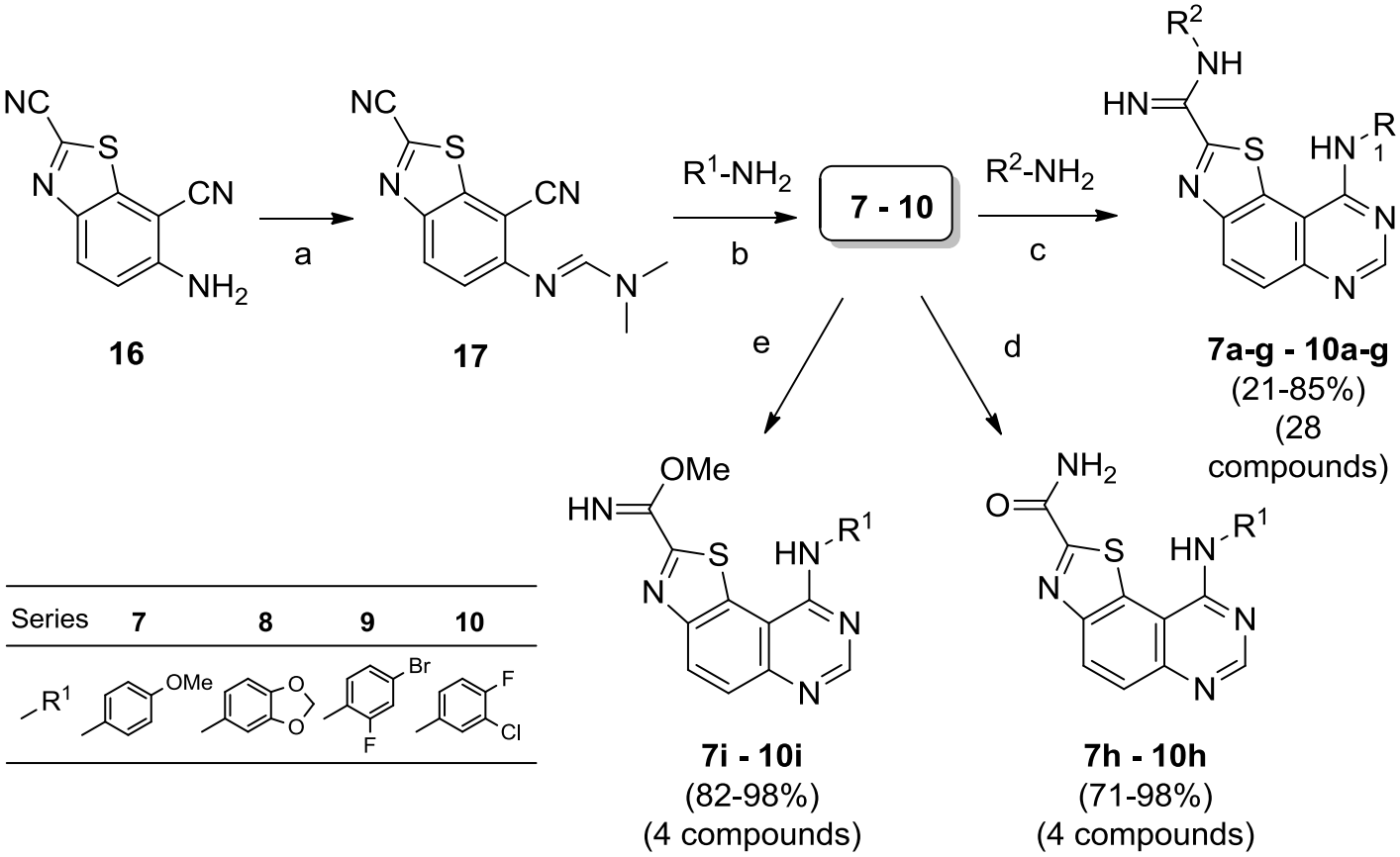
This molecular system was designed as an efficient precursor of various target molecules.

Possible transformations of benzothiazole **16** as a versatile molecular platform.



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) $NaOH_{aq}$ (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)

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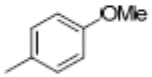
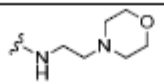
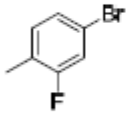
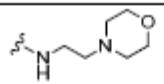
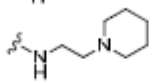
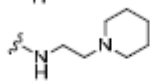
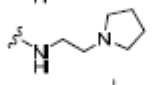
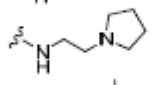
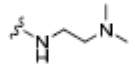
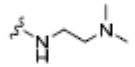
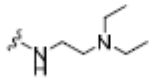
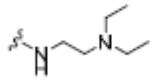
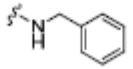
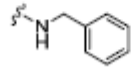
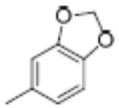
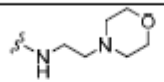
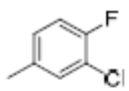
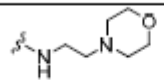
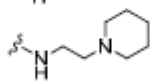
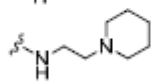
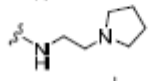
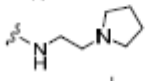
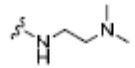
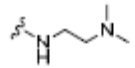
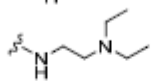
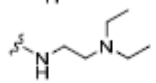
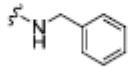
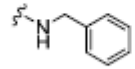
		7a	41			9a	85
		7b	43			9b	72
		7c	47			9c	68
		7d	53			9d	64
		7e	50			9e	86
		7f	28			9f	68
		7g	67			9g	40
R1	R2	Compound	Yield [a] (%)	R1	R2	Compound	Yield [a] (%)
		8a	41			10a	71
		8b	34			10b	82
		8c	48			10c	69
		8d	30			10d	50
		8e	66			10e	50
		8f	21			10f	69
		8g	-[b]			10g	43

[a] Isolated yield; [b] Not prepared.

Kinase inhibitory activity [a,b,c] 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.

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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	-[d]	-	-	-	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 μM. 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 μM): DYRK1A: 0.029; CK1: 1.50; CDK5 and GSK3α/β: > 10 [27]; Leucettine L41 (IC_{50} in μM): 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.

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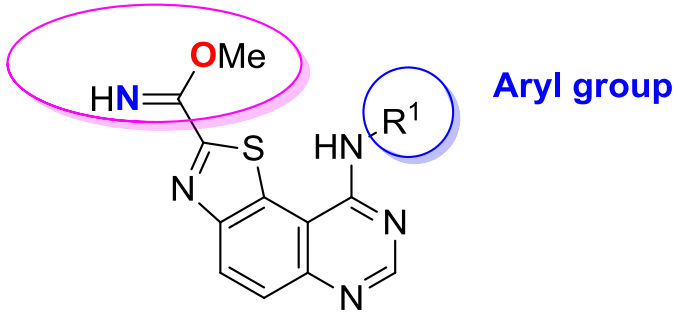
A methyl 9-(arylamino)thiazolo[5,4-*f*]quinazoline-2-carbimidate derivative library with highly potent DYRK1A/1B kinase inhibitory activities

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



Compound series **C**

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..

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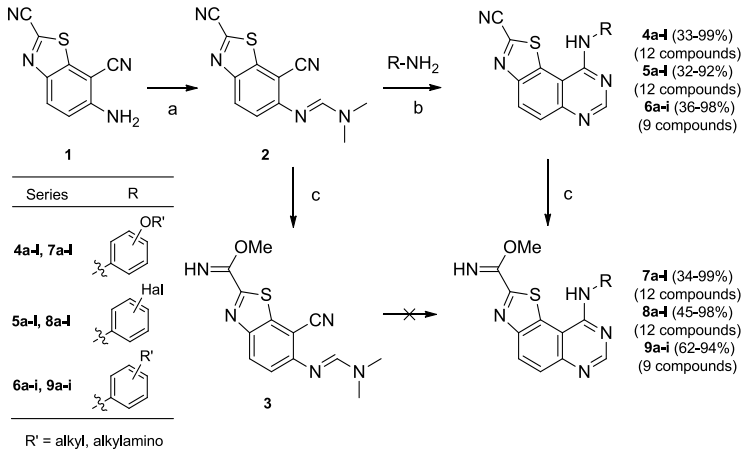
Amine (R-NH_2)	Compound	Yield (%) [a]	Time (min)	Compound	Yield (%) [a]
4-methoxyaniline	**4a**	99	2	**7a**	82
3,4-(methylenedioxy)aniline	**4b**	95	45	**7b**	92
1,4-benzodioxan-6-amine	**4c**	33	15	**7c**	80
2,3-dihydro-1-benzofuran-5-amine	**4d**	95	5	**7d**	66
3,4-dimethoxyaniline	**4e**	74	15	**7e**	89
2,4-dimethoxyaniline	**4f**	59	2	**7f**	71
3,5-dimethoxyaniline	**4g**	98	7	**7g**	58
3-nitro-4-methoxyaniline	**4h**	61	20	**7h**	59
4-aminophenol	**4i**	80	5	**7i**	81
5-amino-2-methoxyphenol	**4j**	54	5	**7j**	99
4-amino-2-nitrophenol	**4k**	60	15	**7k**	34
3,4,5-trimethoxyaniline	**4l**	85	5	**7l**	94
4-chloroaniline	**5a**	89	10	**8a**	62
3-chloroaniline	**5b**	74	20	**8b**	78
2,4-dichloroaniline	**5c**	32	50	**8c**	81
3,4-dichloroaniline	**5d**	42	20	**8d**	45
4-fluoroaniline	**5e**	92	5	**8e**	77
4-bromo-2-fluoroaniline	**5f**	78	30	**8f**	94
3-chloro-4-fluoroaniline	**5g**	82	10	**8g**	98
4-chloro-2-fluoroaniline	**5h**	56	20	**8h**	58
2-fluoro-4-methoxyaniline	**5i**	85	5	**8i**	82
4-amino-2-fluorophenol	**5j**	58	10	**8j**	70
2,4-difluoroaniline	**5k**	68	15	**8k**	71
4-aminobenzotrifluoride	**5l**	61	15	**8l**	53
aniline	**6a**	67	5	**9a**	52
4-toluidine	**6b**	64	2	**9b**	88
4-*tert*-butylaniline	**6c**	99	5	**9c**	69
3-ethynylaniline	**6d**	84	15	**9d**	68
4-aminobenzonitrile	**6e**	36	20	**9e**	52
3-aminobenzonitrile	**6f**	80	10	**9f**	33
6-aminobenzimidazole	**6g**	98	10	**9g**	57
N,N-dimethyl-*p*-phenylene-diamine	**6h**	25	15	**9h**	94
4-(pyrrolidin-1-yl)aniline	**6i**	48	5	**9i**	75

[a] Isolated yields.

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.

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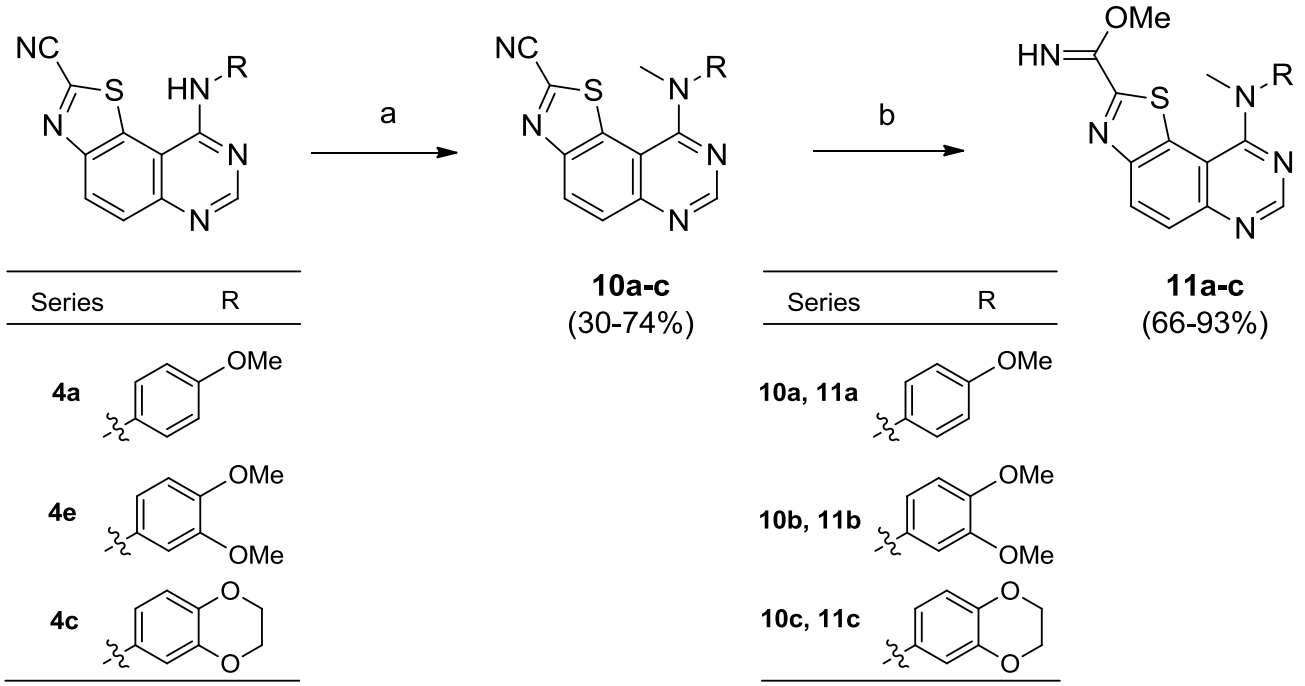
Synthesis of ^{9}N-methylated derivatives of **7a**, **7c** and **7e**.



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**).

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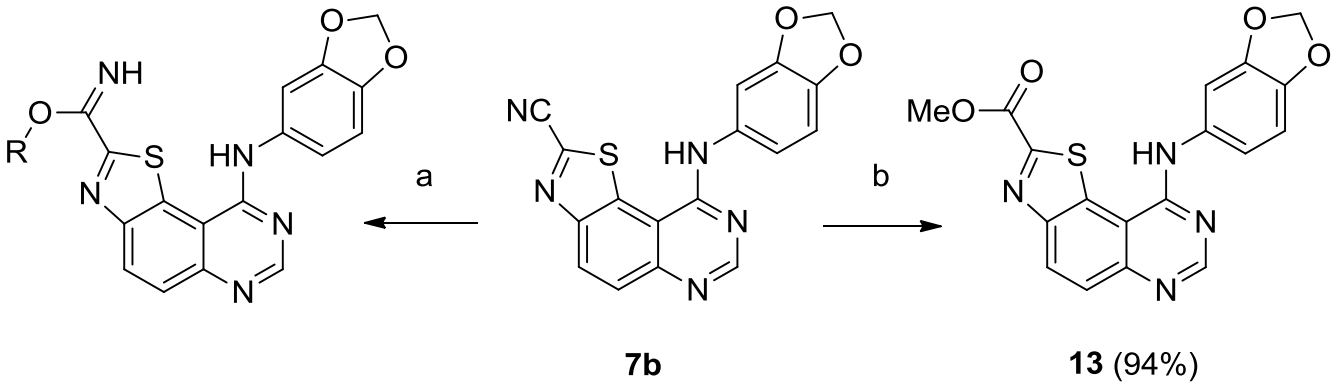
Synthesis of ethyl, isopropyl and benzyl carbimidates **12a–c** and methyl carboxylate **13** from carbonitrile **7b**.

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-H_2O/TFA (0.1%) (6:4, v/v), r.t., 12 h.

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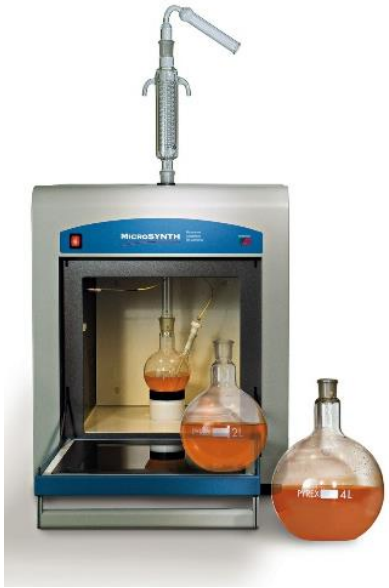
Note concerning microwave-assisted methods used in this work

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.



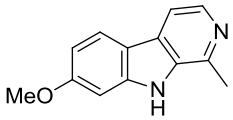
Our choice was also guided by the tendency of pressure to accumulate when a product as DMF/DMA was heated into pressurized vials, especially under microwaves.

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.

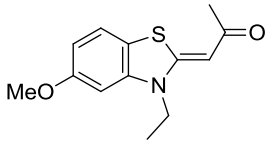
Amine in Position 9 (R-NH_2)	Compound	DYRK1A IC_{50} (nM)	DYRK1B IC_{50} (nM)
4-methoxyaniline	**7a**	13.08 [c]	19.22
3,4-(methylenedioxy)aniline	**7b**	1.65 [c]	4.20
1,4-benzodioxan-6-amine	**7c**	8.00	17.60
2,3-dihydro-1-benzofuran-5-amine	**7d**	$1 < IC_{50} < 1000$	- [b]
3,4-dimethoxyaniline	**7e**	128.80	160.6
2,4-dimethoxyaniline	**7f**	9.53	11.13
3,5-dimethoxyaniline	**7g**	298.90	530.90
3-nitro-4-methoxyaniline	**7h**	123.50	599.80
4-aminophenol	**7i**	$1 < IC_{50} < 1000$	- [b]
5-amino-2-methoxyphenol	**7j**	$1 < IC_{50} < 1000$	- [b]
4-amino-2-nitrophenol	**7k**	4.91	5.68
3,4,5-trimethoxyaniline	**7l**	436.10	485.80
4-chloroaniline	**8a**	1.13	4.74
3-chloroaniline	**8b**	13.64	18.78
2,4-dichloroaniline	**8c** (EHT 5372)	0.22	0.28
3,4-dichloroaniline	**8d**	66.82	99.34
4-fluoroaniline	**8e**	6.06	9.64
4-bromo-2-fluoroaniline	**8f**	3.6 [c]	6.55
3-chloro-4-fluoroaniline	**8g**	$1 < IC_{50} < 1000$	- [b]
4-chloro-2-fluoroaniline	**8h** (EHT 6840)	0.99	1.63
2-fluoro-4-methoxyaniline	**8i** (EHT 1610)	0.36	0.59
4-amino-2-fluorophenol	**8j**	8.63	11.00
2,4-difluoroaniline	**8k** (EHT 9851)	0.94	1.07
4-aminobenzotrifluoride	**8l**	54.84	186.40
aniline	**9a**	1.81	3.48
4-toluidine	**9b** (EHT 3356)	0.98	2.83
4-*tert*-butylaniline	**9c**	39.03	93.84
3-ethynylaniline	**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-yl)aniline	**9i**	n.t.[d]	n.t.
4-methoxyaniline	**11a**	79.85	84.94
3,4-dimethoxyaniline	**11b**	3768.00	4458.00
1,4-benzodioxan-6-amine	**11c**	$1 < IC_{50} < 1000$	- [b]
3,4-(methylenedioxy)aniline	**12a**	6.02	7.72
3,4-(methylenedioxy)aniline	**12b**	124.7	217.80
3,4-(methylenedioxy)aniline	**12c**	33.93	37.34
3,4-(methylenedioxy)aniline	**13**	$1 < IC_{50} < 1000$	- [b]
harmine		21.83	27.87
TG003		24.01	34.39
NCGC-00189310		2.20	20.57
leucettine L41		7.60	37.00

[a] IC_{50} values are reported in nM. The most significant results are presented in bold; [b] Not determined; [c] Compared to our previous studies (see data given in Scheme 1 for **7a**, **7b** and **8f**) the Reaction Biology Corporation DYRK1A kinase assay was about ten times more sensitive and new values given for these three compounds were found closer to the nanomolar range; [d] Not tested.

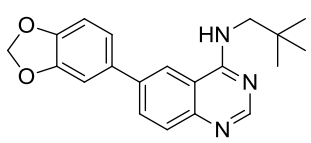
DYRK1A and DYRK1B kinase inhibitory activity of the four methyl thiazolo[5,4-*f*]quinazoline carbimidate series (**7**, **8**, **9**, and **11**); ethyl, isopropyl and benzyl carbimidates (**12a–c**) and methyl carboxylate (**13**).



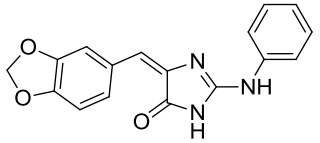
Harmine



TG003



NCGC-00189310

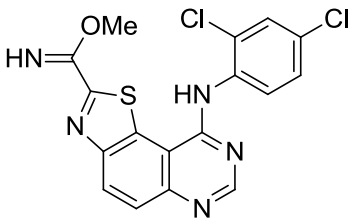


Leucettine L41

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

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

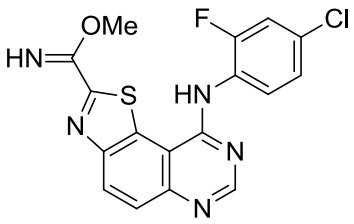
Structures and DYRK1A/1B IC_{50} values of the five lead compounds identified in this study.



EHT 5372 (**8c**)

CLogP: 4.56

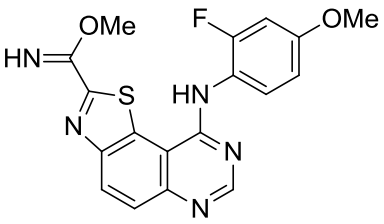
DYRK1A IC50 = 0.22 nM
DYRK1B IC50 = 0.28 nM



EHT 6840 (**8h**)

CLogP: 3.99

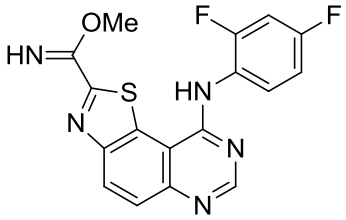
DYRK1A IC50 = 0.99 nM
DYRK1B IC50 = 1.63 nM



EHT 1610 (**8i**)

CLogP: 3.24

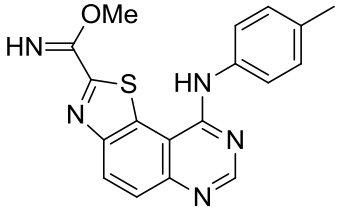
DYRK1A IC50 = 0.36 nM
DYRK1B IC50 = 0.59 nM



EHT 9851 (**8k**)

CLogP: 3.42

DYRK1A IC50 = 0.94 nM
DYRK1B IC50 = 1.07 nM



EHT 3356 (**9b**)

CLogP: 3.62

DYRK1A IC50 = 0.98 nM
DYRK1B IC50 = 2.83 nM

Foucourt A.; Hédou, D.; Dubouilh-Benard, C.; Girard, A.; Taverne, T.; Désiré, L.; Casagrande, A.-S.; Leblond, B.; Loaëc, N.; Meijer, L.; Besson, T.
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.

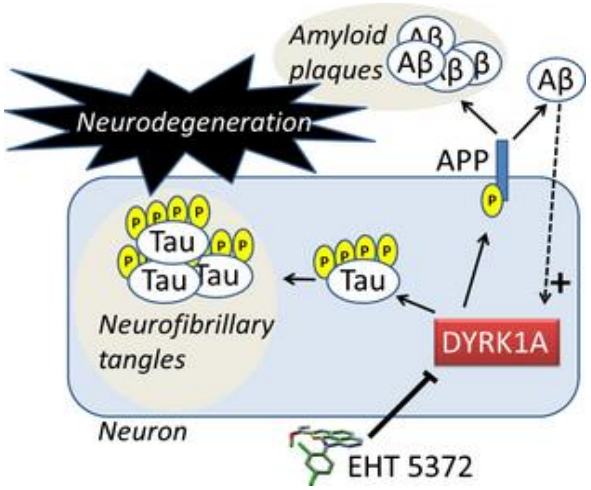
ClogP were calculated with Chemdraw V12.0.

In collaboration with:

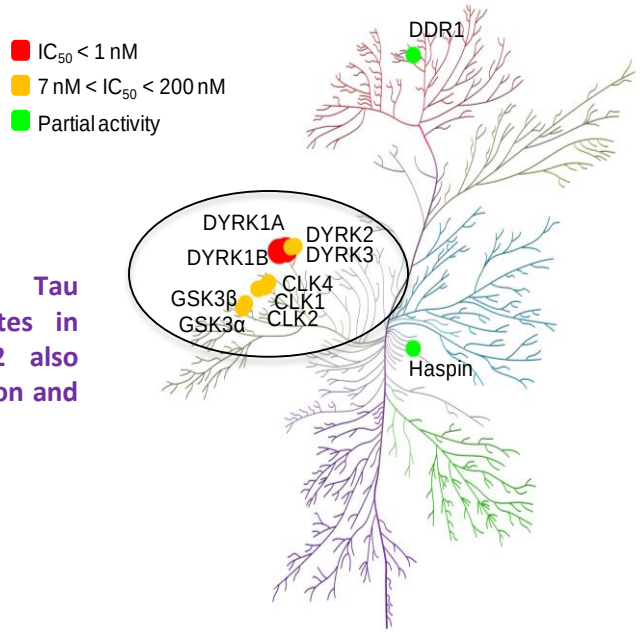
diaxonhit
Specialty Diagnostic Solutions

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
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.



The kinome activity map for EHT 5372 with identified hits highlighted

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 :

Dr Eileen FRIEDMAN
Department of Obstetrics and Gynecology, Upstate Medical University, Syracuse, N.Y., USA

Genes & Cancer, **2014**, *5*, 337
Genes & Cancer, **2014**, *5,* 201
Genes & Cancer, **2014**, *5*, 22
Int. J. Cancer **2013**, *132*, 2258
Cancers **2010**, *2*, 1492 .

Results concerning EHT 1610 and DYRK1A :

Prof John CRISPINO
Division of Hematology/Oncology,
Northwestern University, Chicago, IL, USA

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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