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Research article

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# Synthesis of New *N,N'*-Bis(5-arylidene-4-oxo-4,5-dihydrothiazolin-2-yl)piperazine Derivatives Under Microwave Irradiation and Preliminary Biological Evaluation

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## Abstract

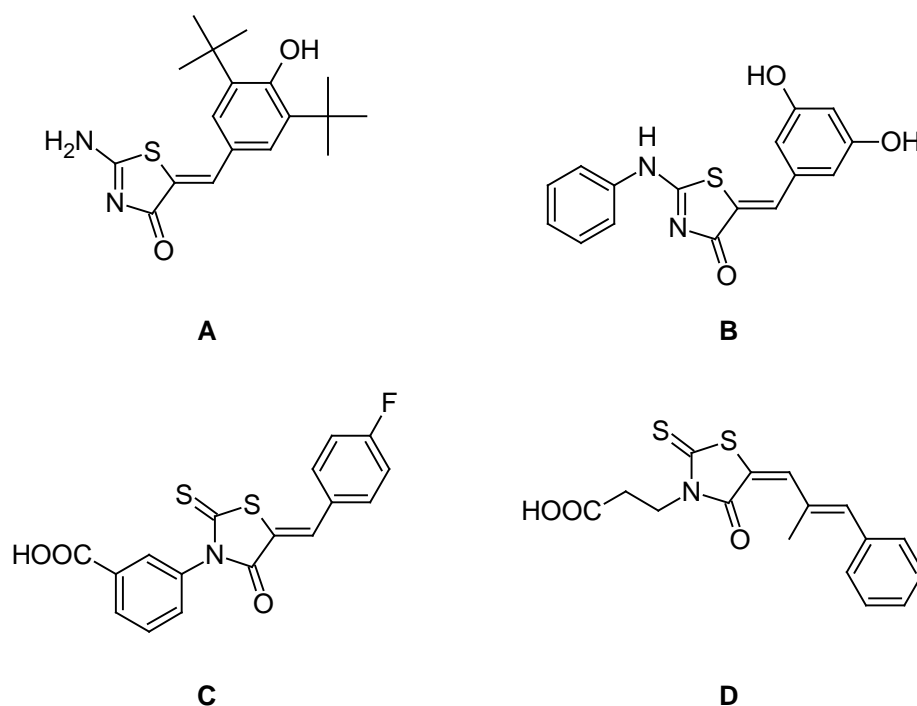
New *N,N'*-bis(5-arylidene-4-oxo-4,5-dihydrothiazoline-2-yl)diamine derivatives **5** were prepared in two steps from rhodanine and piperazine, or 1,4-bis(3-amino-propyl)piperazine, under microwave reaction conditions with retention of configuration. Some of these compounds were tested for *in vitro* antiproliferative activities and for their kinase inhibitory potencies towards six kinases (CDK5/p25, GSK3 $\alpha/\beta$ , DYRK1A, DYRK2, CLK1, and CLK2). The compound **5d** showed nanomolar activity towards DYRK1A kinase (IC<sub>50</sub> = 0.041  $\mu$ M).

## Keywords

5-Arylidene rhodanine • 2,2'-(Piperazine-1,4-diyl)bis(5-benzylidene-1,3-thiazol-4(5*H*)-one) • Microwave irradiation • Cytotoxicity • Protein kinase • Diamines

## Introduction

The 2-amino-5-arylidene-5*H*-thiazol-4-ones and their 5-arylidene rhodanine precursors are a class of five-membered heterocyclic rings (FMHRs) considered as "privileged scaffolds" in the medicinal chemistry community [1]. Considerable work has been published over decades about their chemistry and biology. A number of compounds containing the 2-amino-5-arylidene-5*H*-thiazol-4-one moiety have been shown to exhibit anti-inflammatory [2], antimicrobial [3], and antitumor [4] effects. Among these compounds, Darbufelone® **A** [5] (Figure 1) is orally active in animal models of inflammation [6] and DBPT **B** is under clinical trials for colon cancer [7]. 5-Arylidene rhodanines have also proven to be attractive for the discovery of new candidates. A series of rhodanine-based hits **C** (Figure 1) were found as potent and selective inhibitors of the "atypical" dual-specificity phosphatase (DSP) family member-JNK-stimulating phosphatase-1 (JSP-1). Compounds of this class may be useful for the treatment of inflammatory and proliferative disorders [8]. As the last example, epalrestat **D** reduced the symptoms of diabetic neuropathy [9].



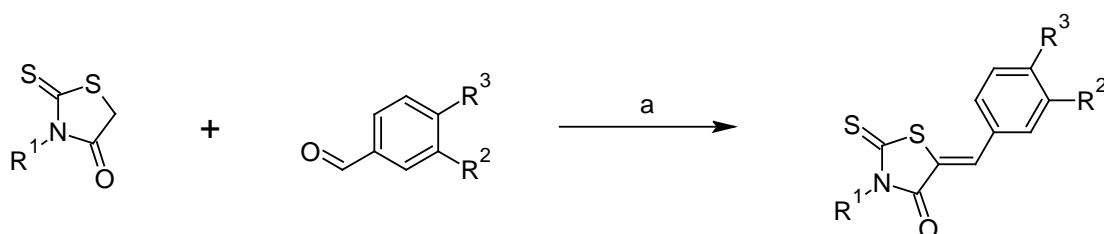
**Fig. 1.** Structures of Darbufelone (**A**), DBPT (**B**), inhibitor of DSP (**C**), and epalrestat (**D**).

Protein kinases are the enzymes which control the phosphorylation of protein in cellular life [10] which is frequently deregulated in human diseases. For the pharmaceutical industry, the protein kinases represent interesting targets for new therapeutic agents [11] and this interest was boosted by the approval of the first marketed inhibitor Gleevec™ used in myeloid leukemia [12]. Due to the biological activity associated with the 2-amino-thiazolidinone moiety, we decided in this paper to explore the synthesis of *N,N'*-bis(5-arylidene-4-oxo-4,5-dihydrothiazolidin-2-yl)diamines derived from piperazine or 1,4-bis(3-aminopropyl)piperazine as linkers, and to study their effects on cells and protein kinases.

## Results and Discussion

### Chemistry

The strategy used for the synthesis of the symmetric derivatives **5** is outlined in Scheme 1. The reactions have been realized under microwave irradiation [13]. The main benefits of microwave irradiation technology are the significant rate-enhancements and sometimes elevated product yields enabling the rapid synthesis of molecules of potential value in medicinal chemistry [14]. The synthesis started by the solution-phase Knoevenagel condensation of aryl aldehydes **2** and commercial rhodanine **1a**. The expected compounds **3a–c** were prepared in yields ranging from 65 to 88% with a reaction time of 10 min. under microwave irradiation (MWI) at 65°C in the presence of sodium acetate. In a similar approach, the 5-arylidene rhodanine propanoic derivatives **3d–g** were easily synthesized using solvent-less reaction conditions under microwave irradiation (130°C, 10 min.). The geometric double bond of **3** was attributed as being *Z* by the shielding effect of the carbonyl group C-4 on the olefinic proton H-5 ( $\delta$  7.5 ppm) in the  $^1\text{H}$  NMR spectra.



**1a**  $R^1 = \text{H}$

**1b**  $R^1 = (\text{CH}_2)_2\text{CO}_2\text{H}$

**2a**  $R^2 = R^3 = \text{H}$

**2b**  $R^2 = \text{H}, R^3 = \text{MeO}$

**2c**  $R^2, R^3 = \text{OCH}_2\text{O}$

**2d**  $R^2, R^3 = \text{O}(\text{CH}_2)_2\text{O}$

**3a**  $R^1 = R^2 = R^3 = \text{H}$

**3b**  $R^1 = R^2 = \text{H}, R^3 = \text{MeO}$

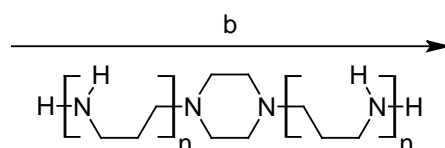
**3c**  $R^1 = \text{H}, R^2, R^3 = \text{OCH}_2\text{O}$

**3d**  $R^1 = (\text{CH}_2)_2\text{CO}_2\text{H}, R^2, R^3 = \text{H}$

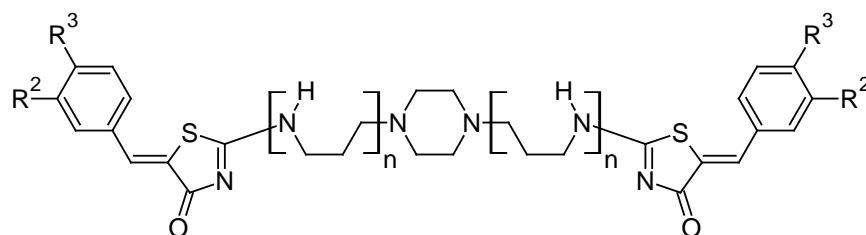
**3e**  $R^1 = (\text{CH}_2)_2\text{CO}_2\text{H}, R^2 = \text{H}, R^3 = \text{MeO}$

**3f**  $R^1 = (\text{CH}_2)_2\text{CO}_2\text{H}, R^2, R^3 = \text{OCH}_2\text{O}$

**3g**  $R^1 = (\text{CH}_2)_2\text{CO}_2\text{H}, R^2, R^3 = \text{O}(\text{CH}_2)_2\text{O}$



**4a**  $n = 0$ ; **4b**  $n = 1$



**5a**  $R^2 = R^3 = \text{H}, n = 0$

**5b**  $R^2 = \text{H}, R^3 = \text{MeO}, n = 0$

**5c**  $R^2, R^3 = \text{OCH}_2\text{O}, n = 0$

**5d**  $R^2 = \text{H}, R^3 = \text{MeO}, n = 1$

**5e**  $R^2, R^3 = \text{OCH}_2\text{O}, n = 1$

**Sch. 1.** a) for **3a–c**: MeOH, AcONa 3 eq., MWI, 65°C, 10 min. and for **3d–g**: MWI, 130°C, 10 min. b) MWI, 80–120°C, 30 min.

Transformation of 5-arylidene rhodanine **3** into 2-amino-5-arylidene-5*H*-thiazol-4-one after addition of a primary amine [15] usually involves activation of the C=S bond of rhodanine via the thioether intermediate that subsequently undergoes a thioalkyl/nitrogen displacement. In order to be able to carry out such sulfur/nitrogen displacement in a faster and more efficient way – avoiding the preparation of the thioether intermediate – we examined the influence of microwave irradiation on the reaction between compound **3** and the symmetric diamino linkers **4a,b**. The experiments revealed that optimal reaction conditions were obtained at 80–120°C after 30 minutes. It is noteworthy that sulfur/nitrogen displacement reactions at 120°C under microwave irradiation have been realized in solution with hexane to avoid decomposition of compound **5**. The desired compounds **5a–e** were prepared in poor to moderate yields (13–26%) and their structures were substantiated by <sup>1</sup>H, <sup>13</sup>C NMR, and HRMS analyses and only the more thermodynamically stable *Z*-isomers were obtained.

### Biology

To evaluate the potency of the compounds **3a–c**, **5a**, and **5c** for their *in vitro* antiproliferative activities, we used six representative tumor cell lines of liver (Huh7), colon (Caco2, HCT 116), breast (MDA-MB 231), prostate (PC3), lung (NCI), and one normal cell line (fibroblats) and measured survival. Results are reported in Table 1. The 5-arylidene rhodanines **3a–c** and two compounds **5a** and **5c** showed measurable, albeit very poor, cytotoxic activity. No clear tendency for higher activity of these compounds can be deduced from these results. Since the log P values of all tested compounds are in the same range, influences of lipophilicity on cytotoxic activity cannot be deduced as well.

**Tab. 1.** Cell effects of the products and calculated partition coefficients log P (calculated with Chem Draw Pro, Cambridge Soft)

Cpd.	Cell lines IC <sub>50</sub> (μM)							Log P <sub>calc.</sub>
	Huh7	Caco2	MDA-MB 231	HCT 116	PC3	NCI	Fibroblats	
<b>3a</b>	> 25	> 25	> 25	> 25	> 25	> 25	> 25	2.0
<b>3b</b>	> 25	> 25	> 25	> 25	> 25	> 25	> 25	1.9
<b>3c</b>	> 25	> 25	> 25	> 25	> 25	> 25	> 25	1.8
<b>5a</b>	> 25	25	> 25	> 25	> 25	> 25	> 25	4.8
<b>5c</b>	> 25	20	> 25	> 25	40	> 25	40	5.3
Roscovitine	10	10	15	8	8	20	> 25	–
DMSO	> 25	> 25	> 25	> 25	> 25	> 25	> 25	–

The kinase inhibitory potencies of compounds **3a–c** and **5d** were evaluated as IC<sub>50</sub> values towards six protein kinases (CDK5/p25, GSK3α/β, DYRK1A, DYRK2, CLK1 and CLK2) and the results are reported in Table 2. The 5-arylidene rhodanines **3a,b** appeared to be inactive towards these six protein kinases, but interesting results were obtained with compounds **5d** and **3c**. The 1,4-bis[(5*Z*)-5-(4-methoxybenzylidene)methylene-4-oxo-4,5-dihydrothiazol-2-yl]piperazine **5b** and the 5-arylidene rhodanine **3c** are very active on DYRK1A [16] and a noteworthy IC<sub>50</sub> = 41 nM was measured for **5b**. The compound **5d** has also shown submicromolar inhibition potencies towards DYRK2 (IC<sub>50</sub> = 0.6 μM) and CLK1 (IC<sub>50</sub> = 0.5 μM). Regarding these results, the potential of the (5*Z*) 5-arylidene-4-oxo-4,5-

dihydro-thiazolidine-2-yl moiety appended on 1,4-bis(3-aminopropyl)piperazine **4b** as a linker could be highly interesting in the development of a new class of inhibitors of DYRK1A kinase which is known to be involved in Alzheimer's disease/Down syndrome [17].

**Tab. 2.** CDK5/p25, GSK3 $\alpha/\beta$ , DYRK1A, DYRK2, CLK1, CLK3 inhibitions.

Cpd.	IC <sub>50</sub> ( $\mu$ M)					
	CDK5/p25	GSK3 $\alpha/\beta$	DYRK1A	DYRK2	CLK1	CLK2
<b>3a</b>	> 10	> 10	> 10	> 10	> 10	> 10
<b>3b</b>	> 10	> 10	> 10	> 10	> 10	> 10
<b>3c</b>	> 10	8.5	0.070	–	–	–
<b>5d</b>	> 10	> 10	0.041	0.6	0.5	7.7

## Conclusion

In conclusion, we worked out a short and practical synthesis under microwave irradiation of *N,N'*-(5-arylidene-4-oxo-4,5-dihydrothiazolidin-2-yl)diamines **5a–e** derived from piperazine **4a** [18, 19] and 1,4-bis(3-aminopropyl)piperazine **4b**. The *in vitro* anti-proliferative activities are extremely weak and this could be due to a lower cellular penetration of compounds **3** and **5** or a lower interaction with the cellular targets. Surprisingly, the compound **5d** has shown nanomolar inhibition potency towards DYRK1A and this interesting inhibition led us to expand our efforts in the synthesis of diversely disubstituted *N,N'*-bispiperazine derivatives with the 5-arylidene thiazolidinone moiety as new potential inhibitors of this kinase. Work is in progress to gain deeper insight into the structure-activity relationships (SAR) of this new interesting class of diamines.

## Experimental

### General

Elemental analysis: Flash EA1112 CHN/O Thermo Electron; HRMS (MS/MS ZABSpec ToF Micromass, EBE TOF geometry, IP 8 eV); NMR: BRUKER AC 300P (<sup>1</sup>H: 300 MHz, <sup>13</sup>C: 75 MHz); melting points: Leica System Kofler VMHB Melting Point apparatus (not corrected); microwave reactor: Monowave 300 Anton-Paar (850 W), monowave software package.

### General procedure I: Preparation of 5-arylidene-2-thioxo-thiazolidine-4-one **3a–c** under microwave irradiation.

A mixture of rhodanine **1a** (1 g, 7.5 mmol), aldehyde **2** (8.95–9 mmol), sodium acetate (1.85 g, 22.55 mmol), and methanol (5 ml) was placed in a borosilicate glass vial (10 ml) with a Teflon® magnetic stir bar and sealed with a snap cap. The glass tube was then introduced into the Monowave 300 Anton-Paar microwave cavity (P = 850 Watt) and the stirred mixture was irradiated at 65°C (with a power of 10 Watt) for 30 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down to room temperature, and then was filtered on a Buchner funnel and the insoluble compound **3** was washed with methanol (2x5 ml). The crude compound **3** was purified by recrystallization

from methanol and further dried under high vacuum ( $10^{-2}$  Torr) for 1 hour, which gave the desired compound **3** as a powder.

**General procedure II: Preparation of 3-(5-arylidene-4-oxo-2-thioxo-thiazolidine-3-yl)propanoic acid 3d–g under solvent-free microwave irradiation.**

A mixture of rhodanine **1b** (0.5 g, 2.44 mmol) and aldehyde **2** (2.44 mmol) was placed in a borosilicate glass vial (10 ml) with a Teflon® magnetic stir bar and sealed with a snap cap. The glass tube was then introduced into the Monowave 300 Anton-Paar microwave cavity ( $P = 850$  Watt) and the stirred mixture was irradiated at  $130^{\circ}\text{C}$  for 10 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down to room temperature and 5 ml of a mixture of ethanol/hexane (1:1) were added directly to the glass vial. The resulting precipitated product **3** was filtered on a Buchner funnel and the insoluble compound **3** was washed with the same mixture (2x5 ml). The crude compound **3** was further dried under high vacuum ( $10^{-2}$  Torr) for 1 hour, which gave the desired compound **3** as a powder.

**General procedure III: Synthesis of N,N'-bis(5-arylidene-4-oxo-4,5-dihydro-thiazolidine-2-yl)piperazine derivatives 5a-e under microwave irradiation.**

A mixture of 5-arylidene-2-thioxo-thiazolidine-4-one **3** (4 mmol), piperazine **4a** (172 mg, 2 mmol) or 1,4-bis(3-aminopropyl)piperazine **4b** (400 mg, 2 mmol) was placed in a borosilicate glass vial (10 ml) with a Teflon® magnetic stir bar and sealed with a snap cap. The glass tube was then introduced into the Monowave 300 Anton-Paar microwave cavity ( $P = 850$  Watt) and the stirred mixture was irradiated at  $80$ – $120^{\circ}\text{C}$  (with a power of  $5$ – $200$  Watt) for 30 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down to room temperature and 10 ml of cooled ethanol ( $4^{\circ}\text{C}$ ) were added directly in the glass vial. The resulting precipitated product **5** was filtered off, washed with 2 x 5 ml of ethanol and dried under high vacuum ( $10^{-2}$  Torr) at room temperature for 1 hour. After  $^1\text{H}$  NMR analysis, the product **5** was purified by recrystallization from methanol, which gave the desired compound **3** as a powder.

**(5Z)-5-Benzylidene-2-thioxo-1,3-thiazolidin-4-one (3a)**

Prepared following General procedure I from benzaldehyde **2a** (0.95 g, 8.95 mmol) to give 1.08 g (65%) as an orange powder.  $\text{Mp} = 208$ – $210^{\circ}\text{C}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) = 7.44–7.55 (m, 5H, Ar), 7.57 (s, 1H, =CH), 13.12 (br s, 1H, NH).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) = 126.88 (C-1), 129.20 (C-2), 130.30 (C-3), 130.37 (C-4), 130.45 (C=, C-5), 133.22 (=CH), 171.28 (C=S, C-2); 196.64 (C=O, C-4). HRMS,  $m/z = 243.9868$  found (calculated for  $\text{C}_{10}\text{H}_7\text{NONaS}_2$ ,  $[\text{M}+\text{Na}]^+$  requires 243.9867). Anal. Calcd. for  $\text{C}_{10}\text{H}_7\text{NOS}_2$ : C, 54.27; H, 3.19. Found: C, 54.23; H, 3.16.

**(5Z)-5-(4-Methoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-one (3b)**

Prepared following General procedure I from 4-methoxybenzaldehyde **2b** (1.23 g, 9 mmol) to give 1.36 g (74%) as an orange powder.  $\text{Mp} = 250$ – $252^{\circ}\text{C}$ .  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) = 3.82 (s, 3H,  $\text{OCH}_3$ ), 7.10 (d,  $J = 8.8$  Hz, 2H, H-3, Ar), 7.55 (d,  $J = 9.1$  Hz, 2H, H-2, Ar), 7.57 (s, 1H; =CH), 13.76 (br s, 1H, NH).  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) = 55.45 ( $\text{OCH}_3$ ), 114.92 (C-3'), 124.90 (C=, C-5), 126.02 (C-1'), 129.71 (=CH), 132.28 (C-2'), 160.82 (C-4'), 173.024 (C=S, C-2), 197.25 (C=O, C-4). HRMS,  $m/z = 295.9792$  found

(calculated for  $C_{11}H_9NO_2Na_2S_2$ ,  $[M-H+2Na]^+$  requires 295.9792). Anal. Calcd. for  $C_{11}H_9NO_2S_2$ : C, 52.57; H, 3.61. Found: C, 52.65; H, 3.67.

**(5Z)-5-(1,3-Benzodioxol-5-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one (3c)**

Prepared following General procedure I from piperonaldehyde **2c** (1.35 g, 9 mmol) to give 1.74 g (88%) as an orange powder. Mp > 260°C.  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 6.13 (s, 2H; OCH<sub>2</sub>O), 7.11–7.45 (m, 3H; H-5', H-6', Ar), 7.52 (s, 1H, =CH), 7.55 (s, 1H, H-2'; Ar), 13.74 (br s, 1H, NH).  $^{13}C$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 102.10 (OCH<sub>2</sub>O), 109.26 (C=, C-5), 109.45 (C-6'), 123.02 (C-1'), 126.65 (C-5'), 127.16 (=CH), 131.81 (C-2'), 148.27 (C-4'), 149.60 (C-3'), 169.58 (C=S, C-2), 195.51 (C=O, C-4). HRMS,  $m/z$  = 287.9765 found (calculated for  $C_{11}H_7NO_3Na_2S_2$ ,  $[M+Na]^+$  requires 287.9765). Anal. Calcd. for  $C_{11}H_7NO_3S_2$ : C, 49.80; H, 2.66. Found: C, 49.91; H, 2.69.

**3-[(5Z)-5-Benzylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]propanoic acid (3d)**

Prepared following General procedure II from benzaldehyde **2a** (0.256 g, 2.44 mmol) to give **3d** in 60% yield as a brown powder. Mp = 224–226°C.  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 2.33 (m, 2H, CH<sub>2</sub>), 4.15 (m, 2H, CH<sub>2</sub>), 7.51–7.65 (m, 5H, H-2, H-3, H-4, Ar), 7.80 (s, 1H, =CH), 13.16 (br s, 1H, OH).  $^{13}C$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 33.30 (CH<sub>2</sub>), 41.78 (CH<sub>2</sub>), 122.6 (C=, C-5), 129.46 (C-2'), 130.57 (C-3'), 130.84 (C-4'), 132.63 (=CH), 133.02 (C-1), 166.76 (C=O, C-4), 171.94 (CO<sub>2</sub>H), 193.15 (C=S, C-2). HRMS,  $m/z$  = 337.9904 found (calculated for  $C_{13}H_{10}NO_3Na_2S_2$ ,  $[M-H+2Na]^+$  requires 337.9898).

**3-[(5Z)-5-(4-Methoxybenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]propanoic acid (3e)**

Prepared following General procedure II from 4-methoxybenzaldehyde **2b** (0.332 g, 2.44 mmol) to give **3e** in 60% as a brown powder. Mp > 260°C.  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 2.24 (t, 2H, J = 8.2 Hz, CH<sub>2</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 4.12 (t, 2H, J = 8.2 Hz, CH<sub>2</sub>), 7.10 (d, 2H, J = 8.8 Hz, H-3, Ar), 7.64 (d, 2H, J = 8.8 Hz, H-2, Ar), 7.86 (s, 1H, =CH), 13.26 (br s, 1H, OH).  $^{13}C$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 34.11 (CH<sub>2</sub>), 42.20 (CH<sub>2</sub>), 55.56 (OCH<sub>3</sub>), 115.11 (C-3'), 119.26 (C=, C-5), 125.58 (C-1'); 129.90 (=CH), 132.84 (C-2'), 161.41 (C-4'), 166.86 (C=O, C-4), 171.98 (CO<sub>2</sub>H), 192.86 (C=S, C-2). HRMS,  $m/z$  = 346.0185 found (calculated for  $C_{14}H_{13}NO_4Na_2S_2$ ,  $[M+Na]^+$  requires 346.0184).

**3-[(5Z)-5-(1,3-Benzodioxol-5-ylmethylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]propanoic acid (3f)**

Prepared following General procedure II from piperonal **2c** (0.366 g, 2.44 mmol) to give **3f** in 63% as a brown powder. Mp = 220–224°C.  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 2.61 (t, 2H, J = 3.9 Hz, CH<sub>2</sub>), 4.21 (t, 2H, J = 4.7 Hz, CH<sub>2</sub>), 6.15 (s, 2H, OCH<sub>2</sub>O), 7.09–7.23 (m, 3H, H-2, H-5, H-6, Ar), 7.74 (s, 1H, =CH), 12.50 (br s, 1H, OH).  $^{13}C$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 30.74 (CH<sub>2</sub>), 40.30 (CH<sub>2</sub>), 102.21 (OCH<sub>2</sub>O), 109.35 (C-2'), 109.61 (C-5'), 119.71 (C=, C-5), 126.98 (C-6'), 127.14 (C-1'), 133.21 (=CH), 148.35 (C-4'), 149.88 (C-3'), 166.67 (C=O, C-4), 171.72 (CO<sub>2</sub>H), 192.97 (C=S, C-2). HRMS,  $m/z$  = 346.0185 found (calculated for  $C_{14}H_{13}NO_4Na_2S_2$ ,  $[M+Na]^+$  requires 346.0184).

**3-[(5Z)-5-(2,3-Dihydro-1,4-benzodioxin-6-ylmethylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]propanoic acid (3g)**

Prepared following General procedure II from 1,4-benzodioxane-6-carboxaldehyde (**2d**)



(0.401 g, 2.44 mmol) to give **3g** in 54% yield as a brown powder. Mp = 226–228°C.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 2.55 (t, 2H, J = 7.3 Hz, CH<sub>2</sub>), 4.18 (t, 2H, J = 7.4 Hz, CH<sub>2</sub>), 4.30 (m, 4H, OCH<sub>2</sub>CH<sub>2</sub>O), 7.02 (d, 1H, J = 8.6 Hz, H-5, Ar), 7.12 (d, 1H, J = 2.2 Hz, H-6, Ar), 7.15 (s, 1H, H-2, Ar), 7.70 (s, 1H; =CH), 12.46 (br s, 1H, OH).  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 31.30 (CH<sub>2</sub>), 40.30 (CH<sub>2</sub>), 64.01 (OCH<sub>2</sub>CH<sub>2</sub>O), 118.22 (C-2'), 119.47 (C-5'), 119.79 (C=, C-5), 124.46 (C-6'), 126.31 (C-1'), 132.96 (=CH), 143.82 (C-4'), 146.25 (C-3'); 166.67 (C=O, C-4), 171.80 (CO<sub>2</sub>H), 192.93 (C=S, C-2). HRMS,  $m/z$  = 374.0138 found (calculated for C<sub>15</sub>H<sub>13</sub>NO<sub>5</sub>NaS<sub>2</sub>, [M+Na]<sup>+</sup> requires 374.0133).

**(5Z,5'Z)-2,2'-(Piperazine-1,4-diyl)bis(5-benzylidene-1,3-thiazol-4(5H)-one)**  
**(1,4-Bis[(5Z)-5-benzylidene-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]piperazine, 5a)**

Prepared following General procedure III from 5-benzylidene-2-thioxothiazolidin-4-one (**3a**) (885 mg, 4 mmol) and piperazine **4a** (172 mg, 2 mmol) in hexane (2 ml) at 120°C to give **5a** in 13% yield as a brown powder. Mp > 260°C.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 3.34 (br s, 8H, N(CH<sub>2</sub>)<sub>4</sub>N), 7.28–7.7 (m, 12H, H-2', H-3', H-4', Ar, =CH).  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 42.45 (N(CH<sub>2</sub>)<sub>4</sub>N), 129.08 (C-2'), 129.16 (=CH), 129.22 (C=), 129.55 (C-3'), 129.82 (C-4'), 129.94 (C-1'); 130.41 (C=N), 159.56 (C=O). HRMS,  $m/z$  = 483.0918 found (calculated for C<sub>24</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>NaS<sub>2</sub>, [M+Na]<sup>+</sup> requires 483.0925). Anal. Calcd. for C<sub>24</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub>: C, 62.59; H, 4.38. Found: C, 62.56; H, 4.41.

**(5Z,5'Z)-2,2'-(Piperazine-1,4-diyl)bis[5-(4-methoxybenzylidene)-1,3-thiazol-4(5H)-one]**  
**(1,4-Bis[(5Z)-5-(4-methoxybenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]piperazine, 5b)**

Prepared following General procedure III from 5-(4-methoxybenzylidene)-2-thioxothiazolidin-4-one (**3b**) (1.005 g, 4 mmol) and piperazine **4a** (172 mg, 2 mmol) at 80°C to give **5b** in 36% yield as a yellow powder. Mp > 260°C.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 2.99 (s, 8H, N(CH<sub>2</sub>)<sub>4</sub>N), 3.79 (s, 6H, OCH<sub>3</sub>), 7.04 (d, J = 5 Hz, 4H, H-3', Ar), 7.16 (s, 2H, =CH), 7.43 (d, J = 8.7 Hz, 4H, H-2', Ar).  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 42.99 (N(CH<sub>2</sub>)<sub>4</sub>N), 55.27 (OCH<sub>3</sub>), 114.54 (C-3'), 114.73 (C-1'), 124.13 (=CH), 127.55 (C=, C-5), 131.29 (C-2'), 131.38 (C-4'), 132.14 (C=N, C-2), 159.56 (C=O, C-4). HRMS,  $m/z$  = 521.1317 found (calculated for C<sub>26</sub>H<sub>25</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>, [M+H]<sup>+</sup> requires 521.1310). Anal. Calcd. for C<sub>26</sub>H<sub>24</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>: C, 59.98; H, 4.65. Found: C, 59.87; H, 4.64.

**(5Z,5'Z)-2,2'-(Piperazine-1,4-diyl)bis[5-(1,3-benzodioxol-5-ylmethylene)-1,3-thiazol-4(5H)-one]**  
**(1,4-Bis[(5Z)-5-(1,3-benzodioxol-5-ylmethylene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]piperazine, 5c)**

Prepared following General procedure III from 5-(1,3-benzodioxol-5-ylmethylene)-2-thioxothiazolidin-4-one (**3c**) (1.061 g, 4 mmol) and piperazine **4a** (172 mg, 2 mmol) in hexane (2 ml) at 120°C to give **5a** in 15% yield as a brown powder. Mp > 260°C.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 3.02 (s, 8H, N(CH<sub>2</sub>)<sub>4</sub>N), 6.11 (s, 4H, OCH<sub>2</sub>O), 7.02–7.18 (m, 6H, H-2', H-5', H-6', Ar), 7.58 (s, 2H, =CH).  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  (ppm) = 52.72 (N(CH<sub>2</sub>)<sub>4</sub>N), 101.88 (OCH<sub>2</sub>O), 108.71 (C-2'), 125.13 (C-5'), 126.04 (C=, C-5), 127.86 (C-1'), 130.41 (C-6'), 144.21 (=CH), 146.02 (C=N, C-2), 148.11 (C-4'), 148.78 (C-3'), 182.22 (C=O, C-4). HRMS,  $m/z$  = 571.0726 found (calculated for C<sub>26</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub>NaS<sub>2</sub>, [M+Na]<sup>+</sup> requires 571.0722). Anal. Calcd. for C<sub>26</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub>: C, 56.92; H, 3.67. Found: C, 56.96; H, 3.71.

**(5*Z*,5'*Z*)-2,2'-[Piperazine-1,4-diylbis(propane-3,1-diylimino)]bis[5-(4-methoxybenzylidene)-1,3-thiazol-4(5*H*)-one]  
(1,4-Bis(3-[(5*Z*)-5-(4-methoxybenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino)propyl)piperazine, 5d)**

Prepared following General procedure III from 5-(4-methoxybenzylidene)-2-thioxothiazolidin-4-one (**3b**) (1.005 g, 4 mmol) and 1,4-bis(3-aminopropyl)piperazine (**4b**) (0.4 g, 2 mmol) in hexane (2 ml) at 120°C to give **5d** in 25% yield as a yellow powder. Mp = 220–222°C. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 1.68 (quint, *J* = 6.9 Hz, 4H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 2.37 (t, *J* = 6.7 Hz; 4H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 2.57 (s, 8H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 2.84 (t, *J* = 7.1 Hz, 4H; NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 3.79 (s, 6H, OCH<sub>3</sub>), 7.02 (d, *J* = 8.8 Hz, 4H, H-3', Ar), 7.18 (s, 2H; =CH), 7.44 (d, *J* = 8.8 Hz, 4H, H-2', Ar). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 23.39 (NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 37.41 (NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 52.03 (NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 54.42 (NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 55.27 (OCH<sub>3</sub>), 114.58 (C-3'), 125.04 (=CH), 127.28 (C-1'), 130.99 (C=), 131.44 (C-2'), 159.77 (C-4'), 201.61 (C=N, C-2), 206.74 (C=O, C-4). HRMS, *m/z* = 635.2396 found (calculated for C<sub>32</sub>H<sub>39</sub>N<sub>6</sub>O<sub>4</sub>S<sub>2</sub>, [M+H]<sup>+</sup> requires 635.1819). Anal. Calcd. for C<sub>32</sub>H<sub>38</sub>N<sub>6</sub>O<sub>4</sub>S<sub>2</sub>: C, 60.54; H, 6.03. Found: C, 60.57; H, 6.07.

**(5*Z*,5'*Z*)-2,2'-[Piperazine-1,4-diylbis(propane-3,1-diylimino)]bis[5-(1,3-benzodioxol-5-ylmethylene)-1,3-thiazol-4(5*H*)-one]  
(1,4-Bis(3-[(5*Z*)-5-(1,3-benzodioxol-5-ylmethylene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino)propyl)piperazine, 5e)**

Prepared following General procedure III from 5-(1,3-benzodioxol-5-ylmethylidene)-2-thioxothiazolidin-4-one (**3c**) (1.061 g, 4 mmol) and 1,4-bis(3-aminopropyl)piperazine (**4b**) (0.4 g, 2 mmol) in hexane (2 ml) at 120°C to give **5e** in 15% yield as a brown powder. Mp = 222–224°C. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 1.69 (quint, *J* = 6.9 Hz, 4H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 2.37 (t, *J* = 6.6 Hz, 4H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 2.37 (s, 8H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 2.83 (t, *J* = 7.1 Hz, 4H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 6.07 (s, 4H, OCH<sub>2</sub>O), 7.02 (m, 6H, H-2', H-5', H-6', Ar), 7.14 (s, 2H, =CH). <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) = 23.47 (NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 37.45 (NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 52.22 (NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 54.54 (NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>4</sub>N), 101.52 (OCH<sub>2</sub>O), 108.74 (C-2'), 108.82 (C-5'), 124.21 (C-6'), 124.84 (=CH), 147.72 (C-4'), 147.89 (C-3'), 182.66 (C=, C-5), 202.14 (C=N, C-2), 206.72 (C=O, C-4). HRMS, *m/z* = 663.1981 found (calculated for C<sub>32</sub>H<sub>35</sub>N<sub>6</sub>O<sub>6</sub>S<sub>2</sub>, [M+H]<sup>+</sup> requires 663.7790). Anal. Calcd. for C<sub>32</sub>H<sub>34</sub>N<sub>6</sub>O<sub>6</sub>S<sub>2</sub>: C, 57.99; H, 5.17. Found: C, 57.92; H, 5.16.

***In vitro* kinase inhibition assays**

*Buffer A*: 10 mM MgCl<sub>2</sub>, 1 mM EGTA, 1 mM DTT, 25 mM Tris-HCl pH 7.5, 50 µg heparin/ml. *Buffer C*: 60 mM β-glycerophosphate, 15 mM *p*-nitrophenylphosphate, 25 mM Mops (pH 7.2), 5 mM EGTA, 15 mM MgCl<sub>2</sub>, 1 mM DTT, 1 mM sodium vanadate, 1 mM phenylphosphate. Kinase activities were assayed in *Buffer A* or *C*, at 30°C, at a final ATP concentration of 15 µM. Blank values were subtracted and activities expressed in % of the maximal activity, i.e. in the absence of inhibitors. Controls were performed with appropriate dilutions of DMSO. The kinase peptide substrates were obtained from Millegen (Labege, France). *DYRK1A* and *DYRK2* (human, recombinant, expressed in *E. coli* as a GST fusion protein) were purified by affinity chromatography on glutathione-agarose and assayed in *buffer A* (+ 0.5 mg BSA /ml) using Woodtide (KKISGRLSPIMTEQ) (1.5 µg/assay) as a

substrate, in the presence of 15  $\mu\text{M}$  [ $\gamma$ - $^{33}\text{P}$ ] ATP (3,000 Ci/mmol; 10 mCi/ml) in a final volume of 30  $\mu\text{L}$ . After 30 min incubation at 30°C, the reaction was stopped by harvesting onto P81 phosphocellulose papers (Whatman) using a FilterMate harvester (Packard) and were washed in 1% phosphoric acid. Scintillation fluid was added and the radioactivity was measured in a Packard counter. *CLK1* and *CLK3* (human, recombinant, expressed in *E. coli* as GST fusion proteins) were assayed in buffer A (+ 0.15 mg BSA /ml) with RS peptide (GRSRSRSRSRSR) (1 $\mu\text{g}$ /assay). *CDK5/p25* (human, recombinant) was prepared as previously described [26]. Its kinase activity was assayed in buffer C, with 1  $\mu\text{g}$  histone H1 /ml. *GSK-3 $\alpha/\beta$*  (porcine brain, native) was assayed in Buffer A and using a GSK-3 specific substrate (GS-1: YRRAAVPPSPSLSRHSSPHQSpEDEEE) (pS stands for phosphorylated serine) [20].

### **Cell culture and survival assays**

Skin diploid fibroblastic cells were provided by BIOPREDIC International Company (Rennes, France). Caco-2 cells and Huh7 cells were obtained from the ECAC collection. Cells were grown according to ECAC recommendations. The RLEC-F1 clone was derived from an established rat biliary epithelial cell line as previously described [21]. The toxicity test of the compounds on these cells was as follows: 4 x 10<sup>3</sup> cells were seeded in 96 multiwell plates and left for 24 h for attachment, spreading, and growing. Then they were exposed for 48 h to increasing concentrations of the compounds, ranging from 0.1 to 25  $\mu\text{L}$  in a final volume of 80  $\mu\text{L}$  of culture medium. They were then fixed with 4% paraformaldehyde solution and the nuclei were stained with Hoechst 3342 and counted using automated imaging analysis (Simple PCI software).

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### **Authors' Statement**

#### **Competing Interests**

The authors declare no conflict of interest.

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