New 5-ylidene rhodanine derivatives based on the dispacamide A model.

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Abstract A practical approach for the preparation of (5*Z*) 5-ylidene rhodanine derivatives bearing the (4,5-dihalogeno-pyrrol-2-yl)carbamoyl fragment of dispacamide A is reported. The new compounds were obtained in good yields (19–88 %) by Knoevenagel condensation according to a solution-phase microwave dielectric heating protocol in the presence of organic bases (piperidine, TEA, and AcONa) from a set of *N*-substituted rhodanines **2**(**a**–**i**). The ten synthetic products **3**(**a**–**j**) have been synthesized with a *Z*-geometry about their exocyclic double bond and the structure of one of these compounds (**3**) was confirmed by a single X-ray diffraction analysis. The new (5*Z*) 5-ylidene rhodanine derivatives **3**(**a**–**j**) were tested against eight protein kinases.

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Introduction

During the two last decades, the 5-arylidene-2-thioxo-thiazolidine-4-ones and 5-arylidene rhodanine derivatives have been the subject of intensive research by organic chemists and biologists because such compounds represent privileged scaffolds in drug discovery. A survey of recent literature showed that these compounds display a wide range of pharmaceutical properties. For example, epalrestat **I** (Fig. 1) was used in the treatment of diabetic peripheral neuropathy [1] and has been evaluated as aldose reductase inhibitor [2]. The 5-benzylidene rhodanine core (compound **II**) has been shown to inhibit the pancreatic cholesterol esterase [3] (CEase). A series of dimeric analogs based on BH3I [4] have been developed as small-molecule Bcl-2 antagonists (compounds **III**) for apoptosis through a complete SAR study [5]. To discover chemical probes to further understand the function of human DNA polymerase λ in cancer by high-throughput screening (HTS) using SYBR Green-based assay [6] and three 5-arylidene-2-thioxo-thiazolidine-4-ones (compounds **IV**) were identified as potent inhibitors. For Alzheimer's disease, compounds containing the 5-arylidene rhodanine moiety are reported to have an inhibitory effect (compounds **V**) of tau aggregation [7], amyloid polypeptide fibril formation [8,9], regulation of cathepsin-D immunoreactivity (compound **VI**) in the senile plaques [10,11]. In addition, rhodanine-based molecules have become a popular small-molecule family of inhibitors for numerus targets in malaria [12,13], Hepatitis C [14], HIV infection [15,16],

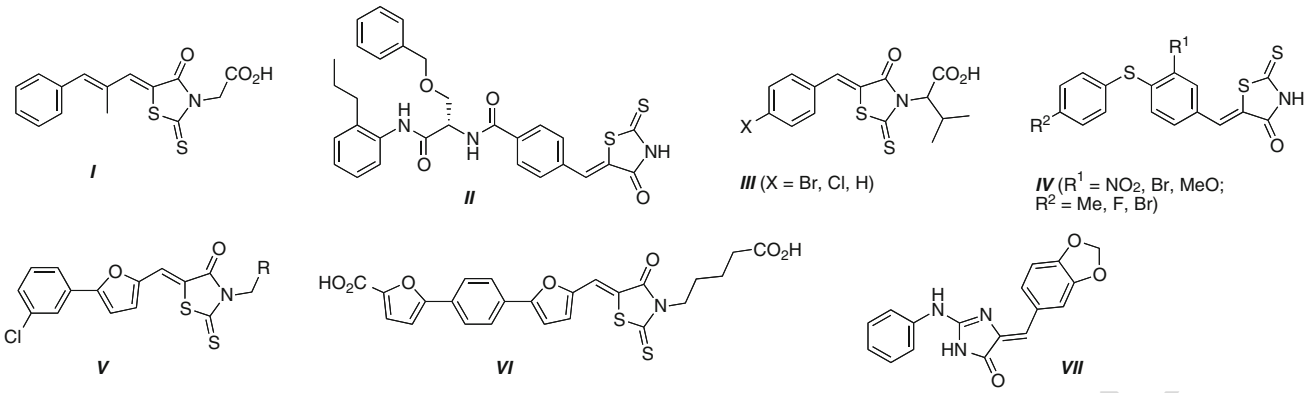


Fig. 1 Structures of some bioactive 5-arylidene rhodanine derivatives (**I**–**VI**) and leucettine L_{41} (**VII**)

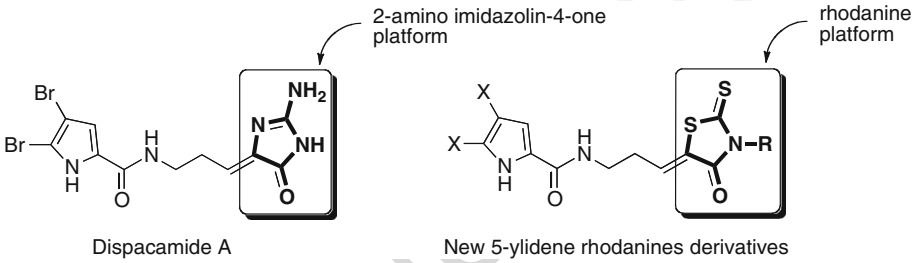


Fig. 2 *N*-3-substituted 5-ylidene rhodanine derivatives based on dispacamide A model

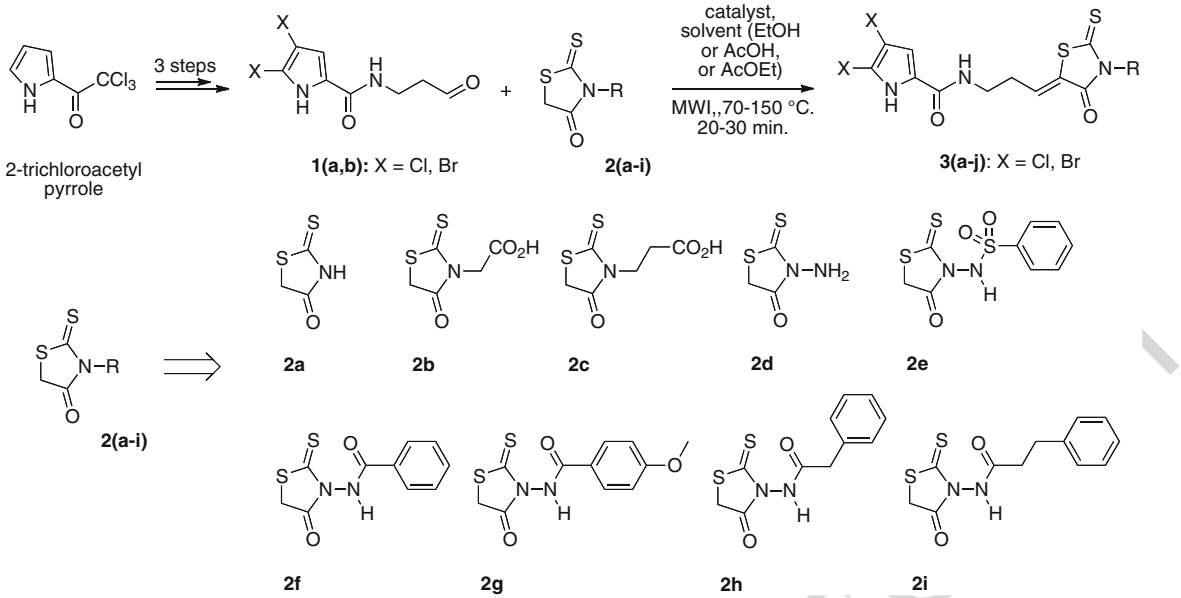
obstructive pulmonary disease and asthma [17], anthrax and botulinum [18].

Our group, during the last 10 years, has investigated the chemical development of analogs of marine sponge alkaloid as inhibitors of protein kinases. Protein kinases represented a class of enzymes, which catalyze protein phosphorylation, a key cellular regulatory mechanism that is frequently deregulated in human diseases. We have recently identified the marine sponge alkaloid leucettamine B as an inhibitor of DYRKs/CLKs [19,20]. The synthesis of analogs of leucettamine B named leucettines (leucettine L_{41} **VII**) and the biological characterization of leucettines [21] showed that this family of kinase inhibitors deserves futher optimization as potential therapeutics against neurodegenerative diseases such as Alzheimer's diseases [22,23]. In parallel, the 2-amino imidazoline-4-one moiety present in the marine sponge alkaloid dispacamide A (Fig. 1) [24] represented also an attractive scaffold for the search of potential new inhibitor of protein kinases. Recently, we have developed an efficient approach to dispacamide A and its analogs [25] in seven steps with an overall yield ranging from 12 to 33 %. Unfortunately, the preliminary biological screening results of these new dispacamide A derivatives [26] showed moderate inhibition activities against serine/threonine kinases. In our efforts to discover new low molecular weight inhibitors of disease-relevant protein kinases, we focused now our attention on the synthesis of *N*-3-substituted 5-ylidene rhodanine derivatives based on dispacamide A model (Fig. 2). In this context, the 2-amino-imidazoline-4-one platform of dispacamide A was replaced by a rhodanine platform.

In this approach, the planned retrosynthesis of these 5-ylidene rhodanine derivatives is based around the key aldol condensation between the *N*-(4,5-dihalogeno pyrrol-2-yl) carbamoyl aldehyde building-block and various 2-thioxo-thiazolidine-4-ones. This route was envisaged to be amenable to the design of new 5-ylidene rhodanine derivatives for their preliminary screening as kinase inhibitors. Our goal in this study is the development of a convenient, high yielding and robust reaction protocol for the preparation of new *N*-3-substituted 5-yliden-2-thioxo-thiazolidine-4-one derivatives.

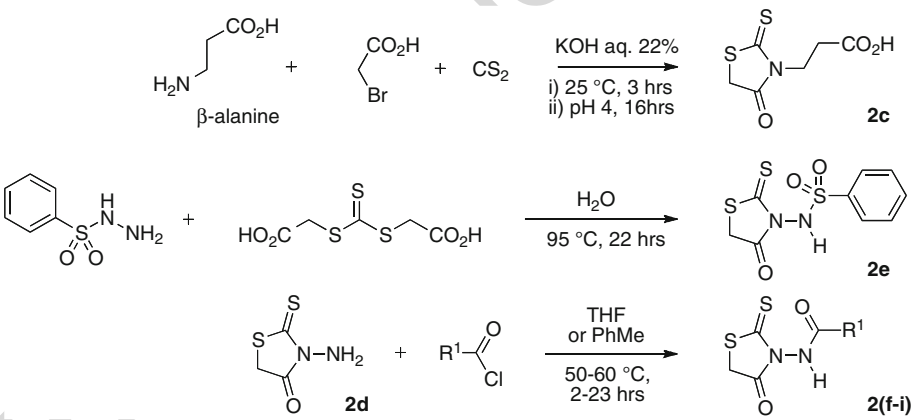
Results and discussion

The overall strategy to the target 5-ylidene *N*−substituted rhodanine derivatives is outlined in Scheme 1. For this study, we have examined the reactivity of various 2-thioxo-thiazolidine-4-ones **2**(**a**–**i**) with the *N*-(4,5-dihalogeno pyrrol-2-yl) carbamoyl aldehydes **1**(**a**,**b**) in Knœvenagel condensation under microwave dielectric heating. For the synthesis of small molecules with potential biological activity, the use of microwave irradiation is growing in importance [27,28] because the major benefits of performing reaction under microwave irradiation are higher product yields and shorter reaction times as compared to reactions which run with conventional heating (i.e., in oil bath). A key advan-



Scheme 1 General synthetic approach for 5-ylidene rhodanines derivatives **3**(**a**–**j**) and structure of the starting rhodanines **2**(**a**–**i**)

Scheme 2 Synthetic approach used for the preparation of *N*-substituted rhodanines **2c**, **2**(**e**–**i**)

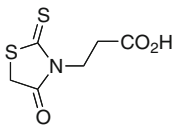
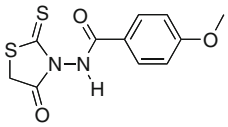
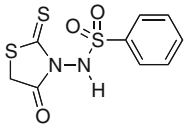
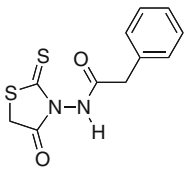
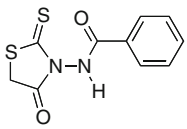
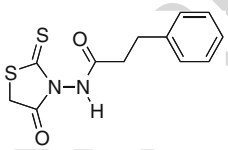


tage of modern commercial scientific laboratory microwave apparatus is their ability to control reaction conditions precisely, by monitoring temperature/pressure, and reaction times.

The *N*-(4,5-dihalogeno pyrrol-2-yl) carbamoyl aldehyde partners **1**(**a**,**b**) were prepared in three steps according to our previously published method [24]. Starting from commercial readily available 2-trichloroacetyl pyrrole, a regioselective halogenation was conducted by addition of bromine (X = Br) or sulfuryl chloride (X = Cl) to give the corresponding C-4, C-5 dihalogeno pyrroles (70–90 %), which were then coupled with 3,3-diethoxy-1-aminopropane (75–88 %). The corresponding *N*-(4,5-dihalogenopyrrol-2-yl) carbamoyl acetals were deprotected with p-TsOH at 55 °C after 6 h (98 %) and led to the aldehyde building-blocks **1**(**a**,**b**) in good overall yields (**1a** 60 % for X = Br; **1b** 66 % for X = Cl).

For the present study, we have investigated the chemical reactivity of a series of various *N*-substituted rhodanines **2**(**a**–**i**) for Knoevenagel condensation in the presence of aldehydes **1**(**a**,**b**). Among these compounds, rhodanine **2a**, 2-(4-*oxo*-2-thioxo-thiazolidin-3-yl)acetic acid **2b** and 3-amino rhodanine **2d** are commercially available. Access to 3-(4-*oxo*-2-thioxo-thiazolidin-3-yl)propanoic acid **2c** (Scheme 2) could be accomplished by the reaction of β-alanine with carbon disulfide and bromoacetic acid in aqueous potassium hydroxide [29]. After 3 h at room temperature, the reaction mixture was acidified at pH 4 and the desired insoluble compound **2c** was obtained in 44 % yield (Table 1) by simple filtration. To introduce the arylsulfonamide functionality on the rhodanine moiety in compound **2e**, we used the Power's approach [14]: firstly, the formation of the arylsulfonyl hydrazide was accomplished by treatment of sulfonyl chloride at 0 °C with hydrazine in THF followed by aqueous work-up and, secondly, the arylsulfonyl hydrazide treated with *bis*-(carbomethyl)trithiocarbonate [30,31] in water at 95 °C for 22 h produced 3-(arylsulfonylamino)rhodanine **2e** in 41 % yield after purification by crystallization from ethanol.

Table 1 Results for the preparation of *N*-substituted rhodanines **2c**, **2(e–i)**

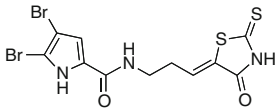
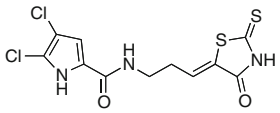
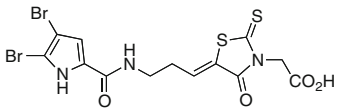
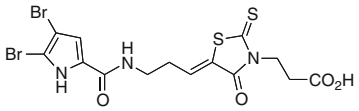
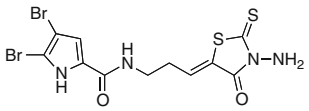
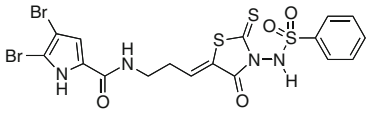
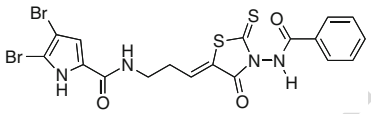
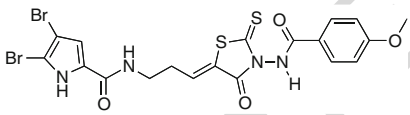
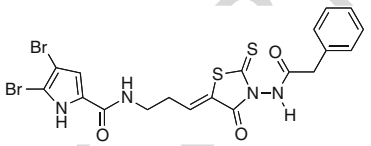
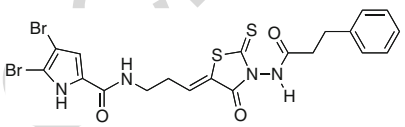
Compound	Structure	Yield[a] (%)	Compound	Structure	Yield[a] (%)
2c		44	**2g**		98
2e		41	**2h**		98
2f		90	**2i**		84

[a] Isolated yields after purification

Next, the preparation of compounds **2(f–i)** involved the use of commercial 3-amino rhodanine **2d** as starting product. Among the conditions studied, we found that reaction of **2d** with benzoyl chloride in THF at 60 °C gave good conversion to **2f** (90 %) after 2 h. For compounds **2(g–i)**, optimal reaction conditions were obtained only in dry toluene at 50 °C. After a reaction time ranging from 8 (for **2g**, **h**) to 23 h (for **2i**) which were monitored by thin-layer chromatography on silica gel using dichloromethane/ethanol (9:1) as eluent, we obtained the crystallized compounds **2(g–i)** in good to high yields (84–98 %). With the desired *N*-substituted rhodanines **2(a–i)** and the *N*-(4,5-dihalogeno pyrrol-2-yl)carbamoyl aldehydes **1(a**, **b)** in hand, we proceeded to examine the Knoevenagel condensation under microwave dielectric heating for the synthesis of new 5-ylidene rhodanines **3(a–j)** based on the dispacamide A model. In literature, the condensation of an aryl aldehyde to 2-thioxo-thiazolidine-4-one required the presence of a base such as piperidine in ethanol [32,33], piperidine/AcOH in ethanol under microwave irradiation [34–37] or with a catalytic amount of piperidinium acetate in refluxing toluene [38], AcONa in refluxed AcOH [39,40] or concentrated ammonia solution in the presence of NH_4Cl [41]. The use of solventless reaction conditions has also been employed with task specific ionic liquids (TSILs) [42,43] or with a solid inorganic support (Al_2O_3 or KSF) under microwave [44]. In this context, we decided to perform the condensation reaction under microwave dielectric heating and we screened a range of reaction parameters in order to find optimal reaction conditions. Reaction optimization for the synthesis of compounds **3(a–j)** consisted of varying the reaction temperature (70–150 °C), the irradiation power (50–200 W), the reaction time (20–40 min), the nature of the solvent (EtOH, AcOH, or AcOEt), the base (piperidine, Et_3N or AcONa) and the ratio of rhodanine **2** with the base. The reactions were conducted in borosilicate vials of 10 mL equipped with snap caps (at the end of the irradiation reaction time, cooling was realized automatically by compressed air). As shown in Table 2, the use of 0.1 equivalent of piperidine/AcOH in ethanol has been employed for the synthesis of *N*-3-substituted 5-ylidene rhodanine derivatives **3(a–c)** and**3f** in poor (**3f** 19 %), moderate (**3c** 46 %) to good yields (**3a** 88 % and **3b** 82 %). In contrast, any effort to obtain Knoevenagel condensation adducts from the reaction of the other *N*-substituted rhodanines **2** with aldehydes **1(a**, **b)** was unsuccessful using these reaction conditions. This implies that new specific synthetic protocols has to be devised for the others products **3**. Finally, treatment of **1** and **2** with a stoichiometric mixture of AcONa/AcOH (1 equivalent) during 20 min at 120–140 °C afforded the compounds **3d** and **3(g–j)** in yields ranging from 46 to 74 %. It is noteworthy that access to compound **3e** required the use of triethylamine (TEA) in glacial acetic acid instead of piperidine or AcONa and the condensation reaction was conducted in ethyl acetate (AcOEt). Compound **3e** was synthesized in 71 % yield after a reaction time of 30 min using moderate reaction temperature (70 °C) and irradiation power (50 W) in a glass vial without snap caps (or in open vessel at atmospheric pressure).

Structures of the desired compounds **3(a–j)** were substantiated by ^1H, ^{13}C NMR and HRMS analyses. In theory, *E* and *Z* geometrical isomers around the exocyclic double (CH=C) are possible for the *N*-3-substituted 5-ylidene rhodanine derivatives **3(a–j)**. ^1H NMR spectra of these compounds **3** show only one signal for the methylene proton (CH=) in the range of 6.82–7.20 ppm, at lower field val-

Table 2 Results for the preparation of *N*-3-substituted 5-ylidene rhodanine derivatives **3**(**a**–**j**) from *N*-substituted rhodanines **2**(**a**–**i**) and 4,5-dihalogeno-1*H*-pyrrole-2-carboxylic acid (3-oxopropyl)-amide **1**(**a**, **b**)

Compound	Structure of compound **3**	Reaction conditions used under microwave[a]					Yield[b] (%)
		Reagents	Solvent reaction	Reac. temp. (°C)	Reac. time (min)	Power (W)	
3a		piperidine/AcOH (0.1 eq.)	EtOH	150	20	200[c]	88
3b		piperidine/AcOH (0.1 eq.)	EtOH	150	20	200[c]	82
3c		piperidine/AcOH (0.1 eq.)	EtOH	110	40	–[d]	46
3d		AcONa/AcOH 1 eq.	AcOH	140	20	60[c]	46
3e		Et_3N /AcOH (0.1 eq.)	AcOEt	70	30	50[c,e]	71
3f		piperidine /AcOH (0.1 eq.)	EtOH	150	20	–[d]	19
3g		AcONa /AcOH (1 eq.)	AcOH	120	20	100[c]	52
3h		AcONa /AcOH (1 eq.)	AcOH	120	20	100[c]	74
3i		AcONa /AcOH (1 eq.)	AcOH	120	20	100[c]	58
3j		AcONa /AcOH (1 eq.)	AcOH	120	20	100[c]	49

[a] Microwave irradiation of the reaction mixture was realized in a glass tube sealed with a snap cap (closed vessel)
[b] Isolated yield after workup and purification by preparative chromatography (on a Combi Flash R_f 200 psi, Serlabo Technologies France using pre-packed column of silica gel 60 F 254 Merck equipped with a DAD UV/Vis 200–360 nm detector) unless indicated otherwise
[c] Explorer®24 (CEM France) used as microwave reactor
[d] Monowave®300 (Anton Paar France) used as microwave reactor
[e] The reaction was conducted in glass tube without snap cap (open vessel mode)

ues than those expected for the *E*-isomers, which strongly indicates that the compounds have the *Z*-configuration. The *Z*-configuration of compounds **3**(**a**–**j**)was confirmed from the ^{1}H-coupled ^{13}C NMR spectrum of these compounds followed by examination of the splitting pattern and coupling constant of the signal of the C=O group in the rhodanine sys-

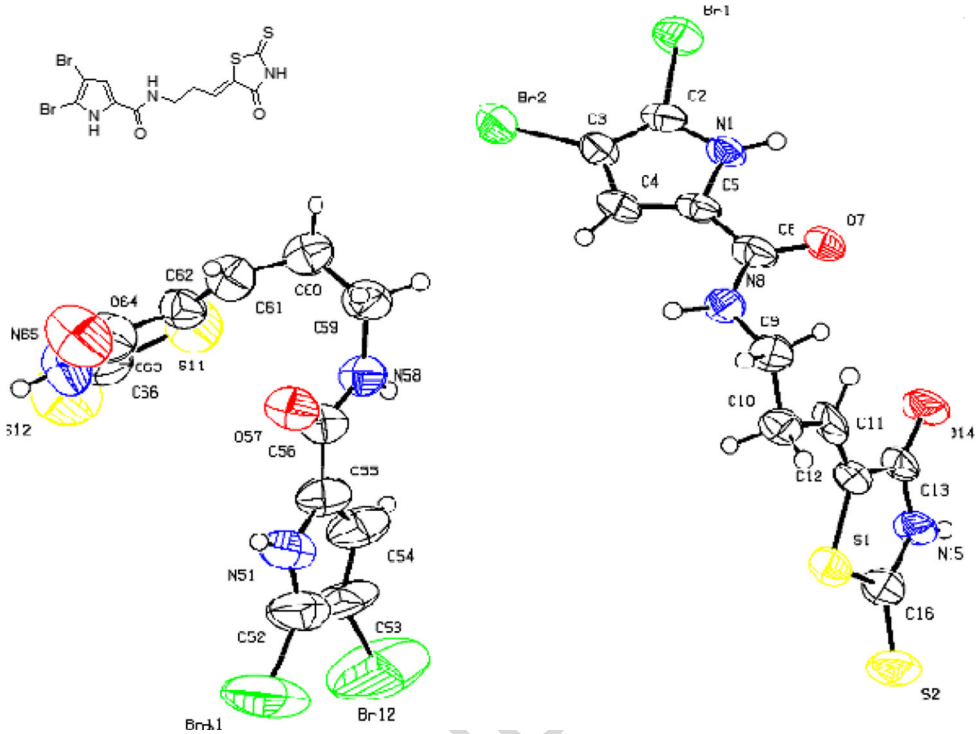


Fig. 3 Ortep diagram of 4,5-dibromo-1*H*-pyrrol-2-carboxylic acid [3-(4-*oxo*-2-thioxo-thiazolidin-5-ylidene)-propyl]-amide **3a** obtained by X-ray diffraction

Table 3 Effects of compounds **3**(**a**–**j**) on the catalytic activity of eight purified protein kinases[a]

Compound	CDK1	CDK2	CDK5/p25	GSK3α/β	CK1	DYRK1A	CLK1
Dispacamide A	–	–	–	>10	–	>10	–
3a	>10	>10	>10	–	–	5.7	–
3b	>10	>10	>10	>10	>10	>10	>10
3(**c**–**j**)	–	–	–	–	–	–	–

[a] Compounds were tested at various concentrations on each kinase as described in "Experimental" section. IC_{50} values are reported in μM, – inactive at the highest concentration tested (10 μM); >10 inhibitory but IC_{50} >10 μM

tem [45]. Finally, the *Z*-configuration and also the chemical structure of **3** were confirmed by the single X-ray diffraction analysis of 4,5-dibromo-1*H*-pyrrol-2-carboxylic acid [3-(4-*oxo*-2-thioxo-thiazolidin-5-ylidene)-propyl]-amide **3a** (Fig. 3).

As an initial effort to investigate their in vitro bioactivity, the new 5-ylidene rhodanine derivatives **3**(**a**–**j**) were tested against three protein kinases relevant to Alzheimer's disease, CK1α/β (casein kinase 1α/β), CDK5 (cyclin-dependent kinase 5)/p25 and GSK-3α/β glycogen synthase kinase 3α/β. All assays were run in the presence of 15 μM ATP and appropriate protein substrates (RRKHAAIGpSAYSITA peptide for CK1α/β, histone H1 for CDK5/p25, GS-1 (YRRAAVPPSPSLSRHSSPHQSpEDEEE) peptide for GSK-3α/β). IC_{50} values were determined from dose–response curves and are provided in Table 3.

These results are summarized in Table 3. The unsubstituted compound **3a** showed promising inhibitory activity against DYRK1A with IC_{50} value in the single-digit micromolar range (**3a**: IC_{50} 5.7 μM). Yet the other new 5-ylidene rhodanine derivatives **3**(**c**–**j**) substituted in position *N*-3 were considered inactive on CDKs, GSK3α/β,CK1, CLK1 and DYRK1A since they displayed IC_{50} values above 10 μM, these results suggested that these structures cannot be accommodated in the ATP binding site of these protein kinases by hydrogen bond interactions with specific amino-acids of the ATP-binding pocket of each protein kinase.

Conclusion

In summary, the present study described a practical approach to new 5-ylidene rhodanine derivatives **3**(**a**–**j**) bearing the (4,5-dihalogeno-pyrrol-2-yl)carbamoyl fragment of dispacamide A as potential inhibitors of protein kinases for therapeutics against neurodegenerative diseases. The key step of this solution phase organic synthesis involved a Knoevenagel condensation under microwave dielectric heat-

ing from *N*-(4,5-dihalogeno-pyrrol-2-yl) carbamoyl aldehydes **1**(**a**, **b**) and *N*-substituted rhodanines **2**(**a**–**i**) partners. This microwave-assisted condensation afforded new (5*Z*) 5-ylidene rhodanines derivatives in a stereo-controlled fashion with yields ranging from 19 to 88 % and in high purity after purification by preparative chromatography on silica gel. This work should enable further biological evaluations, new analogs though the simple synthetic process described here, and further studies towards a complete structure–activity relationship (SAR). These studies are on going in our laboratory.

Chemistry experimental part

Melting points were determined on a Kofler melting point apparatus and were uncorrected. Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. ^{1}H NMR spectra were recorded on BRUKER AC 300 P (300 MHz) spectrometer, ^{13}C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Data are given in the following order: δ value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants J is given in Hz. The mass spectra (HRMS) were taken respectively on a MS/MS ZAB-Spec Tof Micromass (EBE TOF geometry) at an ionizing potential of 8 eV and on a VARIAN MAT 311 at an ionizing potential of 70 eV in the "Centre Régional de Mesures Physiques de l'Ouest" (CRMPO, Rennes). Reactions under microwave irradiations were realized in the Explorer®24 CEM microwave reactor (CEM France) and also in the Anton Paar Monowave 300®microwave reactor (Anton Paar France) using borosilicate glass vials of 10 mL equipped with snap caps (at the end of the irradiation, cooling reaction was realized by compressed air). The microwave instrument consists of a continuous focused microwave power output from 0 to 300 W for the Explorer®24 CEM apparatus and from 0 to 800 W for the Anton Paar Monowave 300®apparatus. All the experiments were performed using stirring option. The target temperature was reached with a ramp of 2 min and the chosen microwave power stay constant to hold the mixture at this temperature. The reaction temperature is monitored using calibrated infrared sensor and the reaction time included the ramp period. The microwave irradiation parameters (power and temperature) were monitored by the ChemDriver software package for the Explorer®24 CEM apparatus and by the Monowave software package for the Anton Paar Monowave 300®reactor. Preparative chromatographies were realized on a Combi Flash R_f 200 psi (Serlabo Technologies France) using pre-packed column of silica gel 60 F 254 Merck equipped with a DAD UV/Vis 200–360 nm detector. Elemental analyses were performed on a Flash Microanalyzer EA1112 CHNS/O Thermo Electron in the "Centre Régional de Mesures Physiques de l'Ouest" (CRMPO, Rennes). Solvents were evaporated with a BUCHI rotary evaporator. All reagents and solvents were purchased from Acros, Aldrich Chimie, and Fluka France and were used without further purification. The starting aldehydes 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3-*oxo*-propyl)-amide **1a** and 4,5-dichloro-1*H*-pyrrole-2-carboxylic acid (3-*oxo*-propyl)-amide **1b** were synthesized according to our previous methods described in literature [19].

*3-(4-Oxo-2-thioxo-thiazolidin-3-yl)-propionic acid (**2c**)*

In a 25 mL two-necked round-bottomed flask provided with a magnetic stirrer and condenser, β-alanine (500 mg, 5.61 mmol) was solubilized in a solution of 22 % potassium hydroxide at room temperature. To this homogeneous solution was added carbon disulfide (0.37 mL, 6.12 mmol) dropwise during 10 min at 25 °C. After stirring over a period of 3 h, commercial bromoacetic acid (781 mg, 5.61 mmol) was added in small portions to the reaction mixture. The yellowish solution was vigorously stirred at 25 °C during 3 h. The resulting orange solution was acidified at pH 4 with conc sulfuric acid then, stirred over a period of 16 h and orange needles appeared in the suspension. The insoluble product **2c** was collected by filtration and dried under high vacuum (10^{-2} Torr) at 25 °C for 2 h. The product **2c** (503 mg, 44 % yield) was further used without purification. Mp = 162–164 °C. ^{1}H NMR (DMSO-d_6) δ: 4.05 (m, 4H, H-3, C$\underline{H}_2$); 4.22 (s, 2H, H-5′, C$\underline{H}_2$). ^{13}C NMR (DMSO-d_6) δ: 30.57 (C-2, $\underline{C}H_2$CO); 35.90 (C-3, N$\underline{C}H_2$); 39.57 (C-5′, $\underline{C}H_2$S); 171.04 (C-1, $\underline{C}$=O); 174.04 (C-4′, $\underline{C}$=O); 202.96 (C-2′, $\underline{C}$=S). HRMS, m/z: 249.9585 found (calculated for $C_6H_6NO_3Na_2S_2$ $[M–H+2Na]^+$ requires 249.9585).

*N-(4-Oxo-2-thioxo-thiazolidin-3-yl)-benzenesulfonamide (**2e**)*

In a 25 mL two-necked round-bottomed flask provided with a magnetic stirrer and condenser, a suspension of commercial phenylsulfonyl hydrazine (500 mg, 2.9 mmol) in 3 mL of deionized water was vigorously stirred at 95 °C during 2 h and produced an homogeneous yellow solution. To this solution was added commercial *bis*-(carboxymethyl)trithiocarbonate (657 mg, 2.9 mmol). The reaction mixture was stirred at 95 °C over a period of 22 h. Water was evaporated in vacuo during 7 h and the desired insoluble compound **2e** was collected by filtration then was submitted to purification by recrystallization in 3 mL of absolute ethanol. The product **2e** was obtained as white needles in 41 % yield (344 mg). Mp = 152–154 °C. ^{1}H NMR (DMSO-d_6) δ: 4.75 (s, 2H, H-5′, C$\underline{H}_2$);

8.03 (m, 2H, H-3, Ar); 8.13 (m, 1H, H-4, Ar); 8.37 (m, 2H, H-3, Ar); 11.31 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 32.95 (C-5′, $\underline{C}H_2S$); 127.23 (C-2, Ar); 128.97 (C-3, Ar); 133.34 (C-4, Ar); 140.78 (C-1, Ar); 170.30 (C-4′, $\underline{C}$=O); 199.40 (C-2′, $\underline{C}$=S). HRMS, m/z: 310.9594 found (calculated for $C_9H_8N_2O_3NaS_3$ $[M+Na]^+$ requires 310.9594).

*N-(4-Oxo-2-thioxo-thiazolidin-3-yl)-benzamide (**2f**)*

In a 25 mL round-bottomed flask provided with a magnetic stirrer and condenser, a mixture of commercial 3-amino rhodanine **2d** (500 mg, 3.37 mmol) and benzoyl chloride (0.39 mL, 3.37 mmol) was stirred in 5 mL of dry tetrahydrofuran at 60 °C during 2 h. The solvent of the reaction mixture was eliminated in a rotary evaporator under reduced pressure and the yellowish crude residue crystallized after cooling down to room temperature. The crude solid was washed with toluene (2×5 mL) and was collected by filtration. The desired product **2f** was obtained as a yellowish powder in 90 % yield (767 mg) and was further used without purification. Mp = 196–198 °C. ^{1}H NMR (DMSO-d_6) δ: 4.53 (s, 2H, H-5′, $C\underline{H}_2$); 7.56 (m, 2H, H-3, Ar); 7.66 (m, 1H, H-4, Ar); 7.93 (m, 2H, H-2, Ar); 11.56 (br s, 1H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6) δ: 33.43 (C-5′, $\underline{C}H_2S$); 127.75 (C-2, Ar); 128.72 (C-3, Ar); 130.90 (C-1, Ar); 132.76 (C-4, Ar); 164.44 (NH$\underline{C}$=O); 170.42 (C-4′, $\underline{C}$=O); 200.14 (C-2′, $\underline{C}$=S). HRMS, m/z: 274.9927 found (calculated for $C_{10}H_8N_2O_2NaS_2$ $[M+Na]^+$ requires 274.9925).

*4-Methoxy-N-(4-oxo-2-thioxo-thiazolidin-3-yl)-benzamide (**2g**)*

In a 25 mL round-bottomed flask provided with a magnetic stirrer and condenser, a mixture of commercial 3-amino rhodanine **2d** (300 mg, 2.02 mmol) and *p*−methoxybenzoyl chloride (345 mg, 2.02 mmol) was dispersed in 3 mL of dry toluene. The reaction mixture was heated at 50 °C under vigorous magnetic stirring and the reaction was monitored by TLC on silica plates using dichloromethane/ethanol (9:1) as eluent (**2g** R_f 0.8). After 8 h, the solvent of the reaction mixture was eliminated in a rotary evaporator under reduced pressure and the crude oil was dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The crude oil crystallized after standing at room temperature. The desired product **2g** was obtained as yellowish powder in 98 % yield (570 mg) and was further used without purification. Mp = 190–192 °C. ^{1}H NMR (DMSO-d_6) δ: 3.84 (s, 3H, $C\underline{H}_3O$); 4.51 (s, 2H, H-5′, $C\underline{H}_2S$); 7.08 (d, 2H, J = 8.9 Hz, H-3, Ar); 7.92 (d, 2H, J = 8.9 Hz, H-2, Ar); 11.39 (br s, 1H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6) δ: 33.34 (C-5′, $\underline{C}H_2S$); 55.48 ($\underline{C}H_3O$); 113.95 (C-3, Ar); 122.96 (C-1, Ar); 129.79 (C-2, Ar); 162.67 (C-4, Ar); 163.79 (NH$\underline{C}$=O); 170.51 (C-4′, $\underline{C}$=O); 200.29 (C-2′, $\underline{C}$=S). HRMS, m/z: 305.0031 found (calculated for $C_{11}H_{10}N_2O_3NaS_2$ $[M+Na]^+$ requires 305.0030).

*N-(4-Oxo-2-thioxo-thiazolidin-3-yl)-2-phenyl-acetamide (**2h**)*

In a 25 mL round-bottomed flask provided with a magnetic stirrer and condenser, a mixture of commercial 3-amino rhodanine **2d** (300 mg, 2.02 mmol) and phenylacetyl chloride (0.27 mL, 2.02 mmol) was dispersed in 3 mL of dry toluene. The reaction mixture was heated at 50 °C under vigorous magnetic stirring and the reaction was monitored by TLC on silica plates using dichloromethane/ethanol (9:1) as eluent (**2h** R_f 0.75). After 8 h, the solvent of the reaction mixture was eliminated in a rotary evaporator under reduced pressure and the crude product was dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The desired product **2h** was obtained as yellowish powder in 98 % yield (538 mg) and was further used without purification. Mp = 172–174 °C. ^{1}H NMR (DMSO-d_6) δ: 3.66 (s, 2H, $C\underline{H}_2$); 4.40–4.41 (br s, 2H, H-5′, $C\underline{H}_2S$); 7.31–7.32 (m, 5H, H-2, H-3, H-4, Ar); 11.41 (br s, 1H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6) δ: 33.38 (C-5′, $\underline{C}H_2S$); 126.52 (C-4, Ar); 128.19 (C-3, Ar); 129.11 (C-2, Ar); 134.65 (C-1, Ar); 168.39 (NH$\underline{C}$=O); 170.18 (C-4′$\underline{C}$=O); 199.99 (C-2′, $\underline{C}$=S). HRMS, m/z: 289.0082 found (calculated for $C_{11}H_{10}N_2O_2NaS_2$ $[M+Na]^+$ requires 289.0081).

*N-(4-Oxo-2-thioxo-thiazolidin-3-yl)-3-phenyl-propionamide (**2i**)*

In a 25 mL round-bottomed flask provided with a magnetic stirrer and condenser, a mixture of commercial 3-amino rhodanine **2d** (50 mg, 0.34 mmol) and 2-phenylpropionyl chloride (50 µL, 0.34 mmol) was dispersed in 1 mL of dry toluene. The reaction mixture was heated at 50 °C under vigorous magnetic stirring and the reaction was monitored by TLC on silica plates using dichloromethane/ethanol (9:1) as eluent (**2i** R_f 0.75). After 23 h, the solvent of the reaction mixture was eliminated in a rotary evaporator under reduced pressure. The crude residue was dissolved in dichloromethane (15 mL) then, this organic layer was washed with 4 mL of saturated hydrogen carbonate $NaHCO_3$ and was dried over $MgSO_4$. After filtration, the solvent of the filtrate was eliminated in vacuo and the crude residue was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. The desired product **2i** was obtained as orange powder in 84 % yield (80 mg) and was further used without purification. Mp = 190–192 °C . ^{1}H NMR (DMSO-d_6) δ: 2.67 (dd, 2H, J = 6.3, 8.3 Hz, 2H, $C\underline{H}_2$Ar); 2.95 (m, 2H, $C\underline{H}_2$CO); 4.47–4.48 (br s, 1H, H-5′, $C\underline{H}_2S$); 7.32–7.35 (m, 5H, H-2, H-3, H-4, Ar); 11.05 (br s, 1H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6) δ: 30.41 ($\underline{C}H_2$Ar); 33.32 ($\underline{C}H_2$CO); 34.49 (C-5′, CH_2S); 126.02–128.27 (C-2, C-3, C-4, Ar); 140.53 (C-1, Ar); 169.79 (NH$\underline{C}$=O); 170.24 (C-4′, $\underline{C}$=O); 200.03 (C-2′, $\underline{C}$=S). HRMS, m/z: 303.0239 found (calculated for $C_{12}H_{12}N_2O_2NaS_2$ $[M+Na]^+$ requires 303.0238).

*Standard procedure for the preparation of 4,5-dihalogeno-1H-pyrrol-2-carboxylic acid [3-(4-oxo-2-thioxo-thiazolidin-5-ylidene) -propyl]-amide **3(a, b)***

In a 10 mL glass tube were placed successively 4,5-dihalogeno-1*H*-pyrrole-2-carboxylic acid (3-*oxo*-propyl)-amide **1**(**a**, **b**) (3.09 mmol), commercial rhodanine **2a** (3.09 mmol, 1 equiv.), piperidine (0.31 mmol, 0.1 equiv.) and glacial acetic acid (0.31 mmol, 0.1 equiv.) in 12 mL of absolute ethanol. The glass tube was sealed with a snap cap and placed in the Explorer®24 CEM microwave cavity (P = 300 W). The mixture was irradiated at 150 °C (with a power of 200 W) for 20 min under vigorous magnetic stirring. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and the volatile compounds of the reaction mixture were eliminated in a rotary evaporator under reduced pressure. The crude residue was submitted to purification by preparative chromatography (Combi Flash R_f 200 psi apparatus, detector UV 254 nm) on pre-packed column of silica gel 60F 254 Merck using dichloromethane/ethanol (9:1) as eluent. Pooling and evaporation of the solvents in vacuo gave the expected compounds **3**(**a**, **b**) which, were dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h.

*4,5-Dibromo-1H-pyrrol-2-carboxylic acid [3-(4-oxo-2-thioxo-thiazolidin-5-ylidene)-propyl]-amide (**3a**)*

Orange powder. R_f = 0.83. Yield = 88 %. Mp = 156 °C (decomposition). ^{1}H NMR (DMSO-d_6) δ: 2.41 (m, 2H, C$\underline{H}_2$CH=); 3.41 (m, 2H, NHC$\underline{H}_2$); 6.81 (t, 1H, J = 7.6 Hz, =C$\underline{H}$); 6.87 (d, 1H, J = 2.3 Hz, H-3, =C$\underline{H}$, Ar); 8.31 (t, 1H, J = 6.0 Hz, N$\underline{H}$CO); 12.71 (br s, 1H, H-1, N$\underline{H}$, Ar); 13.60 (br s, 1H, H-3′, N$\underline{H}$). ^{13}C NMR (DMSO-d_6) δ: 32.27 (C$\underline{H}_2$CH=); 36.79 (NH$\underline{C}$H$_2$); 97.79 (C-4, =$\underline{C}$Br, Ar); 104.69 (C-4′, $\underline{C}$=O); 112.59 (C-3, =$\underline{C}$H, Ar); 124.74 (C-5′, $\underline{C}$=CH); 127.88 (C-5, =$\underline{C}$Br, Ar); 130.36 (C-2, Ar); 135.02 (=$\underline{C}$H); 159.00 (NH-$\underline{C}$=O); 167.49 (C-4′, $\underline{C}$=O); 195.95 (C-2′, $\underline{C}$=S). HRMS, m/z: 459.8403 found (calculated for $C_{11}H_9N_3O_2^{79}Br_2NaS_2$ [M+Na]$^+$ requires 459.8401).

*4,5-Dichloro-1H-pyrrol-2-carboxylic acid [3-(4-oxo-2-thioxo-thiazolidin-5-ylidene)-propyl]-amide (**3b**)*

Orange powder. R_f = 0.79. Yield = 82 %. Mp = 180 °C (decomposition). ^{1}H NMR (DMSO-d_6) δ: 2.40 (q, 2H, J = 6.5 Hz, C$\underline{H}_2$CH=); 3.43 (q, 2H, J = 6.5 Hz, NHC$\underline{H}_2$); 6.82 (m, 1H, =C$\underline{H}$); 6.84 (s, 1H, H-3, =C$\underline{H}$, Ar); 8.34 (t, 1H, J = 5.8 Hz, N$\underline{H}$CO); 12.74 (br s, 1H, N$\underline{H}$, Ar); 13.58 (br s, 1H, H-3′, N$\underline{H}$). ^{13}C NMR (DMSO-d_6) δ: 32.26 (C$\underline{H}_2$CH=); 36.80 (NH$\underline{C}$H$_2$); 107.92 (C-4, =$\underline{C}$Cl, Ar); 109.65 (C-3, =$\underline{C}$H, Ar); 114.94 (C-4′, $\underline{C}$=O); 124.61 (C-5, =$\underline{C}$Cl, Ar); 124.74 (C-5′, $\underline{C}$=CH; 130.38 (C-2, Ar); 134.96 (=$\underline{C}$H); 159.12 (NH-$\underline{C}$=O); 167.48 (C-4′, $\underline{C}$=O); 195.94 (C-2′, $\underline{C}$=S). HRMS, m/z: 371.9411 found (calculated for $C_{11}H_9N_3O_2^{35}Cl_2NaS_2$ [M+Na]$^+$ requires 371.9411).

*(5-{3-[(4,5-Dibromo-1H-pyrrol-2-carbonyl)-amino]-propylidene} -4-oxo-2-thioxo–thiazolidin-3-yl)-acetic acid (**3c**)*

In a 10 mL glass tube were placed successively 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3-*oxo*-propyl)-amide **1a** (200 mg, 0.62 mmol), commercial 2-(4-*oxo*-2-thioxo-thiazolidin-3-yl)-acetic acid **2b** (118 mg, 0.62 mmol, 1 equiv.), piperidine (6 μL, 0.062 mmol, 0.1 equiv.), glacial acetic acid (4 μL, 0.062 mmol, 0.1 equiv.) in 2.5 mL of absolute ethanol. The glass tube was sealed with a snap cap and placed in the Monowave®200 Anton-Paar microwave cavity (P = 800 W). The mixture was irradiated at 110 °C for 40 min under vigorous magnetic stirring. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and the volatile compounds of the reaction mixture were eliminated in a rotary evaporator under reduced pressure. The crude residue was submitted to purification by preparative chromatography (Combi Flash R_f 200 psi apparatus, detector UV 254 nm) on pre-packed column of silica gel 60F 254 Merck using dichloromethane/methanol (9:1) as eluent (**3c**: R_f 0.10). Pooling and evaporation of the solvents in vacuo gave the desired compound **3c** which, was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. **3c** was obtained as yellow powder in 46 % yield (140 mg). Mp = 210–212 °C. ^{1}H NMR (DMSO-d_6) δ: 2.50 (m, 2H, C$\underline{H}_2$CH=); 3.42 (m, 2H, NHC$\underline{H}_2$); 4.63 (s, 2H, C$\underline{H}_2$CO); 6.87 (s, 1H, =C-$\underline{H}$, Ar); 7.07 (t, 1H, J = 7.5 Hz, =C$\underline{H}$); 8.35 (t, 1H, J = 5.5 Hz, N$\underline{H}$CO); 12.71 (br s, 1H, N$\underline{H}$). ^{13}C NMR (DMSO-d_6) δ: 30.64 (C$\underline{H}_2$CH=); 36.79 (NH$\underline{C}$H$_2$); 44.81 (C$\underline{H}_2$CO); 97.77 (C-4, =$\underline{C}$Br, Ar); 104.48 (C-5′, $\underline{C}$=CH); 112.49 (C-3, =$\underline{C}$H, Ar); 126.72 (C-5, =$\underline{C}$Br, Ar); 127.88 (C-2, Ar); 137.84 (C=$\underline{C}$H); 159.05 (NH-$\underline{C}$=O); 164.55 (C-4′, $\underline{C}$=O); 167.10 (C=O, $\underline{C}$O$_2$H); 193.66 (C-2′, $\underline{C}$=S). HRMS, m/z: 517.8448 found (calculated for $C_{13}H_{11}N_3O_4^{79}Br_2NaS_2$ [M+Na]$^+$ requires 517.8455).

*(5-{3-[(4,5-Dibromo-1H-pyrrol-2-carbonyl)-amino]-propylidene} -4-oxo-2-thioxo–thiazolidin-3-yl)-propionic acid (**3d**)*

In a 10 mL glass tube were placed successively 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3-*oxo*-propyl)-amide **1a** (79 mg, 0.24 mmol), 3-(4-*oxo*-2-thioxo-thiazolidin-3-yl)-propionic acid **2c** (50 mg, 0.24 mmol, 1 equiv.), commercial sodium acetate AcONa (20 mg, 0.24 mmol, 1 equiv.), and glacial acetic acid (90 μL, 1.6 mmol, 6.58 equiv.). The glass tube was sealed with a snap cap and placed in the Explorer®24 CEM microwave cavity (P = 300 W). The mixture

was irradiated at 140 °C (with a power of 60 W) for 20 min under vigorous magnetic stirring. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and to the oily crude reaction mixture was added 1 mL of deionized water. After triturating, the insoluble product **3d** was collected by filtration and was submitted to purification by preparative chromatography (Combi Flash R_f 200 psi apparatus, detector UV 254 nm) on pre-packed column of silica gel 60F 254 Merck using dichloromethane/ethanol (9:1) as eluent (**3d** R_f 0.49). Pooling and evaporation of the solvents in vacuo gave the desired compound **3d** which, was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. **3d** was obtained as yellowish needles in 46 % yield (58 mg). Mp = 90 °C (decomposition). ^{1}H NMR (DMSO-d_6) δ: 2.45 (m, 2H, C$\underline{H}_2$CH=); 2.56 (m, 2H, C$\underline{H}_2$CO); 3.41 (m, 2H, NHC$\underline{H}_2$); 4.15 (t, 2H, J = 7.8 Hz, 2H, NC$\underline{H}_2$); 6.89 (s, 1H, H-3, =C-$\underline{H}$, Ar); 7.01 (t, 1H, J = 7.5 Hz, C=C$\underline{H}$); 8.32 (t, 1H, J = 5.5 Hz, 1H, N$\underline{H}$CO); 12.72 (br s, 1H, H-1, N$\underline{H}$, Ar). ^{13}C NMR (DMSO-d_6) δ: 30.70 (C$\underline{H}_2$CH=); 32.23 (C$\underline{H}_2$CO); 36.82 (NC$\underline{H}_2$); 97.80 (C-4, =C$\underline{C}$Br, Ar); 104.72 (C-5, =C$\underline{C}$Br, Ar); 112.60 (C-3, =C$\underline{H}$, Ar); 127.17 (C-5′, C$\underline{C}$=CH); 127.87 (C-2, Ar); 136.61 (C$\underline{H}$=); 159.04 (NH-C$\underline{C}$=O); 164.86 (C-4′, C=O); 171.67 (C$\underline{C}$O$_2$H); 193.65 (C-2′, C$\underline{C}$=S). HRMS, m/z: 507.8636 found (calculated for $C_{14}H_{12}N_3O_4^{79}Br_2S_2$ [M-H]$^-$ requires 507.8636).

*4,5-Dibromo-1H-pyrrol-2-carboxylic acid [3-(3-amino-4-oxo- 2-thioxo-thiazolidin-5-ylidene)-propyl]-amide (**3e**)*

In a 10 mL glass tube were placed successively 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3-*oxo*-propyl)-amide **1a** (100 mg, 0.31 mmol), commercial 3-amino rhodanine **2d** (46 mg, 0.31 mmol, 1 equiv.), dry triethylamine Et$_3$N (4 μL, 0.031 mmol, 0.1 equiv.), glacial acetic acid AcOH (2 μL, 0.031 mmol, 0.1 equiv.) in 1 mL of ethyl acetate AcOEt. The glass tube was placed (open vessel) in the Explorer®24 CEM microwave cavity (P = 300 W) and the mixture was irradiated at 70 °C (with a power of 50 W) for 30 min under vigorous magnetic stirring. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and to the crude reaction mixture was added 5 mL of cyclohexane. This heterogeneous mixture in the tube was submitted to ultrasound in a Branson 1510 apparatus at 25 °C during 30 min. The yellowish desired compound **3e** was collected by filtration, washed with Et$_2$O (2 × 5 mL) and was purified by preparative chromatography (Combi Flash R_f 200 psi apparatus, detector UV 254 nm) on pre-packed column of silica gel 60F 254 Merck using dichloromethane/methanol (9:1) as eluent (**3e** R_f 0.69). Pooling and evaporation of the solvents in vacuo gave the desired compound **3e** which, was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. **3e** was obtained as a yellowish powder in 71 % yield (100 mg). ^{1}H NMR (DMSO-d_6) δ: 2.45 (m, 2H, C$\underline{H}_2$CH=); 3.41 (m, 2H, NC$\underline{H}_2$); 5.99 (m, 1H, C=C$\underline{H}$); 6.95 (s, 1H, H-3, Ar); 8.28 (m, 1H, N$\underline{H}$-CO); 12.79 (br s, 1H, N$\underline{H}$, Ar). HRMS, m/z: 452.8693 found (calculated for $C_{11}H_{11}N_4O_2^{79}Br_2S_2$ [M+H]$^+$ requires 452.8690).

*4,5-Dibromo-1H-pyrrol-2-carboxylic acid [3-(3-benzenesulfonylamino-4-oxo-2-thioxo-thiazolidin-5-ylidene)-propyl]-amide (**3f**)*

In a 10 mL glass tube were placed successively 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3-*oxo*-propyl)-amide **1a** (100 mg, 0.31 mmol), *N*-(4-*oxo*-2-thioxo-thiazolidin-3-yl)-benzenesulfonamide **2e** (89 mg, 0.31 mmol, 1 equiv.), piperidine (3 μL, 0.031 mmol, 0.1 equiv.), glacial acetic acid (2 μL, 0.031 mmol, 0.1 equiv.) in 1.2 mL of absolute ethanol. The glass tube was sealed with a snap cap and placed in the Monowave®200 Anton-Paar microwave cavity (P = 800 W). The mixture was irradiated at 150 °C for 20 min under vigorous magnetic stirring. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and the volatile compounds of the reaction mixture were eliminated in a rotary evaporator under reduced pressure. To the black crude residue was added Et$_2$0 (5 mL) and after triturating, the insoluble compound **3f** was collected by filtration. Then, **3f** was submitted to purification by preparative chromatography (Combi Flash R_f 200 psi apparatus, detector UV 254 nm) on pre-packed column of silica gel 60F 254 Merck using dichloromethane/methanol (9:1) as eluent (**3f** R_f 0.69). Pooling and evaporation of the solvents in vacuo gave the desired compound **3f** which, was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. **3f** was obtained as an orange powder in 19 % yield (35 mg). Mp = 2424–226 °C. ^{1}H NMR (DMSO-d_6) δ: 2.45 (m, 2H, C$\underline{H}_2$CH=); 3.42 (m, 2H, NC$\underline{H}_2$); 6.87 (d, 1H, J = 2.7 Hz, =C$\underline{H}$, Ar); 7.07 (t, 1H, J = 7.6 Hz, =C$\underline{H}$); 7.56 (m, 2H, H-3″, Ar); 7.67 (m, 1H, H-4″, Ar); 7.80 (m, 2H, H-2″, Ar); 8.34 (t, 1H, J = 5.9 Hz, N$\underline{H}$CO); 11.51 (br s, 1H, N$\underline{H}$SO$_2$); 12.71 (br s, 1H, N$\underline{H}$Pyr). ^{13}C NMR (DMSO-d_6) δ: 31.77 (C$\underline{H}_2$CH=); 36.66 (NC$\underline{H}_2$); 97.79 (C-4, =C$\underline{C}$Br, Ar); 104.74 (C-5, =C$\underline{C}$Br, Ar); 11260 (C-3, =C$\underline{H}$, Ar); 123.41 (C-5′, C$\underline{C}$=CH); 127.22 (C-2″, Ar); 127.87 (C-2, =C$\underline{C}$-H, Ar); 129.07 (C-3″, Ar); 133.48 (C-4″, Ar); 138.92 (C=C$\underline{H}$); 140.59 (C-1″, Ar); 159.05 (NH-C$\underline{C}$=O); 161.73 (C-4′, C$\underline{C}$=O); 190.37 (C-2′, C$\underline{C}$=S). HRMS, m/z: 614.8438 found (calculated for $C_{17}H_{14}N_4O_4^{79}Br_2NaS_2$ [M+Na]$^+$ requires 614.8442).

*Standard procedure for the preparation of 4,5-dibromo-1H-pyrrol-2-carboxylic acid [3-(3-substituted amino-4-oxo-2-thioxo-thiazolidin-5-ylidene)-propyl]-amide (**3g**) and **3(i, j)**.*

In a 10 mL glass tube were placed successively 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3-*oxo*-propyl)-amide **1a** (52–

122 mg, 0.16–0.38 mmol), *N*-acyl rhodanine **2**(**f**–**i**) (45–100 mg, 0.16–0.38 mmol, 1 equiv.), commercial sodium acetate AcONa (14–31 mg, 0.16–0.38 mmol, 1 equiv.), and glacial acetic acid (61–140 μL, 1.06–2.47 mmol, 6.58 equiv.). The glass tube was sealed with a snap-cap and placed in the Explorer®24 CEM microwave cavity ($P = 300$ W). The mixture was irradiated at 120 °C (with a power of 100 W) for 20 min under vigorous magnetic stirring. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and deionized water (2 mL) was added to the brown crude reaction mixture. The resulting suspension was submitted to ultrasound in a Branson 1510 apparatus at 25 °C during 30 min and the beige insoluble product **3** was collected by filtration. Then, compound **3** was triturated in 5 mL of Et_2O for compounds **3g** and **3**(**i**, **j**) or in 5 mL of dichloromethane for compound **3h*** and again was collected by filtration. The crude products **3g** and **3**(**i**, **j**) were purified by preparative chromatography (Combi Flash R_f 200 psi apparatus, detector UV 254 nm) on pre-packed column of silica gel 60F 254 Merck using dichloromethane/methanol (9:1) as eluent. Pooling and evaporation of the solvents it in vacuo gave the expected compound **3g** and **3**(**i**, **j**) and were dried under high vacuum (10^{-2} Torr) at 25 °C during 1 h. (*) The compound **3h** was purified by recrystallization in dichloromethane CH_2Cl_2.

*4,5-Dibromo-1H-pyrrol-2-carboxylic acid [3-(3-benzoylamino-4-oxo-2-thioxo-thiazolidin-5-ylidene)-propyl]-amide (**3g**)*

Compound **3g** (R_f 0.69) was prepared in 52% yield (90 mg) from 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3-*oxo*-propyl)-amide **1a** (100 mg, 0.31 mmol), *N*-(4-*oxo*-2-thioxo-thiazolidin-3-yl)-benzamide **2f** (78 mg, 0.31 mmol), sodium acetate AcONa (25 mg, 0.31 mmol) in glacial acetic acid (120 μL, 2 mmol, 6.58 equiv.) according to the standard procedure. Mp = 242–244 °C. ^{1}H NMR (DMSO-d_6) δ: 2.50 (m, 2H, C$\underline{H}_2$CH=); 3.33 (m, 2H, NC$\underline{H}_2$); 6.89 (d, 1H, $J = 2.7$ Hz, =C$\underline{H}$, Ar); 7.20 (t, 1H, $J = 7.6$Hz, =C$\underline{H}$); 7.57 (m, 2H, H-3″, Ar); 7.67 (m, 1H, H-4″, Ar); 7.94 (m, 2H, H-2″, Ar); 8.39 (t, 1H, $J = 6.1$ Hz, N$\underline{H}$CO); 11.72 (br s, 1H, NN$\underline{H}$CO); 12.74 (br s, 1H, N$\underline{H}$, Ar). ^{13}C NMR (DMSO-d_6) δ: 31.98 (C$\underline{H}_2$CH=); 36.75 (NC$\underline{H}_2$); 97.80 (C-4, =C$\underline{Br}$, Ar); 104.76 (C-5, =C$\underline{Br}$, Ar); 112.61 (C-3, =C$\underline{H}$, Ar); 123.84 (C-5′, =$\underline{C}$); 127.73 (C-2″, Ar); 127.88 (C-2, =$\underline{C}$-CO, Ar); 128.79 (C-3″, Ar); 130.66 (C-1″, Ar); 132.89 (=$\underline{C}$); 139.36 (C-4″, Ar); 159.08 (NH-$\underline{C}$=O); 161.70 (C-4′, $\underline{C}$=O); 164.43 (NNH$\underline{C}$=O); 191.14 (C-2′, $\underline{C}$=S). HRMS, m/z: 578.8774 found (calculated for $C_{18}H_{14}N_4O_4^{79}Br_2NaS_2$ $[M+Na]^+$ requires 578.8772).

*4,5-Dibromo-1H-pyrrol-2-carboxylic acid {3-[3-(4-methoxy-benzoylamino)-4-oxo-2-thioxo-thiazolidin-5-ylidene]-propyl}-amide (**3h**)*

Compound **3h** was prepared in 74% yield (154 mg) from 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3-*oxo*-propyl)-amide **1a** (115 mg, 0.35 mmol), 4-methoxy-*N*-(4-*oxo*-2-thioxo-thiazolidin-3-yl)-benzamide **2g** (100 mg, 0.35 mmol), sodium acetate AcONa (29 mg, 0.35 mmol) in glacial acetic acid (130 μL, 2.33 mmol, 6.58 equiv.) according to the standard procedure. Mp = 190 °C(decomposition). ^{1}H NMR (DMSO-d_6) δ: 2.53 (m, 2H, C$\underline{H}_2$CH=); 3.45 (m, 2H, NC$\underline{H}_2$); 3.84 (s, 3H, C$\underline{H}_3$O); 6.89 (d, 1H, $J = 2.6$ HZ, H-3, =C$\underline{H}$, Ar); 7.09 (m, 2H, H-3″, Ar); 7.18 (t, 1H, $J = 7.7$ Hz, C=C$\underline{H}$); 7.91 (m, 2H, H-2″, Ar); 8.38 (t, 1H, $J = 5.5$ Hz, 1H, N$\underline{H}$CO); 11.53 (s, 1H, NN$\underline{H}$CO); 12.73 (br s, 1H, N$\underline{H}$, Ar). ^{13}C NMR (DMSO-d_6)δ: 31.95 (C$\underline{H}_2$CH=); 36.74 (NC$\underline{H}_2$); 55.49 (C$\underline{H}_3$O); 97.81 (C-4, =C$\underline{Br}$, Ar); 104.76 (C-5, =C$\underline{Br}$, Ar); 112.60 (C-3, =C$\underline{H}$, Ar); 114.03 (C-3″, Ar); 114.82 (C-3″, Ar); 122.70 (C-5′, =$\underline{C}$); 123.90 (C-2, =$\underline{C}$-CO, Ar); 127.81 (C-2″, Ar); 129.80 (C-2″, Ar); 139.21 (C$\underline{H}$=); 159.09 (C-1″, Ar); 160.55 (C-4″, Ar); 162.77 (NH-$\underline{C}$=O); 163.84 (C-4′, $\underline{C}$=O); 166.31 (NNH$\underline{C}$=O); 196.11 (C-2′, $\underline{C}$=S). HRMS, m/z: 608.8875 found (calculated for $C_{20}H_{20}N_4O_5^{79}Br_2NaS_2$ $[M+Na]^+$ requires 608.8874).

*4,5-Dibromo-1H-pyrrol-2-carboxylic acid [3-(4-oxo-3-phenylacetylamino-2-thioxo-thiazolidin-5-ylidene)-propyl]-amide (**3i**)*

Compound **3i** (R_f 0.71) was prepared in 58% yield (126 mg) from 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3-*oxo*-propyl)-amide **1a** (122 mg, 0.38 mmol), *N*-(4-*oxo*-2-thioxo-thiazolidin-3-yl)-2-phenyl-acetamide **2h** (100 mg, 0.38 mmol), sodium acetate AcONa (31 mg, 0.38 mmol) in glacial acetic acid (140 μL, 2.47 mmol, 6.58 equiv.) according to the standard procedure. Mp = 100 °C (decomposition). ^{1}H NMR (DMSO-d_6) δ: 2.53 (m, 2H, C$\underline{H}_2$CH=); 3.43 (m, 2H, NC$\underline{H}_2$); 3.66 (s, 2H, C$\underline{H}_2$CONH); 6.87 (d, 1H, $J = 2.7$ Hz, =C$\underline{H}$, Ar); 7.12 (t, 1H, $J = 7.6$ Hz, C=C$\underline{H}$); 7.29–7.33 (m, 5H, H-2″, H-3″, H-4″, Ar); 8.36 (t, 1H, $J = 5.9$ Hz, N$\underline{H}$CO); 11.36 (s, 1H, NN$\underline{H}$CO); 12.71 (br s, 1H, N$\underline{H}$, Ar). ^{13}C NMR (DMSO-d_6) δ: 28.98 (C$\underline{H}_2$CH=); 31.89 (NHCOC$\underline{H}_2$); 36.74 (NC$\underline{H}_2$); 97.81 (C-4, =C$\underline{Br}$, Ar); 104.74 (C-5′, $\underline{C}$=CH); 122.62 (C-3, =C$\underline{H}$, Ar); 123.98 (C-5, =C$\underline{Br}$, Ar); 126.72 (C-4″, Ar); 127.87 (=$\underline{C}$-CO, Ar); 128.26 (C-3″, Ar); 129.11 (C-2″, Ar); 134.53 (C-1″, Ar); 138.81 (C=C$\underline{H}$); 159.08 (NH-$\underline{C}$=O); 161.53 (C-4′, $\underline{C}$=O); 168.53 (NNH$\underline{C}$=O); 190.99 (C-2′, $\underline{C}$=S). HRMS, m/z: 592.8927 found (calculated for $C_{19}H_{16}N_4O_3^{79}Br_2NaS_2$ $[M+Na]^+$ requires 592.8928).

*4,5-Dibromo-1H-pyrrol-2-carboxylic acid {3-[4-oxo-3-(3-phenyl-propionylamino)-2-thioxo-thiazolidin-5-ylidene]-propyl}-amide (**3j**)*

Compound **3j** (R_f 0.77) was prepared in 49 % yield (46 mg) from 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3-*oxo*-propyl)-amide **1a** (52 mg, 0.16 mmol), *N*-(4-*oxo*-2-thioxo-thiazolidin-3-yl)-3-phenyl-propionamide **2i** (45 mg, 0.16 mmol), sodium acetate AcONa (14 mg, 0.16 mmol) in glacial acetic acid (61 µL, 1.06 mmol, 6.58 equiv.) according to the standard procedure. Mp = 100 °C (decomposition). ^{1}H NMR (DMSO-d_6) δ: 2.62 (m, 2H, C$\underline{H}_2$CO); 2.88 (m, 2H, C$\underline{H}_2$Ar); 3.43 (m, 2H, NC$\underline{H}_2$); 6.88 (d, 1H, J = 2.5 Hz, =C$\underline{H}$, Ar); 7.13 (t, 1H, J = 7.6 Hz, C=C$\underline{H}$); 7.23-7.31 (m, 5H, H-2″, H-3″, H-4″, Ar); 8.36 (t, 1H, J = 5.9 Hz, N$\underline{H}$CO); 11.15 (s, 1H, NN$\underline{H}$CO); 12.72 (br s, 1H, H-1, N$\underline{H}$, Ar). ^{13}C NMR (DMSO-d_6) δ: 30.36 (C$\underline{H}_2$CH=); 31.87 (C$\underline{H}_2$Ar); 34.45 (C$\underline{H}_2$CO); 36.75 (NHC$\underline{H}_2$); 97.79 (C-4, =C$\underline{C}$Br, Ar); 104.74 (C-5, =C$\underline{C}$Br, Ar); 112.60 (C-3, =C$\underline{C}$H, Ar); 123.99 (C-5′, C$\underline{C}$=CH); 126.04 (C-4″, Ar); 127.87 (C-2, =C$\underline{C}$CO, Ar); 128.23 (C-2″, Ar); 128.28 (C-3″, Ar); 138.73 (=C$\underline{C}$H); 140.45 (C-1″, Ar); 159.07 (NH-C$\underline{C}$=O); 161.58 (C-4′, C$\underline{C}$=O); 169.91 (NNHC$\underline{C}$=O); 191.02 (C-2′, C$\underline{C}$=S). HRMS, m/z: 606.9084 found (calculated for $C_{20}H_{18}N_4O_3^{79}Br_2NaS_2$ $[M+Na]^+$ requires 606.9085).

*X-ray crystallographic data for 4,5-dibromo-1H-pyrrol-2-carboxylic acid [3-(4-oxo-2-thioxo-thiazolidin-5-ylidene)-propyl]-amide (**3a**)*

($2(C_{11}$ H_9 Br_2 N_3 O_2 $S_2)$); M = 878.3. APEXII, Bruker-AXS diffractometer, Mo-Kα radiation (λ = 0.71073 Å), T = 150(2) K; triclinic P-1 (I.T.#2), a = 7.0648(6), b = 14.9877(13), c = 17.6708(13)Å, α = 75.216(3), β = 87.475(3), γ = 78.233(3)°, V = 1771.1(3) Å^3, Z = 2, d = 1.647 g cm^{-3}, μ = 4.815 mm^{-1}. The structure was solved by direct methods using the *SIR97* program [46], and then refined with full-matrix least-square methods based on F^2 (*SHELXL-97*) [47] with the aid of the *WINGX* [48]program. The contribution of the disordered solvents to the calculated structure factors was estimated following the *BYPASS* algorithm [49], implemented as the *SQUEEZE* option in *PLATON* [50]. A new data set, free of solvent contribution, was then used in the final refinement. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions. A final refinement on F^2 with 8064 unique intensities and 361 parameters converged at $\omega R(F^2) = 0.2134 (R(F) = 0.0795)$ for 2888 observed reflections with $I > 2\sigma(I)$. Crystallographic data for the structure of **3a** in this paper have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 938832. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44-0-1223-336033 or e-mail:deposit@ccdc.cam.ac.uk].

Biochemistry part

Protein kinase assay buffers

Buffer A 10 mM $MgCl_2$, 1 mM EGTA, 1 mM DTT, 25 mM Tris–HCl pH 7.5, 50 µg heparin/mL. *Buffer B* 50 mM $MgCl_2$, 90 mM NaCl, 30 mM Tris–HCl pH 7.4.

Kinase preparations and assays

Kinase activities for each enzyme were assayed in buffer A or B, with their corresponding substrates, in the presence of 15 µM ATP in a final volume of 30 µL. After 30-min incubation at 30 °C, the reaction was stopped by harvesting, using a FilterMate harvester (Packard), onto P81 phosphocellulose papers (GE Healthcare) which were washed in 1 % phosphoric acid. Scintillation fluid was added and the radioactivity measured in a Packard counter. Blank values were subtracted and activities calculated as pmoles of phosphate incorporated during the 30-min incubation. The activities were expressed in % of the maximal activity, i.e., in the absence of inhibitors. Controls were performed with appropriate dilutions of DMSO.

CDK1/cyclin B (M phase starfish oocytes, native), *CDK2/cyclin E* (human, recombinant, from A. Echalier), and *CDK5/p25* (human, recombinant, expressed in *E. coli*) [51] were assayed in Buffer A (supplemented extemporaneously with 0.15 mg BSA/mL, except for CDK2) with 25 µg of histone H1.

DYRK1A (rat, recombinant, expressed in *E. coli* as GST fusion protein, provided by Dr. W. Becker), *DYRK1A* (human, recombinant, expressed in *E. coli* as GST fusion proteins), *DYRK4* (human, recombinant, expressed in insect cells), *CLK1, 2, 3, and 4* (mouse, recombinant, expressed in *E. coli* as GST fusion proteins) was assayed as described for CDK1/cyclin B with 1 µg of RS peptide (GRSRSRSRSRSR) as a substrate. Native DYRK1A was purified from rat brain, taking advantage of the natural poly-histidine sequence located in the C-terminal domain of DYRK1A, by affinity chromatography on cobalt–sepharose beads (Clontech). Briefly, after a 30-min preclearing incubation at 4 °C with sepharose beads, rat brain lysates were incubated with cobalt-sepharose beads (400 µg total proteins/20 µL beads). Kinase activity of native DYRK1A was directly assessed on the beads in buffer A (+0.5 mg BSA/mL) using the Woodtide substrate (KKISGRLSPIMTEQ).

GSK-3α/β (porcine brain, native, affinity purified on axin–sepharose beads), *GSK-3α and GSK3β* (human, recombinant, expressed in insect cells) and *PfGSK-3* (*Plasmodium falciparum*, recombinant, expressed in *E. coli*) were assayed

as described for CDK1/cyclin B, but using a GSK-3 specific substrate (GS-1: YRRAAVPPSPSLSRHSSPHQpSEDEEE, where pS stands for phosphorylated serine) [52].

Casein kinase 1 (CK1δ/ε) (porcine brain, native) was assayed with 0.67 μg of CKS peptide (RRKHAAIGpSAYSITA), a CK1 specific substrate [53].

CLK1 (mouse, recombinant, expressed in *E. coli* as GST fusion proteins) was assayed in buffer A (+0.15 mg BSA/mL) with RS peptide (GRSRSRSRSRSR) (1 μg/assay).

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