Med Chem Res (2015) 24:1653–1661
DOI 10.1007/s00044-014-1186-7

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Prospective study directed to the synthesis of unsymmetrical linked bis-5-arylidene rhodanine derivatives via "one-pot two steps" reactions under microwave irradiation with their antitumor activity

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Received: 22 April 2014 / Accepted: 10 July 2014 / Published online: 5 September 2014

Abstract We here report on the synthesis of new unsymmetrical linked bis-5-arylidene rhodanine derivatives with stereocontrolled *Z*-configuration. The 6 steps synthesis was achieved and the key steps are the construction of the two 5-arylidene rhodanine moieties using an "one-pot two-steps" method under microwave dielectric heating in a closed reactor. The intermediates **6**, **7** and desired unsymmetrical compounds **9** have been also evaluated for their in vitro inhibition of cell proliferation (Huh7 D12, Caco2, MDA-MB 231, HCT116, and NCI-H727 tumoral cell lines). Two of all compounds have shown potent activity against Huh7 D12, Caco2, and MDA-MB 231.

Electronic supplementary material The online version of this article (doi:10.1007/s00044-014-1186-7) contains supplementary material, which is available to authorized users.

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Keywords Microwave · Knoevenagel condensation · Rhodanine · 5-Arylidene-2-thioxo-1,3-thiazolidine-4-one · Unsymmetrical bis-rhodanine · Tumoral lines

Introduction

The 5-arylidene-2-thioxo-1,3-thiazolidinine-4-ones or 5-arylidene rhodanines and their 2-amino-5-arylidene-5*H*-thiazol-4-one derivatives belong to five-membered heterocyclic rings (FMHRs) and are considered as "privileged scaffolds" in the medicinal chemistry community because they presented an inherent tendency for a large panel of biological activities (Mentgen *et al.*, 2012). These low-molecular weight inhibitors have been previously studied (Singh *et al.,* 1981; Tomasic and Masic, 2009) and have been subjected to controversies (Lesyk and Zimenkovsky, 2004) due to the high potential of these scaffolds to form intermolecular interactions in diverse receptors. The FMHRs have been known to possesses a wide range of biological properties such as potent and selective inhibitors of the "atypical" dual-specificity phosphatase (DSP) family member-JNK-stimulating phosphatase-1 (JSP-1) (Cutshall *et al.*, 2005), as aldose reductase inhibitor on diabetic peripheral neuropathy (Hotta *et al.,* 2006), as DDX3 inhibitor for HIV replication (Maga *et al.,* 2008).

Our research group is mainly invested in the synthesis of marine alkaloid derivatives as low-molecular weight-inhibitors (Bazureau *et al.,* 2009) of dual specificity, tyrosine phosphorylation-regulated kinases (DYRKs) (Debdab *et al.,* 2011; Tahtouh *et al.,* 2012) and CLKs (cdc2-like kinases) (Aranda *et al.,* 2011). Recently, we have realized a complete structure activity relationship (SAR) study and have identified leucettine L_{41} (Fig. 1), a synthetic derivative of the marine alkaloid leucettamine B, as first potent inhibitor of DYRK1A (IC_{50} 40 nM) and CLKs, two families of kinase involved in various

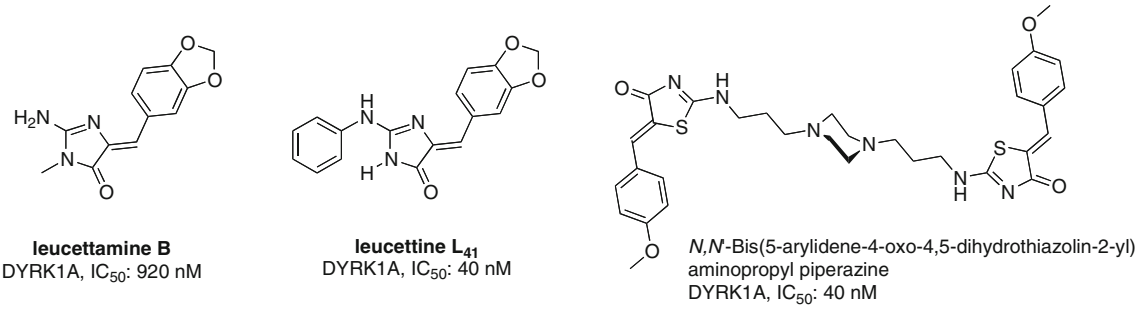


Fig. 1 Inhibitors of the protein kinase DYRK1A identified and developed in our group

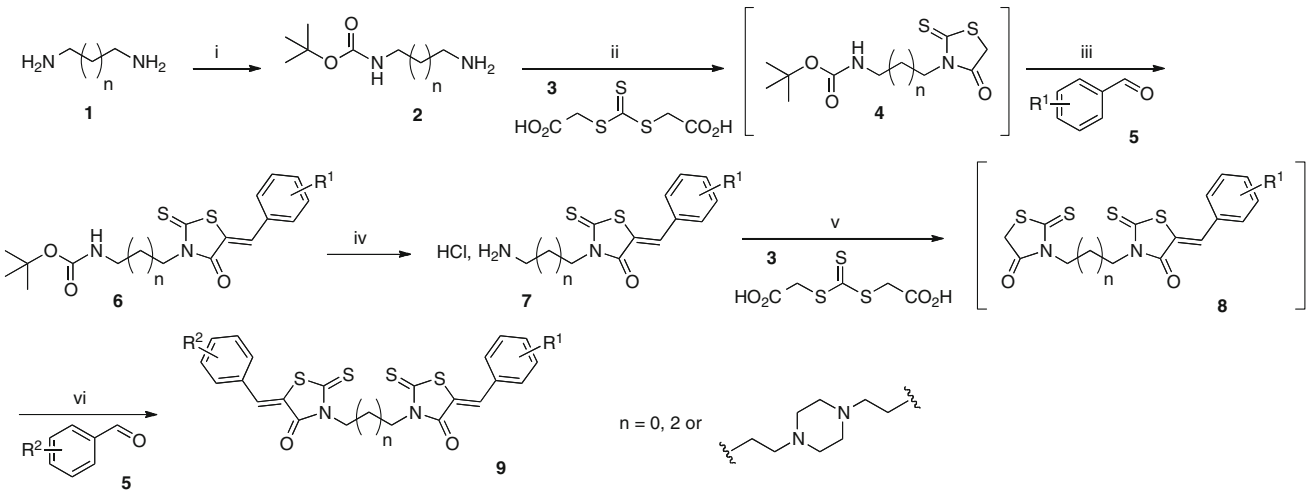
diseases including Alzheimer's disease (AD), Down syndrome (Smith *et al.,* 2012), and also cancer (Ionescu *et al.,* 2012; Xiao *et al.,* 2013; Ling *et al.,* 2013). Encouraged by these preliminary results, we continued to explore the design and the synthesis of an expanded series of *N,N'*-bis-(5-arylidene-4-oxo-3,5-dihydro-4*H*-imidazol-2-yl)diamines as potential protein kinase inhibitors from appropriate symmetric alkyldiamines as flexible linkers (Coulibaly *et al*., 2012a). Starting from 1,4-bis(3-aminopropyl)piperazine, this strategy was also extended to the synthetic preparation of symmetric *N,N'*-disubstituted diamines bearing 5-arylidene-1,3-thiazolidine-4-one moiety and to our surprise one of these compounds has shown nanomolar inhibition potency (IC_{50} 40 nM) towards DYRK1A (Fig. 1) (Coulibaly *et al*., 2012b). This result prompted us to explore now the use of symmetric 1,2-diamino linker grafted on *N*-3 position of two different 5-arylidene rhodanine platforms in order to modulate potential biological activities. The goal of the present study was to develop unsymmetrical linked bis-5-arylidene rhodanine derivatives, via "one-pot two steps" reactions under microwave irradiation to build heterocyclic platforms and evaluate biological activities on six representative tumoral cell lines.

Results and discussion

Chemistry

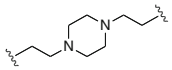
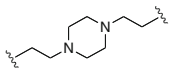
The overall strategy to the target linked bis-5-arylidene rhodanine derivatives is outlined in Scheme 1. Starting from various commercial symmetric diamines **1** as linkers (i.e., ethylenediamine **1a**, 1,4-diaminobutane **1b,** and 1,4-bis-(3-aminopropyl)piperazine **1c**), these diamino building block **1** was subjected to 0.1–0.2 equivalent of di-*tert*-butyldicarbonate (Boc_2O) to afford mainly the mono-Boc-protected amine **2** (Bonger *et al.,* 2009) in 26–56 % yield (Table 1). For the construction of the first 5-arylidene rhodanine moiety grafted on the mono-Boc-protected diamino linker **2**, we decided to test a "one-pot two-steps" described protocol (Radi *et al.,* 2010) involving the "Holmberg method" (Holmberg, 1910) (which is based on the reaction of bis(carboxymethyl)-trithiocarbonate **3** with primary amine) and Knoevenagel condensation to afford directly the 5-arylidene rhodanine **6** under microwave irradiation. This choice was guided by the fact that the major benefits of performing reaction under microwave irradiation are higher product yields and significant rate enhancements compared to reactions which run with conventional heating (i.e., in oil bath). A real advantage of commercial laboratory microwave apparatus is their ability to control reaction conditions precisely, by monitoring reaction times and temperature/pressure (de la Hoz and Loupy, 2012; Bazureau and Draye, 2011; Krstenansky and Cotteril, 2000).

For the preparation of **4**, reaction optimization consisted in varying the reaction time (5-20 min.), the reaction temperature (80–100 °C), the ratio of reagents (ratio **2/3**:1–1.3), the use of a polar or no polar solvent (hexane, Et_2O, 1,4-dioxane, dimethoxyethane), and the use of closed or open vessel mode and the choice of an organic base (pyridine, *i*-PrN_2Et, Et_3N). After all these experiments, the optimal reaction conditions were obtained at 90 °C after 10 min; with a stoichiometric mixture of **2** and **3** solubilized in dimethoxyethane with one equivalent of Et_3N. The reaction is conducted in a closed reactor (in this case, the reaction under microwave irradiation is realized in commercial glass tube closed with a snap cap). It is noteworthy that initial attempts to isolate the compound **4** after a time-consuming chromatographic purification were unsuccessful. In this context, we decided to drop the structural identification of **4** in this second step and after the first microwave irradiation period (10 min.), aromatic aldehyde **5** was added directly in the reaction mixture. The resulting mixture was irradiated at 110 °C for 5 min. For this present protocol, we have also examined the chemical reactivity of two commercially available aldehydes **5** (i.e., 4-methoxybenzaldehyde **5a** and 3,4-methylenedioxybenzaldehyde **5b**). After elimination of the volatiles compounds in vacuo, the desired products **6a–e** were isolated after a simple



Scheme 1 Reagents and reaction conditions: (i) $(t\text{-}BuO_2C)_2O$, 1,4-dioxane, 25 °C, 24 h. (ii) **3** 1 equiv., Et_3N 1 equiv., DME, 90 °C, MWI, 10 min. (iii) **5** 1 equiv., 110 °C, MWI, 5 min. (iv) HCl 6 M, 1,4-dioxane, 25 °C, 4 h. (v) **3** 1 equiv., Et_3N 2 equiv., DME, 90 °C, MWI, 10 min. (vi) **5** 1 equiv., 110 °C, MWI, 5 min

Table 1 Results for the preparation of carbamates **2**, 5-arylidene-2-thioxo-1,3-thiazolidine carbamate **6**, the deprotected derivatives **7** and the bis-*N,N'*-(5-arylidene rhodanine-3-yl) derivatives **9**

Compound	n	R^1	R^2	Yield[a] (%)
2a	0	–	–	26
2b	2	–	–	28
2c		–	–	56
6a	0	4-MeO	–	23
6b	0	3,4-(OCH_2O)	–	59
6c	2	4-MeO	–	44
6d	2	3,4-(OCH_2O)	–	35
6e		3,4-(OCH_2O)	–	36
7a	0	4-MeO	–	91
7b	0	3,4-(OCH_2O)	–	98
7c	2	3,4-(OCH_2O)	–	65
9a	0	4-MeO	H	47
9b	0	3,4-(OCH_2O)	H	43
9c	0	3,4-(OCH_2O)	4-MeO	27

[a] Isolated yields

precipitation in MeOH followed by washing with methylene chloride. A set of five designed compounds **6** was prepared in 23–59 % yield (Table 1) and characterized by ^1H, ^{13}C NMR, and HRMS. The geometry of the exocyclic double bond (=CH) of these new 5-arylidene rhodanine derivatives **6a–e** was performed; the thermodynamically more stable *Z*-isomers predominated and *Z*-configuration was assigned as previously reported in literature (Xia *et al.*, 2009). Deprotection of compounds **6** into their corresponding salts **7** was conducted in 1,4-dioxane with a solution of 6 M HCl at room temperature after 4 h of reaction time. The expected hydrochloride salts **7** were synthesized in good yields (65–98 %). Finally, for the installation of the second 5-arylidene-4-oxo-2-thioxo-1,3-thiazolidine-1-yl moiety, we employed again the "one-pot two-steps" protocol under microwave irradiation. To a solution of bis(carboxymethyl)-trithiocarbonate **3** in dimethoxyethane, was added successively two equivalents of triethylamine and appropriate quantity of hydrochloride salt **7**. The resulting suspension in a closed reactor was heated at 90 °C under microwave irradiation for 10 min. After this first period of irradiation, aromatic aldehyde **5** (4-methoxybenzaldehyde **5a** or benzaldehyde **5c**) was added and the mixture was submitted immediately to microwave dielectric heating at 110 °C for 5 min. The desired product **9** was obtained as precipitate after addition of methanol in the solventless crude residue and triturating, followed by washings with cooled hexane, methylene chloride and finally was recrystallized in ethanol to increase the quality of the precipitated product **9**. At this stage, the compounds **9a–c** were fully analyzed and characterized before entering the biological tests. The structure identification of all these new compounds was based on the ^1H and ^{13}C assignments and was performed extensive 1D and 2D NMR spectroscopy. Examination of the ^1H NMR spectrum in DMSO-d_6 for **9a** showed two separated signals for the two methylene protons (CH=), one appears at δ 7.78 ppm and the second shifted to 7.83 ppm and hence confirmed the unsymmetrical structure of **9a**. It is interesting to note that these two methylene protons appear at lower field values than those expected for the *E*-isomers,

Table 2 Antiproliferative activity of compounds **6a–e**, **7a–c** and **9a–c** on six representative tumor cell lines

Compound	% of survival[a] and IC_{50} (μM) of selected compounds[b]						
	Huh7 D12	Caco 2	MDA-MB231	HCT 116	PC3	NCI-H727	Fibroblats
6a	100	92	114	94	95	110	–
6b	76	76	97	ND	94	86	–
6c	108	68	109	97	95	110	–
6d	108	68	109	97	95	110	–
6e	48 (8)	19 (8)	60 (15)	37 (12)	54 (12)	33 (15)	– (>25)
7a	85 (>25)	94 (>25)	13 (7)	45 (15)	93 (>25)	94 (40)	– (>25)
7b	75 (17)	71 (20)	83 (20)	64 (15)	94 (>25)	74 (18)	– (>25)
7c	109	105	109	109	114	97	–
9a	110	106	113	92	103	119	–
9b	111	111	111	119	143	119	–
9c	122	123	125	115	110	116	–
Roscovitine	(12)	(5)	(12)	(7)	(10)	(20)	(>25)
DMSO	NE	NE	NE	NE	NE	NE	NE

ND not determined, *NE* no effect at 0.25 % (from a solution of DMSO 25 μM)

[a] Percentage of survival measured at 25 μM (after 48 h using a single dose, triplicate)

[b] IC_{50} values in brackets are expressed in μM and are the average of three assays, standard error ± 0.5 μM

which strongly indicates that the two 5-arylidene-4-oxo-2-thioxo-1,3-thiazolidine-1-yl moieties have both the *Z*-configuration (Guiheneuf *et al*., 2014). The unsymmetrical structure of **9a** was also confirmed in the ^{13}C NMR spectrum because we observed two separated signals for the two methylene (CH=) carbons (δ 133.1 and 133.4 ppm).

Biology

To evaluate the potency of selected compounds **6a–e**, **7a–c** and **9a–c** for their in vitro inhibition of cell proliferation, we used a panel of 6 representative tumoral cell lines, namely Huh7 D12 (differential hepatocellular carcinoma), Caco2 (differentiating colorectal adenocarcinoma), HCT (actively proliferating colorectal carcinoma), PC3 (prostate carcinoma), NCI-H2 (lung carcinoma), MDA-MB 231 (breast carcinoma), and diploid skin fibroblasts as normal cell lines for control. Roscovitine was also used as a positive control and it IC_{50} values were compared with those obtained for the compounds **6**, **7,** and **9**. Results of the in vitro antiproliferative data activity are reported in Table 2. The most active compound was clearly **6e** and exhibited antitumor activities in the Huh7 D12 and Caco2 cell lines with IC_{50} values lower than 10 μM (Huh7 D12 IC_{50} 8 μM and Caco2 IC_{50} 8 μM). In addition, **7a** presented also a selective activity in the MDA MB231 cell line (IC_{50} 7 μM) and did not exhibit the growth of normal fibroblasts ($IC_{50} > 25$ μM). On the other hand, in the desired unsymmetrical linked bis-5-arylidene rhodanine derivatives **9a–c**, none of these compounds presented a significant activity against the six representative tumoral cell lines.

Conclusion

In summary, the synthesis of unsymmetrical linked bis-5-arylidene rhodanine derivatives was realized in six steps. The key steps of this sequence involved the construction of 5-arylidene-4-oxo-2-thioxo-1,3-thiazolidine-1-yl moieties by "one-pot two-steps" protocol under microwave dielectric heating using primary amine (i.e., intermediates **2** and **7**), bis(carboxymethyl)-trithiocarbonate **3** and aromatic aldehydes **5**. The intermediates **6**, **7** and unsymmetrical compounds **9** have been built with a *Z*-geometry and their in vitro inhibition of cell proliferation was carried out. None of unsymmetrical compounds showed a significant activity against the six tumoral cell lines, but the intermediates **6e** and **7a** exhibit activity against Huh7 D12, Caco 2, and MDA MB231 cell lines.

Experimental section

Chemistry

General remarks

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 and ^{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: *d* value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad), number of protons, coupling constants *J* is given in Hertz. The mass spectra (HRMS) were taken, respectively, on a MS/MS ZABSpec 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 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 800 W for this Monowave 300® apparatus. All the experiments in the microwave reactor were performed using stirring option. The target temperature was reached with a ramp of 3 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 Monowave software package of the Monowave 300® microwave reactor. Solvents were evaporated with a BUCHI rotary evaporator. All reagents and solvents were purchased from Acros, Sigma-Aldrich Chimie, TCI France and Fluka France and were used without further purification.

*Tert-butyl (2-aminoethyl)carbamate (**2a**)*

In a 250 ml two-necked round-bottomed flask, provided with magnetic stirrer and condenser, commercial 1,2-diaminoethane **1a** (14.42 g, 16.03 ml, 0.24 mol.) was solubilized in 1,4-dioxane (69 ml). To this mixture was added dropwise a solution of di-*tert*-butyldicarbonate (6.5 g, 30 mmol.) in 85 ml of 1,4-dioxane over a period of 3 h at room temperature. After vigorous stirring at 25 °C during 12 h, the volatile compounds of the reaction mixture were removed in vacuo and to the crude reaction mixture was poured 150 ml of deionized water. The mixture was extracted with methylene chloride (5 × 50 ml), organic phases were collected and dried over anhydrous magnesium sulfate. The filtrate was concentrated in a rotary evaporator under reduced pressure and was dried under high vacuum (10^{-2} Torr) at 25 °C for 10 min. The desired carbamate **2a** (1.25 g) was obtained as colorless mobile oil in 26 % yield and was further used without purification. ^{1}H NMR (DMSO-d_6) δ: 1.20 (s, 9H, Me_3C); 2.60 (t, 2H, J = 5.8 Hz, $C\underline{H}_2$); 2.96 (t, 2H, J = 4.3 Hz, $C\underline{H}_2NH$); 4.93 (br s, 2H, NH_2); 5.71 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 28.2 (CH_3); 41.1 ($\underline{C}H_2$); 66.8 ($\underline{C}H_2NH$); 78.7 ($Me_3\underline{C}O$); 156.3 ($NH\underline{C}O$). HRMS, *m/z*: 161.1289 found (calculated for $C_7H_{17}N_2O_2$ $[M+H]^+$ requires 161.1290).

*Tert-butyl (4-aminobutyl)carbamate (**2b**)*

In a 250 ml two-necked round-bottomed flask, provided with magnetic stirrer and condenser, commercial 1,4-diaminobutane **1a** (14.3 ml, 12.5 g, 0.14 mol.) was solubilized in 1,4-dioxane (69 ml). To this mixture was added dropwise a solution of di-*tert*-butyldicarbonate (6.5 g, 30 mmol.) in 85 ml of 1,4-dioxane over a period of 3 h at room temperature. After vigorous stirring at 25 °C during 12 h, the volatile compounds of the reaction mixture were eliminated in vacuo and to the crude reaction mixture was poured 150 ml of deionized water. The mixture was extracted with methylene chloride (5 × 50 ml), organic phases were collected and dried over anhydrous magnesium sulfate. The filtrate was concentrated in a rotary evaporator under reduced pressure and was dried under high vacuum (10^{-2} Torr) at 25 °C for 10 min. The desired carbamate **2b** (1.58 g) was obtained as colorless mobile oil in 28 % yield and was further used without purification. ^{1}H NMR (DMSO-d_6) δ: 1.34 (s, 9H; Me_3CO); 1.40 (m, 4H, CH_2); 2.61 (t, 2H, J = 6.7 Hz, CH_2); 3.02 (m, 2H, CH_2NH); 4.93 (br s, 2H, NH_2); 5.71 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 27.2 (CH_2); 28.4 (Me_3CO); 29.5 (CH_2); 40.2 (CH_2); 41.1 (CH_2); 78.9 (CO); 156.1 (NHCO). HRMS, *m/z*: 189.1600 found (calculated for $C_9H_{21}N_2O_2$ $[M+H]^+$ requires 189.1603).

*Tert-butyl {2-[4-(3-aminopropyl)piperazin-1-yl]propyl}carbamate (**2c**)*

In a 250 ml two-necked round-bottomed flask, provided with magnetic stirrer and condenser, commercial 1,4-bis-(3-aminopropyl)piperazine **1c** (4.32 ml, 4.21 g, 21 mol.) was solubilized in 1,4-dioxane (34 ml). To this mixture was added a solution of di-*tert*-butyldicarbonate (812 mg., 37 mmol.) in 16 ml of 1,4-dioxane over a period of 3 h at room temperature. After vigorous stirring at 25 °C during 12 h, the volatile compounds of the reaction mixture were eliminated in vacuo and to the crude reaction mixture was poured 80 ml of deionized water. The mixture was extracted with methylene chloride (5 × 25 ml), organic phases were collected and dried over anhydrous magnesium sulfate. The filtrate was concentrated in a rotary evaporator under reduced pressure and was dried under high vacuum (10^{-2} Torr) at 25 °C for 10 min. The desired carbamate **2c** (3.52 g) was obtained as colorless mobile oil in 56 % yield and was further used without purification.

^{1}H NMR (DMSO-d_6) δ: 1.37 (s, 9H, Me_3C); 1.60 (m, 4H, CH_2); 2.35 (m, 12H, CH_2); 2.68 (t, 2H, $J = 6.6$ Hz, CH_2NH_2); 3.11 (m, 2H, CH_2NH); 4.88 (br s, NH_2); 5.42 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 26.3 (CH_2); 28.4 (Me_3CO); 29.9 (CH_2); 39.8 (CH_2NH_2); 40.6 (CH_2NH); 53.1 (CH_2N); 56.5 (NCH_2); 78.7 (Me_3CO); 156.1 (NHCO). HRMS, *m/z*: 301.2603 found (calculated for $C_{15}H_{33}N_4O_2$ $[M+H]^+$ requires 301.2603).

*Standard procedure for the preparation of 5-arylidene-2-thioxo-1,3-thiazolidine-4-one carbamates **6a-e** under microwave irradiation*

In a 10 ml glass tube was placed successively bis(carboxymethyl)trithiocarbonate **3** (0.2 g, 0.88 mmol., 1 equiv.), dimethoxyethane (1 ml), triethylamine (119 µl, 89 mg., 0.88 mmol., 1 equiv.), and carbamate **2** (0.88 mmol., 1 equiv.). The glass tube was sealed with a snap cap and placed in the Monowave 300® Anton Paar microwave cavity ($P = 800$ Watt). The reaction mixture was irradiated at 90 °C for 10 min. under vigorous magnetic stirring. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature, aldehyde **5** (0.88 mol, 1 equiv.) was added to the cooled reaction mixture which was immediately submitted to microwave irradiation at 110 °C for 5 min. After cooling, the volatile compounds of the reaction mixture were eliminated in a rotary evaporator under reduced pressure. To the crude reaction mixture was added 2 ml of MeOH and after triturating, the insoluble product **6** was collected by filtration on a Büchner funnel (porosity N°4), washed with cooled methylene chloride (2 × 0.5 ml) and was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. The desired compound **6** was further used without purification.

*(5Z)-Tert-butyl [2-(5-(4-methoxybenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)ethyl]carbamate (**6a**)*

Compound **6a** was prepared in 23 % yield (80 mg) as yellow powder from *tert*-butyl (2-aminoethyl)carbamate **2a** (9 mg., 0.88 mmol.) and 4-methoxybenzaldehyde **5a** (120 mg., 0.88 mmol.) according to the standard procedure. Mp = 134–136 °C. ^{1}H NMR (DMSO-d_6) δ: 1.31 (s, 9H, Me_3C); 3.25 (q, 2H, $J = 5.1$ Hz, CH_2NH); 3.83 (s, 3H, OCH_3); 4.10 (t, 2H, $J = 5.3$ Hz, CH_2); 6.94 (br t, 1H, $J = 6.1$ Hz, $NHCH_2$); 7.10 (d, 2H, $J = 8{,}8$ Hz, H-3′, Ar); 7.60 (d, 2H, $J = 8{,}8$ Hz, H-2′, Ar); 7,70 (s, 1H, CH=). ^{13}C NMR (DMSO-d_6) δ: 28.1 (CMe_3); 36.9 (CH_2NH); 44.5 (CH_2N); 55.5 (OCH_3); 77.7 ($OCMe_3$); 115.2 (C-3′, Ar); 119.4 (C-1′, Ar); 125.6 (C=); 132.5 (CH=); 132.7 (C-2′, Ar); 155.7 (NHCO); 161.4 (C-4′, Ar); 167.3 (C=O); 193.7 (C=S). HRMS, *m/z*: 417.0921 found (calculated for $C_{18}H_{22}N_2O_4S_2Na$ $[M+Na]^+$ requires 417.0918).

*(5Z)-Tert-butyl [2-(5-(1,3-benzodioxol-5ylmethylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)ethyl]carbamate (**6b**)*

Compound **6b** was prepared in 59 % yield (212 mg) as yellow powder from *tert*-butyl (2-aminoethyl)carbamate **2a** (9 mg., 0.88 mmol.) and 3,4-methylendioxybenzaldehyde **5b** (132 mg., 0.88 mmol.) according to the standard procedure. Mp = 154–156 °C. ^{1}H NMR (DMSO-d_6) δ: 1.32 (s, 9H, Me_3C); 3.25 (q, 2H, $J = 5.1$ Hz, 2H, CH_2NH); 4.10 (t, 2H, $J = 5{,}3$ Hz, 2H, CH_2N); 6.15 (s, 2H, OCH_2O); 6.93 (t, 1H, $J = 6.1$ Hz, 1H, NH); 7.10–7.20 (m, 3H, H-2′, H-3′, H-5′, Ar); 7.70 (s, 1H, CH=). ^{13}C NMR (DMSO-d_6) δ: 28.1 (Me_3C); 36.9 (CH_2NH); 44.5 (CH_2N); 77.7 (Me_3C); 102.1 (OCH_2O); 109.3 (C-2′, Ar); 109.5 (CH=); 120.1 (C=); 126.7 (C-5′, Ar); 127.3 (C-1′, Ar); 132.5 (C-6′, Ar); 148.3 (C-4′, Ar); 149.7 (C-3′, Ar); 155.7 (NHCO); 167.2 (C=O); 193.6 (C=S). HRMS, *m/z*: 431.0709 found (calculated for $C_{18}H_{20}N_2O_5S_2Na$ $[M+Na]^+$ requires 431.0711).

*(5Z)-Tert-butyl [2-(5-(4-methoxybenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)butyl]carbamate (**6c**)*

Compound **6c** was prepared in 44 % yield (163 mg) as yellow powder from *tert*-butyl (2-aminobutyl)carbamate **2b** (166 mg., 0.88 mmol.) and 4-methoxybenzaldehyde **5a** (120 mg., 0.88 mmol.) according to the standard procedure. Mp = 142–146 °C. ^{1}H NMR (DMSO-d_6) δ: 1.35 (s, 9H, Me_3C); 1.61 (quint, 2H, $J = 7.4$ Hz, CH_2); 2.91 (q, 2H, $J = 6.2$ Hz, CH_2NH); 3.83 (s, 3H, OCH_3); 4.00 (t, 2H, $J = 7$ Hz, CH_2N); 6.80 (br s, 1H, NH); 7.12 (d, 2H, $J = 9.1$ Hz, H-3′, Ar); 7.60 (d, 2H, $J = 8.9$ Hz, H-2′, Ar); 7.70 (s, 1H, CH=). ^{13}C NMR (DMSO-d_6) δ: 23.9 (CH_2); 26.7 (CH_2); 28.1 (Me_3C); 40.3 (CH_2N); 55.6 (OCH_3); 77.4 (Me_3C); 115.2 (C-3′, Ar); 119.0 (C=); 125.5 (C-1′, Ar); 132.9 (C-2′, Ar); 133.2 (CH=); 155.5 (NHCO); 161.5 (C-4′, Ar); 167.0 (C=O); 193.3 (C=S). HRMS, *m/z*: 445.1234 found (calculated for $C_{20}H_{26}N_2O_4S_2Na$ $[M+Na]^+$ requires 445.1232).

*(5Z)-Tert-butyl [2-(5-(1,3-benzodioxol-5ylmethylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)butyl]carbamate (**6d**)*

Compound **6d** was prepared in 35 % yield (134 mg) as yellow powder from *tert*-butyl (2-aminobutyl)carbamate **2b** (166 mg., 0.88 mmol.) and 3,4-methylenedioxybenzaldehyde **5b** (132 mg., 0.88 mmol.) according to the standard procedure. Mp = 226–228 °C. ^{1}H NMR (DMSO-d_6) δ: 1.40 (s, 9H, Me_3C); 1.44 (m, 2H, CH_2); 1.67 (m, 2H, CH_2); 2.97 (q, 2H, $J = 6.8$ Hz, CH_2NH); 4.07 (t, 2H, $J = 7.2$ Hz, CH_2N); 6.13 (s, 2H, OCH_2O); 6.42 (br s, 1H, NH); 7.07–7.20 (m, 3H, H-2′, H-5′, H-6′, Ar); 7.72 (s, 1H, CH=). ^{13}C NMR (DMSO-d_6) δ: 23.9 (CH_2); 26.8 (CH_2); 28.2 (Me_3C); 44.0 (CH_2NH); 56.0 (CH_2N); 77.5 (CMe_3); 102.1 (OCH_2O); 109.2 (C-2′, Ar); 109.4 (C-5′, Ar); 120.0 (C=); 126.8 (C-6′, C_{ipso}, Ar); 127.3 (C-1′,

C_{ipso}, Ar); 133.1 (CH=); 148.4 (C-4′, Ar); 149.8 (C-3′, Ar); 155.5 (NHCO); 166.9 (C=O); 193.1(C=S). HRMS, *m/z*: 459.1023 found (calculated for $C_{20}H_{24}N_2O_5S_2Na$ $[M+Na]^+$ requires 459.1024).

*(5Z)-Tert-butyl [(4-{[5-(1,3-benzodioxol-5-ylmethylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]propyl}piperazin-1-yl)propyl]carbamate (**6e**)*

Compound **6e** was prepared in 36 % yield (174 mg) as yellow powder from *tert*-butyl {2-[4-(2-aminopropyl)piperazin-1-yl]propyl}carbamate **2c** (263 mg., 0.88 mmol.) and 3,4-methylenedioxybenzaldehyde **5b** (132 mg., 0.88 mmol.) according to the standard procedure. Mp = 132–134 °C. ^{1}H NMR (DMSO-d_6) δ: 1.34 (s, 9H, Me_3C); 1.41 (m, 2H, CH_2); 1.80 (m, 2H, CH_2); 2.10 (t, 4H, J = 7.1 Hz, 4H, CH_2N); 2,25 (m, 8H, 4xNCH_2); 2.84 (q, 2H, J = 6.1 Hz, CH_2NH); 4.08 (t, 2H, J = 6.9 Hz, CH_2N); 6.14 (s, 2H, OCH_2O); 6.73 (s, 1H, NH); 7.10–7.21 (m, 3H, H-2′, H-5′, H-6′, Ar); 7.72 (s, 1H, CH=). ^{13}C NMR (DMSO-d_6) δ: 26.5 (CH_2); 28.1 (CMe_3); 38.3 (CH_2); 40.0 (CH_2NH); 43.2 (CH_2N); 52.8 (CH_2N); 52.9 (CH_2N); 55.5 (CH_2N); 77.3 (CMe_3); 102.2 (OCH_2O); 109,3 (CH=); 109.5 (C-2′, Ar); 120,0 (C=); 126.8 (C-5′, Ar); 127.3 (C-1′, Ar); 132.9 (C-6′, Ar); 148.3 (C-4′, Ar); 149.8 (C-3′, Ar); 155.5 (NHCO); 167.2 (C=O); 193.0 (C=S). HRMS, *m/z*: 549.2195 found (calculated for $C_{26}H_{37}N_4O_5S_2$ $[M+H]^+$ requires 549.2205).

*Standard procedure for the preparation of salts **7a–e** after deprotection of the 5-arylidene-2-thioxo-1,3-thiazolidine-4-one carbamates **6***

In a 50 ml two-necked round-bottomed flask provided with a magnetic stirrer and condenser, carbamate **6** (0.4 mmol., 1 equiv.) was solubilized in 1,4-dioxane (2 ml) at room temperature under vigorous stirring during 10 min. To this homogeneous solution was added dropwise for 30 min; a solution of 6 M HCl (2 ml) in 1,4-dioxane (2 ml). The reaction mixture was stirred during 4 h at 25 °C and was concentrated in a rotary evaporator under reduced pressure for elimination of volatile compounds. To the crystallized crude reaction mixture was added 5 ml of Et_2O and after triturating, the insoluble salt **7** was collected by filtration, then washed with 2 × 5 ml of Et_2O. The desired salt **7** was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h that gave a yellowish powder and was further used without purification.

*(5Z)-3-(2-Aminoethyl)-5-(4-methoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-one hydrochloride (**7a**)*

Compound **7a** was prepared in 91 % yield (107 mg) as yellow powder from *(5Z)-tert*-butyl [2-(5-(4-methoxybenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)ethyl]carbamate **6a** (158 mg., 0.4 mmol.) according to the standard procedure. Mp = 260–262 °C. ^{1}H NMR (DMSO-d_6) δ: 3.13 (t, 2H, J = 6 Hz, CH_2); 3.84 (s, 3H, OCH_3); 4.20 (t, 2H, J = 6 Hz, CH_2); 7.13 (d, 2H, J = 8.9 Hz, H-3′, Ar); 7.63 (d, 2H, J = 8.8 Hz, H-2′, Ar); 7.79 (s, 1H, CH=); 7.94 (br s, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ: 36.2 (CH_2); 41.7 (CH_2); 55.6 (OCH_3); 115.2 (C-3′, Ar); 119.4 (C=); 125.5 (C-1′, Ar); 132.8 (C-2′, Ar); 132.9 (CH=); 161.5 (C-4′, Ar); 167.5 (C=O); 193.8 (C=S). HRMS, *m/z*: 295.0577 found (calculated for $C_{13}H_{15}N_2O_2S_2$ $[M+H]^+$ requires 295.0575); 278.0316 found (calculated for $C_{13}H_{12}NO_2S_2$ $[M-NH_3+H]^+$ requires 278.0309).

*(5Z)-3-(2-Aminoethyl)-5-(1,3-benzodixol-5-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one hydrochloride (**7b**)*

Compound **7b** was prepared in 98 % yield (121 mg) as yellow powder from *(5Z)-tert*-butyl [2-(5-(1,3-benzodixol-5-ylmethylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)ethyl]carbamate **6b** (163 mg., 0.4 mmol.) according to the standard procedure. Mp = 260–262 °C. ^{1}H NMR (DMSO-d_6) δ: 3.13 (t, 2H, J = 5,9 Hz, CH_2NH_2); 4.26 (t, 2H, J = 5.9 Hz, CH_2N); 6.15 (s, 2H, OCH_2O); 7.11–7.25 (m, 3H, H-2′, H-5′, H-6′, Ar); 7.75 (s, 1H, CH=); 7.87 (br s, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ: 36.3 (CH_2NH); 41.7 (CH_2N); 102.2 (OCH_2O); 109.4 (CH=); 109.6 (C-2′, Ar); 120.1 (C=); 126.9 (C-5′, Ar); 127.1 (C-1′, Ar); 133.0 (C-6′, Ar); 148.4 (C-4′, Ar); 149.9 (C-3′, Ar); 167.5 (C=O); 193.7 (C=S). HRMS, *m/z*: 309.0369 found (calculated for $C_{13}H_{12}N_2O_3S_2$ $[M+H]^+$ requires 309.0367); 292.0109 found (calculated for $C_{13}H_{10}NO_3S_2$ $[M-NH_3+H]^+$ requires 292.0102).

*(5Z)-3-(4-Aminobutyl)-5-(1,3-benzodixol-5-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one hydrochloride (**7c**)*

Compound **7c** was prepared in 65 % yield (87 mg) from *(5Z)-tert*-butyl [2-(5-(1,3-benzodixol-5-ylmethylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)butyl]carbamate **6d** (174 mg., 0.4 mmol.) according to the standard procedure. Mp = 259–260 °C. ^{1}H NMR (DMSO-d_6) δ: 1.16 (m, 2H, CH_2); 1.75 (m, 2H, CH_2); 2.86 (m, 2H, CH_2NH_2); 4.12 (t, 2H, J = 6.7 Hz, CH_2N); 6.22 (s, 2H, OCH_2O); 7.17–7.28 (m, H-2′, H-5′, H-6′, Ar); 7.82 (s, 1H, CH=). ^{13}C NMR (DMSO-d_6) δ: 23.7 (CH_2); 38.3 (CH_2); 43.6 (CH_2NH_2); 66.3 (CH_2N); 102.2 (OCH_2O); 109.4 (C-2); 109.6 (C-5′, Ar); 119.6 (C=); 127.1 (C-6′, Ar); 133.3 (CH=); 148.4 (C-4′, Ar); 149.9 (C-3′, Ar); 167.1 (C=O); 195.3 (C=S). HRMS, *m/z*: 337.0681 found (calculated for $C_{15}H_{17}N_2O_3S_2$ $[M+H]^+$ requires 337.0681).

*Standard procedure for the preparation of the linked bis-N,N'-(5-arylidene rhodanin-3-yl) derivatives **9** under microwave irradiation*

In a 10 ml glass tube was placed successively bis(carboxymethyl)trithiocarbonate **3** (0.13 g, 0.58 mol., 1 equiv.), dimethoxyethane (1 ml), triethylamine (155 µl, 116 mg., 1.16 mmol., 2 equiv.), and hydrochloride salt **7** (0.58 mmol., 1 equiv.). The glass tube was sealed with a snap cap and placed in the Monowave 300® Anton Paar microwave cavity ($P = 800$ Watt). The reaction mixture was irradiated at 90 °C for 10 min. under vigorous magnetic stirring. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature, aldehyde **5** (0.58 mol, 1 equiv.) was added to the cooled reaction mixture which was immediately submitted to microwave irradiation at 110 °C for 5 min. After cooling, the volatile compounds of the reaction mixture were eliminated in a rotary evaporator under reduced pressure. To the crude reaction mixture was added 2 ml of MeOH and after triturating, the insoluble product **9** was collected by filtration on a Büchner funnel (porosity N°4), washed successively with cooled hexane (5 × 2 ml), methylene chloride (3 × 1 ml) and was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. The desired compound **9** was purified by recrystallization in EtOH.

*(5Z)-5-Benzylidene-3-{2-[(5Z)-5-(4-methoxybenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]ethyl}-2-thioxo-1,3-thiazolidin-4-one (**9a**)*

Compound **9a** was prepared in 47 % yield (136 mg) as yellow powder from *(5Z)*-3-(2-aminoethyl)-5-(4-methoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-one hydrochloride **7a** (363 mg., 0.58 mmol.) and benzaldehyde **5c** (62 mg., 0.58 mmol.) according to the standard procedure. Mp = 222–224 °C. ^{1}H NMR (DMSO-d_6) δ: 3.84 (s, 3H, OCH_3); 4.43 (s, 4H, CH_2); 7.11 (d, 2H, $J = 8.8$ Hz, H-3, Ar); 7.53–7.63 (m, 7H, H-2, H-2′, H-3′, H-4′, Ar); 7.78 (s, 1H, CH=); 7.83 (s, 1H, CH=). ^{13}C NMR (DMSO-d_6) δ: 40.4 (CH_2N); 55.7 (OCH_3); 115.1 (C-3, Ar); 118,5 (C=); 121.8 (C-1, C_{ipso}, Ar); 125.4 (C-1′, C_{ipso}, Ar); 129.5 (C-2′, Ar); 130.8 (C-3′, C-4′, Ar); 132.8 (C-2, Ar); 133.1 (CH=); 133.4 (CH=); 161.6 (C-4, C_{ipso}, Ar); 167.2 (C=O); 193.7 (C=S). HRMS, *m/z*: 521.0097 found (calculated for $C_{23}H_{18}N_2O_3S_4Na$ $[M+Na]^+$ requires 521.0098).

*(5Z)-5-(1,3-Benzodioxol-5-ylmethylidene)-3-{2-[(5Z)-5-benzylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]ethyl}-2-thioxo-1,3-thiazolidin-4-one (**9b**)*

Compound **9b** was prepared in 43 % yield (128 mg) from *(5Z)*-3-(2-aminoethyl)-5-(1,3-benzodixol-5-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one hydrochloride **7b** (200 mg., 0.58 mmol.) and benzaldehyde **5c** (62 mg., 0.58 mmol.) according to the standard procedure. Mp = 260–262 °C. ^{1}H NMR (DMSO-d_6) δ: 4.43 (t, 4H, $J = 3.9$ Hz, CH_2); 6.15 (s, 2H, OCH_2O); 7.10–7.23 (m, 3H, H-2′, H-5′, H-6′, Ar); 7.53 (d, 3H, $J = 7.3$ Hz, H-3′, H-4′, Ar); 7.66 (d, 2H, $J = 5.7$ Hz, H-2′, Ar); 7.75 (s, 1H, CH=); 7.83 (s, 1H, CH=). ^{13}C NMR (DMSO-d_6) δ: 41.5 (CH_2); 102.2 (OCH_2O); 109.4 (C-2, Ar); 109.7 (C-5, Ar); 119.1 (C=); 119.4 (C=); 121.8 (C-6, Ar); 121.8 (C-1, C_{ipso}, Ar); 127.2 (C-2′, Ar); 129.5 (C-3′, Ar); 130.8 (C-4′, Ar); 132.7 (CH=); 133.4 (C-1′, C_{ipso}, Ar); 148.4 (C-3, C_{ipso}, Ar); 150,0 (C-4, C_{ipso}, Ar); 167.2 (C=O); 193.6 (C=S). HRMS, *m/z*: 513.0070 found (calculated for $C_{23}H_{17}N_2O_4S_4$ $[M+H]^+$ requires 513.0071).

*(5Z)-5-(1,3-Benzodioxol-5-ylmethylidene)-3-{2-[(5Z)-5-(4-methoxybenzylidene)-4-oxo-2-thioxo-1,3-thiazolidin-3-yl]ethyl}-2-thioxo-1,3-thiazolidin-4-one (**9c**)*

Compound **9c** was prepared in 27 % yield (85 mg) from *(5Z)*-3-w(2-aminoethyl)-5-(1,3-benzodixol-5-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one hydrochloride **7b** (200 mg., 0.58 mmol.) and 4-methoxybenzaldehyde **5a** (79 mg., 0.58 mmol.) according to the standard procedure. Mp = 164–166 °C. ^{1}H NMR (DMSO-d_6) δ: 3.84 (s, 3H, OCH_3); 4.41 (s, 4H, CH_2); 6.15 (s, 2H, OCH_2O); 7.10 (d, 2H, $J = 8.8$ Hz, H-2′, Ar); 7.09-7.20 (m, 7H, H-2, H-5, H-6, Ar); 7.60 (d, 2H, $J = 8.8$ Hz, H-3′, Ar); 7.74 (s, 1H, CH=); 7.78 (s, 1H, CH=). ^{13}C NMR (DMSO-d_6) δ: 41.6 (CH_2); 55.6 (OCH_3); 99.5 (OCH_2O); 115.2 (C-3′, C-2, Ar); 118.5 (C=); 119.1 (C-1′, C_{ipso}, Ar); 125.4 (C-1, C_{ipso}, Ar); 127.0 (C-6, Ar); 133.1 (C-2′, C-5, Ar); 133.4 (CH=); 148.4 (C-4, C_{ipso}, Ar); 150.0 (C-3, C_{ipso}, Ar); 161.6 (C-4′, C_{ipso}, Ar); 167.2 (C=O); 213.1 (C=S). HRMS, *m/z*: 543.0172 found (calculated for $C_{21}H_{19}N_2O_4S_4$ $[M+H]^+$ requires 543.0177).

Cell culture and survival assays

Skin diploid fibroblastic cells were provided by BIOPREDIC International Company (Rennes, France). Caco2 (Ref ECACC: 86010202), Huh-7D12 (Ref ECACC: 01042712), MDA-MB-231 (Ref ECACC: 92020424), HCT-116 (Ref ECACC: 91091005), PC3 (Ref ECACC: 90112714) and NCI-H727 (Ref ECACC: 94060303) cell lines were obtained from the ECACC collection. Cells were grown according to ECACC recommendations (Nakabayashi *et al.*, 1982). The toxicity test of the compounds on these cells was as follows: 2 × 10^3 cells for HCT-116 cells or 4 x 10^3 for the other cells were seeded in 96 multiwell plates in triplicate and left for 24 h for attachment, spreading, and growing. Then, cells were exposed for 48 h to increasing

concentrations of the compounds, ranging from 0.1 to 25 μM in a final volume of 120 μl of culture medium. Cells were fixed in cooled solution of acetic acid/ethanol (90:5 %), nuclei were stained with Hoechst 3342 (Sigma) and counted using automated imaging analysis (Cellomics Arrayscan VTI/HCS Reader, Thermo/Scientific). The IC_{50} were graphically determined.

Acknowledgments One of us (K.W.C.) wishes to thank the Agence Universitaire de la Francophonie AUF, contract N°0486″ for a research fellowship. Financial support of this program carried out under the French National Cancer Institute "Cancéropôle Grand Ouest" by contracts PRIR 04-8390 and ACI 04-2254, is gratefully acknowledged.

Conflict of interest The authors declare that they have no competing interests.

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