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Synthesis of *N*,*N*′-bis(5-arylidene-4-oxo-3,5-dihydro-4*H*-imidazol-2-yl)diamines bearing various linkers and biological evaluation as potential inhibitors of kinases

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ABSTRACT

The synthesis in 4 steps of new *N*,*N*′-bis(5-arylidene-4-oxo-3,5-dihydro-4*H*-imidazol-2-yl)diamines issued from various symmetric primary diamines as linkers was reported. The key step of our strategy has been the sulphur/nitrogen displacement of (5*Z*)-5-arylidene-2-ethylsulfanyl-3,5-dihydro-4*H*-imidazol-4-ones **6** with respectively ethylenediamine **7a**, piperazine **7b** and *N*,*N*′-bis(3-aminopropyl)piperazine **7c** using solvent-free reaction conditions under microwave irradiation with retention of configuration. These compounds were tested for their kinase inhibitory potencies toward four kinases (GSK-3α/β, DYRK1A, CLK1 and CLK3).

1. Introduction

According to the World Heath Organisation (WHO), between 300 million and 500 million clinical case of malaria occur every year [1]. Malaria is one of the most severe infectious diseases, primarily affecting the world's most disadvantaged populations. This parasite infection is estimated to kill more than 1 million people annually and possibly as many as 3 million, with most of the deaths among children under age six living in undeveloped sub-Saharian Africa [2]. Despite the presence of commercially available anti-malarial drugs, the disease is gaining ground as the parasite's resistance to drugs and the parasite-carrying mosquito's resistance to insecticides expand. Of the four typically recognized *Plasmodium* species causing diseases in humans, which can be transmitted by about 60 species of *Anopheles* mosquito, *Plasmodium falciparum* causes most mortality, mainly in children below the age of 5, and *Plasmodium vivax* most morbidity additionally representing a reservoir of latent infections [3]. The infection stages of the malaria parasite reside in the salivary glands of female mosquito that bite humans for a blood meal. The mosquito injects its saliva into the wound, then transferring approximatively 15–20 so-called sporozoites into the blood stream [4]. Anti-malarial agents are classified by the stages of the malaria life cycle that are targeted by the blood. Currently there are only limited safe drugs for the treatment of the disease, however, reports of emerging resistance against existing drugs warrant the introduction of new drugs. Recently, the re-emergence of malaria as a public health problem demonstrates the urgent need for the discovery and development of new anti-malarial drugs.

Traditionally, the chemotherapy of malaria involves killing of the asexual parasites and providing supportive therapy to the host to boots its immune system. In this context and prior to the 2nd world war, quinine and its derivatives (pamaquine, chloroquine) were used intensively. They were followed by proguanyl and amodiaquine in the 1940s, followed by primaquine and pyrimethamine (1950s), sulfadoxine (1960s) [5]. The use of medicinal

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plants such as the Chinese "sweet wormwood" *Artemisia annua*, has a long tradition in the treatment of malaria [6] and identification of the major active metabolite of this plant, artemisin, gave rise the development of numerous anti-malarial drug derivatives, such as artemether, artesunate and dihydroartemisin in the 1980s [7].

Due to the intensive use of chloroquine (CQ) as a drug of choice for treating malaria since the 1950s, the CQ-resistance appeared in East-Asian countries and then, in most part of the world. Around the world, the CQ-resistance induced several efforts of the researchers to develop new anti-malarial drugs derived from 4-aminoquinolines moieties connected by linkers of various lengths and chemical nature. The interest of such bis-quinolines has been explained by the fact of their steric bulk prevents them from fitting into the substrate binding site of *P. falciparum* CQ-resistance transporter (*Pf*CRT). So, the role of bis-quinolines in malaria chemotherapy has been extensively reviewed [8]. Piperaquine [9] (Fig. 1) is the most advanced representative of this family and was developed in 1960s; it has been extensively used in China. The increasing spread of malaria together with the emergence of resistance against conventional anti-malarial drugs has put enormous pressure on the public health systems to introduce new therapeutics. Unfortunately, the number of drug classes is very restricted. Cocktails of anti-malarial drugs are now recommended to prevent chemoresistance. This emphasizes that alternative drugs with a novel mechanism of action need to be urgently developed. Pentamidine (Fig. 1) is a diamidine, which has a long history as antiprotozoal agent against trypanosomiasis and leishmaniasis since 1930s. Recently, it was proposed that diamidines act against *Plasmodium* species through the ferri-protophorphyrin binding and the inhibition of mitochondrial functions [10]. The curative effect of *N*-alkylamidine [11], as M34, inhibits the *P. falciparum* parasite's multiplication in low nanomolar range (IC_{50} = 0.3 nM) and was demonstrated in an animal model. This agent was able to inhibit plasmodial phosphatidylcholine de novo biosynthesis in infected erythrocytes [12]. The strategy was then confirmed with the bis-thiazolium salt [13] (T3, Fig. 1) active against rodent and non-human primate malaria.

Regarding the anti-malarial activity issued from *N*-alkylamidine, we decided to explore 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 candidates in the anti-malarial chemotherapy. Thus, taking into account our experience in the field of the synthesis of new bioactive heterocyclic compounds based on imidazoline-4-one heterocyclic core [14], we used the 2-amino-5-arylidene-imidazoline-4-one moiety linked through various symmetric diamino linkers (Fig. 2). Thus, an investigation into the potential of these compounds for this purpose was investigated and also their biological evaluation as protein kinase inhibitors. The 518 protein kinases of the human kinome constitute a wide family of disease-relevant targets for the identification and optimization of potential therapeutic agents.

2. Chemistry

Concerning the strategy used, we envisaged to prepare a series of novel *N*,*N*′-bis-(5-arylidene-4-oxo-3,5-dihydro-4*H*-imidazol-2-yl)diamines from appropriate symmetric alkyldiamines as flexible linkers with various 5-arylidene-2-ethylsulfanyl-3,5-dihydro-4*H*-imidazoline-4-one partners by sulphur/nitrogen displacement [15] as key step of the process. The overall strategy for the synthesis of the symmetric derivatives **8**–**10** is outlined in Scheme 1.

The synthesis started with the solution preparation of *N*-alkyl thiohydantoines **1**(**a**,**b**) from methyl glycinate hydrochloride and commercial isothiocyanates **1**(**a**,**b**) (**1a**: R^1 = Me, **1b**: R^1 = Bu). In the second step for the Knoevenagel products **5**(**a**–**h**), an equimolecular mixture of the starting hydantoine **2** and arylaldimine **4** was heated at 80 °C under microwave (μω, in the Explorer® 24 CEM microwave reactor) using solventless reaction conditions for a reaction time of 30 min. The arylaldimines **4**(**a**–**e**) were prepared in good yields (93–99%, Table 1) according to a solvent-free microwave protocol developed in our laboratory [16]. In all cases, compounds **5**(**a**–**h**) were obtained in a stereospecific way and the geometric double bond was attributed as being *Z* by the shielding effect of the carbonyl group C-4 on the olefinic proton H-5 ($\delta_{H\text{-}5}$ ~6.6 ppm) in the ^{1}H NMR spectra. Accessibility to the S-ethyl compounds **6**(**a**–**f**) involved the solution reaction of 5-arylidene thiohydantoines **5** with 1.5 equiv of ethyliodide in the presence of 0.5 equiv of potassium carbonate. After 24 h at 60 °C and work-up (elimination of the salts and the solvent under vacuum), all the 5-arylidene-2-ethylsulfanyl-3,5-dihydro-4*H*-imidazol-4-one **6**(**a**–**f**) were easily purified by recrystallization with a mixture of pentane/ethanol (1:1). As seen from the results in Table 1, it can be observed that the alkylation's step gave yields ranging from 54 to 88%. The structure assignment of the compounds **6**(**a**–**f**) is based on spectroscopic data (^{1}H, ^{13}C NMR, HRMS) and the diversity on these compounds has been introduced at the *N*-2 position and at the C-5 position by Knoevenagel condensation. It should be noted that this alkylation step gave regioselective *S*-alkylation with retention of the (5*Z*)-stereochemistry ($\delta_{H\text{-}5}$ = 6.81–6.92 ppm).

With the 5-arylidene-3,5-dihydro-4*H*-imidazol-4-ones **6**(**a**–**f**) in hand, activated with an alkylthio group in position C-2 for a subsequent sulphur/nitrogen displacement from a primary diamine, we continued to study the influence of microwave irradiation in order to obtain a large number of *N*,*N*′-bis(5-arylidene-imidazolinone) compounds suitable for the biological screening. The main benefits of performing the reaction under microwave conditions are the significant rate-enhancements and the better product yields that can be observed. It is clear that the use of microwave irradiation technology to rapid synthesis of potential molecules is a useful tool for medicinal community [17]. In this context we examined the influence of microwave irradiation on a neat mixture of 5-arylidene-2-ethylsulfanyl-3,5-dihydro-4*H*-imidazol-4-one **6** and diamine reagent **7**. For this

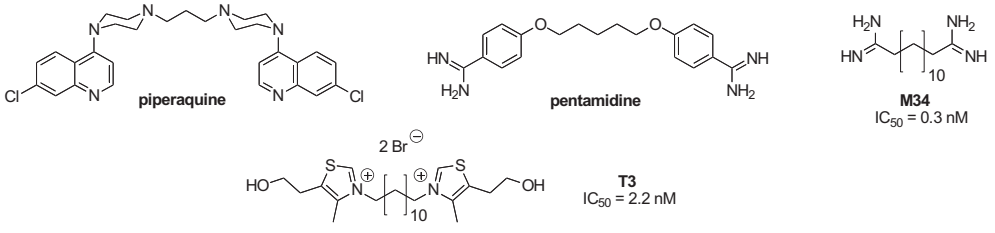


Fig. 1. Anti-plasmodial compounds.

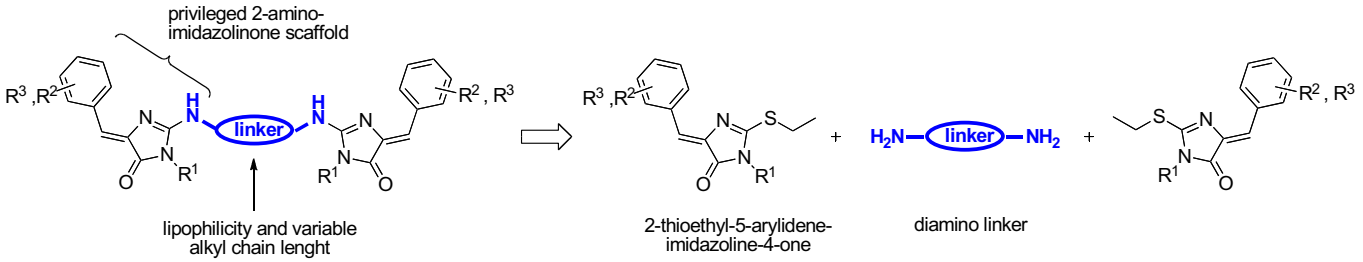
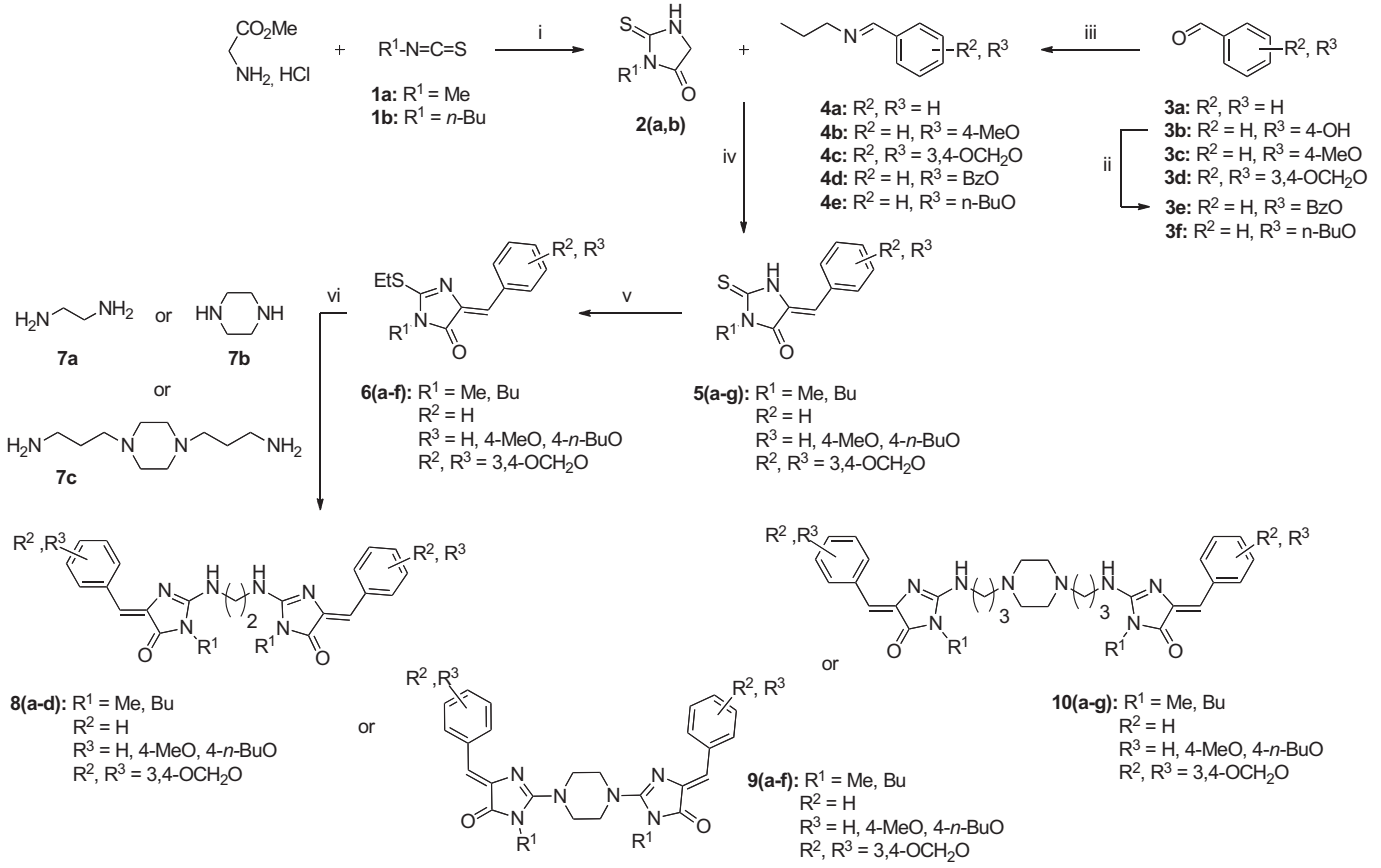


Fig. 2. Retrosynthetic strategy toward *N*,*N*′-bis-(5-arylidene-4-oxo-3,5-dihydro-4*H*-imidazol-2-yl)diamines.

study, the primary diamines employed were, ethylenediamine **7a**, piperazine **7b** and *N*,*N*′-bis(3-aminopropyl)piperazine **7c**. Reaction optimization for the preparation of compounds **8** derived from ethylenediamine **7a** or compounds **9** issued from piperazine **7b** or compounds **10** obtained from the *N*,*N*′-disubstituted piperazine **7c** consisted in varying the reaction temperature (from 60 to 160 °C), the reaction concentration (ratio **7**/**6** from 0.5 to 2), the power for microwave irradiation (100, 150 and 200 W) and the reaction time (from 15 to 60 min). After performing the test reactions, the experiments revealed that the optimal microwave reaction conditions were obtained when the optimal ratio **6**/**7** was obtained with 1.5 equiv of ethylenediamine **7a**, 1 equiv of piperazine **7b** and 0.5 equiv of **7c**. For the other parameters, the reaction mixture was irradiated at 100–160 °C (200 W) during a reaction time of 20–45 min. It is noteworthy that for safety reasons, a 3-min heating ramp was performed before the temperature was maintained at the selected reaction temperature.

As seen from the results of Table 2, the reaction time is dependent upon the nature of the diamino reagent **7** and also the substituents on the 5-arylidene-3,5-dihydro-4*H*-imidazolin-4-one **6** (R^1, R^2, R^3 or R^2–R^3). For example, access to compound **8a** from **5b** (R^1 = Me, R^2 = H, R^3 = 4-MeO) and **7a** requires a reaction time of 30 min but for **10b** from **5b** and **7c**, it was necessary to heat at 160 °C with the same reaction time (30 min). In fact, the versatility of this sulphur/nitrogen displacement [18] was demonstrated through the preparation of a small library of 17 new *N*,*N*′-bis(5-arylidene-4-oxo-3,5-dihydro-4*H*-imidazol-2-yl)diamines **8**(**a**–**d**), **9**(**a**–**f**) and **10**(**a**–**g**) with various linkers in yields ranging from 9 to 72%. The structures of all compounds **8**, **9** and **10** were substantiated by ^{1}H, ^{13}C and HRMS analyses and only the thermodynamically more stable *Z*-isomers were obtained.



Scheme 1. Reagents and reaction conditions. (i) 1 1 equiv., Et_3N, Et_2O, reflux, oil bath, 18 hrs. (ii) K_2CO_3 1.5 equiv., RX 1.05 equiv., MeCN, reflux, 96 hrs. (iii) Pr-NH2 2 equiv., 60°C, 30 min., μω (Explorer® 24CEM microwave reactor). (iv) 4 1 equiv., 80°C, 30 min., μω , 200 W (v) EtI 1.5 equiv., K_2CO_3 0.5 equiv., MeCN, 60°C, oil bath, 24 hrs. (vi) ethylenediamine 7a 1-1.5 equiv. or piperazine 7b 1 equiv. or N,N′-bis(3-aminopropoyl)piperazine 7c 0.5 equiv., 100-160°C, 20-45 min., μω, 300 W.

Table 1
Results for the preparation of thiohydantoines **2**(**a**,**b**), aldehydes **3**(**e**,**f**), arylaldimines **4**(**a**–**e**), 5-arylidene thiohydantoines **5**(**a**–**h**) and 5-arylidene-2-ethylsulfanyl-3,5-dihydro-4*H*-imidazoline-4-ones **6**(**a**–**f**).

Compound	R^1	R^2	R^3	Yield[a] (%)
2a	Me	–	–	95
2b	Bu	–	–	96
3e	–	H	4-$C_6H_5CH_2O$	92
3f	–	H	4-BuO	70
4a	–	H	H	92
4b	–	H	4-MeO	99
4c	–	H	4-$C_6H_5CH_2O$	93
4d	–	H	4-BuO	93
4e	–	3,4-OCH_2O		99
5a	Me	H	H	86
5b	Me	H	4-MeO	95
5c	Me	3,4-OCH_2O		77
5d	Me	H	4-BuO	24
5e	Me	H	4-$C_6H_5CH_2O$	66
5f	Bu	H	4-MeO	67
5g	Bu	3,4-OCH_2O		75
6a	Me	H	H	21
6b	Me	H	4-MeO	54
6c	Me	3,4-OCH_2O		72
6d	Me	H	4-$C_6H_5CH_2O$	70
6e	Me	H	4-BuO	88
6f	Bu	H	4-$C_6H_5CH_2O$	78

[a] Isolated yields.

3. Biology

Chloroquinine (CQ) and the other anti-malarial drugs are believed to act within the malaria food vacuole by binding heme and thereby converting free heme, a toxic compound for the host cell and the malarial parasite, into hemozoin [19] which is the non-toxic malarial pigment. Current reports indicate that this chemical transformation can be readily used for anti-malarial screening. Egan *et al.* [20] reported that, ferriprotophorphyrin IX chloride under acidic condition (pH 5.0) similar to that found in the lysosomal vacuole of *P. falciparum*, evolved to yield a precipitate of β-hematin (the synthetic form of hemozoin). In the presence of some chemicals (quinine, chloroquine, amodiaquin) this reaction can be inhibited and constituted a simple test enabling to identify potential anti-*P. falciparum* agents [21]. Investigation of the anti-plasmodial activity according to the *in vitro* β-hematin formation revealed that none of the prepared compounds **8**, **9** and **10** was active ($IC_{50} > 100$ μM).

Protein kinases are the enzymes, which catalyze protein phosphorylation, a key cellular regulatory mechanism that is deregulated in human diseases. Consequently, protein kinases represent interesting targets for the pharmaceutical industry in its search for new therapeutic agents. As an initial effort to investigate their *in vitro* bioactivity, compounds **8**, **9** and **10** were tested against four protein kinases as GSK-3α/β (glycogen synthase kinase 3α/β), DYRK-1A (dual-specificity, tyrosine phosphorylation activated kinase 1A) [22], CLK1 and CLK3 (cdc2-like kinases). All assays were run in the presence of 15 μM ATP and appropriate protein substrates GS-1 (YRRAAVPPSPSLSRHSSPHQSpEDEE) peptide for GSK-3α/β [23], RS peptide (GRSRSRSRSRSR) for CLK1 and CLK3, Wooltide (KKISGRLSPIMTEQ) for DYRK-1A. IC_{50} values were determined from dose–response curves and are provided in Table 3.

Considering the CLK1 kinase, the best inhibitory potencies were sub-micromolar inhibition for compounds **9b** ($IC_{50} = 0.68$ μM) and **10c** ($IC_{50} = 0.61$ μM). These derivatives are substituted either by a (4-methoxyphenyl)methylene group or a (benzo [1,3]dioxol-5-yl) methylene group on the C-5 position of the imidazolinone moiety grafted to a piperazinyl or a (3-aminopropyl)piperazinyl linker. The other compounds (**8a**, **8b**, **9c** and **10d**) were mildly active toward this kinase with IC_{50} values in the micromolar range ranging from 1.4 (**8b**) to 7.6 μM (**8a**). It is noteworthy that compound **10c** has shown micromolar inhibition potencies toward GSK-3α/β ($IC_{50} = 2.7$ μM), DYRK-1A ($IC_{50} = 5.4$ μM) and CLK3 ($IC_{50} = 1.5$ μM). Regarding these results, these new series of *N*,*N*′-bis(5-arylidene-imidazolinone) appended on ethylenediamine, piperazine or *N*,*N*′-bis(3-aminopropyl)piperazine as linkers could be particularly interesting in the development of new inhibitors of CLK1 kinase. Further biological investigations are underway.

Table 2
Results for the preparation of *N*,*N*′-bis-(5-arylidene-4-oxo-3,5-dihydro-4*H*-imidazol-2-yl)diamines **8**(**a**–**e**), **9**(**a**–**g**) and **10**(**a**–**g**) issued from ethylenediamine **7a**, piperazine **7b** and 1,4-bis(3-aminopropyl)piperazine **7c**.

Compound	R^1	R^2	R^3	Reaction temperature (°C)	Reaction time (min)	Yield[a] (%)
8a	Me	H	4-MeO	120	30	20
8b	Me	3,4-OCH_2O		120	30	25
8c	Me	H	4-$C_6H_5CH_2O$	120	30	11
8d	Me	H	4-BuO	100	20	10
9a	Me	H	H	160	30	47
9b	Me	H	4-MeO	160	35	72
9c	Me	3,4-OCH_2O		140	45	22
9d	Me	H	4-$C_6H_5CH_2O$	160	30	62
9e	Bu	H	4-$C_6H_5CH_2O$	160	30	15
9f	Me	H	4-BuO	160	30	26
10a	Me	H	H	150	30	22
10b	Me	H	4-MeO	160	30	32
10c	Me	3,4-OCH_2O		160	30	36
10d	Bu	3,4-OCH_2O		150	30	9
10e	Me	H	4-$C_6H_5CH_2O$	160	30	24
10f	Bu	H	4-$C_6H_5CH_2O$	160	30	16
10g	Me	H	4-BuO	140	30	21

[a] Isolated yields.

Table 3
Kinase inhibition[a] values (IC_{50} in μM) for compounds **8**, **9** and **10**.

Compound	R^1	R^2	R^3	GSK-3α/β	DYRK-1A	CLK1	CLK3
8a	Me	H	4-MeO	>10	>10	7.6	–
8b	Me	3,4-OCH_2O		>10	>10	1.4	–
9a	Me	H	4-$C_6H_5CH_2O$	>10	>10	>10	–
9b	Me	H	4-BuO	>10	>10	0.68	–
9c	Me	H	H	>10	>10	4	–
9d	Me	H	4-MeO	>10	>10	>10	>10
10a	Me	3,4-OCH_2O		>10	>10	>10	>10
10b	Me	H	4-$C_6H_5CH_2O$	>10	>10	≥10	>10
10c	Bu	H	4-$C_6H_5CH_2O$	2.7	5.4	0.61	1.5
10d	Me	H	4-BuO	>10	>10	4.1	6.7
10e	Me	H	H	>10	>10	>10	>10
10f	Me	H	4-MeO	>10	>10	>10	>10
10g	Me	3,4-OCH_2O		>10	>10	>10	>10

[a] Kinase inhibition experiments were carried out as described previously [14a–23].

4. Conclusion

In summary, new *N*,*N*′-bis(5-arylidene-4-oxo-3,5-dihydro-4*H*-imidazol-2-yl)diamines **8**, **9** and **10** with two diversity points have been prepared according to a solvent-free microwave irradiation protocol in the last key step by sulphur/nitrogen displacement. To our knowledge, this approach for this new family of symmetric *N*,*N*′-disubstituted diamines bearing 5-arylidene-imidazolinone moiety as new model of diamidine has never been reported and may be a complement to those existing in literature. The interesting inhibition of compounds **9b** and **10c** toward the CLK1 kinase, which is known to be involved in Alzheimer's disease [14a] as key regulator of pre-mRNA splicing, lead us to expand our effort in the synthesis of new derivatives as new potential inhibitors of this

kinase. This work should enable further biological evaluations, analogs through the synthesis process described here, and studies of the structure–activity relationship (SAR). Unfortunately, none of the compounds **8**, **9** and **10** showed inhibition activity as potential anti-*P. falciparum* agents using the inhibition assay of β-hematin formation. But the studies on kinase inhibitory potencies are on going in our laboratory.

5. Experimental section

5.1. Chemistry

5.1.1. 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 300P (300 MHz) spectrometer, ^{13}C NMR spectra on BRUKER AC 300P (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; br, broad), number of protons, coupling constants *J* is given in Hertz. The mass spectra (HRMS) were taken respectively on an 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 Explorer® 24 CEM microwave reactor (CEM 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. All the experiments 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 ChemDriver software package for the Explorer® 24 CEM apparatus. 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 thiohydantoines **2**(**a**,**b**) and aldimines **4**(**a**–**e**) were synthesized according to our previous method [16].

*5.1.1.1. 4-Benzyloxybenzaldehyde (**3e**).* In a 50 ml two-necked round-bottomed flask provided with a magnetic stirrer and condenser, a mixture of 4-hydroxybenzaldehyde **3b** (3 g, 24.6 mmol) and potassium carbonate (1.57 g, 15.9 mmol, 1.5 equiv) in dry acetonitrile (20 ml) was stirred at room temperature for 30 min. To this suspension, a solution of benzylbromide (3.08 ml, 25.83 mmol, 1.05 equiv) in 10 ml of acetonirile was added dropwise during 30 min. The resulting mixture was heated at 81 °C over a period of 96 h under vigorous magnetic stirring. Then, the reaction was allowed to cool down to room temperature and the insoluble salt (KBr) was filtered off and the filtrate was concentrated in a rotary evaporator under reduced pressure. The crude residue was dried under vacuum (10^{-2} Torr) for 1 h. The 4-benzyloxybenzaldehyde **3e** (92% yield) was used without further purification. ^{1}H NMR (DMSO-d_6) δ: 5.22 (s, 2H, Ar–CH_2–O–Ar); 7.18 (d, 2H, J = 8.1 Hz, H-3, Ar); 7.30 (d, 2H, J = 4.3 Hz, H-2′); 7.35 (q, 1H, J = 2.5 Hz, H-4′); 7.42 (t, 2H, J = 1.5 Hz, H-3′); 7.47 (d, 2H, J = 1.6 Hz, H-2′); 7.85 (dd, 2H, J = 2.6 Hz, H-3, Ar); 9.86 (s, 1H, CHO). ^{13}C NMR (DMSO-d_6) δ: 69.91 (Ar–CH_2–Ar); 115.24 (C-2); 127.81 (C-3); 128.04 (C-1); 128.47 (C-3′); 136.26 (C-2′); 163.24 (C-1′); 191.25 (C=O). HRMS, *m*/*z*: 213.0915 found (calculated for $C_{14}H_{13}O_2$ $[M + H]^{+\cdot}$ requires 213.0916).

*5.1.1.2. 4-Butyloxybenzaldehyde (**3f**).* The 4-butyloxybenzaldehyde **3f** was prepared from 4-hydroxybenzaldehyde **3b** (3 g, 24.6 mmol), potassium carbonate (1.57 g, 15.9 mmol, 1.5 equiv) and potassium iodide (4.08 g, 25.83 mmol, 1.05 equiv) in dry acetonitrile (20 ml), a solution of bromobutane (2.77 ml, 25.83 mmol, 1.05 equiv) in acetonitrile (10 ml) according to the procedure used for the synthesis of 4-benzyloxybenzaldehyde **3e**. Yield: 70%. ^{1}H NMR (DMSO-d_6) δ: 0.92 (t, J = 7.4 Hz; 3H, $CH_3CH_2CH_2CH_2O$); 1.41 (sext, J = 2.1 Hz, 2H, $CH_3CH_2CH_2CH_2O$); 1.71 (qint, J = 2.8 Hz, 2H; $CH_3CH_2CH_2CH_2O$); 4.06 (t, J = 6.5 Hz, 2H; $CH_3CH_2CH_2CH_2O$); 7.08 (d, J = 8.7 Hz; 2H, H-3, Ar); 7.83 (d, J = 8.8 Hz; 2H, H-2, Ar); 9.85 (s, CHO). ^{13}C NMR (DMSO-d_6) δ: 13.51 ($CH_3(CH_2)_4O$; 18.58 ($CH_3CH_2CH_2CH_2O$); 30.47 (CH_3CH_2-CH_2CH_2O); 67.64 ($CH_3CH_2CH_2CH_2O$); 114.74 (C-2); 129.44 (C-4); 131.7 (C-3); 163.64 (C-1); 191.04 (C=O). HRMS, *m*/*z*: 179.1070 found (calculated for $C_{11}H_{15}O_2$ $[M + H]^+$. requires 179.1072).

5.1.2. Standard procedure for the synthesis of 5-arylidene-2-thioxo-imidazoline-4-one **5**(***a***–***g***) under microwave irradiation

A mixture of *N*-methyl thiohydantoine **2a** (0.5 g, 3.84 mmol) or *N*-butyl thiohydantoine **2b** (0.4 g, 1.83 mmol) and arylaldimine **4** (3.84 mmol for **2a** or 1.83 mmol for **2b**) was placed in a borosilicate glass vial (10 ml) with a Teflon® magnetic stir bar and sealed with a snap cap. The glass tube was then introduced into an Explorer® 24 CEM microwave cavity (P = 300 W). The stirred mixture was irradiated at 80 °C (with a power of 200 W) for 30 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down to room temperature and was extracted with methylene chloride (3 × 5 ml). The combined organic phases were dried over $MgSO_4$, filtered and the volatile solvent was eliminated in a rotary evaporator under reduced pressure. The desired compound **5** was purified by recrystallization from a mixture of pentane/chloroforme (1:1). The precipitated product **5** was filtered and further dried under high vacuum (10^{-2} Torr) for 1 h, which gave the desired the *N*-methyl or *N*-butyl-2-thioxo-5-arylidene-imidazoline-4-one **5** as a powder. The compound **5** was characterized by ^{1}H, ^{13}C NMR and HRMS.

*5.1.2.1. (5Z)-5-Benzylidene-3-methyl-2-thioxo-imidazolidin-4-one (**5a**).* Yield = 86%. Brown powder. Mp = 206–208 °C. ^{1}H NMR (DMSO-d_6) δ = 3.19 (s, 3H, NCH_3); 6.60 (s, 1H; =CH); 7.40 (d, 2H, J = 7.3 Hz, H-2′, Ar); 7.77 (dd, 3H, J = 2 Hz, H-3′, H-4′, Ar); 11.22 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ = 27.21 (NCH_3); 112.47 (C=CH); 128.74 (C-2); 129.24 (C-4); 130.24 (C-3); 132.41 (C-1); 164.36 (C=S, C-2); 179.26 (C=O, C-4). HRMS, *m*/*z* = 218.0515 found (calculated for $C_{11}H_{10}N_2OS$, M^+ requires 218.0514).

*5.1.2.2. (5Z)-5(4-Methoxybenzylidene)-3-methyl-2-thioxo-imidazolidin-4-one (**5b**).* Yield = 95%. Brown powder. Mp = 170–172 °C. ^{1}H NMR (DMSO-d_6) δ = 3.18 (s, 3H, NCH_3); 3.81 (s, 3H, OCH_3); 6.60 (s, 1H, =CH); 6.97 (d, 2H, J = 8.5 Hz, H-2′, Ar); 7.75 (d, 2H, J = 8.5 Hz, H-3′, Ar); 11.32 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ = 27.18 (NCH_3); 55.33 (OCH_3); 113.28 (=CH); 114.36 (C-2′, Ar); 124.31 (C-1′, Ar); 124.78 (C=, C-5); 132.28 (C-3′, Ar); 160.34 (C=S, C-2); 164.14 (C-4′, Ar); 178.45 (C=O, C-4). HRMS, *m*/*z* = 248.0617 found (calculated for $C_{12}H_{12}N_2O_2S$, M^+ requires 248.0619).

*5.1.2.3. (5Z)-5-(Benzo[1,3]dioxol-5-yl)methylene-3-methyl-2-thioxo-imidazolidin-4-one (**5c**).* Yield = 75%. Yellow powder. Mp = 118–120 °C. ^{1}H NMR (DMSO-d$_6$) δ = 3.18 (s, 3H, NCH_3); 6.09 (s, 2H, OCH_2O); 6.54 (s, 1H, =CH); 6.96 (d, 1H, J = 8 Hz, H-5′, Ar); 7.27 (d, 1H, J = 8 Hz, H-6′, Ar); 7.45 (s, 1H, H-2′, Ar); 12.22 (br s, 1H, NH). ^{13}C NMR (DMSO-d$_6$) δ = 27.61 (NCH_3); 102.10 (OCH_2O); 109.10 (C-5′, Ar);

109.81 (C-2′, Ar); 113.72 (=CH); 125.13 (C=, C-5); 126.9 (C-6′, Ar); 126.91 (C-1′, Ar); 148.42 (C-3′, C-4′, Ar); 149.01 (C-3′, C-4′, Ar); 164.61 (C=O, C-4); 179.02 (C=S, C-2). HRMS, m/z = 262.0409 found (calculated for $C_{12}H_{10}N_2O_3S$, M^+ requires 262.0412).

*5.1.2.4. (5Z)-5(4-Butyloxybenzylidene)-3-methyl-2-thioxo-imidazolidin-4-one (**5d**).* Yield = 24%. Yellow powder. Mp = 142–144 °C. ^{1}H NMR (DMSO-d_6) δ = 0.92 (t, 3H, J = 7.3 Hz, $CH_3CH_2CH_2CH_2O$); 1.44 (sext, 2H, J = 7.5 Hz, $CH_3CH_2CH_2CH_2O$); 1.69 (quint, 2H, J = 7.5 Hz, $CH_3CH_2CH_2CH_2O$); 3.18 (s, CH_3N); 4.01 (t, *2H*, J = 6.4 Hz, $CH_3CH_2CH_2CH_2O$); 6.58 (s, 1H, =CH); 6.97 (d, 2H, J = 8.7 Hz, H-2′, Ar); 7.73 (d, 2H, J = 8.6 Hz, H-3′, Ar); 12.23 (br s, 1H; NH). ^{13}C NMR (DMSO-d_6) δ = 13.63 ($CH_3CH_2CH_2CH_2O$); 18.65 ($CH_3CH_2CH_2CH_2O$); 27.16 ($CH_3CH_2CH_2CH_2O$); 30.60 (CH_3N); 67.32 ($CH_3CH_2CH_2CH_2O$); 113.33 (=CH); 114.76 (C-2′, Ar); 124.31 (C-4′, Ar); 124.64 (C-1′, Ar); 132.28 (C-3′, Ar); 159.80 (C=, C-5); 164.15 (C=S, C-2); 178.41 (C=O, C-4). HRMS, m/z = 290.1085 found (calculated for $C_{15}H_{18}N_2O_2S$, M^+ requires 290.1089).

*5.1.2.5. (5Z)-3-Methyl-5(4-phenylmethyloxybenzylidene)-2-thioxo-imidazolidin-4-one (**5e**).* Yield = 66%. Yellow powder. Mp > 260 °C. ^{1}H NMR (DMSO-d_6) δ = 3.18 (s, 3H, NCH_3); 5.17 (s, 2H, $PhCH_2O$); 6.60 (s, 1H, =CH); 7.08 (d, 2H, J = 8.7 Hz, H-2′, Ar); 7.43–7.47 (m, 5H, J = 5.3, 9.1 Hz, H-2″, H-3″, H-4″, Ar); 7.75 (d, 2H, J = 8.7 Hz, H-3′, Ar); 12.26 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ = 27.18 (CH_3N); 69.32 ($PhCH_2O$); 113.15 (=CH); 115.19 (C-2′, C-3′); 124.52 (C-1′); 125.01 (C-1″); 127.72 (C-2″, C-3″); 127.91 (C-4′); 128.43 (Ar); 132.25 (Ar); 136.66 (Ar); 159.41 (C=, C-5); 164.21 (C=S, C-2); 178.52 (C=O, C-4). HRMS, m/z = 324.0936 found (calculated for $C_{18}H_{16}N_2O_2S$, M^+ requires 324.0932).

*5.1.2.6. (5Z)-3-Butyl-5-(4-methoxybenzylidene)-2-thioxo-imidazolidin-4-one (**5f**).* Yield = 67%. Yellow powder. Mp = 110–112 °C. ^{1}H NMR (DMSO-d_6) δ = 0.88 (t, 3H, J = 4.1 Hz, $CH_3CH_2CH_2CH_2N$); 1.28 (sext, 2H, J = 7.3 Hz, $CH_3CH_2CH_2CH_2N$); 1.58 (quint, 2H, J = 7 Hz, $CH_3CH_2CH_2CH_2N$); 3.76 (t, 2H, J = 7.3 Hz, $CH_3CH_2CH_2CH_2N$); 3.80 (s, 3H, OCH_3); 6.57 (s, 1H, =CH); 6.96 (d, 2H, J = 8.8 Hz, H-2′, Ar); 7.74 (d, 2H, J = 8.8 Hz, H-3′, Ar); 12.21 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ = 13.53 ($CH_3CH_2CH_2CH_2N$); 19.4 ($CH_3CH_2CH_2CH_2N$); 29.30 ($CH_3CH_2CH_2CH_2N$); 40.25 ($CH_3CH_2CH_2CH_2N$); 55.31 (OCH_3); 113.30 (=CH); 114.34 (C-2′, Ar); 124.31 (C-1′, Ar); 124.37 (C=, C-5); 132.27 (C-3′, Ar); 160.32 (C-4′, Ar); 164.16 (C=S, C-2); 178.01 (C=O, C-4). HRMS, m/z = 290.1086 found (calculated for $C_{15}H_{18}N_2O_2S$, M^+ requires 290.1089).

*5.1.2.7. (5Z)-5-(Benzo[1,3]dioxol-5-yl)methylene-3-butyl-2-thioxo-imidazolidin-4-one (**5g**).* Yield = 75%. Yellow powder. Mp = 118–120 °C. ^{1}H NMR ($CDCl_3$) δ = 0.94 (t, 3H, J = 7 Hz, CH_3); 1.37 (sext, 2H, J = 7 Hz, CH_2CH_3); 1.70 (quint, 2H, J = 7.5 Hz, $CH_3CH_2CH_2$); 3.89 (t, 2H, J = 7.5 Hz, CH_2N); 6.02 (s, 2H, OCH_2O); 6.65 (s, 1H, CH=); 6.86 (d, 1H, J = 8Hz, H-5′, Ar); 6.94 (d, 1H, J = 1.5 Hz, H-6′, Ar); 7.00 (dd, 1H, J = 8.1, 1.5 Hz, H-2′, Ar); 9.40 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ = 10.77 ($CH_3CH_2CH_2CH_2N$); 13.55 ($CH_3CH_2CH_2CH_2N$); 29.71 (tm, J = 130 Hz, $CH_3CH_2CH_2$); 41.32 (tt, J = 141 Hz, CH_2N); 101.91 (t, J = 174 Hz, OCH_2O); 108.71 (dt, J = 164 Hz, C-5′, Ar); 110.81 (d, J = 167 Hz, C-2′, Ar); 114.02 (dt, J = 162 Hz, CH=); 125.03 (dt, J = 163 Hz, C=, C-5); 125.11 (d, J = 5 Hz, C-6′, Ar); 126.81 (C-1′, Ar); 148.62 (C-3′, C-4′, Ar); 149.12 (C-3′, C-4′, Ar); 164.02 (C=O, C-4); 178.11 (C=S, C-2). HRMS, m/z = 304.0880 found (calculated for $C_{15}H_{16}N_2O_3S$, M^+ requires 304.0882).

*5.1.3. Standard procedure of S-alkylation of 5-arylidene-2-thioxo-imidazoline-4-one 5 for the synthesis of 5-arylidene-2-ethylsulfanyl-3,5-dihydro-4H-imidazoline-4-one 6(**a**–**f**)*

In a 25 ml two necked room-bottomed flask, provided with a magnetic stirrer and reflux condenser, a suspension of 5-arylidene thiohydantoine **5** (6 mmol), commercial potassium carbonate (0.42 g, 3.02 mmol, 0.5 equiv) and ethyliodide (580 μl, 7.25 mmol, 1.5 equiv) in dry acetonitrile (16 ml) was heated in a thermostated oil bath at 60 °C during 24 h under vigorous magnetic stirring. After cooling down to room temperature, the reaction mixture was concentrated in a rotary evaporator under reduced pressure. To the crude residue was added methylene chloride (20 ml) and the insoluble salt was filtered off. The volatile solvent of the filtrate was eliminated under reduced pressure in a rotary evaporator. The crude product **6** was recrystallized from a mixture of pentane/ethanol (1:1) and further dried under high vacuum (10^{-2} Torr) for 1 h, which gave the desired 5-arylidene-2-ethylthio-imidazoline-4-one **6** as a powder and was characterized by ^{1}H, ^{13}C and HRMS.

*5.1.3.1. (5Z)-5-Benzylidene-2-ethylsulfanyl-3-methyl-3,5-dihydro-4H-imidazol-4-one (**6a**).* Yield = 21%. Yellow powder. Mp = 108–110 °C. ^{1}H NMR ($CDCl_3$) δ = 1.46 (t, 3H, J = 7.4 Hz, SCH_2CH_3); 3.09 (s, 3H, NCH_3); 3.30 (q, 2H, J = 8.1 Hz, SCH_2CH_3); 6.87 (s, 1H; =CH); 7.28–7.36 (m, 4H, J = 5.3 Hz, H-3′-H-4′, Ar); 8.08 (dd, 2H, J = 1.6 Hz, H-2′, Ar). ^{13}C NMR ($CDCl_3$) δ = 14.32 (CH_3CH_2S); 25.21 (NCH_3); 26.52 (CH_3CH_2S); 123.51 (=CH); 128.61 (C-3′, Ar); 129.65 (C-4′, Ar); 131.84 (C-2′, Ar); 134.55 (C-1′, Ar); 138.54 (C=, C-5); 164.91 (C=N, C-2); 169.92 (C=O, C-4). HRMS, m/z = 248.0875 found (calculated for $C_{13}H_{14}N_2OS$, M^+ requires 246.0872).

*5.1.3.2. (5Z)-2-ethylsulfanyl-3-methyl-5-(4-methyloxybenzylidene)-3,5-dihydro-4H-imidazol-4-one (**6b**).* Yield = 54%. Yellow powder. Mp = 132–134 °C. ^{1}H NMR (DMSO-d_6) δ = 1.44 (t, 3H, J = 7.3 Hz, SCH_2CH_3); 3.05 (s, 3H, NCH_3); 3.34 (q, 2H, J = 4.3 Hz, SCH_2CH_3); 3.81 (s, 3H, OCH_3); 6.83 (s, 1H, =CH); 7.1 (d, 2H, J = 8.9 Hz, H-2′, Ar); 8.16 (d, 2H, J = 8.8 Hz, H-3′, Ar). ^{13}C NMR (DMSO-d_6) δ = 14.25 (CH_3CH_2S); 24.55 (CH_3CH_2S); 26.23 (NCH_3); 55.27 (OCH_3); 114.28 (=CH); 122.31 (C-2′, Ar); 126.91 (C-3′, Ar); 133.44 (C-1′, Ar); 136.41 (C-4′, Ar); 160.54 (C=, C-5); 163.72 (C=N, C-2); 168.71 (C=O, C-4). HRMS, m/z = 276.0936 found (calculated for $C_{14}H_{16}N_2O_2S$, M^+ requires 276.0932).

*5.1.3.3. (5Z)-5-(Benzo[1,3]dioxol-5-yl)methylene-2-ethylsulfanyl-3-methyl-3,5-dihydro-4H-imidazol-4-one (**6c**).* Yield = 72%. Yellow powder. Mp = 152–154 °C. ^{1}H NMR (DMSO-d_6) δ = 1.55 (t, 3H, J = 7.4 Hz, SCH_2CH_3); 3.17 (s, 3H, NCH_3); 3.40 (q, 2H, J = 7 Hz, SCH_2CH_3); 6.01 (s, 2H, OCH_2O); 6.82 (d, 1H, J = 8 Hz, H-5′, Ar); 6.83 (s, 1H, =CH); 7.37 (dd, 1H, J = 8.1 Hz, H-6′, Ar); 8.05 (s, 1H, H-2′, Ar). ^{13}C NMR (DMSO-d_6) δ = 14.71 (SCH_2CH_3); 25.60 (SCH_2CH_3); 26.91 (NCH_3); 101.80 (OCH_2O); 108.82 (C-5′, Ar); 11.21 (C-2′, Ar); 124.02 (CH=); 128.41 (C-6′, Ar); 129.51 (C-1′, Ar); 137.50 (C=, C-5); 148.31 (C-3′, C-4′, Ar); 149.51 (C-3′, C-4′, Ar); 164.11 (C=N, C-2); 170.31 (C=O, C-4). HRMS, m/z = 290.0730 found (calculated for $C_{14}H_{14}N_2O_3S$, M^+ requires 290.725).

*5.1.3.4. (5Z)-2-Ethylsulfanyl-3-methyl-5-(4-phenylmethyloxybenzylidene)-3,5-dihydro-4H-imidazol-4-one (**6d**).* Yield = 70%. Yellow powder. Mp = 174–176 °C. ^{1}H NMR (DMSO-d_6) δ = 1.43 (t, 3H, J = 7.3 Hz, CH_3CH_2S); 3.04 (s, 3H, NCH_3); 3.31 (q, 2H, J = 7.1 Hz, CH_3CH_2S); 5.17 (s, 2H, $PhCH_2O$); 6.83 (s, 1H, =CH); 7.07 (d, 2H, J = 8.8 Hz, H-2′, Ar); 7.37–7.46 (m, 5H, J = 7.1 Hz, H-2″, H-3″, H-4″, Ar); 8.15 (d, 2H, J = 8.8 Hz, H-3′, Ar). ^{13}C NMR (DMSO-d_6) δ = 14.25 (CH_3CH_2S); 24.54 (NCH_3); 26.24 (CH_3CH_2S); 69.27 ($PhCH_2O$); 115.15 (=CH); 122.22 (C=, C-5); 127.13 (C-4′, Ar); 127.73 (C-2′, C-3′, Ar); 127.91 (C-2″, Ar); 128.41 (C-2′, C-3′, Ar); 133.43 (C-3″, Ar); 136.49 (C-1′, Ar); 136.66 (C-4″, Ar); 159.62 (C-1″, Ar); 163.79 (C=N, C-2); 168.75 (C=O, C-4). HRMS, m/z = 352.1241 found (calculated for $C_{20}H_{20}N_2O_2S$, M^+ requires 352.1245).

*5.1.3.5. (5Z)-5-(4-Butyloxybenzylidene)-2-ethylsulfanyl-3-methyl-3,5-dihydro-4H-imidazol-4-one (**6e**).* Yield = 88%. White powder. Mp = 108–110 °C. ^{1}H NMR ($CDCl_3$) δ = 0.99 (t, 3H, J = 7.4 Hz, $CH_3CH_2CH_2CH_2O$); 1.51 (sext, 2H, J = 7.8 Hz, $CH_3CH_2CH_2CH_2O$); 1.52 (t, 3H, J = 7.4 Hz, CH_3CH_2S); 1.82 (quint, 2H, J = 6.8 Hz, $CH_3CH_2CH_2CH_2O$); 3.15 (s, 3H, CH_3N); 3.75 (qt, 2H, J = 7.4 Hz, CH_3CH_2S); 4.02 (t, 2H, J = 6.5 Hz, $CH_3CH_2CH_2CH_2O$); 6.92 (dd, 2H, J = 8.9 Hz, H-2′, Ar); 6.92 (s, 1H, =CH); 8.11 (dd, 2H, J = 8.6 Hz, H-3′, Ar). ^{13}C NMR ($CDCl_3$) δ = 13.83 ($CH_3CH_2CH_2CH_2O$); 14.33 (CH_3CH_2S); 19.21 ($CH_3CH_2CH_2CH_2O$); 25.11 ($CH_3CH_2CH_2CH_2O$); 26.49 (NCH_3); 31.19 (CH_3CH_2S); 67.77 ($CH_3CH_2CH_2CH_2O$); 114.71 (C-2′, Ar); 123.99 (=CH); 127.24 (C=, C-5); 133.68 (C-3′, Ar); 136.76 (C-1′, Ar); 160.57 (C-4′, Ar); 163.11 (C=N, C-2); 170.04 (C=O, C-4). HRMS, m/z = 341.1300 found (calculated for $C_{17}H_{22}N_2O_2SNa$, $[M + Na]^+$ requires 341.12997).

*5.1.3.6. (5Z)-2-Ethylsulfanyl-3-methyl-5-(4-phenylmethyloxybenzylidene)-3,5-dihydro-4H-imidazol-4-one (**6f**).* Yield = 78%. Yellow powder. Mp = 136–138 °C. ^{1}H NMR (DMSO-d_6) δ = 0.88 (t, 3H, J = 7.2 Hz, $NCH_2CH_2CH_2CH_3$); 1.22 (sext, 2H, J = 7.6 Hz, $NCH_2CH_2CH_2CH_3$); 1.43 (t, 3H, J = 7.4 Hz, CH_3CH_2S); 1.54 (sext, 2H, J = 7.7 Hz, $NCH_2CH_2CH_2CH_3$); 3.33 (q, 2H, J = 7.3 Hz, CH_3CH_2S); 6.08 (s, 2H, $PhCH_2O$); 6.81 (s, CH=); 7.55 (dd, 5H, J = 6.9 Hz, H-2″, H-3″, H-4′, Ar); 8.02 (d, 4H, J = 1.7 Hz, H-2′, H-3′, Ar). ^{13}C NMR (DMSO-d_6) δ = 13.41 ($CH_3CH_2CH_2CH_2N$); 14.18 (CH_3CH_2S); 19.31 ($CH_3CH_2CH_2CH_2N$); 24.76 ($CH_3CH_2CH_2CH_2N$); 30.30 (CH_3CH_2S); 40.29 ($CH_3CH_2CH_2CH_2N$); 101.52 ($PhCH_2O$); 108.57 (=CH); 110.01 (C=, C-5); 122.38 (Ar); 127.89 (Ar); 128.59 (Ar); 136.53 (Ar); 147.57 (Ar); 148.79 (Ar); 163.64 (C=N, C-2); 168.64 (C=O, C-4). HRMS, m/z = 394.1712 found (calculated for $C_{22}H_{26}N_2O_2S$, M^+ requires 394.1715).

*5.1.4. Standard procedure for the synthesis of N,N′-bis[(5Z)-5-arylidene-4-oxo-3,5-dihydro-4H-imidazolin-2-yl]diamine **8**(**a**–**d**), **9**(**a**–**f**), **10**(**a**–**g**) by sulphur/nitrogen displacement under microwave irradiation*

A mixture of 5-arylidene-2-ethylsulfanyl-3,5-dihydro-4*H*-imidazoline-4-one **6** (2 mmol, 1 equiv) and ethylenediamine **7a** (120 or 180 mg, 1 or 1.5 mmol, 1 or 1.5 equiv) or piperazine **7b** (172 mg, 2 mmol, 1 equiv) or *N*,*N*′-bis(3-aminopropyl)piperazine **7c** (0.2 g, 1 mmol, 0.5 equiv) was placed in a borosilicate glass vial (10 ml) with a Teflon® magnetic stir bar and sealed with a snap cap. The glass tube was then introduced into an Explorer® 24 CEM microwave cavity (P = 300 W). The stirred mixture was irradiated at 100–160 °C (with a power of 200 W) for 20–45 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down to room temperature and 10 ml of cooled methanol (4 °C) were added directly in the glass vial. The resulting precipitated product **8** was filtered off, washed with 2 × 5 ml of methanol and dried under high vacuum (10^{-2} Torr) at room temperature for 1 h. After ^{1}H NMR analysis, the desired product **8** was purified by recrystallization from methanol.

*5.1.4.1. 1,2-Bis-[(5Z)-3-methyl-5-(4-methoxyphenyl)methylene-4-oxo-3,5-dihydro-4H-imidazol-2-yl]ethylene diamine (**8a**).* Prepared from **7a**: 1 equiv. Reaction conditions: 120 °C, 30 min. Yield = 20%. Orange powder. Mp > 260 °C. ^{1}H NMR (DMSO-d_6) δ = 2.96 (s, 6H, NCH_3); 3.74 (s, 4H, $NH(CH_2)_2NH$); 3.74 (s, 6H, OCH_3); 6.39 (s, 2H, =CH); 6.85 (d, J = 8.6 Hz, 4H, H-2′, Ar); 7.76 (br s, 2H, NH); 8.01 (d, 4H, J = 8.6 Hz, H-3′, Ar). ^{13}C NMR (DMSO-d_6) δ = 25.39 (NCH_3); 40.62 ($N(CH_2)_2N$); 54.98 (OCH_3); 112.90 (C=CH), 113.83 (C-2′, Ar); 128.54 (C-1′, Ar); 131.71 (C-3′, Ar); 138.49 (C = , C-5); 158.20 (C-4′, Ar); 158.63 (C=N, C-2); 169.55 (C=O, C-4). HRMS, m/z = 489.2240 found (calculated for $C_{26}H_{29}N_6O_4$, $[M + H]^+$ requires 489.2248).

*5.1.4.2. 1,2-Bis-[(5Z)-5-(1,3-benzodioxol-5-yl)methylene-3-methyl-4-oxo-3,5-dihydro-4H-imidazol-2-yl]ethylene diamine (**8b**).* Prepared from **7a**: 1 equiv. Reactions conditions: 120 °C, 30 min. Yield = 25%. Orange powder. Mp > 260 °C. ^{1}H NMR (DMSO-d_6) δ = 2.96 (s, 6H, NCH_3); 3.72 (s, 4H, $NH(CH_2)_2NH$); 5.98 (s, 4H, OCH_2O); 6.37 (s, 2H, =CH); 6.84 (d, 2H, J = 8.1 Hz, H-6′, Ar); 7.40 (dd, 2H, J = 7.2 Hz, H-5′, Ar); 7.80 (br s, 2H, NH); 7.90 (s, 2H, H-2′, Ar). ^{13}C NMR (DMSO-d_6) δ = 25.41 (NCH_3); 40.30 ($N(CH_2)_2N$); 100.93 (OCH_2O); 108.25 (C-2′, Ar); 109.52 (C-5′, Ar); 112.97 (C-6′, Ar); 125.13 (C=CH); 130.28 (C-1′, Ar); 138.73 (C = , C-5); 146.62 (C-4′, Ar); 147.16 (C-3′, Ar); 158.26 (C=N, C-2); 169.48 (C=O, C-4). HRMS, m/z = 517.1838 found (calculated for $C_{26}H_{25}N_6O_6$, $[M + H]^+$ requires 517.1830).

*5.1.4.3. 1,2-Bis-[(5Z)-5-(4-benzyloxyphenyl)methylene-3-methyl-4-oxo-3,5-dihydro-4H-imidazol-2-yl]ethylene diamine (**8c**).* Prepared from **7a**: 1 equiv. Reactions conditions: 120 °C, 30 min. Yield = 11%. Orange powder. Mp > 260 °C. ^{1}H NMR (DMSO-d_6) δ = 2.96 (s, 6H, NCH_3); 3.72 (s, 4H, $NH(CH_2)_2NH$); 5.09 (s, 4H, $PhCH_2O$); 6.40 (s, 2H, =CH); 6.92 (d, 4H, J = 8.3 Hz, H-2′, Ar); 7.38 (m, 10H, J = 6.1 Hz, H-2″, H-4″, Ar); 7.77 (br s, 2H, NH); 8.01 (d, 4H, J = 8.4 Hz, H-4″, Ar). ^{13}C NMR (DMSO-d_6) δ = 25.38 ($NH(CH_2)_2NH$); 40.29 (NCH_3); 69.09 ($PhCH_2O$); 112.83 (=CH); 114.70 (C=, C-5); 127.60 (C-2); 127.79 (C-2′, Ar); 128.39 (C-3′, Ar); 128.75 (C-4″, Ar); 131.70 (C-3″, Ar); 136.92 (C-1′, Ar); 138.57 (C-4′, Ar); 157.71 (C-1″, Ar); 158.24 (C=N, C-2); 170.01 (C=O, C-4). HRMS, m/z = 641.2872 found (calculated for $C_{38}H_{37}N_6O_4$, $[M + H]^+$ requires 641.2871).

*5.1.4.4. 1,2-Bis-[(5Z)-5-(4-butyloxyphenyl)methylene-3-methyl-4-oxo-3,5-dihydro-4H-imidazol-2-yl]ethylene diamine (**8d**).* Prepared from **7a**: 1.5 equiv. Reactions conditions: 100 °C, 20 min. Yield = 10%. Orange powder. Mp = 220 °C. ^{1}H NMR (DMSO-d_6) δ = 0.92 (t, 6H, J = 6.2 Hz, $CH_3(CH_2)_3O$); 1.42 (sext, 4H, J = 3.3 Hz, $CH_3CH_2CH_2CH_2O$); 1.67 (quint, 4H, J = 3.2 Hz, $CH_3CH_2CH_2CH_2O$); 2.96 (s, 6H, NCH_3); 3.72 (s, 4H, $N(CH_2)_2N$); 3.92 (t, 4H, J = 7.5 Hz, $CH_3CH_2CH_2CH_2O$); 6.36 (s, 2H, =CH); 6.83 (d, 4H, J = 8.5 Hz, H-2′, Ar); 7.78 (br s, 2H, NH); 8.01 (d, 4H, J = 7.9 Hz, H-3′, Ar). ^{13}C NMR (DMSO-d_6) δ = 13.66 ($CH_3(CH_2)_2CH_2O$); 18.67 ($CH_3CH_2CH_2CH_2O$); 25.47 (NCH_3); 30.64 ($CH_3CH_2CH_2CH_2O$); 40.61 ($NH(CH_2)_2NH$); 67.03 ($CH_3(CH_2)_2CH_2O$); 112.95 (=CH); 114.30 (C-2′, Ar); 128.35 (C-1′, Ar); 131.74 (C-3′, Ar); 138.42 (C=, C-5); 158.07 (C=N, C-2); 158.16 (C-4′, Ar); 169.55 (C=O, C-4). HRMS, m/z = 541.2865 found (calculated for $C_{32}H_{41}N_6O_4$, $[M + H]^+$ requires 541.2871).

*5.1.4.5. 1,4-Bis-[(5Z)-5-phenylmethylene-3-methyl-4-oxo-3,5-dihydro-4H-imidazol-2-yl]piperazine (**9a**).* Prepared from **7b**: 1 equiv. Reaction conditions: 160 °C, 30 min. Yield = 47%. Orange powder. Mp > 260 °C. ^{1}H NMR (DMSO-d_6) δ = 3.25 (s, 6H, NCH_3); 3.81 (s, 8H, $N(CH_2)_4N$); 6.60 (s, 2H, C=CH); 7.28–7.43 (m, 8H, J = 7.3 Hz, H-3, H-4, Ar); 8.10 (d, 4H, J = 7.3 Hz, H-2, Ar). ^{13}C NMR (DMSO-d_6) δ = 29.60 (NCH_3); 46.68 ($N(CH_2)_4N$); 112.04 (=CH); 127.72 (C-4′, Ar); 128.28 (C-3′, Ar); 130.26 (C-2′, Ar); 134.99 (C-1′, Ar); 140.52 (C=, C-5); 162.54 (C=N, C-2); 169.66 (C=O, C-4). HRMS, m/z = 477.2007 found (calculated for $C_{26}H_{26}N_6O_2Na$, $[M + Na]^+$ requires 477.2009).

*5.1.4.6. 1,4-Bis-[(5Z)-3-methyl-5-(4-methoxyphenyl)methylene-4-oxo-3,5-dihydro-4H-imidazol-2-yl]piperazine (**9b**).* Prepared from **7b**: 1 equiv. Reaction conditions: 160 °C, 35 min. Yield = 72%. Orange powder. Mp > 260 °C. ^{1}H NMR (DMSO-d_6) δ = 3.22 (s, 6H, NCH_3); 3.74 (br s, 8H, $C_4H_{10}N_2$); 3.78 (s, 6H, OCH_3); 6.61 (s, 2H, =CH); 6.95 (d, 4H, J = 8.8 Hz, H-2′, Ar); 8.08 (d, 4H, J = 8.8 Hz, H-3′, Ar). ^{13}C NMR (DMSO-d_6) δ = 29.62 (NCH_3); 46.68 ($N(CH_2)_4N$); 55.80 (OCH_3); 114.70 (C-3′, Ar); 117.56 (=CH); 128.75 (C-1′, Ar); 132.86 (C-2′, Ar); 137.73 (C=, C-5); 160.23 (C-4′, Ar); 161.04 (C=N, C-2); 171.45 (C=O, C-4). HRMS, m/z = 515.2399 found (calculated for $C_{28}H_{31}N_6O_4$, $[M + H]^+$ requires 515.2401).

*5.1.4.7. 1,4-Bis-[(5Z)-5-(1,3-benzodioxol-5-yl)methylene-3-methyl-4-oxo-3,5-dihydro-4H-imidazol-2-yl]piperazine (**9c**).* Prepared from **7b**: 1 equiv. Reaction conditions: 140 °C, 45 min. Yield = 22%. Orange powder. Mp > 260 °C. ^{1}H NMR (DMSO-d_6) δ = 3.22 (s, 6H, NC$\underline{H}_3$); 3.75 (s, 8H, N(C$\underline{H}_2$)$_4$N); 6.05 (s, 4H, OC$\underline{H}_2$O); 6.58 (s, 2H, =CH); 6.94 (d, 2H, J = 1.5 Hz, H-6′, Ar); 7.48 (dd, 2H, J = 9.6 Hz, H-5′, Ar); 7.94 (s, 2H, H-2′, Ar). ^{13}C NMR (DMSO-d_6) δ = 29.68 (N$\underline{C}$H$_3$); 46.64 (N($\underline{C}$H$_2$)$_4$N); 101.54 (O$\underline{C}$H$_2$O); 108.69 (C-2′, Ar); 110.44 (C-5′, Ar); 117.38 (C-1′, Ar); 126.52 (C-6′, Ar); 127.89 (=$\underline{C}$H); 130.39 ($\underline{C}$=, C-5); 146.53 (C-4′, Ar); 148.03 (C-3′, Ar); 157.71 ($\underline{C}$=N, C-2); 161.14 ($\underline{C}$=O, C-4). HRMS, m/z = 543.1986 found (calculated for $C_{28}H_{27}N_6O_6$, $[M + H]^+$ requires 543.1986).

*5.1.4.8. 1,4-Bis-[(5Z)-5-(4-benzyloxyphenyl)methylene-3-methyl-4-oxo-3,5-dihydro-4H-imidazol-2-yl]piperazine (**9d**).* Prepared from **7b**: 1 equiv. Reaction conditions: 160 °C, 30 min. Yield = 62%. Orange powder. Mp > 260 °C. ^{1}H NMR (DMSO-d_6) δ = 3.22 (s, 6H, NC$\underline{H}_3$); 3.74 (s, 8H, $C_4H_{10}N_2$); 5.15 (s, 4H, PhC$\underline{H}_2$O); 6.61 (s, 2H, =CH); 7.02 (d, 4H, J = 8.9 Hz, H-2′, Ar); 7.36–7.44 (m, 10H, J = 4.5 Hz, H-2″, H-3″, H-4″, Ar); 8.07 (d, 2H, J = 7.6 Hz, H-3′, Ar). ^{13}C NMR (DMSO-d_6) δ = 29.4 (N$\underline{C}$H$_3$); 46.07 (N($\underline{C}$H$_2$)$_4$N); 69.21 (O$\underline{C}$H$_2$Ar); 114.85 (C-3′, Ar); 116.81 (=$\underline{C}$H); 127.74 (C-2″, Ar); 127.90 (C-4″, Ar); 128.13 (C-1′, Ar); 128.43 (C-3″, Ar); 132.42 (C-2′, Ar); 136.82 ($\underline{C}$=, C-5); 136.97 (C-1′, Ar); 158.49 (C-4′, Ar); 160.36 ($\underline{C}$=N, C-2); 170.93 ($\underline{C}$=O, C-4). HRMS, m/z = 667.3023 found (calculated for $C_{40}H_{39}N_6O_4$, $[M + H]^+$ requires 667.3028).

*5.1.4.9. 1,4-Bis-[(5Z)-5-(4-benzyloxyphenyl)methylene-3-butyl-4-oxo-3,5-dihydro-4H-imidazol-2-yl]piperazine (**9e**).* Prepared from **7b**: 1 equiv. Reaction conditions: 160 °C, 30 min. Yield = 15%. Yellow powder. Mp = 252–254 °C. ^{1}H NMR (DMSO-d_6) δ = 0.90 (t, 6H, J = 5.8 Hz, C$\underline{H}_3$(CH$_2$)$_3$N); 1.25 (m, 4H, J = 5.5 Hz, CH$_3$C$\underline{H}_2$CH$_2$CH$_2$N); 1.61 (m, 4H, J = 3.3 Hz, CH$_3$CH$_2$C$\underline{H}_2$CH$_2$N); 3.71 (t, 4H, J = 3.2 Hz, CH$_3$CH$_2$CH$_2$C$\underline{H}_2$N); 5.15 (s, 4H, ArC$\underline{H}_2$O); 6.61 (s, 2H, =C$\underline{H}$); 7.03 (d, 4H, J = 8 Hz, H-3′, Ar), 7.40–7.44 (m, 10H, J = 4.3–8.18 Hz, H-2″, H-4″, Ar); 8.08 (d, 4H, J = 8 Hz, H-2′, Ar). ^{13}C NMR (DMSO-d_6) δ = 13.64 ($\underline{C}$H$_3$CH$_2$CH$_2$CH$_2$N); 19.78 (CH$_3$$\underline{C}H_2CH_2CH_2$N); 30.43 (CH$_3CH_2$$\underline{C}H_2CH_2$N); 41.18 (CH$_3CH_2CH_2$$\underline{C}H_2$N); 46.91 (N($\underline{C}H_2$)$_4$N); 70.34 (O$\underline{C}H_2$Ar); 115.73 (C-3′, Ar); 117.79 (=$\underline{C}$H); 127.86 (C-2″, Ar); 128.144 (C-4″, Ar); 128.77 (C-3″, Ar); 128.98 (C-1″, Ar); 132.91 (C-1′, Ar); 132.91 (C-2′, Ar); 137.58 ($\underline{C}$=, C-5); 159.37 (C-4′, Ar); 160.84 ($\underline{C}$=N, C-2); 171.62 ($\underline{C}$=O, C-4). HRMS, m/z = 751.3962 found (calculated for $C_{46}H_{51}N_6O_4$, $[M + H]^+$ requires 751.3966).

*5.1.4.10. 1,4-Bis-[(5Z)-5-(4-butyloxyphenyl)methylene-3-methyl-4-oxo-3,5-dihydro-4H-imidazol-2-yl]piperazine (**9f**).* Prepared from **7b**: 1 equiv. Reaction conditions: 160 °C, 30 min. Yield = 26%. Yellow powder. Mp > 260 °C. ^{1}H NMR (DMSO-d_6) δ = 0.92 (t, 6H, J = 7.3 Hz, C$\underline{H}_3$(CH$_2$)$_3$O); 1.42 (sext, 4H, J = 7.2 Hz, CH$_3$C$\underline{H}_2$CH$_2$CH$_2$O); 1.69 (quint, 4H, J = 7.2 Hz, CH$_3$CH$_2$C$\underline{H}_2$CH$_2$O); 3.22 (s, 6H, NCH$_3$); 3.73 (N(CH$_2$)$_4$N); 4.01 (t, 4H, J = 6 Hz, CH$_3$(CH$_2$)$_2$C$\underline{H}_2$O); 6.61 (s, 2H, =CH); 6.94 (d, 4H, J = 8.6 Hz, H-2′, Ar); 8.06 (d, 4H, J = 8.5 Hz, H-3′, Ar). ^{13}C NMR (DMSO-d$_6$) δ = 13.75 ($\underline{C}$H$_3$CH$_2$CH$_2$CH$_2$O); 19.04 (CH$_3$$\underline{C}H_2CH_2CH_2$O); 29.60 (N$\underline{C}H_3$); 31.30 (CH$_3CH_2$$\underline{C}H_2CH_2$O); 46.71 (N($\underline{C}H_2$)$_4$N); 68.30 (CH$_3CH_2CH_2$$\underline{C}H_2$O); 115.35 (C-3′, Ar); 117.69 (=$\underline{C}$H); 128.65 (C-1′, Ar); 132.87 (C-2′, Ar); 137.68 ($\underline{C}$=, C-5); 159.71 (C-4′, Ar); 161.05 ($\underline{C}$=N, C-2); 171.46 ($\underline{C}$=O, C-4). HRMS, m/z = 599.3334 found (calculated for $C_{34}H_{43}N_6O_4$, $[M + H]^+$ requires 599.3340).

*5.1.4.11. N,N′-Bis-[(5Z)-5-phenylmethylene-3-methyl-4-oxo-3,5-dihydro-4H-imidazol-2-yl)-1,4-bis-(3-aminopropyl)piperazine (**10a**).* Prepared from **7c**: 0.5 equiv. Reaction conditions: 150 °C, 30 min. Yield = 26%. Yellow powder. Mp > 260 °C. ^{1}H NMR (DMSO-d$_6$) δ = 1.79 (t, 4H, J = 6.3 Hz, NCH$_2$C$\underline{H}_2$CH$_2$N(CH$_2$)$_4$N); 2.28 (t, 4H, J = 6.6 Hz; NC$\underline{H}_2$CH$_2$CH$_2$N(CH$_2$)$_4$N); 2.28 (s, 8H; NCH$_2$CH$_2$CH$_2$N(C$\underline{H}_2$)$_4$N); 3.02 (s, 6H, NC$\underline{H}_3$); 3.44 (quint, 4H, J = 6.7 Hz, NCH$_2$CH$_2$C$\underline{H}_2$N(CH$_2$)$_4$N); 3.75 (s, 6H, OC$\underline{H}_3$); 6.35 (s, 2H; =CH); 6.90 (d, 4H, J = 9.7 Hz, H-2′, Ar); 7.59 (br s, 2H, N$\underline{H}$); 8.20 (d, 4H, J = 9.6 Hz, H-3′, Ar). ^{13}C NMR (DMSO-d$_6$) δ = 25.52 (N$\underline{C}$H$_3$); 25.92 (NCH$_2$$\underline{C}H_2CH_2$N(CH$_2$)$_4$N); 40.30 (N$\underline{C}H_2CH_2CH_2$N(CH$_2$)$_4$N); 52.82 (N($\underline{C}H_2$)$_4$N); 55.48 (NCH$_2CH_2$$\underline{C}H_2$N(CH$_2$)$_4$N); 112.04 (=$\underline{C}$H); 127.19 (C-4′, Ar); 128.18 (C-3′, Ar); 130.06 (C-2′, Ar); 135.99 (C-1′, Ar); 140.52 ($\underline{C}$ = , C-5); 158.54 ($\underline{C}$=N, C-2); 169.62 ($\underline{C}$=O, C-4). HRMS, m/z = 569.3354 found (calculated for $C_{32}H_{41}N_8O_2$, $[M + H]^+$ requires 569.3347).

*5.1.4.12. N,N′-bis-[(5Z)-3-methyl-5-(4-methoxyphenylmethylene-4-oxo-3,5-dihydro-4H-imidazol-2-yl]-1,4-bis-(3-aminopropyl)piperazine (**10b**).* Prepared from **7c**: 0.5 equiv. Reaction conditions: 160 °C, 30 min. Yield = 22%. Yellow powder. Mp > 260 °C. ^{1}H NMR (DMSO-d_6) δ = 1.79 (t, 4H, J = 6.3 Hz, NCH$_2$C$\underline{H}_2$CH$_2$N(CH$_2$)$_4$N); 2.28 (t, 4H, J = 6.6 Hz, NC$\underline{H}_2$CH$_2$CH$_2$N(CH$_2$)$_4$N); 2.28 (s, 8H, NCH$_2$CH$_2$CH$_2$N(C$\underline{H}_2$)$_4$N); 3.02 (s, 6H, NC$\underline{H}_3$); 3.44 (quint, 4H, J = 6.7 Hz, NCH$_2$CH$_2$C$\underline{H}_2$N(CH$_2$)$_4$N); 3.75 (s, 6H, OC$\underline{H}_3$); 6.35 (s, 2H, =C$\underline{H}$); 6.90 (d, 4H, J = 9.7 Hz, H-2′, Ar); 7.59 (br s, 2H, N$\underline{H}$); 8.20 (d, 4H, J = 9.6 Hz, H-3, Ar). ^{13}C NMR (DMSO-d_6) δ = 25.45 (N$\underline{C}$H$_3$); 25.92 (NCH$_2$$\underline{C}H_2CH_2$N(CH$_2$)$_4$N); 40.28 (NCH$_2CH_2$$\underline{C}H_2$N(CH$_2$)$_4$N); 52.84 (NCH$_2CH_2CH_2$N(CH$_2$)$_4$N); 55.51 (N$\underline{C}H_2CH_2CH_2$N(CH$_2$)$_4$N); 112.61 (=$\underline{C}$H); 113.78 (C-2′, Ar); 128.65 (C-1′, Ar); 138.57 (C-4′, Ar); 157.84 ($\underline{C}$=N, C-2); 158.62 ($\underline{C}$=, C-5); 169.60 ($\underline{C}$=O, C-4). HRMS, m/z = 629.3557 found (calculated for $C_{34}H_{45}N_8O_4$, $[M + H]^+$ requires 629.3558).

*5.1.4.13. N,N′-bis-[(5Z)-5-(1,3-benzodioxol-5-yl)methylene-3-methyl-4-oxo-3,5-dihydro-4H-imidazol-2-yl]-1,4-bis-(3-aminopropyl)piperazine (**10c**).* Prepared from **7c**: 0.5 equiv. Reaction conditions: 160 °C, 30 min. Yield = 36%. Yellow powder. Mp > 260 °C. ^{1}H NMR (DMSO-d_6) δ = 1.79 (t, 4H, J = 13.9 Hz, NC$\underline{H}_2$CH$_2$CH$_2$N(CH$_2$)$_4$N); 2.37 (t, 4H, J = 6.2 Hz, NCH$_2$CH$_2$C$\underline{H}_2$N(CH$_2$)$_4$N); 2.37 (s, 8H; N(CH$_2$)$_4$N); 3.02 (s, 6H, NCH$_3$); 3.44 (t, 4H, J = 13.2 Hz, NC$\underline{H}_2$CH$_2$CH$_2$N(CH$_2$)$_4$N); 5.99 (s, OC$\underline{H}_2$O); 6.34 (s, 2H, =C$\underline{H}$); 6.87 (d, 2H, J = 8.0 Hz, H-6′, Ar); 7.35 (d, 2H, J = 7.9 Hz, H-5′, Ar); 7.65 (br s, 2H, NH); 7.96 (s, 2H, H-2′, Ar). ^{13}C NMR (DMSO-d_6) δ = 25.46 (N$\underline{C}$H$_3$); 25.84 (NCH$_2$$\underline{C}H_2CH_2$N(CH$_2$)$_4$N); 40.22 (N$\underline{C}H_2CH_2CH_2$N(CH$_2$)$_4$N); 52.75 (N($\underline{C}H_2$)$_4$N); 55.48 (NCH$_2CH_2$-$\underline{C}H_2$N(CH$_2$)$_4$N); 100.91 (O$\underline{C}H_2$O); 108.20 (=$\underline{C}$H); 109.34 (C-6′, Ar); 112.61 (C-5′, Ar); 125.15 (C-2′, Ar); 130.34 (C-1′, Ar); 138.84 ($\underline{C}$=, C-5); 146.58 (C-4′, Ar); 147.14 (C-3′, Ar); 157.94 ($\underline{C}$=N, C-2); 169.51 ($\underline{C}$=O, C-4). HRMS, m/z = 657.3146 found (calculated for $C_{34}H_{41}N_8O_6$, $[M + H]^+$ requires 657.3144).

*5.1.4.14. N,N′-bis-[(5Z)-3-butyl-5-(1,3-benzodioxol-5-yl)methylene-4-oxo-3,5-dihydro-4H-imidazol-2-yl]-1,4-bis-(3-aminopropyl)piperazine (**10d**).* Prepared from **7c**: 0.5 equiv. Reaction conditions: 150 °C, 30 min. Yield = 36%. Yellow powder. Mp = 262 °C. ^{1}H NMR (DMSO-d_6) δ = 0.87 (t, 6H, J = 7.1 Hz, C$\underline{H}_3$CH$_2$CH$_2$CH$_2$N); 1.23 (sext, 4H, J = 6.5 Hz, CH$_3$C$\underline{H}_2$CH$_2$CH$_2$N); 1.46 (quint, 4H, J = 6.6 Hz, CH$_3$CH$_2$C$\underline{H}_2$CH$_2$N); 1.79 (t, 4H, J = 5.4 Hz, NCH$_2$CH$_2$C$\underline{H}_2$N(CH$_2$)$_4$N); 2.36 (t, 8H, J = 5.9 Hz, NCH$_2$CH$_2$CH$_2$N(C$\underline{H}_2$)$_4$N); 3.44 (t, 4H, J = 4.2 Hz, NC$\underline{H}_2$CH$_2$CH$_2$N-(CH$_2$)$_4$N); 3.53 (t, 4H, J = 6.3 Hz, CH$_3$CH$_2$CH$_2$C$\underline{H}_2$N); 5.99 (s, 4H, OC$\underline{H}_2$O); 6.32 (s, 2H, =C$\underline{H}$); 6.87 (d, 2H, J = 8.1 Hz, H-6′, Ar); 7.35 (d, 2H, J = 8.2 Hz, H-5′, Ar); 7.59 (br s, 2H, NH); 7.95 (s, 2H, H-2′, Ar). ^{13}C NMR (DMSO-d_6) δ = 13.56 (CH$_3$CH$_2$CH$_2$CH$_2$N); 19.27 (CH$_3$$\underline{C}H_2CH_2CH_2$N); 21.13 (CH$_3CH_2$$\underline{C}H_2CH_2$N); 25.93 (NCH$_2$$\underline{C}H_2CH_2$N(CH$_2$)$_4$N); 30.36 (CH$_3CH_2$-$\underline{C}H_2CH_2$N); 38.15 (N$\underline{C}H_2CH_2CH_2$N(CH$_2$)$_4$N); 52.81 (NCH$_2CH_2CH_2$-N($\underline{C}H_2$)$_4$N); 55.48 (NCH$_2CH_2$$\underline{C}H_2$N(CH$_2$)$_4$N); 100.91 (O$\underline{C}H_2$O); 108.20 (=$\underline{C}$H); 109.34 (C-6′, Ar); 112.57 (C-5′, Ar); 125.14 (C-2′, Ar); 130.39 (C-4′, Ar); 133.90 (C-1′, Ar); 138.64 (C-3′, Ar); 138.90 ($\underline{C}$=, C-5); 146.58 ($\underline{C}$=N, C-2); 147.15 ($\underline{C}$=O, C-4). HRMS, m/z = 741.4083 found (calculated for $C_{40}H_{53}N_8O_6$, $[M + H]^+$ requires 741.4083).

*5.1.4.15. N,N′-bis-[(5Z)-5-(4-benzyloxyphenyl)methylene-3-methyl-4-oxo-3,5-dihydro-4H-imidazol-2-yl]-1,4-bis-(3-aminopropyl)piperazine (**10e**).* Prepared from **7c**: 0.5 equiv. Reaction conditions: 160 °C, 30 min. Yield = 24%. Yellow powder. Mp > 260 °C. ^{1}H NMR (DMSO-d_6) δ = 1.80 (quint, 4H, J = 6.7 Hz, HNCH$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 2.41 (t, 4H, J = 6.6 Hz, HNCH$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 2.43 (s, 8H, HNCH$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 2.99 (s, 6H, NCH$_3$); 3.42 (t, 4H, J = 5.2 Hz, HNCH$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 5.09 (s, 4H, PhCH$_2$O); 6.35 (s, 2H, =CH); 6.96 (d, 4H, J = 8.8 Hz, H-2′, Ar); 7.32–7.42 (m, 10H, J = 7.1 Hz, H-2′, H-4′, Ar); 8.02 (d, 4H, J = 8.8 Hz, H-3′, Ar). ^{13}C NMR (DMSO-d_6) δ = 25.42 (NCH$_3$); 25.94 (HNCH$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 39.15 (N(CH$_2$)$_4$N); 52.85 (HNCH$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 55.52 (HNC H$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 69.10 (PhCH$_2$O); 112.52 (=CH); 114.62 (C-2′, Ar); 127.58 (C-2″, Ar); 127.77 (C-4′, Ar); 128.35 (C-3′, Ar); 128.87 (C-1′, Ar); 131.63 (C-3″, Ar); 136.88 (C-1″, Ar); 138.67 (C-4′, Ar); 157.67 (C=, C-5); 157.86 (C=N, C-2); 169.56 (C=O, C-4). HRMS, m/z = 781.4185 found (calculated for $C_{46}H_{53}N_8O_4$, $[M + H]^+$ requires 781.4183).

*5.1.4.16. N,N′-Bis-[(5Z)-3-butyl-5-(4-benzyloxyphenyl)methylene-4-oxo-3,5-dihydro-4H-imidazol-2-yl]-1,4-bis-(3-aminopropyl)piperazine (**10f**).* Prepared from **7c**: 0.5 equiv. Reaction conditions: 160 °C, 30 min. Yield = 16%. Yellow powder. Mp = 222–224 °C. ^{1}H NMR (DMSO-d_6) δ = 0.86 (t, 6H, J = 7.3 Hz, CH$_3$CH$_2$CH$_2$CH$_2$N); 1.22 (quint, 4H, J = 7.4 Hz, CH$_3$CH$_2$CH$_2$CH$_2$N); 1.44 (quint, 4H, J = 6.1 Hz, CH$_3$CH$_2$CH$_2$CH$_2$N); 1.79 (quint, 4H, J = 6.3 Hz, HNCH$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 2.37 (t, 4H, J = 6.1 Hz, HNCH$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 2.39 (s, 8H, HNCH$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 3.45 (t, 4H, J = 5.1 Hz, NHCH$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 3.51 (t, 4H, J = 6.6 Hz, CH$_3$CH$_2$CH$_2$CH$_2$N); 5.10 (s, 4H, PhCH$_2$O); 6.34 (s, 2H, =CH); 6.97 (d, 4H, J = 8.8 Hz, H-2′, Ar); 7.30–7.41 (m, 10H, J = 6.8 Hz, H-2″, H-3″, H-4″, Ar); 7.53 (br s, 2H, NH); 8.02 (d, 4H, J = 8.7 Hz, H-3′, Ar). ^{13}C NMR (DMSO-d_6) δ = 13.56 (CH$_3$(CH$_2$)$_3$N); 19.27 (CH$_3$CH$_2$(CH$_2$)$_2$N); 25.96 (CH$_3$CH$_2$CH$_2$CH$_2$N); 30.37 (CH$_3$CH$_2$CH$_2$CH$_2$N); 38.11 (N(CH$_2$)$_4$N); 52.88 (HNCH$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 55.53 (HNC H$_2$CH$_2$CH$_2$(CH$_2$)$_4$N); 69.11 (PhCH$_2$O); 112.48 (=CH); 114.63 (C-2′, Ar); 127.60 (C-2″, Ar); 127.78 (C-4″, Ar); 128.36 (C-3″, Ar); 128.89 (C-1′, Ar); 131.64 (C-3′, Ar); 136.90 (C-4′, Ar); 157.30 (C=, C-5); 157.68 (C=N, C-2); 169.60 (C=O, C-4). HRMS, m/z = 865.5125 found (calculated for $C_{52}H_{65}N_8O_4$, $[M + H]^+$ requires 865.5123).

*5.1.4.17. N,N′-Bis-[(5Z)-5-(4-butoxyphenyl)methylene-3-methyl-4-oxo-3,5-dihydro-4H-imidazol-2-yl]-1,4-bis-(3-aminopropyl)piperazine (**10g**).* Prepared from **7c**: 0.5 equiv. Reaction conditions: 160 °C, 30 min. Yield = 21%. Yellow powder. Mp = 262–264 °C. ^{1}H NMR (DMSO-d_6) δ = 0.89 (t, 6H, J = 7.4 Hz, CH$_3$CH$_2$CH$_2$CH$_2$O); 1.40 (sext, 4H, J = 7.5 Hz, CH$_3$CH$_2$CH$_2$CH$_2$O); 1.65 (quint, 4H, J = 6.7 Hz, CH$_3$CH$_2$CH$_2$CH$_2$O); 1.79 (quint, 4H, J = 6.3 Hz, HNCH$_2$CH$_2$CH$_2$N(CH$_2$)$_4$N); 2.39 (t, 4H, J = 6.8 Hz, HNCH$_2$CH$_2$CH$_2$N(CH$_2$)$_4$N); 2.41 (s, 8H, HNCH$_2$CH$_2$CH$_2$N(CH$_2$)$_4$N); 3.02 (s, 6H, NCH$_3$); 3.44 (t, 4H, J = 5.6 Hz, HNCH$_2$CH$_2$CH$_2$N(CH$_2$)$_4$N); 3.94 (t, 4H, J = 6.5 Hz, CH$_3$CH$_2$CH$_2$CH$_2$O); 6.34 (s, 2H, =CH); 6.87 (d, 4H, J = 8.8 Hz, H-2′, Ar); 7.59 (br s, 2H, NH); 8.01 (d, 4H, J = 8.8 Hz, H-3′, Ar). ^{13}C NMR (DMSO-d_6) δ = 14.12 (CH$_3$(CH$_2$)$_3$O); 19.17 (CH$_3$CH$_2$CH$_2$CH$_2$O); 25.94 (NCH$_3$); 26.47 (HNCH$_2$CH$_2$CH$_2$N(CH$_2$)$_4$N); 31.17 (CH$_3$CH$_2$CH$_2$CH$_2$O); 40.81 (HNCH$_2$CH$_2$CH$_2$N(CH$_2$)$_4$N); 53.37 (HNCH$_2$CH$_2$CH$_2$N(CH$_2$)$_4$N); 56.02 (HNCH$_2$CH$_2$CH$_2$N(CH$_2$)$_4$N); 67.57 (CH$_3$CH$_2$CH$_2$CH$_2$O); 113.23 (=CH); 114.73 (C-2′, Ar); 129.01 (C-1′, Ar); 132.18 (C-3′, Ar); 139.01 (C=, C-5); 158.30 (C-4′, Ar); 158.59 (C=N, C-2); 170.11 (C=O, C-4). HRMS, m/z = 713.4493 found (calculated for $C_{40}H_{57}N_8O_4$, $[M + H]^+$ requires 713.4497).

5.2. In vitro kinase inhibition assays

5.2.1. Buffer

Buffer A. 10 mM $MgCl_2$, 1 mM EGTA, 1 mM DTT, 25 mM Tris–HCl at pH 7.5, and 50 μg heparin/mL.

5.2.2. Kinase preparations and assays

Kinase activities were assayed in buffer A, at 30 °C, at a final ATP concentration of 15 μM. Blank values were subtracted and activities expressed in percent of the maximal activity, i.e., in the absence of inhibitors. Controls were performed with appropriate dilutions of DMSO. The kinase peptide substrates were obtained from Proteogenix (Oberhausbergen, France).

DYRK1A (rat recombinant, expressed in *Escherichia coli* as a GST fusion protein) was purified by affinity chromatography on glutathione-agarose and assayed in buffer A (+0.15 mg BSA/mL) using Woodtide (KKISGRLSPIMTEQ) (1.5 μg/assay) as a substrate, in the presence of 15 μM [γ-^{33}P] ATP (3000 Ci/mmol; 10 mCi/mL) in a final volume of 30 μL. After 30 min, incubation at 30 °C, the reaction was stopped by harvesting onto P81 phosphocellulose papers (Whatman) using a FilterMate harvester (Packard) and were washed in 1% phosphoric acid. Scintillation fluid was added and the radioactivity measured in a Packard counter.

CLK1 and CLK3 (mouse, recombinant, and expressed in *E. coli* as GST fusion proteins) were assayed in buffer A (+0.15 mg BSA/mL) with RS peptide (GRSRSRSRSRSR) (1 μg/assay).

GSK-3α/β (porcine brain, native) was assayed in buffer A and using a GSK-3 specific substrate (GS-1: YRRAAVPPSPSLSRHSSPHQSpEDEEE) (pS stands for phosphorylated serine) [24].

5.3. Cell-free assay for inhibition of β-hematin formation

Inhibition of formation of β-hematin in a cell-free assay was observed by using the following procedure. A stock solution (10 mL) of the studied compound (solution A) was prepared by dissolving 2 μmol of that compound in a mixture of DMSO (1 mL) and HEPES buffer 0.2 M (pH 7.0). A stock solution (10 mL) of hemin (solution B) was prepared by dissolving 2 μmol (1.3 mg) of hemin in a mixture of aqueous sodium hydroxide 0.1 M (5 mL) and HEPES buffer 0.2 M. The test solution of the studied compound was obtained by mixing solution A (1 mL), solution B (1 mL), acetate buffer pH 5 (1 mL) and HEPES buffer 0.2 M (2 mL). In the absence of compound **8** or **9** or **10**, β-hematin precipitated within a few minutes.

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