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Original paper

Synthesis and structure determination of 2,3-diaryl-9,9-dioxo-1*H*-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ols

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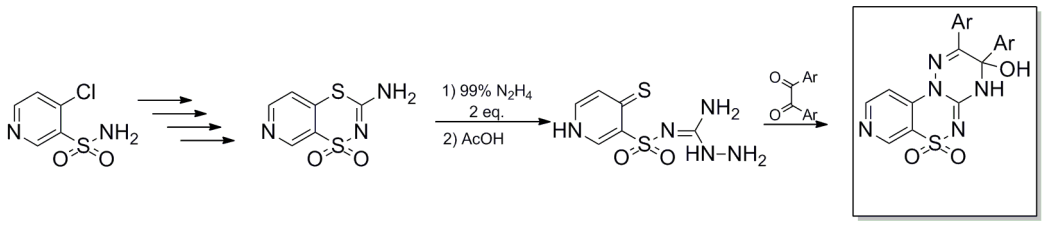
Graphical Abstract

Synthesis and structure determination of ~~novel~~ 2,3-diaryl-9,9-dioxo-1*H*-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ols, Jarosław Sławiński*, Aneta Pogorzelska, Beata Żołnowska, Tomasz Laskowski, Paweł Sowiński



ABSTRACT

3-Amino-1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine has been synthesized and applied to the synthesis of 3-amino-2-(4-thioxo-1,4-dihydropyridin-3-ylsulfonyl)guanidine. The reaction of the aminoguanidine with the appropriate 1,2-diarylethane-1,2-diones afforded 2,3-diaryl- 9,9-dioxo-1*H*-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol derivatives**.** The structure of these compounds, which represent a novel heterocyclic ring system, was confirmed on the basis of elemental analysis and spectroscopic data including COSY, NOESY, ROESY, HSQC and HMBC.

KEYWORDS:

4-Chloropyridine-3-sulfonamide

1,1-Dioxopyrido[4,3-*e*]-1,4,2-dithiazine

Synthesis

NMR studies

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1. Introduction

Arylsulfonamides have been shown to exhibit a variety of biological activities.[1] Among them, the derivatives modified by substition of the arylsulfonamide core by pyridothiadiazine ring system as well as 1,2,4-triazine scaffold constitute an important class of compounds with pharmacological properties .[2,3]

Pyridothiadiazines act as AMPA potentiators[4,5] (Figure 1, **I**), K_{ATP} channel openers[6,7] (Figure 1, **II**), CCK receptor ligands,[8] antibacterial and anticancer agents[2,3] (Figure 1, **III**, **IV, V**). The aforementioned biological activity of these compounds means it could find diverse therapeutic applications including the treatment of cognitive disorders,[4-6,9,10] gastro-intestinal disturbances,[8] anxiety,[8] cancer,[2,3] bacterial infections,[2,3] pancreatitis,[8] pain,[8] schizophrenia,[8,11] drug abuse,[8] arterial hypertension,[6,7] depression and Parkinson's disease.[12]

The 1,2,4-triazine scaffold has been found in numerous biologically active compounds.[13] An array of biological activities related to 1,2,4-triazine containing compounds, including antitumor[3,13-15] (Figure 1, **VI**) and antiviral[16,17] properties, has been reported. It is worth noting that various condensed 1,2,4-triazines also display a broad spectrum of therapeutically interesting activity.[18-24]

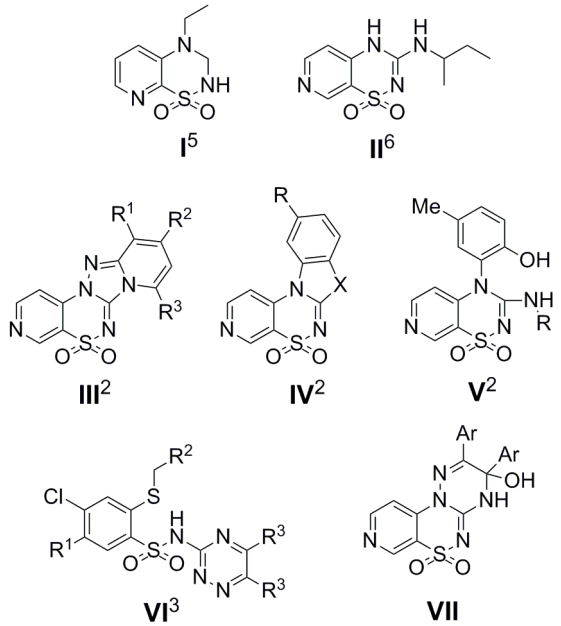


Figure 1. Structures of known AMPA potentiators **I**[5], potassium channel openers **II**[6], antibacterial and anticancer pyridothiadiazine derivatives **III-V**[2], antitumor *N*-(1,2,4-triazin-3-yl)benzenosulfonamides **VI**[3] and novel 9,9-dioxo-1*H*-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol derivatives **VII**.

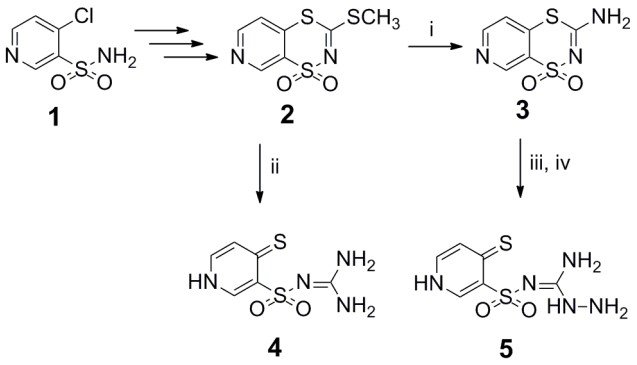
Due to a number of biological properties of nitrogen-containing heterocycles, the synthesis of these compounds is an important point of the search for new therapeutic agents. One of the general strategies in the preparations of these molecules is reaction between

dicarbonyl compounds and an amine group. Depending on the chemical structure of the two substrates, the reaction product can give mono- or polyazacycles. In the case of guanidine and 1,2-dicarbonyl compounds, the documented product is an appropriately substituted imidazole derivative,[25,26] while use of aminoguanidine leads to the corresponding triazine.[3,27-29] Herein we report the unexpected course of reaction between an aminoguanidine component, i.e. 3-amino-2-(4-thioxo-1,4-dihydropyridin-3-ylsulfonyl)guanidine, and benzil derivatives, which consequently led to formation of the new ring system 9,9-dioxo-1*H*-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol (Figure 1, **VII**). It could be seen that this structure may be consider as a condensed system of pyridothiadiazine with a 1,2,4-triazine ring.

2. Results and discussions

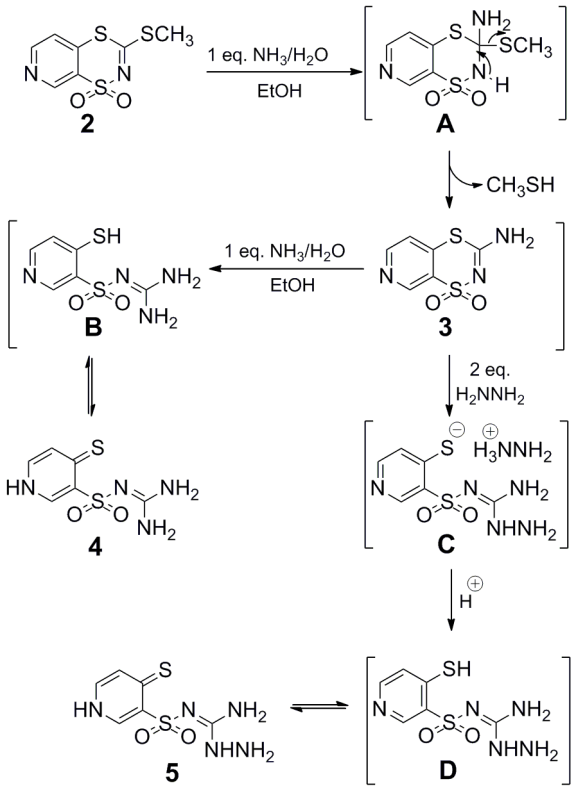
2.1. Synthetic chemistry

As presented in Scheme 1 the synthesis of the starting 2-(4-thioxo-1,4-dihydropyridin-3-ylsulfonyl)guanidine derivatives **4** and **5** was achieved in a multi-step reaction sequence starting from commercially available 4-chloropyridine-3-sulfonamide **1**. At first, 3-methylthio-1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine **2** was readily obtained according to the previously described procedure.[30] Further treatment of **2** with one molar equivalent of 25% ammonium hydroxide in ethanolic solution resulted in the formation of 3-amino-1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine **3** in an excellent yield 95%. On the other hand, when a two molar excess of ammonium hydroxide was used the ring opening reaction readily proceeded to furnish 2-(4-thioxo-1,4-dihydropyridin-3-ylsulfonyl)guanidine **4**. Similarly, reaction of **3** with two molar equivalents of hydrazine hydrate afforded 3-amino-2-(4-thioxo-1,4-dihydropyridin-3-ylsulfonyl)guanidine **5**. Yields of these reactions were high, 88% for both **4** and **5** (Schemes 1 and 2). Inspection of the IR and NMR spectroscopic data (see Experimental section) revealed that compounds **4** and **5**, in the solid state as well as DMSO solution, exist in a single 4-thioxopyridine tautomeric form.



Scheme 1. Reagents and conditions: (i) 1 eq. 25% $NH_{3\,aq}$, EtOH, 120 h, rt, 95%; (ii) 2 eq. 25% $NH_{3\,aq}$, EtOH, 90 h, rt then 3 h, reflux, 88%; (iii) 2 eq. 99% N_2H_4 hydrate, dry MeOH, 30-40 h, 88%; (iv) AcOH, 88%

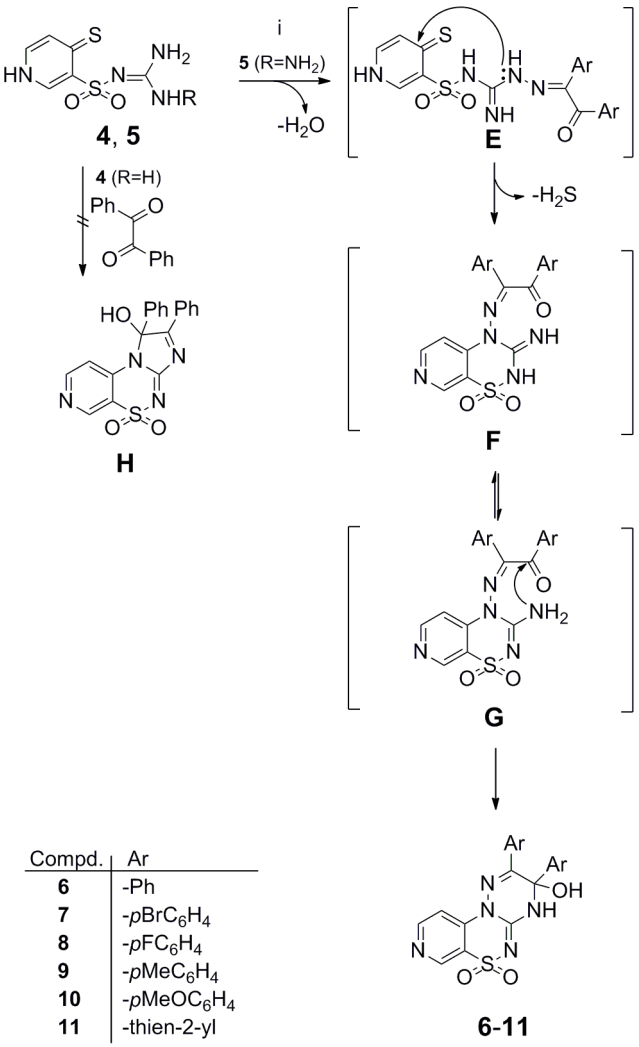
The proposed mechanism for the formation of 2-(4-thioxo-1,4-dihydropyridin-3-ylsulfonyl)guanidine derivatives **4** and **5** is shown in Scheme 2. The reaction sequence involved the initial formation of 3-aminopyridodithiazine **3** by nucleophilic substitution of thiomethyl group *via* a non-isolable adduct of type **A**. The subsequent transformation of **3** led to the formation of an intermediate guanidine **B**, containing a 4-mercaptopyridine ring which tautomerized to the stable 4-thioxopyridine giving compound **4**. In turn, reaction of **3** with an excess of hydrazine hydrate yielded an intermediate salt **C**, which upon acidification afforded 4-mercaptopyridine **D**. Further **D** tautomerization resulted in the stable 4-thioxopyridine derivative **5**.



Scheme 2. Proposed mechanism for the formation of 2-(4-thioxo-1,4-dihydropyridin-3-ylsulfonyl)guanidine derivatives **4**, **5**.

The reaction of aminoguanidine **5** with the appropriate 1,2-diarylethane-1,2-diones carried out in anhydrous dimethylsulfoxide (DMSO) at 80-85 ˚C for 42-58 h afforded the novel pentaazaphenanthrene ring system **6-11.** The proposed mechanism leading to the formation of products **6-11** is outlined in Scheme 3. The initial step is believed to be the formation of intermediate condensation/tautomerization product of type **E** which undergoes S_NAr addition-elimination process on the activated 4-position of pyridine ring to form pyridothiadiazine intermediate **F** with simultaneous H_2S elimination. The formation of **G** is due to the **F** tautomerization privileged because of the formation of the preferred thiadiazine system.[31] The final six-membered ring closure leading to the desired 2,3-diaryl-9,9-dioxo-1*H*-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol derivatives **6-11** was ensued upon attack of the amino group on the next carbonyl carbon atom (Scheme 3).

An attempt was also made to apply 2-(4-thioxo-1,4-dihydropyridin-3-ylsulfonyl)guanidine **4** to the reaction with benzil, that would allow the preparation of the corresponding cyclocondensation product of type **H** (Scheme 3). However, the reaction failed, even at a prolonged reaction time of over 60 hours, apparently due to the relatively low nucleophilicity of the sulfonylguanidine nitrogen atoms. As a result, a mixture of several products was obtained, of which only isolated in a pure state was disulfide derivative of compound **4**.



Compd.	Ar
6	-Ph
7	-*p*BrC$_6$H$_4$
8	-*p*FC$_6$H$_4$
9	-*p*MeC$_6$H$_4$
10	-*p*MeOC$_6$H$_4$
11	-thien-2-yl

Scheme 3. Proposed mechanism of the formation of 2,3-diaryl-9,9-dioxo-1*H*-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol derivatives **6-11**; (i) 1,2-diarylethane-1,2-dione, dry DMSO, 80-85 °C, 42-58 h, 17-60%.

The structures of **6-11** were confirmed by IR, NMR and MS data and elemental analyses.

In the IR spectra of compounds **6-11** the characteristic OH and NH groups appeared as overlapping broad absorption bands in the 3378-3302 cm^{-1}. In the ^{1}H NMR spectra (DMSO-d$_6$) of the compounds **6-11** the chemical shifts of the two singlets in the 8.24-8.57 ppm and 10.31-10.73 ppm regions were assigned to the protons of OH and NH groups respectively. The presence of these groups was also confirmed by the rapid exchange observed in the NMR spectra of compounds **10** made in DMSO with deuterium oxide (D$_2$O). Moreover, signals of protons H-8, H-5 and H-6 from the pyridine ring of the tricyclic pentaazaphenathrene system shifted downfield in comparison with the analogous 4-thioxo-1,4-dihydropyridine protons H-2, H-5 and H-6 of **2**.

2.2. NMR spectroscopy studies

The NMR spectroscopy studies, consisting of COSY, NOESY, ROESY, HSQC and HMBC experiments, resulted in structure confirmation of 9,9-dioxo-2,3-di(thien-2-yl)-1*H*-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol **11** (Figure 2) by proton and carbon assignments which are given in **Tables 1** and **2**, respectively. The resonance signal of proton H8 was identified as the only one singlet showing a correlation to a sp^2 carbon in HSQC spectrum. The COSY spectrum of **11** allowed the connectivities within three structural blocks, namely C5-C6, C14-C16 and C19-C21 to be traced. The C14-C16 and C19-C21 spin systems were distinguished by the presence of H5/H19 ROE and upon the C2/H14 and C2/H16 heteronuclear correlations. The chemical shift of carbon C2 in the ^{13}C NMR spectrum (77.5 ppm) indicated its sp^3 hybridization. The H11/H14 and H11/H19 ROEs with C2/H11 and C14/H11 HMBC correlations determined the position of the hydroxyl group. The presence of H1/H11 and H1/H14 ROEs with C2/H1, C3/H1, C4b/H1, C10a/H1, C13/H1 and C18/H1 HMBC correlations revealed the position of the protonated nitrogen. The assignments of quaternary sp^2 carbons C3, C4b, C8a, C10a, C13 and C18 were made upon several heteronuclear correlations observed in the HMBC spectrum, listed in **Table 2**.

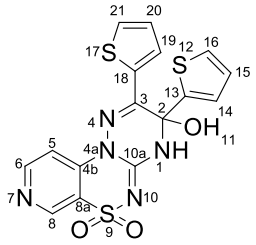


Figure 2. The structure of 9,9-dioxo-2,3-di(thien-2-yl)-1*H*-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol **11**; the atom numbers are correlated with the NMR results

Table 1. ^{1}H NMR data for 11.

Proton no.	^{1}H δ (ppm)	^3J (HH) contacts (Hz)	NOE/ROE contacts
H-1	10.72	-	H-11; H-14
H-5	7.87	5.94 (H-6)	H-6; H-19
H-6	8.86	5.94 (H-5)	H-5
H-8	8.98	-	-
H-11	8.56	-	H-1; H-14; H-19
H-14	7.22	3.41 (H-15)	H-1; H-11; H-15; H-19
H-15	7.00	3.41 (H-14); 4.78 (H-16)	H-14; H-16
H-16	7.59	4.78 (H-15)	H-15
H-19	7.47	3.34 (H-20)	H-5; H-11; H-14; H-20
H-20	7.05	3.34 (H-19); 4.84 (H-21)	H-19; H-21
H-21	7.73	4.84 (H-20)	H-20

Table 2. ^{13}C NMR data for 11 with long-range C/H couplings observed in HMBC spectrum.

Carbon no.	^{13}C δ (ppm)	HMBC to proton [see: Table 1]
C-2	77.5	H-11; H-14; H-16
C-3	148.5	H-1; H-11; H-19; H-20; H-21
C-4b	142.7	H-1; H-5; H-6; H-8
C-5	110.3	H-6; H-8
C-6	153.6	H-5; H-8
C-8	145.5	H-6
C-8a	121.5	H-5; H-6; H-8
C-10a	148.5	H-1
C-13	145.5	H-1; H-11; H-14; H-15; H-16
C-14	127.8	H-11; H-15; H-16
C-15	127.9	H-14; H-16
C-16	127.9	H-14; H-15
C-18	135.9	H-1; H-19; H-20; H-21
C-19	132.0	H-20; H-21
C-20	128.4	H-19; H-21
C-21	131.2	H-19; H-20

3. Conclusion

We have demonstrated that the reactions of 3-methylthio-1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine **2** with one molar equivalent of 25% ammonium hydroxide leads to the formation of 3-amino-1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine **3** while the two molar excess of ammonium hydroxide proceeded to furnish 2-(4-thioxo-1,4-dihydropyridin-3-ylsulfonyl)guanidine **4**. Reaction of **3** with two molar equivalents of hydrazine hydrate afforded 3-amino-2-(4-thioxo-1,4-dihydropyridin-3-ylsulfonyl)guanidine **5** which reacting with the appropriate 1,2-diarylethane-1,2-diones gave the new ring system 9,9-dioxo-1*H*-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol (**6-11**) with potential biological activity.

4. Experimental section

4.1. General

The following instruments and parameters were used: melting points Stuart SMP30; IR spectra: KBr pellets, 400-4000 cm^{-1} Thermo Mattson Satellite FTIR spectrometer; ^{1}H NMR and ^{13}C NMR: Varian Gemini 200 apparatus; chemical shifts (δ) are reported in parts per million downfield from TMS; coupling constants (*J*) are given in hertz; multiplicity in ^{1}H NMR is reported as singlet (s), broad singlet (br s), doublet (d), triplet (t), and multiplet (m). Mass spectra were recorded on Applied Biosystem QStar XL MS/MS mass spectrometer with an electrospray ionization (ESI) and hybrid quadrupole time-of-flight analyzer (Q-TOF). The

results of elemental analyses for C, H, and N were in agreement with the calculated values within ±0.4% range. Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60F254 plates and visualized with UV. The starting substrate 3-methylthio-1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine (**2**) was obtained from commercially available 4-chloropyridine-3-sulfonamide **1** applying procedure described previously.[30]

4.2. NMR studies

NMR spectra for **11** were recorded with a Varian Unity 500 Plus spectrometer in DMSO-d_6 solvent at temperature of 302 K. The spectra of ^{13}C and one-dimensional ^{1}H were collected with standard parameters.

NOESY and ROESY spectra were acquired in phase-sensitive mode with a spectral width of 3398 Hz. The NOESY spectrum was acquired with mix time 350 ms in 1024 × 200 matrix with 32 accumulations per increment and processed in 1 K × 1 K matrix. The ROESY spectrum was acquired with mix time 300 ms in 1024 × 200 matrix with 24 accumulations per increment and processed in 1 K × 1 K matrix.

COSY, HSQC and HMBC experiments were performed with pulse field gradients. The COSY spectrum was acquired in 1024 × 256 matrix with 4 accumulations and processed in 1 K × 1 K matrix. The HSQC spectrum was acquired in phase sensitive mode. The spectral windows for ^{1}H and ^{13}C axes were 3398 Hz and 16341 Hz, respectively. Data were collected in 672 × 170 matrix and processed in 1 K × 1 K matrix. The HMBC spectrum was acquired in phase sensitive mode. The spectral windows for ^{1}H and ^{13}C axes were 3398 Hz and 16341 Hz, respectively. Data were collected in 736 × 180 matrix and processed in 1 K × 1 K matrix.

4.3. 3-Amino-1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine (3)

To a suspension of 3-methylthio-1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine (**2**) (9.0 g, 36.5 mmol) in ethanol (36 mL) 25% NH_3 aq. (2.87 mL, 38.33 mmol) was added and stirred at rt for 120 h. The reaction mixture was refluxed with stirring until the evolution of MeSH had ceased (25 h). After 12 h the precipitate was collected by filtration, washed with ethanol (3x3 mL), dried and applied without further purification. Yield (solid powder): 95% (7.45 g); mp=256.5-257 °C (dec); IR (KBr) v=3379, 3294, 3206 (NH_2), 1626 ($NH_{2\ def.}$), 1568, 1551 (C=N, C=C), 1298, 1159 (SO_2) cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ=7.79 (d, *J*=5.3 Hz,

1H), 8.74 (d, *J*=5.3 Hz, 1H), 9.03 (s, 1H); 9.33 (br s, 2H). Anal. Calcd for $C_6H_5N_3O_2S_2$, (215.25): C, 33.48; H, 2.34; N, 19.52. Found: C, 33.55; H, 2.30; N, 19.26.

4.4. 2-(4-Thioxo-1,4-dihydropyridin-3-ylosulfonyl)guanidine (4)

According to the procedure for **3**. Starting from **2** (4.92 g, 20 mmol), ethanol (30 mL), 25% NH_3 aq. (3.28 mL, 43.80 mmol) after 90 h at rt and 3 h at reflux the 2-(4-thioxo-1,4-dihydropyridin-3-ylosulfonyl)guanidine (**4**) was obtained. Yield (solid powder): 88% (4.09 g); mp=230-231 °C (dec); IR (KBr) v=3424, 3319, 3205 (NH, NH_2), 1620 (NH $_{def.}$), 1537 (C=N), 1338 ($SO_{2\ asym.}$), 1226 (C=S), 1133 ($SO_{2\ sym.}$) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ=6.55 (br s, 4H), 7.13 (d, *J*=6.2 Hz, 1H), 7.54 (d, *J*=6.2 Hz, 1H), 8.34 (s, 1H). Anal. Calcd for $C_6H_8N_4O_2S_2$ (232.29): C, 31.02; H, 3.47; N, 24.12. Found: C, 31.09; H, 3.50; N, 24.18.

4.5. 3-Amino-2-(4-thioxo-1,4-dihydropyridin-3-ylsulfonyl)guanidine (5)

To a suspension of 3-amino-1,1-dioxopyrido[4,3-*e*]-1,4,2-dithiazine (**3**) (2.15 g, 10 mmol) in dry methanol (10 mL) 99% hydrazine hydrate (1.00 g, 20 mmol) was added and stirred at rt for 30-40 h. The precipitate was collected by filtration, washed with methanol (2x3 mL), water (2x3 mL), methanol (3 mL) then dried to afford 2.47 g (88.4%) of 3-amino-2-(4-thioxo-1,4-dihydropyridin-3-ylsulfonyl)guanidine (**5**) as a hydrazine salt; mp=196-200 °C (dec). The hydrazine salt of **5** (1.0 g, 3.58 mmol) was suspended in glacial acetic acid (5 mL) and stirred for 1 h. The yellow solid was filtered off, washed with methanol (3x3 mL) and dried to give **5**. Yield (solid powder): 99.8% (0.884 g); mp=208-210 °C (dec); IR (KBr) v=3431, 3332, 3290, 3211, 3096 (NH, NH_2), 1625 (NH $_{def.}$), 1576 (C=N), 1351 ($SO_{2\ asym.}$), 1231 (C=S), 1133 ($SO_{2\ sym.}$) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ=4.43 (br s, 2H); 6.95 (br s, 2H); 7.21 (d, *J*=6.7 Hz, 1H); 7.53 (d, *J*=6.7 Hz, 1H); 8.25 (br s, 1H); 8.29 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 132.0, 134.2, 136.4, 142.2, 160.5, 187.4. Anal. Calcd for $C_6H_9N_5O_2S_2$ (247.30): C, 29.11; H, 3.66; N, 28.32. Found: C, 29.14; H, 3.67; N, 28.30.

4.6. General procedure for the synthesis of 2,3-diaryl-9,9-dioxo-1*H*-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol derivatives (6-11)

To a suspension of **5** (0.495 g, 2 mmol) in dry DMSO (3.5-10 mL) appropriate 1,2-diarylethane-1,2-dione (2 mmol) was added and stirred at 80-85 °C for 42-58 h. After cooling

the precipitate of side products was filtered off, then to filtrate methanol (30 mL) was added dropwise and the mixture was left overnight to crystallization at ambient temperature. The crude products were collected by filtration, washed with methanol and dried. A final purification was described below.

4.6.1. 2,3-Diphenyl-9,9-dioxo-1H-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol (***6***). Starting from **5**, DMSO (3.5 mL), benzil (0.420 g) for 42 h the title compound **6** was obtained. The product was purified by extraction of contaminations with boiling mixture of ethanol/DMF (v/v 4:1) (32 mL). Yield (solid powder): (60%) 0.486 g; mp=215-216 °C (dec); IR (KBr) v=3331 (wide) (OH, NH), 2923, 2852, 1619, 1591 (C=N, C=C), 1282, 1162 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ=7.26-7.35 (m, 6H), 7.50-7.58 (m, 2H), 7.78-7.75 (m, 2H), 7.96 (d, *J*=5.9 Hz, 1H), 8.38 (s, 1H), 8.83 (d, *J*=5.9 Hz, 1H), 8.99 (s, 1H), 10.44 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 78.2 (C-OH), 110.5, 121.2, 126.9, 128.4, 128. 5, 128.9, 129.0, 130.5, 132.9, 141.0, 142.6, 142.8, 145.3, 152.2, 153.3. Anal. Calcd for $C_{20}H_{15}N_5O_3S$ (405.43): C, 59.25; H, 3.73; N, 17.27. Found: C, 59.20; H, 3.69; N, 17.20.

4.6.2. 2,3-Di(4-bromophenyl)-9,9-dioxo-1H-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol (***7***). Starting from **5**, DMSO (3.5 mL), 4,4'-dibromobenzil (0.736 g) for 49 h the title compound **7** was obtained. The product was purified by extraction of contaminations with boiling chloroform (25 mL) and dried. Yield (solid powder): 34% (0.378 g); mp=178-180 °C; IR (KBr) v=3378 (wide) (OH, NH), 1617, 1589 (C=N, C=C), 1291, 1163 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ=7.43-7.56 (m, 6H), 7.67 (d, *J*=8.7 Hz, 2H), 7.95 (d, *J*=5.9 Hz, 1H), 8.52 (s, 1H), 8.83 (d, *J*=5.9 Hz, 1H), 9.00 (s, 1H), 10.46 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 77.7 (C-OH), 110.4, 121.1, 122.4, 124.4, 129.3, 130.9, 131.4, 131.6, 132.0, 140.3, 142.5, 142.6, 145.4, 150.5, 153.3. Anal. Calcd for $C_{20}H_{13}Br_2N_5O_3S$ (563.22): C, 42.65; H, 2.33; N, 12.43. Found: C, 42.59; H, 2.23; N, 12.22.

4.6.3. 2,3-Di(4-fluorophenyl)-9,9-dioxo-1H-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol ***(8)***. Starting from **5**, DMSO (6 mL), 4,4'-difluorobenzil (0.492 g) for 48 h the title compound **8** was obtained. Yield (solid powder): 17% (0.150 g); mp=291-293 °C; IR (KBr) v=3302 (wide) (OH, NH), 1608, 1512 (C=N, C=C), 1287, 1161 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ=7.12-7.21 (m, 4H), 7.59-7.66 (m, 2H), 7.74-7.82 (m, 2H), 7.97 (d, *J*=5.9 Hz, 1H), 8.48 (s, 1H), 8.83 (d, *J*=5.9 Hz, 1H), 9.01 (s, 1H), 10.45 (s, 1H). Anal. Calcd for $C_{20}H_{13}F_2N_5O_3S$ (441.41): C, 54.42; H, 2.97; N, 15.87. Found: C, 54.32; H, 2.75; N, 15.48.

*4.6.4. 2,3-Di(4-methylphenyl)-9,9-dioxo-1H-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol (**9**).* Starting from **5**, DMSO (10 mL), 4,4'-dimethylbenzil (0. 477 g) for 58 h the title compound **9** was obtained. The product was purified by crystallization from DMSO (1 mL) at 88 °C. Yield (solid powder): 39% (0.166 g); mp=201-204 °C; IR (KBr) v=3372 (wide) (OH, NH), 2922, 2852 (CH_3), 1614, 1591 (C=N, C=C), 1288, 1161 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ=2.24 (s, 6H), 7.09-7.14 (m, 4H), 7.42 (d, *J*=7.4 Hz, 2H), 7.66 (d, *J*=7.4 Hz, 2H), 7.96 (d, *J*=5.8 Hz, 1H), 8.27 (s, 1H), 8.83 (d, *J*=5.8 Hz, 1H), 8.98 (s, 1H), 10.34 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 20.9, 21.1, 78.2, 110.4, 121.2, 126.7, 128.9, 129.0, 130.2, 138.1, 138.4, 140.3, 142.6, 142.8, 145.3, 152.2, 153.3. Anal. Calcd for $C_{22}H_{19}N_5O_3S$ (433.48): C, 60.96; H, 4.42; N, 16.16. Found: C, 60.81; H, 4.22; N, 15.83.

*4.6.5. 2,3-Di(4-methoxyphenyl)-9,9-dioxo-1H-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol (**10**).* Starting from **5**, DMSO (3.5 mL), 4,4'-dimethoxybenzil (0. 540 g) for 48 h the title compound **10** was obtained. The product was purified by extraction of contaminations with boiling mixture of ethanol/DMF (v/v 4:1) (16 mL). Yield (solid powder): 53% (0.493 g); mp=208-210 °C; IR (KBr) v=3319 (wide) (OH, NH), 2931, 2838 (CH_3), 1609, 1515 (C=N, C=C), 1304, 1169 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ=3.71 (s, 3H), 3.73 (s, 3H), 6.84 (d, *J*=3.3 Hz, 2H), 6.89 (d, *J*=3.3 Hz, 2H), 7.45 (d, *J*=8,8 Hz, 2H), 7.73 (d, *J*=8.8 Hz, 2H), 7.96 (d, *J*=5.9 Hz, 1H), 8.24 (s, 1H), 8.82 (d, *J*=5.9 Hz, 1H), 8.98 (s, 1H), 10.31 (s, 1H); NH and OH protons δ 8.24 (s, 1H, NH), 10.31 (s, 1H, OH) ppm were exchanged with D_2O; ^{13}C NMR (50 MHz, DMSO-d_6) δ 55.4 (OCH_3), 55.5 (OCH_3), 78.1 (C-OH), 110.4, 113.77, 113.82, 121.2, 125.2, 128.1, 130.7, 133.5, 142.7, 142.9, 145.2, 152.0, 153.3, 159.4, 160.9; MS ESI Q-TOF: m/z=466 (M^++1). Anal. Calcd for $C_{22}H_{19}N_5O_5S$ (465.48): C, 56.77; H, 4.11; N, 15.05. Found: C, 56.57; H, 4.05; N, 14.72.

*4.6.6. 9,9-Dioxo-2,3-di(thien-2-yl)-1H-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol (**11**).* Starting from **5**, DMSO (6 mL), 1,2-di(thiofen-2-yl)ethane-1,2-dione (0.495 g) for 50 h the title compound **11** was obtained. The product was purified by extraction of contaminations with boiling chloroform (6 mL) and dried. Yield (solid powder): 29% (0.240 g); mp=190-193 °C; IR (KBr) v=3312 (wide) (OH, NH), 1644, 1592 (C=N, C=C), 1289, 1160 (SO_2) cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ=6.99-7.09 (m, 2H), 7.22-7.25 (m, 1H), 7.48-7.58 (m, 1H), 7.59-7.62 (m, 1H), 7.73-7.76 (m, 1H), 7.89 (d, *J*=5.9 Hz, 1H), 8.57 (s, 1H), 8.88 (d, *J*=5.9 Hz, 1H), 8.99 (s, 1H), 10.73 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 77.2, 110.2, 121.2, 127.7,

128.3, 131.1, 131.9, 135.3, 142.3, 142.4, 145.3, 148.1, 153.5. Anal. Calcd for $C_{16}H_{11}N_5O_3S_3$ (417.5): C, 46.03; H, 2.66; N, 16.78. Found C, 45.73; H, 2.46; N, 16.38.

Supplementary data

Supplementary data related to this article can be found at ...

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