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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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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.

1. Introduction

Arylsulfonamides have been shown to exhibit a variety of biological activities.[1] Among them, the derivatives modified by substitution 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] (Fig. 1, **I**), K_{ATP} channel openers[6,7] (Fig. 1, **II**), CCK receptor ligands,[8] antibacterial and anticancer agents[2,3] (Fig. 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] (Fig. 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]

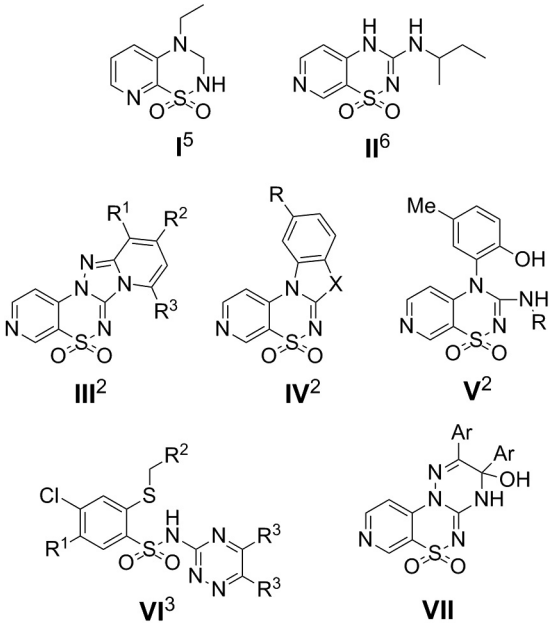

Fig. 1. Structures of known AMPA potentiators **I**[5], potassium channel openers **II**[6], antibacterial and anticancer pyridothiadiazine derivatives **III**–**V**[2], antitumor *N*-(1,2,4-triazin-3-yl)benzenosulfonamides **VI**[3], and novel 9,9-dioxo-1*H*-9-thia-1,4,4a,7,10-pentaazaphenanthrene-2-ol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

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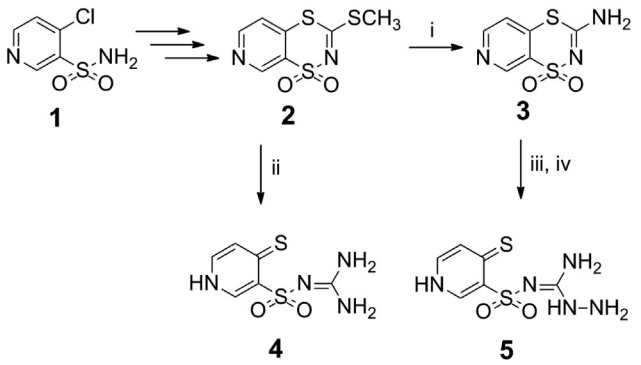
Due to a number of biological properties of nitrogen-containing heterocycles, the synthesis of these compounds is an important point of the search for new therapeutic agents. One of the general strategies in the preparations of these molecules is reaction between dicarbonyl compounds and an amine group.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

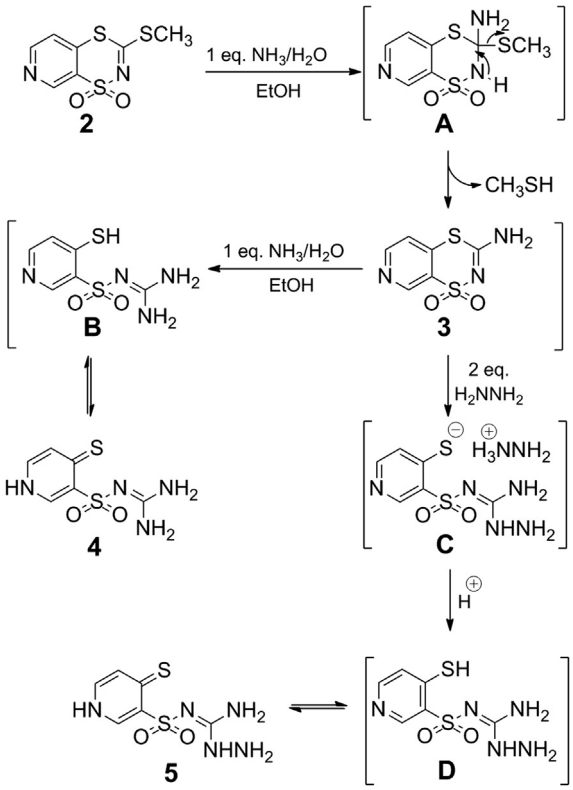
2.1. Synthetic chemistry

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 1 M equiv 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 2 M 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 2 M equiv 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 equiv 25% $NH_{3\ aq}$, EtOH, 120 h, rt, 95%; (ii) 2 equiv 25% $NH_{3\ aq}$, EtOH, 90 h, rt then 3 h, reflux, 88%; (iii) 2 equiv 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



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

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**.

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, and further tautomerization to the more stable 3-aminopyridothiadiazine[2,31] intermediate **G**. 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 h, apparently due to the relatively low nucleophilicity of the sulfonylguanidine nitrogen atoms. As a result, an intractable mixture of products was formed.

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