

6-Amino-4-Aryl-3-Carbamoyl-5-Cyano-1,4-Dihydropyridine-2-Thiolates: Synthesis, Reactions and Docking Studies [†]

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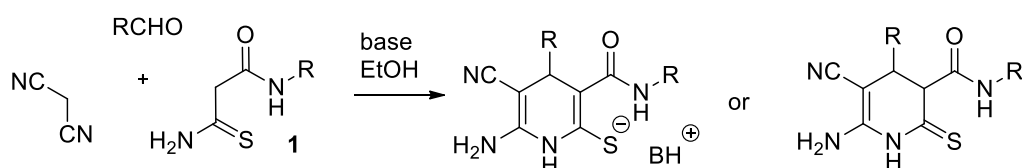
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Abstract: New triethylammonium 6-amino-4-aryl-3-carbamoyl-5-cyano-1,4-dihydropyridine-2-thiolates were prepared in good yields by ternary condensation of malononitrile, aldehydes and monothiomalonamide in the presence of Et₃N. The thiolates undergo S-alkylation under mild conditions to give new 1,4-dihydropyridines. Molecular docking studies were carried out in order to explore the interaction mechanism and to investigate suitable binding modes of the new compounds on the calcium channel proteins. Some of the compounds in experiments in silico were found to be more potent as calcium channel blockers than reference drug Nifedipine.

Keywords: 1,4-dihydropyridines; calcium channel blockers; 3-amino-3-thioxopropanamide; heterocyclization

1. Introduction

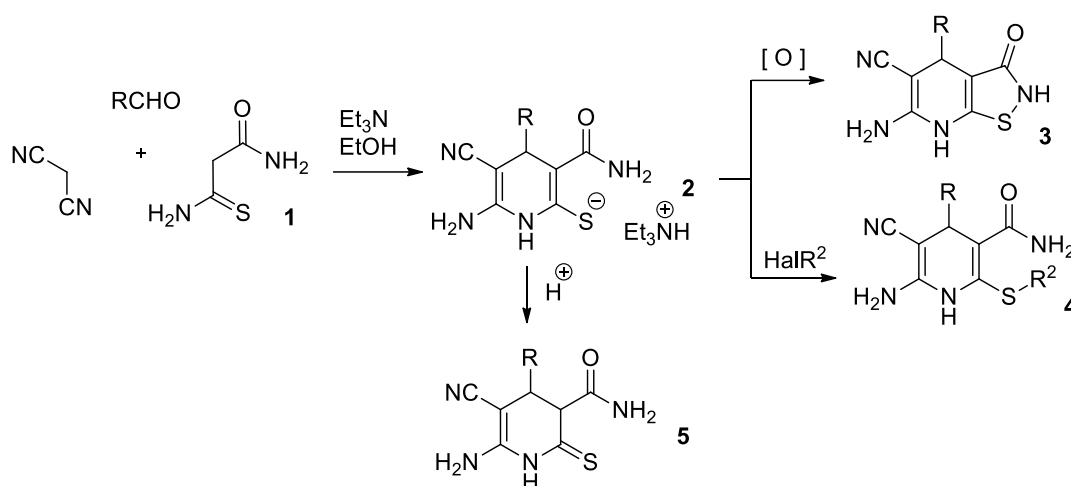
1,4-Dihydropyridines, usually easily available through Hantzsch synthesis, are known for a long time as compounds of practical interest, primarily as cardioprotectors, HIV-1 protease inhibitors and calcium channel blockers (for reviews see [1–7]). Much less is known about sulfur-containing 1,4-dihydropyridine-3-carboxamides which are expected to have a biological activity. The general route towards these compounds is based on the Hantzsch-type ternary reaction of monothiomalonamides with aldehydes and methylene active compounds (Scheme 1). The methods for the synthesis of 2-(R-thio)-1,4-nicotinamides were reported in the papers [8–12]. In continuation of our studies in the chemistry of functionalized pyridines, we decided to prepare new 1,4-dihydropyridine-3-carboxamides starting from monothiomalonamide **1** (R = H) (3-amino-3-thioxopropanamide, thiocarbamoylacetamide) and malononitrile.



Scheme 1. The preparation of 1,4-dihydropyridines from monothiomalonamide.

2. Results and Discussion

We found that new triethylammonium 6-amino-4-aryl-3-carbamoyl-5-cyano-1,4-dihydropyridine-2-thiolates **2** can be prepared in 80–91% yields by ternary condensation of malononitrile, aldehydes and monothiomalonamide **1** in the presence of Et₃N (Scheme 2). The reactions of the thiolates **2** were investigated. Thus, the oxidation under mild conditions afforded isothiazolopyridines **3** and S-alkylation with reactive halides gave 2-(S-alkyl)-1,4-dihydropyridin-5-ylidene-6-amino-3-carbamoyl-4-cyano-1,4-dihydropyridines **4** in 50–80% yields. The acidification of salts leads to the formation of tetrahydropyridines **5** in almost quantitative yields.



Scheme 2. Synthesis and reactions of thiolates **2**.

Some of the prepared compounds were studied *in silico* for possible cardioprotecting effects. Molecular docking study is carried out using Autodock vina program (version 1.5.6) and MOE software in order to explore the interaction mechanism and to investigate suitable binding modes of compounds **2–4** on the calcium channel proteins. The crystal structure of calcium channel blocker alpha 1 was retrieved from the RSCB Protein Data Bank (PDB ID: 3LV3). Binding energy calculations were performed on the compound with the best results **4a** (Figure 1) which has good docking score and H-bond interaction.

The binding energy of active compound **4a** was found to be -9.3 kcal/mol, and the binding energy of other selected active compound **4b** was -8.9 kcal/mol. These compounds have lowest binding energies than combating with (3LV3)-receptor. The compounds, which are having hydrogen bond interactions with ARG 239, ASP 238, TYR 209 active residues shows lowest binding energies. This implies that the active site residues ASP, ARG, TYR are become more favorable to the binding with 3LV3 protein. Noteworthy that Nifedipine, known trading cardioprotecting drug used as reference, in the similar calculations showed the binding energy of only -6.2 kcal/mol.

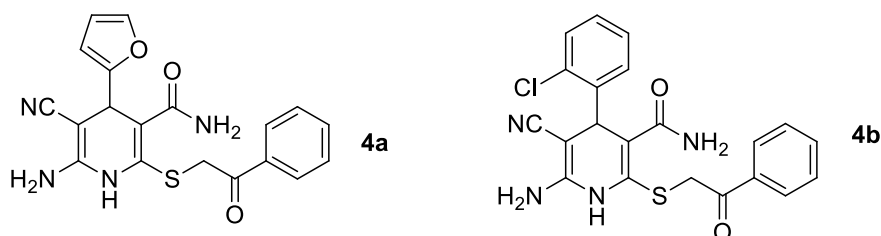


Figure 1. The structures of the most active (according to docking studies) compounds **4a,b**.

The more negative value of binding energy demonstrates higher binding affinity. ARG and TYR (negatively charged residue) formed hydrogen bond with NH group for all compounds, the compound **4a** was best with a strong hydrogen bond (distance C-O...H 2.4 Å) as compared to

compounds **4b**. The Figures 2–5 show the predicted interaction of compounds **4a,b** with 3LV3 protein.

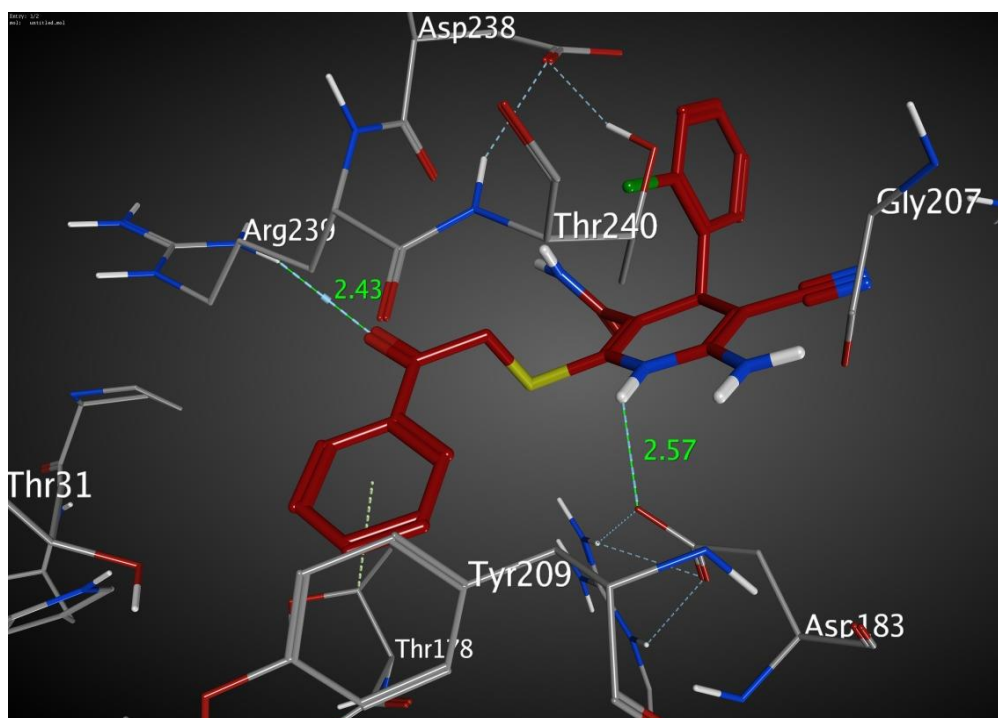


Figure 2. 3D interaction pose of compound **4b** in the active site of the protein (pdb:3LV3).

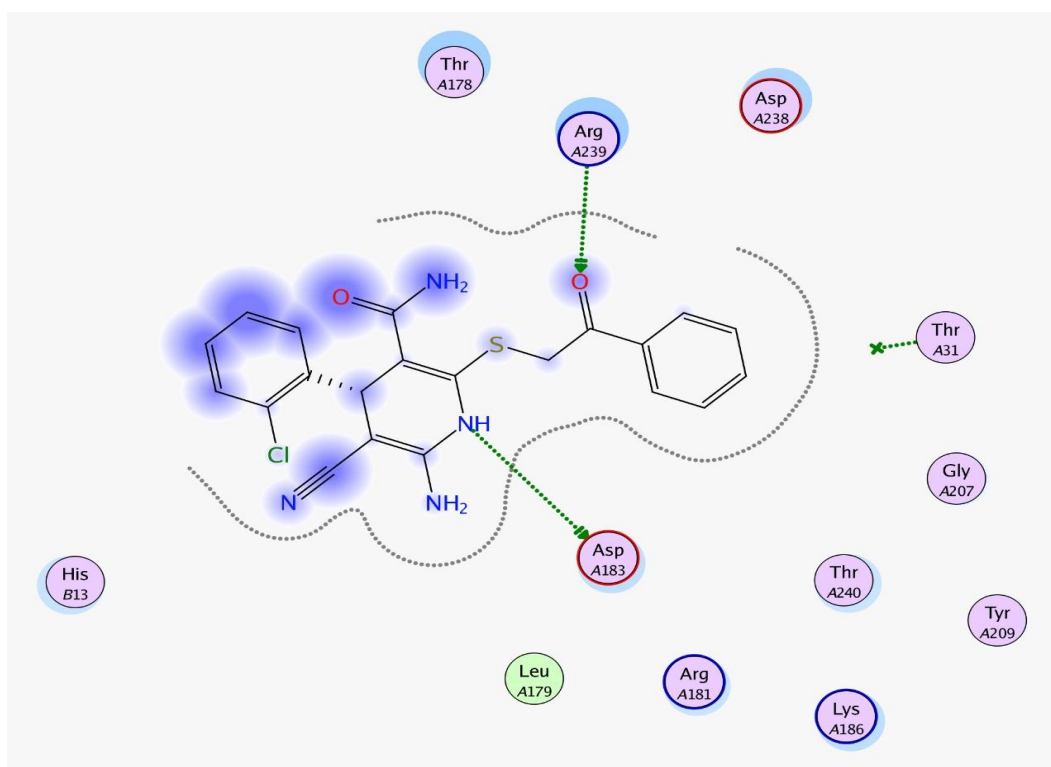


Figure 3. 2D interaction pose of compound **4b** with amino acids of the active site of 3LV3 protein.

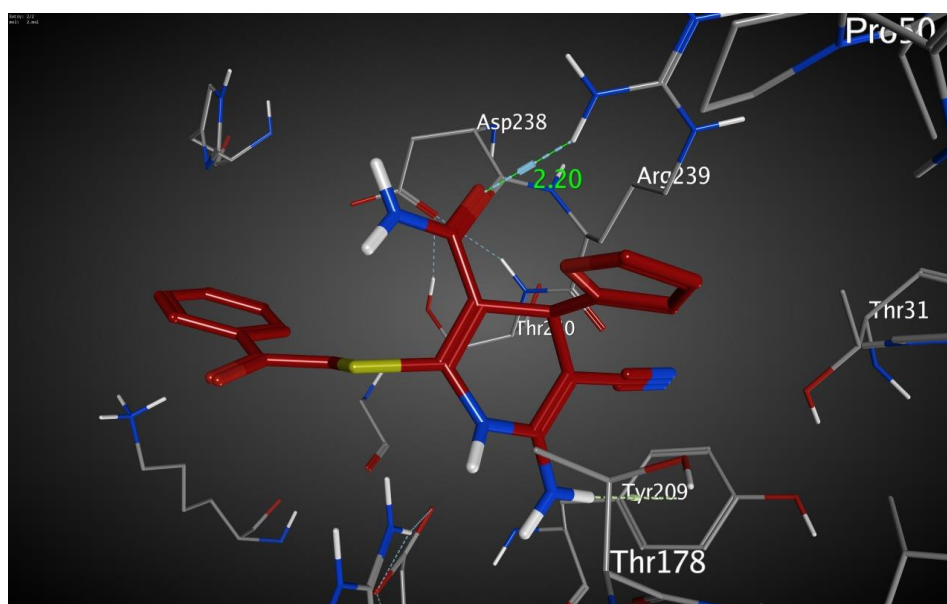


Figure 4. 3D interaction pose of compound 4a in the active site of the protein (pdb:3LV3).

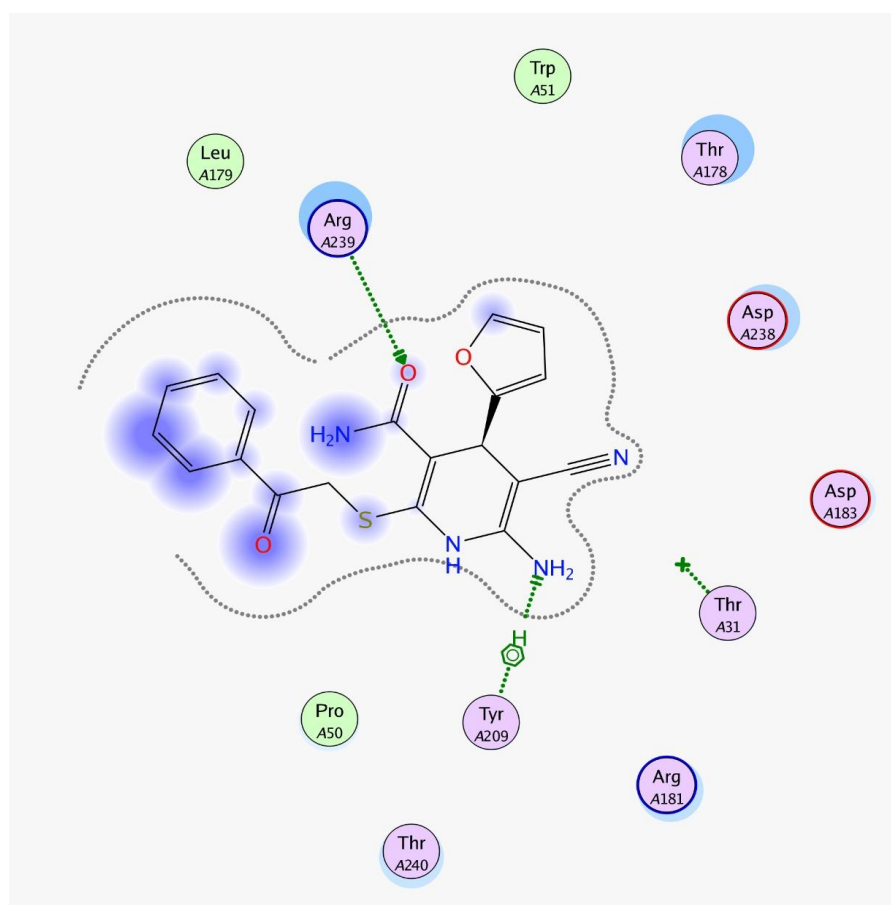


Figure 5. 2D interaction pose of compound 4a with amino acids of the active site of 3LV3 protein.

3. Experimental

3.1. Preparation of triethylammonium 6-amino-4-aryl-3-carbamoyl-5-cyano-1,4-dihydropyridine-2-thiolates

2. General procedure

A mixture of the corresponding aromatic aldehyde (7.6 mmol) with monothiomalonamide (0.89 g, 7.6 mmol), malononitrile (0.5 g, 7.6 mmol) and 1.6 mL of triethylamine in ethanol (10 mL) was

stirred at room temperature (RT) for 0.5 h. A light yellow solid separated was filtered off, washed with acetone and air dried to give thiolates **2** which were used without further purification. The yields were 80–91%.

3.2. Preparation of Compounds **5**. General Procedure

A solution of the corresponding triethylammonium 6-amino-4-aryl-3-carbamoyl-5-cyano-1,4-dihydropyridine-2-thiolate **2** (5 mmol) in 70% aq. EtOH was carefully treated with HCl to adjust pH to 3.0. The yellow powder or crystals were filtered off to give corresponding tetrahyronicotinamide **5** in 90–95% yields. As the example, X-ray and spectroscopic data for selected compounds **5b** (R = 2-ClC₆H₄) are given in the Figures 6–8.

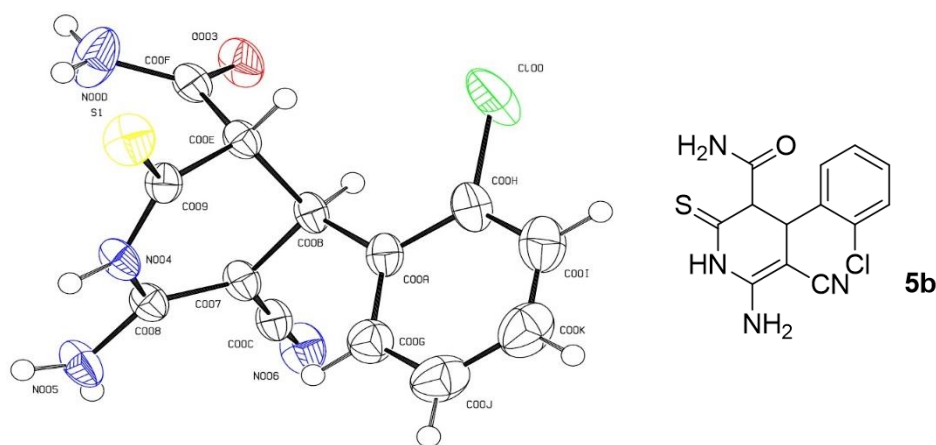


Figure 6. The structure of compound **5b** (X-ray data).

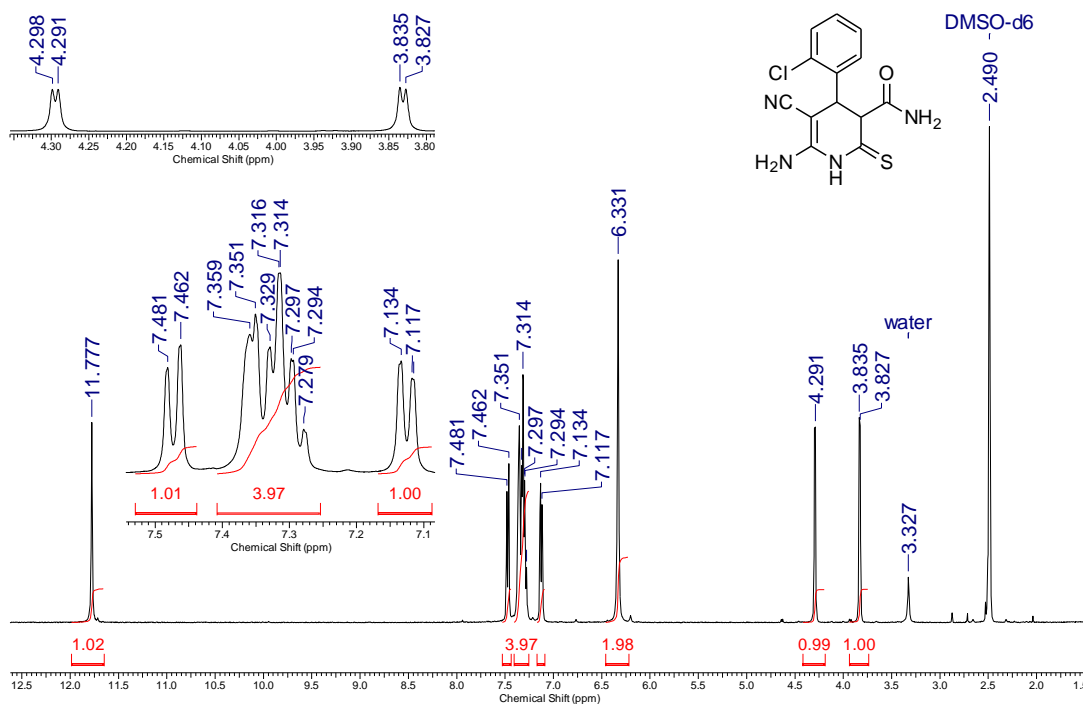


Figure 7. NMR ¹H spectrum (400 MHz, DMSO-d₆) of compound **5b**.

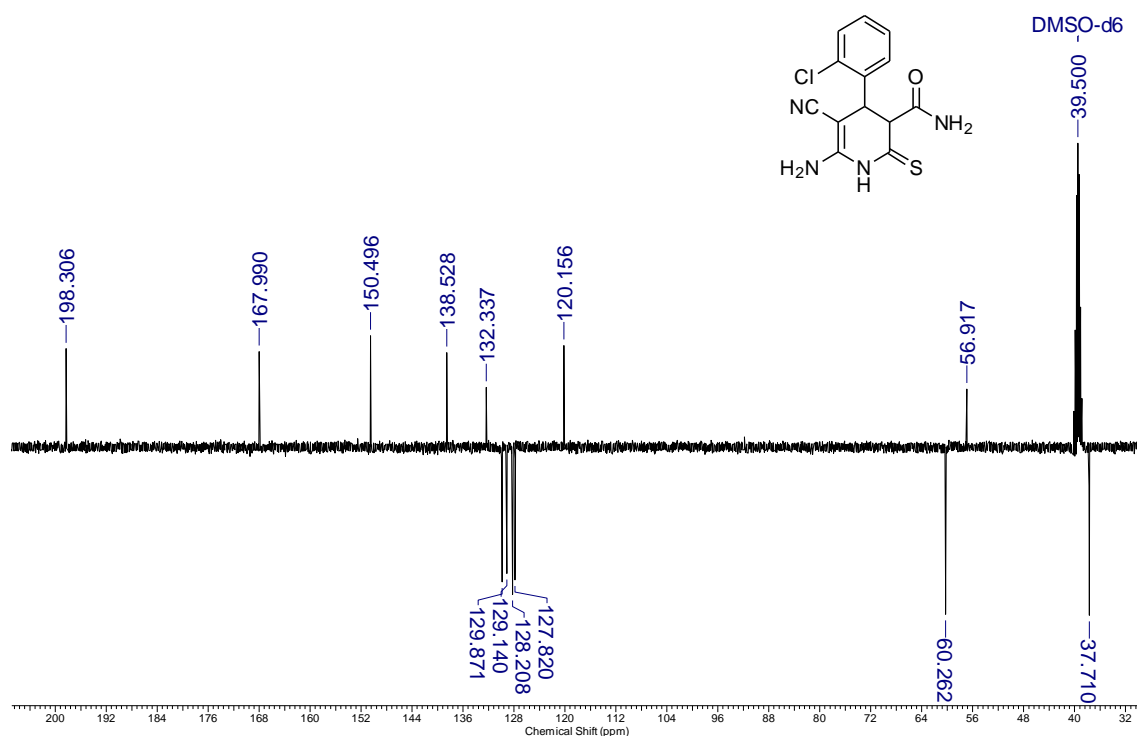


Figure 8. NMR ¹³C DEPTQ spectrum (101 MHz, DMSO-d₆) of compound 5b.

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