chemistry proceedings

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Proceeding Paper

On Synthesis and Determination In Silico of the Biological Activity of New Hybrid Molecules with Fragments of Thieno[2,3-b]Pyridine and 2- Iminothiazoline †

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† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: https://ecsoc-25.sciforum.net/.

Abstract: α-Thiocyanatocarbonyl compounds are the reagents with both electrophilic and nucleophilic reactivity useful as building blocks for many important chemicals and bioactive molecules. These compounds are useful intermediates in the synthesis of sulfur-containing heterocycles such as thiazoles. Starting from α-thiocyanatocarbonyl compounds we succeded to prepare 2-iminothiazolines and chloroacetamides. Chloroacetamides are of interest as reagents for fine organic synthesis, as well as promising agrochemicals or their precursors. Further, compounds were reacted in the presence of bases with a couple of 3-cyanopyridine-2(1*H*)-thiones. As a result, the new products of direct S-alkylation were synthesized in high yields (85–96%).

Keywords: 2-iminothiazoline; N-(chloroacetyl)aminothiazoline; thieno[2,3-b]pyridine; molecular docking

Citation: Kindop, V.K.; Bespalov, A.V.; Dotsenko V.V. On Synthesis and Determination In Silico of the Biological Activity of New Hybrid Molecules with Fragments of Thieno[2,3-b]Pyridine and 2- Iminothiazoline. *Chem. Proc.* **2021**, *3*, x. https://doi.org/10.3390/xxxxx

Academic Editor: Julio A. Seijas

Published: 15 November 2021

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1. Introduction

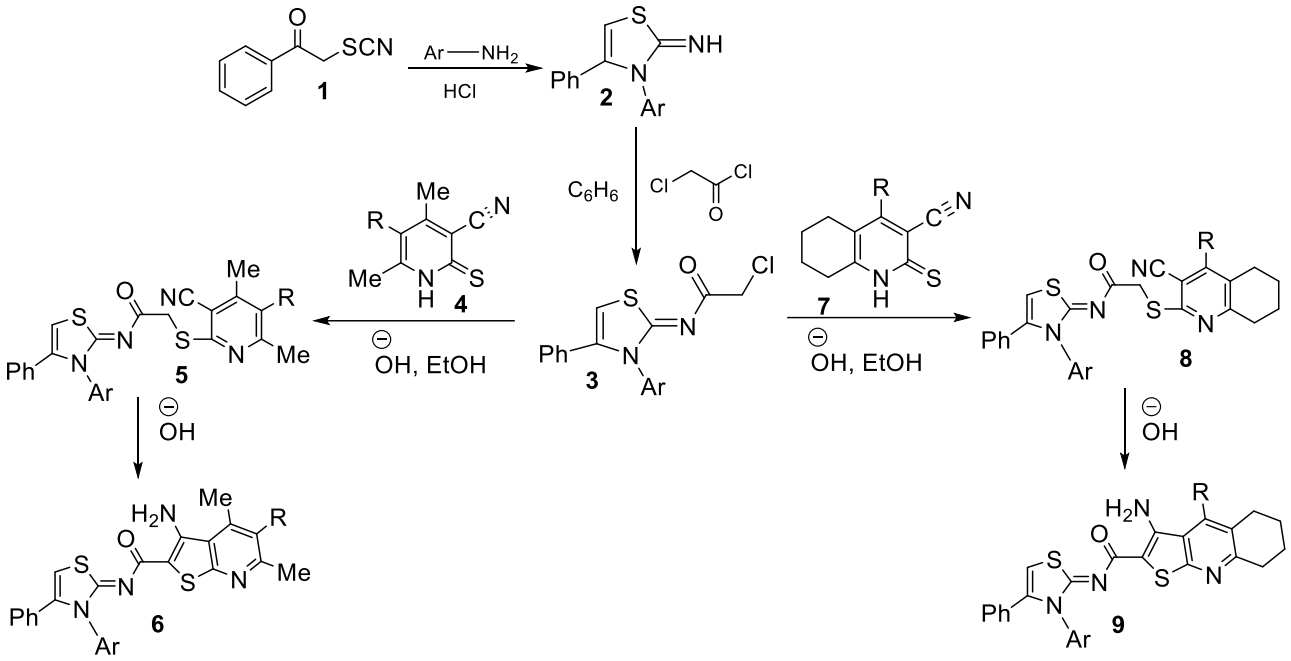
α-Thiocyanatocarbonyl compounds are the reagents with both electrophilic and nucleophilic reactivity useful as building blocks for many important chemicals and bioactive molecules. These compounds are useful intermediates in the synthesis of sulfur-containing heterocycles such as thiazoles [1,2].

2. Results and Discussion

Starting from alpha-thiocyanatocarbonyl compounds 1, we succeded to prepare 2-iminothiazolines 2 and chloroacetamides 3 (Scheme 1). Chloroacetamides 3 are of interest as reagents for fine organic synthesis as well as promising agrochemicals or their precursors.

Further, compounds 3 were reacted in the presence of bases with a couple of 3-cyanopyridine-2(1*H*)-thiones (structures 4 and 7). As a result, the new products of S-alkylation (namely, pyridines 5 and 8) were synthesized in high yields (85–96%).

When a second base equivalent was added to a reaction mixture followed by gentle heating, the Thorpe-Ziegler cyclization of compounds 5 and 8 occurred to afford compounds 6 and 9 (Scheme 1). Compounds 6 and 9 are previously undescribed [3,4] hybrid molecules combining thieno[2,3-b]pyridine and 2-iminothiazoline pharmacophore subunits. It seems likely that the presence of two bounded phramacophore fragments will lead to increase of the pharmacological properties. Moreover, the introducing of thieno[2,3-b]pyridine fragment allow greater variability for the structural modification, as well as the increase in the affinity to a wider range of biological protein receptors is also expected.

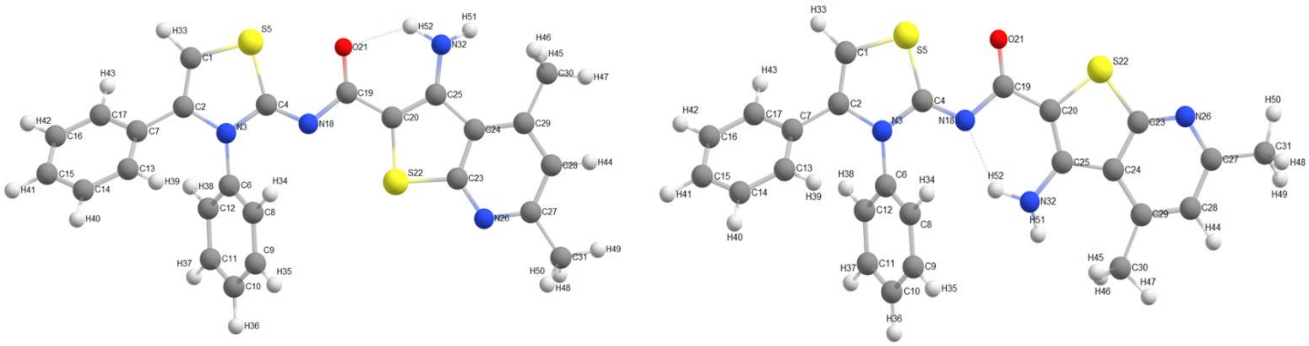


Scheme 1. Preparation of thieno[2,3-b]pyridine/thiazoline hybrid polyheterocyclic ensembles starting from easily available alpha-thiocyanatocarbonyl compounds.

The introduction of the pharmacophore thieno[2,3-b]pyridine fragment enables additional structural modifications as well as increases the affinity to a wide range of protein targets.

We also identified possible protein targets for the resulting compounds using the GalaxyWeb Sagittarius in silico protocols. The structure of the obtained compounds was confirmed by means of NMR, IR spectroscopy and X-ray diffraction analysis.

The prepared products were studied using physico-chemical (IR, NMR, X-ray diffraction analysis) (Figures 1 and 2) as well as quantum chemical methods [5]. We found that thieno[2,3-b]pyridines and thieno[2,3-b]quinolines can exist as two main conformers (structures **a** and **b**, Figure 1).



(**a**) (**b**)

Figure 1. Molecular structures of conformers of compound **6a** optimized at the B3LYP-D3BJ/6-311G(2df,2pd) level: (**a**) s-*trans*, (**b**)—s-*cis*.

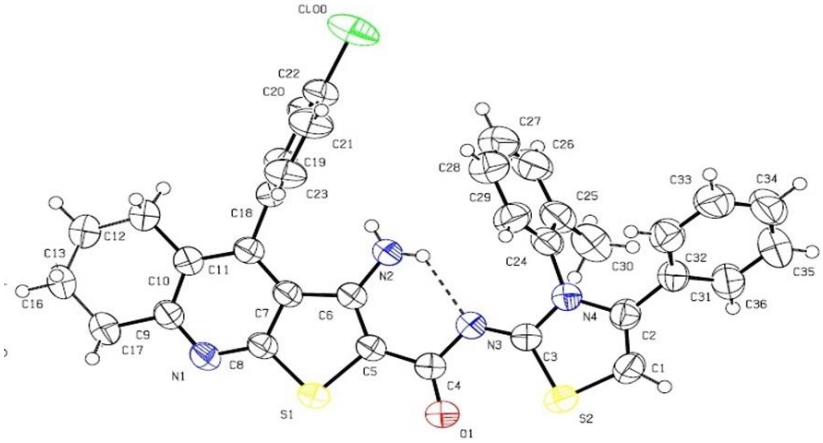
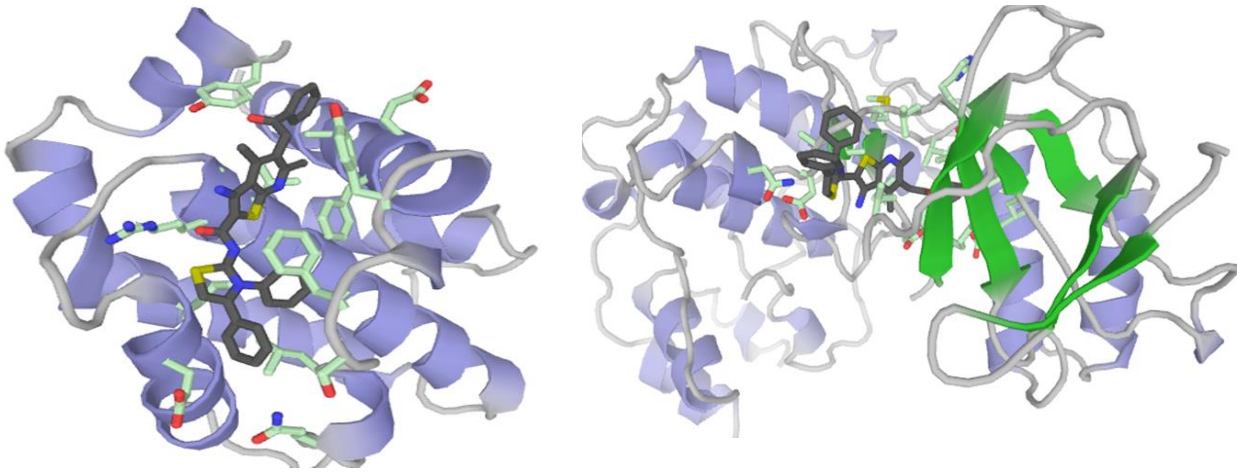


Figure 2. Molecular structure of the prepared thieno[2,3-b]quinoline **9b** according to the X-Ray data.

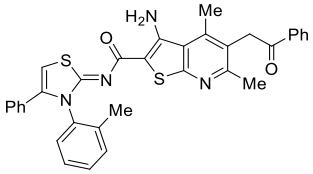
The expected biological activities were evaluated *in silico*. In addition, we predicted possible protein targets for the prepared compounds. For this purpose, we used a new protein-ligand docking protocol Galaxy Web Sagittarius. Possible protein targets are given as PDB IDs (Figure 3, Table 1).



(**a**) (**b**)

Figure 3. Binding poses for one of the prepared compounds to active sites of human proteins (**a**)—3zlo, (**b**)—5tbe.

Table 1. Results of molecular docking.

Structure	*PDB ID*	*Predock Score*	*Docking Score*	*Score*	*The Biological Role of This Protein*
	3ZLO	0.690	−29.478	0.985	Activator/inhibitor of apoptosis
	5TBE	0.150	−29.083	0.446	Transferase Activator
	3U2Z	0.064	−34.427	0.408	Transferase Activator

3. Experimental

Preparation of Chloroacetamides (**3**):

The corresponding 2-iminothiazoline **2** (0.004 mol) was suspended in 15 mL of anhydrous benzene. Then 0.3 mL (0.004 mol, $d = 1.42$ g/cm^3) of chloroacetyl chloride was added dropwise. The mixture was boiled for 4 h. The reaction was monitored by evolution of

hydrogen chloride using a litmus test. After the reaction complete, a mixture was allowed to cool. Colorless crystals of products were filtered off and washed with benzene. The purity of products were checked by TLC (Sorbfil plates, "Imid Ltd." (Krasnodar, Russia)) using a mixture of ethyl acetate and petroleum ether 1:1 as an eluent. The yield of the resulting product (Ar = Ph) was 1.00 g (73%), mp 165–167 °C. The ^{1}H NMR spectrum of **3** is given in the Figure 4.

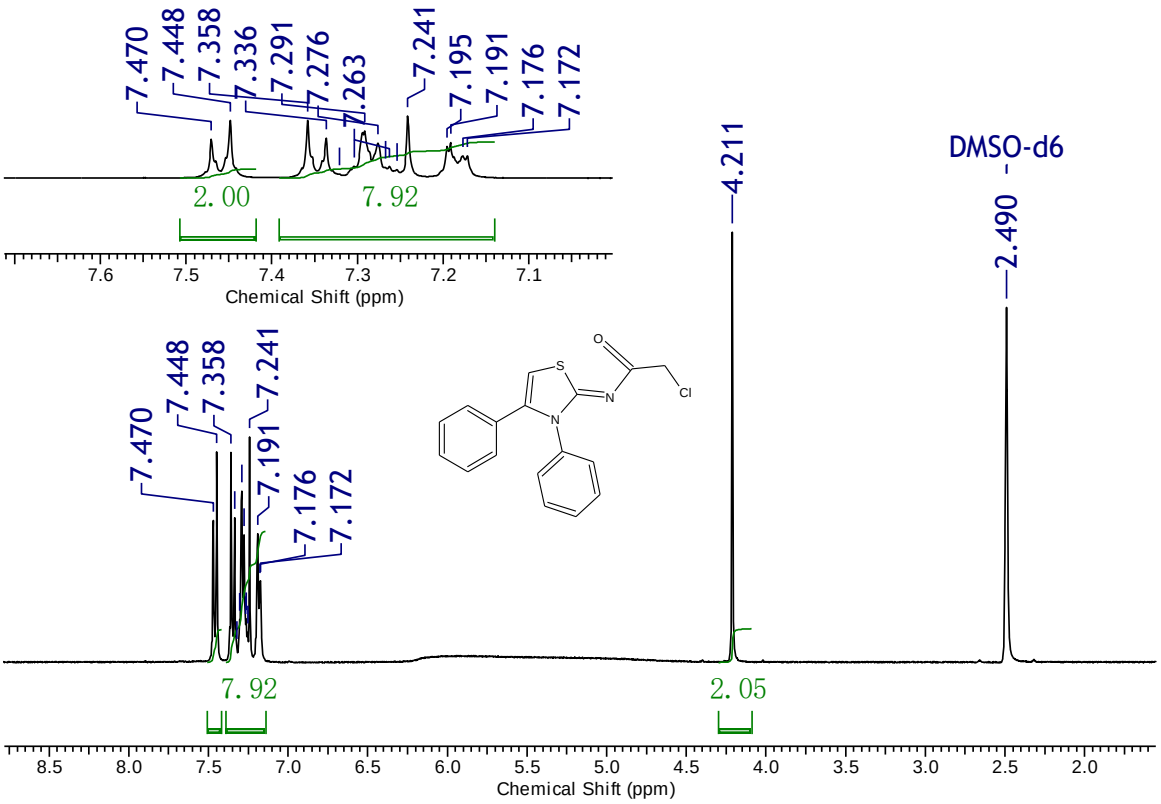


Figure 4. ^{1}H NMR spectrum of compound **3.**

Thieno[2,3-b]pyridines **6** and **9**. General procedure.

2-Thioxopyridines **4** or **7** (0.002 mol) were suspended in EtOH (5 mL), then 1.0 mL of 10% aq. KOH (0.002 mol) was added. As a result, a solution color changed from yellow to light green due to the formation of the corresponding potassium pyridine-2-thiolates. An alkylating agent (0.0022 mol) was added to resulted solution and the mixture was kept under vigorous stirring for 30 min at ambient temperature. The solid product was filtered off and washed with EtOH. The purity was checked by TLC (Sorbfil plates, "Imid Ltd." (Krasnodar)) using a mixture of ethyl acetate and petroleum ether 1:1 as an eluent.

Author Contributions: Conceptualization, V.V.D., A.V.B.; methodology, V.V.D., A.V.B., V.K.K.; synthesis and analysis, V.K.K.; calculations: V.K.K., A.V.B.; writing—original draft preparation, V.V.D., A.V.B., V.K.K.; writing—review and editing, V.V.D.; supervision, V.V.D.; funding acquisition, V.V.D. All authors have read and agreed to the published version of the manuscript.

Funding: The reported study was funded by RFBR and Krasnodar region according to the research project № 19-43-230007.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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