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Proceeding Paper

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

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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 the ternary condensation of malononitrile, aldehydes and monothiomalonamide in the presence of Et_3N. The thiolates underwent S-alkylation under mild conditions to produce new 1,4-dihydronicotinamides. 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 the in silico experiments were found to be more potent as calcium channel blockers than the reference drug, Nifedipine.

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

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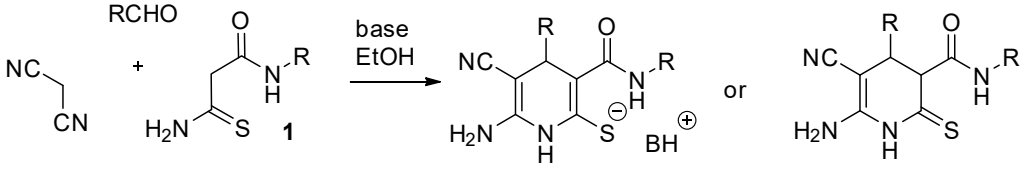
1. Introduction

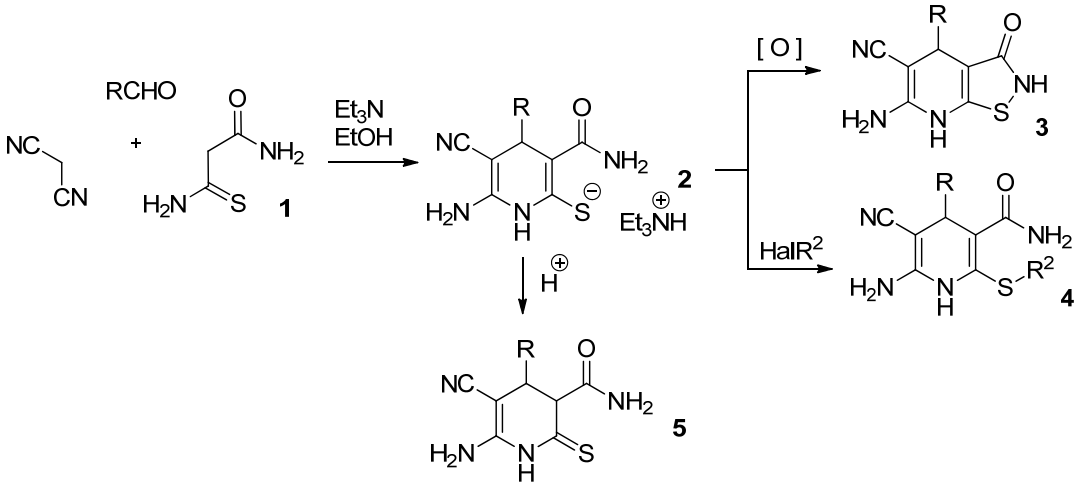
1,4-Dihydropyridines, usually readily available through Hantzsch synthesis, have been known for a long time as compounds of practical interest, primarily as cardioprotectors, HIV-1 protease inhibitors and calcium channel blockers (for reviews, see [1–7]). Much less is known about sulfur-containing 1,4-dihydropyridine-3-carboxamides, which are expected to have biological activity. The general route for 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 [8–12]. In continuation of our studies on 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-dihydronicotinamides 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 the ternary condensation of malononitrile, aldehydes and monothiomalonamide **1** in the presence of Et_3N (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 produced 2-(S-alkyl)-1,4-dihydronicotinamides **4** in 50–80% yields. The acidification of salts led 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 was carried out using the 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 for **4a** (Figure 1), which had a 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 the other selected active compound, **4b**, was −8.9 kcal/mol. These compounds had lower binding energies than combating with the (3LV3) receptor. The compounds, which had hydrogen bond interactions with ARG 239, ASP 238 and TYR 209 active residues, showed the lowest binding energies. This implies that the active site residues, ASP, ARG and TYR, are more favorable compared to the binding with 3LV3 protein. It is noteworthy that Nifedipine, a known trading cardioprotecting drug used as the reference in the similar calculations, showed a binding energy of only −6.2 kcal/mol.

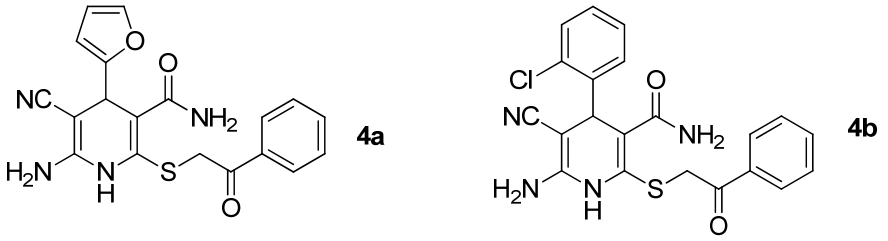


Figure 1. The structures of the most active (according to docking studies) compound **4a,b**.

The more negative value of binding energy demonstrated a higher binding affinity. ARG and TYR (negatively charged residues) formed hydrogen bonds with the NH group

for all compounds; compound **4a** was the best with a strong hydrogen bond (distance C-O...H 2.4 Å) as compared to compound **4b**. Figures 2–5 show the predicted interaction of compound **4a,b** with 3LV3 protein.

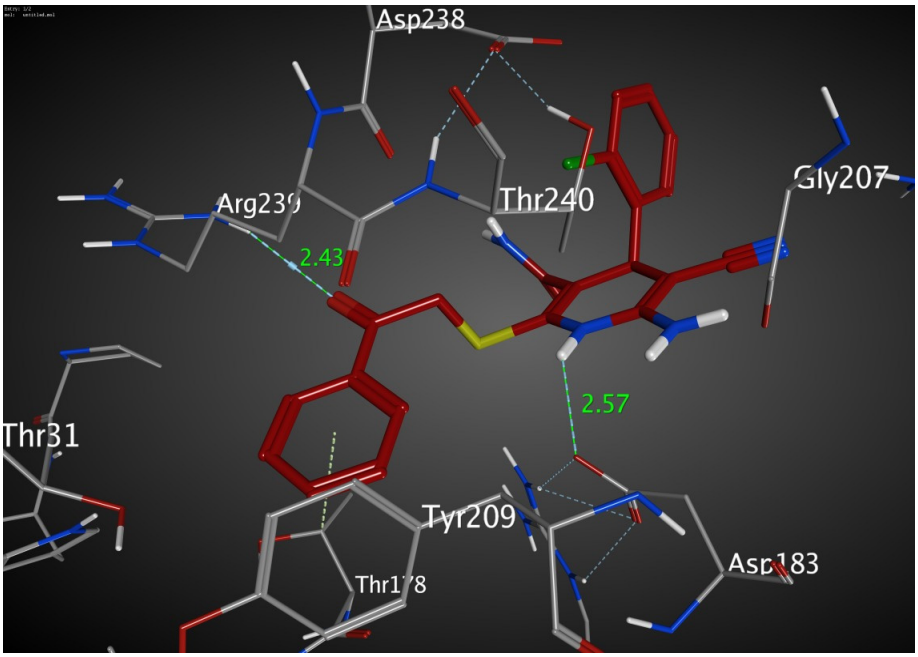


Figure 2. Three-dimensional interaction pose of compound **4b** in the active site of the protein (pdb:3LV3).

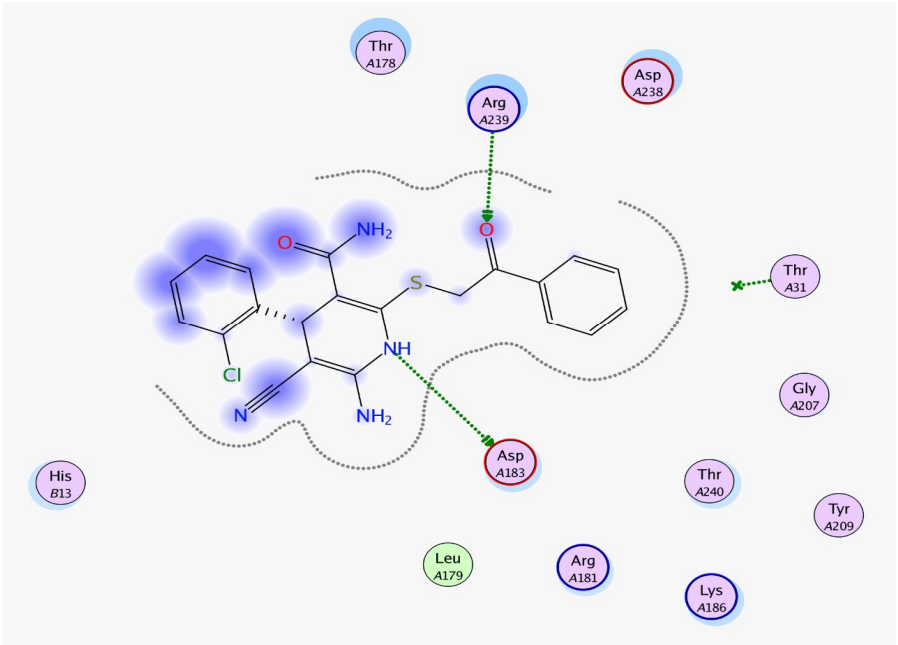


Figure 3. Two-dimensional interaction pose of compound **4b** with amino acids of the active site of 3LV3 protein.

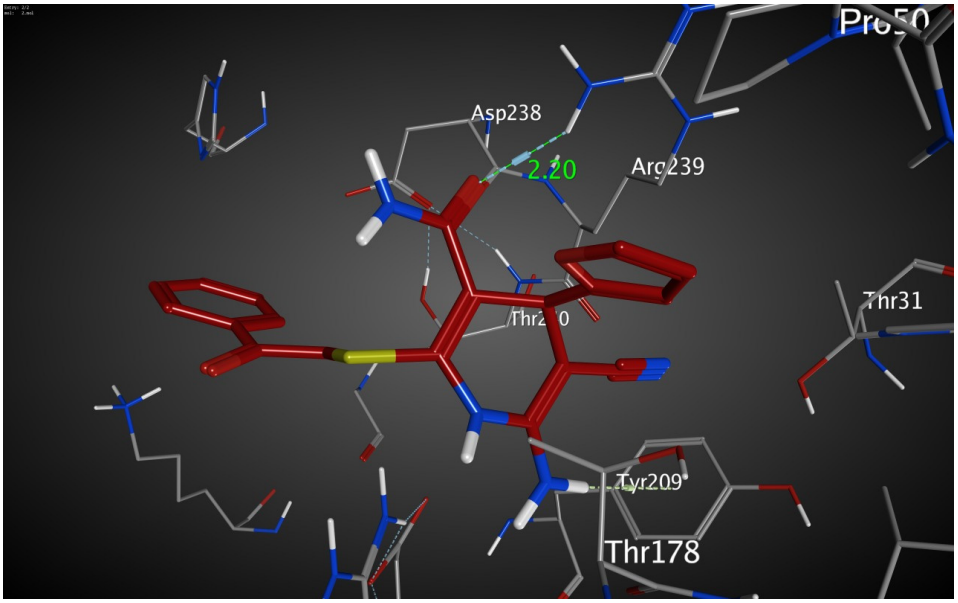


Figure 4. Three-dimensional interaction pose of compound **4a** in the active site of the protein (pdb:3LV3).

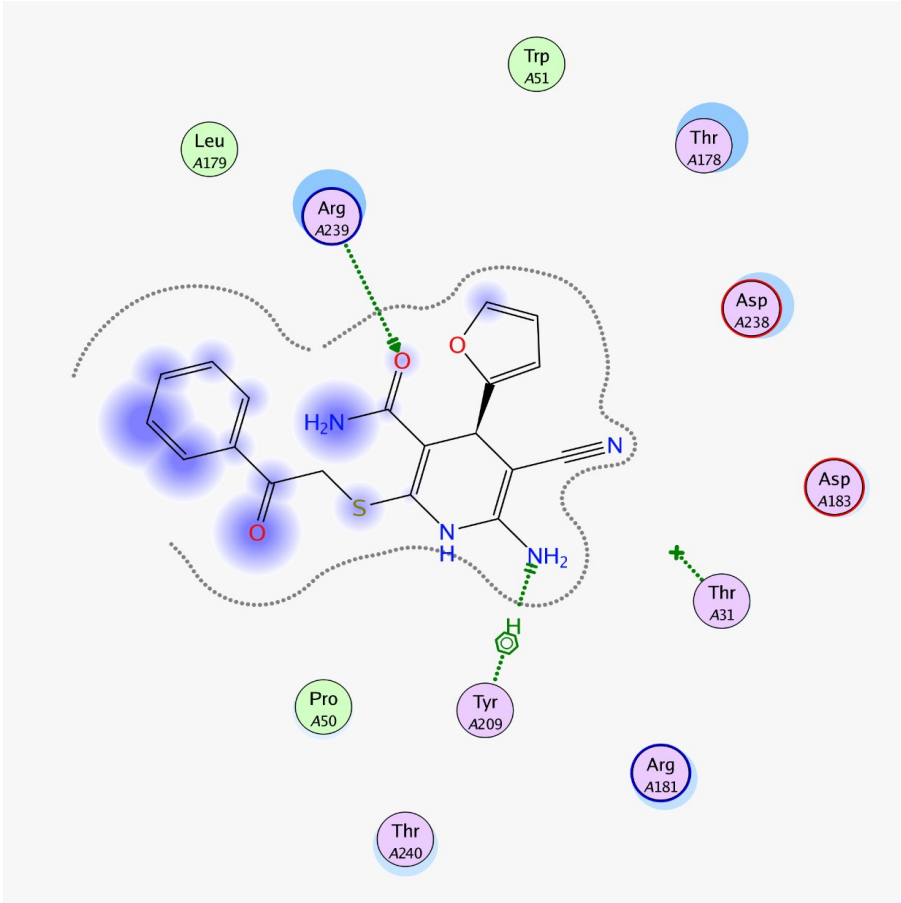


Figure 5. Two-dimensional interaction pose of compound **4a** with amino acids of the active site of 3LV3 protein.

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 and 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 produce 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 produce corresponding tetrahydronicotinamide **5** in 90–95% yields. As an example, X-ray and spectroscopic data for selected compound **5b** (R = 2-ClC$_6$H$_4$) are shown in Figures 6–8.

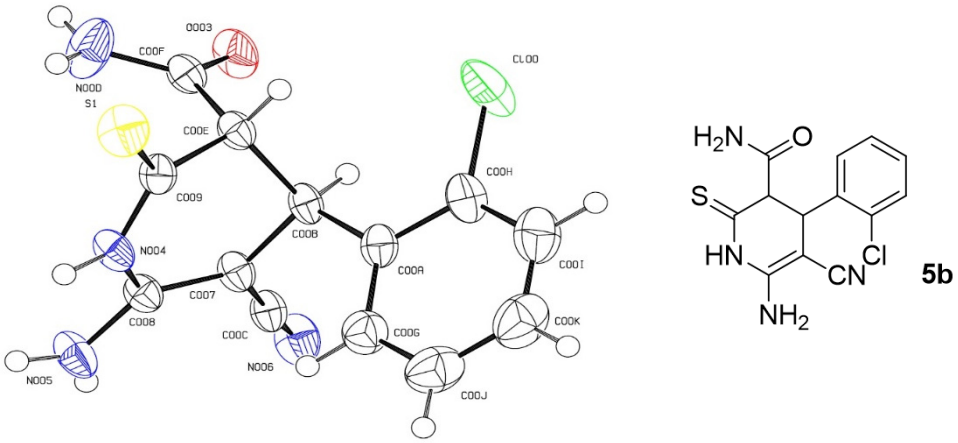


Figure 6. The structure of compound **5b** (X-ray data).

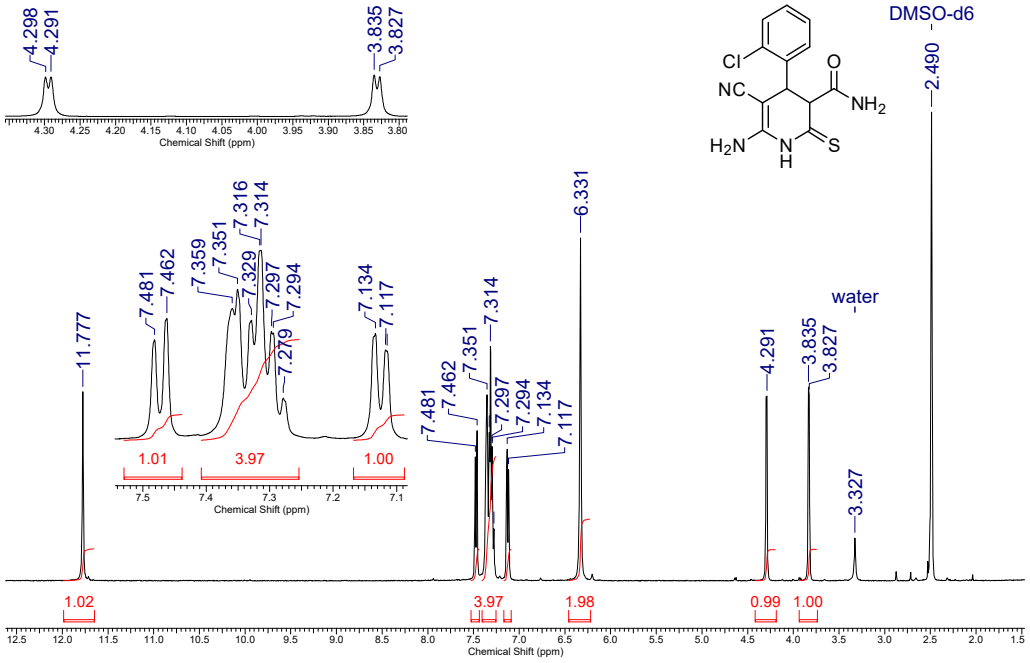


Figure 7. NMR ^{1}H spectrum (400 MHz, DMSO-d$_6$) of compound **5b**.

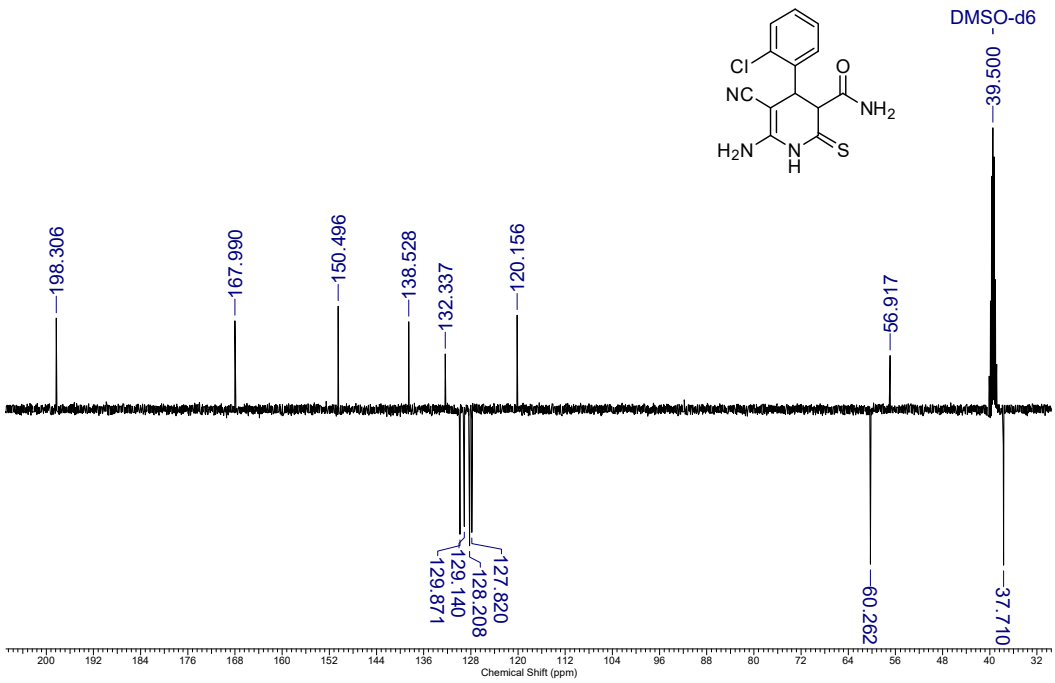


Figure 8. NMR ^{13}C DEPTQ spectrum (101 MHz, DMSO-d_6) of compound **5b**.

Author Contributions: Conceptualization, N.T.J., V.V.D.; methodology, V.V.D..; calculations, N.T.J.; analysis, N.A.A.; investigation, N.T.J., V.V.D..; resources, N.T.J., V.V.D., N.A.A.; writing—original draft preparation, V.V.D.; 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.

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

References

1. Safak, C.; Simsek, R. Fused 1,4-dihydropyridines as potential calcium modulatory compounds. *Mini Rev. Med. Chem.* **2006**, *6*, 747–755, doi:10.2174/138955706777698606.
2. Hilgeroth, A. Dimeric 4-Aryl-1,4-dihydropyridines: Development of a third class of nonpeptidic HIV-1 protease inhibitors. *Mini Rev. Med. Chem.* **2002**, *2*, 235–245, doi:10.2174/1389557023406241.
3. Triggle, D.J. 1, 4-Dihydropyridines as calcium channel ligands and privileged structures. *Cell. Mol. Neurobiol.* **2003**, *23*, 293–303, doi:10.1023/A:1023632419813.
4. Triggle, D.J.; Langs, D.A.; Janis, R.A. Ca^{2+} channel ligands: Structure-function relationships of the 1,4-dihydropyridines. *Med. Res. Rev.* **1989**, *9*, 123–180, doi:10.1002/med.2610090203.
5. Wan, J.P.; Liu, Y. Recent advances in new multicomponent synthesis of structurally diversified 1,4-dihydropyridines. *RSC Adv.* **2012**, *2*, 9763–9777, doi:10.1039/C2RA21406G.
6. Sharma, V.K.; Singh, S.K. Synthesis, utility and medicinal importance of 1,2-& 1,4-dihydropyridines. *RSC Adv.* **2017**, *7*, 2682–2732, doi:10.1039/C6RA24823C.
7. Triggle, D.J. The 1,4-dihydropyridine nucleus: A pharmacophoric template part 1. Actions at ion channels. *Mini Rev. Med. Chem.* **2003**, *3*, 215–223, doi:10.2174/1389557033488141.
8. Krauze, A.; Popelis, J.; Duburs, G. Efficient regioselective one-pot synthesis of partially hydrogenated thiazolo [3, 2-a] pyridines. *Tetrahedron* **1998**, *54*, 9161–9168, doi:10.1016/S0040-4020(98)00553-5.
9. Krauze, A.; Liepinsh, E.; Vilums, M.; Duburs, G. A new regioselective synthesis of 2-methoxymethyl-3-oxo-2,3-dihydro-7H-thiazolo [3,2-a]pyridine-8-carboxylic acid methylamide. *Chem. Heterocycl. Compd.* **2009**, *45*, 250–252, doi:10.1007/s10593-009-0259-x.
10. Krauze, A.; Viļums, M.; Sīle, L.; Duburs, G. Alternative products in one-pot reaction of benzylidenemalononitrile, N-methyl-2-thiocarbamoylacetamide, and ω-bromoacetophenone. *Chem. Heterocycl. Compd.* **2007**, *43*, 653–657, doi:10.1007/s10593-007-0102-1.

11. Krauze, A.; Vilums, M.; Sīle, L.; Duburs, G. Alternative Products in One-Pot Reaction of Benzylidene-Malononitrile, Thiocarbamoylacetamide And Alkyl Halides. *Heterocycl. Commun.* **2009**, *15*, 239–244, doi:10.1515/HC.2009.15.4.239.
12. Dotsenko, V.V.; Krivokolysko, S.G.; Litvinov, V.P. The Mannich reaction in the synthesis of N, S-containing heterocycles 12. First example of aminomethylation involving 2-thioxonicotinamide derivative: Synthesis of 3,5,7,11-tetraazatricyclo [7.3.1.$0^{2,7}$]tridec-2-ene-9-carboxamides. *Russ. Chem. Bull.* **2012**, *61*, 136–140, doi:10.1007/s11172-012-0019-4.