Hybrid molecules with 1,4-dihydropyridine and 1,2,3-triazole heterocyclic systems: novel pharmacologically active compounds with antihypertensive activity

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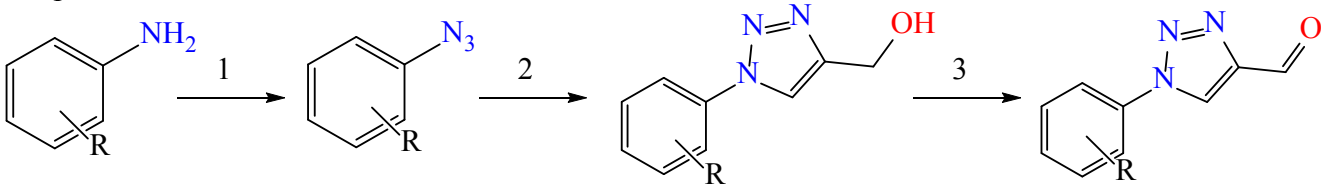
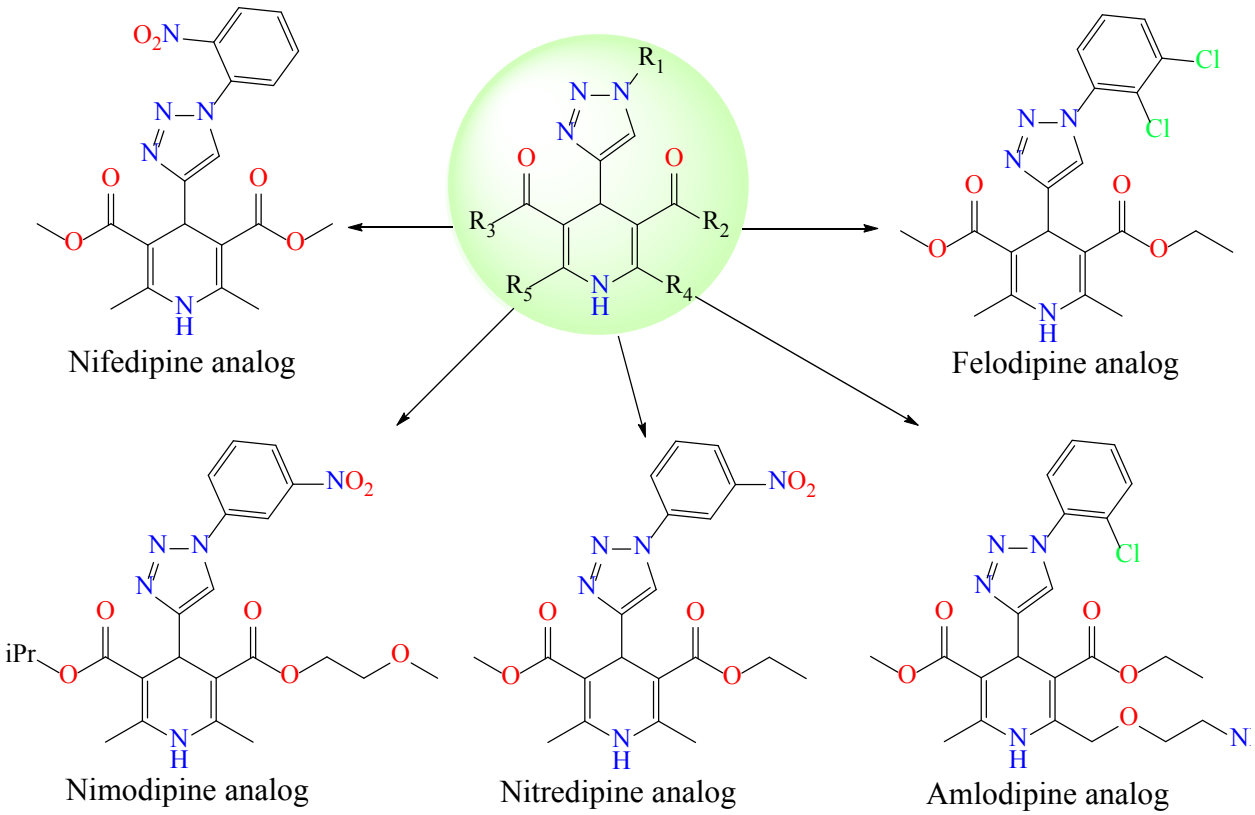
Introduction. Heterocyclic compounds of the 1,4-dihydropyridine series are of interest for scientists from the point of view of fundamental scientific research in the chemistry of heterocycles. 1,4-Dihydropyridine derivatives (1,4-DHP) are widely used in pharmacy due to broad biological activity, namely: anti-inflammatory, anti-tuberculosis, anticonvulsant, inhibit HIV protease, analgesics, antithrombotic, radio- and neuroprotective, antiplatelet activity. They are agents for Multidrug resistance (MDR) in tumor cells. They are also vital agents in the treatment of angina pectoris and hypertension. Some of the dialkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates, such as amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nimodipine, nitrendipine are valuable as calcium channel blockers and are antihypertensive drugs.

The last decade has been marked by increase in the attention of researchers from various fields of science to 1,2,3-triazoles. Therefore, the choice of this heterocycle as a multifunctional structural unit is based on the following aspects:

1. Synthetic accessibility and the possibility to modify the structure at three positions of the heterocycle.
2. High applicability in various fields of fundamental and applied research:
   a) Substrates for organic synthesis;
   b) Medical chemistry (painkillers, anti-inflammatory, anticonvulsant, antimicrobial, antiviral and antineoplastic substances);
   c) Bioorthogonal chemistry – click-reactions proceeding with the formation of triazoles directly in living systems.
3. Heterocyclic peptide bond mimetics, since the triazole ring has similar electronic and topological characteristics to the amide groups.
4. Triazoles gives biostability, bioavailability, efficiency and selectivity to various receptors to new compounds.



Scheme 1 – Synthetic way for 1-phenyl-1*H*-1,2,3-triazole-4-carbaldehydes. Reagents and conditions: 1) $NaNO_2$, HCl, 0 °C; NaN_3, 2–4 h, rt; 2) propargyl alcohol, $CuSO_4$, sodium ascorbate, THF:H_2O (1:1), rt; 3) PCC, CH_2Cl_2, 2 h, rt.



Scheme 2 – Hybrid molecules containing 1,4-dihydropyridine and 1,2,3-triazole rings.

The introduction of the 1,2,3-triazole fragment into the dialkyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates structure can significantly expand the scope of antihypertensive drugs and allow the development of new drugs (Scheme 2).

Materials and methods. Standard methods of organic synthesis were used in the investigation. Structures of the obtained compounds were determined using ^{1}H NMR, ^{13}C NMR spectroscopy, and LC/MS.

Results and discussion. We synthesized triazole aldehydes and derivatives of β-dicarbonyl compounds to obtain the target compounds by the Hantsch reaction. Aldehydes were obtained from the corresponding azides by click-chemistry with propargyl alcohol and then oxidized with Johnson's reagent (Scheme 1). β-Dicarbonyl compounds were prepared from 2,2,6-trimethyl-4H-1,3-dioxin-4-one. Subsequently, the Hantzsch reaction was improved and, as a result, the necessary products were obtained with a yield of 95-99% and a purity of more than 95%.

Conclusions. We have developed synthetic approaches and obtained series of new hybrid molecules containing 1,2,3-triazole and 1,4-dihydropyridine fragments: 4-(1H-1,2,3-triazol-1-yl)-1,4-dihydropyridines.

New 1,2,3-triazolo-1,4-dihydropyridine hybrid molecules are promising biologically active compounds and are of undoubted interest for pharmacological research, including the search for new antihypertensive agents.