SYNTHESIS OF NEW [1,2,4]TRIAZOLO[4,3-a]PYRIDINE-3-YL]ACETAMIDE DERIVATIVES WITH AN 1,2,4-OXADIAZOLE CYCLE

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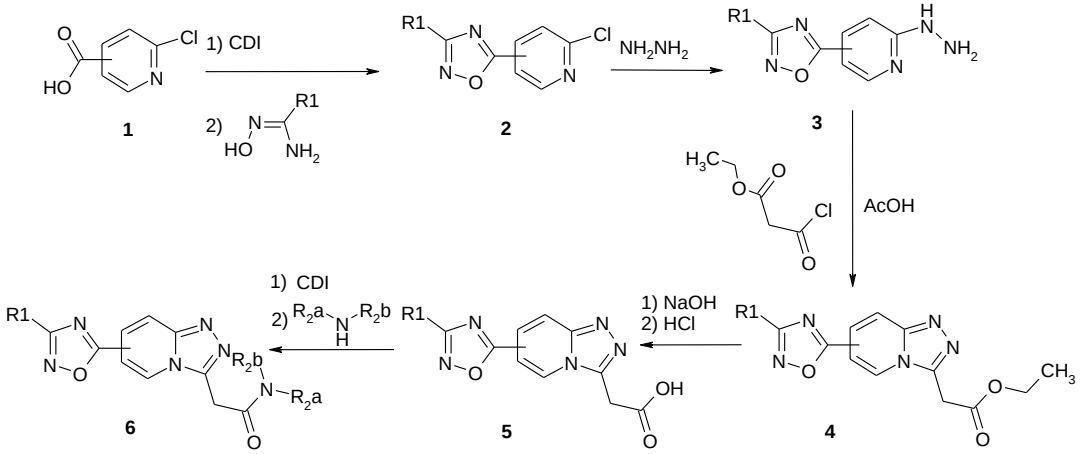
Introduction. Triazole derivatives often exhibit broad biological activities in medicine and agriculture. Pyridine derivatives have also displayed various biological activities. The chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives have received considerable attention owing to their synthetic and effective biological importance. [1,2,4]triazolo[4,3-a]pyridine derivatives possess diverse pharmaceutical and biological activities, i.e., as antibacterial, antithrombotic, anticancer, anti-inflammatory, herbicidal, antifungal, anticonvulsant, anxiolytic, antipsychotic, and antidepressant agents. The incorporation of an [1,2,4]-oxadiazole cycle into the main scaffold is considered to be a good way to produce novel active compounds.

Aim. In view of all these facts, and as a continuation of research on bioactive heterocycles, herein a series of novel 1,2,4-triazolo[4,3-a]pyridines with an [1,2,4]-oxadiazole cycle were synthesized. Prognosis and study of their pharmacological activity was also carried out.

Materials and methods. Our new target compounds 2-[(1,2,4-oxadiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides were prepared following the process presented in Scheme.

Scheme



The reaction sequence starts from known 2-chloropyridine carboxylic acids 1 dissolved in anhydrous DMF (N,N-Dimethylformamide) with an excess of CDI (carbonyldiimidazole). Adding an excess of corresponding amidoxime resulted in the

formation of corresponding 2-chloro-[3-R_1-1,2,4-oxadiazol-5-yl]pyridine 2. 2-hydrazine-[3-R_1-1,2,4-oxadiazol-5-yl]pyridines 3 have been synthesized by hydrazinolysis with hydrazine hydrate and subsequent heating until the end of reaction in dioxane. Further synthesis of ethyl 2-[(3-R_1-1,2,4-oxadiazol-5-yl)-1,2,4-triazolo[4,3-a]pyridine-3-yl]acetates 4 were performed following a procedure of the addition of ethyl malonylchloride to the solution of 2-hydrazine-[3-R_1-1,2,4-oxadiazol-5-yl]pyridines 3 in acetic acid with reflux for 2h. The obtained products 4 then were hydrolysed by sodium hydroxide in aqueous methanol during 12h and then was acidified with hydrochloric acid to obtain corresponding 2-[(3-R_1-1,2,4-oxadiazol-5-yl)-1,2,4-triazolo[4,3-a]pyridine-3-yl]acetic acids 5. The products 5 were further reacted with CDI, in order to activate the carboxyl group for direct reaction with corresponding amines via amide bond formation. As a result, we have obtained novel 2-[(1,2,4-oxadiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides 6.

The purity and structures of the synthesized compounds were confirmed by elemental analysis and ^{1}H NMR spectroscopy data.

In order to predict the pharmacological activity of 2-[(1,2,4-oxadiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides, we performed a pharmacophore-based parallel *in silico* screening experiments. Our collection of structure- and ligand-based interaction models was used, which revealed potential inhibitory activity of the compounds against Cytochrome P 450 (CYP) known to be a heme containing protein superfamily of enzymes metabolizing a broad variety of xenobiotics, including drugs and toxic chemicals. In addition, our experiment also revealed potential inhibitory activity against 5-HT2C (G-protein coupled receptor), known to be a potential target for the treatment of central nervous system (CNS) disorders.

Antimicrobial activity (bacterial and fungal) of some of the synthesized compounds was studied *in vitro*. Antimicrobial screening was performed by CO-ADD (The Community for Antimicrobial Drug Discovery), funded by the Wellcome Trust (UK) and The University of Queensland (Australia). The inhibition of growth was measured against 5 bacteria: *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, and 2 fungi: *Candida albicans* and *Cryptococcus neoformans*.

Results and discussion. New target compounds 2-[(1,2,4-oxadiazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamides have been synthesized and obtained with satisfactory yields. Unfortunately, the compounds deemed active in the Primary Screen (≤32 μg/mL) were not confirmed hits (≤16 μg/mL) in the dose response assay, therefore further development was not prioritized.

Conclusions. However knowing that such type of scaffold could possess wide range of pharmacological activity we would continue searching new biologically active substances among [1,2,4]triazolo[4,3-a]pyridine-3-yl]acetamide derivatives.