NEW BIOACTIVE DERIVATIVES OF ISOXAZOLES AND ISOTHIAZOLES WITH AMINO ACID MOIETIES

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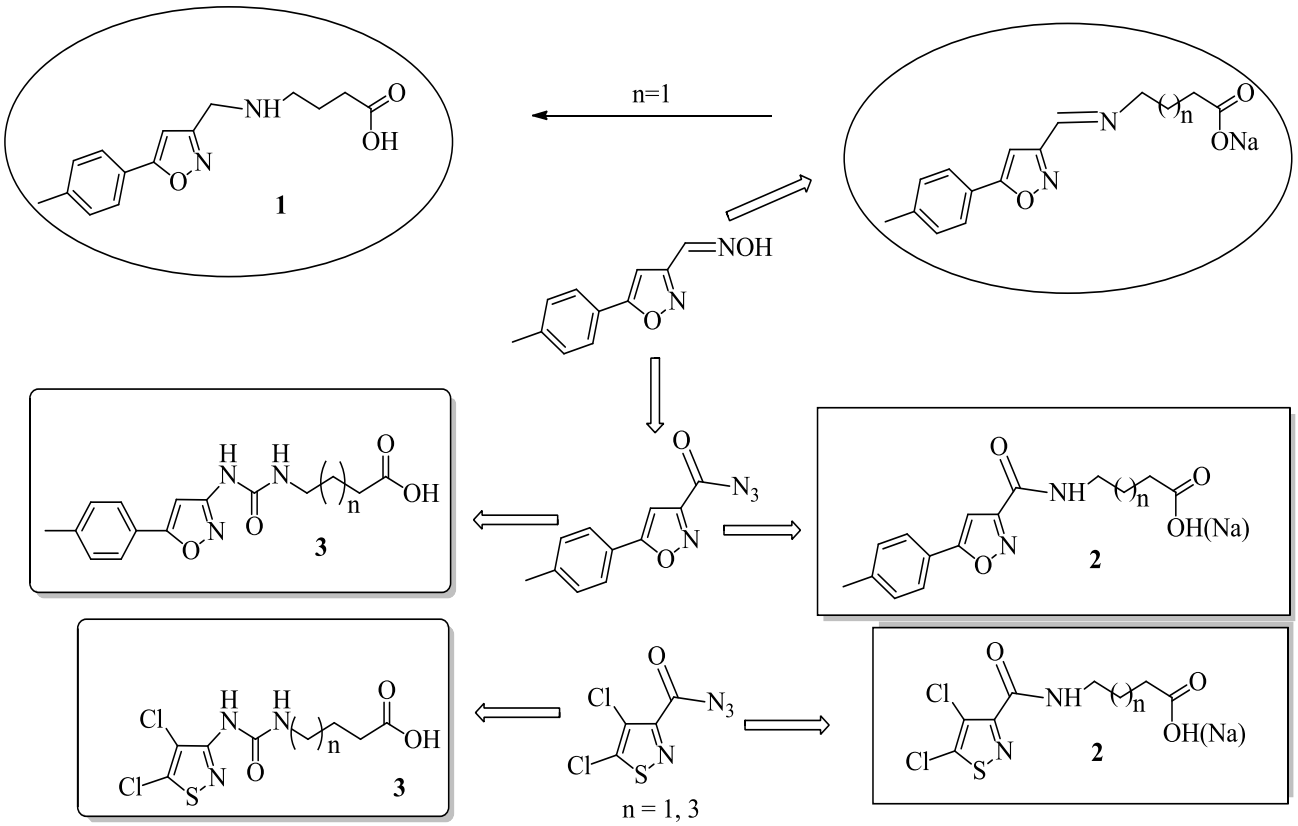
Isothiazole and isoxazole are known to be fragments of wide range of biologically active compounds. For example, 2-amino-3-(3-hydroxy-5-methylisothiazol-4-yl)propionic acid as well as its isoxazole analogue (AMPA) blocks the activation of glutamate receptors which are crucial for different neurodegenerative diseases. Efficiency of the biological action of isothiazoles and isoxazoles is heavily regulated by functional ambience of 1,2-azole scaffold. In this regard, isoxazolyl(isothiazolyl) amines, carboxamides and ureas are very promising for the development of new targeted drugs. Some of the substituted isoxazole carboxamides are FAAH inhibitors and protect against experimental colitis, other are growth hormone secretagogue receptor (GHS-R) antagonists. One representative of (3-benzyloxy-4-carboxamidoisothiazol-3-yl)ureas is an effective inhibitor of tyrosine kinases and it is studied as a promising anticancer agent (CP-547.632).5 Among (isoxazol-3-yl)ureas a perspective Raf kinase inhibitor was spotted [1,2].

We developed the convenient approaches for the synthes of isoxazol-3-yl(isothiazol-3-yl) amines **1**, carboxamides **2** and ureas **3** with amino acid residues. It was expected that the presence of amino acid residue in the molecule would increase the efficiency and selectivity of biological action of the conjugate. Moreover, the amino acid moiety allows to obtain water soluble salt forms, which is important for biological activity and bioassay.



The antitumor activity of some synthesized compounds was studied. The experiments were carried out on primary and linear cultures of neuroepithelial tumors. It was found out that antitumor activity of isoxazoles and isothiazoles conjugates with 4-aminobutanoic acid (carboxamides and ureas) significantly exceeded the effect of the corresponding 1,2-azolyl carboxylic acids. In addition, death of over 40% of cells and decrease in proliferation index ($p \leq 0.05$) were recorded in 24 h of observation after the application of 1M solution of conjugate on glioma cells C6 culture in the experiments in vitro.

References

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