SYNTHESIS OF NOVEL 1,3,5-TRIAZINE DERIVATIVES AS POTENTIAL INHIBITORS OF TUMOR-ASSOCIATED CARBONIC ANHYDRASE IX

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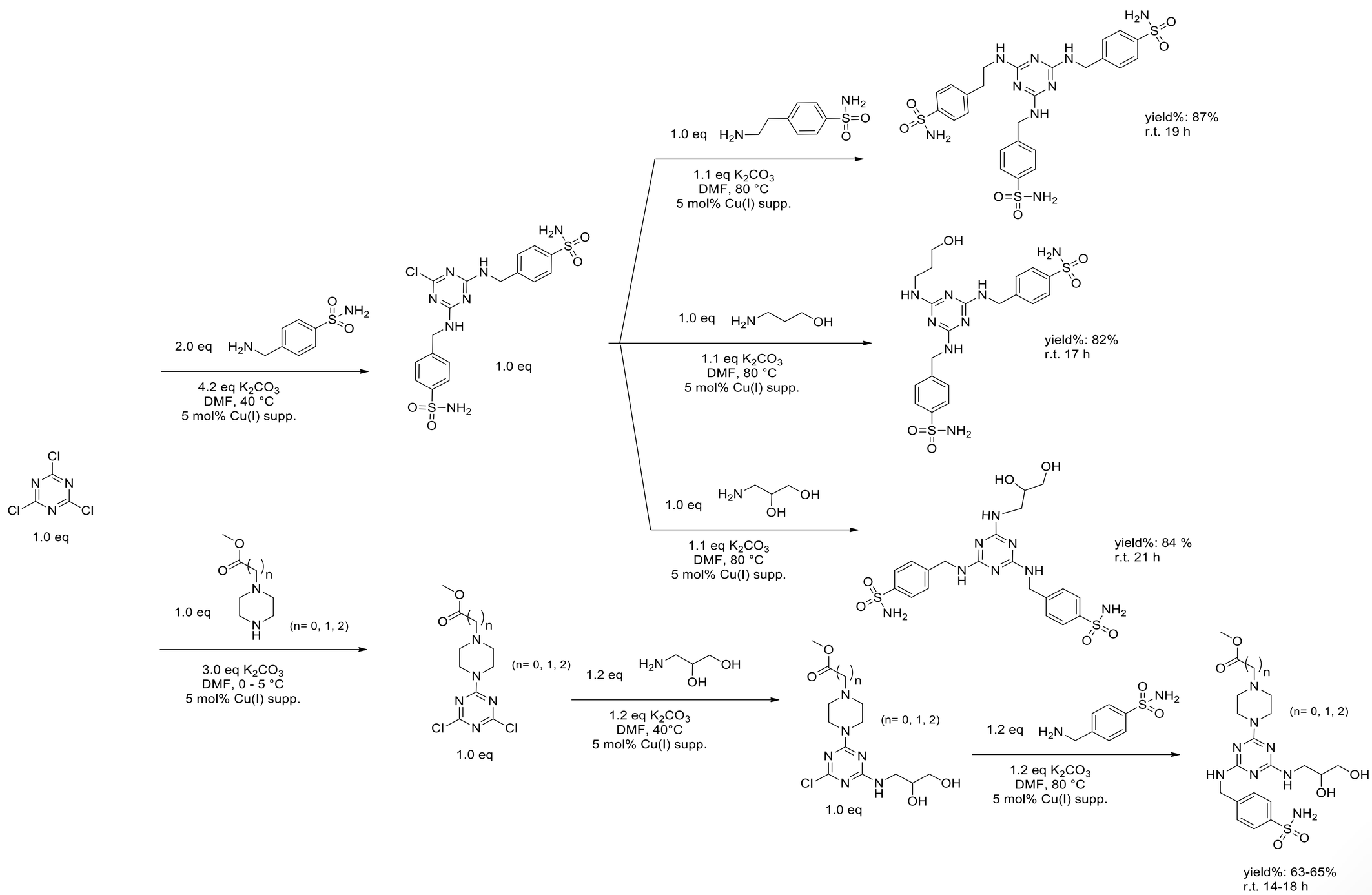
Introduction: In the last few years, the *s*-triazine structural motive, as the carrier of pharmacophores, becomes a subject of many research works. Derivatives of *s*-triazines exhibit a broad spectrum of biological activities, and currently are in the forefront of interest, especially due their anti-tuberculosis, anti-bacterial and anti-cancer properties. [1]
As the target of our interest we chose 1,3,5-triazine derivatives with potential antitumor activity against isozyme carboanhydrase hCAIX (associated with tumor growth). We used forwarded Artificial Neuronal Networks for the prediction of the biological activity of these derivatives. [2, 3]
Syntheses of novel 1,3,5-triazine derivatives starting from cyanuric chloride are shown below. Target structural motives are involved in the *s*-triazine skeleton *via* substitution of chlorine atoms by amino group in various aminobenzensulfonamides, piperazines, amino alcohols and further amino compounds. It was found that substitution of the chlorine atoms in cyanuric chloride can be carried out as C-N coupling catalyzed by Cu(I) supported on weakly acidic macroporous cation exchanger resin of polyacrylate type *via* the oxidative addition - heterolytic addition - reductive elimination processes. The reaction could proceeds as a one-pot/ one-step synthetic process that is carried out under temperature control. Very good and excellent yields were obtained with shorter reaction times in comparison with similar usual syntheses realized step by step. Synthetic procedures optimized by this way can be applied in the preparation of the further various *s*-triazine with respect to the chemical behaviour of the individual nucleophilic reagents.

Method for preparation of catalyst - Cu(I) supported on resin: [4]
Purolite® C104Plus in Na^+ form in amount 75.0 g was stirred in water (200 mL). Cupric acetate monohydrate (49.9 g, 250 mmol) dissolved in water (750 mL) was mixed with aqueous ammonia solution (28 w/w %, 85 mL, 1255 mmol) under good stirring. Furthermore, the dark blue solution was added to the resin suspension and stirred for 30 minutes. Then the aqueous phase was decanted and the blue solid washed twice with water (300 mL). The resin was then stirred for 30 minutes in the water solution (250 mL) containing hydroxylammonium chloride (29.9 g, 430 mmol) at 50 °C until the blue color of resin changed to light gray. After that, the solution was decanted, the solid residue washed twice with water (250 mL), twice with methanol (150 mL) and dried in vacuum. The copper content was determined by flame atomic absorption spectrometry which was approximately 2.2 mmol of Cu/1 g of dry catalyst.



Conclusion: ANNs were used for the prediction of *s*-triazine structures with the potential biological activity against hCAIX. For the syntheses of these triazines were successfully applied procedures mentioned in scheme above. All reactions were proceeded as a one-pot/ one-step synthetic process and they were carried out under temperature control. Furthermore, the efficiency of the supported Cu(I) catalyst was proved. The obtained yields and reaction times were better in comparison with similar usual syntheses realized step by step. Synthetic procedures optimized by this way can be applied in the preparation of the further various *s*-triazines with respect to the chemical behavior of the individual nucleophilic reagents. For prepared triazines and other derivatives, which were predicted by the ANNs, the biological tests are underway.

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