Synthesis of acetamide derivatives of octahydrochromene with arylpiperazine moiety, perspective inhibitors of the Tdp1 enzyme

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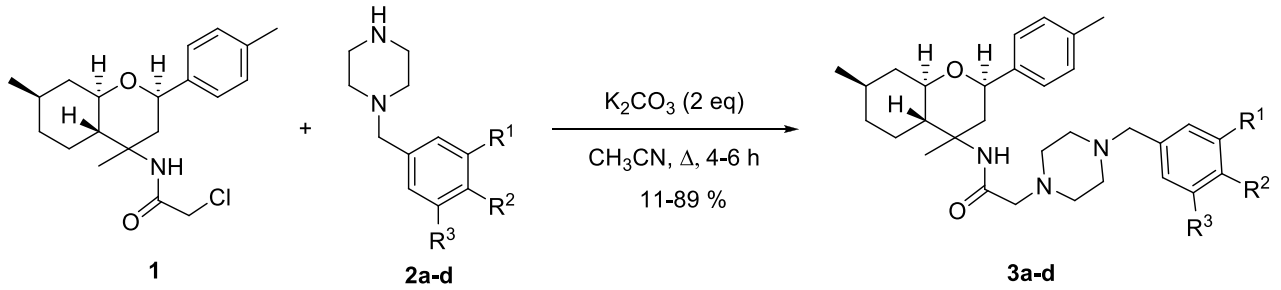
Earlier in our laboratory, amide derivatives of octahydrochromene were obtained by a three-component Prince-Ritter reaction. These compounds exhibited inhibiting activity against the DNA repair enzyme tyrosyl-DNA phosphodiesterase 1 (Tdp1) in the low micromolar range [1]. Based on molecular modeling results, it was proposed that acetamide derivatives of octahydrochromene **3**, which contain an arylpiperazine moiety, may exhibit inhibitory activity against Tdp1.

The purpose of this work is the synthesis of chiral acetamide derivatives of octahydrochromene with an arylpiperazine moiety, starting from 2-chloroacetamide, *p*-tolyloctahydrochromene **1**, and substituted arylpiperazines **2**.

The alkylation reaction was carried out in acetonitrile by boiling in the presence of K_2CO_3, after purification by column chromatography the yields of the target compounds ranged from 11 to 89%.



1 **2a-d** **3a-d**

where R^1, R^3 = OMe (a), H (b-d) , R^2 = OMe (a,b), Me (c), F (d)

Compound **3a** didn't exhibit inhibitory activity against Tdp1, (IC_{50} > 50μM), while compounds **3b-d** showed inhibitory activity ranged from 19.3 to 10.3 μM.

References

[1] A.A. Chepanova et al. // Russian Journal of Bioorganic Chemistry, 2019, Vol. 45, No. 6, pp. 647-655.