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

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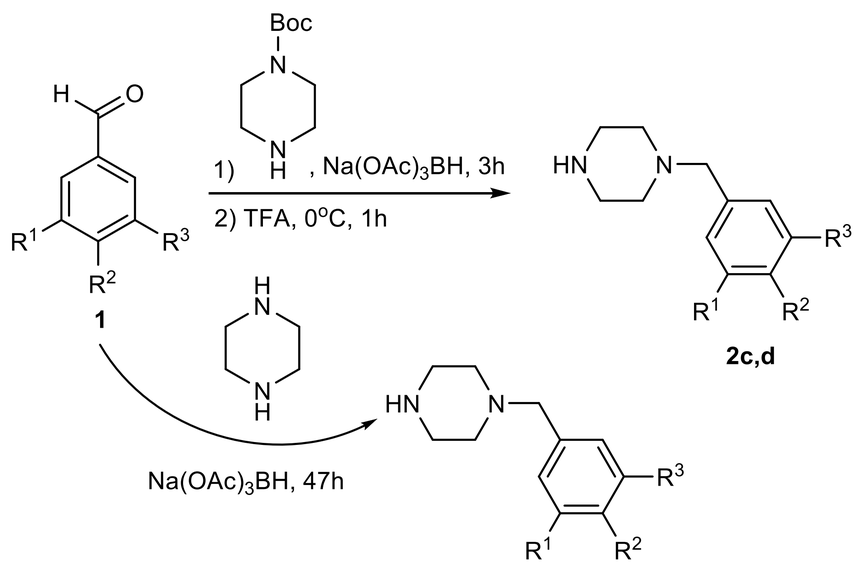
Abstract: *Earlier in our laboratory, amide derivatives of octahydrochromene were obtained by a three-component Prins-Ritter reaction. These compounds exhibited inhibiting activity against the DNA repair enzyme tyrosyl-DNA phosphodiesterase 1 (Tdp1) in the low micromolar range [1].*

Tdp1 is of first importance in the repair of DNA damage, caused by anticancer drugs, such as camptothecin, irinotecan and topotecan. Inhibitors of the Tdp1 may improve efficiency of currently used anticancer therapy, therefore their development is an actual task.

In this work we synthesized number of acetamide derivatives of octahydrochromene, promising inhibitors of the Tdp1, and studied their ability to inhibit of the Tdp1 enzyme.

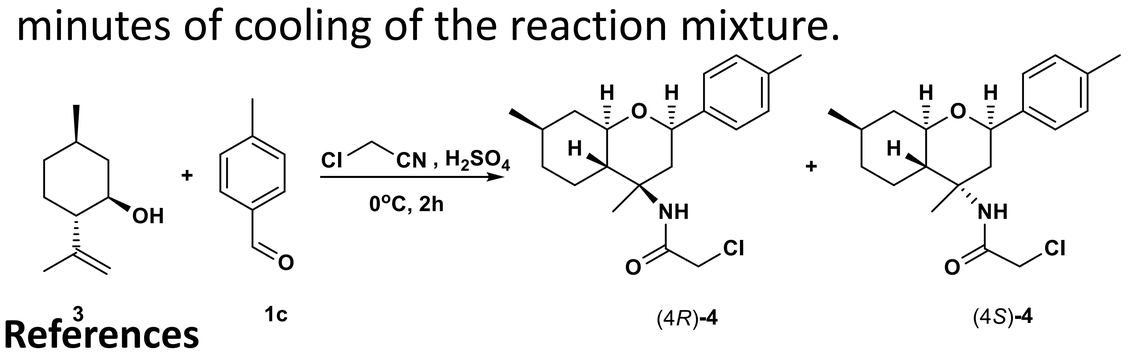
Arylpiperazines were obtained by reducing amination reaction between aromatic aldehydes and piperazine or *N*-Boc-piperazine. During the reduction amination reaction, $Na(OAc)_3BH$ was added an hour after the start of the reaction. When removing the Boc protection, TFA was added drop by drop after 20 minutes of cooling of the reaction mixture. All reactions were carried out in CH_2Cl_2. The advantages of using *N*-Boc-piperazine are the formation of fewer by-products and a faster reaction time.



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

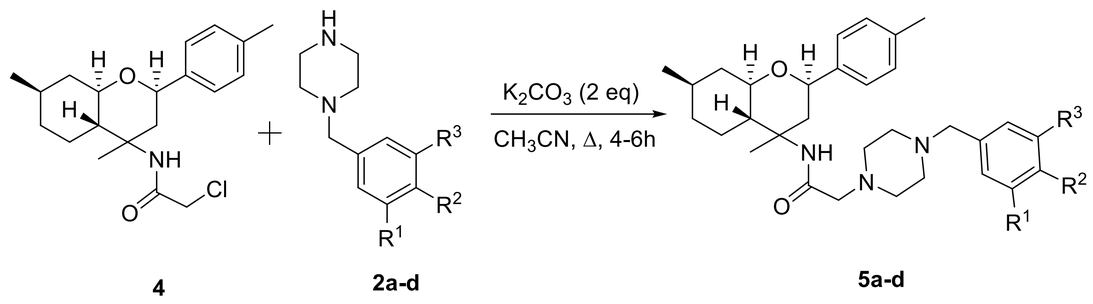
The products **2a** (22%), **2b** (17%), **2c** (45%), **2d** (12%) was isolated by column chromatography (silica gel Macherey-Nagel 0.063-0.20 mm), eluting with 0–20% methanol in dichloromethane.

For obtaining 2-chloroacetamide *p*-tolyloctahydrochromene, (–)-isopulegol **3** and *p*-tolylaldehyde **1c** were introduced into the Prins-Ritter reaction. H_2SO_4 was added after 15 minutes of cooling of the reaction mixture.



Chloroacetonitrile was used as both a reagent and a solvent. The obtaining diastereomers were separated by column chromatography (silica gel, 20 g), eluting with 0–100% ethyl acetate in hexane. The presence of one or the other diastereomer was determined using GC. The yield of the product (4*R*)-**4** was 41%, for the product (4*S*)-**4** the yield was 35%.

The obtaining arylpiperazines were introduced in the alkylation reaction by refluxing in acetonitrile in the presence of K_2CO_3. The target compounds **5a-d** were isolated by column chromatography (silica gel, 5-7 g), eluting with 0–100% ethyl acetate in hexane, then using acetone 100%.



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

The product	The yield, %	*IC_{50}, μM
(4*R*)-**5a**	51	>50
(4*R*)-**5b**	89	19.3±1.7
(4*S*)-**5b**	83	n.d.
(4*R*)-**5c**	73	18.1±1.8
(4*R*)-**5d**	89	19.0±1.0
(4*S*)-**5d**	83	10.3±0.2

*IC_{50} is half-maximal inhibitory concentration, indicating how much an inhibitor ligand is needed to inhibit a biological process by 50%.

References

[1] A.A. Chepanova et al. Effective Inhibitors of Tyrosyl-DNA Phosphodiesterase 1 Based on Monoterpenoids as Potential Agents for Antitumor Therapy // Russian Journal of Bioorganic Chemistry, 2019, Vol. 45, No. 6, pp. 647-655.