PR-11. FLUORINATED 2-CARBONYLPIPERAZINO-1,3-BENZOTHAZIN-4-ONES AS PERSPECTIVE ANTITUBERCULAR AGENTS

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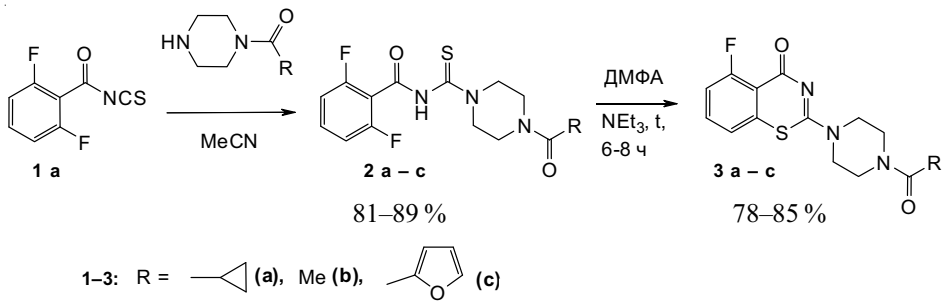
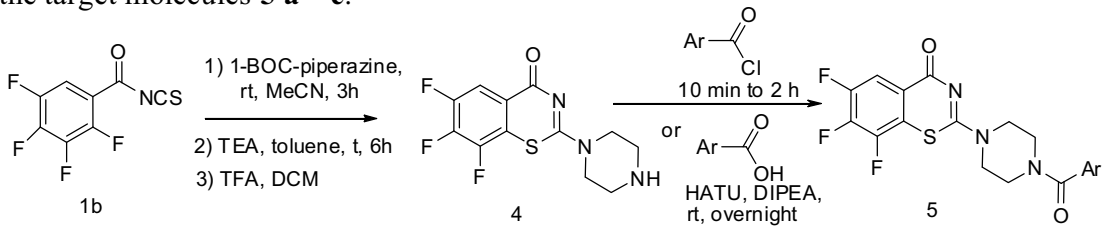
2-Amino substituted 1,3-benzothiazin-4-ones (2-amino-1,3-BTZs) have been discovered as promising agents for the treatment of tuberculosis, 6-trifluoromethyl-8-nitro-1,3-benzothiazin-4-ones bearing not only piperazine but also other cycloalkylimino residues are intensively studied at present [1]. 5-Fluoro-2-(4-ethoxycarbonylpiperazin-1-yl)-1,3-benzothiazin-4-one was found to possess high antitubercular activity [2]. The series of 2-(4-carbonylpiperazino)-6-trifluoro-8-nitro-1,3-benzothiazin-4-ones exhibited high activity towards M. tubercolusis H37Rv and improved solubility in water [3]. For this reason the development of synthetic approaches to novel fluorinated carbonylpiperazino-substituted benzothiazinones is in demand.

2,6-Difluoro-N-piperazinylimino-carbamoyl)benzamides **2** were obtained from benzoylizothiocyanate **1 a** and subjected the cyclization into 5-fluoro-1,3-benzothiazin-4-ones **3 a – c** under refluxing in DMF in the presence of trimethylamine during 6–8 h.



Not many 1-carbonylpiperazine are commercially available, so, we developed the synthetic approach to modification of piperazinyl moiety. The reaction of compound **4** with aroylchlorides or carboxylic acids catalyzed by combination of N-[(dimethylamino)-*1H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-yl-me-thylene]--*N*-methylmethanaminium hexafluorophosphate N-oxide (HATU) and *N,N*-diisopropylethylamine (DIPEA) leads to the target molecules **5 a – e**.



5: Ar = Ph (a), 4-ethylphenyl (b), 4-t-butylphenyl (c), 3-fluorophenyl (d), 2,6-difluorophenyl (e)

References

1. Recent advancements in the development of anti-tuberculosis drugs / S. Chetty [et al.] // Bioorg. Med. Chem. Lett. Pergamon. 2017. Vol. 27, № 3. P. 370–386.

2. Fluorine-containing indoles: Synthesis and biological activity / E. V. Nosova [et al.] // J. Fluor. Chem. Elsevier. 2018. Vol. 212. P. 51–106.

3. Synthesis and antitubercular evaluation of 4-carbonyl piperazine substituted 1,3-benzothiazin-4-one derivatives / C. T. Peng [et al.] // Bioorg. Med. Chem. Lett. Pergamon. 2015. Vol. 25, № 7. P. 1373–1376.

This work was supported by Russian Foundation for Basic Research (grant № 15-13-00077).