Synthesis of novel TDP1 inhibitors – thiazolidinones, thiazolidinediones containing terpenoid substituents

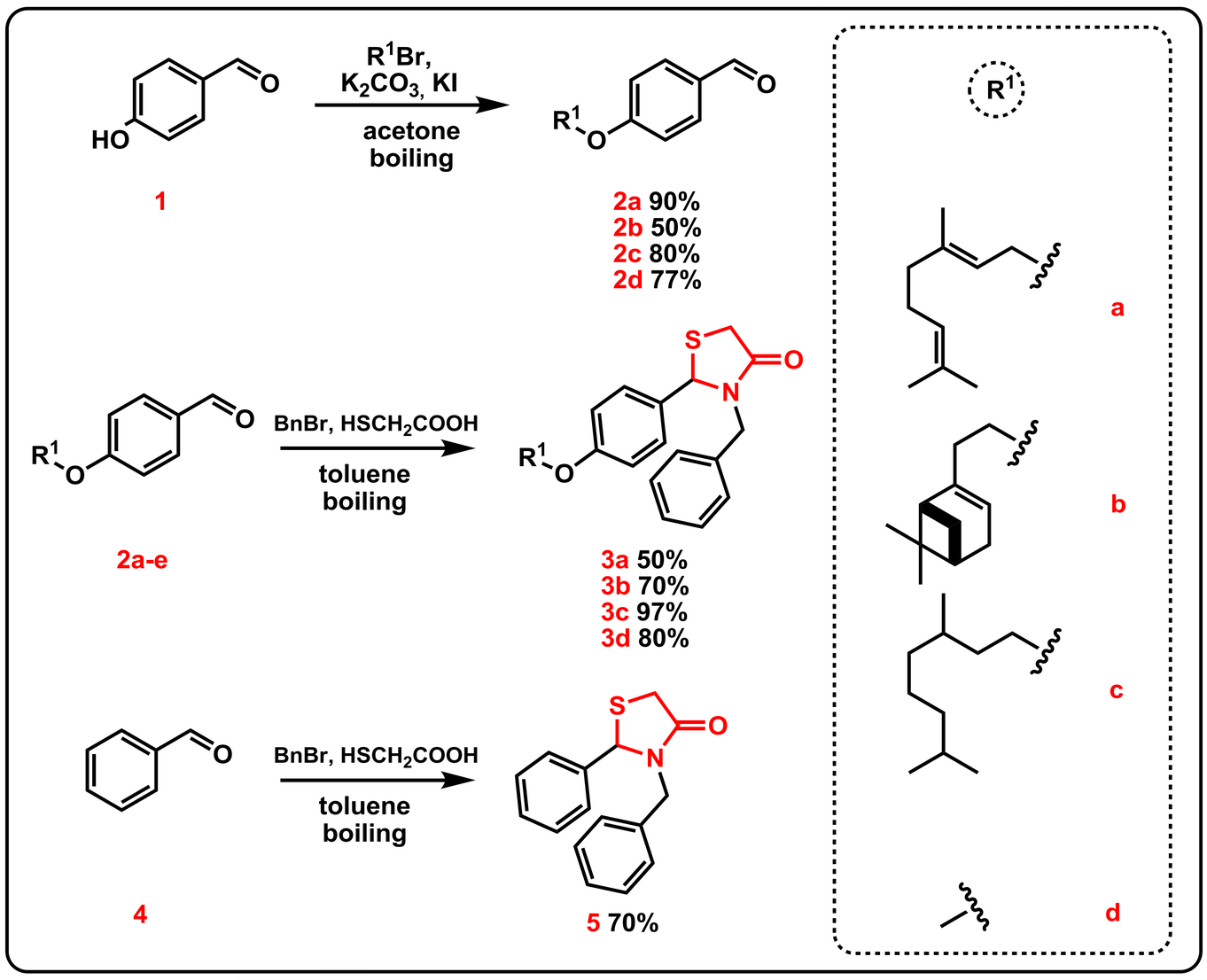
D. I. Ivankin[1]*, A. L. Zakharenko[2], O. A. Luzina[1], O. I. Lavrik[2], N. F. Salakhutdinov[1]

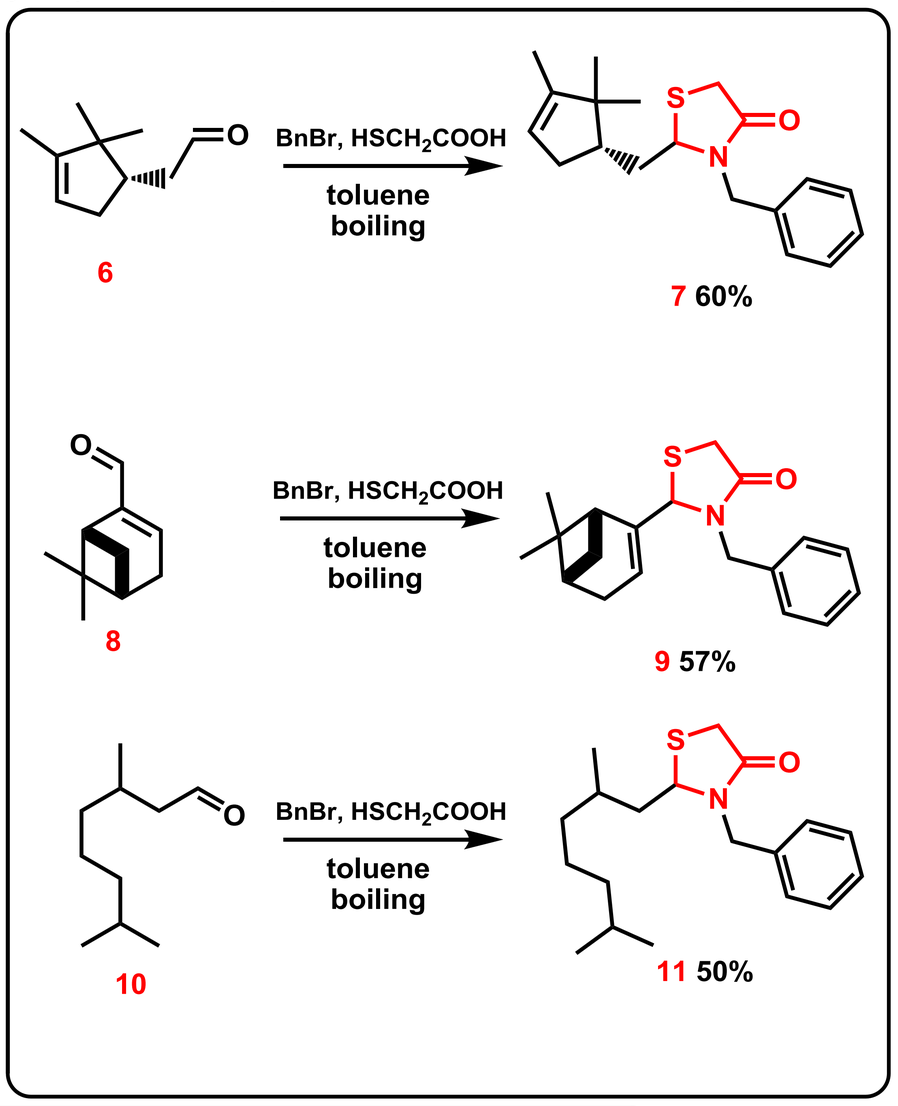
[1]N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry of SB RAS, 630090, Russia, Novosibirsk, 9 Lavrentiev Avenue

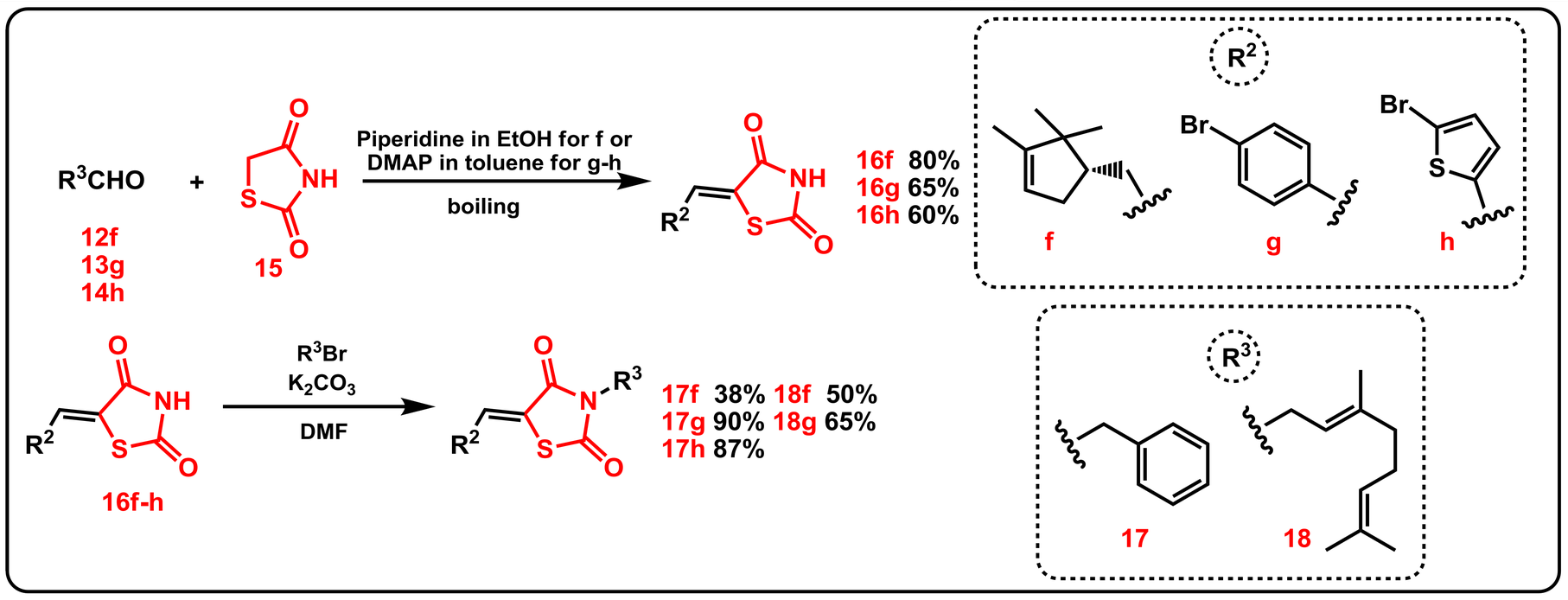
[2]Institute of Chemical Biology and Fundamental Medicine of SB RAS, 630090, Russia, Novosibirsk, 8 Lavrentiev Avenue

*ivankind@nioch.nsc.ru

Tyrosyl-DNA phosphodiesterase 1 (TDP1) is a perspective target-enzyme for creating drugs used in oncological desease therapy for fighting against drug-resistant tumors [1]. Natural compounds are important and renewable sources in modern medicine development. Earlier, it has been found that compounds containing monoterpenoid fragments possess inhibiting activity in relation to TDP1 [2]. In this work, we have synthesized several thiazolidinones and thiazolidinediones containing different terpenoids (cyclic, acyclic, and bicyclic) at different positions in the thiazolidine ring.







Human TDP1 was used as an enzyme and a 15-mer single-stranded oligonucleotide containing both a 5′-FAM fluorophore donor and a quenching 3′-BHQ1 moiety was used as a biosensor for *in vitro* screening [3]. All biological tests were carried out in ICBFM SB RAS. All the results are presented in the table.

Compound	IC_{50}, μM	Compound	IC_{50}, μM	Compound	IC_{50}, μM
3a	2.9 ± 0.6	7	> 100	17f	2.4 ± 1.1
3b	2.1 ± 0.4	9	> 100	17g	1.6 ± 0.3
3c	1.2 ± 0.1	11	> 100	17h	1.9 ± 0.3
3d	> 100	16f	> 100	18f	4.1 ± 0.1
5	> 100	16g	> 100	18g	> 100

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[2] K.Yu. Ponomarev et al. Bioogranic Chemistry, **2017**, *76,* 392-399; K. Volcho et al. Proceedings, **2019**, *22*, 35.
[3] A. Zakharenko et al. Bioorg. Med. Chem., 2015, 23, 2044-2052.

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