NATURAL-LIKE SCAFFOLDS TARGETING THIOREDOXINE REDUCTASE FOR ANTICANCER THERAPY

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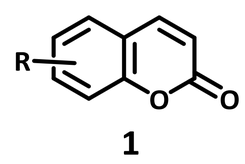
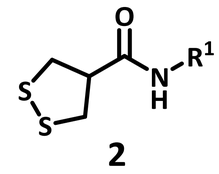
- **INTRODUCTION** Selenoprotein thioredoxin reductase (TrxR) is implied to have several different roles in relation to cancer. Together with selenoprotein thioredoxin reductase (TrxR) and NADPH comprise a highly conserved thioredoxin system that plays a crucial role in redox homeostasis and regulation of different cellular processes.[1] Many studies have suggested that the whole thioredoxin (Trx) system (driven by NADPH comprising TrxR/Trx) is important in carcinogenesis and is implied to have several different roles in relation to cancer, making it promising therapeutic target.
- **AIM** of our research is to design and to synthesize potent inhibitors of TrxR as new anti-cancer agents with higher selectivity against tumor cell. It is also important to notice that utilization of scaffolds of natural products is beneficial because low or no toxicity is expected.
- **TARGET** As part of our interests in discovering and developing small molecules targeting the TrxR/Trx system, herein we report synthesis, and biological evaluation of 3,4-di-unsubstituted coumarins **1** possessing a potential Michael acceptor moiety[2] and 1,2-dithiolanes **2** derivatives.
- **RESULTS** A small library of derivatized coumarins and 1,2-dithiolane analogues has been obtained and tested for its TrxR inhibition activity with promising preliminary biological results



1

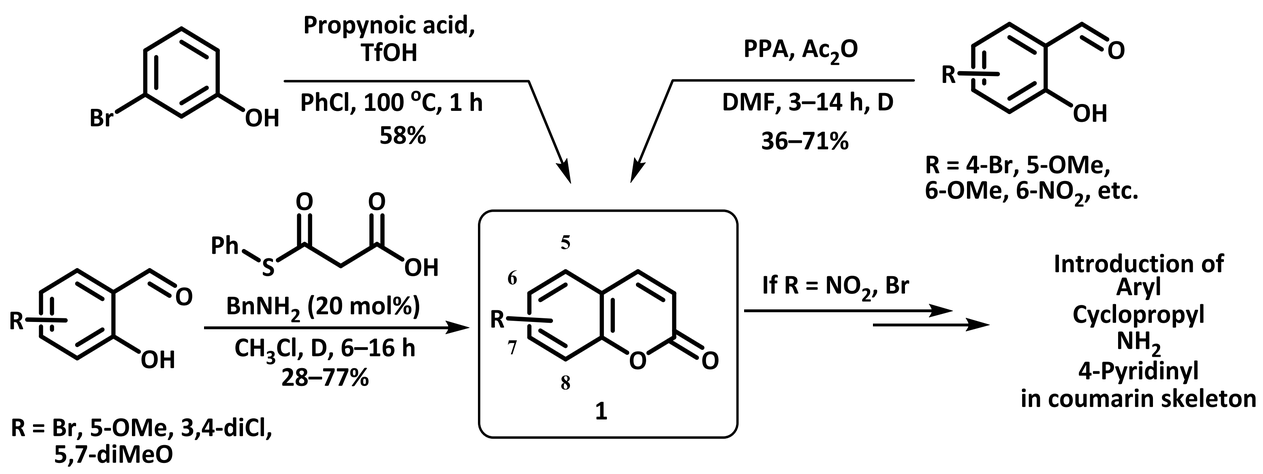
R = alkyl, aryl, heteroaryl, hal, NO_2



2

R^1 = alkyl, aryl, SO_2Me

• SYNTHESIS AND INHIBITORY ACTIVITY OF COUMARIN DERIVATIVES (C=0.2 mM)



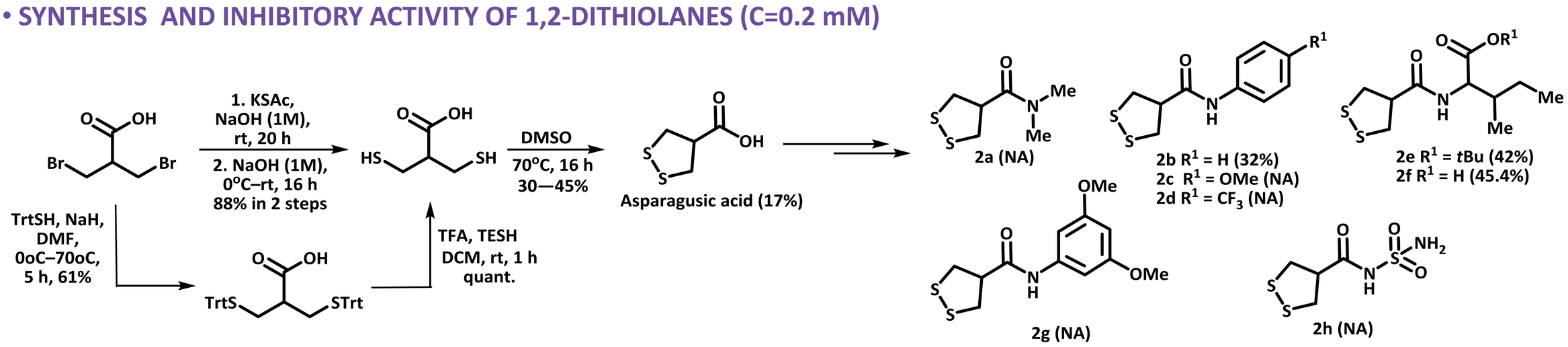
If R (at any coumarin position) is:

H; NO_2; NH_2; 4-$NH_2C_6H_4$; 6,8-diClC_6H_3; 5,7-di$MeOC_6H_3$ – no inhibitory activity observed

R	5	6	7	8
Br	NA	NA	104.6	NA
Ph	78.8	118.9	NA	55.4
4-Py	102.7	NA	NT	NA
OMe	NT	NA	102.0	NT
4-$CF_3C_6H_4$	72.4	35.5	NA	NA
4-$NO_2C_6H_4$	NA	29.3	NA	87.5
Cyclopropyl	109.0	75.8	NA	NA

NT – not tested; NA - not active.

• SYNTHESIS AND INHIBITORY ACTIVITY OF 1,2-DITHIOLANES (C=0.2 mM)



• **SUMMARY** Synthesis and investigation of a set of 42 analogues of 3,4-*di*-unsubstituted coumarins **1** and 9 analogues of 1,2-dithiolanes **2** led to the selection of potent TrxR inhibitors at 0.05 microM range. The presence and the nature of R-groups on coumarin moiety is crucial for biological activity and solubility, comparing to the analog where R = H.

Unfortunately, none of 1,2-dithiolanes derivatives has shown inhibitory activity towards Trx system. We come to the conclusion that 1,2-dithiolane-based substrates are not selective for cellular Trx.[3]

However, the obtained results promt us to the futher investigation in this area, particulary in the direction of selectivity and bioavailability of potent analogs.

• **LITERATURE**

1. Holmgren A. *et al*. *Biochem.Biophys.Res.Commun.* **2010**, 396, 120
2. 2. Krasavin M. *et al*. *J.Enzyme Inhib.Med.Chem*. **2020**, 35, 506
3. Felber, J. G. *et al*. *ChemRxiv2020* (accessed May, **2021**)
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