Development of natural-like small inhibitors of selenoenzymes

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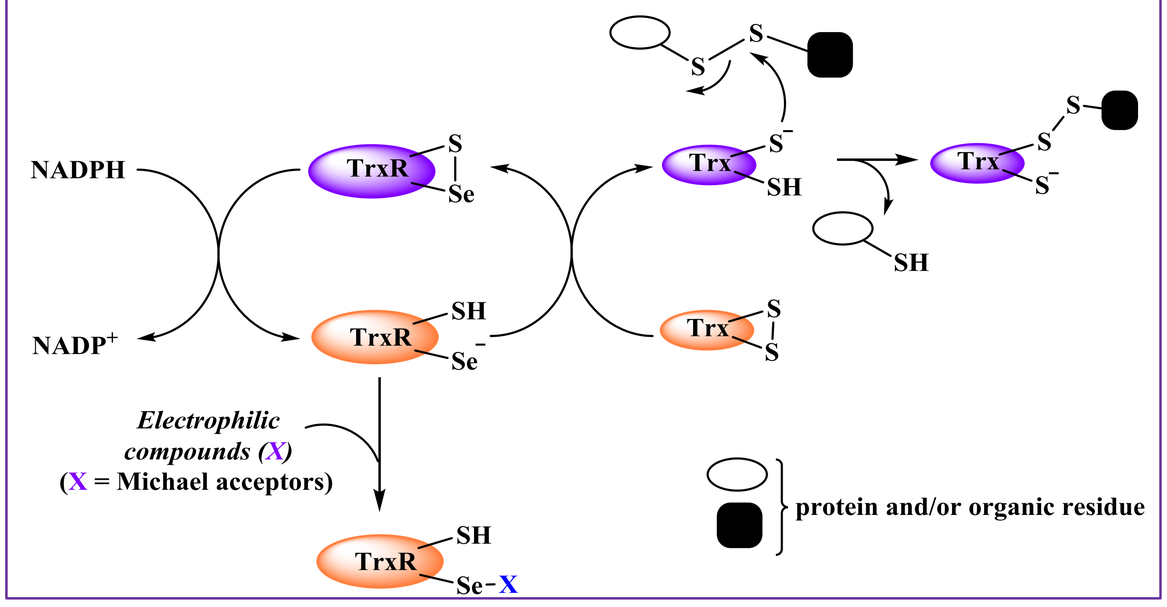
INTRODUCTION

Thioredoxin, 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. Physiological and pathological functions of TrxR1 system in cellular processes have been extensively investigated.[1] It is approved that dysregulation of it results in various human diseases, especially cancer.

AIM

The construction of the specific inhibitors of TrxR over other related enzymes (*e.g.* glutathione reductase) remains a challenge. Herein we present the library of natural-based compound possessing a potential *Michael* acceptor moiety. The use of natural products scaffolds is beneficial because low or no toxicity is expected.

THIOREDOXIN SYSTEM AS DRUG TARGET IN CANCER THERAPY



RESULTS

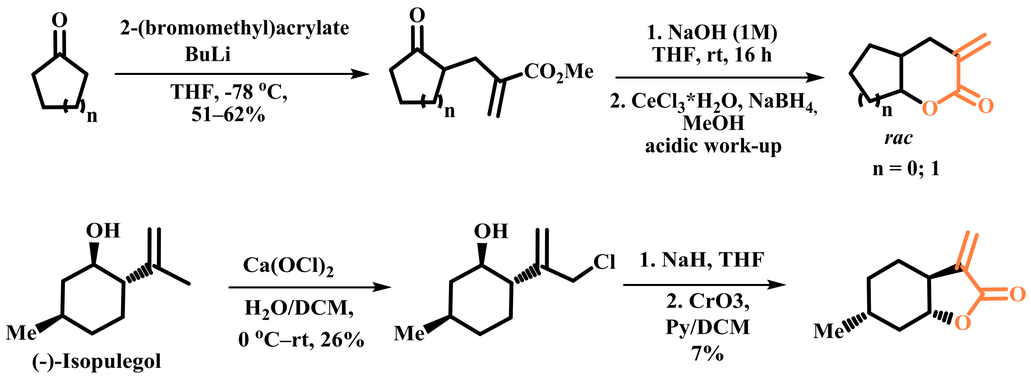
Natural-based library of structurally different *Michael*-type acceptors have been synthesized (>60 compounds) and the preliminary biological activity against TrxR1 has been investigated.

SUMMARY

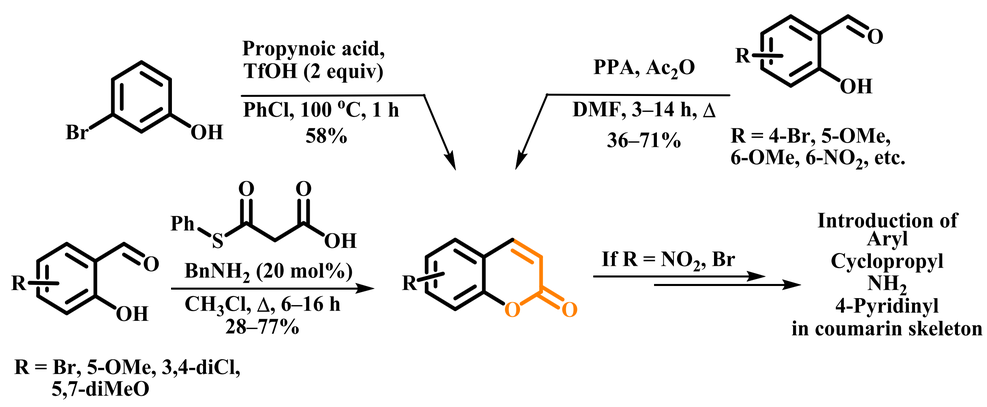
The biological activity results proved the obtained compounds library to be specific TrxR1 inhibitors although the mechanism of action, compound stability and bioavailability is still under investigation. The set of 3,4-*di*-unsubstituted coumarins analogs and *Santamarine* inspired derivatives led to the selection of TrxR1 inhibitors at **micro**molar range.

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

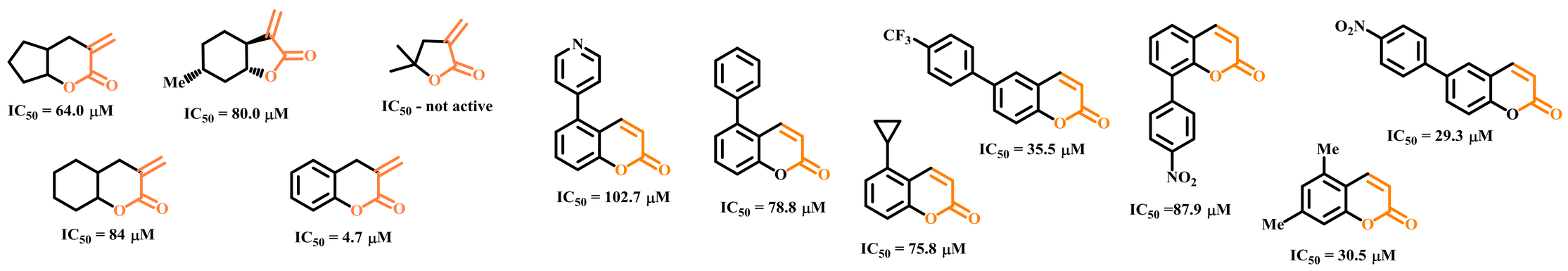
Synthesis of *Santamarine* inspired structures



Synthesis of 3,4-dihydro-coumarins



TrxR1 inhibitors and IC_{50} (mM) values (selected examples)



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Eiropas Reģionālās attīsītības fonds
IEGULDĪJUMS TAVĀ NĀKOTNĒ
PostDoc Latvia
Latvian Institute of Organic Synthesis

References

1. Zhang, J.; Zhang, B.; Li, X.; Han, X.; Liu, R.; Fang, J. *Med. Res. Rev.* **2018**, 1.
2. Zhang, J.; Xu, Q..; Yang, H.-Y.; Yang, M.; Fang, J.; Gao, K. *Front. Mol. Biosci.* , **2021**, *8*, 710676