ICBFM
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IN SILICO–GUIDED IDENTIFICATION AND BIOLOGICAL EVALUATION OF TRITERPENOID-TYPE P-GLYCOPROTEIN INHIBITORS

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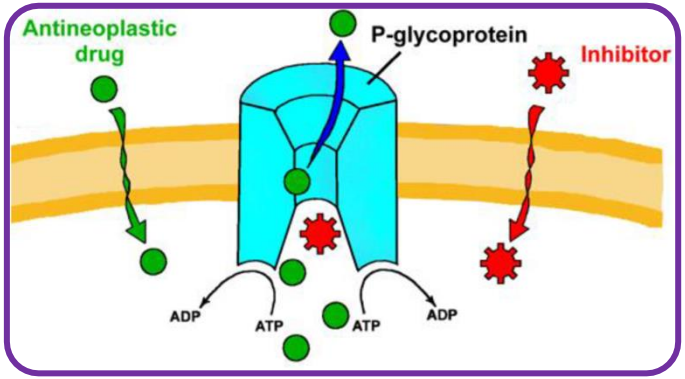
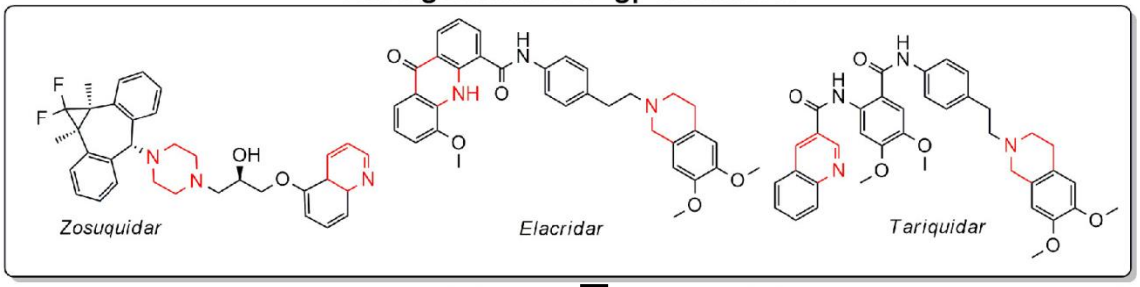
Multidrug resistance (MDR) is a major challenge in cancer chemotherapy



P-glycoprotein is responsible for the active efflux of numerous antitumor drugs from cancer cells.

Substrates	Inhibitors
Vincristine	Verapamil
Vinblastine	Cyclosporin A
Paclitaxel	Zosuquidar
Topotecan	Tariquidar
Etoposide	Tamoxifen
Doxorubicin	Valspodar
Epirubicin	

Third-generation P-gp inhibitors:



clinical trials: toxicity, side effects

search for safer scaffolds, especially among natural metabolites

Objective and methodology

To develop novel small P-gp inhibitors based on semi-synthetic derivatives of 18βH-glycyrrhizic acid (GLA).

In silico modeling and biological validation:

- Molecular docking simulations to predict the binding of GLA derivatives to P-gp
- Cellular assays to assess P-gp transport activity
- RT-PCR and Western blotting to evaluate P-gp expression level.

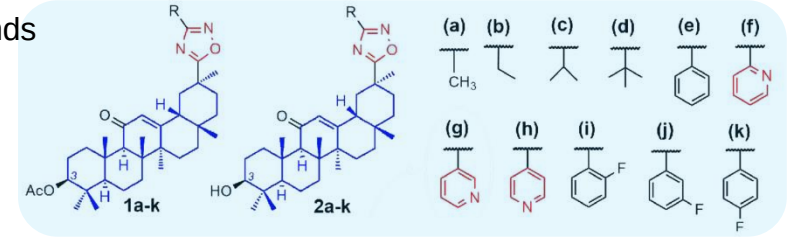
Molecular docking simulations (AutoDock Vina)

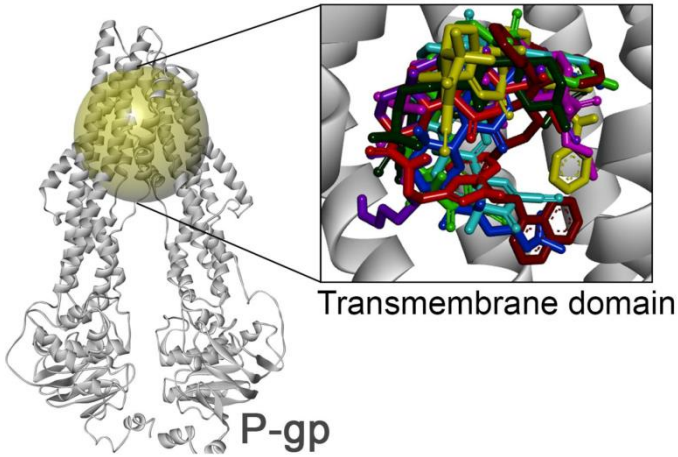
Soloxolone amides

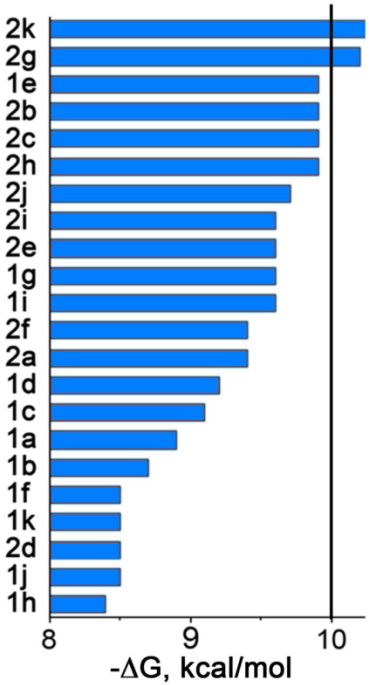
8 compounds

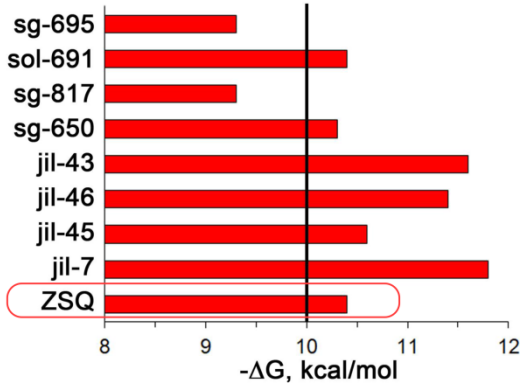
GLA oxadiazoles

22 compounds









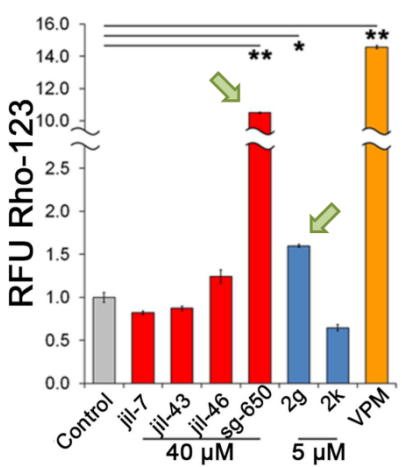
Potential inhibitors:

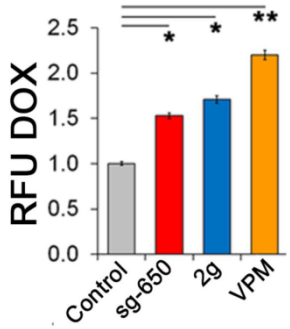
- ✓ **2k, 2g**
- ✓ **Sol-691, sg-650, jil-43, jil-46, jil-45, jil-7**

In vitro functional assays

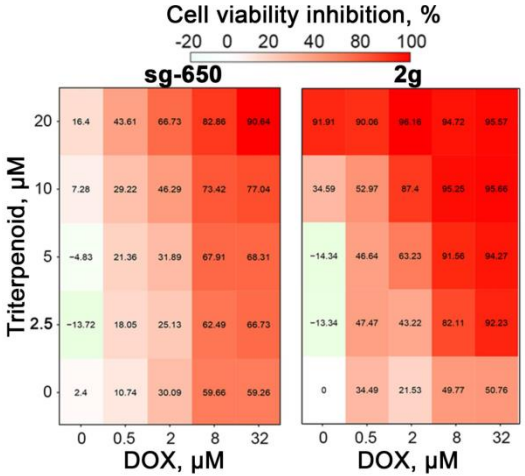
KB-8-5 MDR cells:
- P-gp overexpression
- Low accumulation of P-gp substrates
- Low sensitivity to drugs

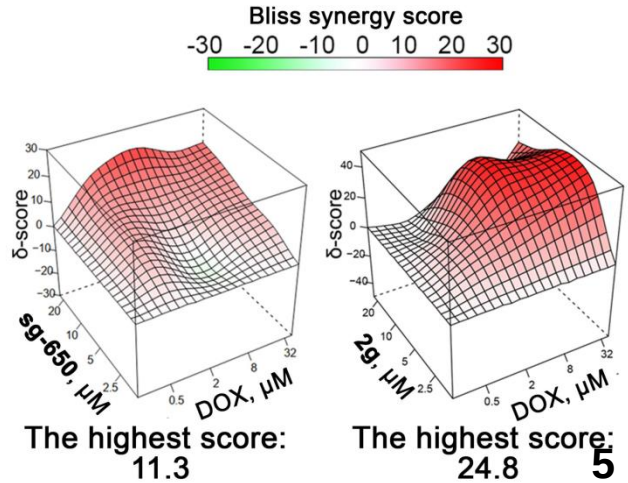
Hit compounds **sg-650** and **2g** increased intracellular accumulation of P-gp substrates Rhodamine 123 (Rho-123) and doxorubicin (DOX). Flow cytometry. VPM – reference inhibitor. *p < 0.05; **p < 0.01





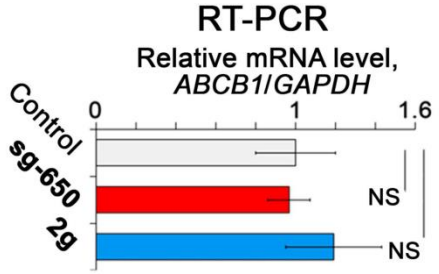
Hit compounds **2g** and **sg-650** desensitize KB-8-5 cells to DOX. MTT assay (left). The Bliss synergy level (right)

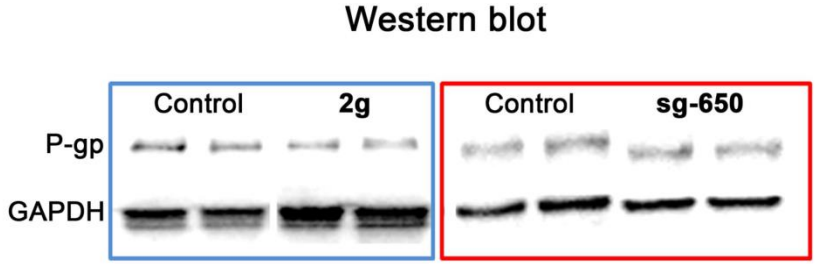




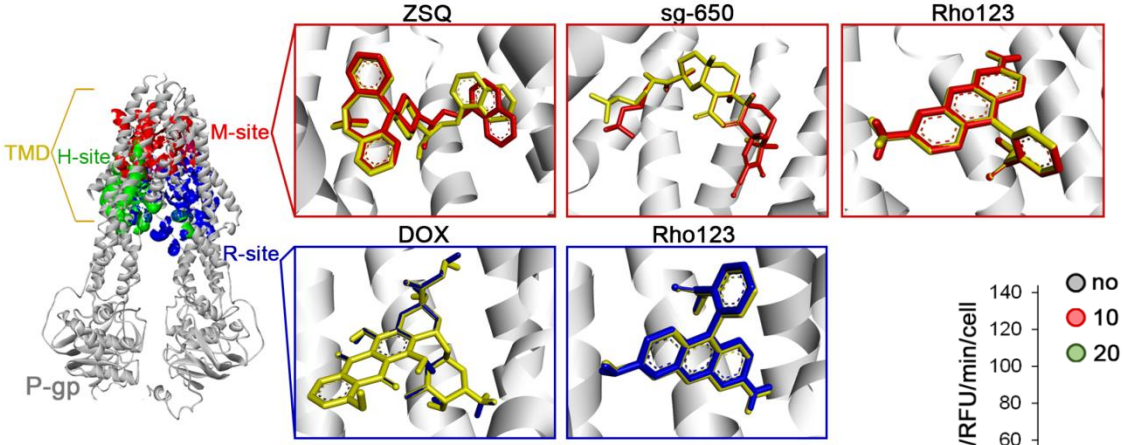
Hit compounds did not affect P-gp expression level

Real-time PCR and Western blotting data after 72 h of incubation with hit compounds.

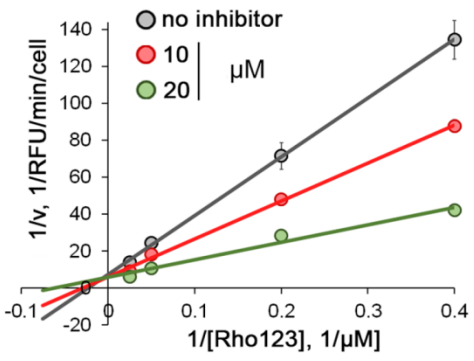




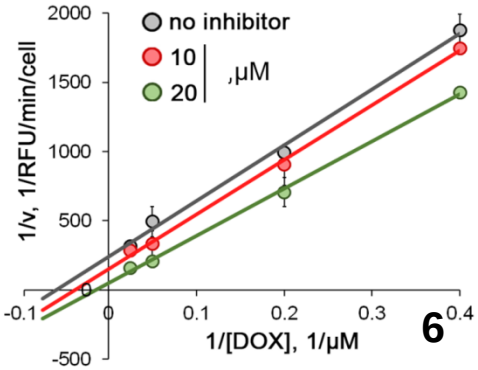
sg-650 directly binds to modulatory (M) site of P-gp transmembrane domain



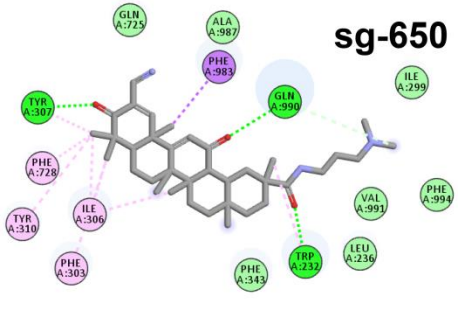
Rho-123
Competitive

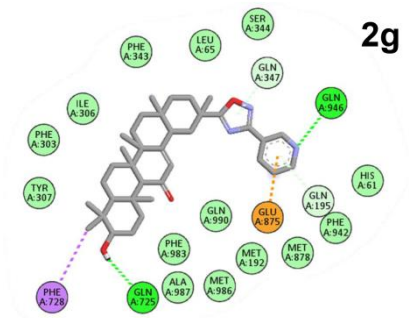


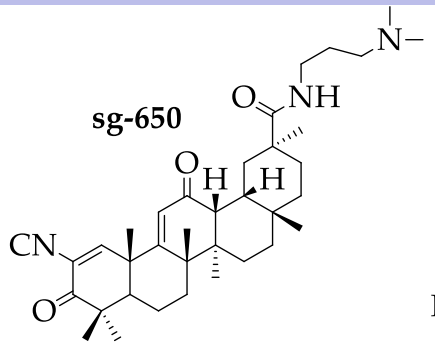
DOX
Uncompetitive

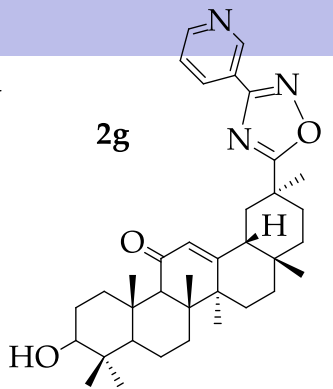


Conclusions









Two semi-synthetic triterpenoids, N,N-dimethylamine-containing amide of soloxolone (sg-650) and meta-pyridine-containing GLA oxadiazole (2g), were shown to:

- ❑ effectively inhibit P-gp transport activity
- ❑ increase the sensitivity of resistant KB-8-5 cells to DOX

Inhibition of P-gp transport activity by **2g** and **sg-650** was associated with their direct interaction with the transmembrane domain.

Thus, the identified compounds can be considered as drug candidates for adjuvant therapy of tumors with an MDR phenotype associated with P-gp overexpression.

Acknowledgments

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