Salicylketoximes as inhibitors of Glucose Transporters

Serena Fortunato,[a] Carlotta Granchi,[a] Raminta Venskutonyté, Jesper S. Hansen,[b] Karin Lindkvist-Petersson,[b] Filippo Minutolo.[a]

[a] *Dept. of Pharmacy, University of Pisa, Via Bonanno, 33, 56126 Pisa, Italy.*
[b] *Dept. of Experimental Medical Science, Lund University, Sölvegatan, 19/221 84-Lund, Sweden.*
E-mail: serena.fortunato@farm.unipi.it

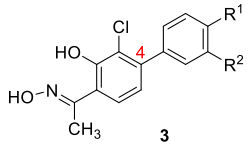
Some derivatives of the 4-arylsalicylketoximes series displayed inhibitory effects on glucose transport and on cell proliferation in several biological assays,[1] resulting to be effective GLUT1 inhibitors also in GLUT1-containing giant vesicles. GLUT1 is one of the 14 glucose transporter isoforms, widely overexpressed in many cancer types. Thus, for the discovered properties, the oximes of interest represent interesting candidates for anticancer therapy.

Variously substituted 4-arylsalicylketoximes (**3**, Fig.1) were synthetized *via* Suzuki cross-coupling and a subsequent condensation of the resulting biaryl-ketone intermediates with hydroxylamine hydrochloride. [1] Rat GLUT1 membrane proteins were produced by *Pichia Pastoris* cultures, and purified following GLUT1 purification protocols, [2] which were largely revised to avoid the protein cleavage.

Compounds **3a**, **3b**, **3e**, and **3f** efficiently inhibited glucose uptake in GLUT1-containing giant vesicle assays. [3] To study the nature of the binding process between GLUT1 and the synthetic compounds, many crystallization attempts were set up with **3a** and **3e** using Lipidic Cubic Phase method, which produced many small crystals.

Since many isoforms of GLUTs are overexpressed in cancer cells, inhibition of other GLUT isoforms, such as GLUT3, will be tested in the near future.

In conclusion, 4-arylsalicylketoximes showed good inhibition of GLUT1 isoform. First results from GLUT3-giant vesicles assays revealed that, within this series of compounds, **3a** is the most selective GLUT1-inhibitor. Further assays with GLUTs-containing giant vesicle and crystallization attempts are currently underway.



3

a. R^1= OCH_3, R^2=F
b. R^1=OH, R^2=H
e. R^1=H, R^2=OH
f. R^1=OH, R^2=Cl

Figure 1: Generic structure of the salicylketoximes 3.

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[2] Venskutonyté R, Elbing K, Lindkvist-Petersson K, *Methods Mol Biol.* **2018**; 1713, 1–13.

[3] Hansen J.H, Elbing K, Thompson J.R, Malmstadt N, Lindkvist-Petersson K, *Chem. Commun*. **2015**; 51, 2316–2319.