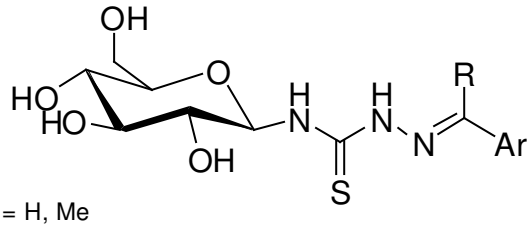
PHARMACEUTICAL CHEMISTRY

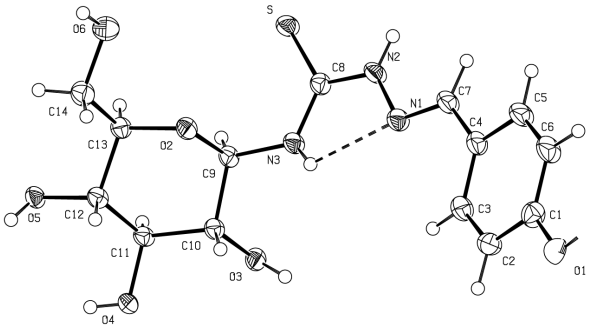
Glucose derivatives are selective and efficient catalytic inhibitors of glycogen phosphorylase (GP), a target for the design of type 2 diabetes therapeutics. On the other hand, thiosemicarbazones are promising compounds in many diseases, in particular cancer. The present work (in collaboration with the Structural Biology and Chemistry Group of IOPC) is aiming to combine these two classes of compounds into one family of organic molecules, and thus a series of β-D-glucopyranosyl-modified thiosemicarbazones have been synthesized. Kinetic experiments showed inhibition (IC_{50} ~5 μM (minimum)) of GP, while crystallographic results for the GP – glucose-thiosemicarbazone complex showed that these derivatives bind both at the new allosteric and the catalytic site, and stabilise the less active quaternary conformation of the enzyme.

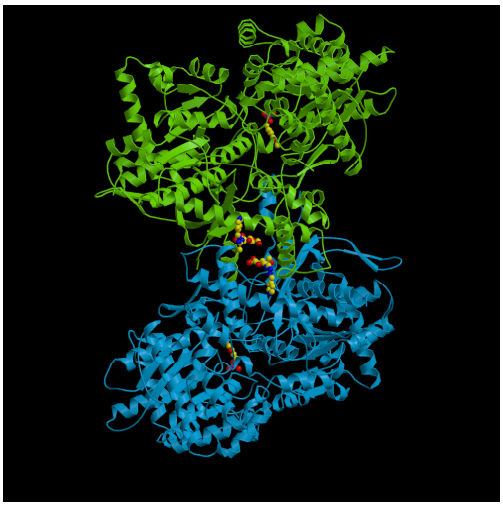
This investigation is part of the project **EURODESY**: A European Research Training Site for the Design and Synthesis of Novel Neuroprotective and Hypoglycaemic Agents through a Multi-disciplinary approach. EURODESY is funded by Marie Curie Early Stage Training program (EST).



R = H, Me
Ar = -C_6H_4-X (*o*,*m*,*p*), pyridyl (2-,3-,4-), ferrocenyl, β-naphthyl
X = F, Cl, Br CF_3, NO_2, OH, OMe, Me, *t*Bu

26 final products





Crystal structure of GP – glucose-thiosemicarbazone complex.

15 crystal structuresIC_{50} ~5 μM (minimum)

Publications

- A.-C. Tenchiu (Deleanu), I.D. Kostas*, D. Kovala-Demertzi, A. Terzis *Carbohydr. Res.* **2009**, *344*, 1352.
- K.-M. Alexacou, A.-C. Tenchiu (Deleanu), E.D. Chrysina, M.-D. Charavgi, I.D. Kostas*, S.E. Zographos, N.G. Oikonomakos, D.D. Leonidas* *Bioorg. Med. Chem.* **2010**, *18*, 7911-7922.