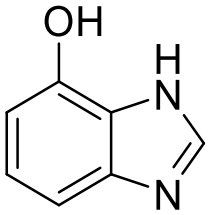
National Research Mordovia State University

FROM IN SILICO DESIGN TO EXPERIMENTAL IMPLEMENTATION:

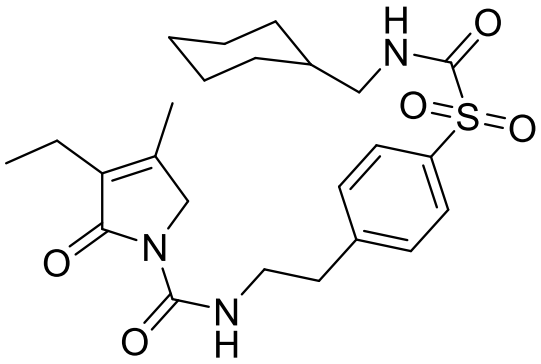
DEVELOPMENT OF A NOVEL GLUCOKINASE ACTIVATOR

K.I. Inzhevatkina, O.I. Balakireva, A.V. Semenov
National Research Mordovia State University, Saransk, Russia

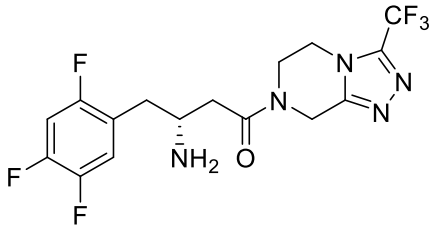
Actuality



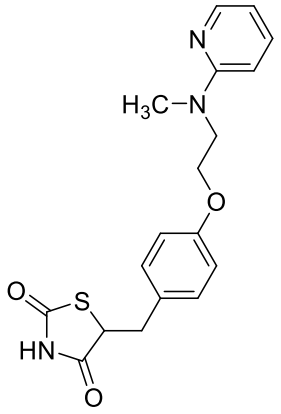
7-hydroxybenzimidazole



Glimepiride



Sitagliptin



Rosiglitazone

DIABETES

Type 2 diabetes is a prevalent disorder characterized by dysregulation of glucose homeostasis

Characterized

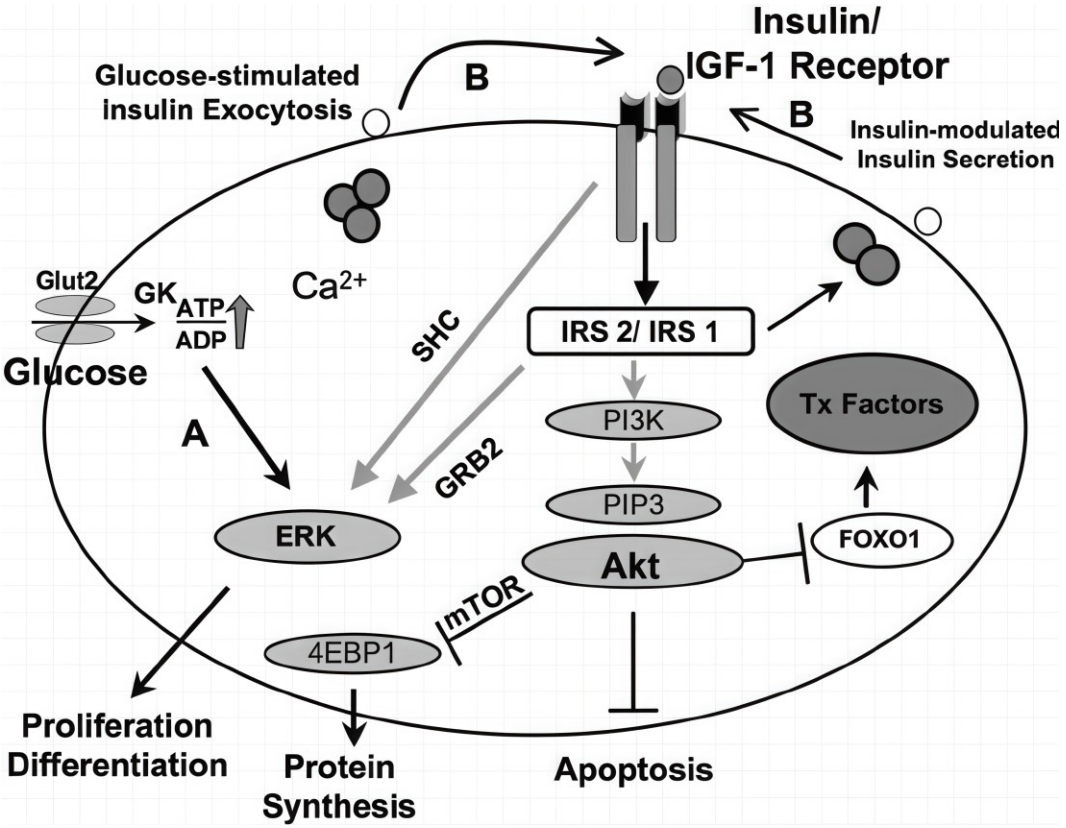
chronic form, disruption of all types of metabolism

At risk

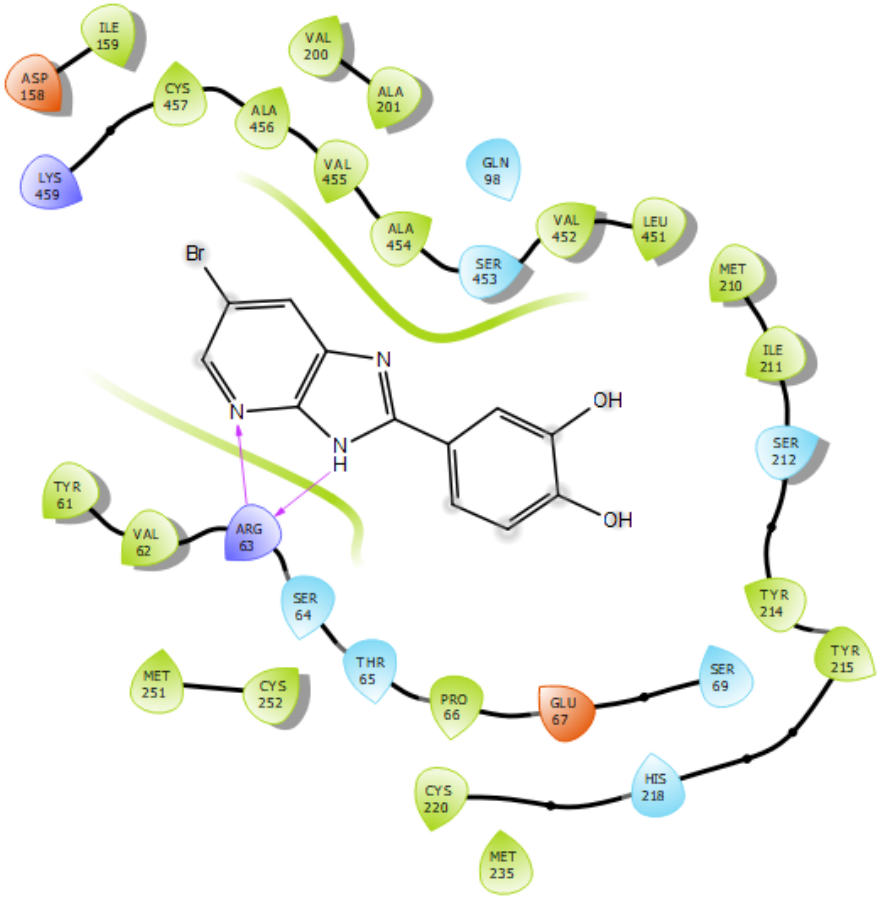
- Those leading a sedentary lifestyle
- over 45 years of age
- with a genetic predisposition

Target

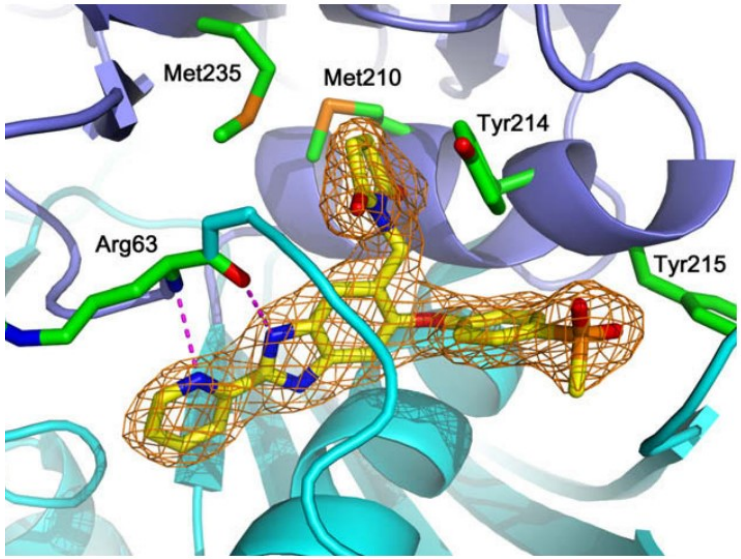
X-ray crystal structure of human glucokinase crystallized in complex with a small molecule glucokinase activator (PDB ID: 3H1V)



Molecular docking



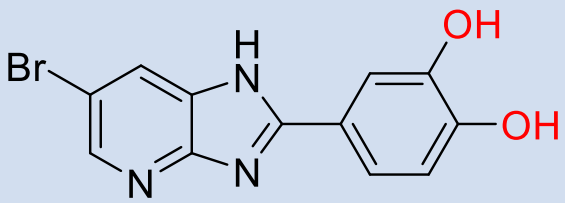
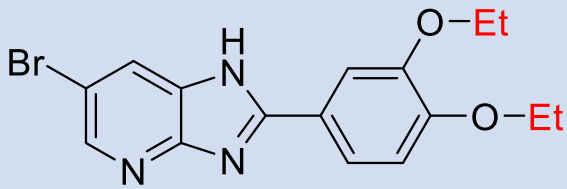
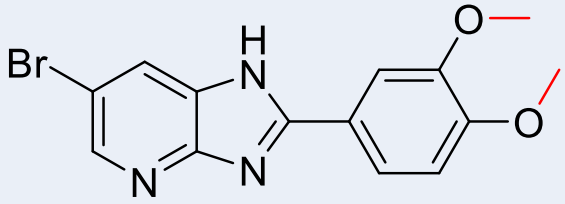
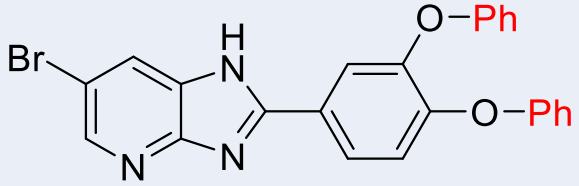
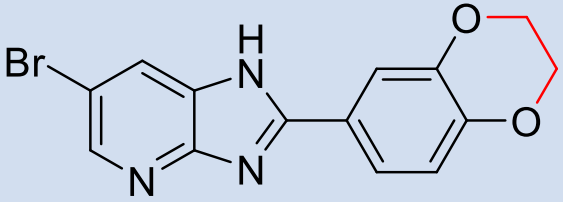
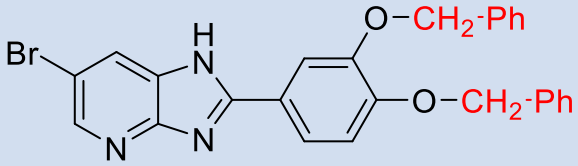
Compound 1



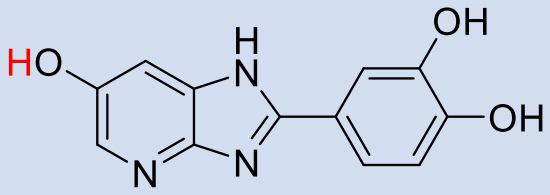
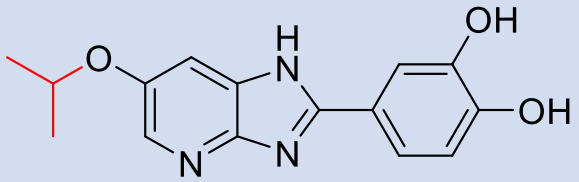
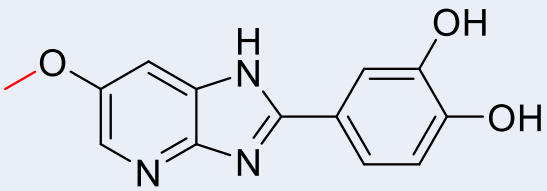
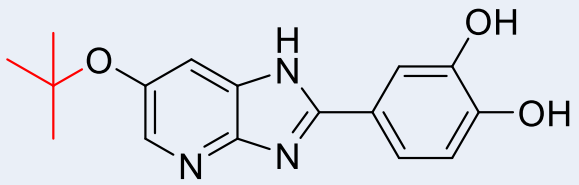
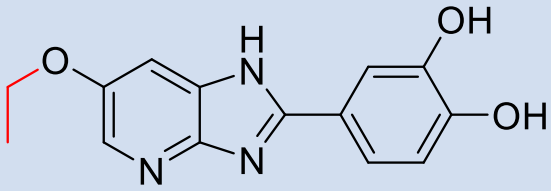
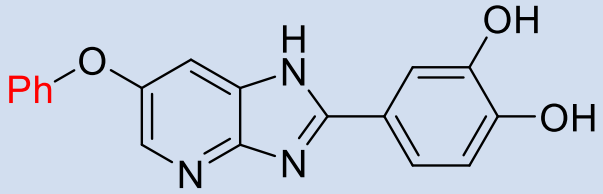
GK activator bound to Glucokinase.

Takahashi, K (2009) Bioorg Med Chem 17: 7042-7051

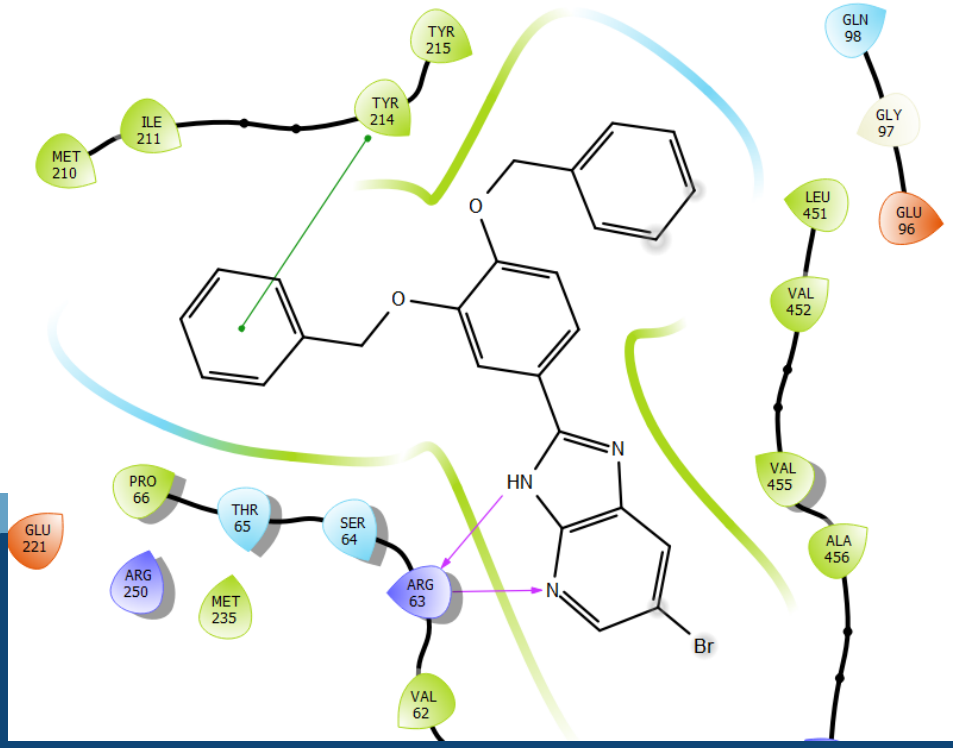
Molecular docking results

	Ligands	XP-GSCORE		Ligands	XP-GSCORE
1		-9.25	2c		-9.60
2a		-9.10	2d		-9.10
2b		-9.40	2e		-12.23

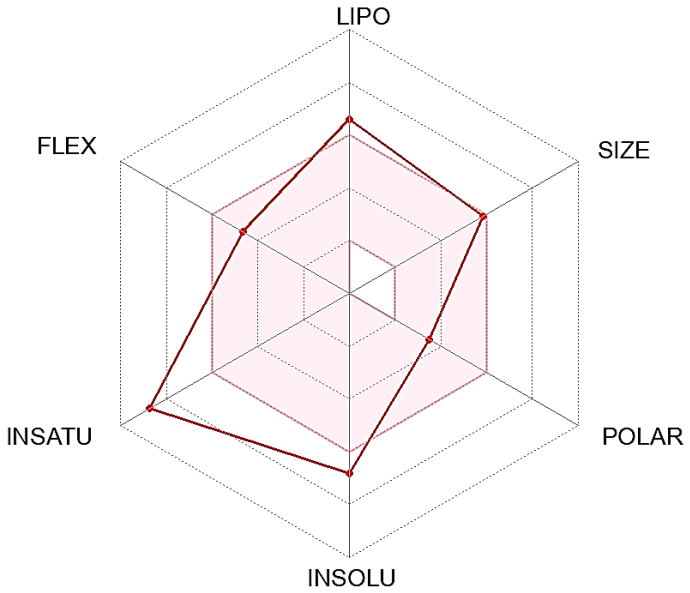
Molecular docking results

	Ligands	XP-GSCORE		Ligands	XP-GSCORE
3a		-9.3	3d		-9.1
3b		-9.7	3e		-8.5
3c		-9.5	3f		-9.7

The binding pocket occupancy and ADME parameters

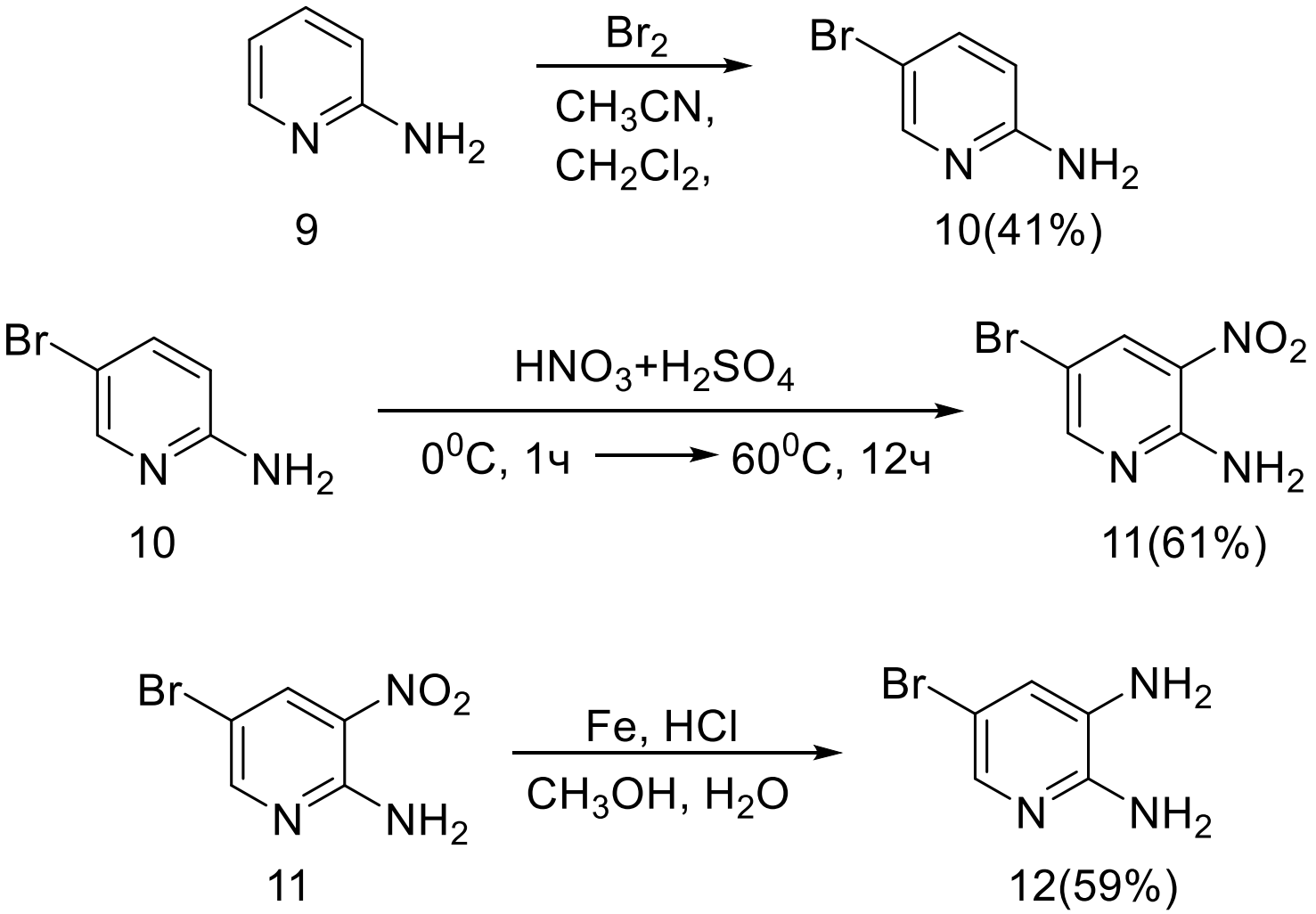


Occupancy of the binding pocket for compound 2e

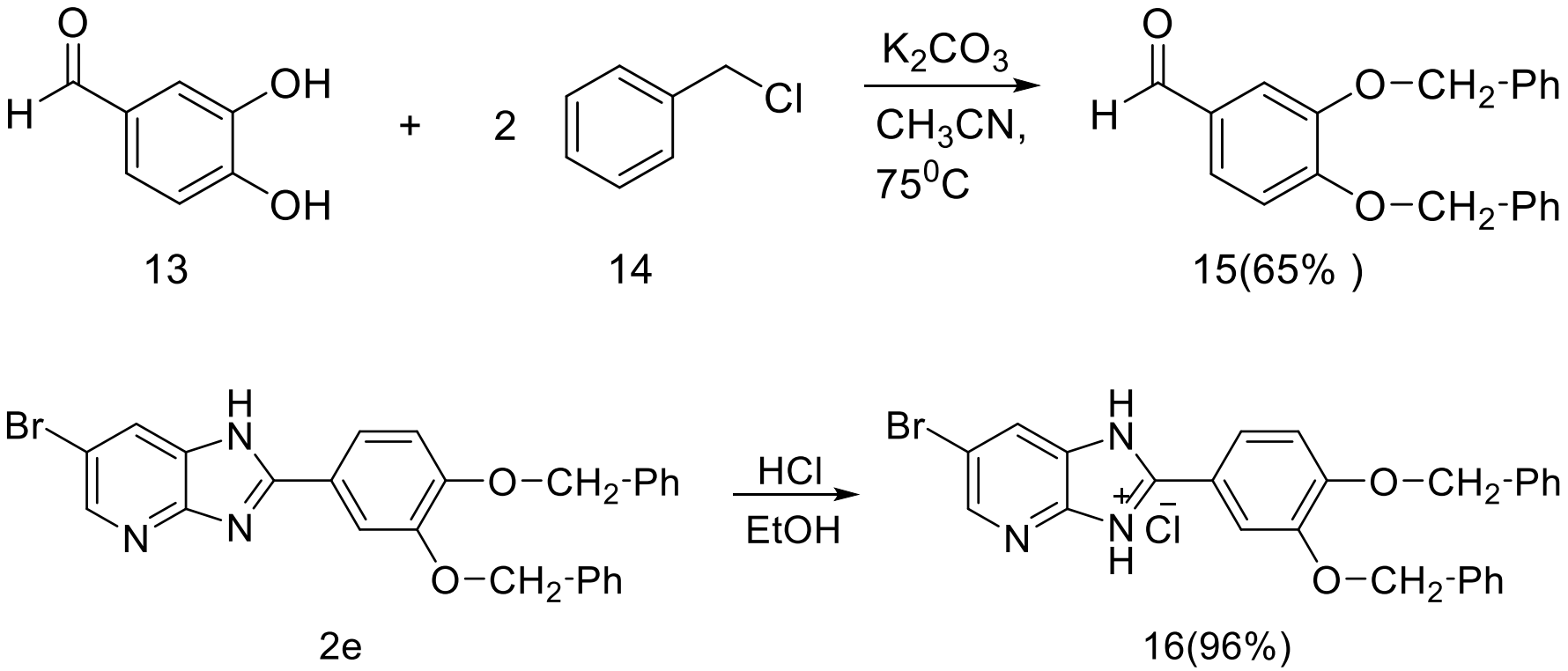


The colored zone is the suitable physicochemical space for oral bioavailability.
LIPO(Lipophility): -0.7 < XLOGP3 < +5.0
SIZE: 150g/mol < MW < 500g/mol
POLAR(Polarity): 20Å² < TPSA < 130Å²
INSOLU(Insolubility): -6 < Log S (ESOL) < 0
INSATU(Insaturation): 0.25 < Fraction Csp3 < 1
FLEX(Flexibility): 0 < Num. rotatable bonds < 9

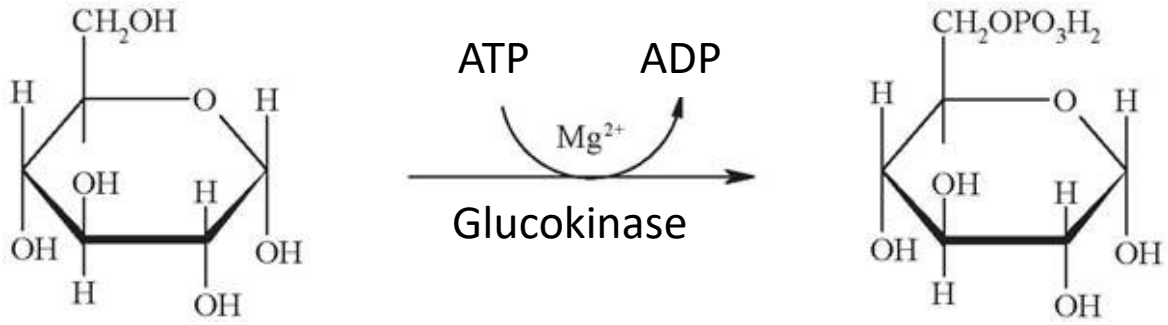
Four-step synthesis of compound (2e)



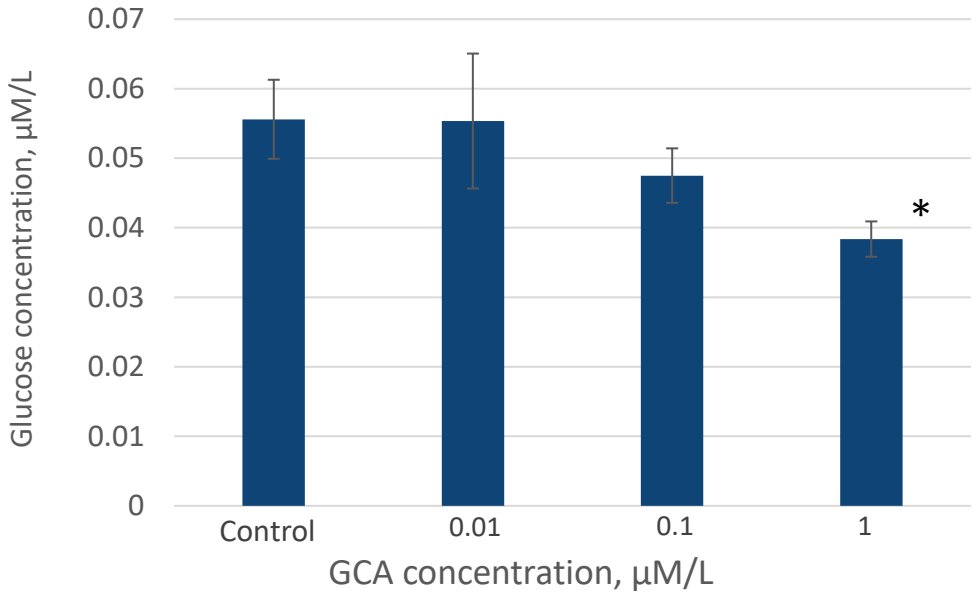
Four-step synthesis of compound (2e) and its hydrochloride salt (16)



Activity determination



Activity determination was performed according to the Long method, based on the enzymatic phosphorylation of glucose followed by colorimetric determination of residual glucose using the Somogyi–Nelson reaction



P<0.95
*Statistically significant

МГУ
им. Н. П. Огарева

Thank you for your attention!