GLIKOGÉN FOSZFORILÁZ GÁTLÁS MONOSZACHARID SZÁRMAZÉKOKKAL

Somsák László

Debreceni Egyetem, Szerves Kémiai Tanszék

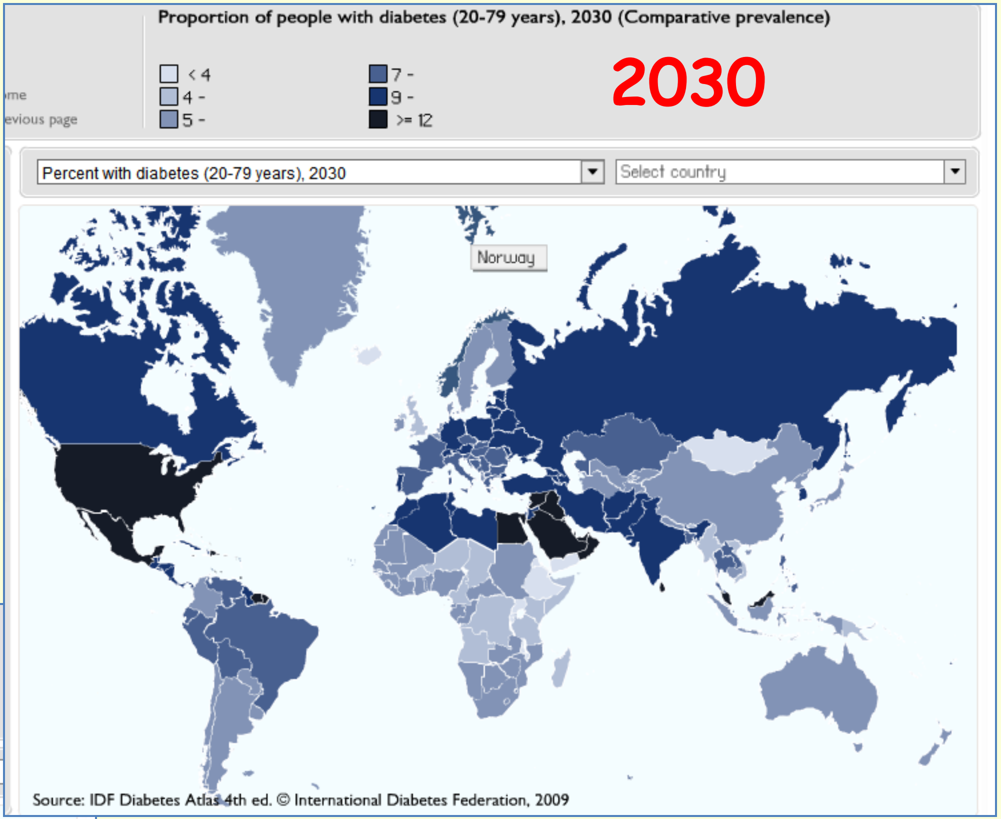
MTA Kémiai Tudományok Osztálya felolvasóülése

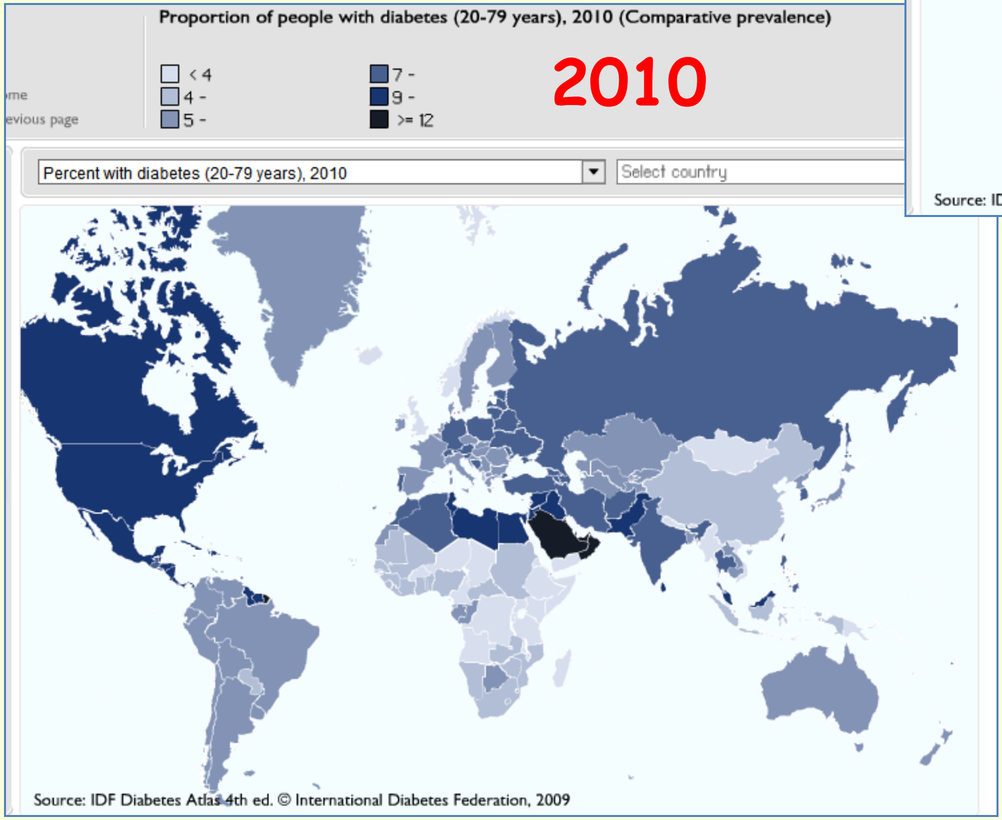
Budapest, 2011. dec. 13.

Prevalence of *diabetes mellitus* in the population (age: 20-79 years)

http://www.idf.org

International Diabetes Federation





International Diabetes Federation

IDF DIABETES ATLAS

http://www.diabetesatlas.org/map

Prevalence of *diabetes mellitus* in the population (age: 20-79 years)

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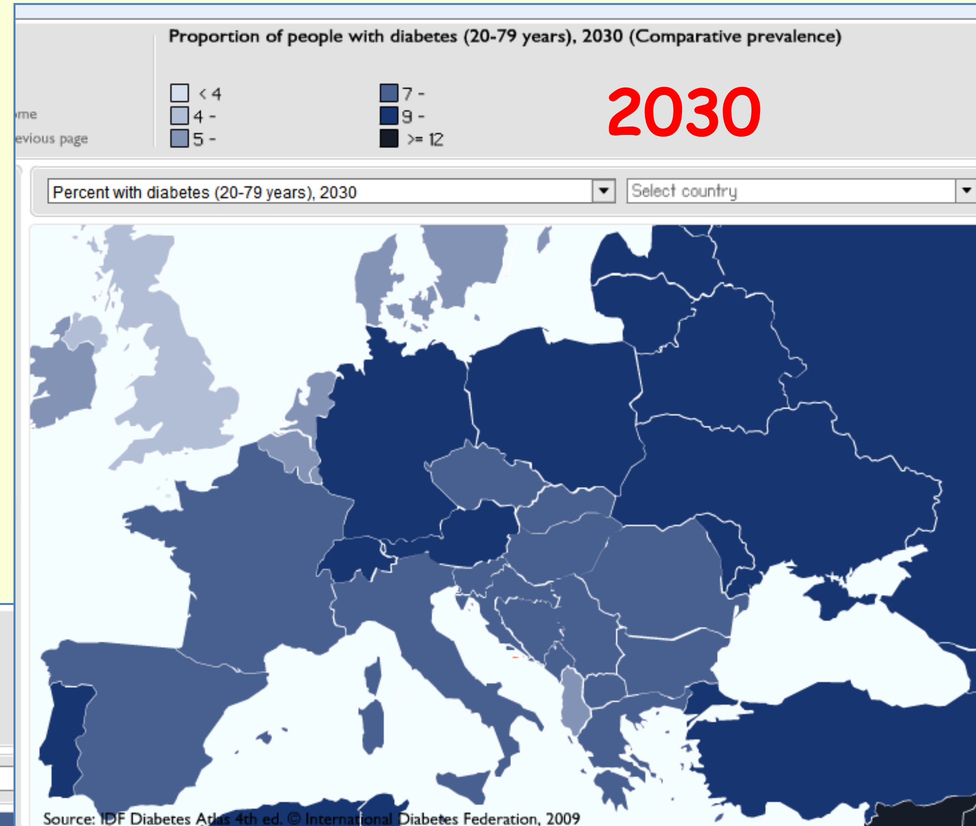
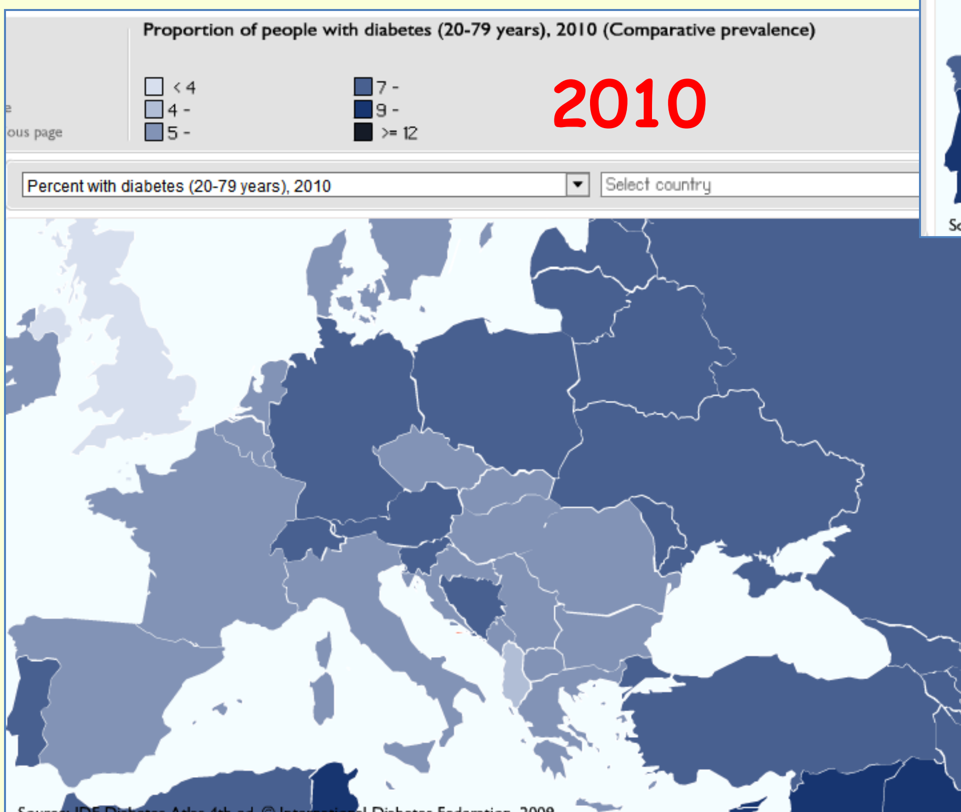




Type 1 diabetes
Total insulin deficiency — **~5 %**

Type 2 diabetes
Impaired insulin secretion or insulin resistance — **~95 %**

Current therapeutic agents for type 2 diabetes

Drug class	Site(s) of action	Molecular target	Adverse effects
Sulphonylureas	Pancreatic β-cells	SU receptor K^+ ATP channel	Hypoglycaemia, weight gain
Metformin - Biguanides	Liver (muscle)	Unknown	Gastrointestinal disturbances, lactic acidosis
Acarbose	Intestine	α-glucosidase	Gastrointestinal disturbances
Thiazolidinediones	Fat, muscle, liver	$PPAR_\gamma$	Weight gain, oedema, anaemia
Insulin	Liver, muscle, fat	Insulin receptor	Hypoglycaemia, weight gain

Source: D. E. Moller, *Nature*, 2001, *414*, 821-827.

Oral hypoglycaemic agents are inadequate for 30-40 % of the patients (A. S. Wagman, J. M. Nuss, *Curr. Pharma. Design*, 2001, *7*, 417-450)

Investigational targets/strategies for type 2 diabetes

Insulin secretagogues	Improving insulin action	Combination therapies	SGLT-2 inhibitors

Strategies altering lipid metabolism

Nutritional therapy

Inhibition of hepatic glucose production

Target	Function
Glucagon	Enhances hepatic glucose output
GCK	Catalyzes the first step of glycolysis
6PF-2-K/F-2,6-P2ase	Regulator of glycolytic and gluconeogenic rates through production of F-2,6-P2
G-6-Pase	Catalyzes the last step of gluconeogenesis
F-1,6-P2ase	Regulates gluconeogenic rates
GSK3	Inhibits glycogen synthase
Glycogen phosphorylase	Catalyzes the conversion of glycogen to glucose-1-phosphate monomers

Source: Morral, N., *Trends Endocrin. Metab.*, 2003, *14*, 169-175.

Diseased states claimed to be affected by glycogen phosphorylase inhibitors

- **Type 2 *diabetes mellitus***
- **Early cardiac and cardiovascular disease in non-diabetics (treatment and/or prevention)**
- **Cardiac arrhythmias (stabilization)**
- **Ischemic injury (protection)**
- **Tumour growth (prevention)**

Structure and binding sites of glycogen phosphorylase

(rabbit muscle GP, RMGP)

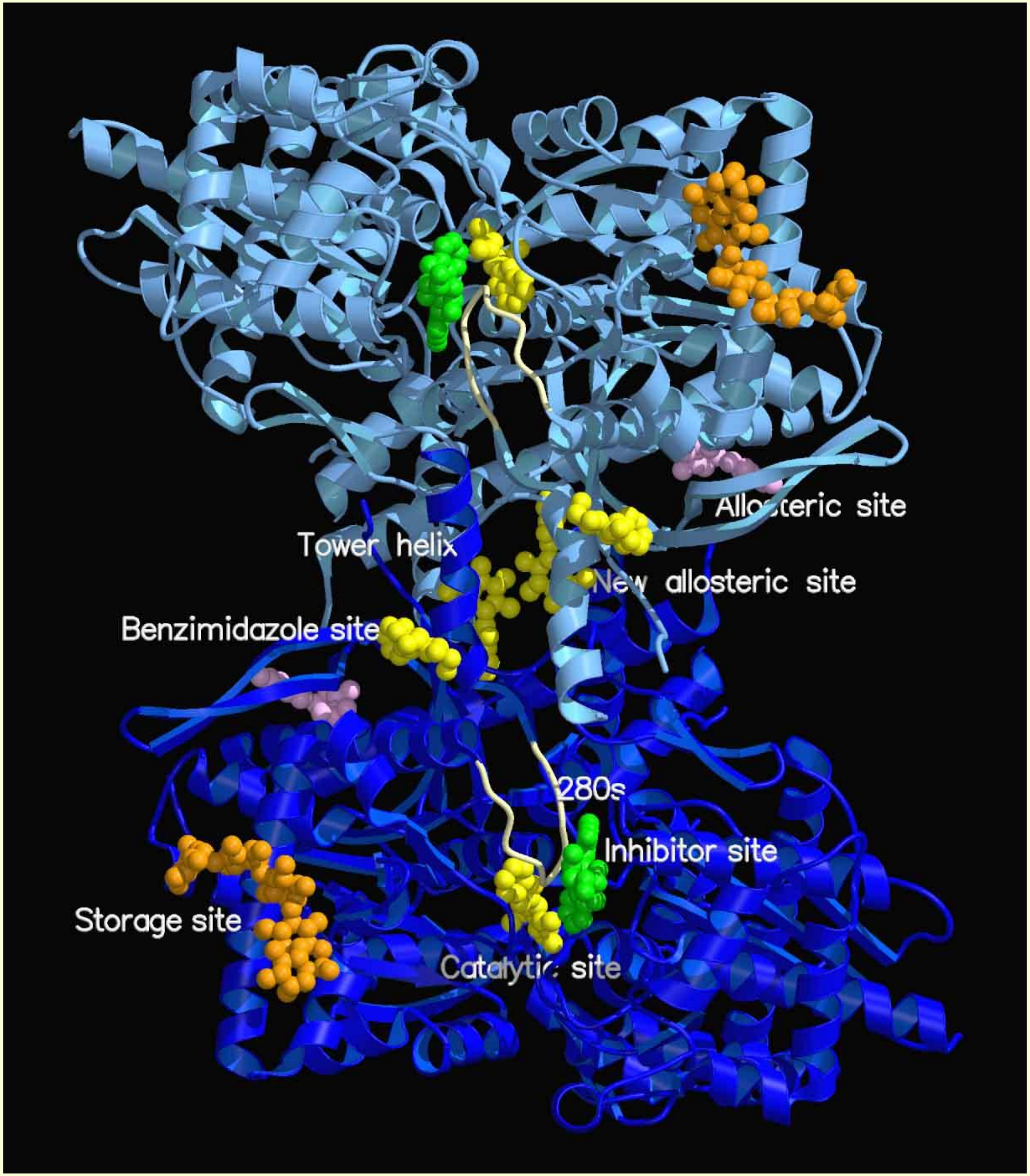
Figure by courtesy of E. D. Chrysina (Institute for Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, Athens, Greece).

Reviews:

Oikonomakos, *Curr. Protein Pept. Sci.*, 2002, *2*, 561-586.

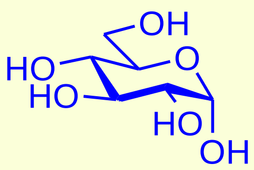
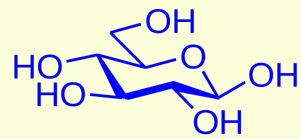
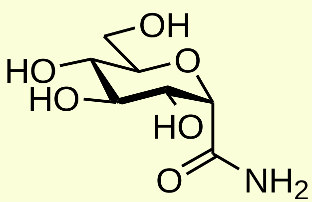
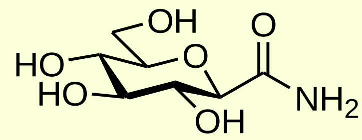
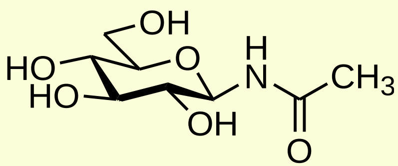
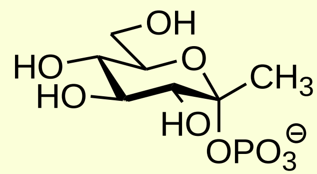
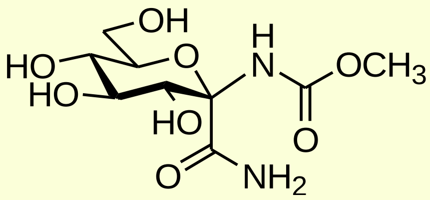
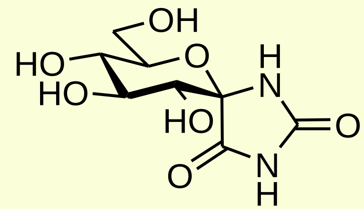
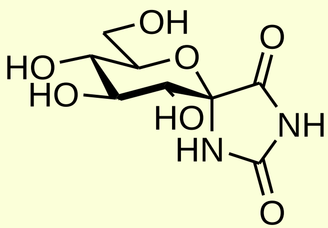
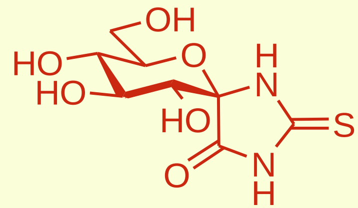
Somsák et al., *Curr. Med. Chem.*, 2008, *15*, 2933-2983.

Thematic issue (Guest editor: L. Somsák) *Mini-Rev. Med. Chem.*, 2010, *10*, 1091-1193.



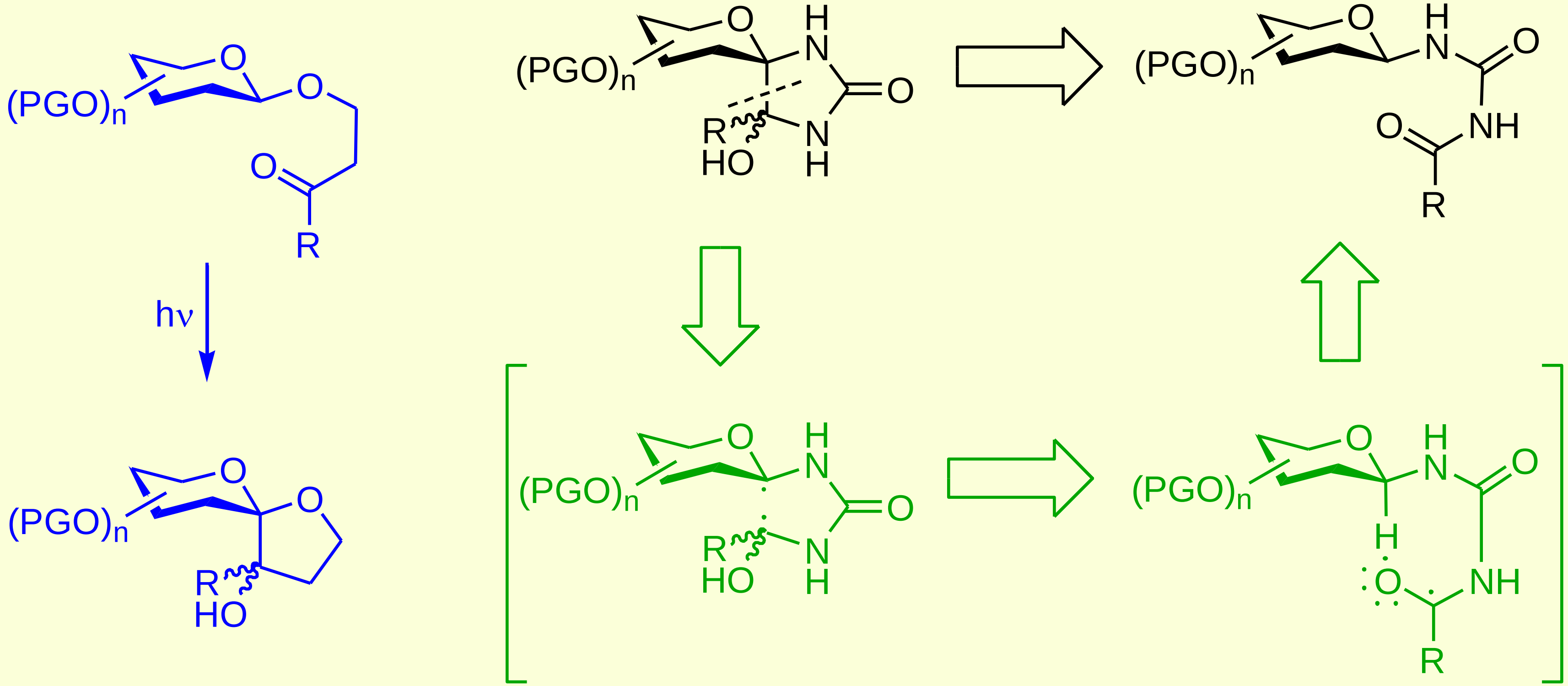
Early glucose analogue inhibitors of RMGPb (K_i [μM])

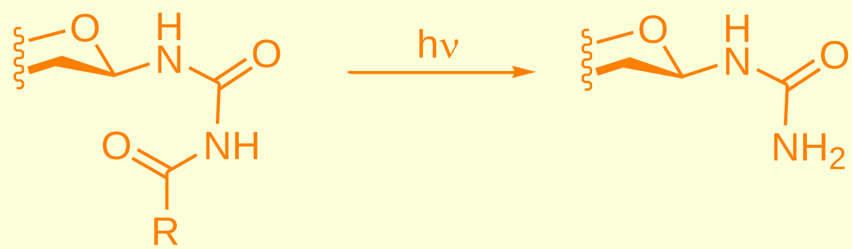
Pioneered by Fleet, Johnson, and Oikonomakos

	1700		7400
	370		440
	32		14
	16		3
	105		5

Review: Somsák et al., *Curr. Pharma. Design*, 2003, *9*, 1177-1189.

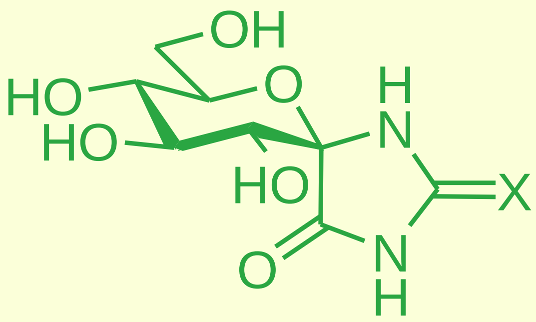
Attempted synthesis of spiro-hydantoin analogues



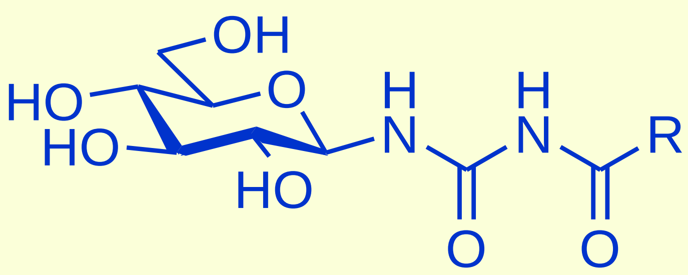


Remy et al.,
***Can. J. Chem.*,**
1980, *58*, 2660-2665.
Descotes, G.
Bull. Soc. Chim. Belges
1982, *91*, 973-983.

Spiro-hydantoins and benzoyl-urea are equipotent inhibitors of RMGPb



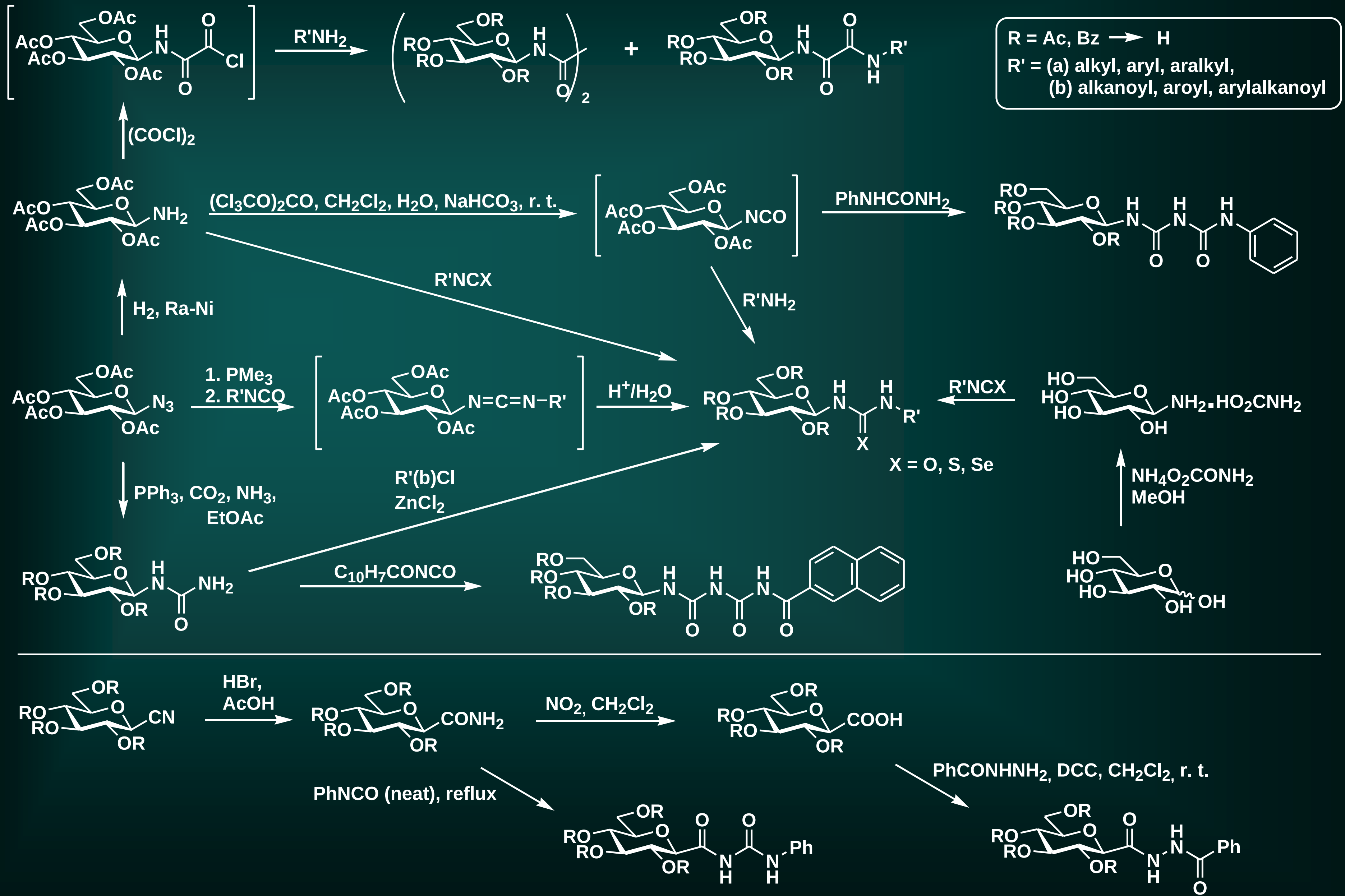
X = O K_i = 3 μM
X = S K_i = 5 μM



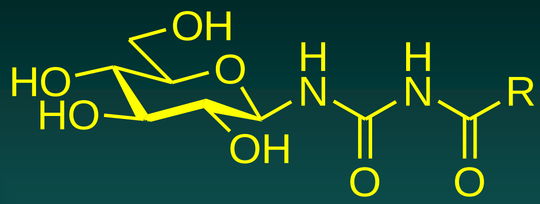
R = CH_3 K_i = 305 μM
R = C_6H_5 K_i = 4.6 μM

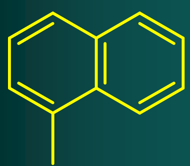
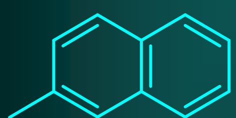
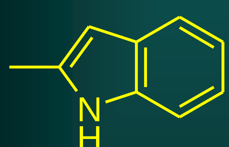
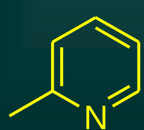
Oikonomakos et al.,
***Eur. J. Biochem.* 2002, *269*, 1684-1696**

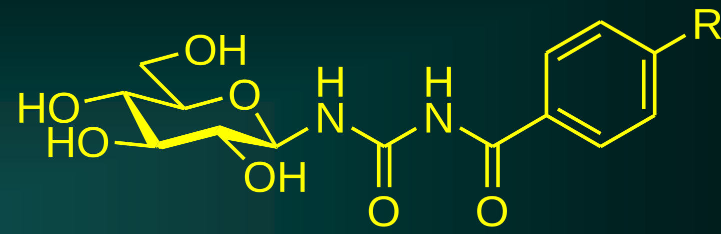
Syntheses of *N*-substituted-*N'*-β-D-glucopyranosylureas and related compounds



Inhibition of RMGPb by *N*-acyl-*N'*-β-D-glucopyranosylureas

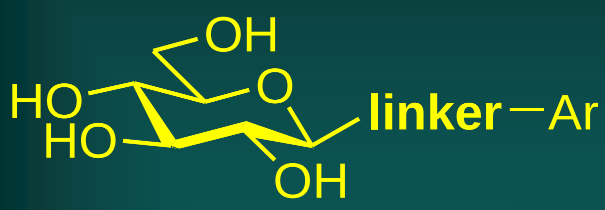
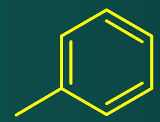
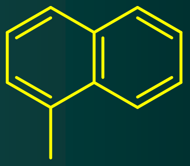
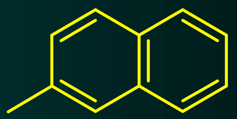


R	K_i [μM]
$-CH_3$	305
	15
	0.35
	4.0
	68
	No inhibition

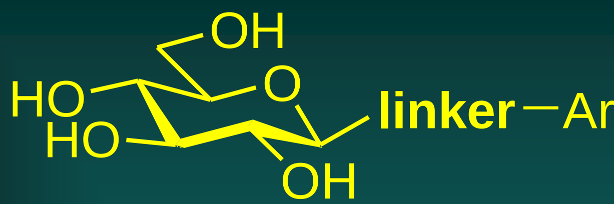


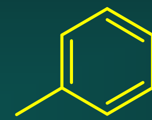
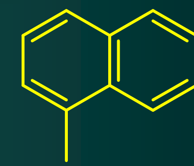
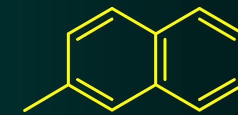
R	K_i [μM]
–H	4.6
$-CH_3$	2.3
$-C_6H_5$	3.7
$-CF_3$	1.8
$-C(CH_3)_3$	0.7
$-NO_2$	3.3
–Cl	4.4
$-NH_2$	6.0
–OH	6.3
$-OCH_3$	3.2
–COOH	IC_{50} 350
$-COOCH_3$	4.0

Influence of the linker length on the inhibition of RMGPb

		Ar	
			
linker		**K_i [µM]**	
NHCO	**81 (144)**	**444**	**10**
NHCONH	**18**	**350 (IC_{50})**	**5.2**
NHCONHCO	**4.6**	**10**	**0.35**
NHCONHCONH	**21**	**-**	**-**
NHCONHCONHCO	**-**	**-**	**45 % (at 625 µM)**

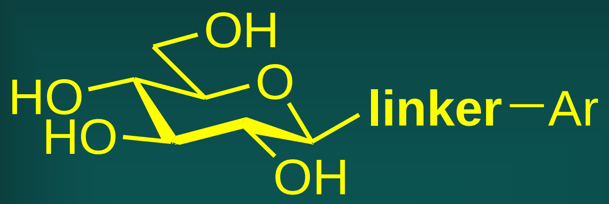
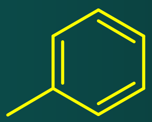
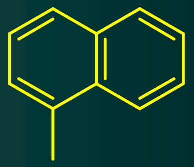
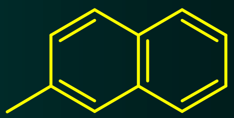
Influence of the linker composition on the inhibition of RMGPb I.



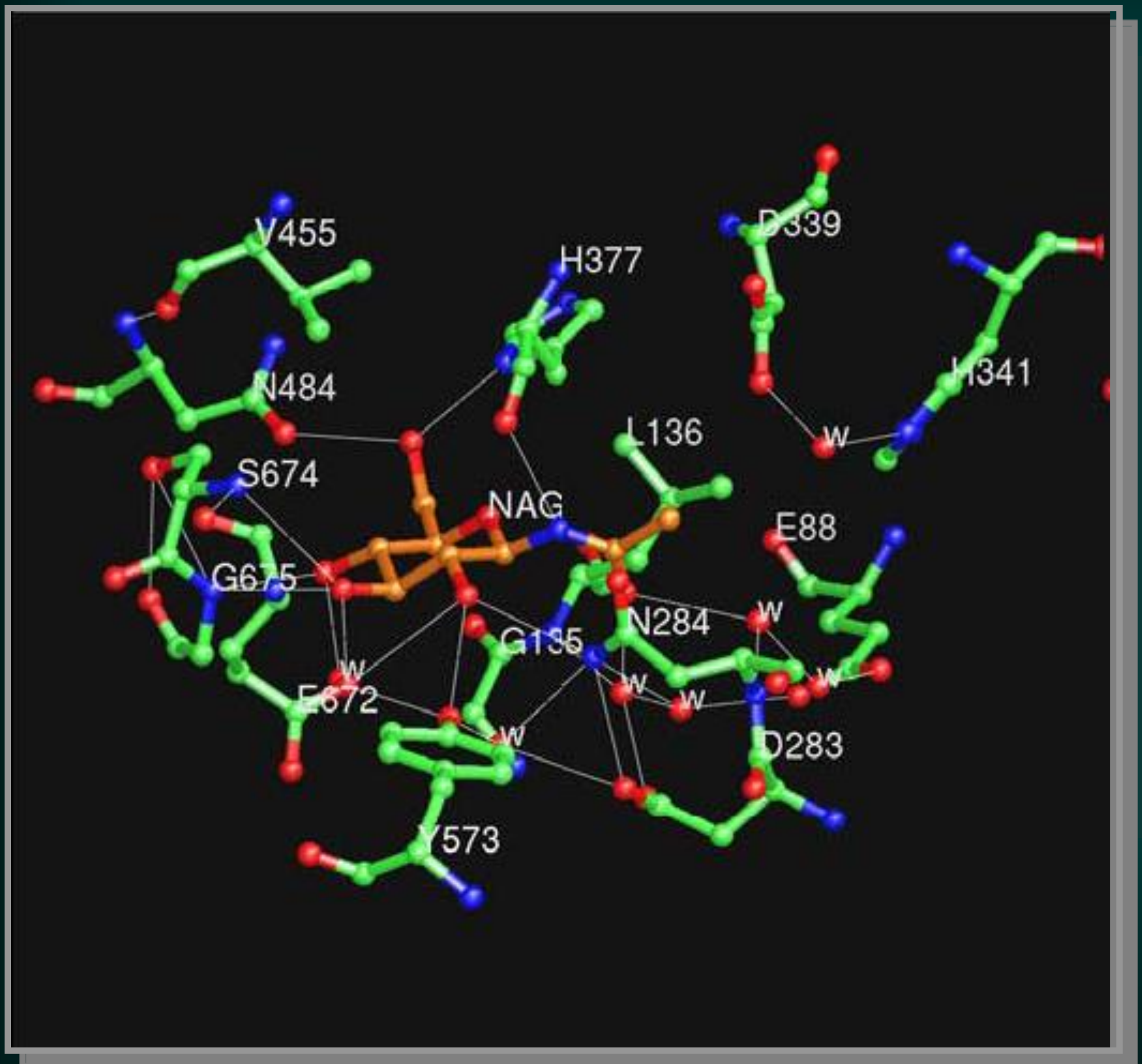
	Ar		
			
linker	K_i [μM]		
NHCONHCO	4.6	10	0.35
$NHCONHCH_2$	750	-	-
$NHCOCH_2CH_2$	85	-	-
NHCOCH=CH	18	-	3.5
NHCOC≡C	61	-	-
$NHCOCH_2O$	34	-	-
$NHCOOCH_2$	350	-	-
$NHCOCH_2NH$	70	-	142
NHCONHCO	2.3		
$NHCONHSO_2$	No inh.		
$NHSO_2NHCO$	No inh.		

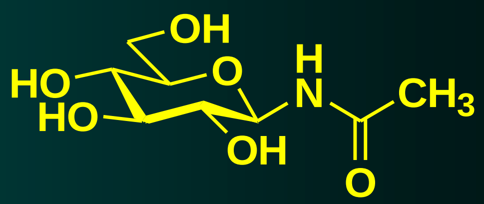
The last three rows are bracketed together: (Ar = 4-CH_3-C_6H_4)

Influence of the linker composition on the inhibition of RMGPb II.

	Ar 		
linker	K_i [μM]		
NHCONHCO	4.6	10	0.35
NHCOCONH	100	144	56
CONHCONH	No inh.	-	-
CONHNHCO	22 % (at 3.75 mM)	-	-

Binding of *N*-acetyl-β-D-glucopyranosylamine at the active site of muscle GPb

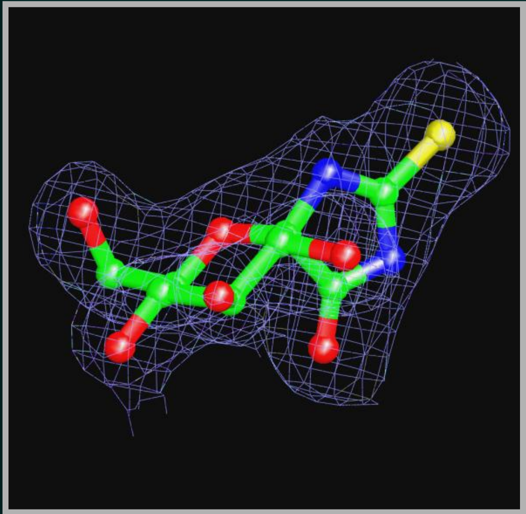


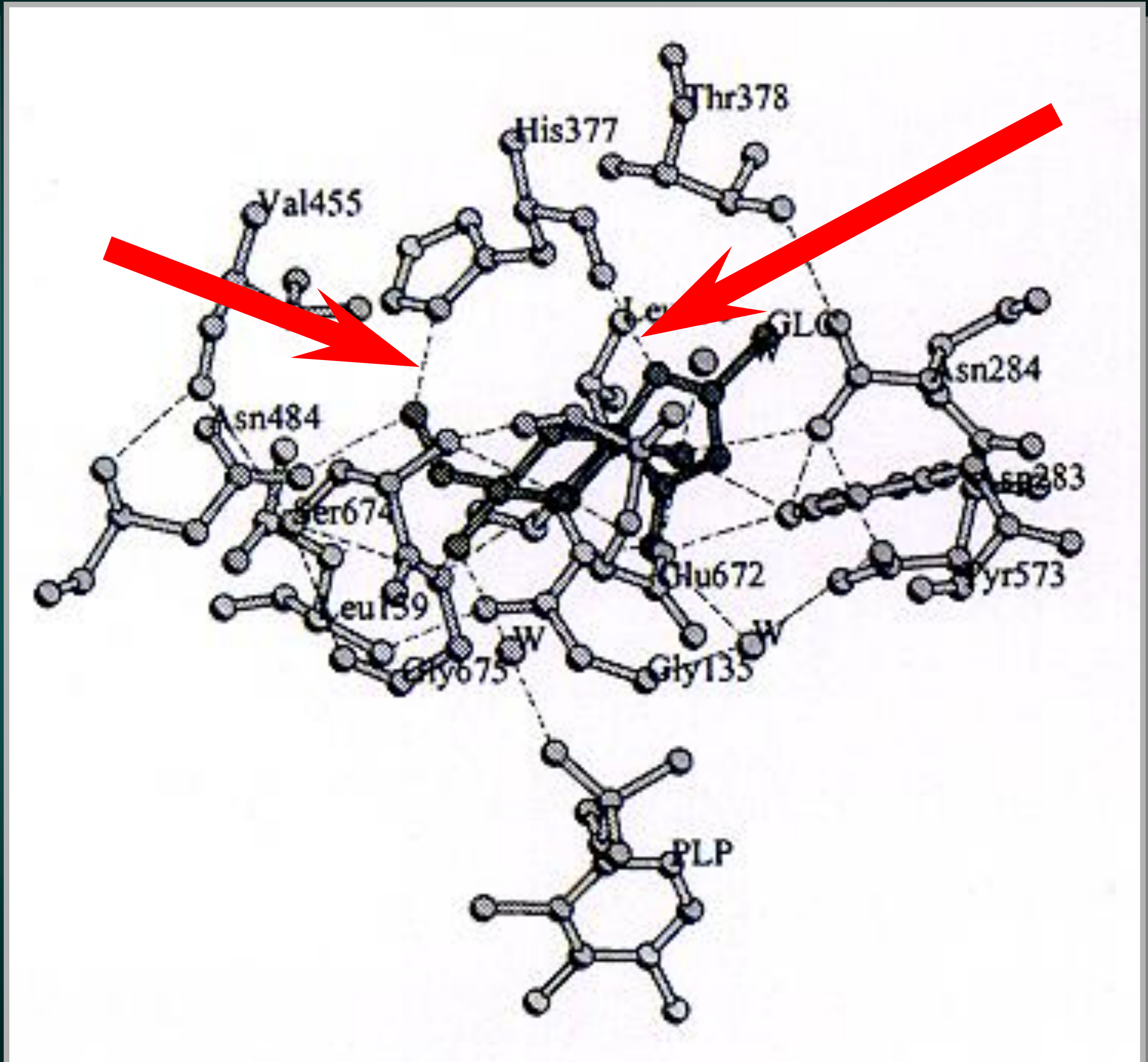


K_i = 32 μM

Anagnostou, E. et al., *Bioorg. Med. Chem.*, 2006, *14*, 181-189.

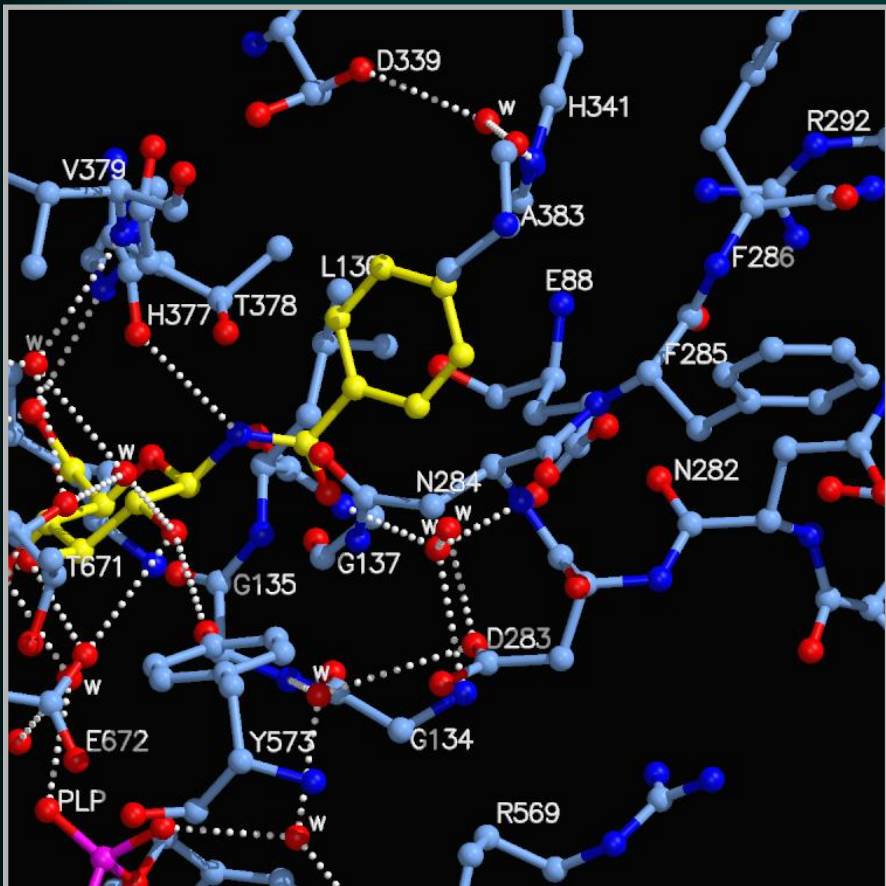
Binding of TH at the active site of muscle GPb

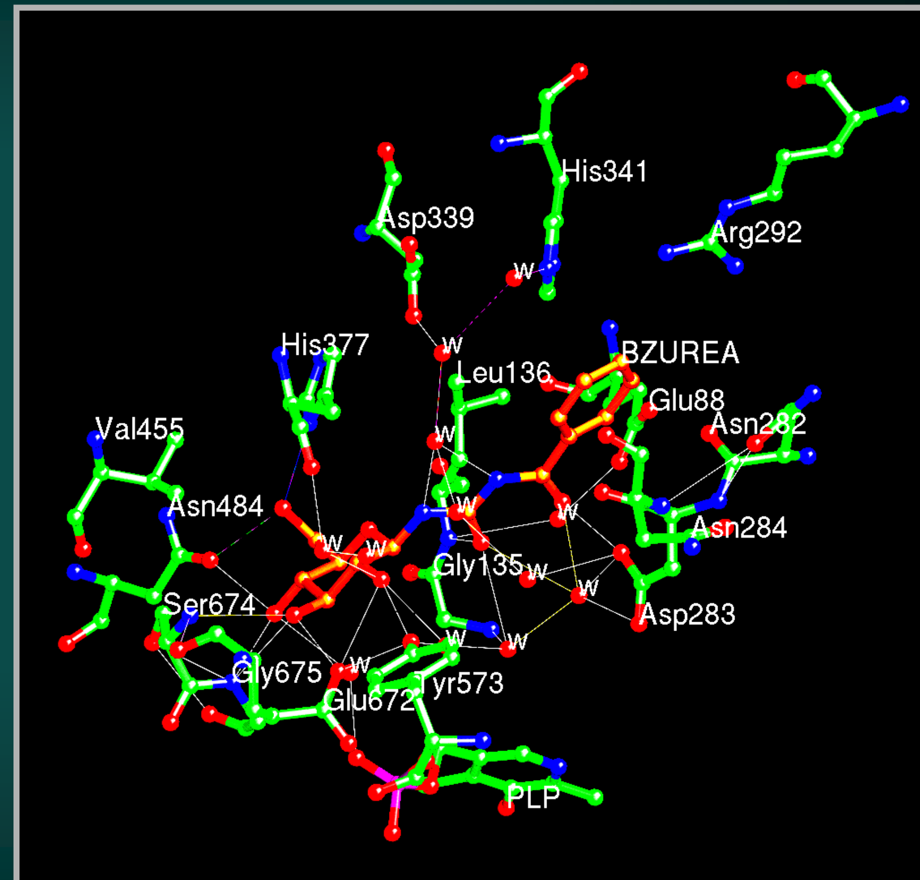


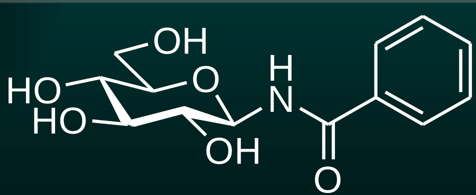


Oikonomakos et al., *Bioorg. Med. Chem.*, 2002, *10*, 261.

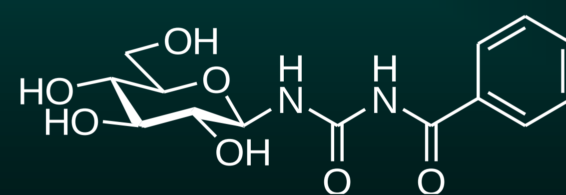
Binding of *N*-benzoyl-β-D-glucopyranosylamine and *N*-benzoyl-*N'*-β-D-glucopyranosyl urea at the active site of muscle GPb





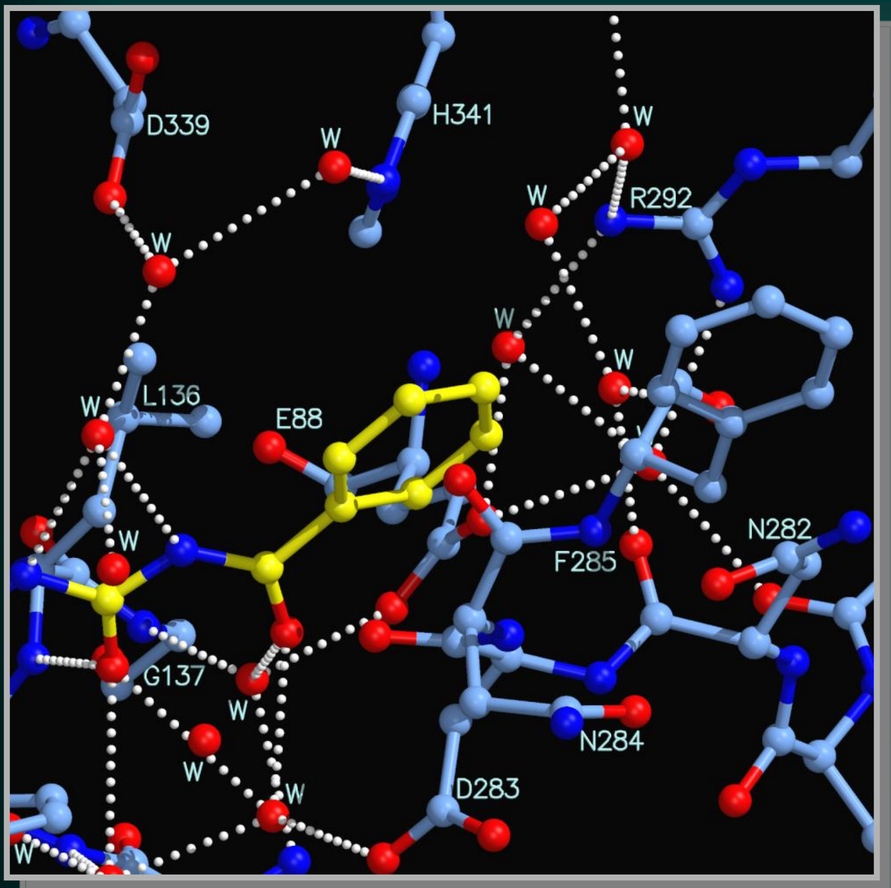


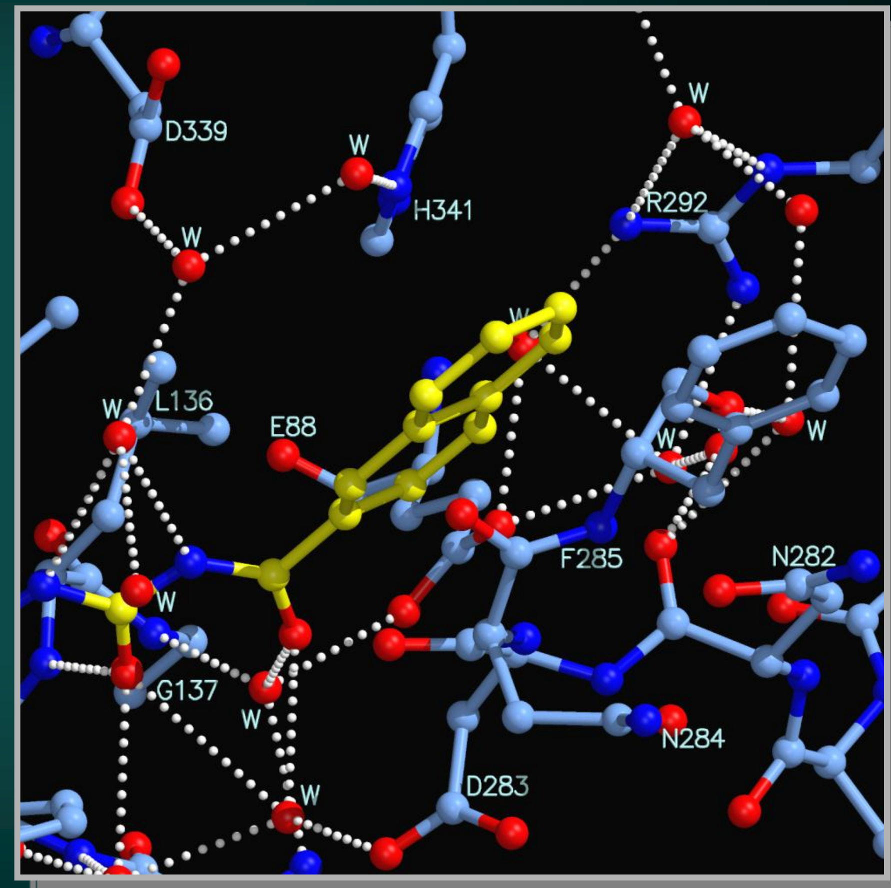
K_i = 81 μM

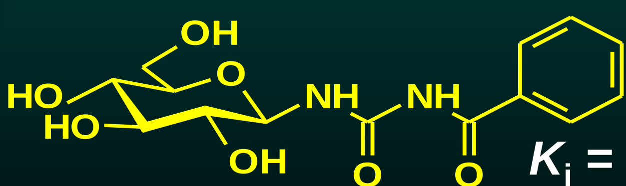


K_i = 4.6 μM

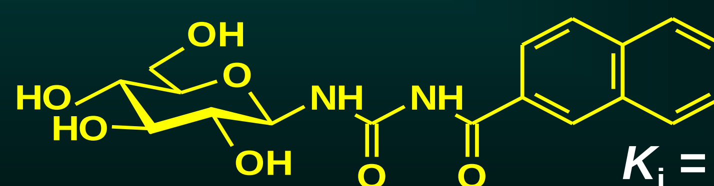
Interactions of *N*-benzoyl- and *N*-2-naphthoyl-*N'*-β-D-glucopyranosylureas in the β-channel of muscle GPb





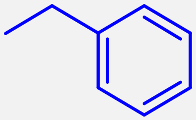
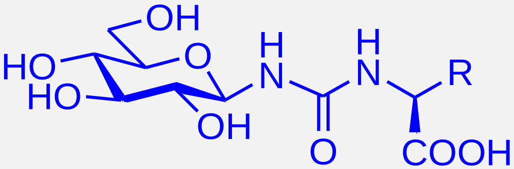
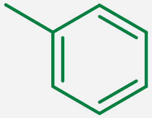
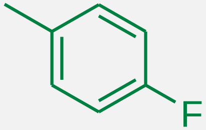
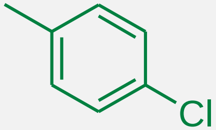
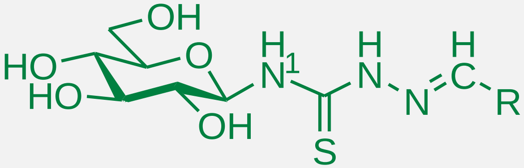


K_i = 4.6 μM



K_i = 0.35 μM

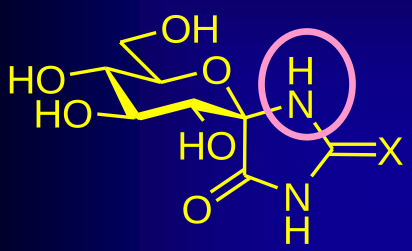
New *N*-β-D-glucopyranosyl derivatives tested as inhibitors of RMGPb

		R		
Gimisis, *Mini-Rev. Med. Chem.*, 2010, *10*, 1127-1138.		$-CH_3$	$-(CH_2)_2SCH_3$	
	**K_i [μM]**	**510**	**1200**	**350**
Alexacou et al., *Bioorg. Med. Chem.*, 2010, *18*, 7911-7922.				
	**IC_{50} [μM]**	**33**	**5.7**	**28**

No H-bond between His377 main chain CO and N[1]-H.

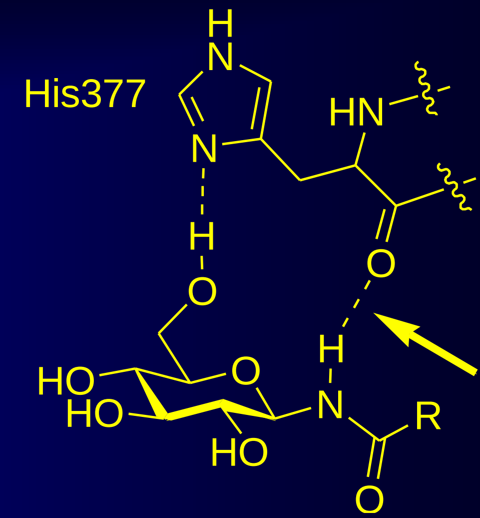
Novel design principle for inhibitors of GP

Leads:

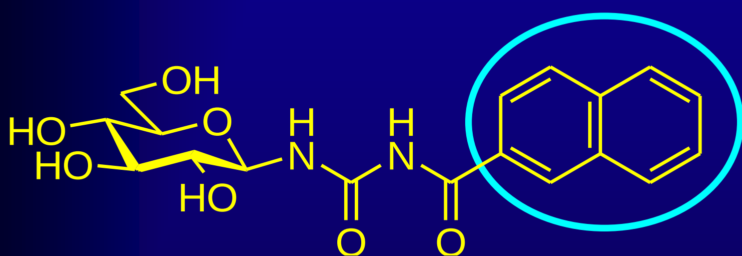


X = O K_i = 3.1 µM

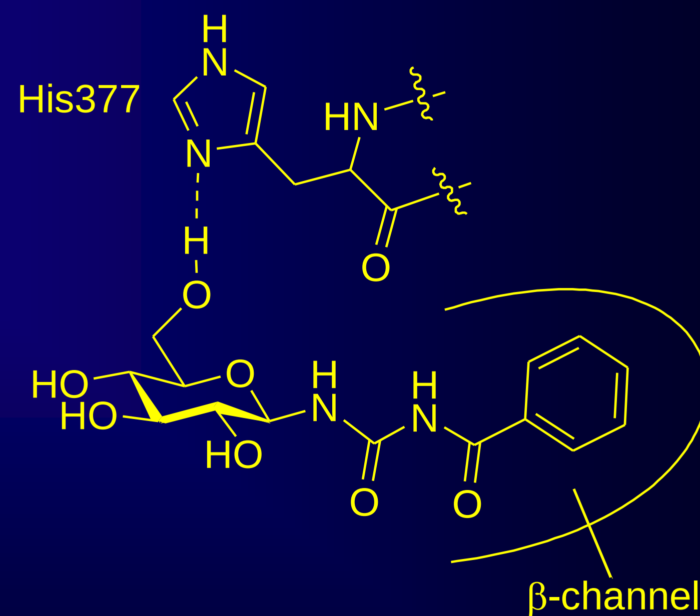
X = S K_i = 5.1 µM



- **rigid, spirobicyclic stucture**
- **H-bridge**

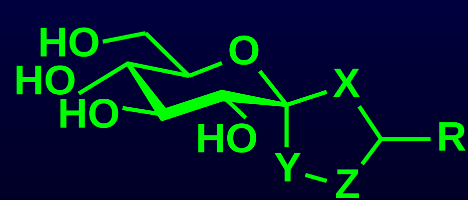


K_i = 0.35 µM

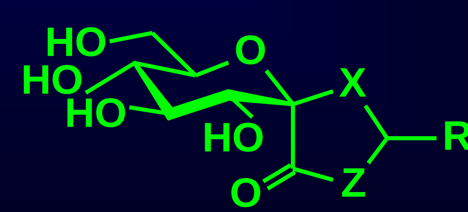


- **interactions in the β-channel**
- **lack of H-bridge**

Target compounds:

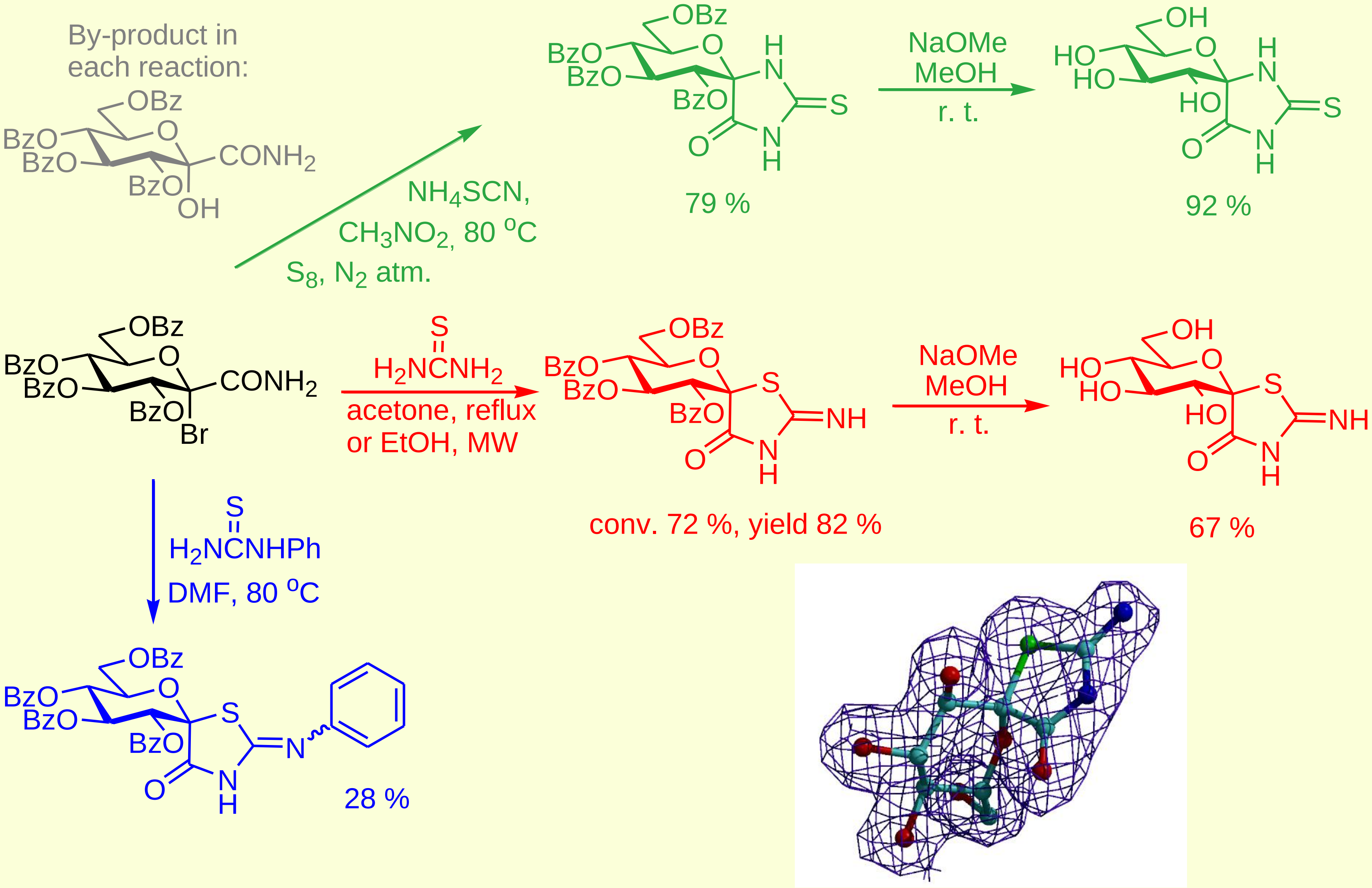


X = O,S, NH

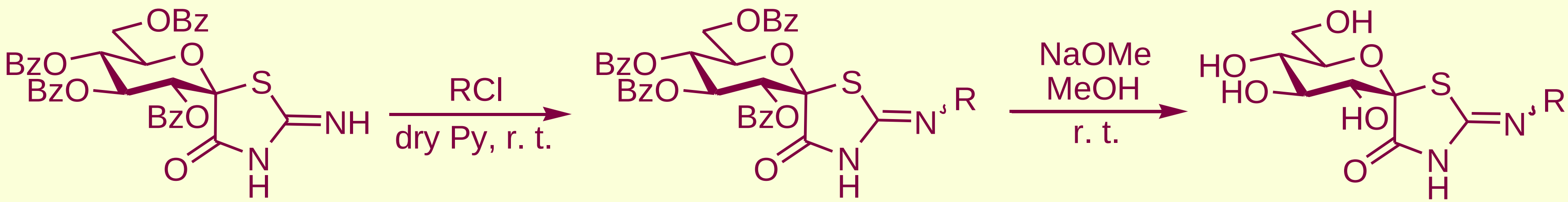


New spirocyclisation of (α-D-*gluco*-hept-2-ulopyranosyl-bromide)onamide

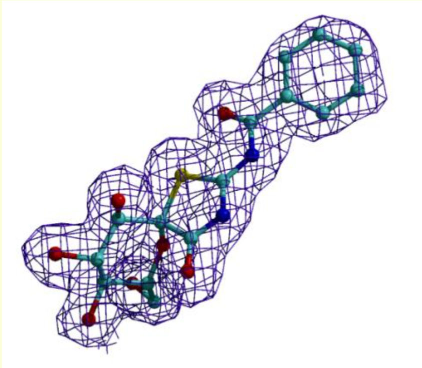
Somsák & Nagy, *Tetrahedron-Asymmetry*, 2000, *11*, 1719-1724.

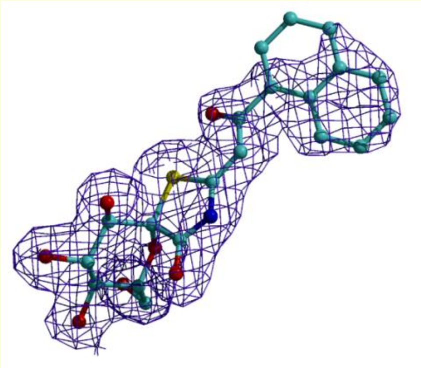


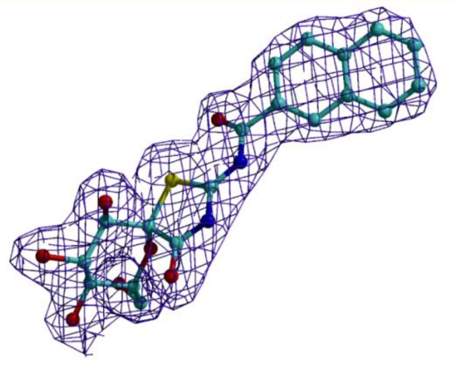
Acylation of glucopyranosylidene-spiro-iminothiazolones



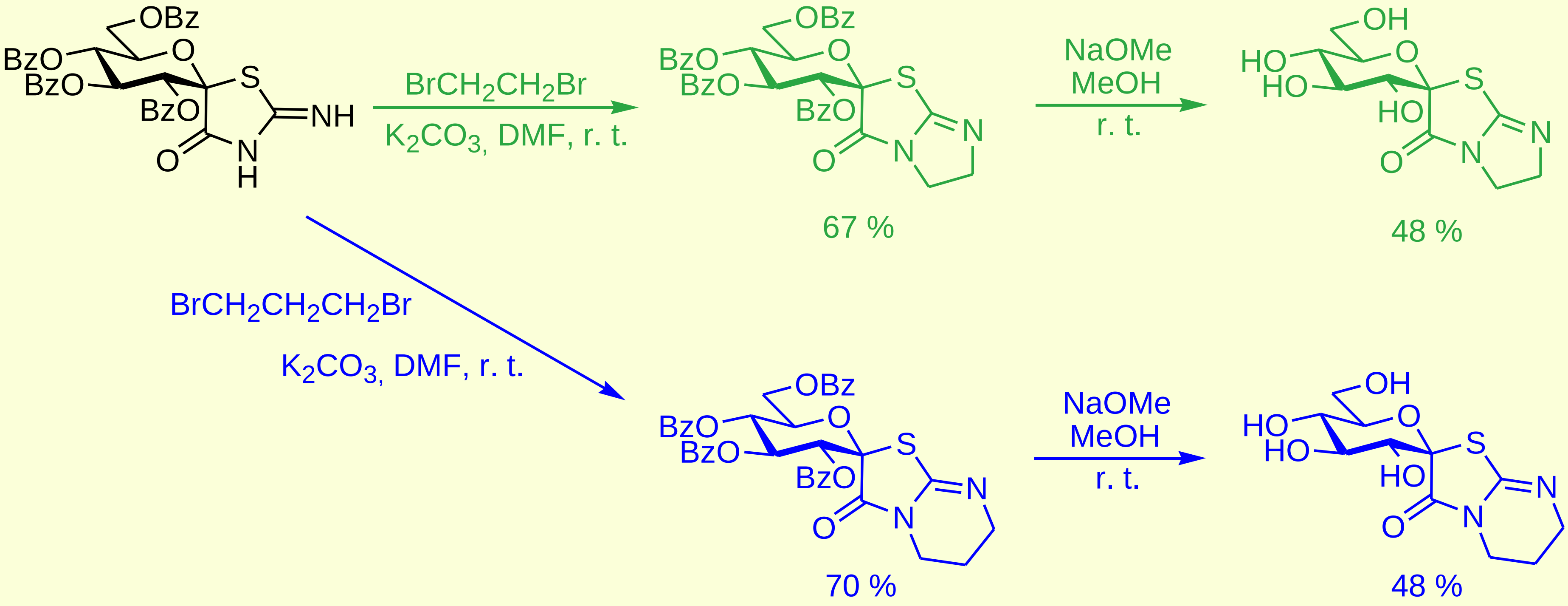
R =	Yield (%)	Yield (%)
Me-CO	76	N-deacylation to give
iPr-CO	81	unprot. thiazolone
tBu-CO	82	26
Ph-CO	84	58
1-Naphth-CO	73	56
2-Naphth-CO	89	50
4-Me-Ph-SO_2	96 (conv. 95 %)	60
1-Naphth-SO_2	91 (conv. 75 %)	
2-Naphth-SO_2	97 (conv. 76 %)	



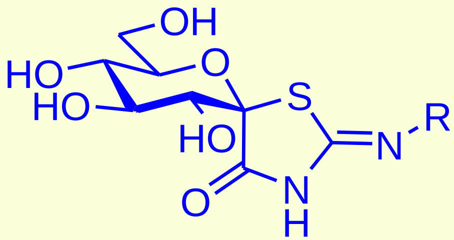


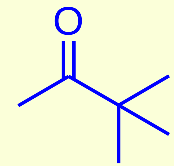
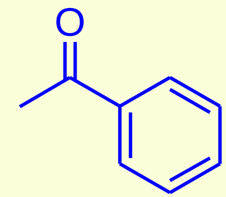


Alkylation of glucopyranosylidene-spiro-iminothiazolones

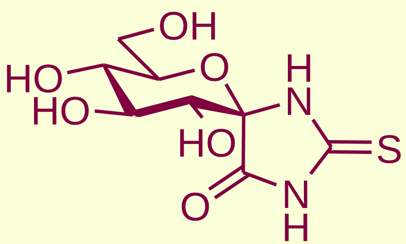


Inhibition of RMGPb by glucopyranosylidene-spiro-iminothiazolone derivatives

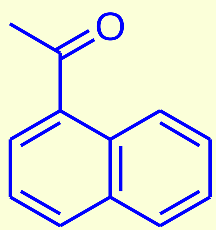


R = H  

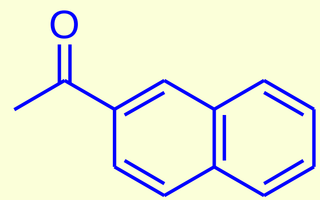
K_i = 14 μM　K_i = 137 μM　K_i = 9 μM



K_i = 5.1 μM

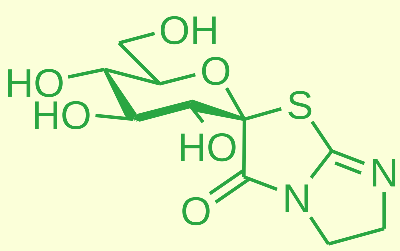


K_i = 8 μM

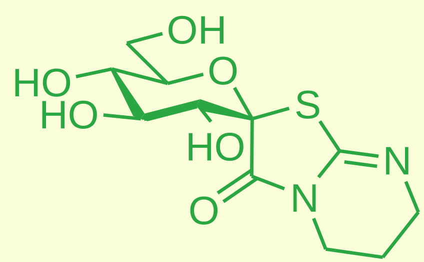


K_i = 4 μM

K_i = 16 μM

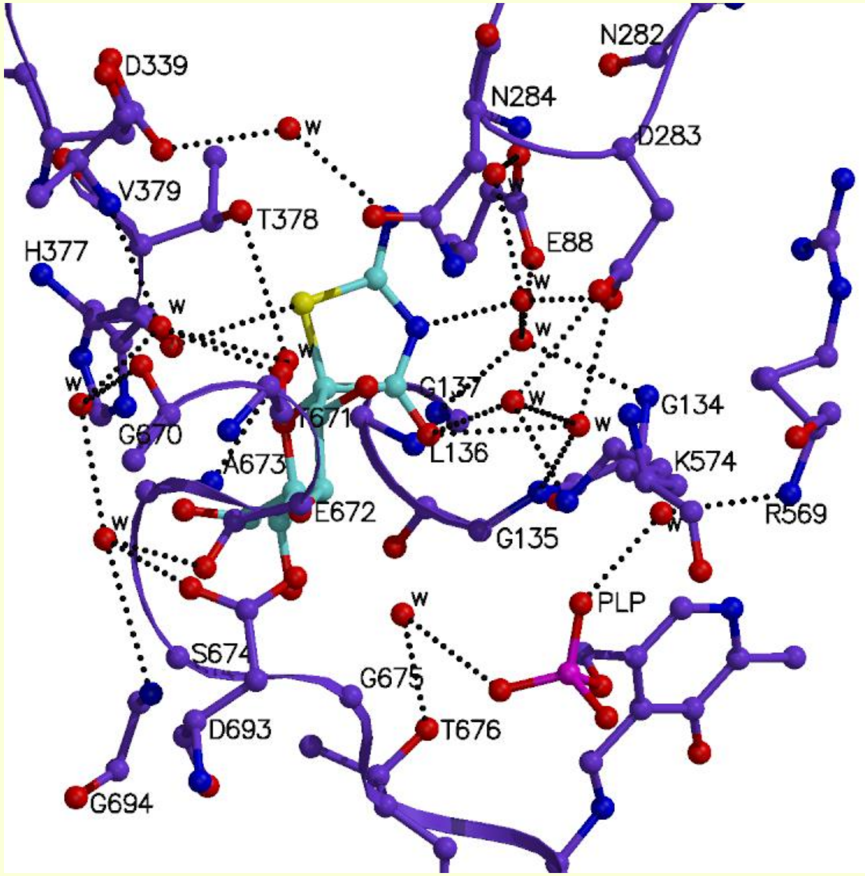


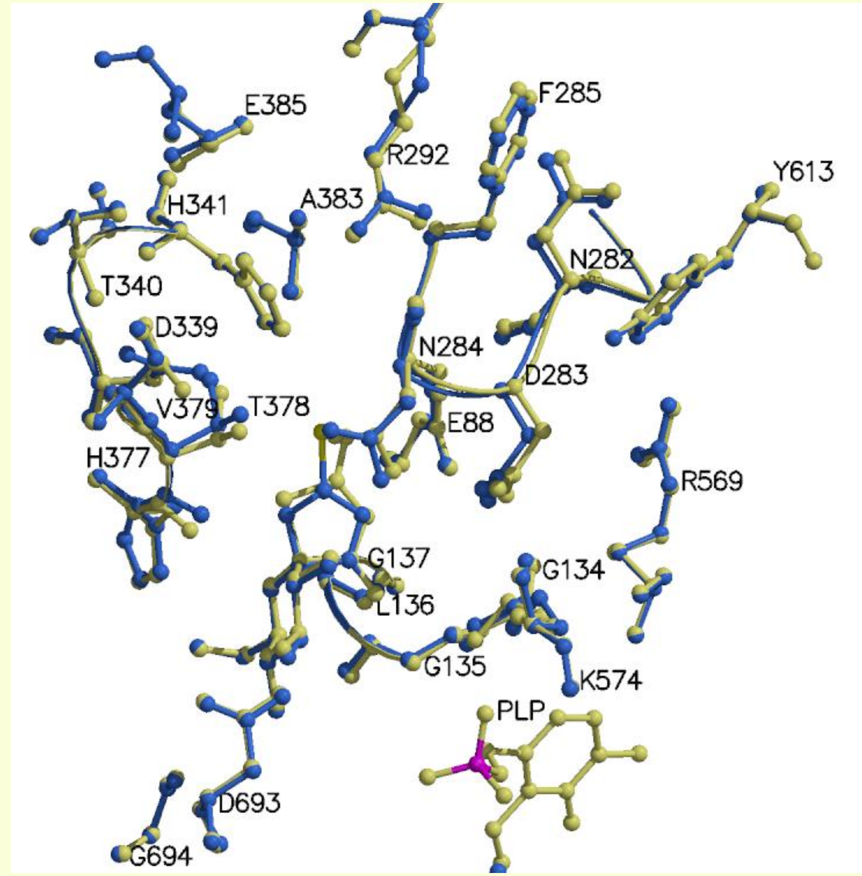
47 % inhibition at 1 mM

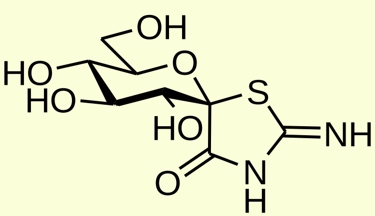


No inhibition up to 1 mM

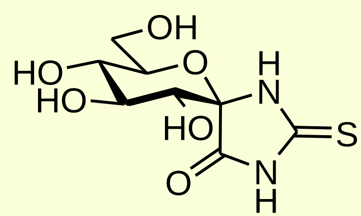
Binding of the spiro-iminothiazolone at the active site of RMGPb and comparison to spiro-thiohydantoin





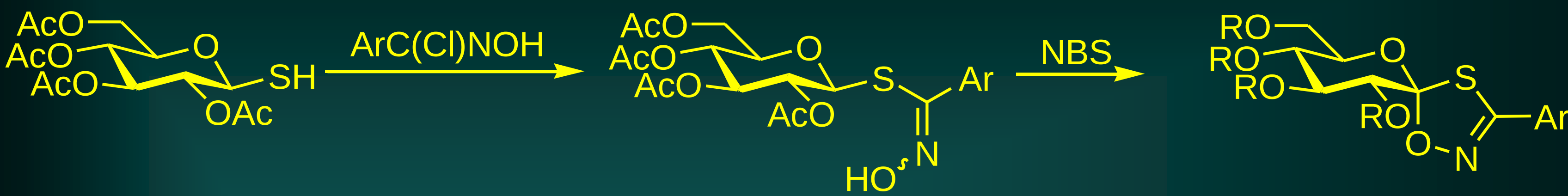


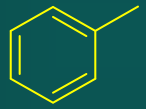
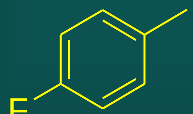
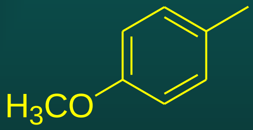
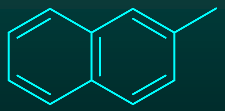
K_i = 14 μM



K_i = 5.1 μM

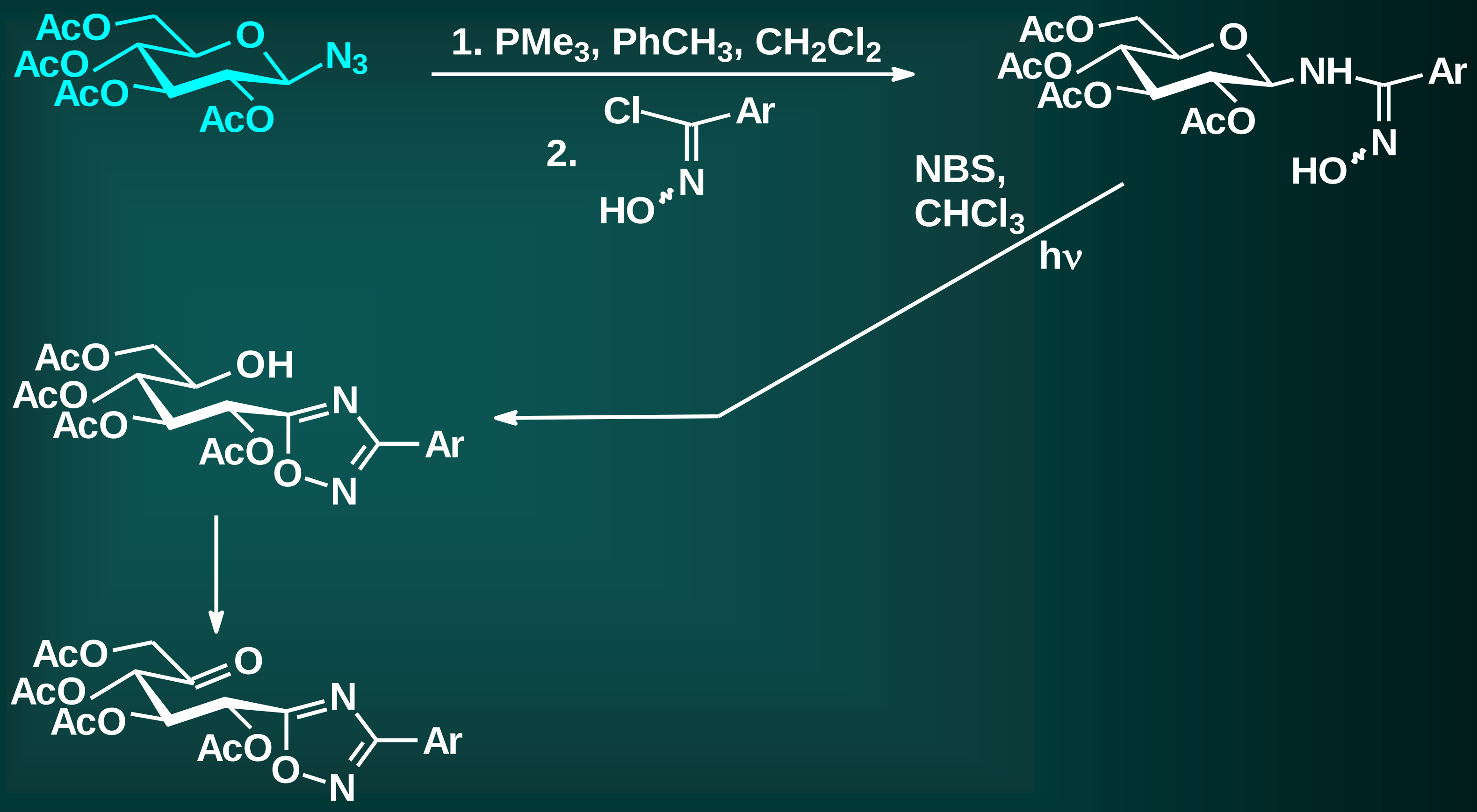
Synthesis of glucopyranosylidene-spiro-oxathiazolines



Ar		R = Ac	R = H
	Yields		
	90	46	90
	65	30	79
	71	69	79
	78	36	94

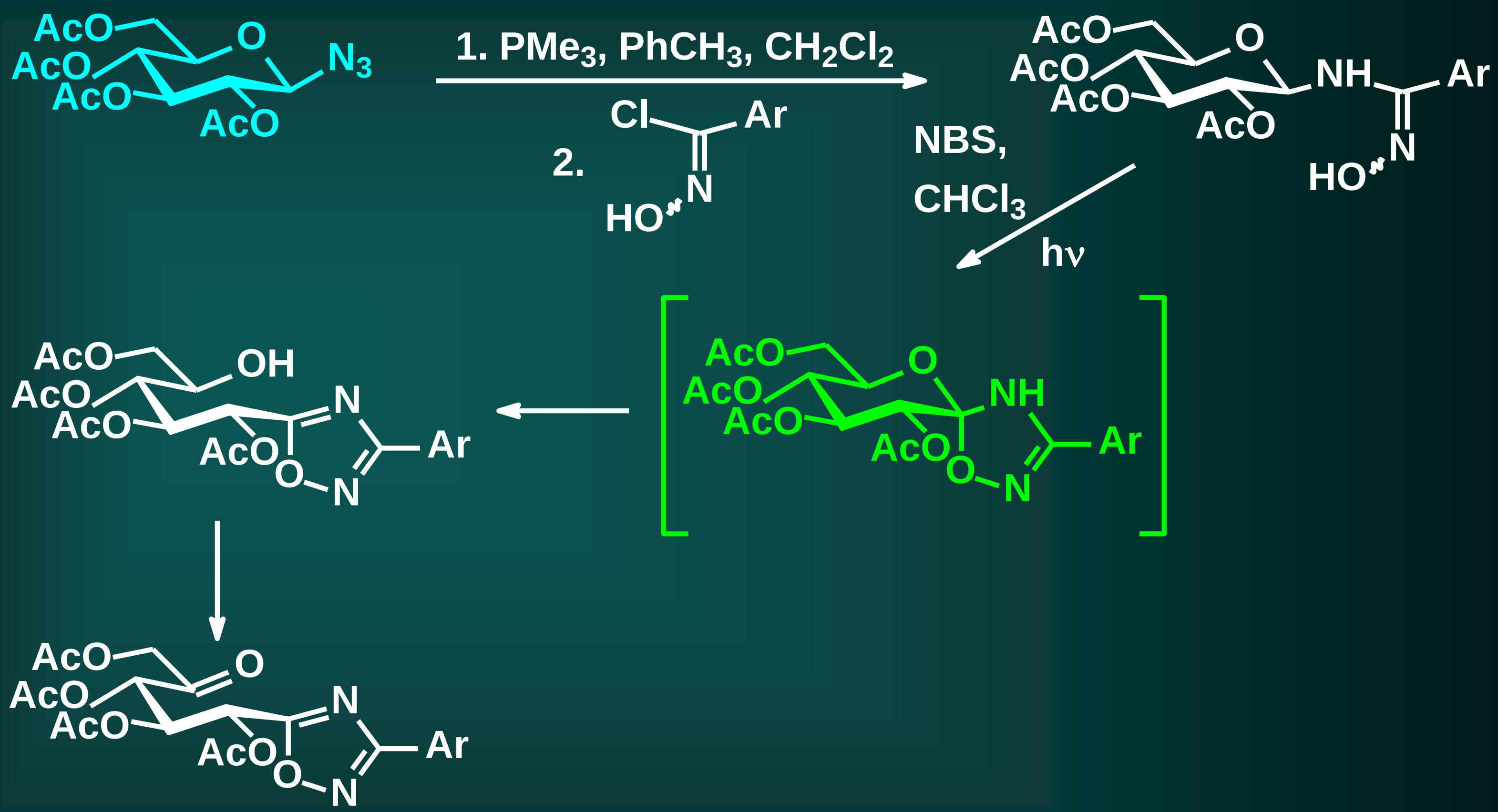
Somsák, Praly, et al., *Bioorg. Med. Chem. Lett.*, 2008, *18*, 5680-5683,
***Bioorg. Med. Chem.* 2009, *17*, 5696-5707.**

Attempted synthesis of a glucopyranosylidene-spiro-oxadiazoline



Somsák, Praly, et al., *Bioorg. Med. Chem.* 2009, *17*, 5696-5707.

Attempted synthesis of a glucopyranosylidene-spiro-oxadiazoline



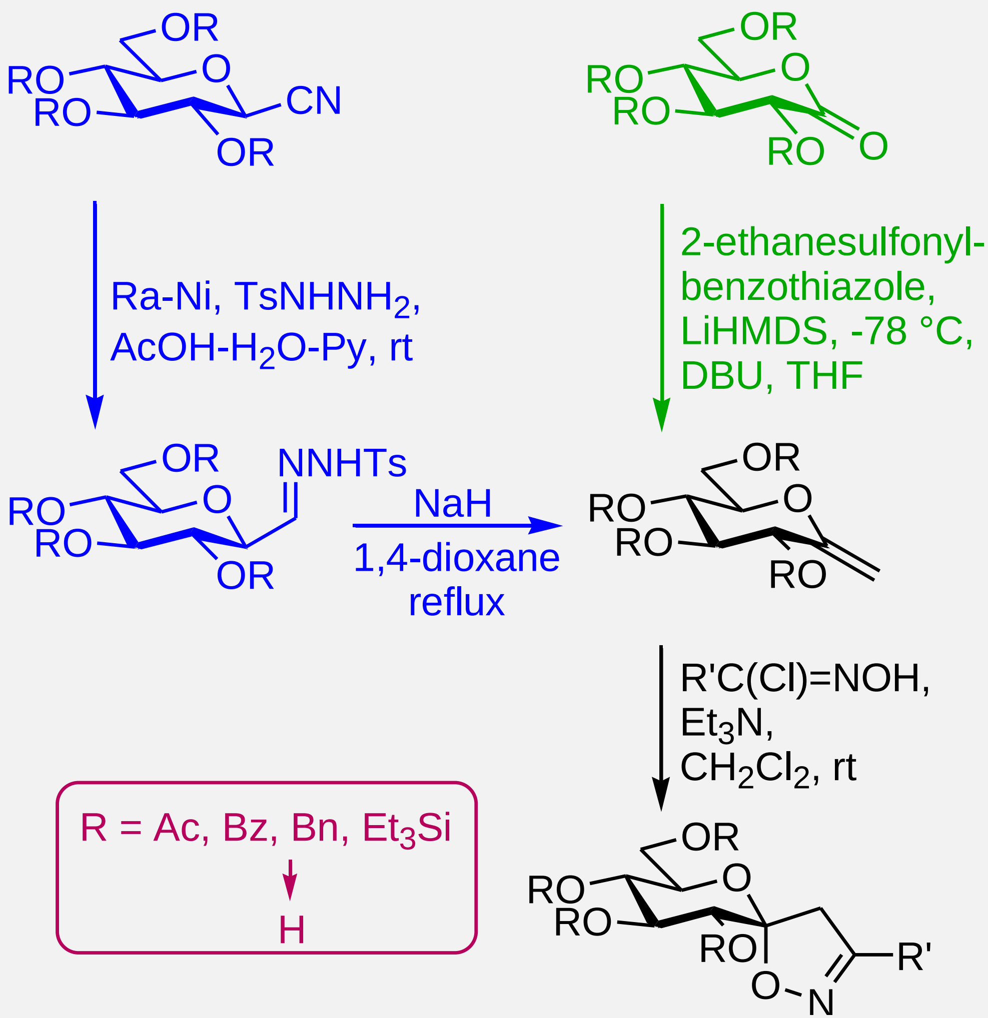
Somsák, Praly, et al., *Bioorg. Med. Chem.* 2009, *17*, 5696-5707.

Synthesis of glycopyranosylidene-spiro-isoxazolines

Tóth & Somsák,
J. Chem. Soc. Perkin 1,
2001, 942-943.

Org. Biomol. Chem.,
2003, *1*, 4039-4046.

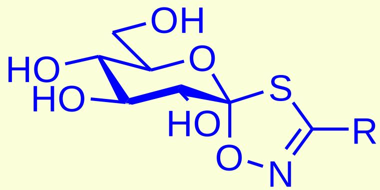
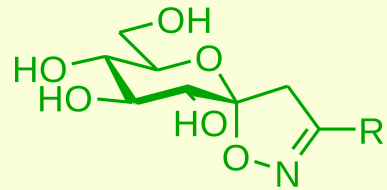
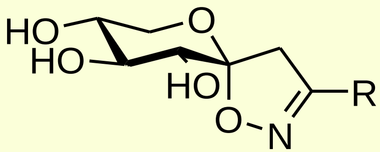
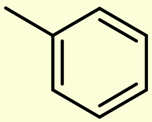
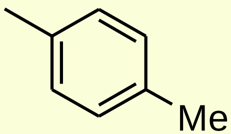
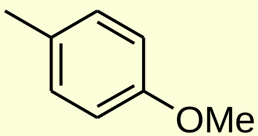
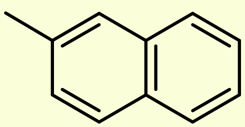
Carbohydrate Chemistry: Proven Synthetic Methods,
2011, in press.



Praly et al.,
Tetrahedron Lett.
2006, *47*, 6143-6147.

Praly et al.,
Bioorg. Med. Chem.,
2009, *17*, 7368-7380.

Inhibition of RMGPb (K_i [μM]) by glycopyranosylidene-spiro-heterocycles

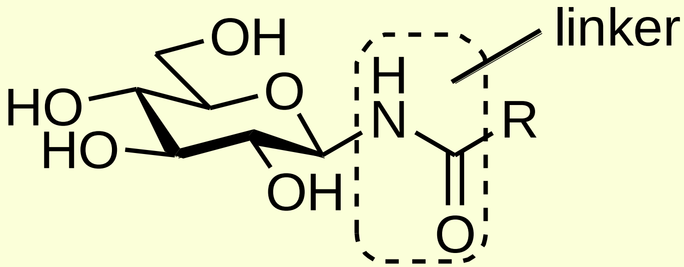
R			
	**26**	**19.6**	**no inh. at 625 μM**
		**7.9**	
	**8.2**	**6.6**	
	**0.16**	**0.63**	**no inh. at 625 μM**

Somsák, Praly et al.,
Bioorg. Med. Chem. Lett.,
2008, *18*, 5680-5683.

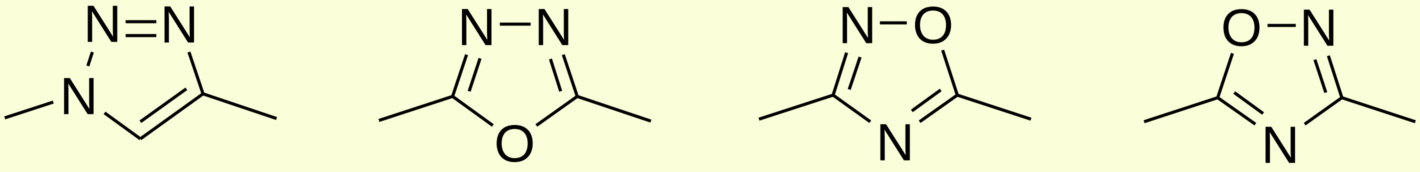
Bioorg. Med. Chem.,
2009, *17*, 5696-5707.

Praly et al.,
Bioorg. Med. Chem.,
2009, *17*, 7368-7380.

Modification of *N*-acyl-β-D-glucopyranosylamines by non-classical bioisosteres*

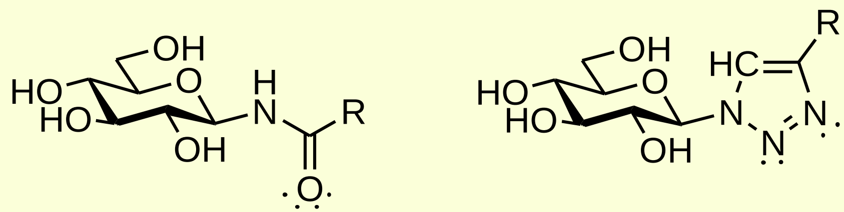


linkers

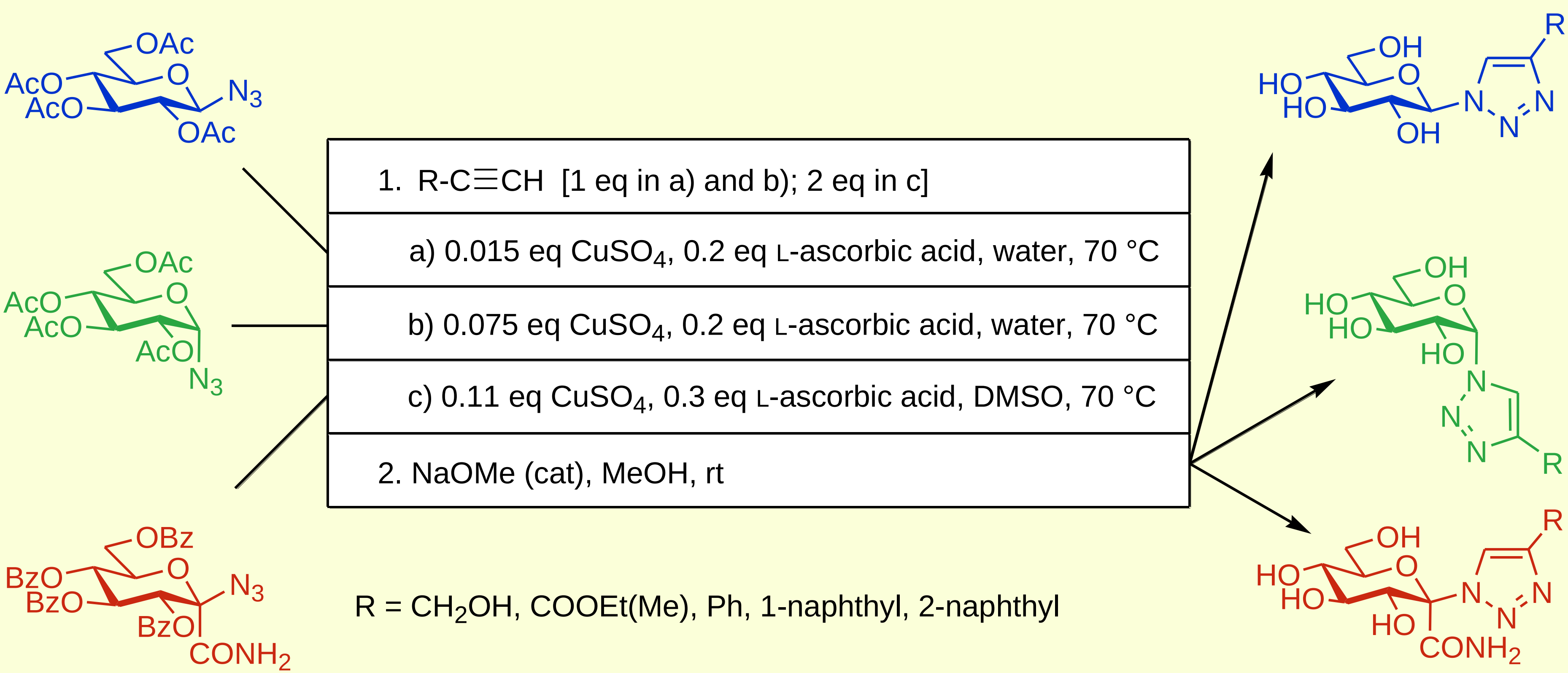


*Patani, G. A.; LaVoie, E. J., *Chem. Rev.,* 1996, *96*, 3147-3176.
Lima, L. M. A.; Barreiro, E. J., *Curr. Med. Chem.,* 2005, *12*, 23-49.

Synthesis of 1-D-glucopyranosyl-4-substituted-1,2,3-triazoles

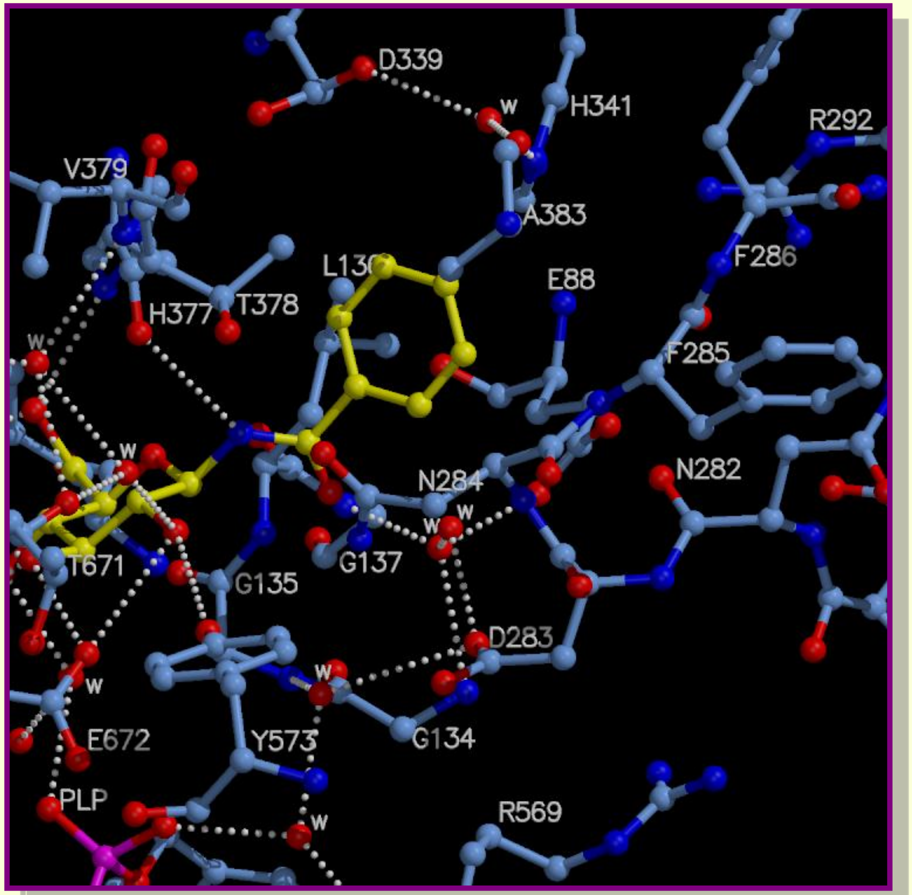


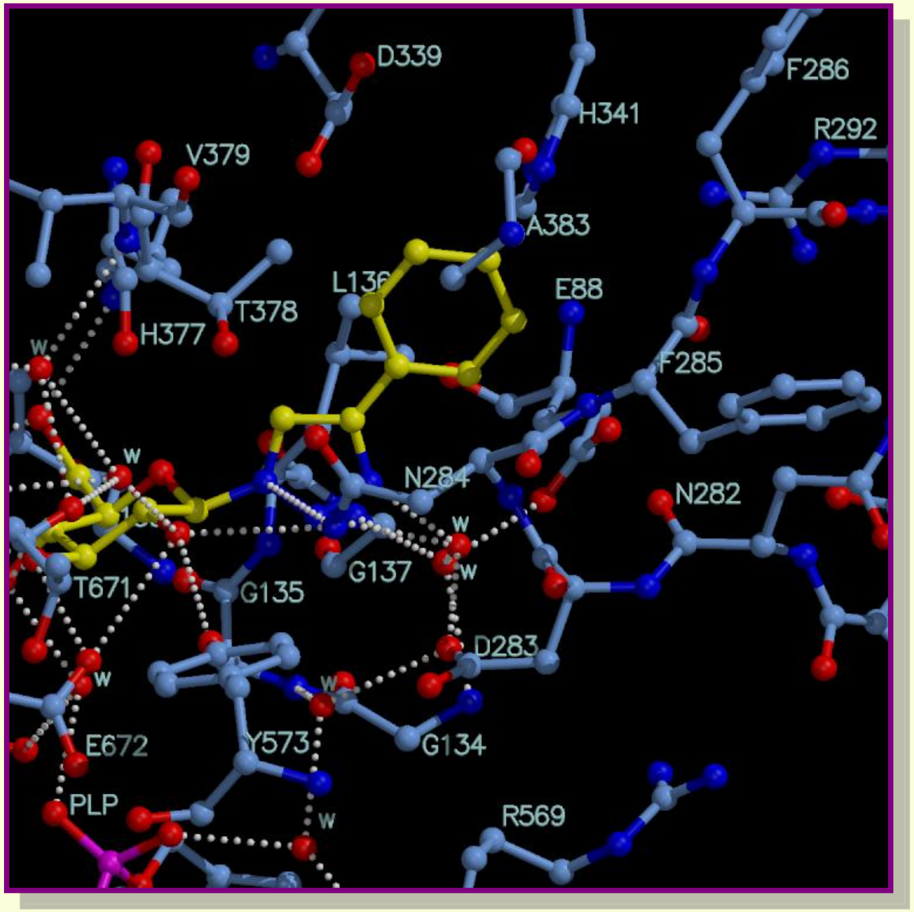
Similarity of the amide moiety and the 1,2,3-triazole ring:
size, dipolar character, and H-bond acceptor capacity
(Angell & Burgess, *Chem. Soc. Rev.* 2007, *36*, 1674-1689).

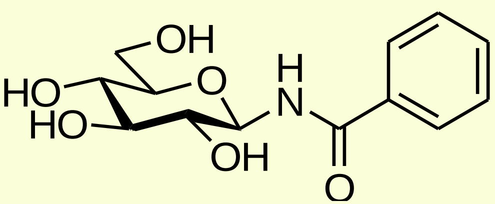


Bokor et al., *Bioorg. Med. Chem.* 2010, *18*, 1171-1180.

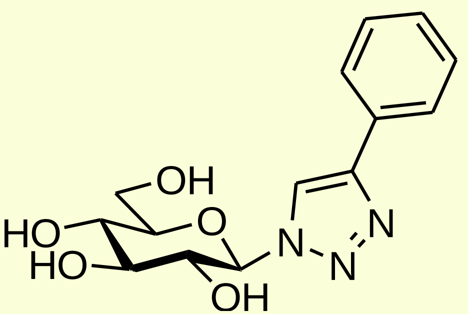
Binding of glucopyranosylamides and -1,2,3-triazoles at the catalytic site of RMGPb I.







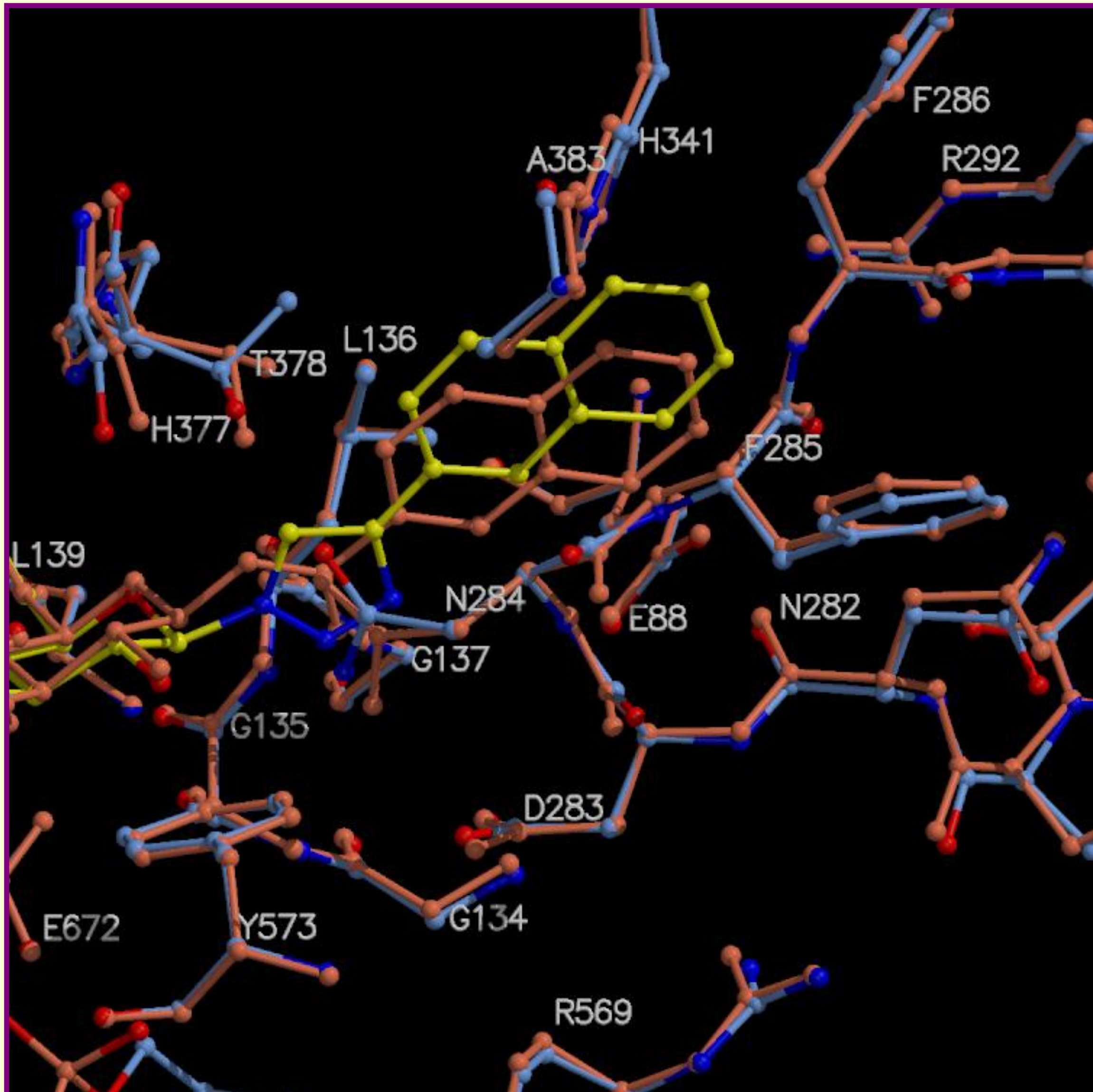
K_i = 81 μM

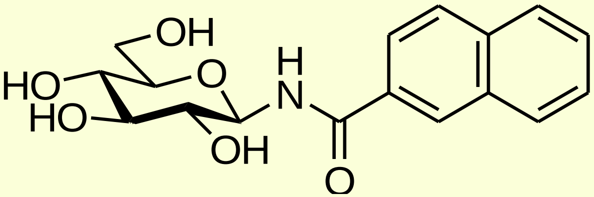


K_i = 151 μM

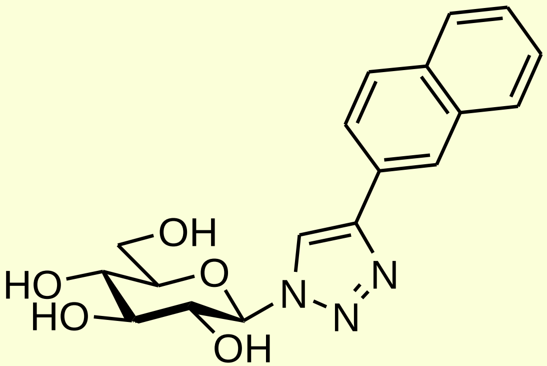
Chrysina et al., *Tetrahedron: Asymm.* 2009, *20*, 733-740.

Binding of glucopyranosylamides and -1,2,3-triazoles at the catalytic site of RMGPb II.





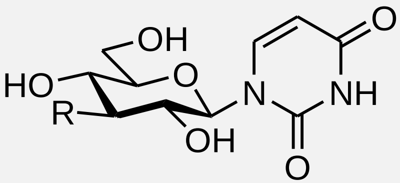
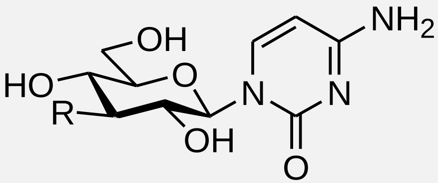
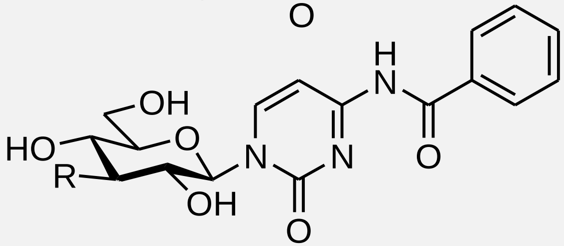
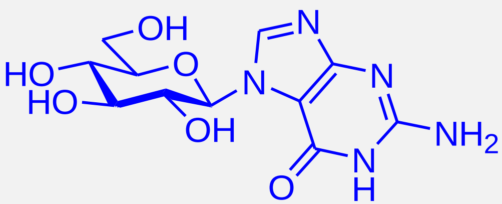
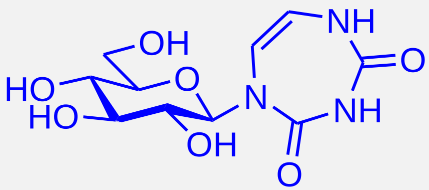
K_i = 13 μM



K_i = 16 μM

Chrysina et al., *Tetrahedron: Asymm.* 2009, *20*, 733-740.

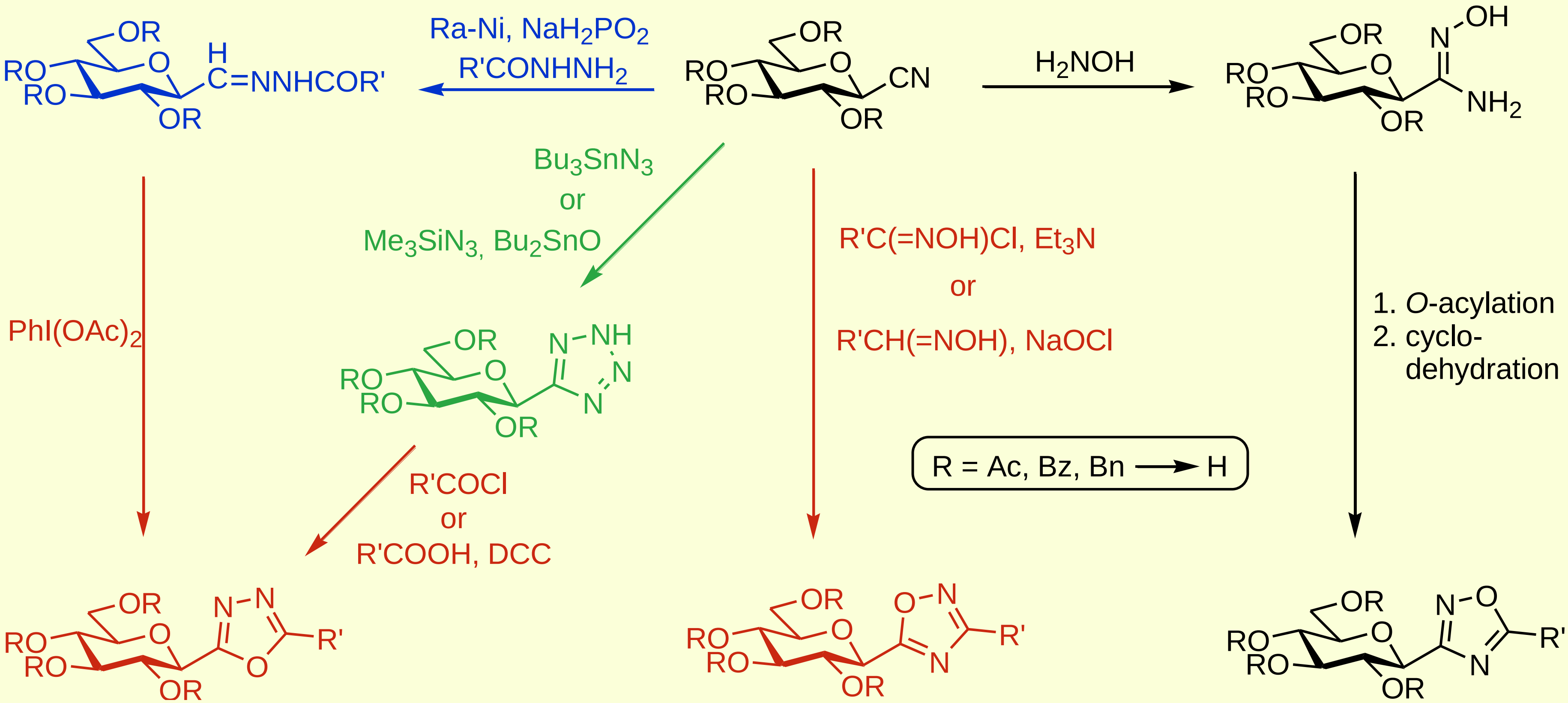
New *N*-β-D-glucopyranosyl heterocycles tested as inhibitors of RMGPb (K_i [μM])

	R = OH	R = F
	6.1	3640
	7.7	4010
		46
	170	
	76	

Gimisis,
***Mini-Rev. Med. Chem.*,**
2010, *10*, 1127-1138.

Tsirkone et al.,
***Bioorg. Med. Chem.*,**
2010, *18*, 3413–3425.

Syntheses of *C*-glucopyranosyl-oxadiazoles



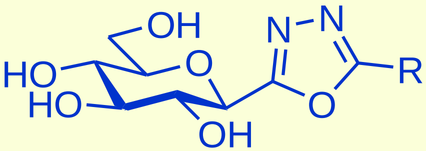
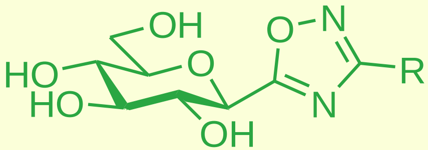
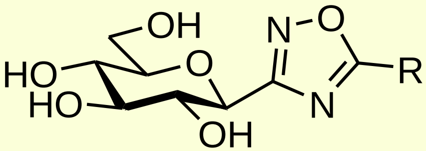
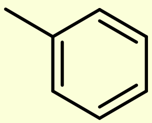
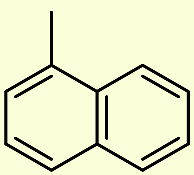
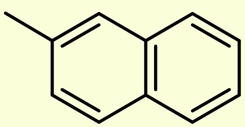
Tóth & Somsák, *Carbohydr. Res.,* 2003, *338*, 1319-1325.

Kun et al., *Carbohydr. Res,* 2011, *346*, 1427-1438.

Tóth et al., *Bioorg. Med. Chem*., 2009, *17*, 4773–4785.

Benltifa et al., *Eur. J. Org. Chem*., 2006, 4242.

Inhibition of RMGPb (K_i [μM]) by *C*-glucopyranosyl-oxadiazoles

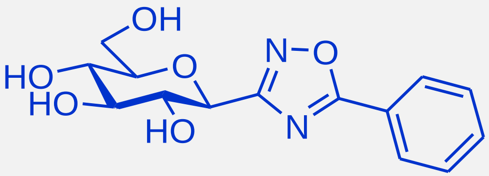
R			
$-CH_3$	**145**	**-**	**no inh. at 625 μM**
	**10 % at 625 μM**	**64**	**10 % at 625 μM**
	**10 % at 625 μM**	**19**	**no inh. at 625 μM**
	**10 % at 625 μM**	**2.4**	**38**

Hadady et al., *Arkivoc*., 2004, *vii*, 140-149.
Chrysina et al., *Prot. Sci.*, 2005, *14*, 873-878.

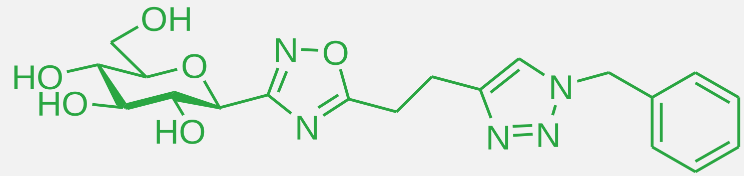
Tóth et al., *Bioorg. Med. Chem*., 2009, *17*, 4773–4785.

Benltifa et al., *Eur. J. Org. Chem*., 2006, 4242.

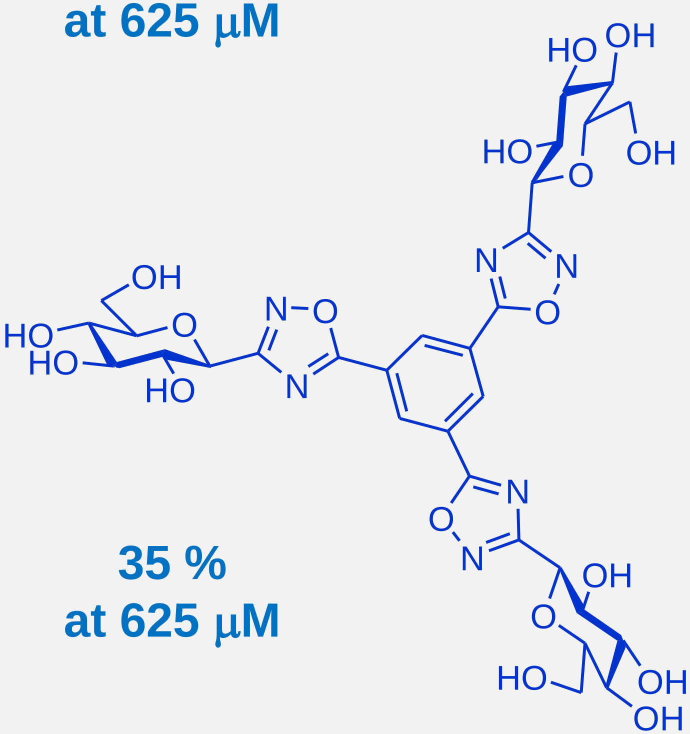
Inhibition of RMGPb by homotrivalent glucose derivatives



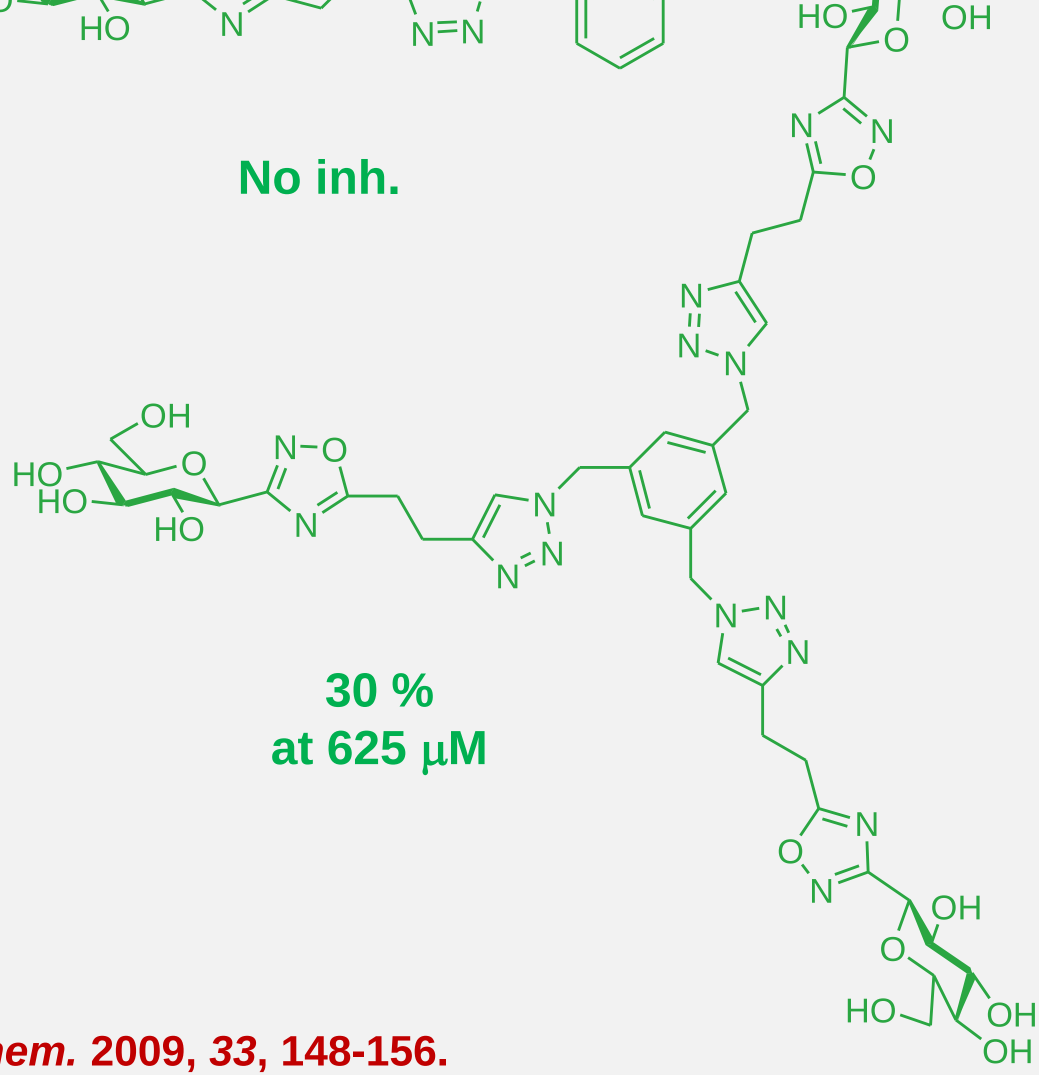
10 %
at 625 μM



No inh.



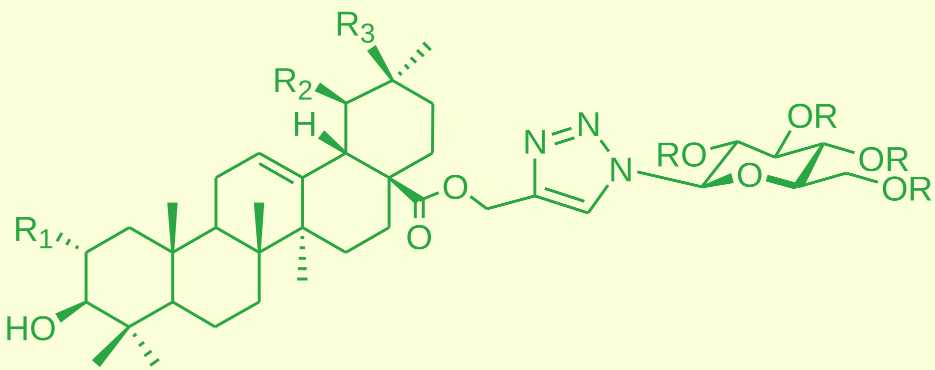
35 %
at 625 μM



30 %
at 625 μM

Cecioni et al., *New J. Chem.* 2009, *33*, 148-156.

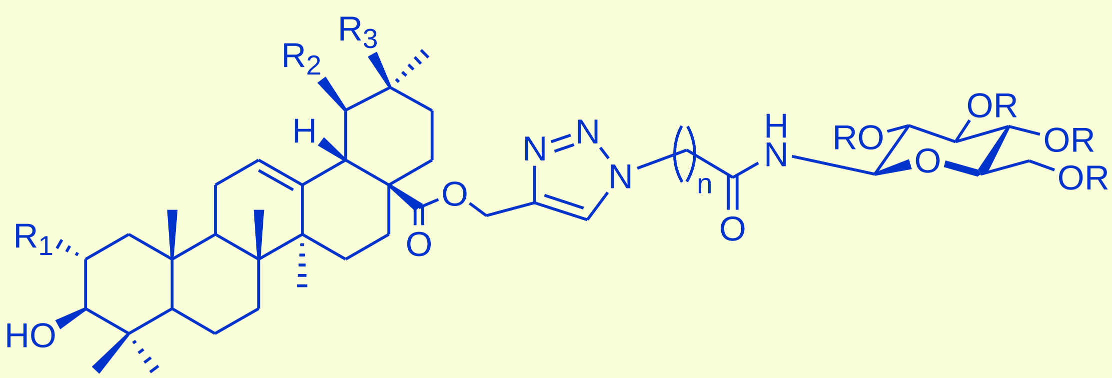
Inhibition of RMGPa by heterobivalent glucose-pentacyclic triterpene derivatives



Oleanolic acid (OA) R_1 = H, R_2 = H, R_3 = CH_3

Ursolic acid (UA) R_1 = H, R_2 = CH_3, R_3 = H

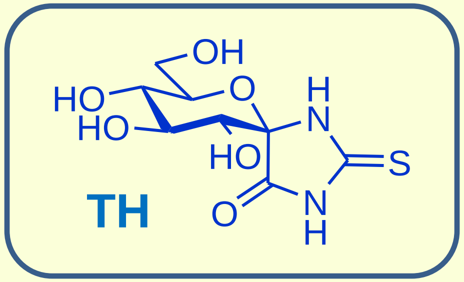
Maslinic acid (MA) R_1 = OH, R_2 = H, R_3 = CH_3

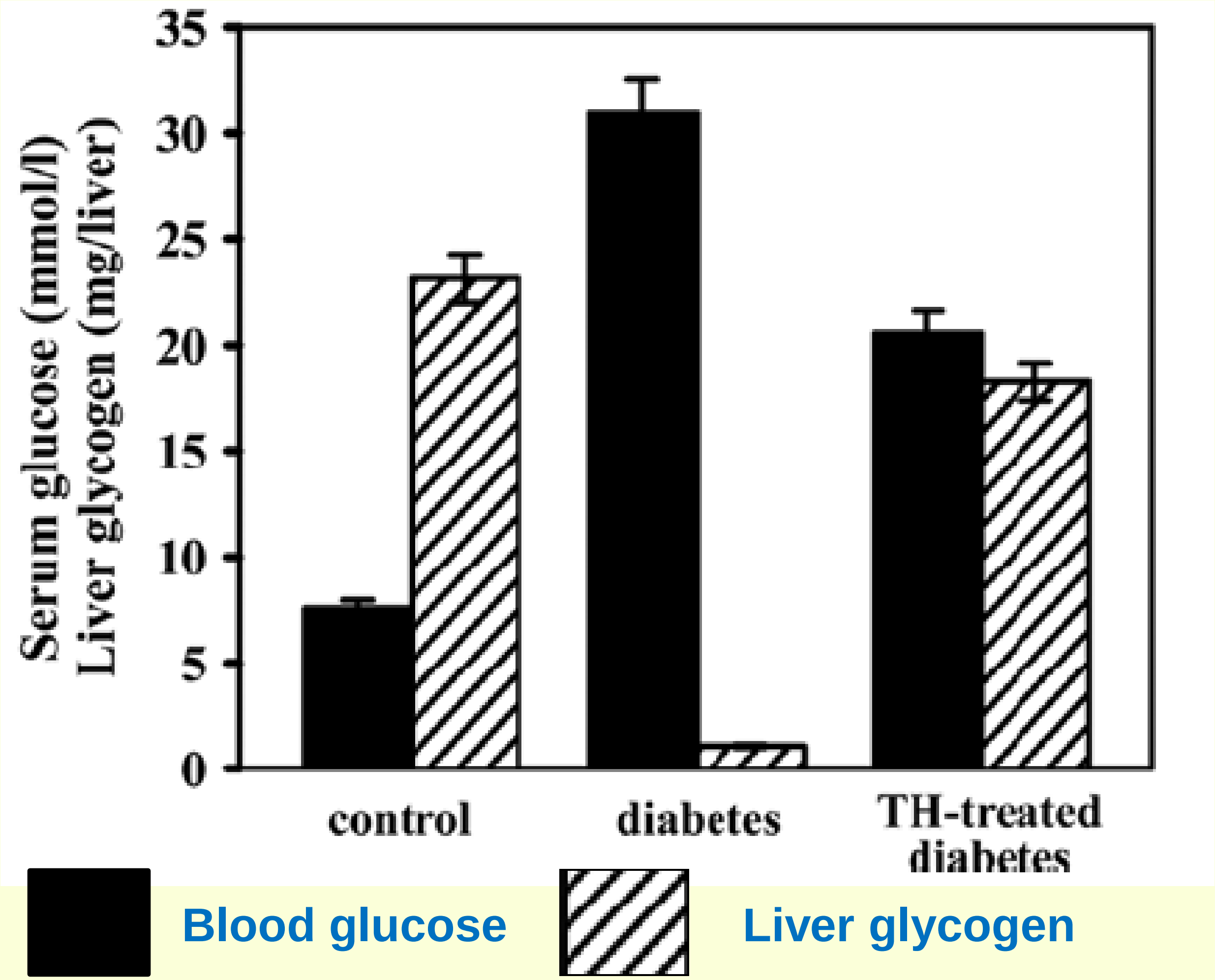


Acid	R	n	IC_{50} [μM]
OA	Ac	-	337
OA	H	-	26
UA	Ac	-	51
UA	H	-	45
MA	Ac	-	no inh.
MA	H	-	779
OA	Ac	1	68
UA	Ac	10	65
MA	Ac	1	78

Cheng et al., *New J. Chem.* 2010, *34*, 1450-1464.

Physiological effects of TH treatment in streptozotocin-induced diabetic rats





The results are the mean ± SD of four independent experiments.

Intravenous administration of TH to Zucker diabetic fatty rats significantly decreased hepatic glycogen phosphorylase *a* levels, and the activation of synthase was initiated without any delay.

Docsa et al., *Mol. Med. Rep.,* 2011, *4*, 477-481.

Summary

Glucose-derived compounds

» *N*-acyl-*N'*-β-D-glucopyranosylureas
» glucopyranosylidene-spiro-heterocycles
(isoxazolines, oxathiazolines)
» *C*-β-D-glucopyranosyl heterocycles

having large aromatic substituents inhibit glycogen phosphorylase in the nanomolar range.

Further inhibitor design may focus on the interactions in the β-channel of the enzyme.

Physiological investigations show glucopyranosylidene-spiro-thiohydantoin to act towards normalizing serum glucose and liver glycogen levels in diabetic rats.

Participants

Organic synthesis

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