Кононов Леонид Олегович

# ХИМИЯ УГЛЕВОДОВ И ГЛИКОБИОЛОГИЯ

https://углеводы.su

# Расписание лекций и семинаров в 2026 г.



***Время:*** понедельник: 14.30–16.00
16.15–17.45

***Даты:***

**ЛЕКЦИИ**

Февраль: 16

Март: 02, 16, 23, 30

Апрель: 06

**СЕМИНАРЫ**

Февраль: 16

Март: 30

Апрель: 06

**ЭКЗАМЕН**

Май : 18 – дату необходимо согласовать заранее

Следите за информацией на сайте углеводы.su

Сдача экзамена возможна только вместе с одной из групп!

# Темы занятий



**ЛЕКЦИИ:**

1. Введение в гликобиологию. Стереохимия углеводов.
2. Химические свойства. Синтез.
3. Гликопротеины
4. Гликолипиды, полисахариды, протеогликаны
5. Структурный анализ гликопротеинов и олигосахаридов.
6. Углевод-связывающие белки.
7. Медицинская гликобиология.

**СЕМИНАРЫ:**

1. Стереохимия углеводов (основы: проекции Фишера, Хеуорса для моносахаридов).
2. Стереохимия углеводов (более сложные вопросы стереохимии).

**ЭКЗАМЕН:**

1) задача (см. семинары),
2) два вопроса: химия + гликобиология (см. вопросы к экзамену).

# Список рекомендуемой литературы



все файлы – на сайте углеводы.su Пароль: **********

**IN ENGLISH:**


6. *Essentials of glycobiology*, A. Varki *et al.* (Eds.), 4th edn., 2022. Открытый доступ к книге (https://www.ncbi.nlm.nih.gov/books/NBK579918). Доступен файл 1-го издания (1999).
7. *Comprehensive Glycoscience. From Chemistry to System Biology,* 2007.
9. *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance,* 2008. *Глава 1: Ch1_General Aspects.*
42. *I. Robina, et al.* Glycosylation Methods in Oligosaccharide Synthesis. *Curr. Org. Synth., 2008.* Доступен файл обобщающего обзора (2005; 75 стр.).


**ПО-РУССКИ:**


3. Т. С. Орецкая и др., *Моно- и дисахариды*, 2010, тт. 1 и 2.
13. Н. К. Кочетков и др. *Химия углеводов*. 1967.
15. А. Ф. Бочков и др., *Углеводы*. 1980.
16. Р. Хьюз. *Гликопротеины*. 1985.


*Примечание:* Нумерация литературы соответствует списку на сайте углеводы.su

# Лекция 1

Введение в гликобиологию

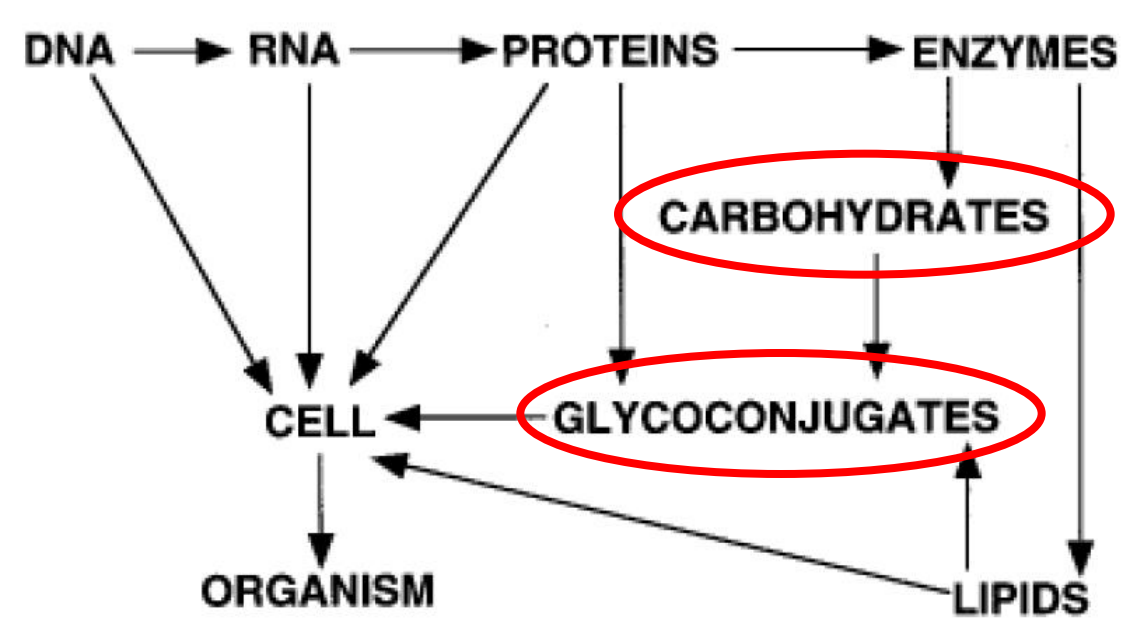
Стереохимия моно- и олигосахаридов

# Место гликобиологии в молекулярной биологии 6

## Традиционный взгляд (сформулирован в 1950-е гг.):

DNA → RNA → PROTEIN → CELL → ORGANISM

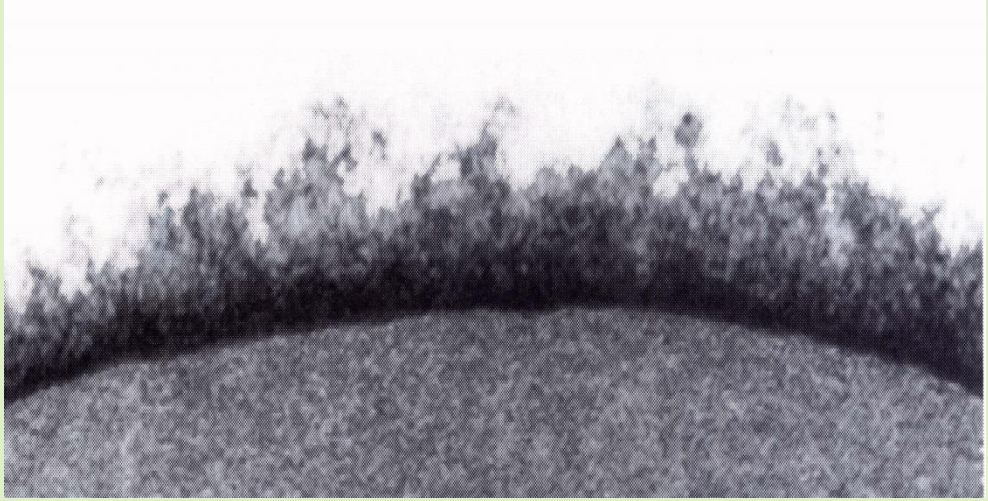
## Современный взгляд (сформулирован в 1980-е гг.):

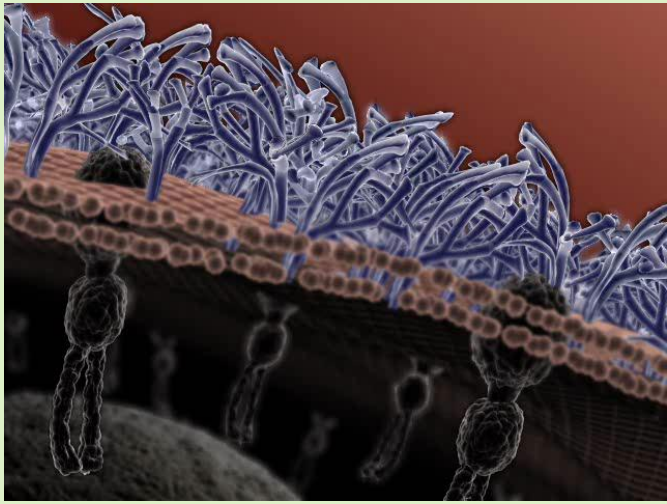


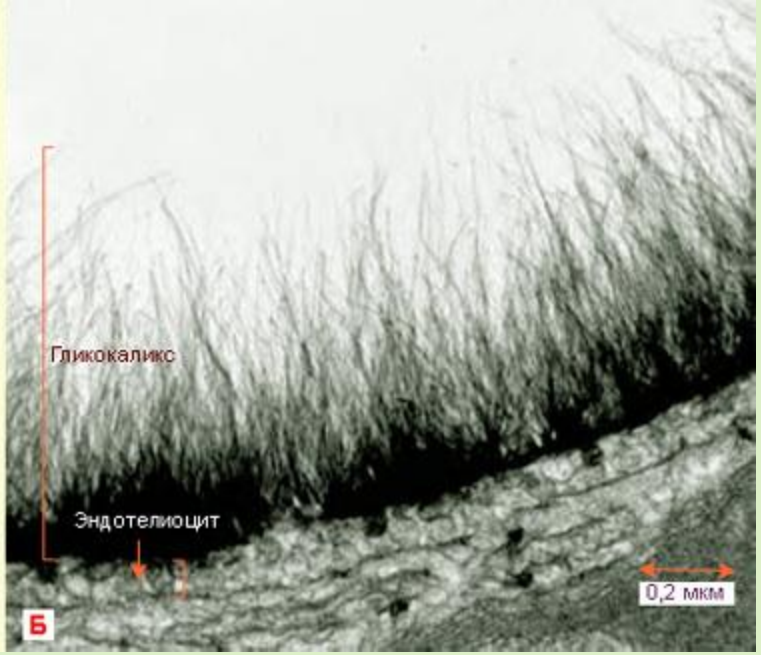

*Essentials of glycobiology*, A. Varki, *et al.* (Eds.), 1nd edn., 1999, p. 7.

# Гликокаликс



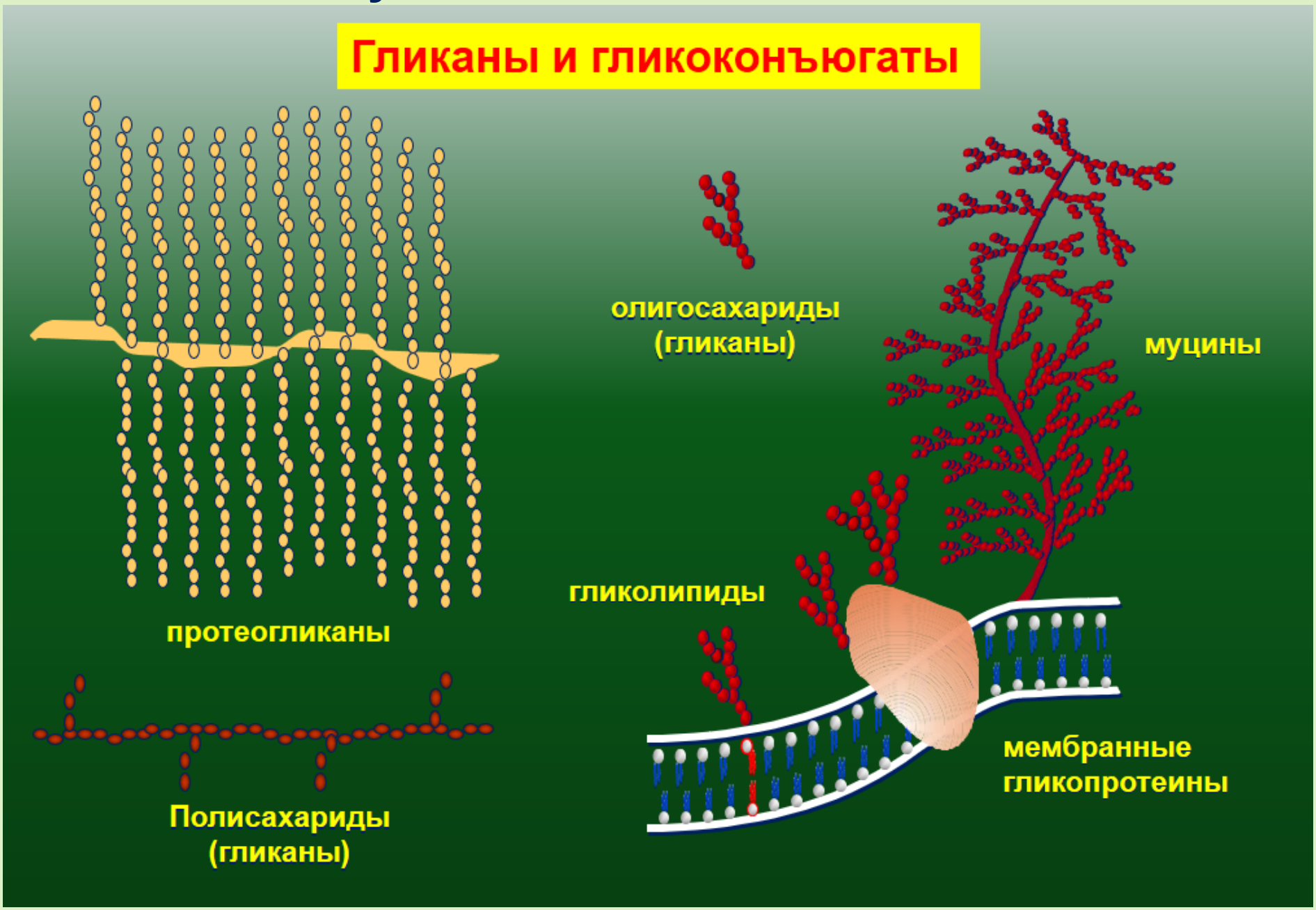






# Глико-молекулы клеток млекопитающих





# Доля гликанов в составе гликоконъюгатов гликана может достигать 85% (масс.)



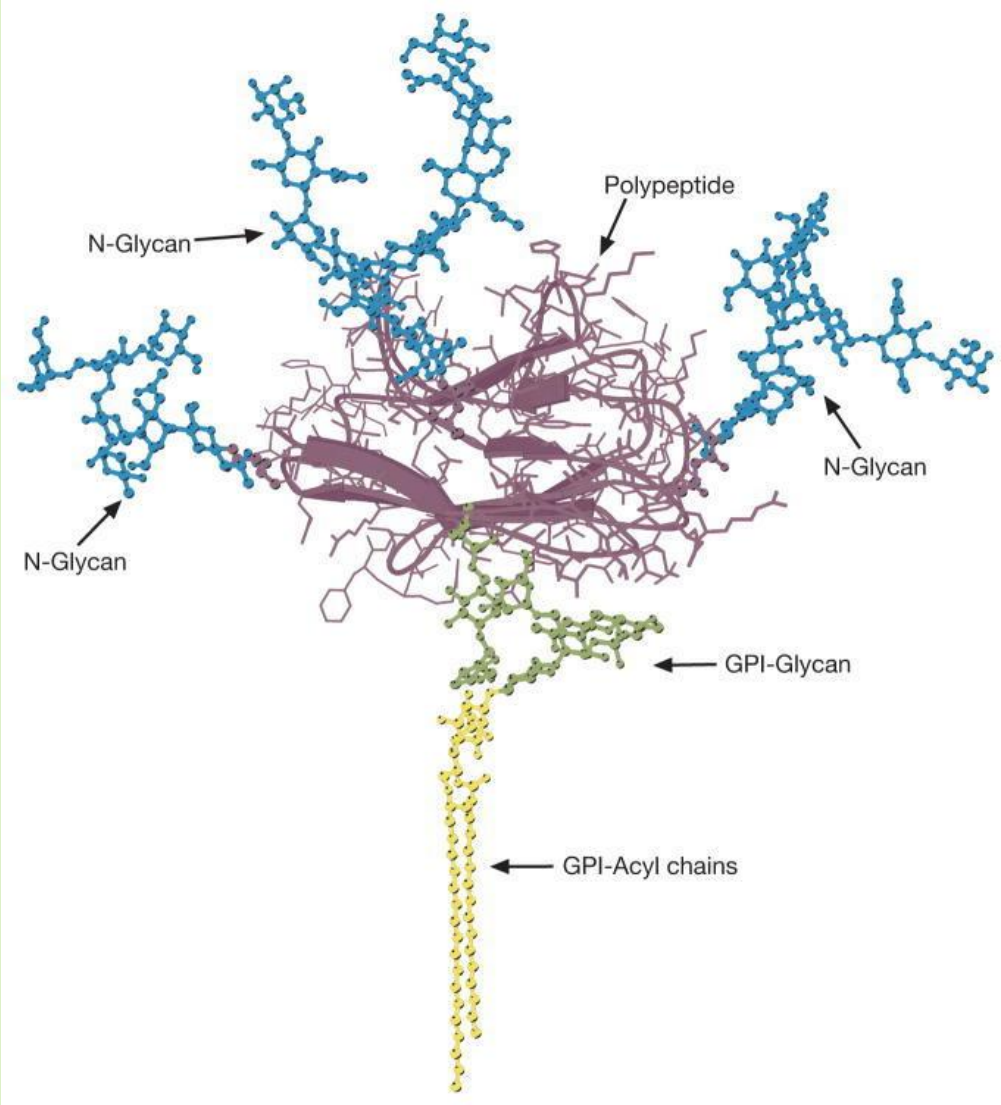
**ПРИМЕР:**

сильно гликозилированный гликопротеин Thy-1

(THYmocyte differentiation antigen 1)

На долю гликанов приходится 30% молекулярной массы гликопротеина Thy-1

($M_w$ 25 кДа → 37 кДа )

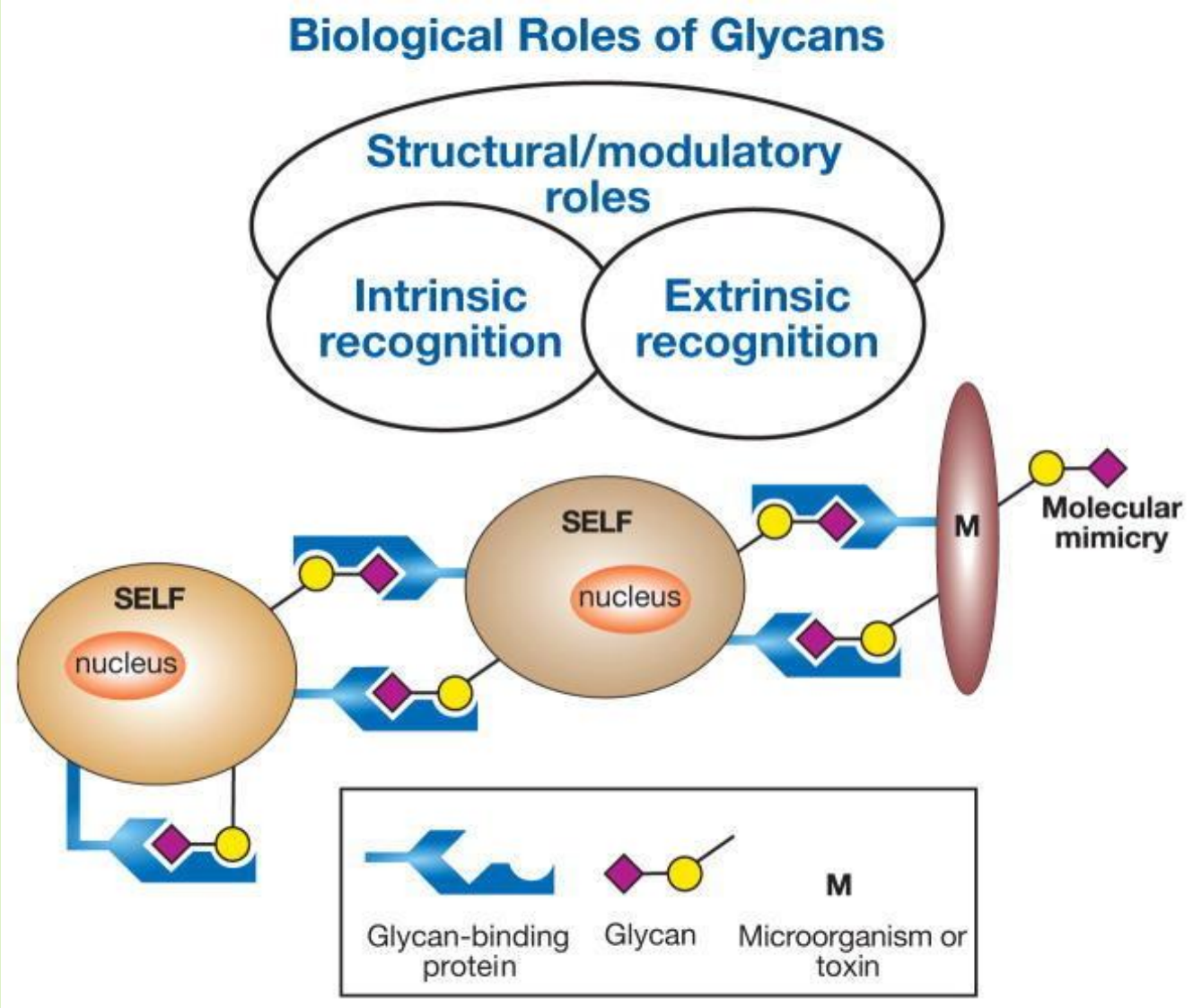



*Essentials of Glycobiology*
Second Edition

Chapter 1, Figure 3

# Биологические функции гликанов



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Second Edition

Chapter 6, Figure 1

# Все теории правильны!



Glycobiology vol. 3 no. 2 pp. 97–130, 1993

SPECIAL INVITED REVIEW

## Biological roles of oligosaccharides: all of the theories are correct

Ajit Varki[1]

Glycobiology Program, UCSD Cancer Center, and Division of Cellular and Molecular Medicine, University of California, San Diego, La Jolla, CA 92093, USA

[1]Correspondence to: University of California, San Diego, Cancer Center, 0063, 9500 Gilman Drive, La Jolla, CA 92093, USA

Many different theories have been advanced concerning the biological roles of the oligosaccharide units of individual

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and cells, the modulation of protein fu
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Most of these discussions have focus

biosynthesis. *Science*, **241**, 1092–1096.

1046. Carlson,J., Sakamoto,Y., Laurell,C.B., Madison,J., Watkins,S. and Putnam,F.W. (1992) Alloalbuminemia in Sweden: structural study and phenotypic distribution of nine albumin variants. *Proc. Natl. Acad. Sci. USA*, **89**, 8225–8229.

1047. Capecchi,M.R. (1989) Altering the genome by homologous recombination. *Science*, **244**, 1288–1292.

1048. Yost,H.J. (1992) Regulation of vertebrate left–right asymmetries by extracellular matrix. *Nature*, **357**, 158–161.

1049. Grosveld,F. and Kollias,G. (1992) *Transgenic Animals*. Academic Press, San Diego.

*Received on December 31, 1992; accepted on January 19, 1993*

31. (a) A. Varki. Biological roles of oligosaccharides: all of the theories are correct. *Glycobiology* **1993**, *3*, 97.

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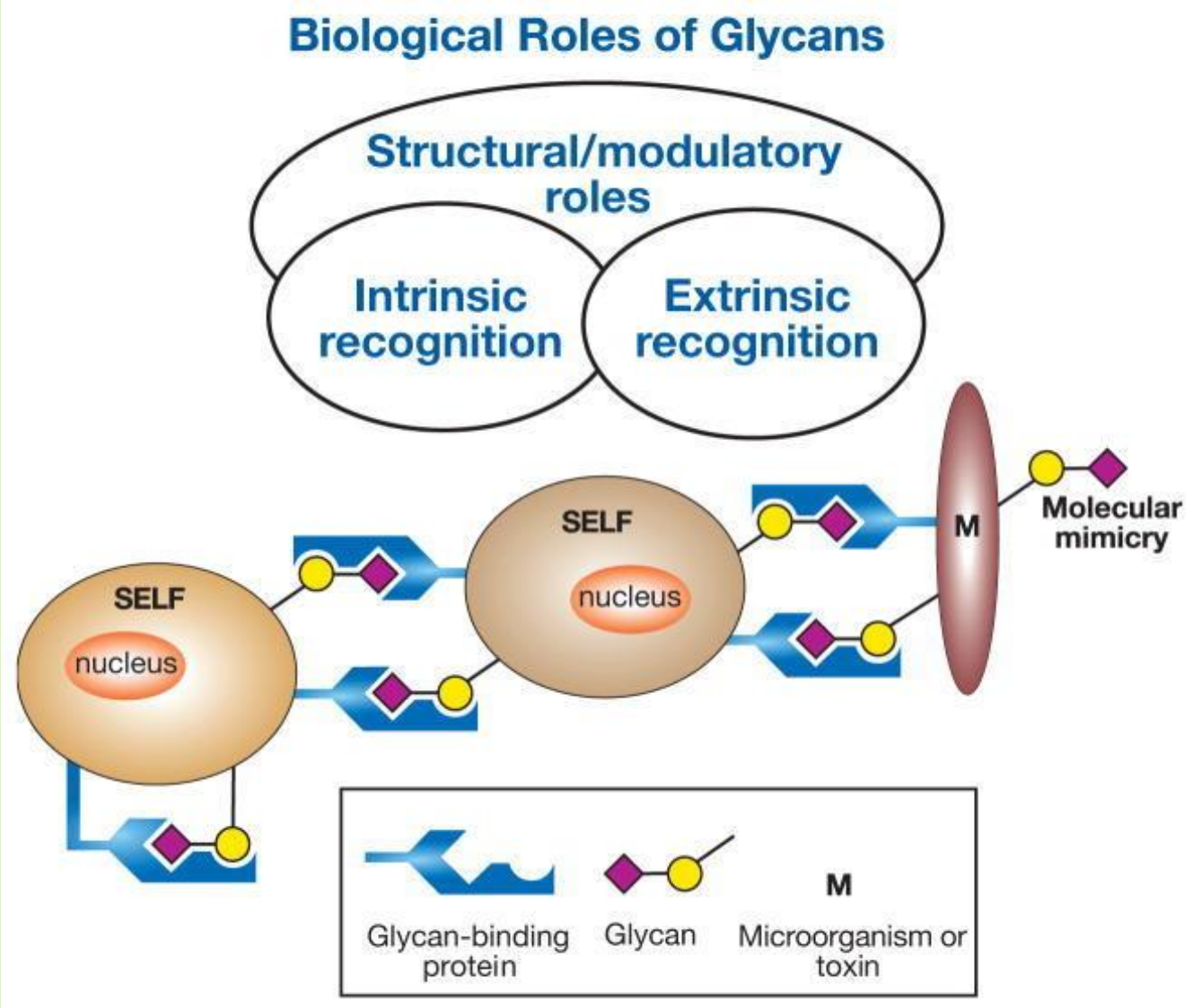
31. (b) A. Varki. Biological roles of glycans. *Glycobiology* **2017**, *27*, 3-49.

# Биологические функции гликанов






*Essentials of Glycobiology*
Second Edition

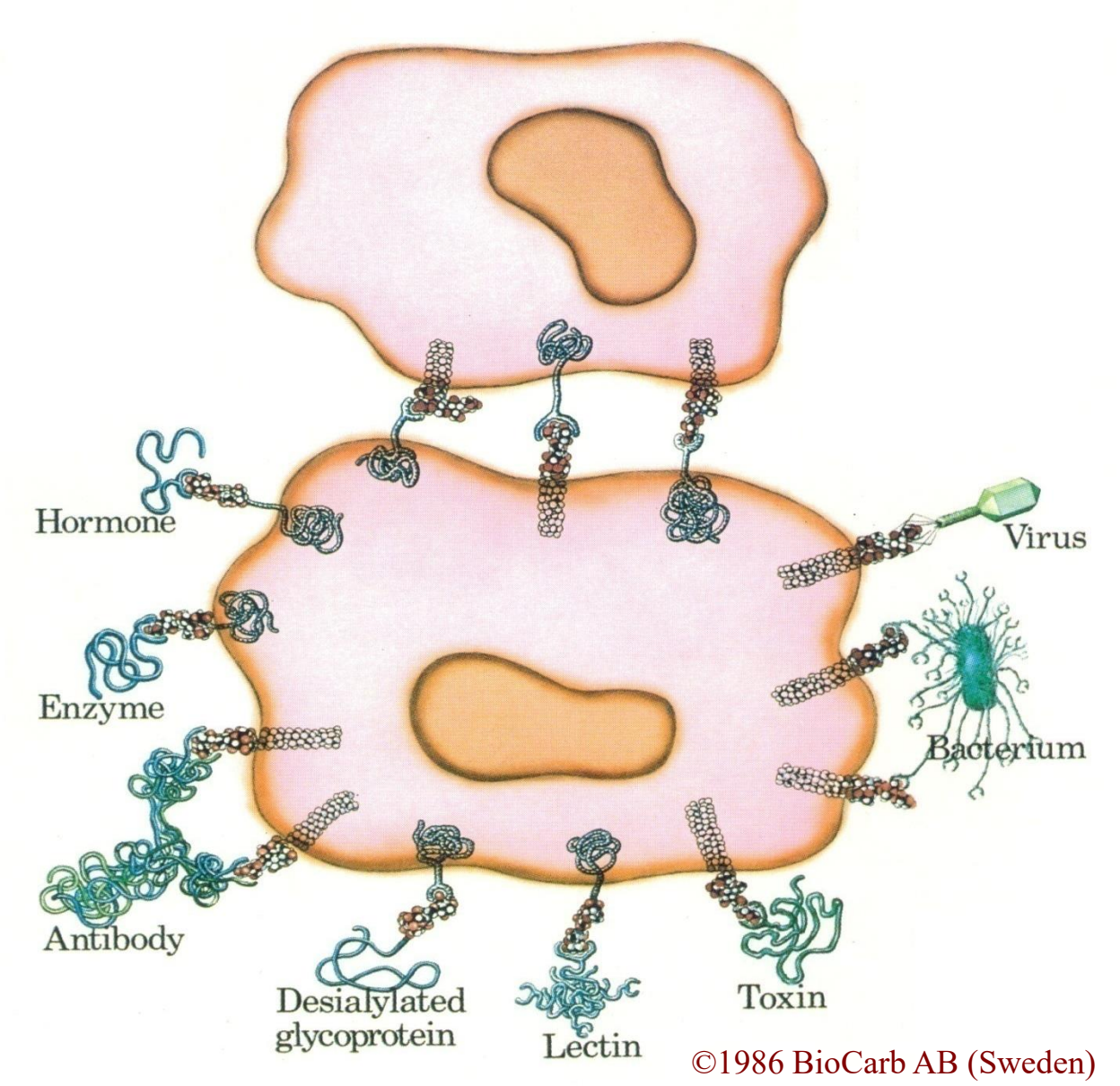
Chapter 6, Figure 1

# Углеводы поверхности клетки



Взаимодействие с:

- другими клетками организма:
  - межклеточное узнавание
  - адгезия и пролиферация клеток
- бактериями и вирусами
- токсинами и антителами
- лектинами
- ферментами углеводного метаболизма
- гормонами

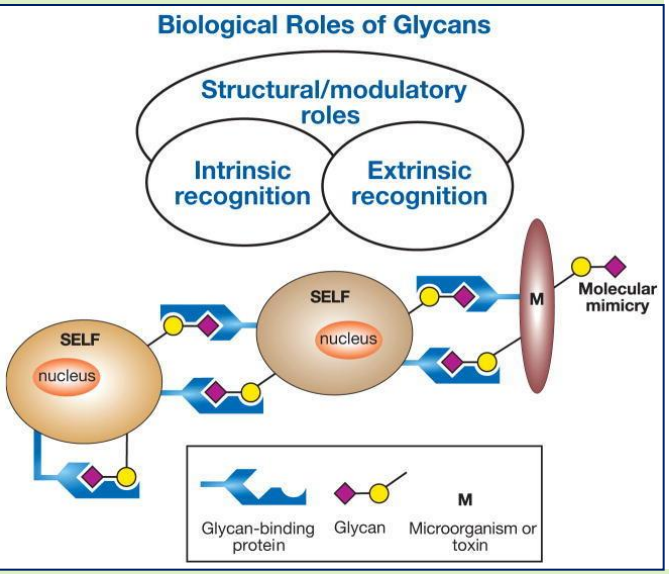


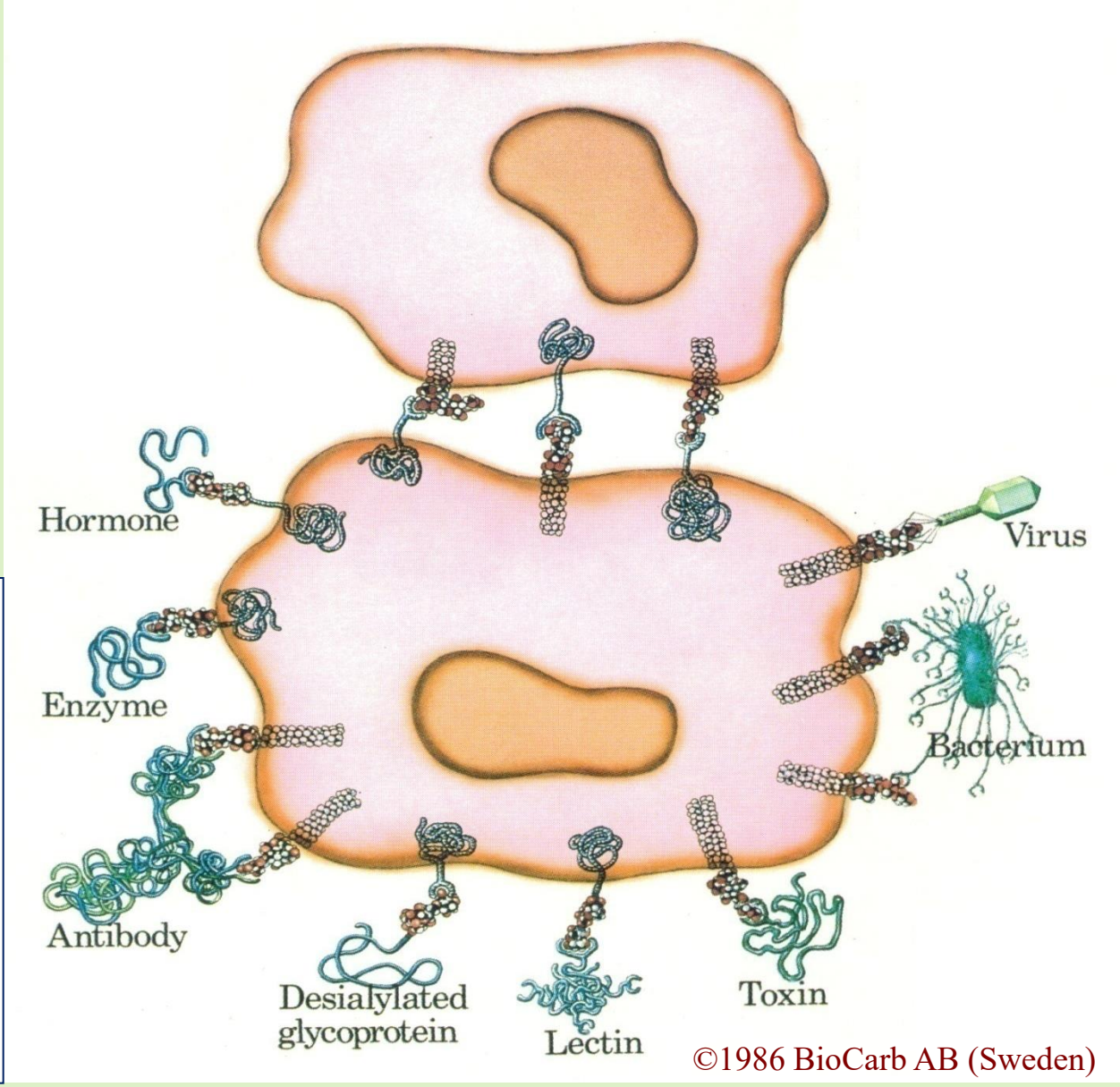
# Углевод-связывающие белки – необходимые участники



Гликобиология узучает не только гликом, но и соответствующий ему протеом:

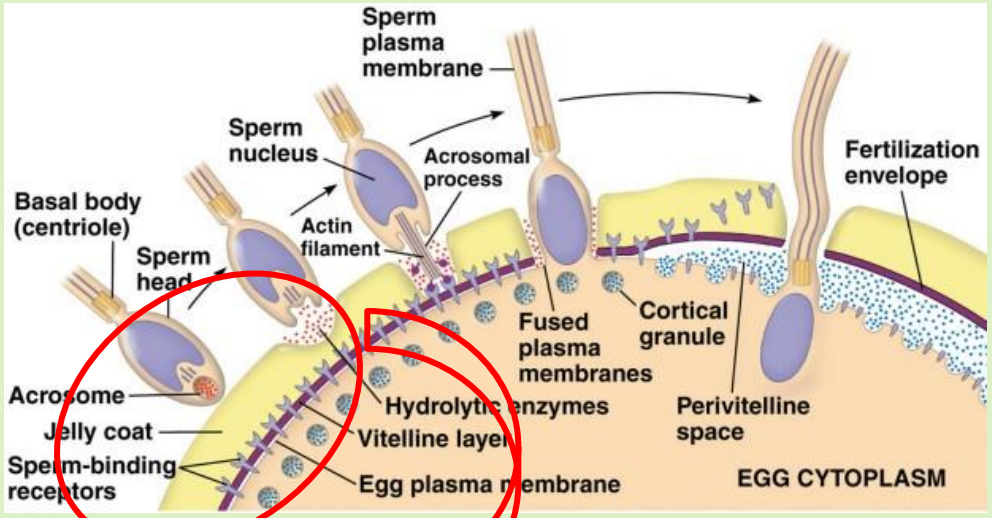
- лектины
- ферменты углеводного метаболизма
- антитела к углеводам

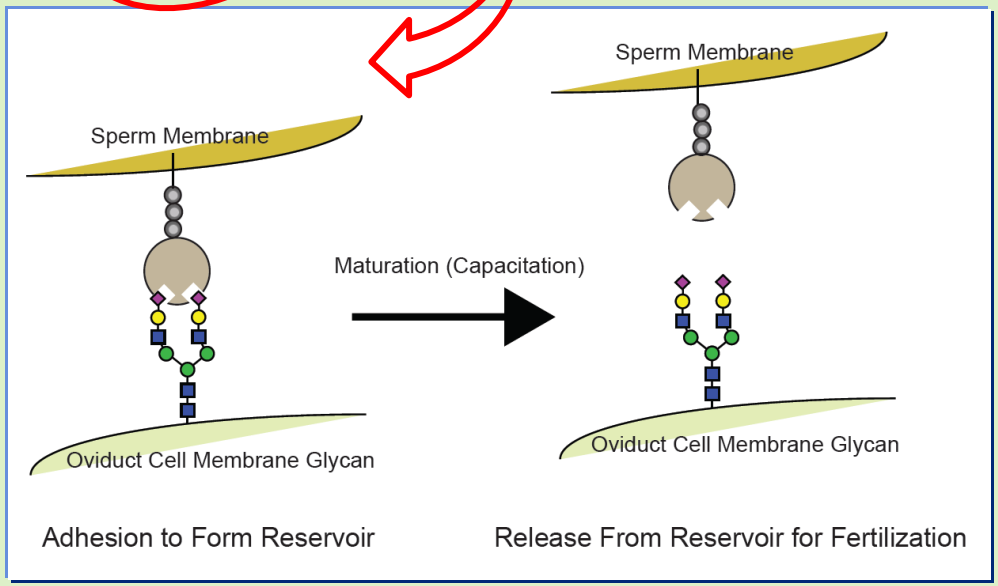


# Роль углеводов в процессе оплодотворения







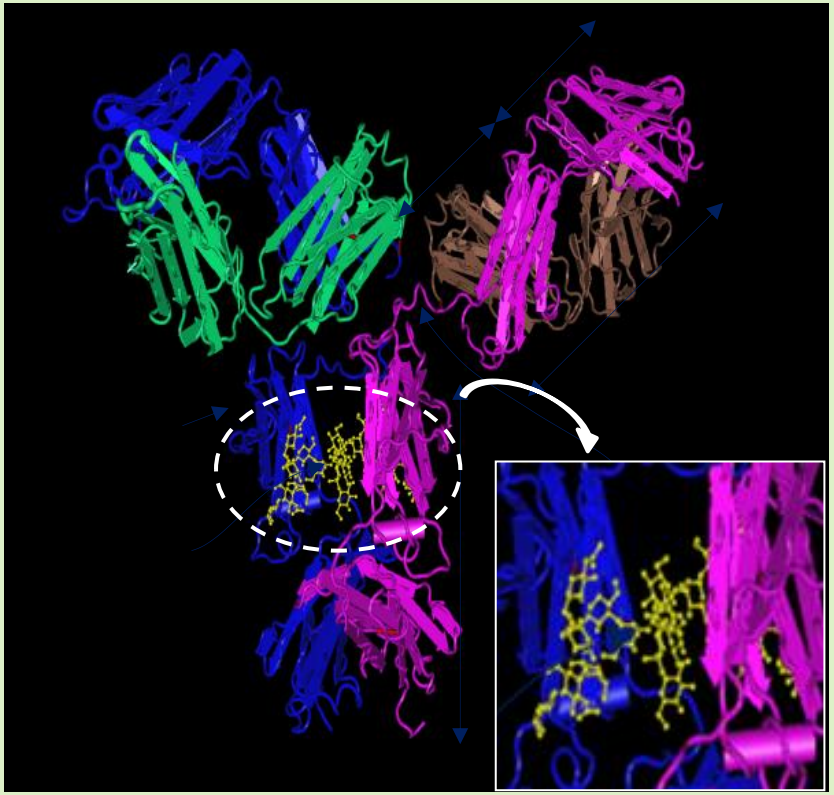

Слиянию сперматозоида с яйцеклеткой предшествует его связывание с гликанами на поверхности яйцеклетки и его активация (capacitation).

7. *Comprehensive Glycoscience. From Chemistry to System Biology*, 2007, Ch. 3.23.5.3, p. 505 (2217).

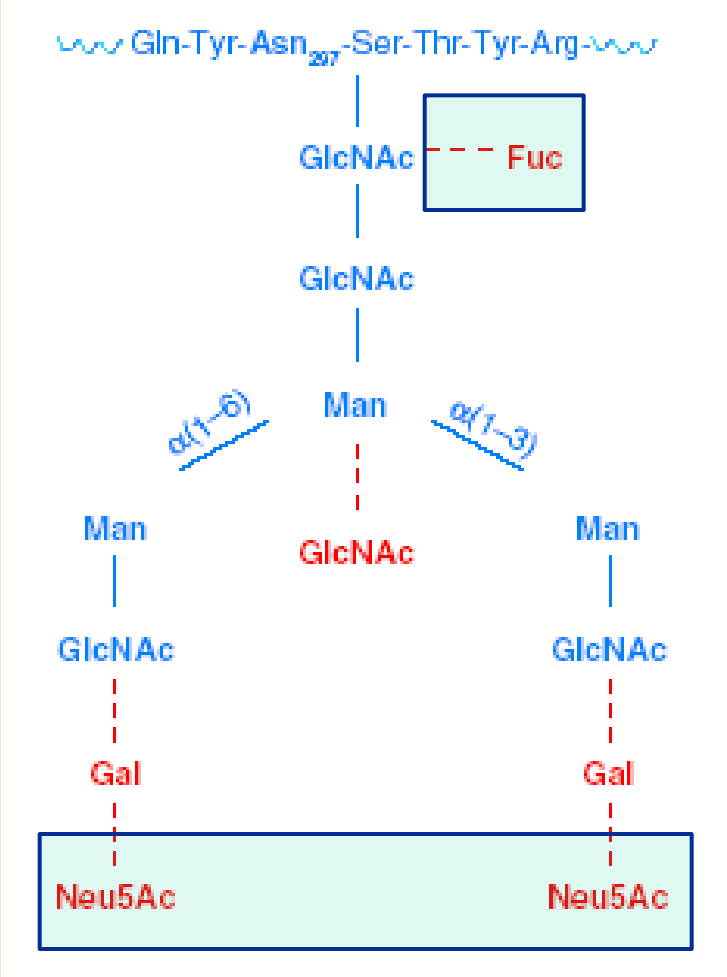
# N-цепи иммуноглобулина IgG человека



**Только вариант без фукозы взаимодействует с цитотоксичными клетками**



**Противовоспалительный эффект Neu5Ac-варианта**



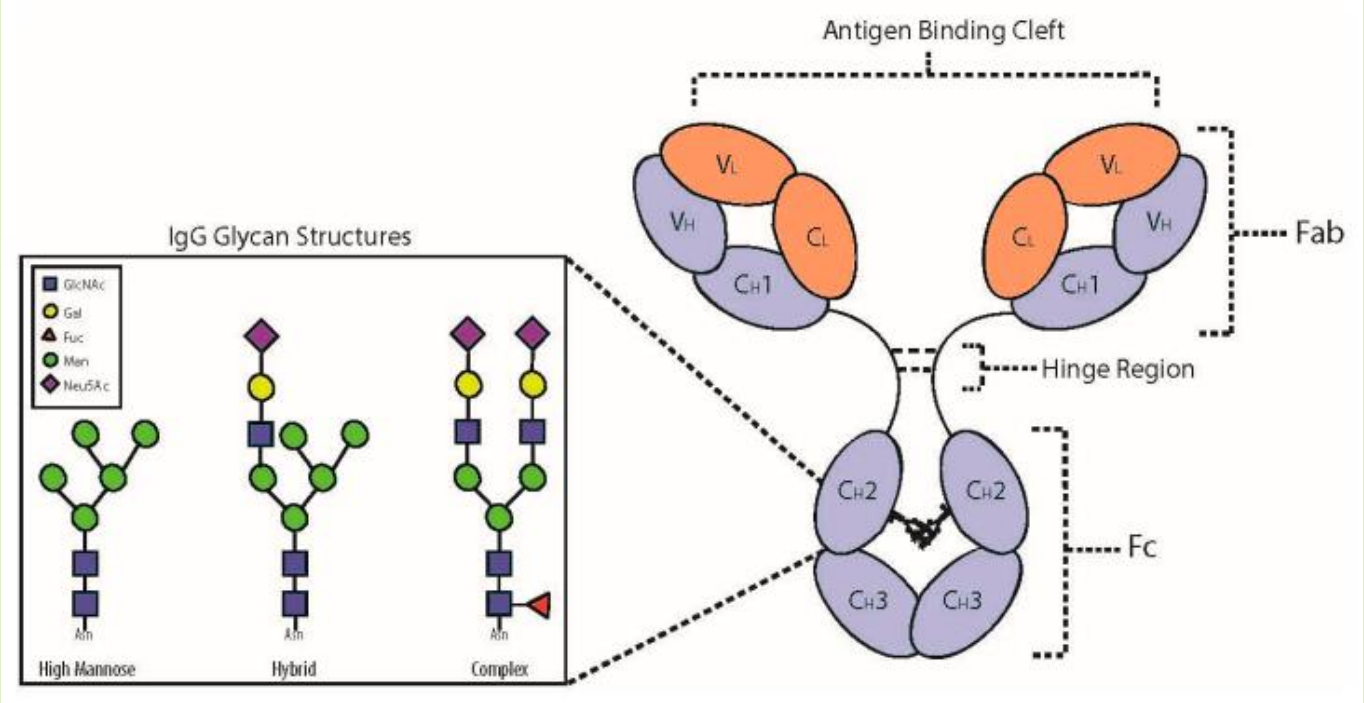
# N-цепи иммуноглобулина IgG человека: динамический маркер для предсказательной, профилактической и персонализированной медицины

International Journal of
*Molecular Sciences*

MDPI

*Review* *Int. J. Mol. Sci.* **2018**, *19*, 390; doi:10.3390/ijms19020390

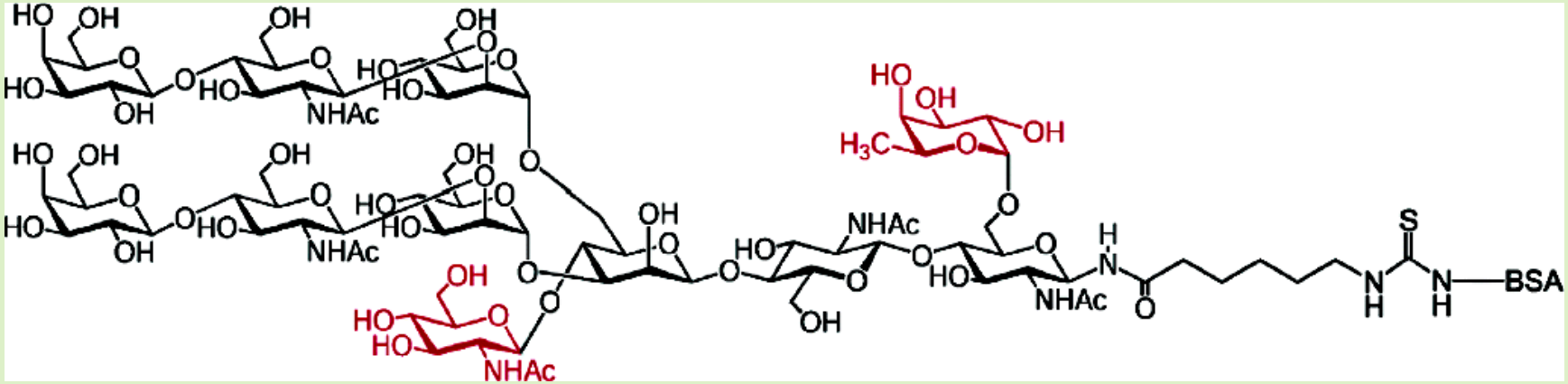
**Unravelling Immunoglobulin G Fc *N*-Glycosylation: A Dynamic Marker Potentiating Predictive, Preventive and Personalised Medicine**



# Неогликопротеины с различными N-гликанами



наличие / отсутствие остатка




наличие / отсутствие остатка

S. André *et al. Biochemistry* **2007**, *46*, 6984. DOI: 10.1021/bi7000467.

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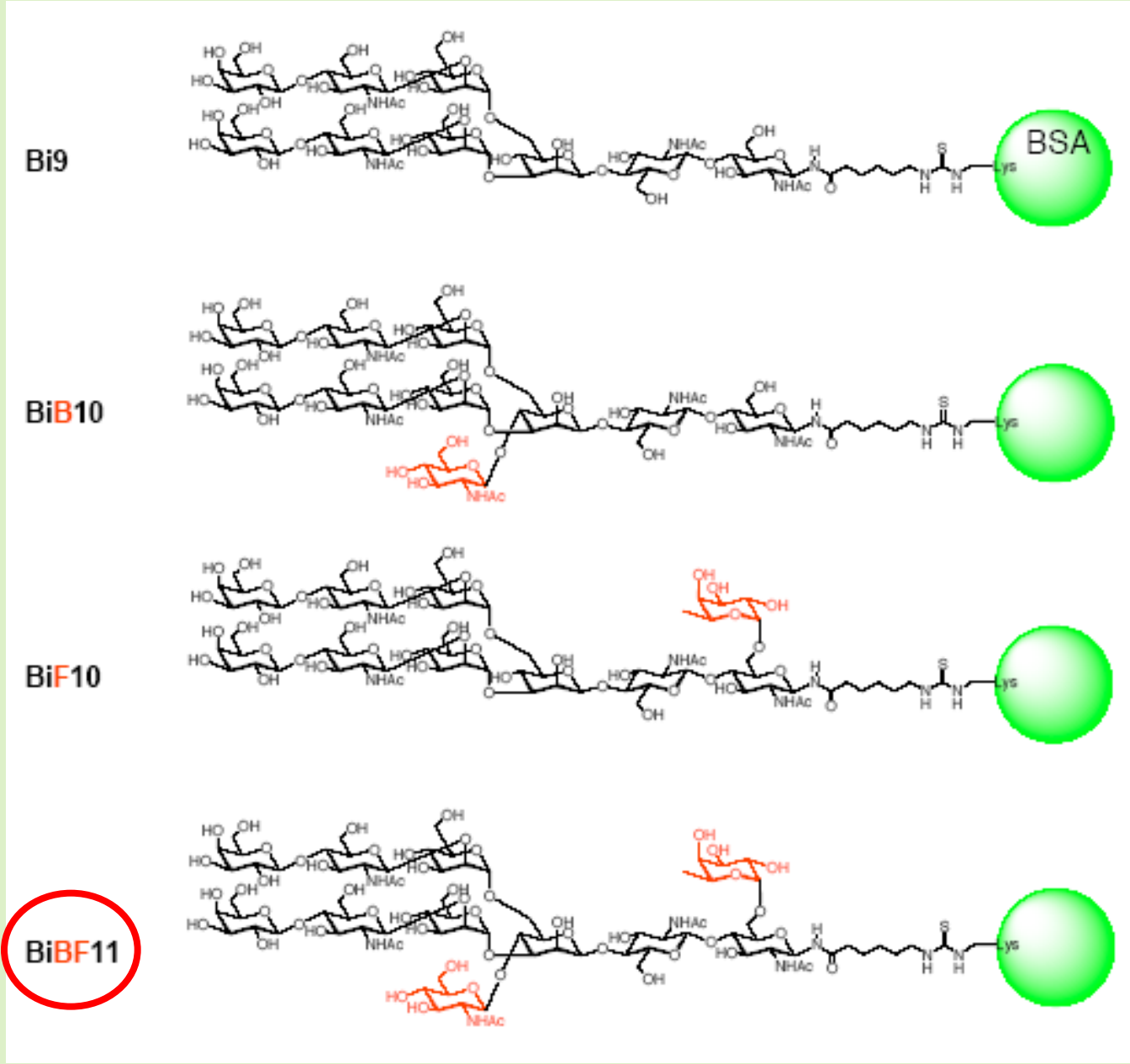
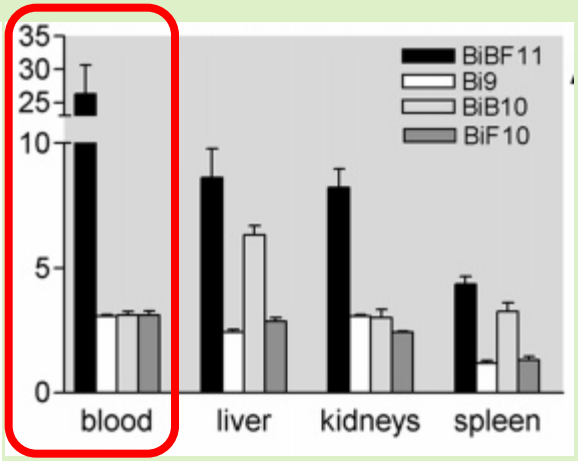


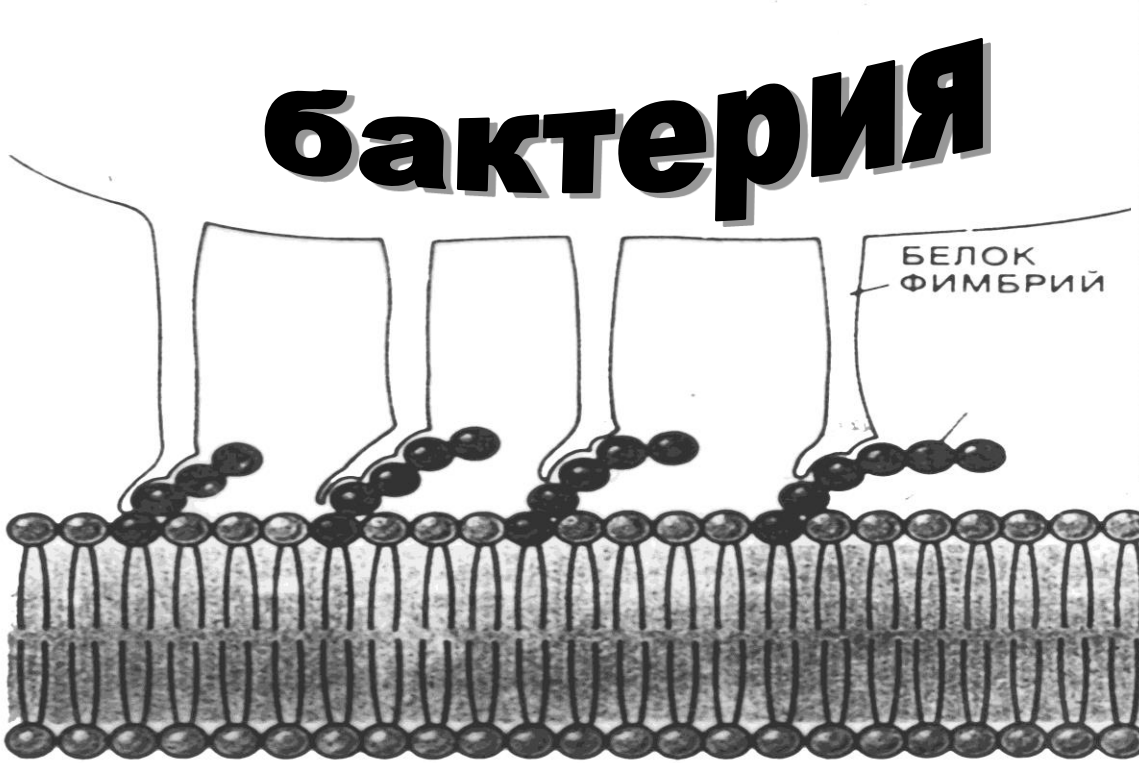



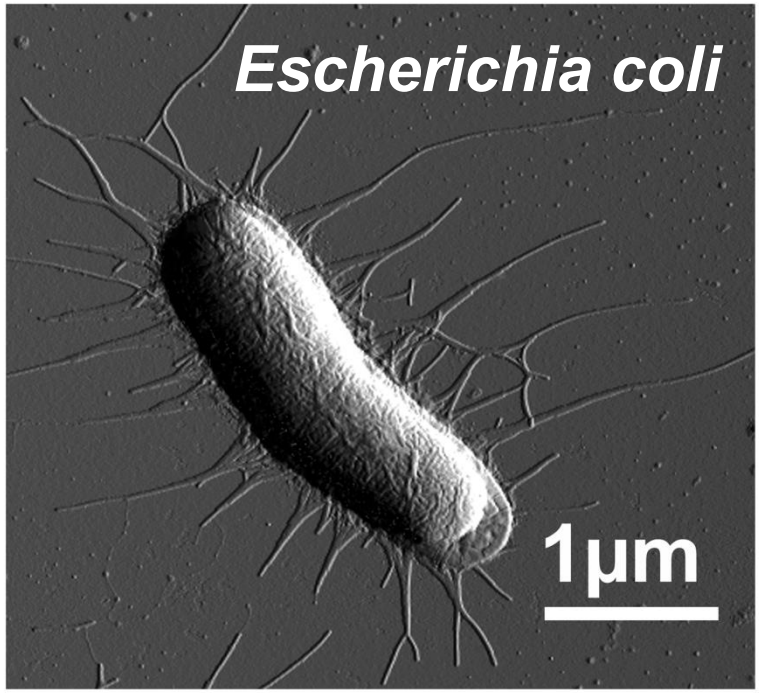

Судьба двухантенных цепей, незначительно различающихся структурой, различна.

# Узнавание углеводов клетки-хозяина лектином бактерии – первый этап адгезии



**P-Фимбрии – PapG:** галабиоза
**Фимбрии типа 1 – FimH:** манноза





7. *Comprehensive Glycoscience. From Chemistry to System Biology*, 2007, Ch. 3.28.3.1, p. 636 (2346).
22. *Glycoscience and Microbial Adhesion*. K. Lindhorst, S. Oscarson (Eds.), 2009, 186 pp.
61. A. Bernardi, *et al.* Multivalent glycoconjugates as anti-pathogenic agents. *Chem. Soc. Rev.* **2013**, *42*, 4709.

# Углеводы поверхности клеток – сайты присоединения бактериальных патогенов



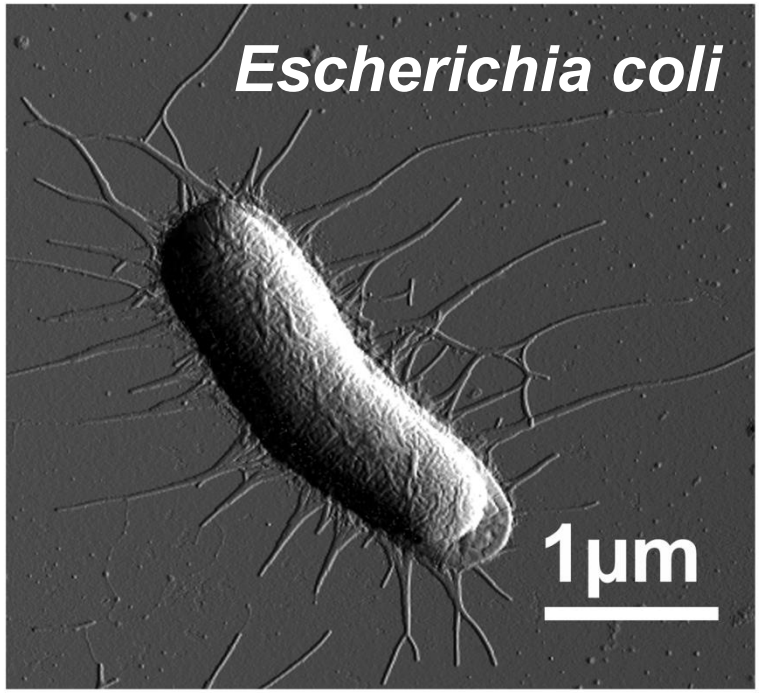
| Organism | Target tissue | Carbohydrate | Structure |
|---|---|---|---|
| *E. coli* Type 1 | Urinary | Manα3Manα6Man | GP |
| *E. coli* P | Urinary | Galα4Gal | GL |
| *E. coli* S | Neural | NeuAc (α2-3)Galβ3GalNAc | GL |
| *E. coli* CFA/1 | Intestinal | NeuAc (α2-8) | GP |
| *E. coli* F1C | Urinary | GalNAcβ4Galβ | GL |
| *E. coli* F17 | Urinary | GlcNAc | GP |
| *E. coli* K1 | Endothelial | GlcNAcβ4GlcNAc | GP |
| *E. coli* K99 | Intestinal | NeuAc(α2-3)Galβ4Glc | GL |
| *C. jejuni* | Intestinal | Fucα2GalβGlcNAc | GP |
| *H. pylori* NP 2005 | Stomach | NeuAc(α2-3)Galβ4GlcNAc | GP |
| | | Fucα2Galβ3(Fucα4)Gal | GP |
| *K. pneumoniae* | Respiratory | Man | GP |
| *N. gonorrhoea* | Genital | Galβ4Glc(NAc) | GL |
| *N. meningitidis* | Respiratory | [NeuAc(α2–3)] Galβ4GlcNAcβ3Galβ4GlcNAc | GL |
| *P. aeruginosa* | Respiratory | L-Fuc | GP |
| | Respiratory | Galβ3Glc(NAc)β3Galβ4Glc | GL |
| *S. typhimurium* | Intestinal | Man | GP |
| *S. pneumoniae* | Respiratory | NeuAcα2-3Galβ1-4GlcNAcβ1-3Galβ1-4Glc | GL |
| *S. suis* | Respiratory | Galα4Galβ4Glc | GL |

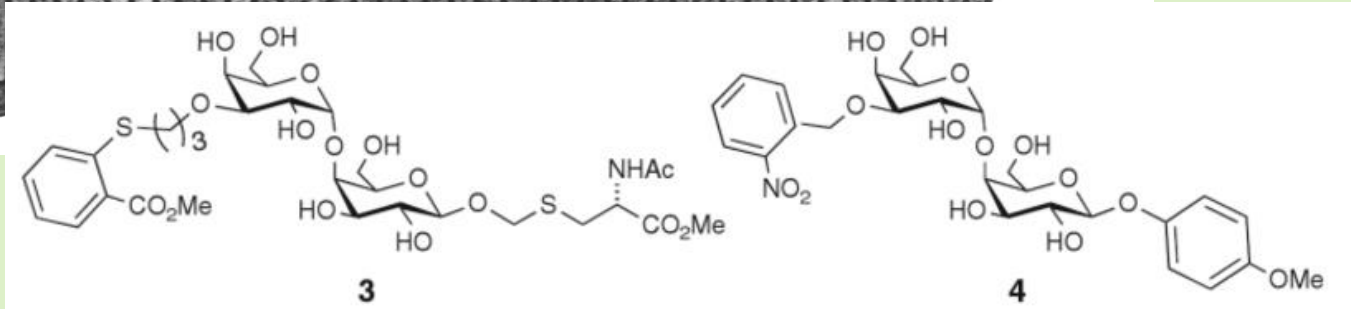
GP = glycoprotein, GL = glycolipids

# Ингибирование связывания лектина бактерии с углеводами клетки – антиадгезионная терапия



**P-Фимбрии – PapG:** галабиоза
**Фимбрии типа 1 – FimH:** манноза



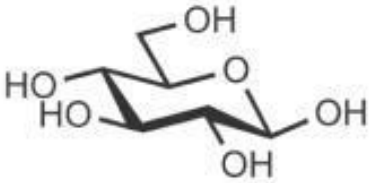
# Примеры «неспецифических» функций гликанов



| гликомолекула | функция |
|---|---|
| GPI-якорь гликопротеинов | конструкционный материал |
| O- и N-цепи гликопротеинов<br>Пример: муцины ЖКТ | защита белка от протеолиза |
| O- и N-цепи гликопротеинов<br>Примеры: IgG | стабилизация оптимальной конформации белка |
| O- и N-цепи гликопротеинов<br>Примеры: липопротеины | гидрофилизация клетки, увеличение растворимости белка |
| O- и N-цепи гликопротеинов<br>Пример: рекомбинантные ГП | защита от действия собственного иммунитета |
| Сиалированные и сульфатированные цепи гликопротеинов | поддержка локального значения pH; развернутая конформация гликопротеинов |
| | |
| | |
| Муцины, протеогликаны | увеличение вязкости среды, барьерная функция |
| O- и N-цепи гликопротеинов | секреция |
| | |
| | |

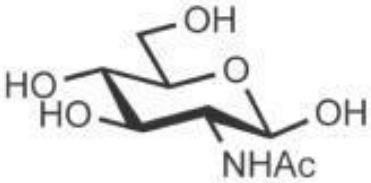
# Типичные моносахариды углеводных цепей гликопротеинов (ГП) и гликосфинголипидов (ГЛ)





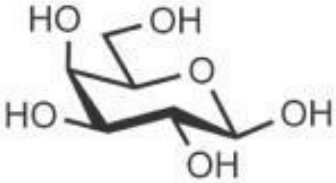

D-Glucose

**Glc**



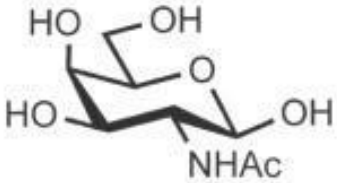

*N*-Acetyl-D-glucosamine

**GlcNAc**



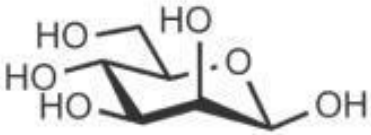

D-Galactose

**Gal**



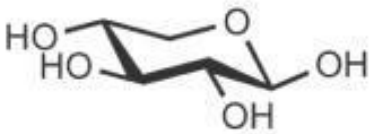

*N*-Acetyl-D-galactosamine

**GalNAc**



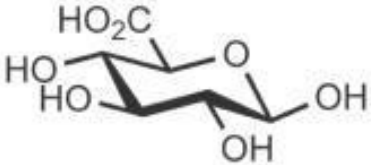

D-Mannose

**Man**



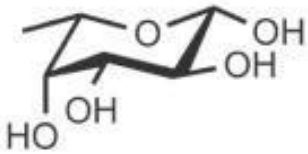

D-Xylose

**Xyl**



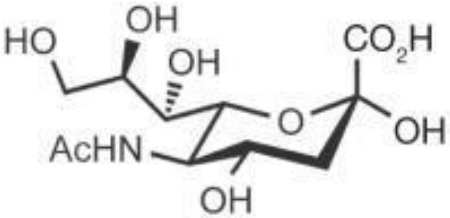

D-Glucuronic acid

**GlcA**




L-Fucose

**L-Fuc**



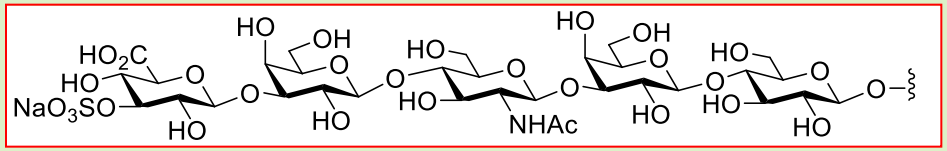

*N*-Acetylneuraminic acid

**Neu5Ac**

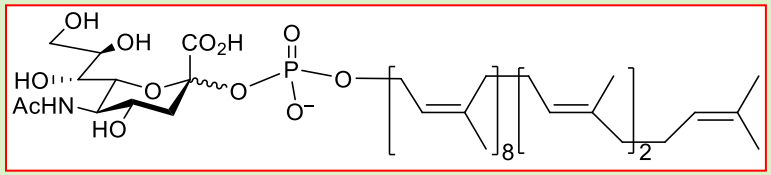
# Модификации по гидроксильной и амино группам



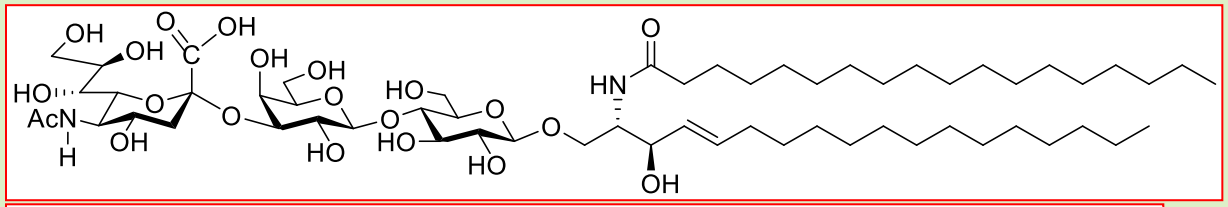
## Пентасахарид антигена HNK-1

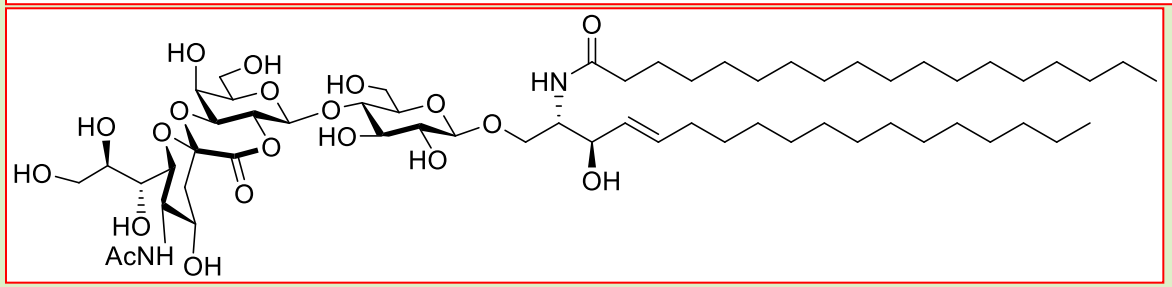



## Сиалил(полипренил)фосфат

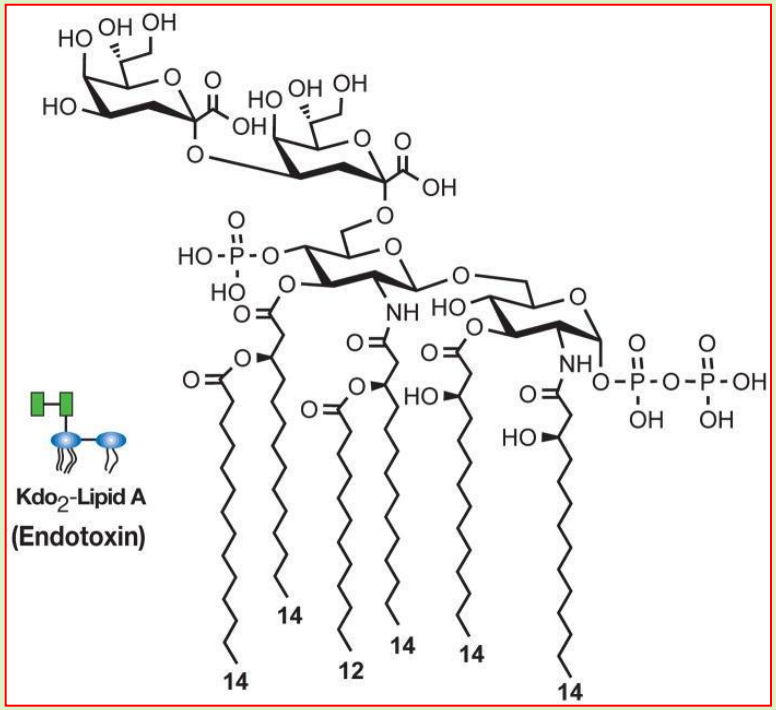



## Ганглиозид $G_{M3}$: кислота и лактон




## Эндотоксин *E. coli*




сульфат

фосфат

ацетил (ацил)

лактон

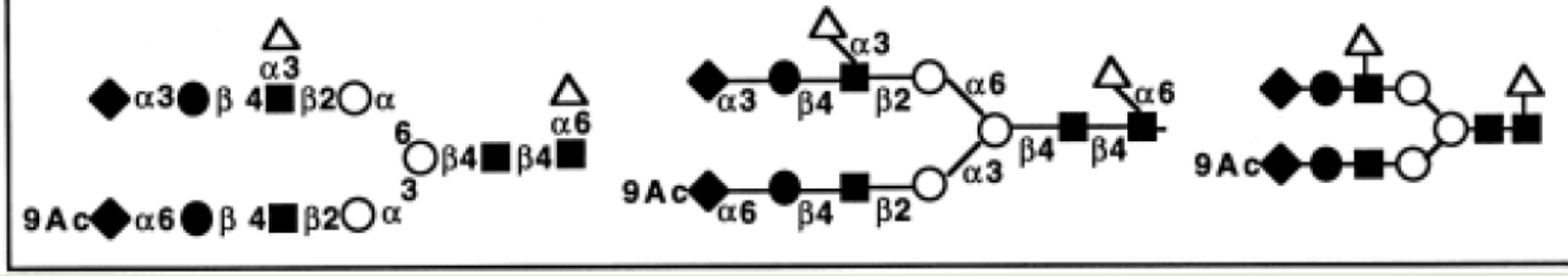
# Символы моносахаридов и типов связей (старая система)



▲ = Glucose (Glc)
○ = Mannose (Man)
● = Galactose (Gal)
■ = N-acetylglucosamine (GlcNAc)
□ = N-acetylgalactosamine (GalNAc)
◪ = N-acetylhexosamine, unspecified (HexNAc)
◐ Hexose, unspecified (Hex)
△ = Fucose (Fuc)
▽ = Xylose (Xyl)
◆ = Sialic acid, unspecified (Sia)
◆ = Glucuronic acid (GlcA)
◆ = Iduronic acid (IdoA)
◇ =Uronic acid, unspecified (HexA)

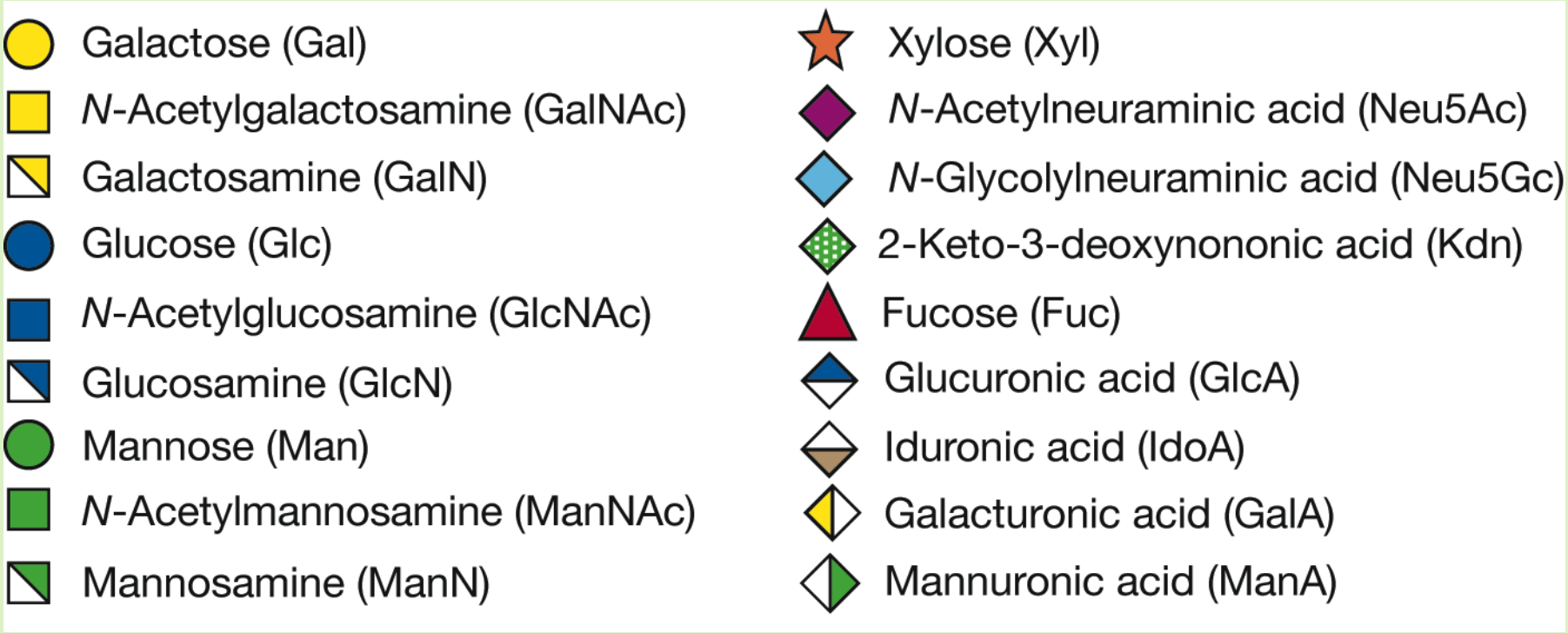
Ac = O-acetyl  P = Phosphate  S = O-Sulfate  NS = N-Sulfate  $NH_2$ = free amino group

***EXAMPLES OF SYMBOLIC REPRESENTATIONS USED IN THIS BOOK***



# Символы моносахаридов (новая система)





# Символы типов связей в олигосахаридах



**FULL REPRESENTATION**

9-O-Ac-Neu5Ac*p*α2-3Gal*p*β1-4GlcNAc*p*β1-2Man*p*α1 Fuc*p*α1
6 6
Man*p*β1-4GlcNAc*p*β1-4GlcNAc*p*β1-Asn
3
3-O-$SO_3$Gal*p*β1-4GlcNAc*p*β1-2Man*p*α1

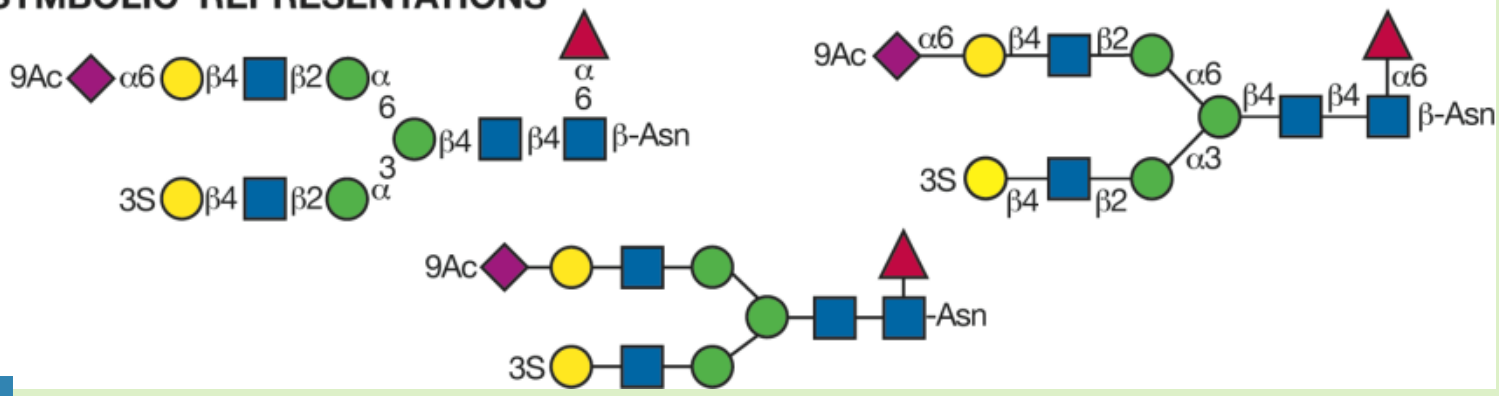
**MODIFIED REPRESENTATION**

9Ac-Neu5Acα2-3Galβ1-4GlcNAcβ1-2Manα1 Fucα1
6 6
Manβ1-4GlcNAcβ1-4GlcNAcβ1-Asn
3
3S-Galβ1-4GlcNAcβ1-2Manα1

**SIMPLIFIED REPRESENTATION**

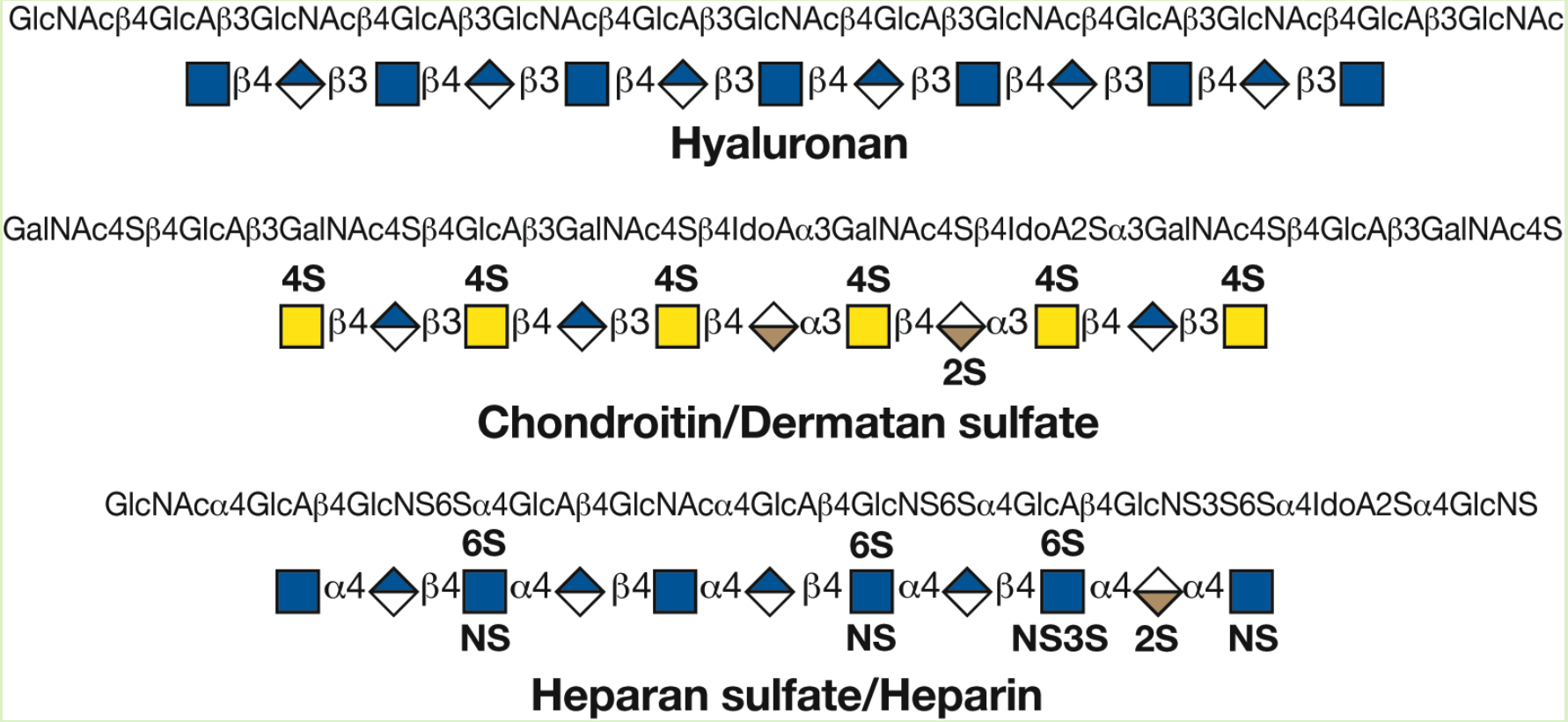
9-O-Ac-Neu5Acα3Galβ4GlcNAcβ2Manα Fucα
6 6
Manβ4GlcNAcβ4GlcNAcβ-Asn
3
3-O-$SO_3$Galβ4GlcNAcβ2Manα

**SYMBOLIC REPRESENTATIONS**



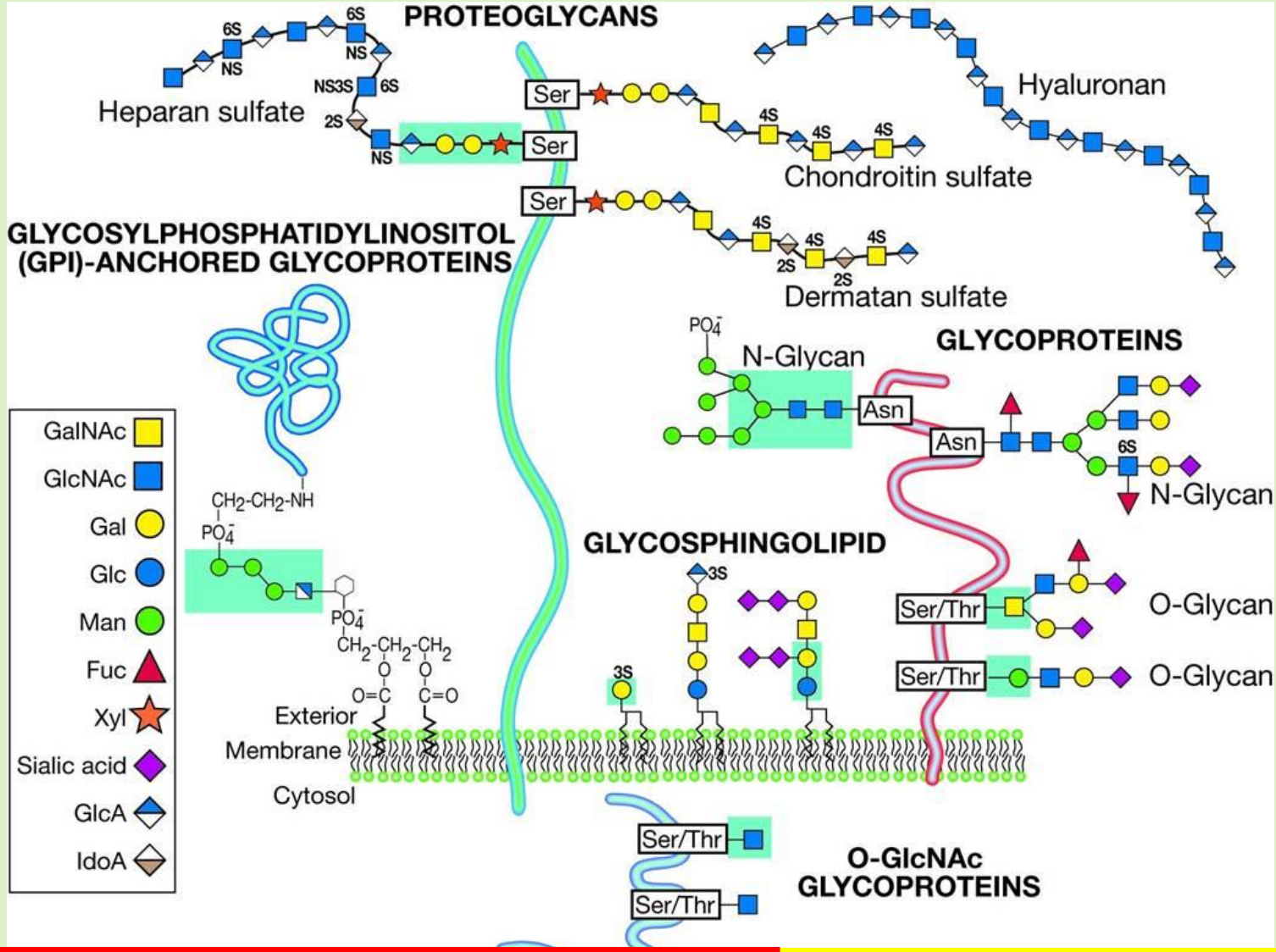
# Символы типов связей в полисахаридах





# Основные классы гликанов животных







10. *The Sugar Code. Fundamentals of glycosciences,* 2009, 569 pp.
49. H.-J. Gabius, *et al*. *Trends Biochem. Sci*. **2011**, *36*, 298.
62. D. Solísa, *et al. Biochim. Biophys. Acta* **2015**, *1850*, 186.


**The Sugar Code**
**Гликокод**

# Лекция 1

Введение в гликобиологию

Стереохимия моно- и олигосахаридов


7. *Comprehensive Glycoscience. From Chemistry to System Biology,* Kamerling, J. *et al*. (Eds.), 2007, Ch. 1.01, p. 1-16.
13. Н. К. Кочетков и др. *Химия углеводов,* 1967, с. 17-31.
18. М.А. Маслов, Н.Г. Морозова. *Основы химии углеводов. Часть 1.* 2005, с. 4-10.
3. Ю. С. Шабаров и др., *Моно- и дисахариды*, 2010, *Часть* I, с. 24-43, *Часть II*, с. 39-50.

# Строение моносахаридов

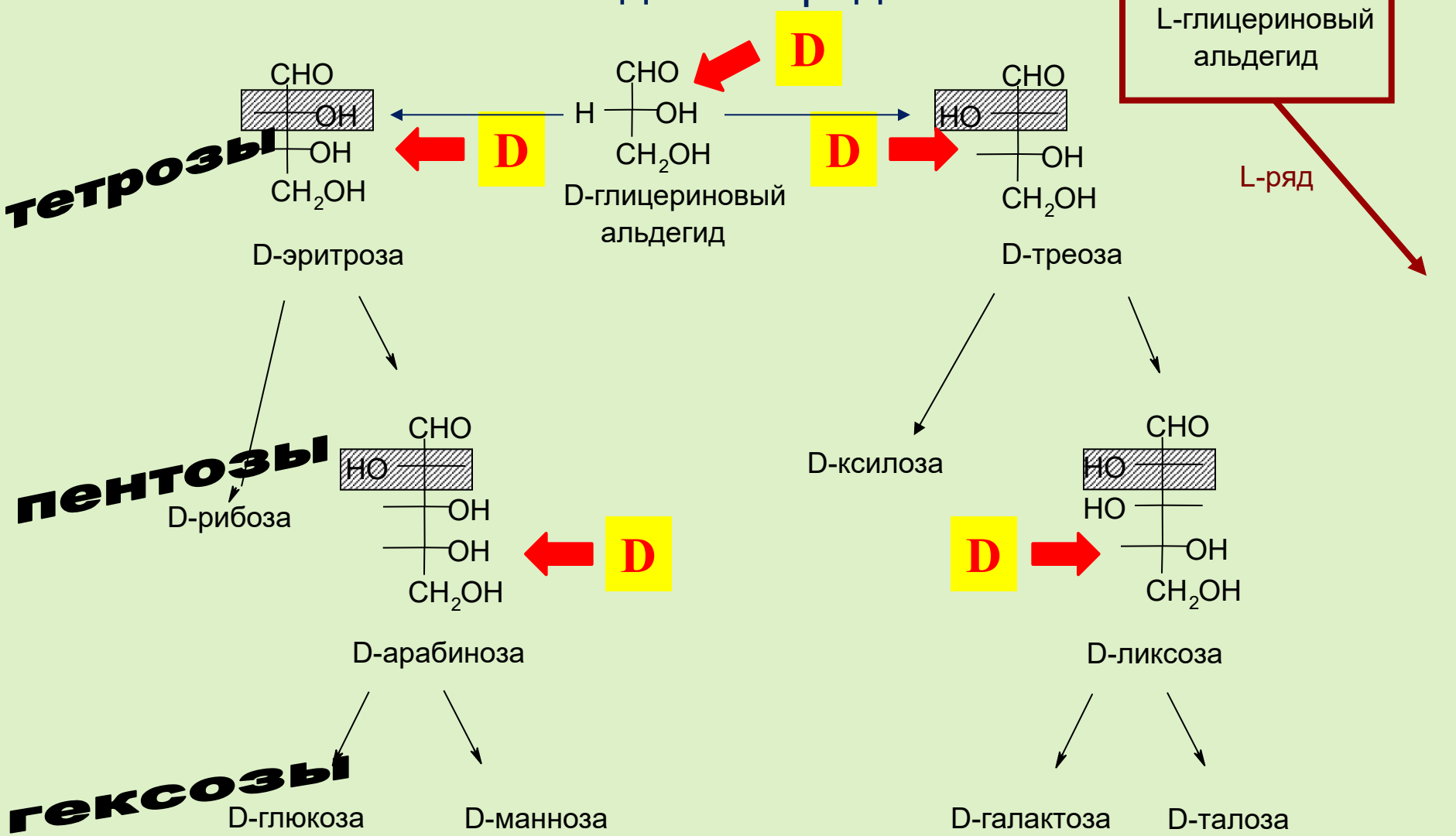


**УГЛЕ-ВОД**
**CARBO-HYDRATE**

$C_n H_{2n} O_n$ или $C_n(H_2O)_n$

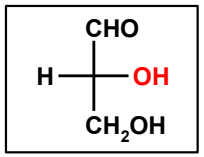
$n = 3–9$

альдозы D-ряда

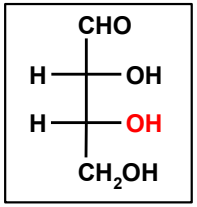


# Альдозы D-ряда

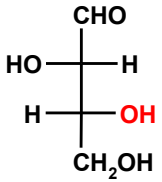





D-глицериновый альдегид




D-эритроза

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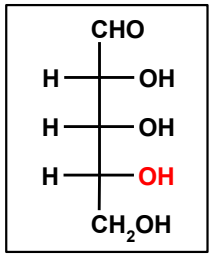


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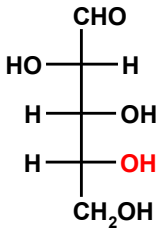


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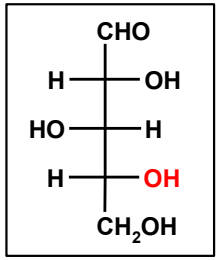


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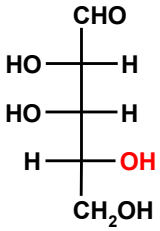


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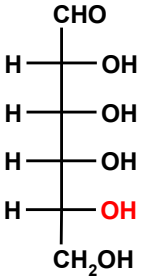


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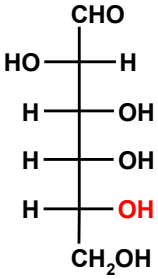


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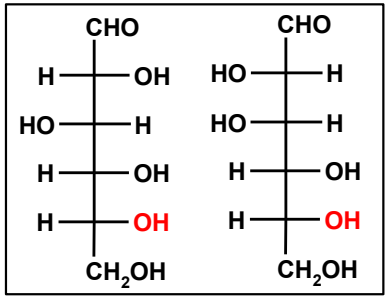
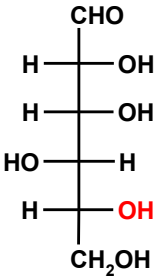



D-глюкоза D-манноза

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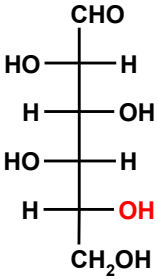


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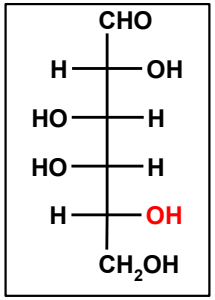


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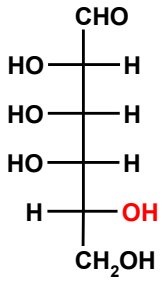
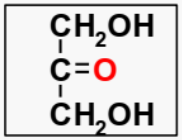



D-талоза

# Кетозы D-ряда



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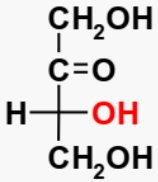


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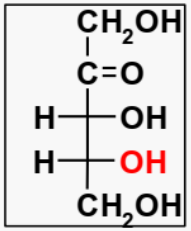
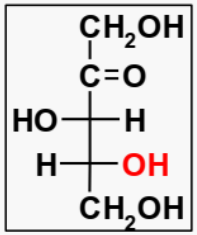
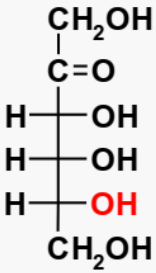



D-рибулоза




D-ксилулоза

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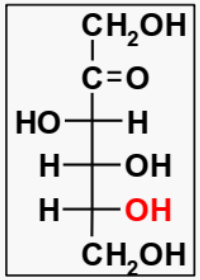


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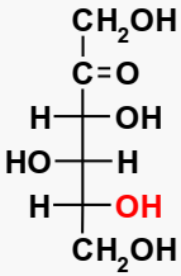


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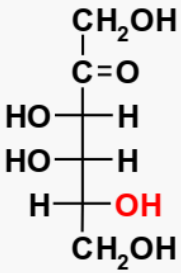
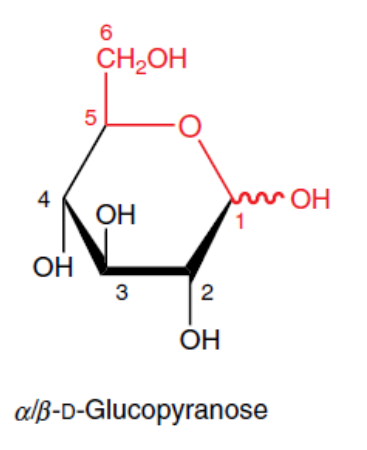



D-тагатоза

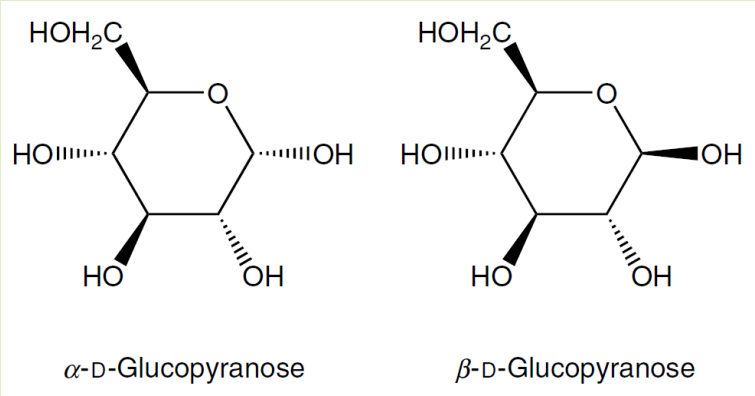
# Способы изображения моносахаридов: Glc



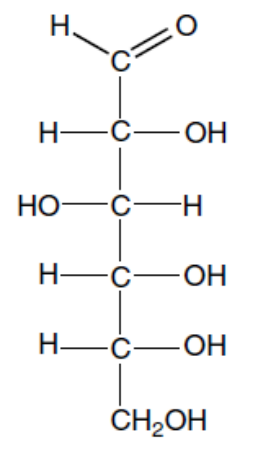
- Хеуорс



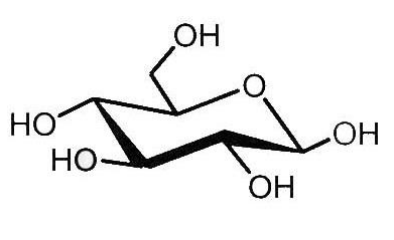

- Миллс




- Фишер

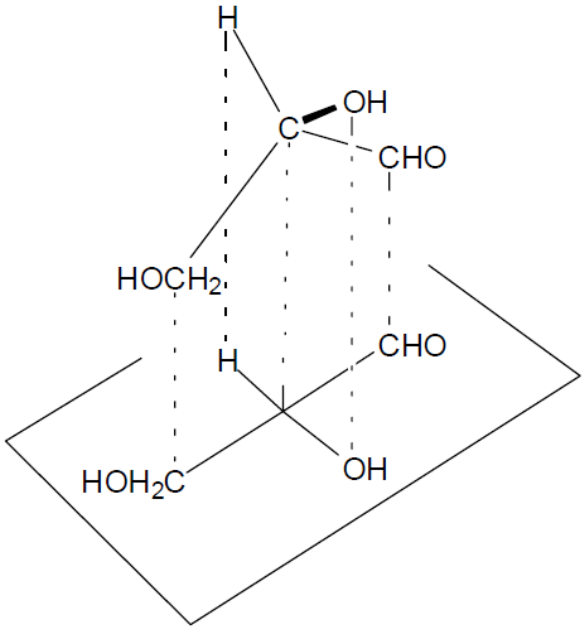


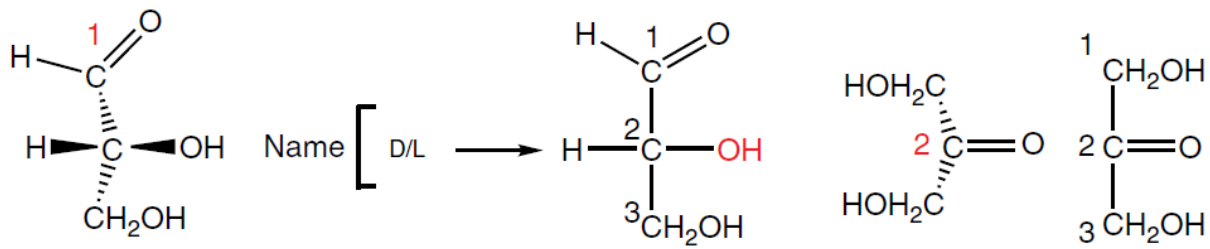

- Конформационный способ («перспективные» формулы)



# Проекция Фишера: простейшие альдоза/кетоза

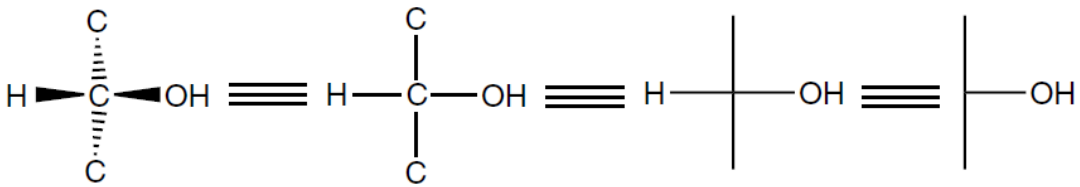


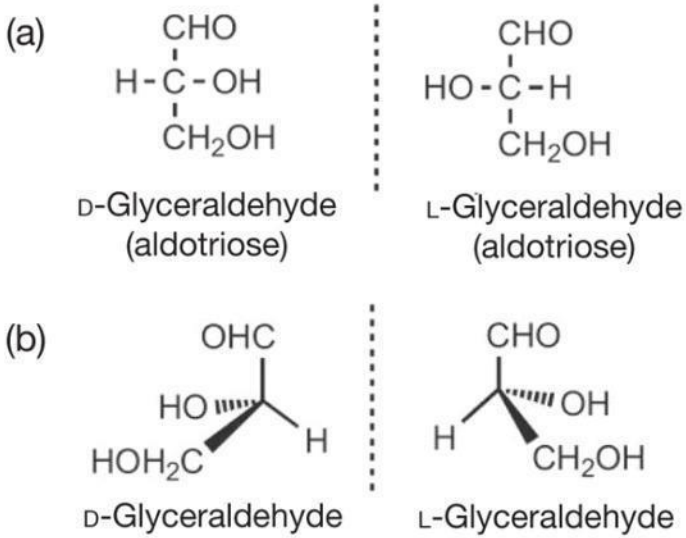



D-Glyceraldehyde

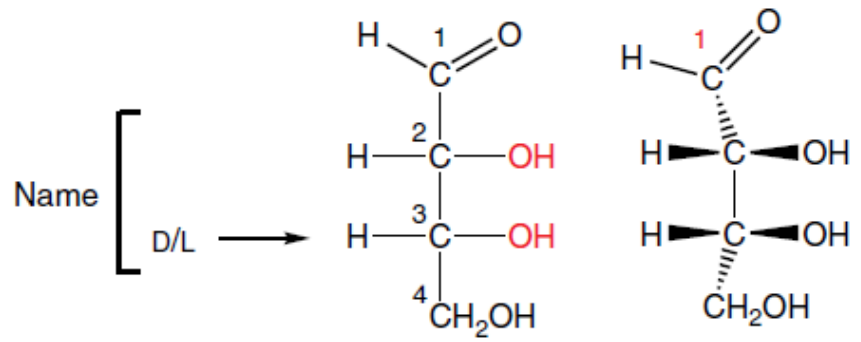
1,3-Dihydroxy-acetone



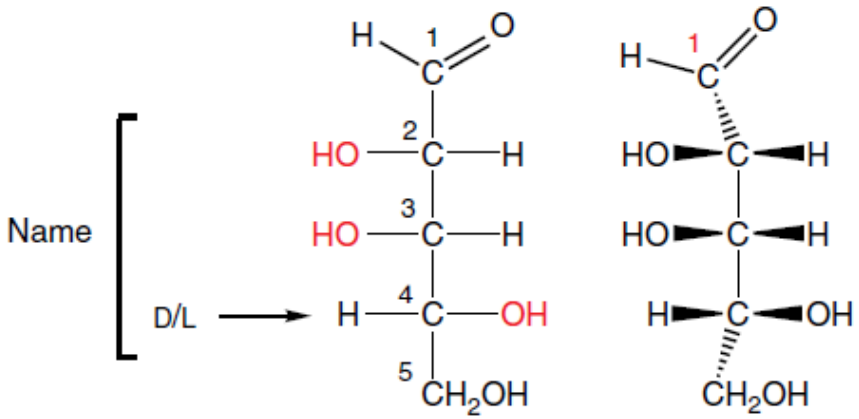



# Проекция Фишера: тетроза, пентоза и гексозы

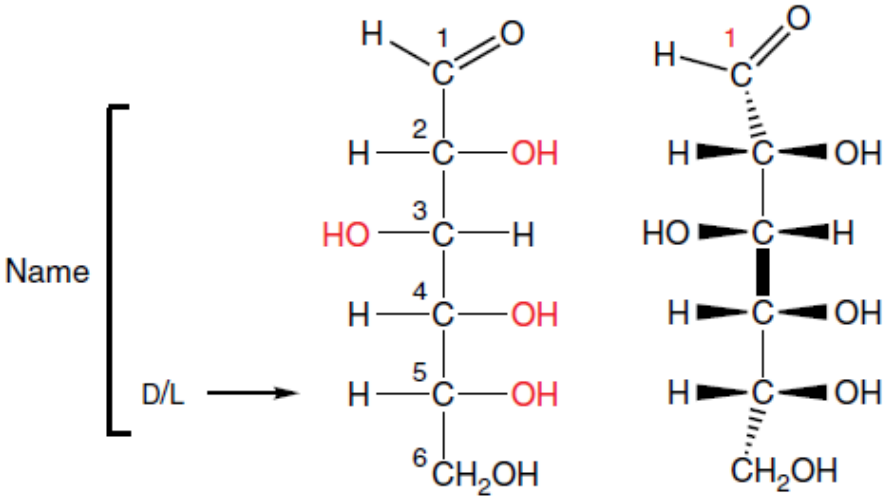




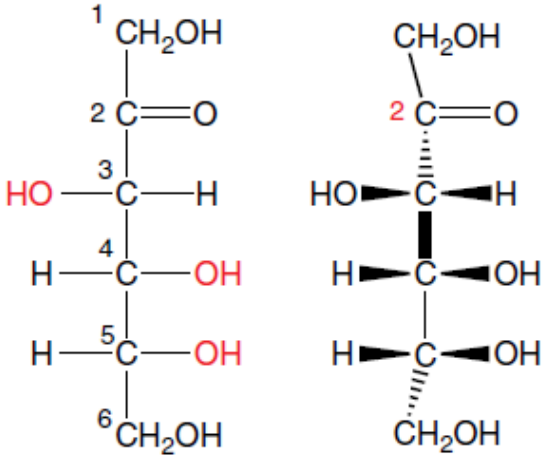

D-Erythrose




D-Lyxose



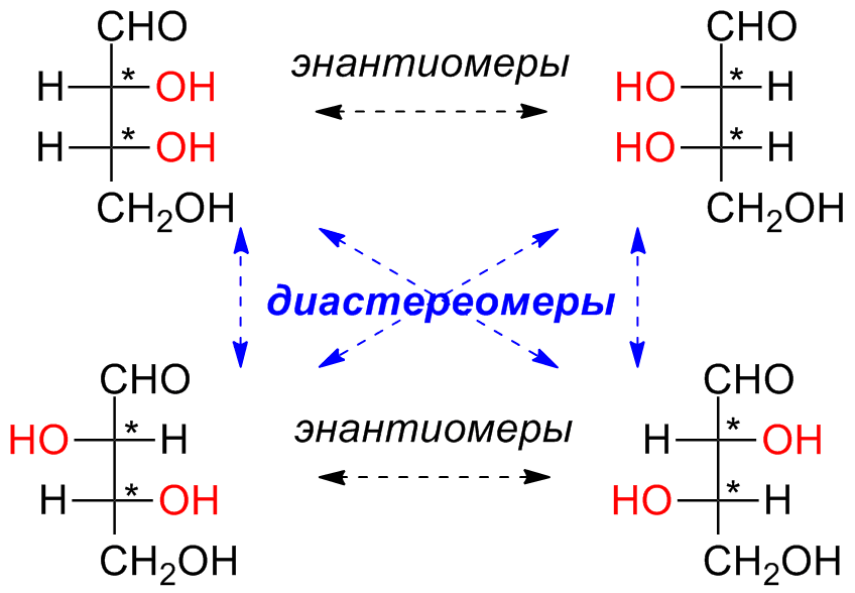

D-Glucose

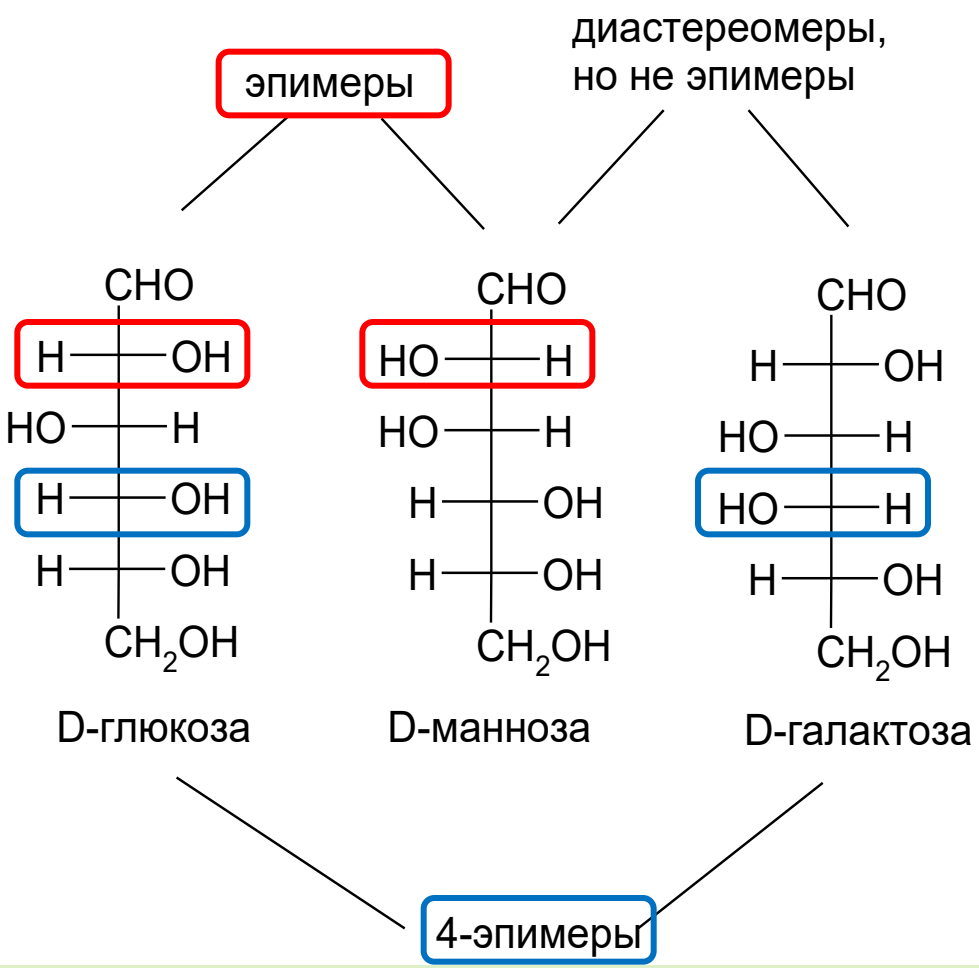



D-Fructose

# Энантиомеры, диастереомеры и эпимеры

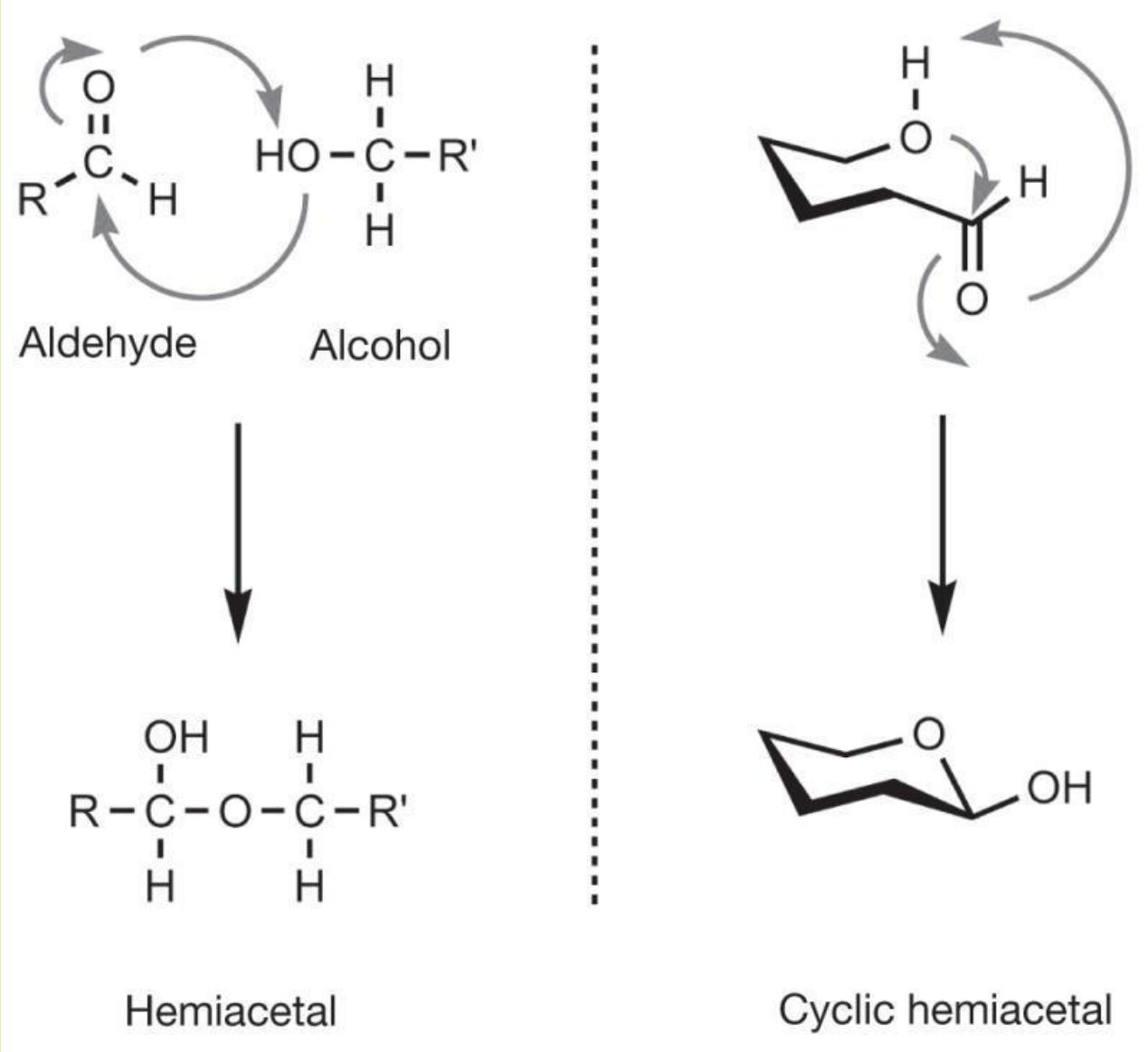




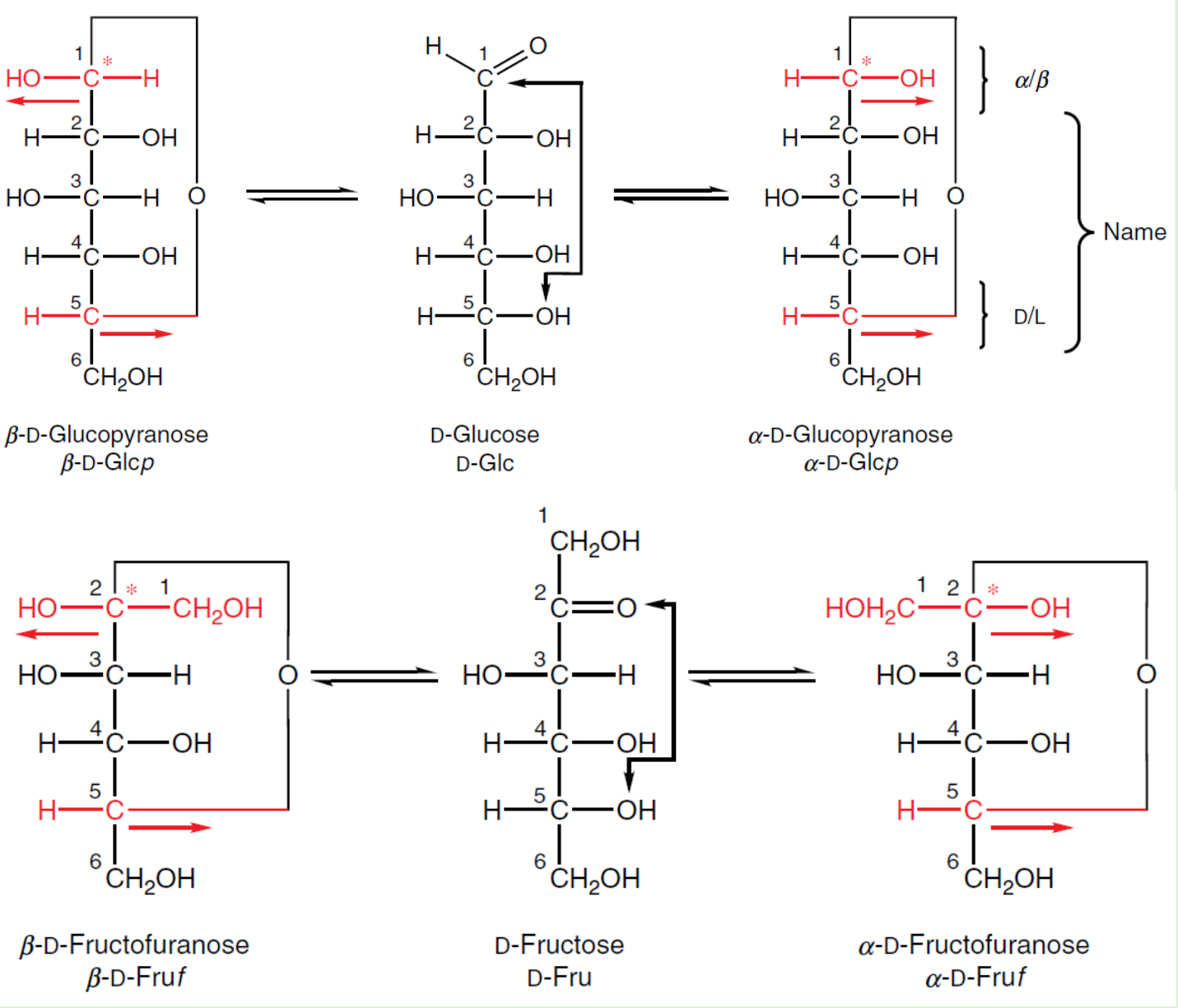
# Полуацетали: циклические формы сахаров



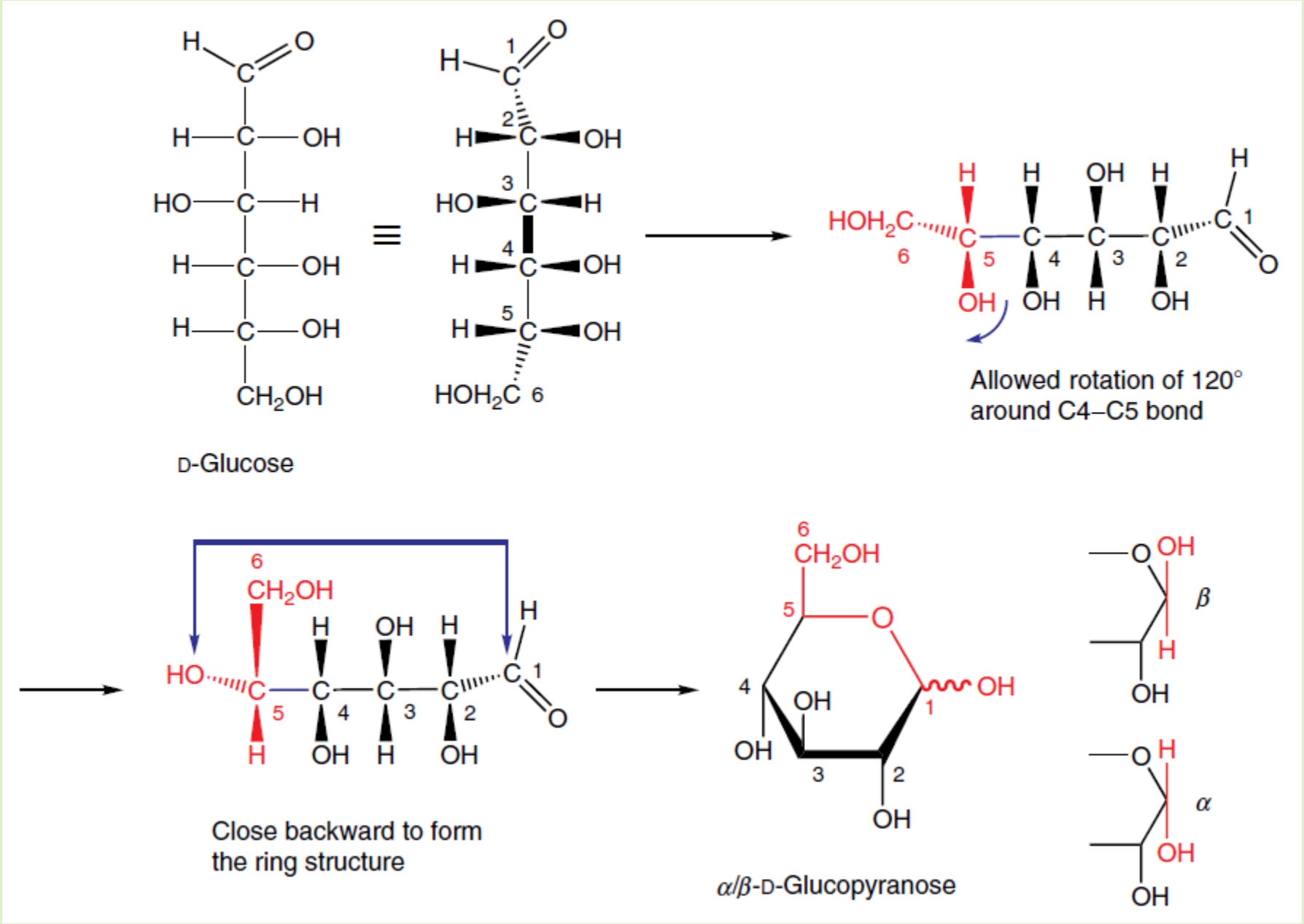


# Проекция Фишера: циклические формы (α и β)

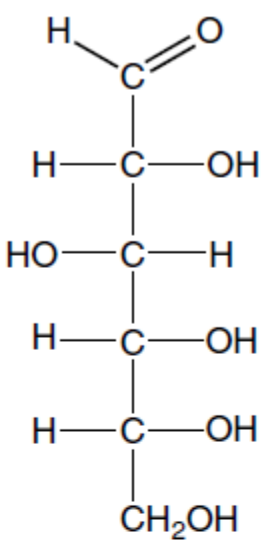




# От проекции Фишера к проекции Хеуорса: D-Glc*p* 42

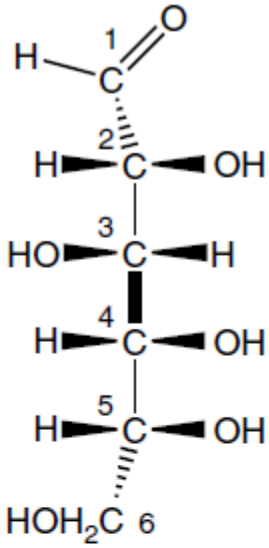


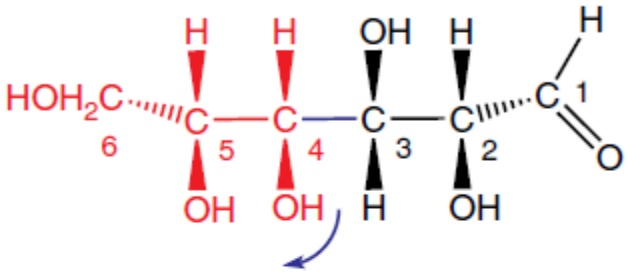
# От проекции Фишера к проекции Хеуорса: Glc*f* 43



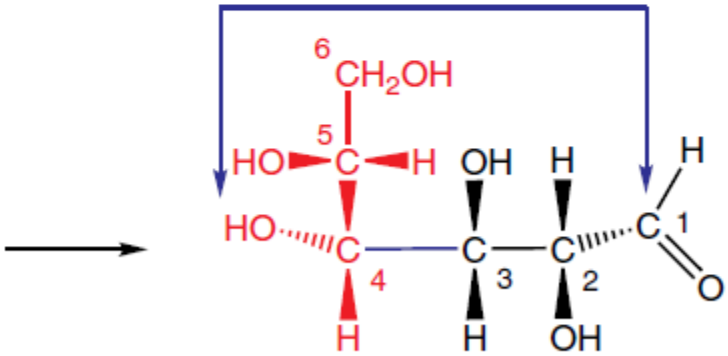

D-Glucose

≡

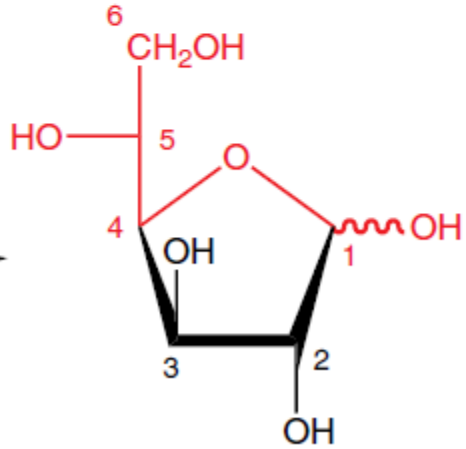


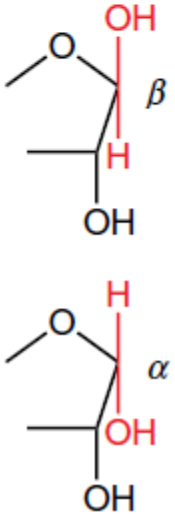




Allowed rotation of 120° around C3–C4 bond




Close backward to form the ring structure



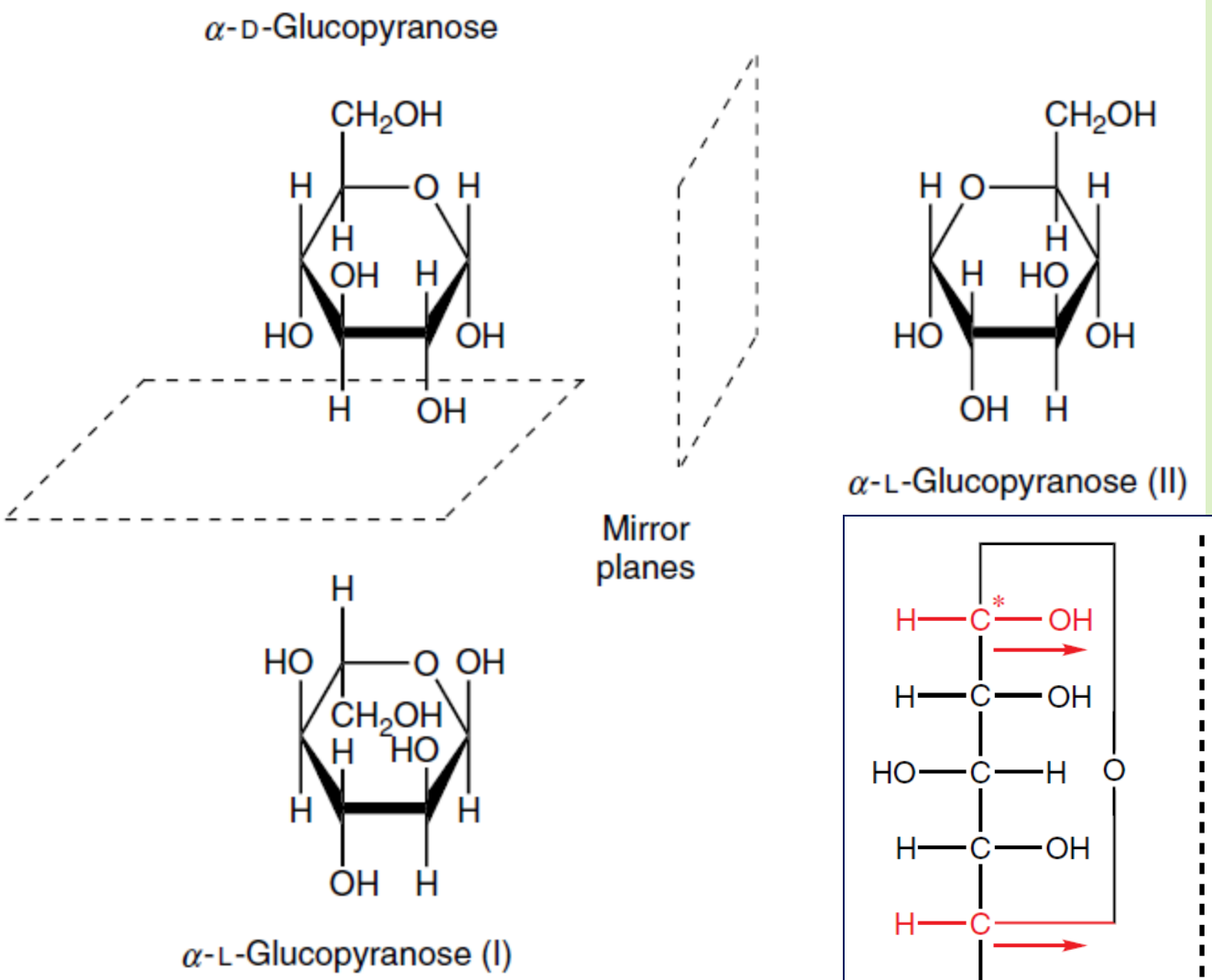




α/β-D-Glucofuranose

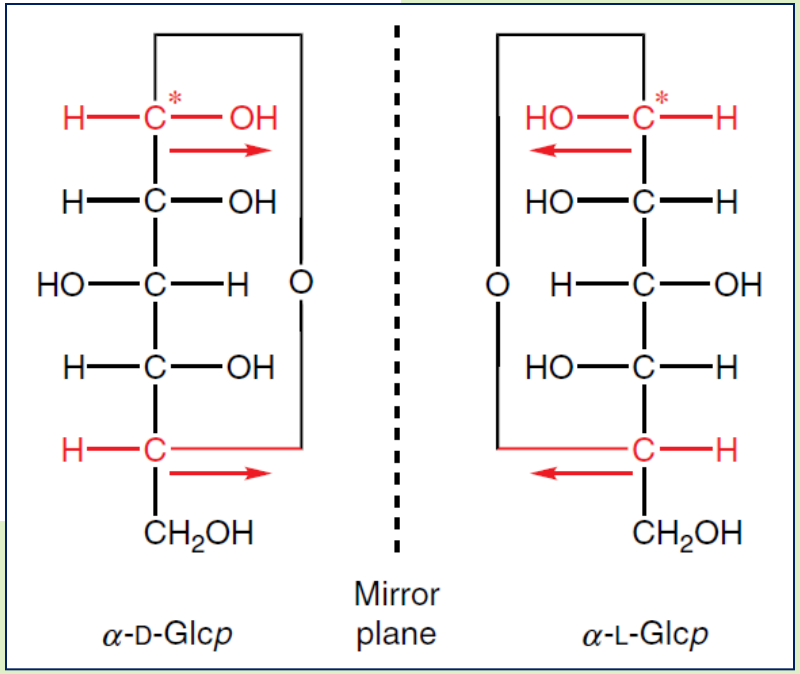
# Изображение D- и L-энантиомеров: α-Glc*p*



Проекция Хеуорса



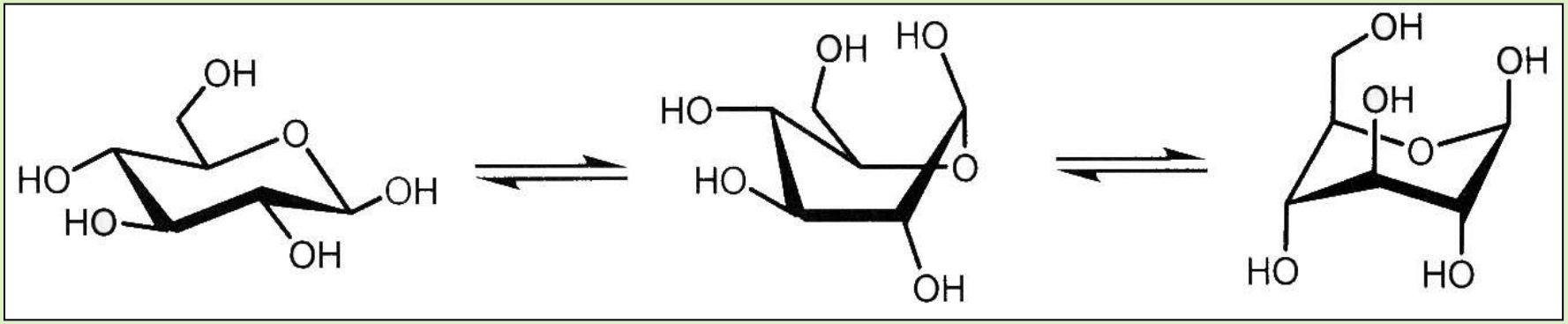

Проекция Фишера

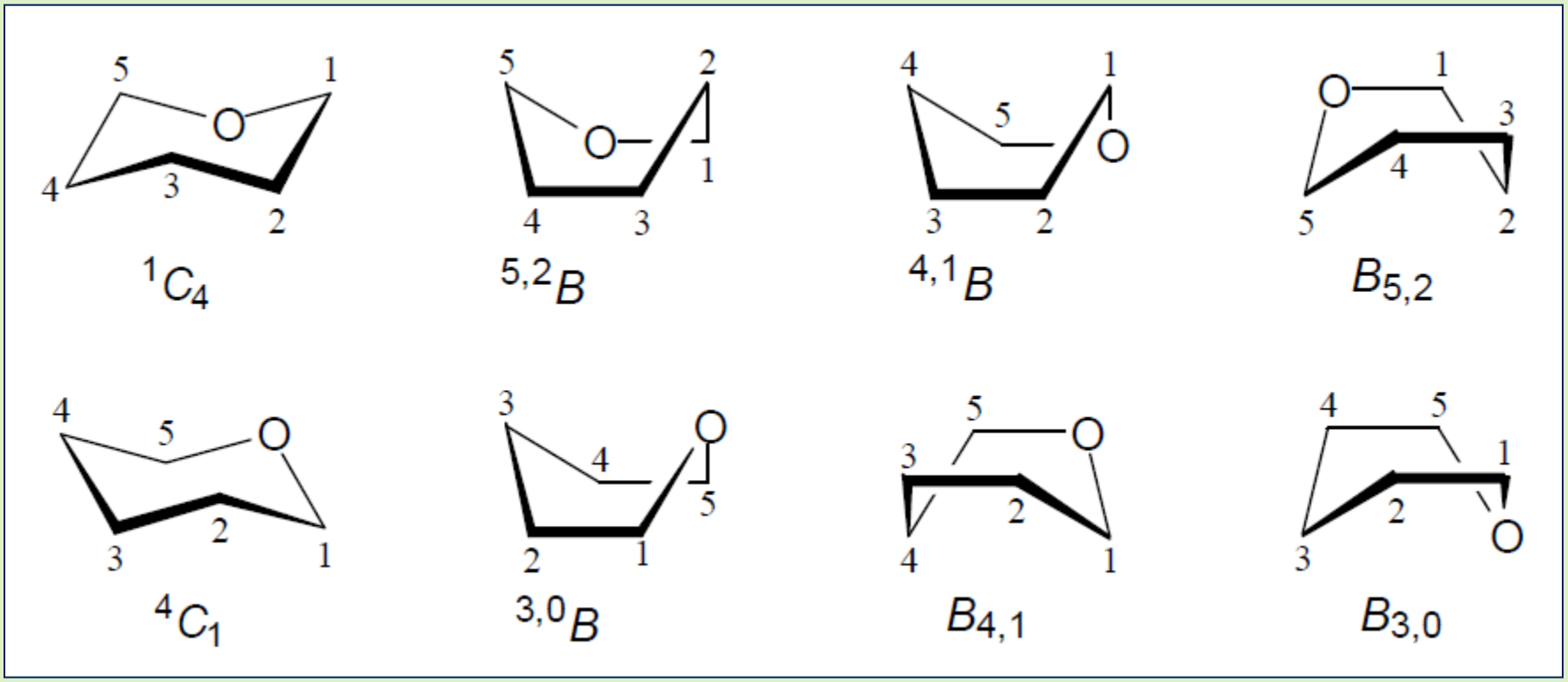


# Реальная конформация пираноз (обозначения)



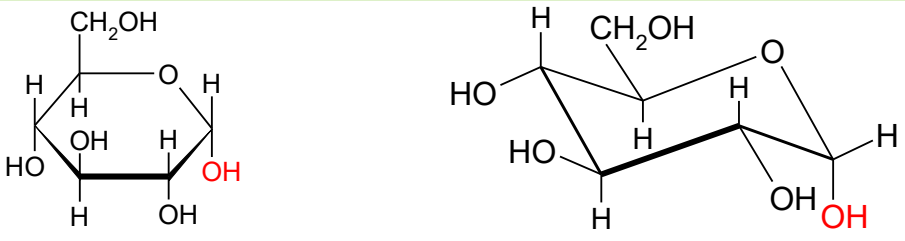
кресло $^4C_1$ ванна кресло $^1C_4$



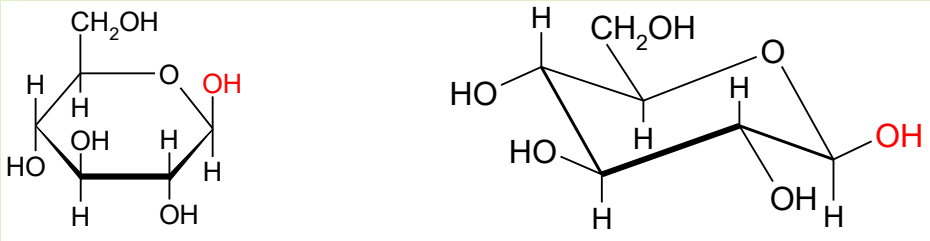



# Конформации моносахаридов: D-Glc*p* и L-Glc*p*

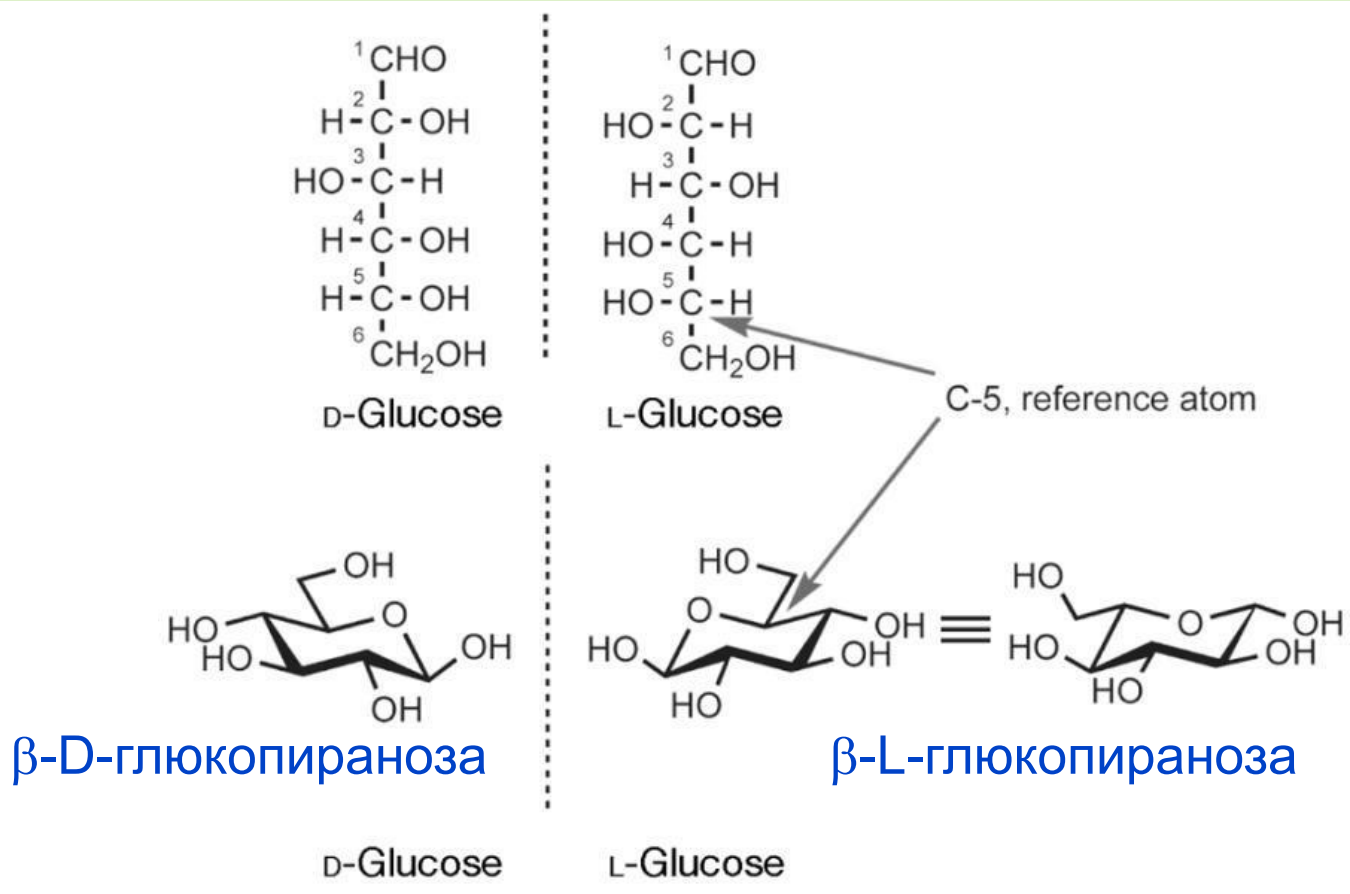




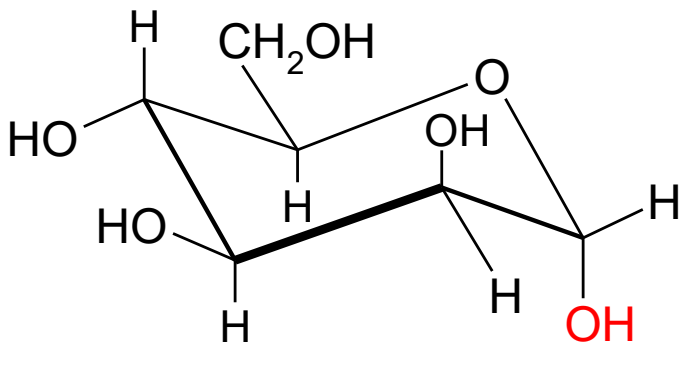
α-D-глюкопираноза



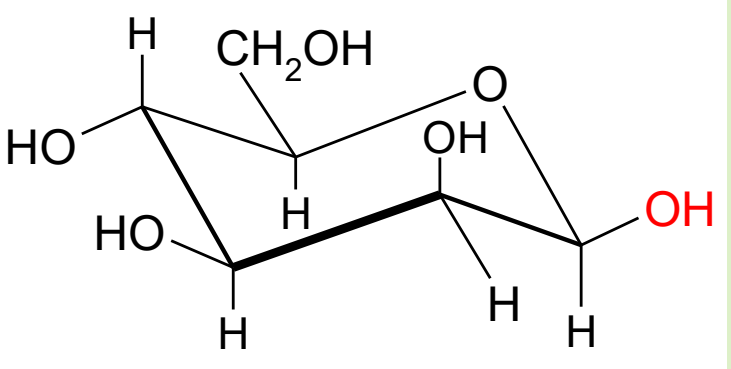
β-D-глюкопираноза



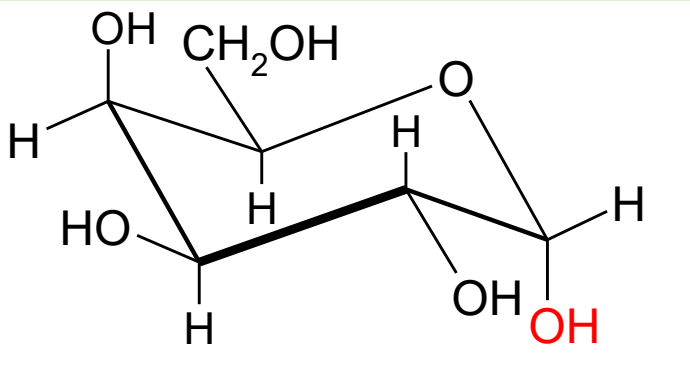
# Конформации моносахаридов: D-Man*p* и D-Gal*p* 47



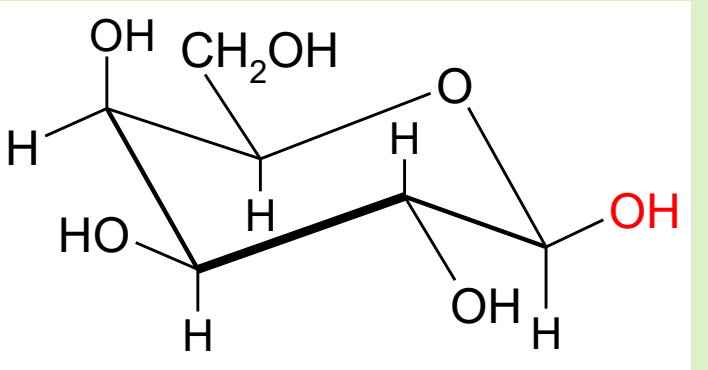

α-D-маннопираноза




β-D-маннопираноза



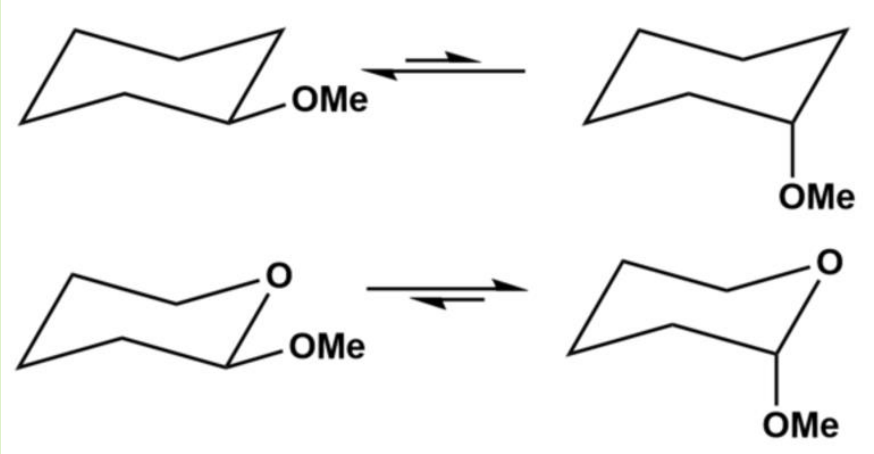

α-D-галактопираноза

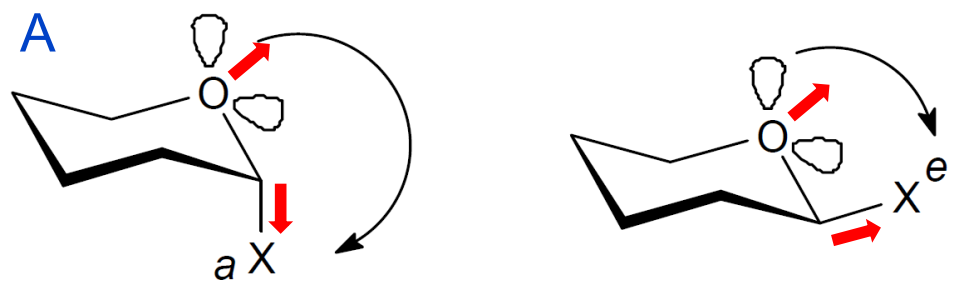


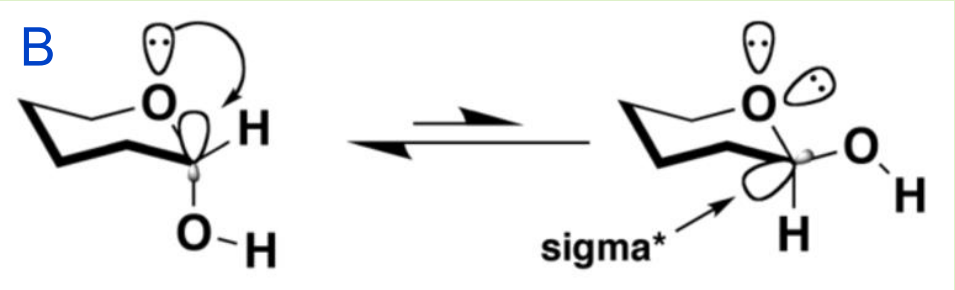

β-D-галактопираноза

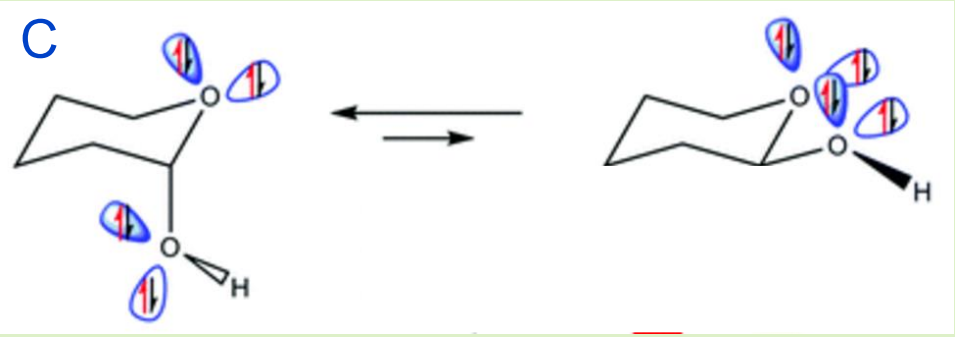
# Аномерный эффект

Br > Cl > OAc > $OCH_3$ > OH > ~~$NH_2$~~




**Причины аномерного эффекта:**

A. Отталкивание диполей

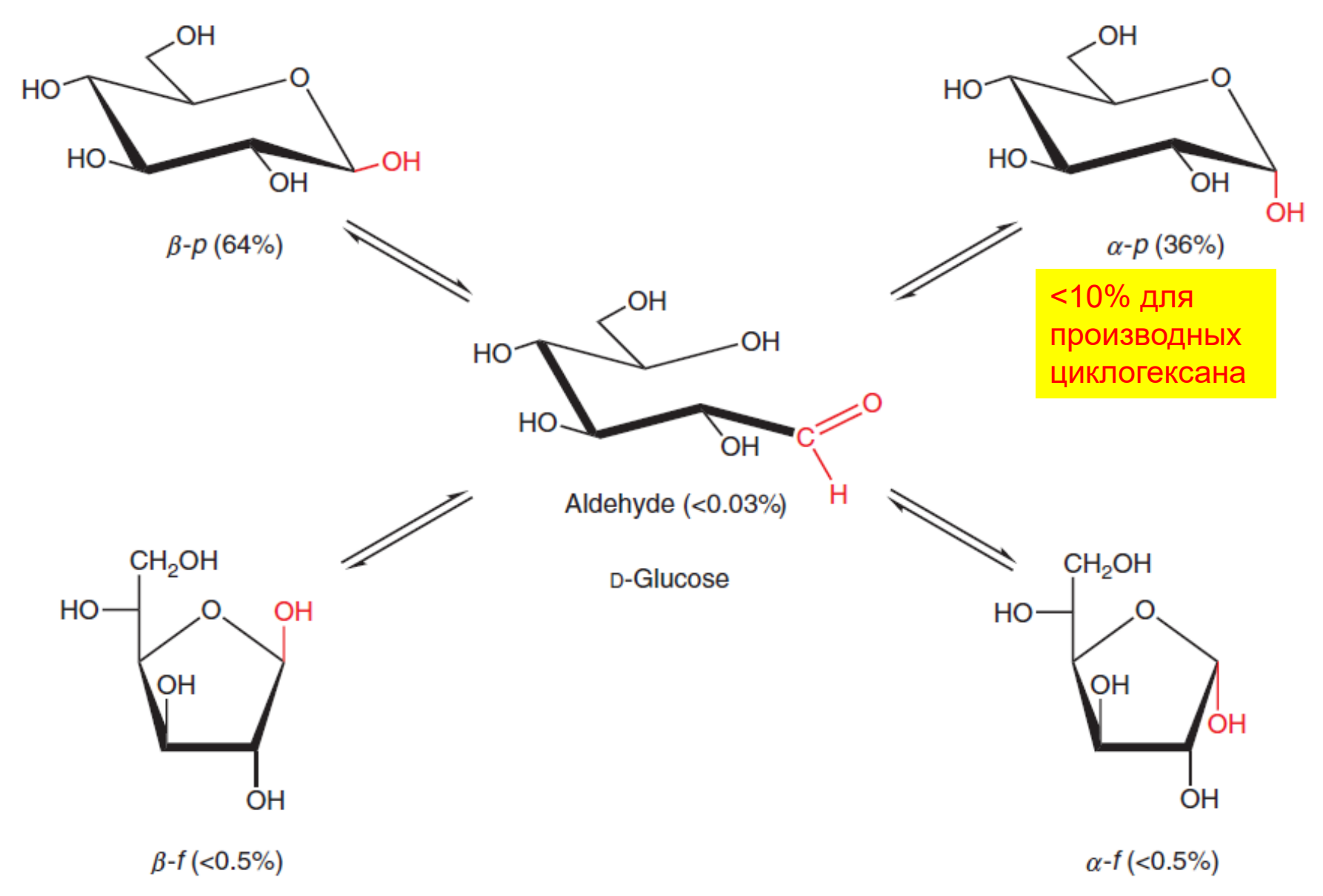
B. Стереоэлектронный эффект (n–σ* гиперконъюгация)

C. Обменные взаимодействия в системах с заполненными электронными оболочками


a) Y. Mo, *Nature Chem.* **2010**, *2*, 666. DOI: 10.1038/nchem.721.
b) C. O. da Silva, *et al., Org. Biomol. Chem.* **2013**, *11*, 299. DOI: 10.1039/c2ob26818c.

# Таутомерные формы D-глюкозы: аномеризация

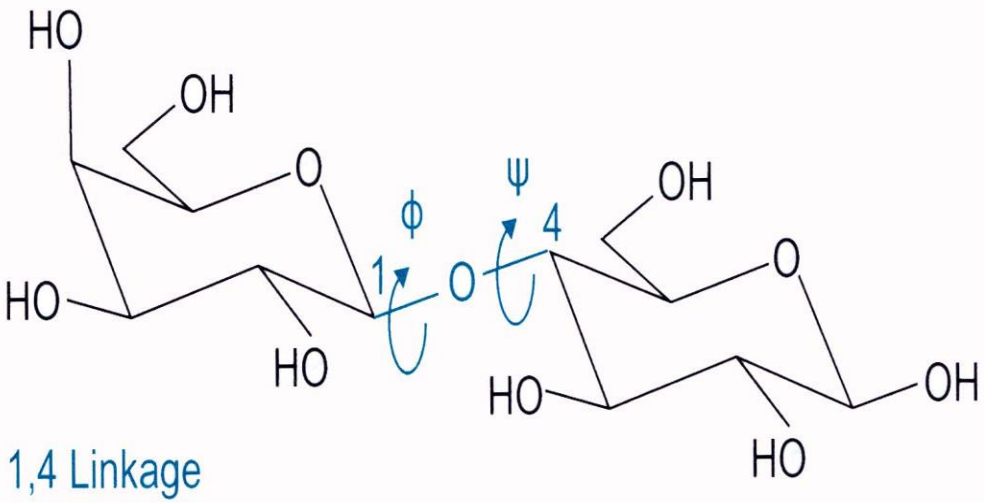




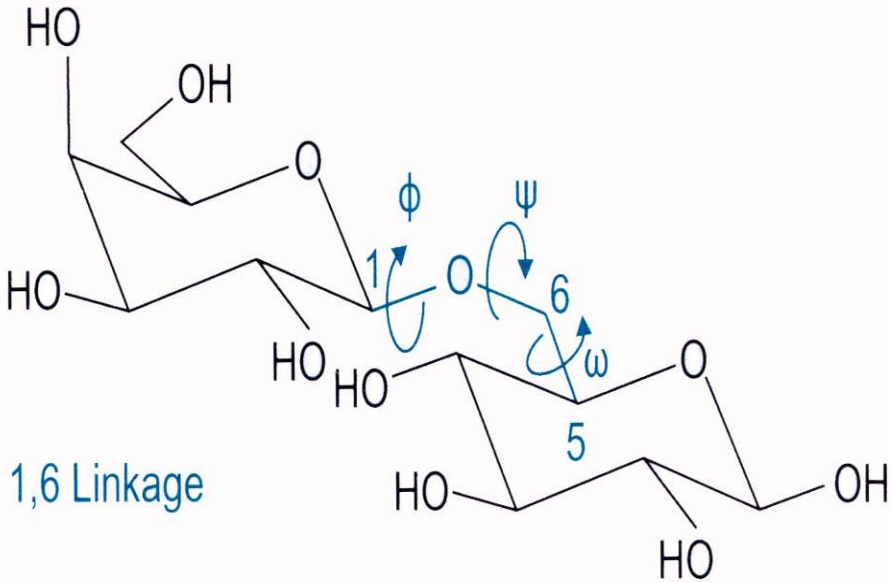

<10% для производных циклогексана

# Конформации олигосахаридов

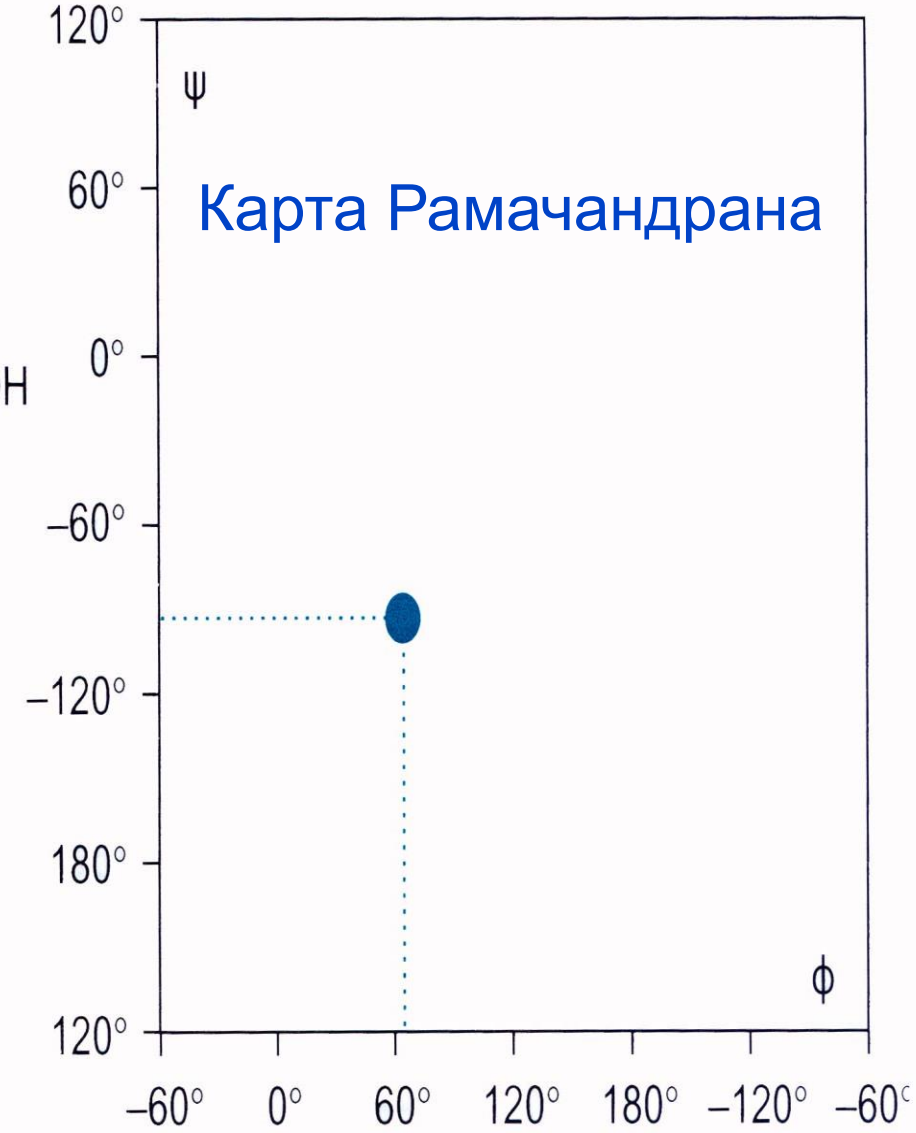





1,4 Linkage

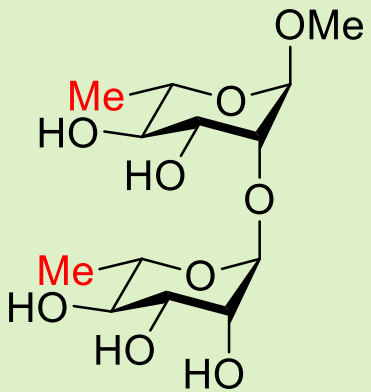


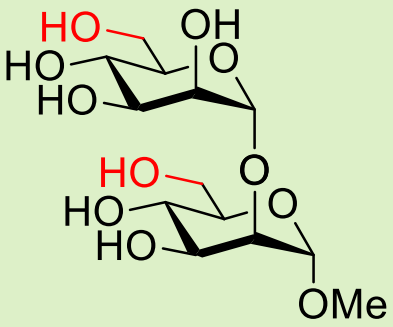

1,6 Linkage



# Конформации олигосахаридов

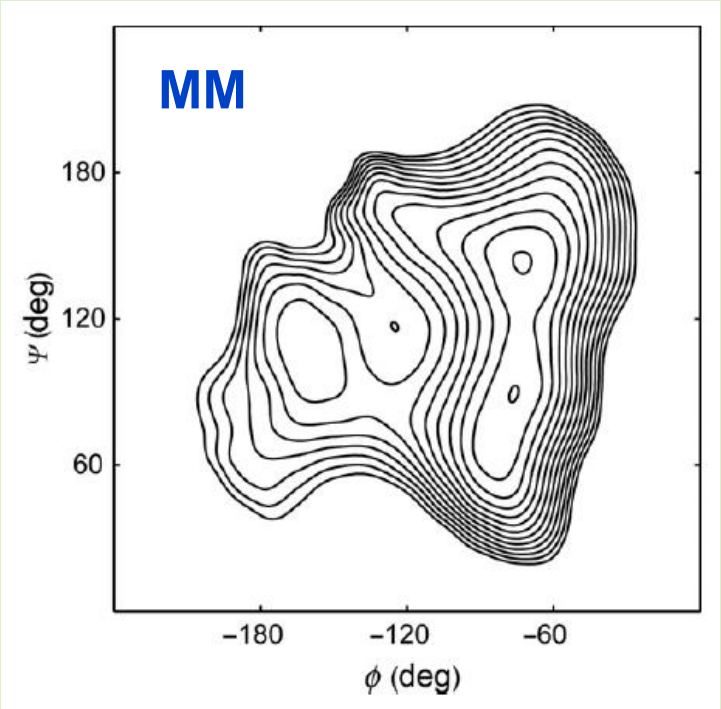


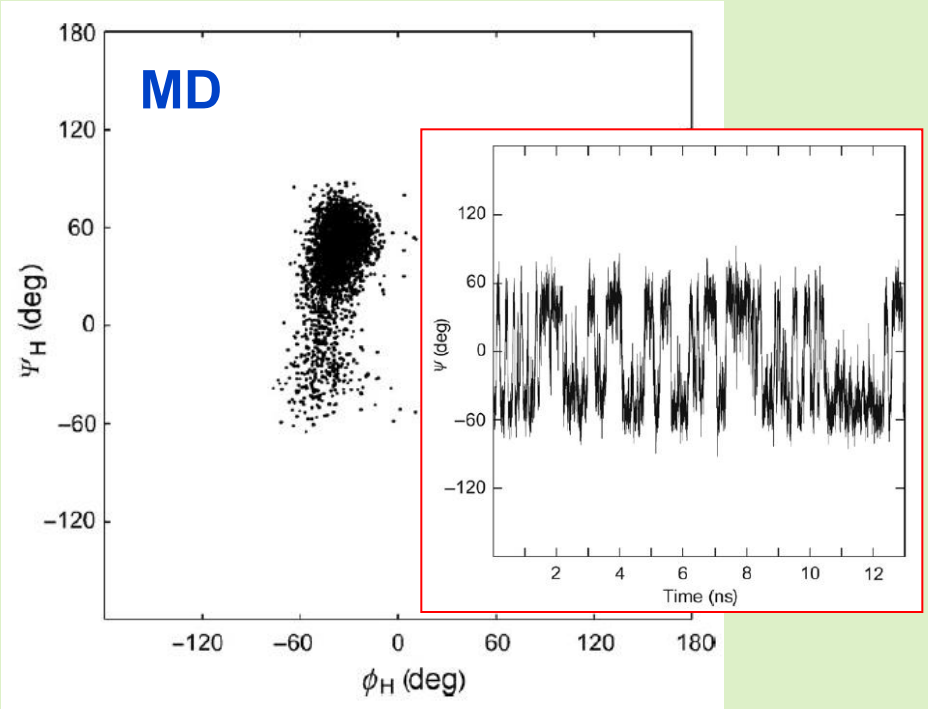



α-L-Rha*p*-(1→2)-α-L-Rha*p*-OMe

α-D-Man*p*-(1→2)-α-D-Man*p*-OMe

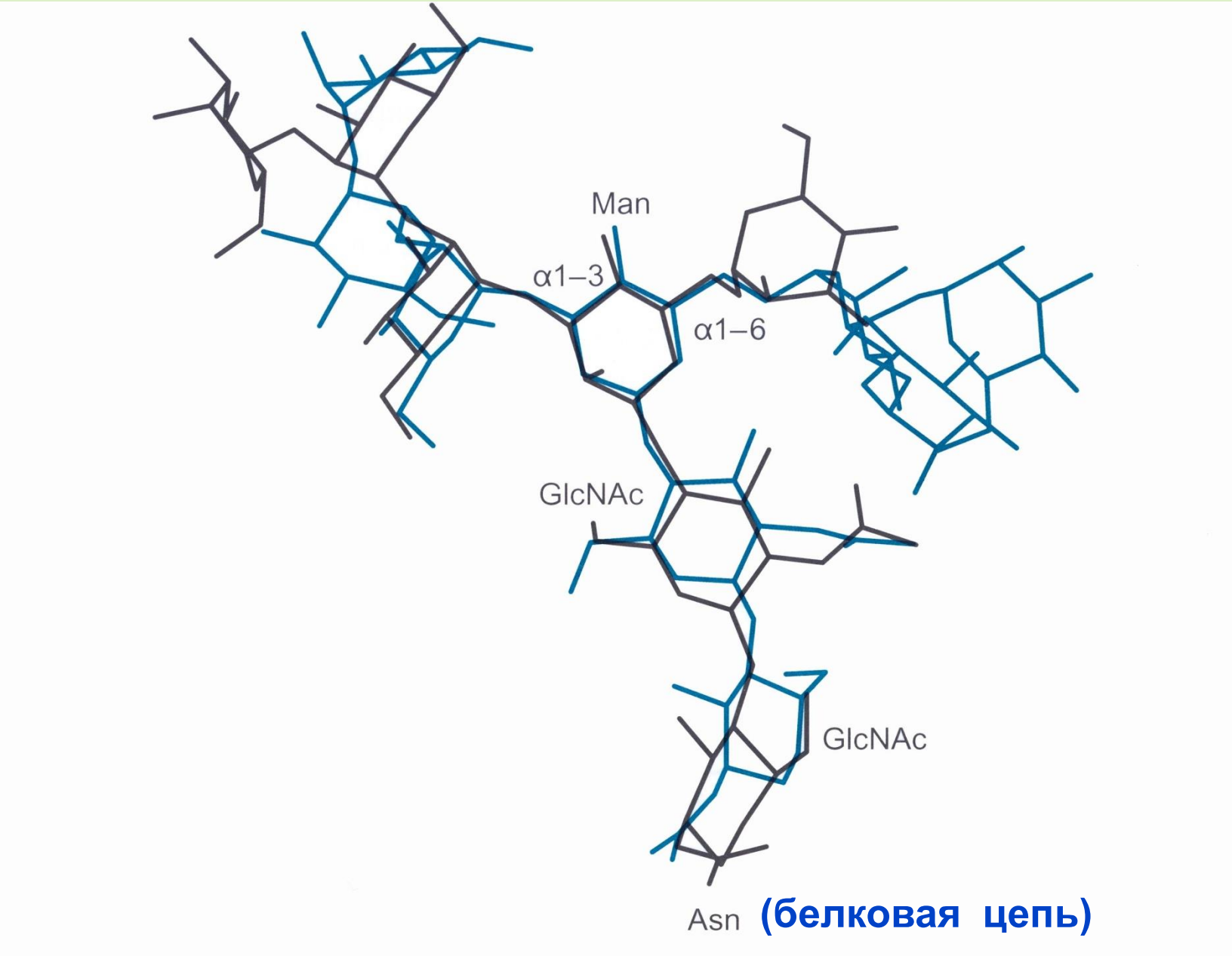



7. *Comprehensive Glycoscience. From Chemistry to System Biology*, 2007, Ch. 2.03.2.3, p. 121 (1063).

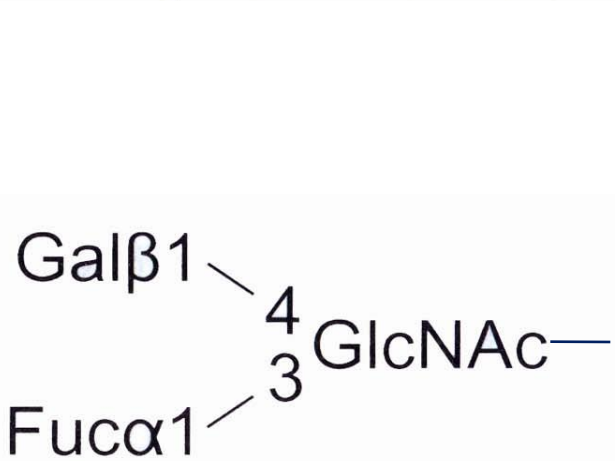
# Конформация ко́рового участка N-цепей



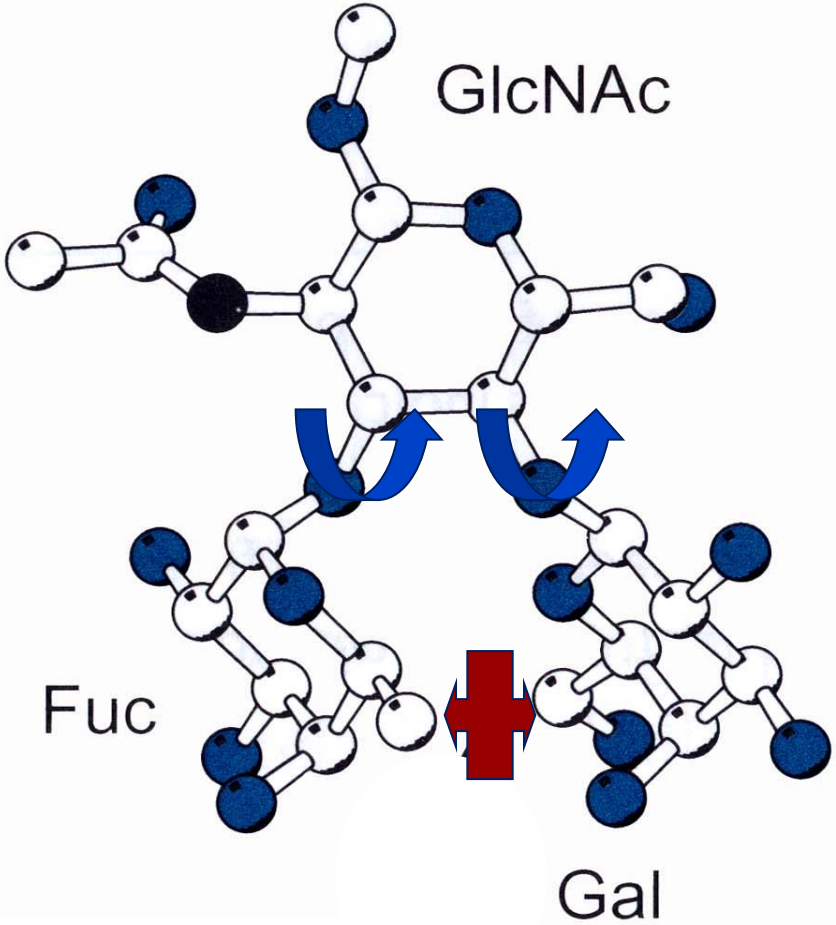


# Рецепторные олигосахариды, как правило:

## 1) относительно жесткие ...

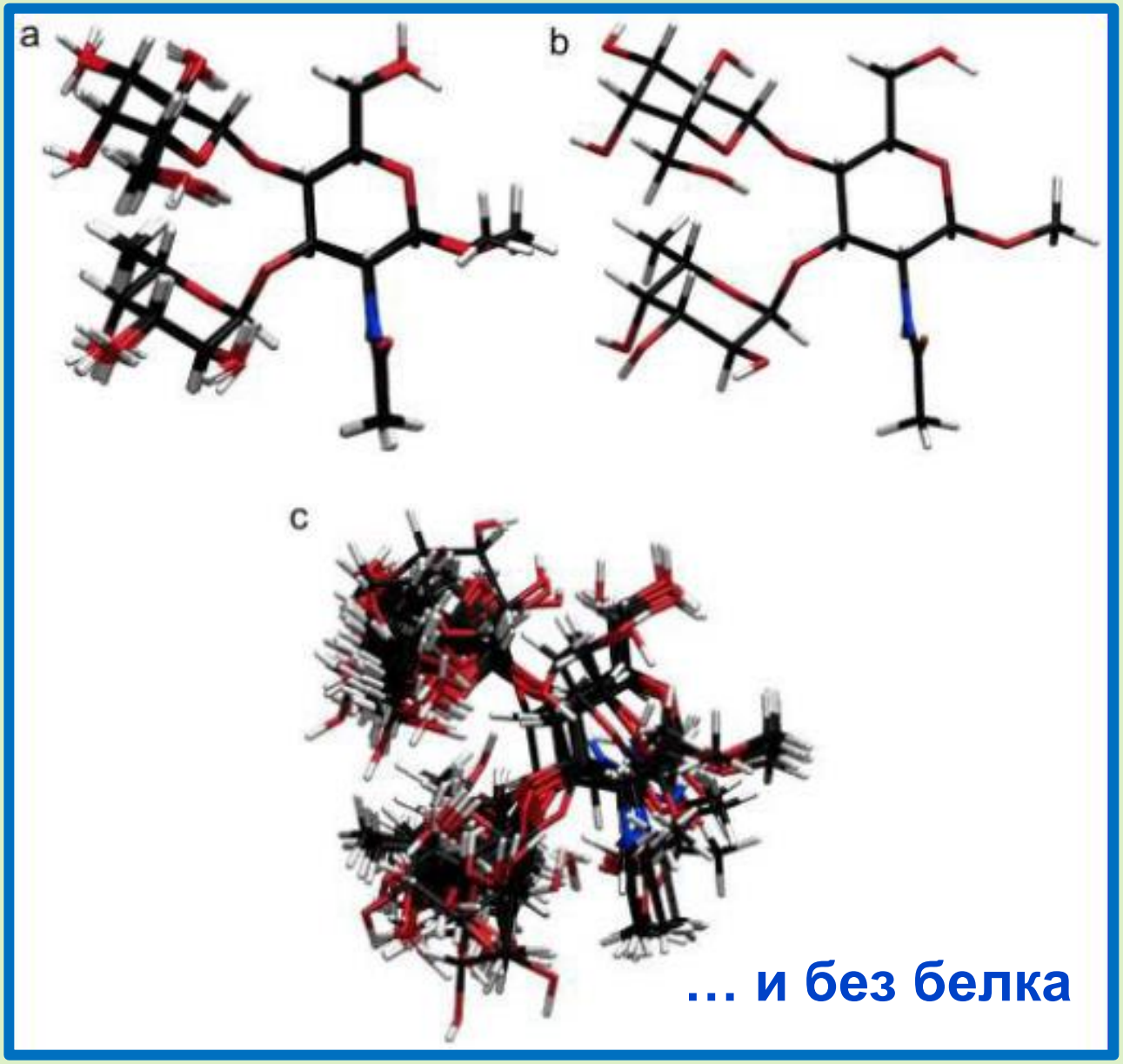



**Le$^{x}$**



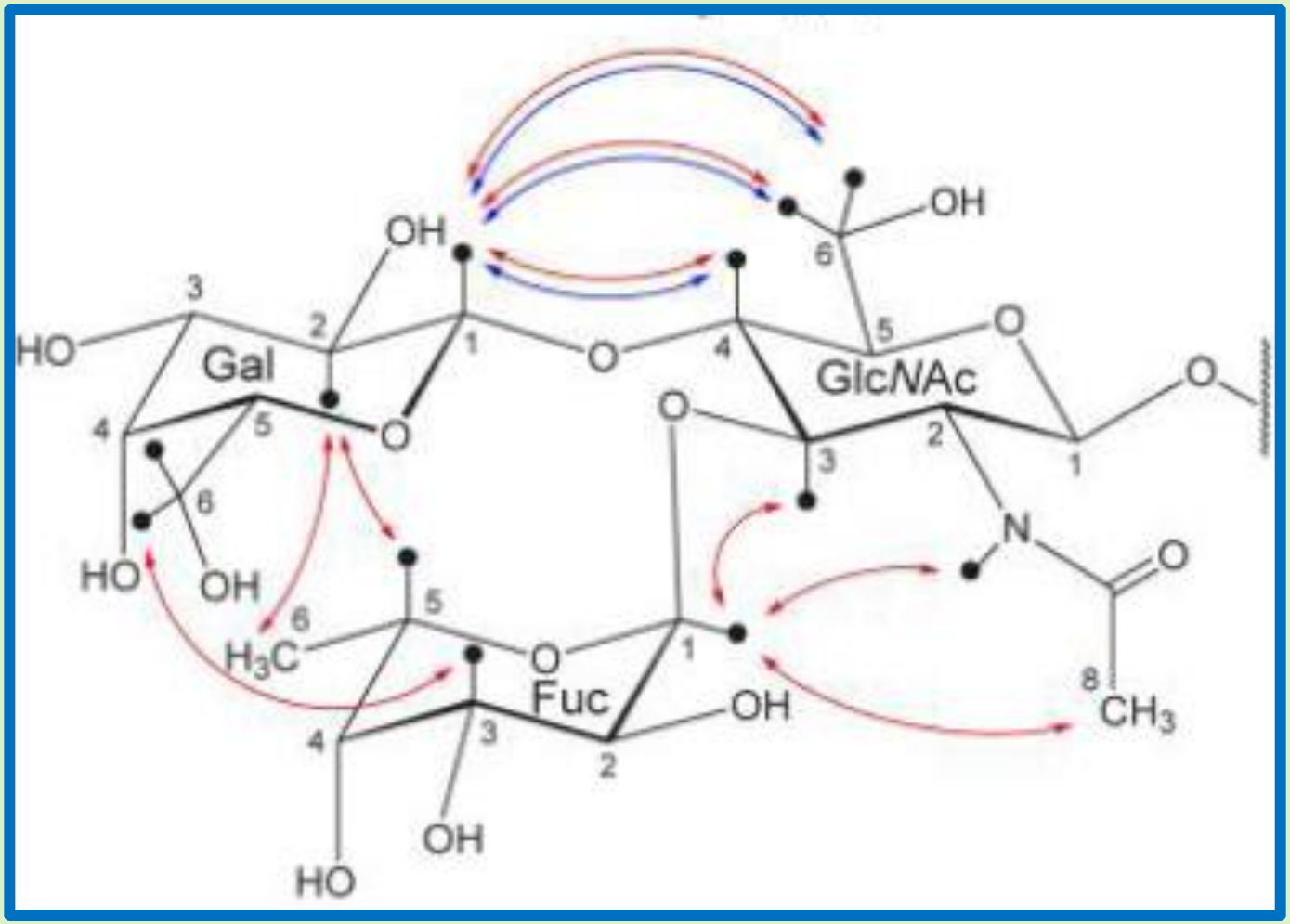
# Тот же трисахарид $Le^X$ в комплексе с белком





# Ядерный эффект Оверхаузера (ЯМР)

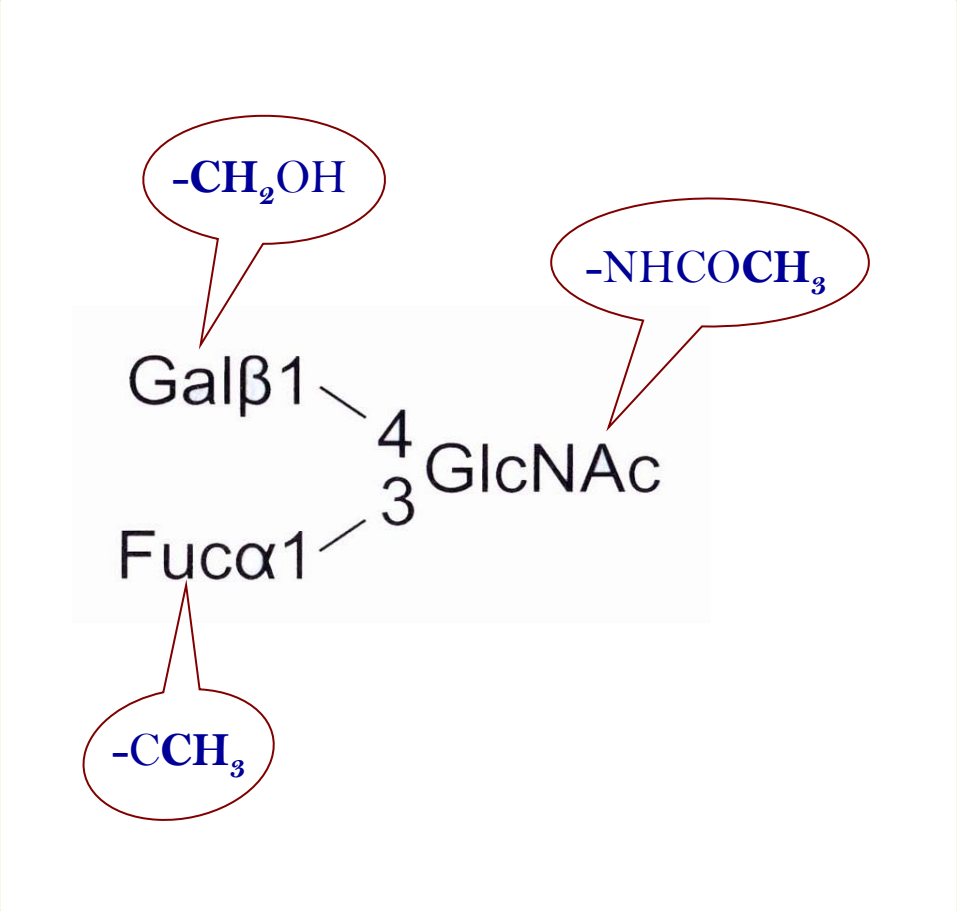





синие стрелки – в отсутствие белка

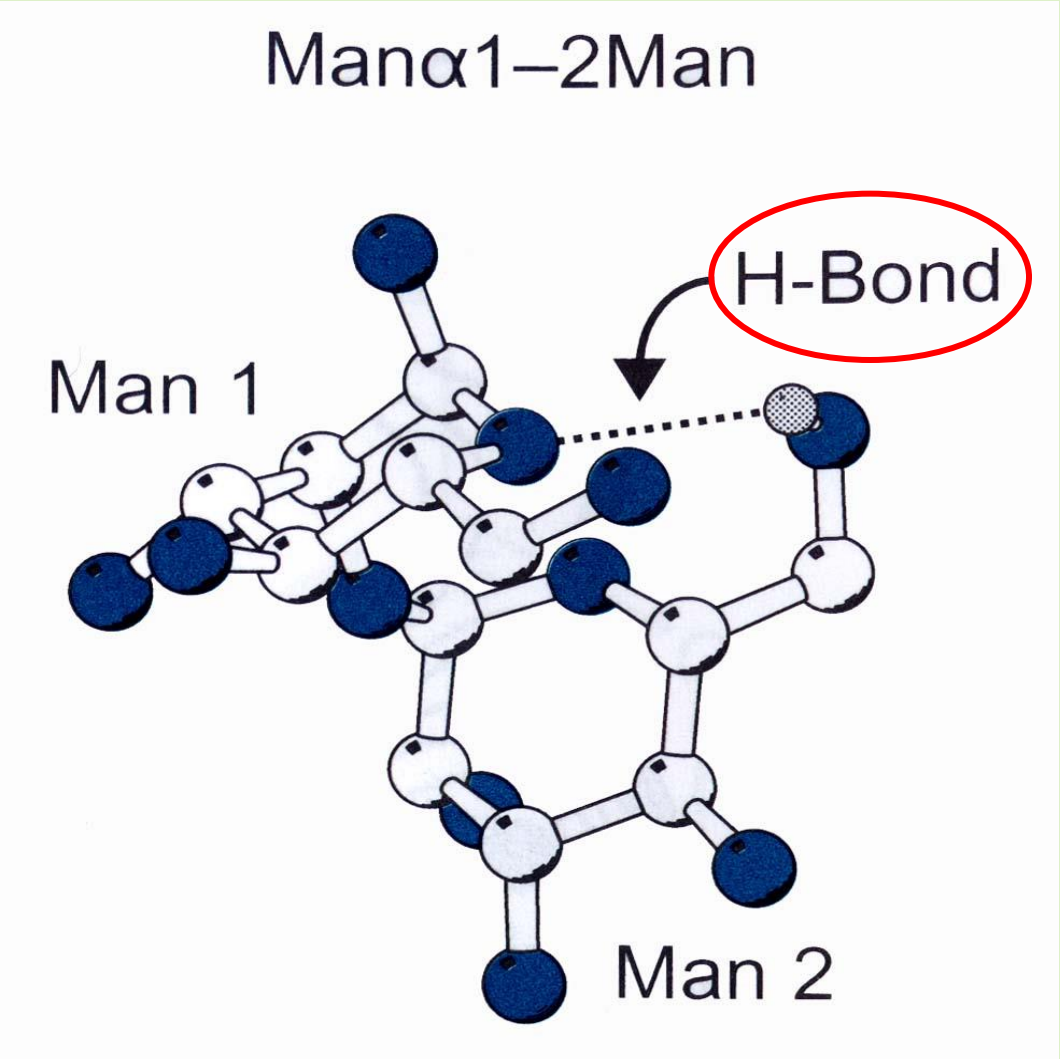
# Рецепторные олигосахариды, как правило:

## 2) имеют гидрофобное “ядро” ...



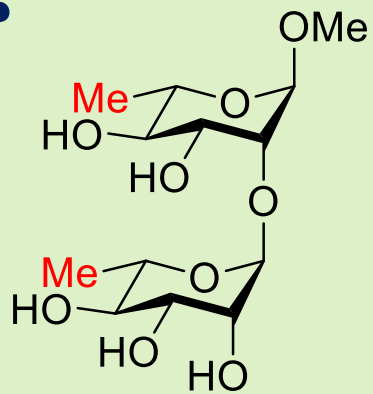
# Рецепторные олигосахариды, как правило:

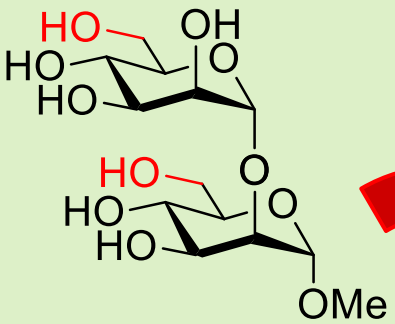
## 3) содержат внутримолекулярные водородные связи



# Конформации олигосахаридов: водородная связь

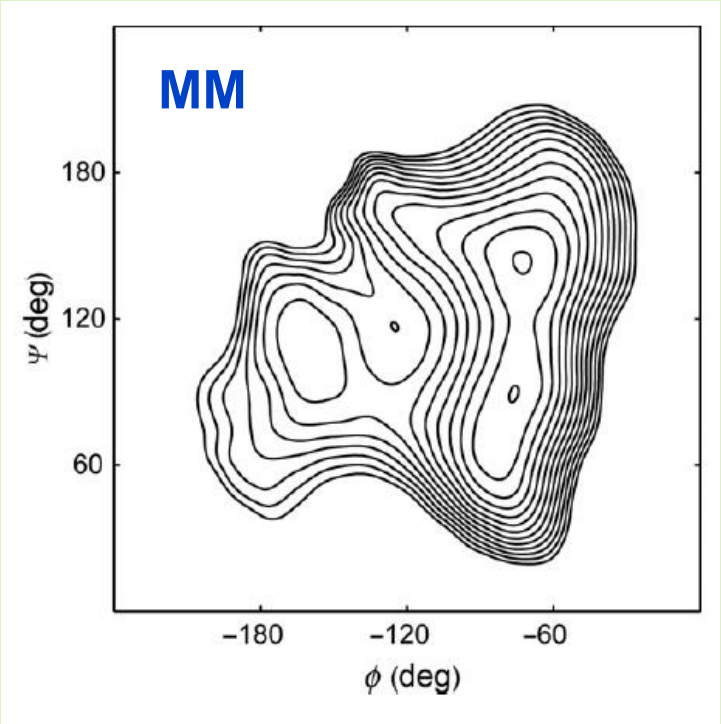


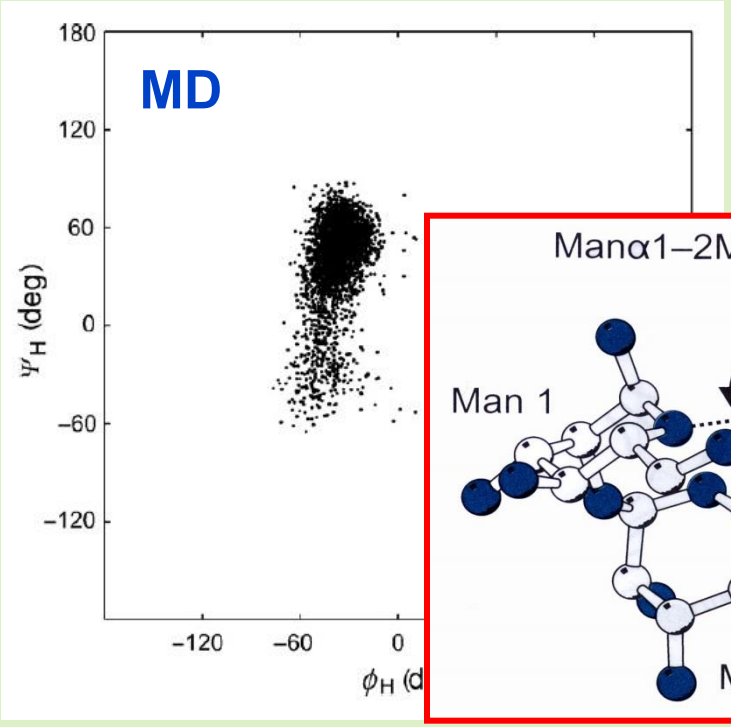


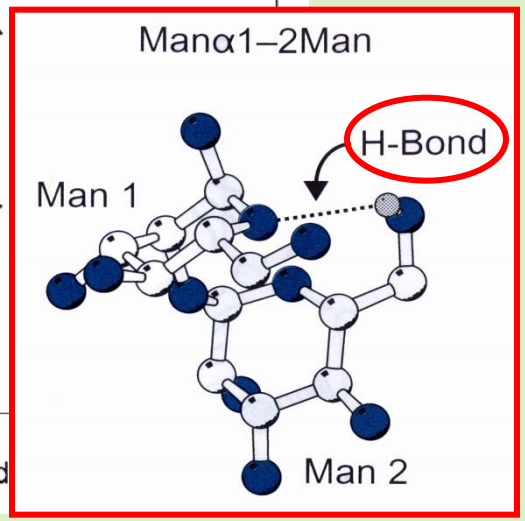




α-L-Rha*p*-(1→2)-α-L-Rha*p*-OMe

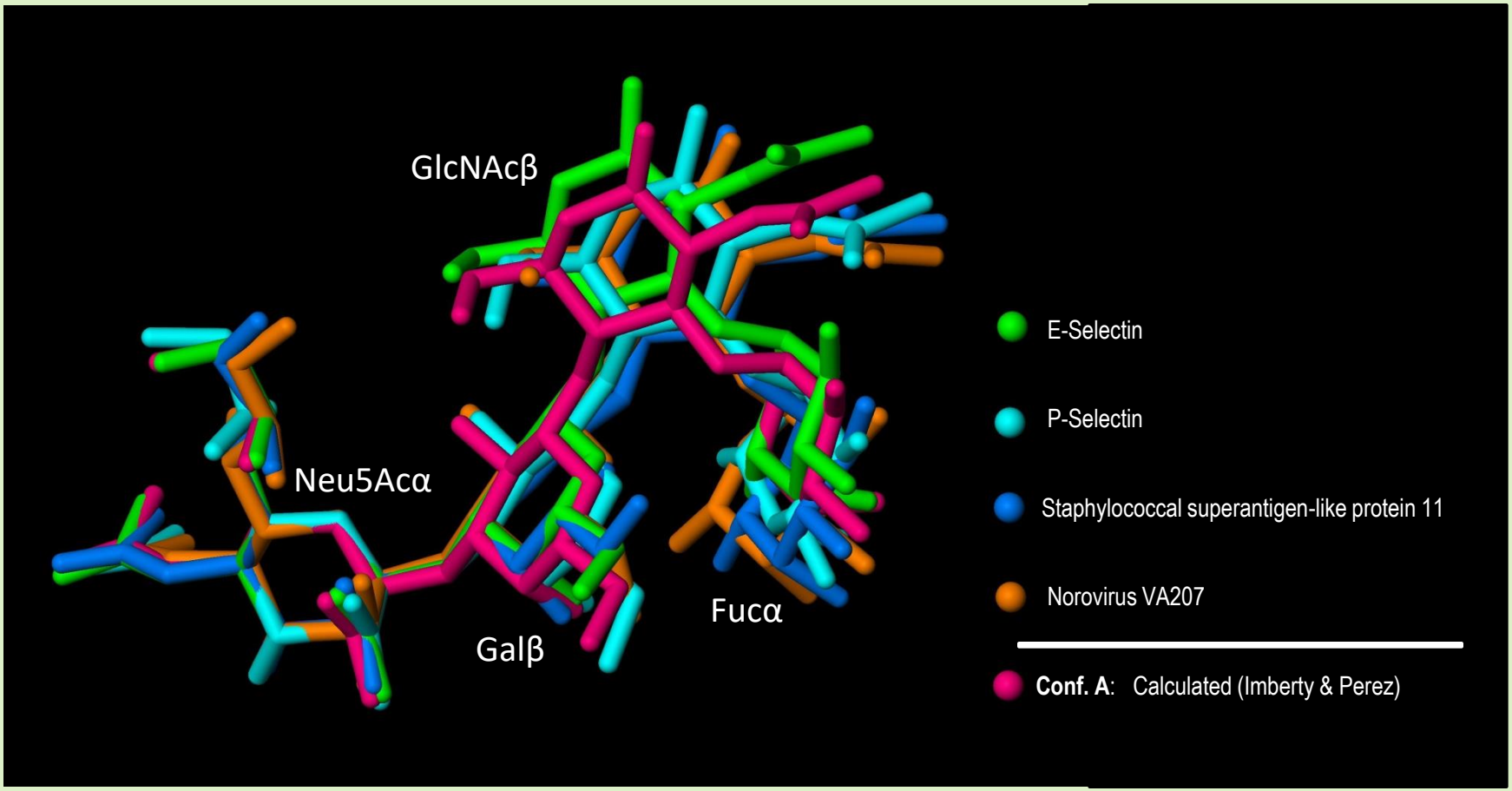
α-D-Man*p*-(1→2)-α-D-Man*p*-OMe



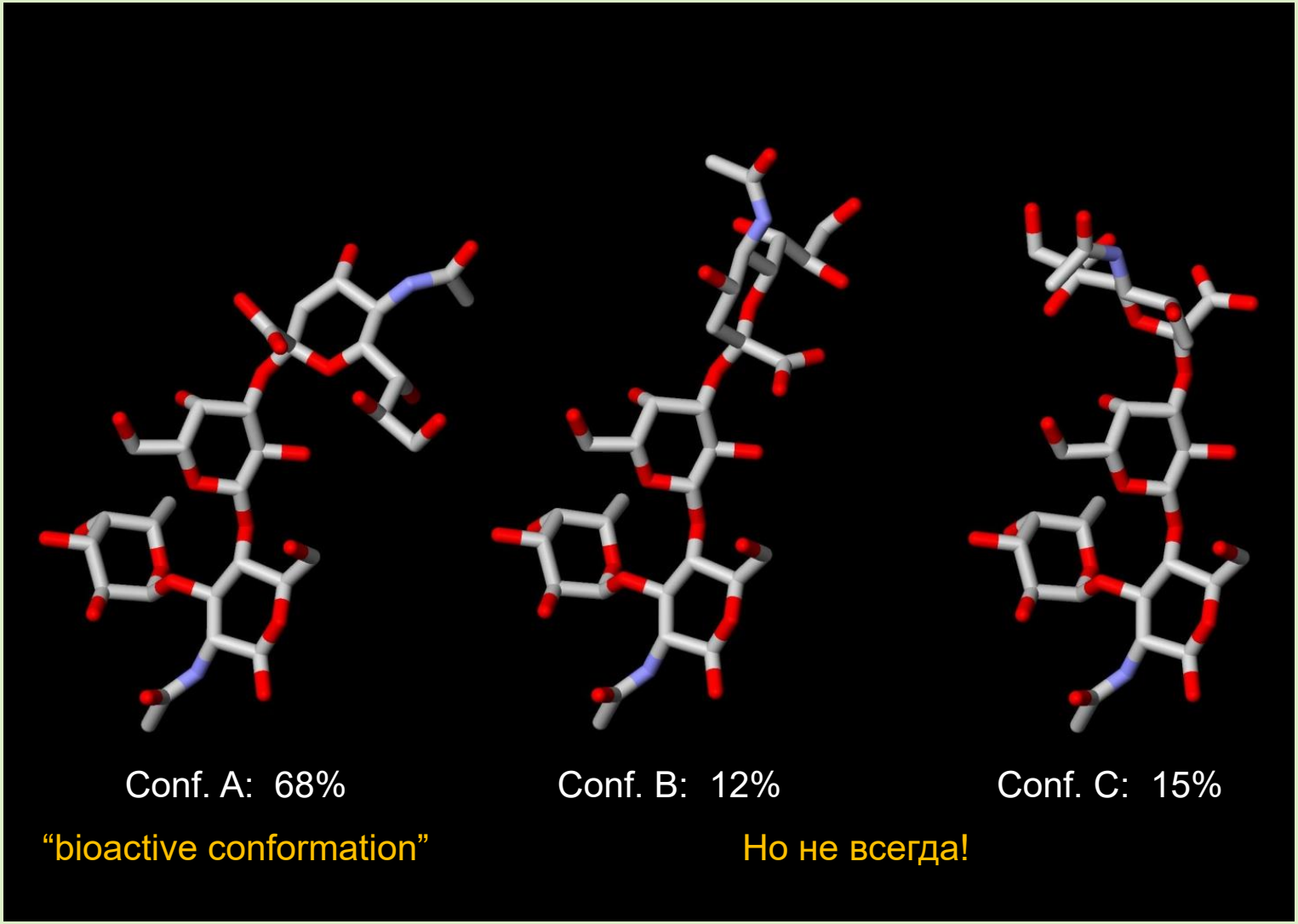
# Данные РСА (комплексы с белками): конформация SiaLe$^X$




Neu5Acα2-3Galβ1-4(Fucα1-3)GlcNAcβ (SiaLe$^X$)

# Вычисленная конформация SiaLe$^{X}$






A. Imberty, S. Perez. In: *Carbohydrate mimics: Concepts and Methods*. Y. Chapleur Y. (Ed.), Wiley VCH: Weinheim, 1998; pp. 349-364.

7. *Comprehensive Glycoscience. From Chemistry to System Biology*, 2007, Ch. 3.35.2.1.1, p. 807 (2510).

Конец лекции 1