Rational Design of Glycomimetics:

Design, Synthesis and Evaluation of Mimics of Ganglioside GM1 as Cholera Toxin Ligands

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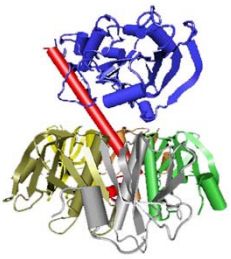
CHOLERA

http://www.who.int/csr/disease/cholera/globaltaskforce/en/

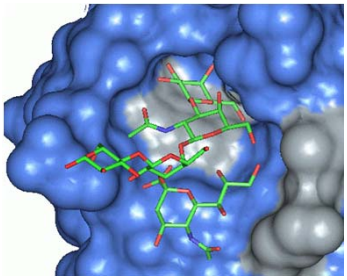


Caused by *Vibrio cholerae*.
Severe disease in ca. 5% of cases.
Estimated 120.000 deaths/year worldwide.

Symptoms: profuse watery diarrhea, vomiting, rapid dehydration and shock. Without treatment, death can occur within hours.
The symptoms are caused by an AB_5 enterotoxin secreted by *V. cholerae* after it reaches the host intestine

The AB_5 Enterotoxins

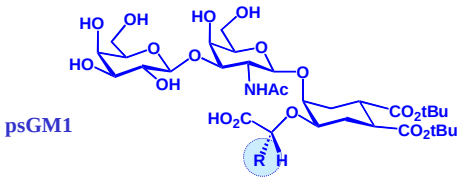
The Cholera Toxin (CT) and the Heat Labile Toxin of *E.coli* (LT) are 80% homologous AB_5 proteins which use the GM1 ganglioside as their selective receptor on the surface of human intestinal epithelial cells.



Non conventional methods for the control of bacterial infections

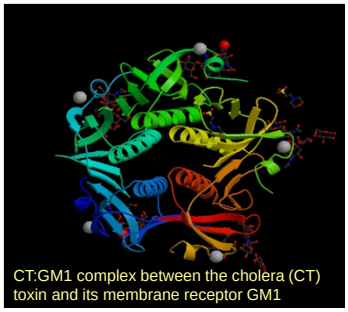
- Infectious diseases are the first cause of mortality in the word.
- The insurgence of **bacterial resistence to antibiotics** requires new strategies for health management and control
- One of the innovative approaches consists in **controlling the infection** and its effects on the organism using **antiadhesive or anti-toxin therapies**.

Design, synthesis and biological activity of cholera toxin (CT) inhibitors



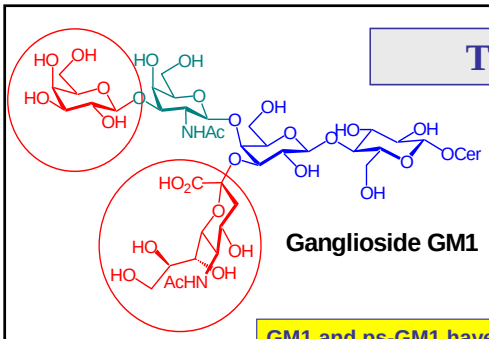
psGM1

psGM1 is the CT ligand developed in our laboratories. Its activity depends on the nature of the R group



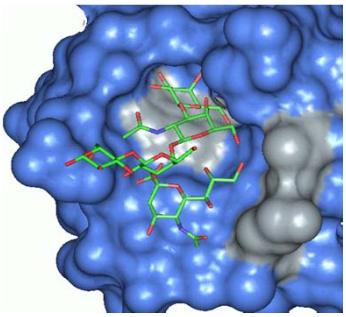
CT:GM1 complex between the cholera (CT) toxin and its membrane receptor GM1

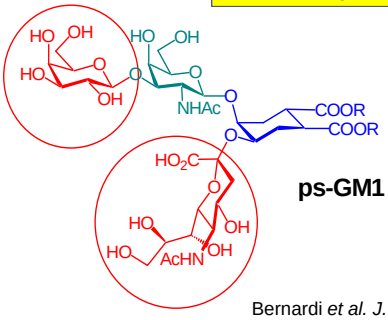
The CT:GM1 Complex



Ganglioside GM1

GM1 and ps-GM1 have the same affinity for CT

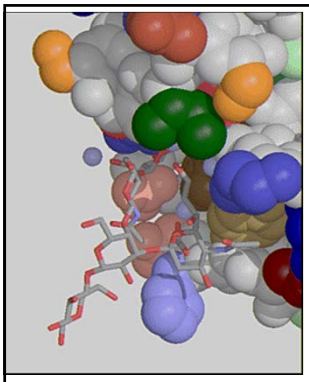




ps-GM1

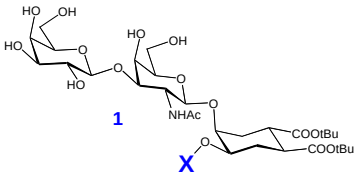
Using CT:GM1 as a model we synthesized a series of ps-GM1 molecules, thus developing a group of structural and functional ganglioside mimics.

Bernardi *et al. J. Am. Chem. Soc. 121*, 2032 (1999)

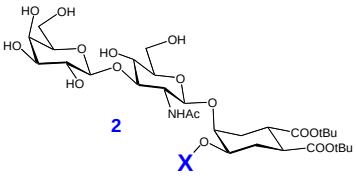


Cholera Toxin:GM1 complex

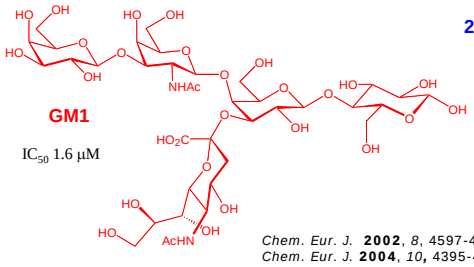
PseudoGM1 CT ligands



1 X=	IC_{50} (μM)
SO_4	400
HO_2C	700
HO_2C, H, Me	1,000
HO_2C, Me, H	200



HO_2C, $PhCH_2$, H	10
HO_2C, $CyCH_2$, H	37
sialic acid	1.3

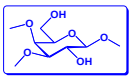


GM1

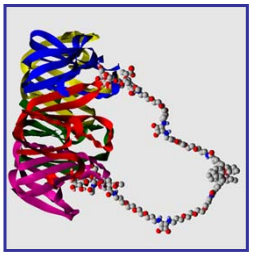
IC_{50} 1.6 μM

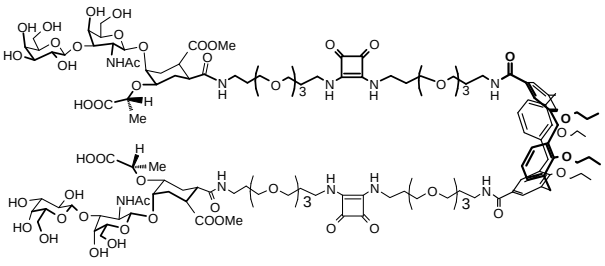
2 X=	
sialic acid	1.8
HO_2C, Me, H	450

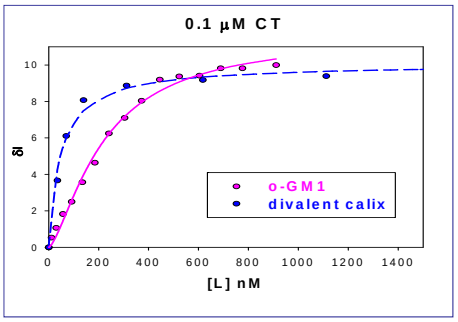
Chem. Eur. J. **2002**, *8*, 4597-4612; *Org. Biomol. Chem.* **2003**, *1*, 785-792; *Chem. Eur. J.* **2004**, *10*, 4395-4406, *Chemistry Eur. J.* **2008**, *14*, 7434-7441



Divalent Calixarene: Fluorescence titrations



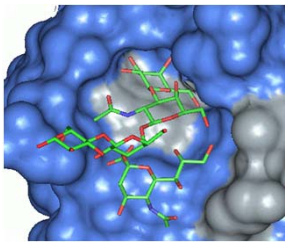




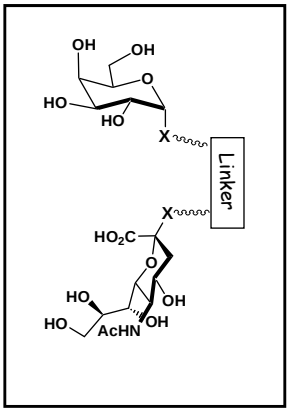
In this assay, the divalent calixarene appears more active than the natural ligand o-GM1

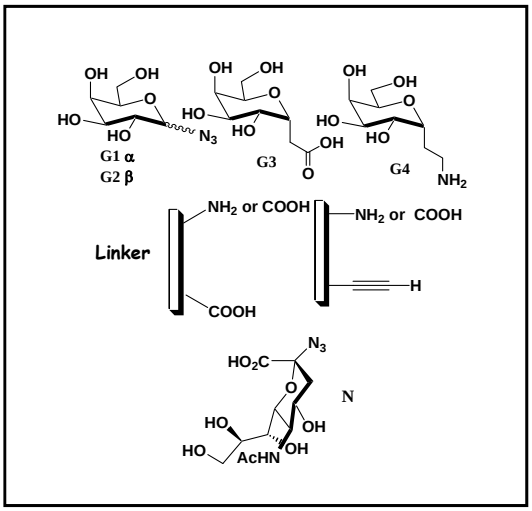
IC_{50}= 48 nM
β = 3950

Casnati, Bernardi *et al J. Am. Chem. Soc.* **2005**,*127*, 3660



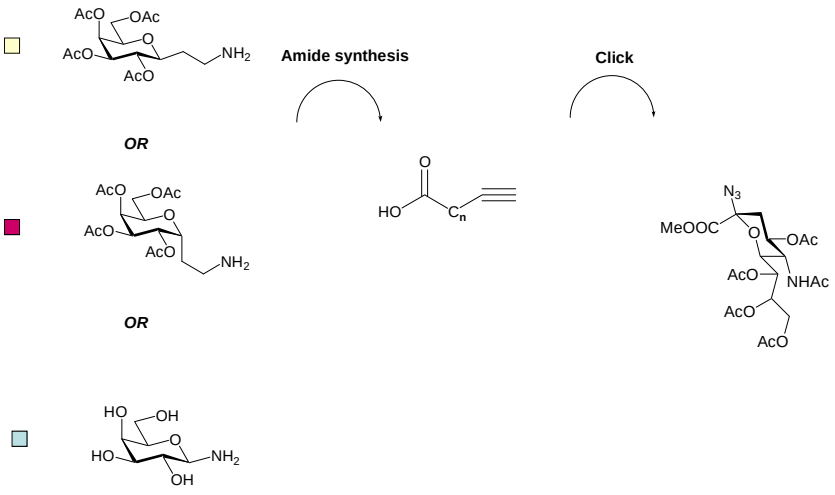
Linker design: Evolution of Cholera Toxin inhibitors



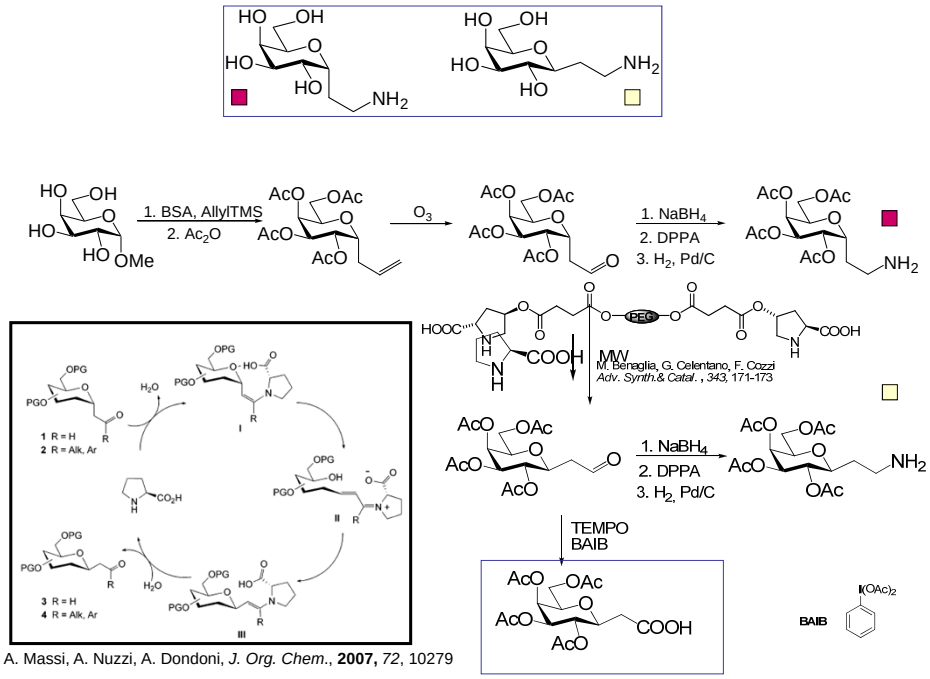


Pavel Cheshev, Crtomir Podlipnik

One simple 3-component library



Pavel Cheshev

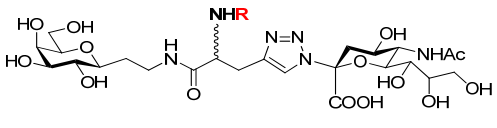


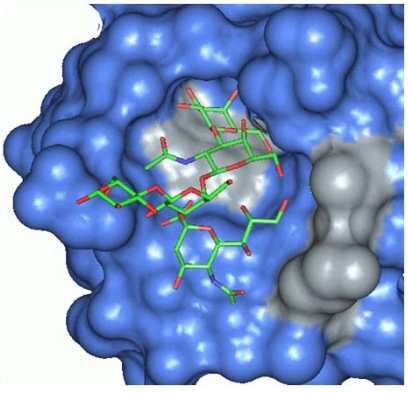
A. Massi, A. Nuzzi, A. Dondoni, *J. Org. Chem.*, **2007,** *72*, 10279

1. Linear structures with lipophylic sidechain

Amides:

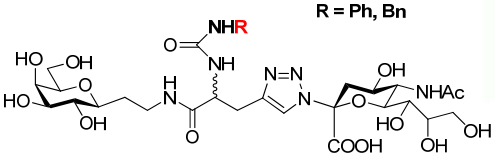
R = Ac, Bz, PhAc





Ureas:

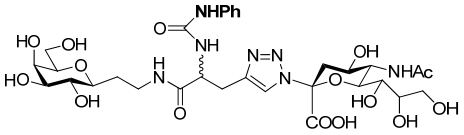
R = Ph, Bn



P. Cheshev *et al* . *Chemistry – Eur. J.* **2010**, 1951 – 1967

The most active so far!

P. Cheshev *et al* . *Chemistry – Eur. J.* **2010**, 1951 – 1967



~3 times more potent then MNPG

WAC test of amides and ureas