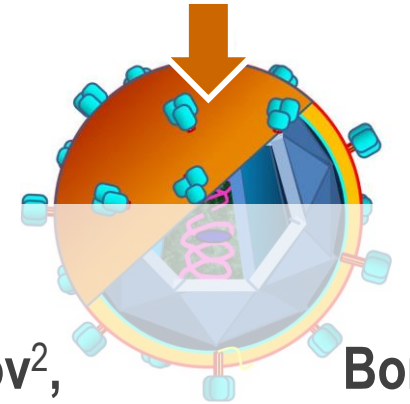
FROM BASIC PRINCIPLES TO COMPUTATIONALLY REFINED MODELS FOR A PRACTIC SYNTHESIS OF THE NANO-COMPETENT POLYMERIC ANTIVIRALS



Alexander V. Serbin[1,2] **Olga L. Alikhanova**[1,2]

Vladimir B. Tsvetkov[2], **Boris D. Bolshchikov**[2]

[1] Biomodulators & Drug Systems RC Health RDF

[2] Institute of Petrochemical Synthesis RAS

Moscow, Russia

serbin@ips.ac.ru / heal@aha.ru

Comments

● Good day, Dear Colleagues

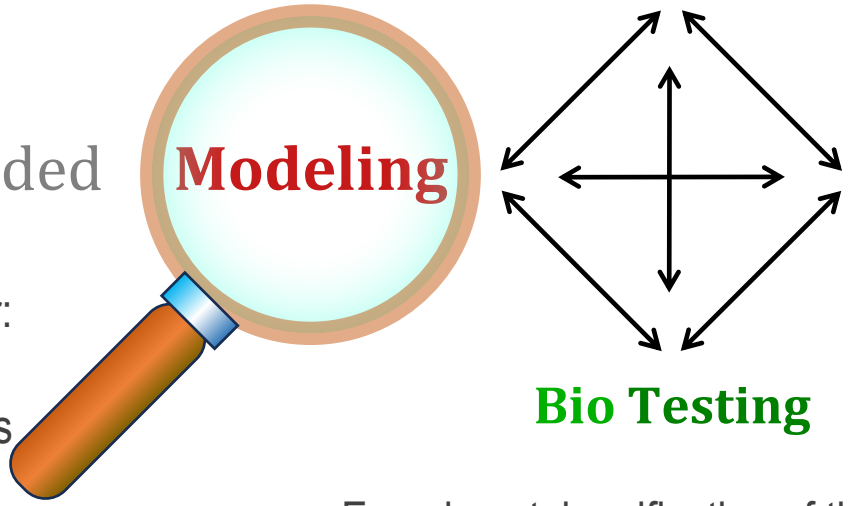
● With thankfulness for this opportunity. ● I would like consider some aspects of not computer but the 'own human brain-aided' generation of fundamental strategies for design, synthesis, and testing the antiviral Drugs. ● And after focusing on the key problems we can search their solutions using the computer-aided modeling capacity

ANTIVIRAL DRUG DEVELOPMENT

Accumulated **Basic Knowledge** ↔
fundamentally predictable principles for

Targets identification ↔ **Design** ↔ **Antivirals** prognosis

Computer-Aided **Modeling**



Detailing - Clarifying the mechanisms & parameters for:

- **Viral Target – Antiviral** interaction in QSAR aspects
- **Synthesis optimization** toward the **desired structures of the Antivirals**

Synthesis

- Realization of desired draggable **(Macro) molecular constructs**
- Stepwise preparation of **drug-candidate samples for (bio) evaluations**

Bio Testing

Experimental verification of the

- **Design & Modeling Prognosis efficiency** or discovery of unpredicted data as new objects for analysis and reinvestigation
- **Prospects** of the **synthesized test-variants** for potential Antivirals for future **biomedical advancement**

Comments

- *It can be summarized by the scheme. From basic knowledge supported Design toward pilot synthesis – bio-testing, and computational modeling if it is relevantly helpful*

ANTIVIRAL DRUG DESIGN

1. FUNDAMENTALLY PREDICTABLE BASIC PRINCIPLES

Comments

- *So, the Design and fundamentally predictable basic principles*

ANTIVIRAL DRUG DESIGN

1. FUNDAMENTALLY PREDICTABLE BASIC PRINCIPLES

1.1. Small and Macro Molecules

Molecular evolution of biological forms of Life

From "**Small**" → to "**Great**"

Covalently ***polymer****ized chains* & *networks*

flexible, but stable self-organization

≈ **300 K** (30°C) ± 50

Temperature & entropy stimuled dissociation & chaos

Bio **Polymer Basis** of **Cells:**

● **Lipides**	***-methylene*** *motifs*	Membranes
● **Proteins**	***-peptides*** *(amides)*	Structuring & Functionali-zation
● **Hydrocarbons**	***-saccharides*** *(ethers)*	
● **Nucleic Acids**	***-nucleotide*** *(esters)*	**Genome**

Comments

● First of all, about small and macro molecules

● The biologic life existence and evolution is naturally progressing from small toward great molecular forms. ● Under the temperature of our Planet only Polymeric chains and networks can covalently accumulate energy sufficient for stable resistance against chaotic dissociation. ● They capable of stepwise self-organizing up to bio life basis, starting from lipides to polysaccharides, proteins and nucleic acids.

ANTIVIRAL DRUG DESIGN

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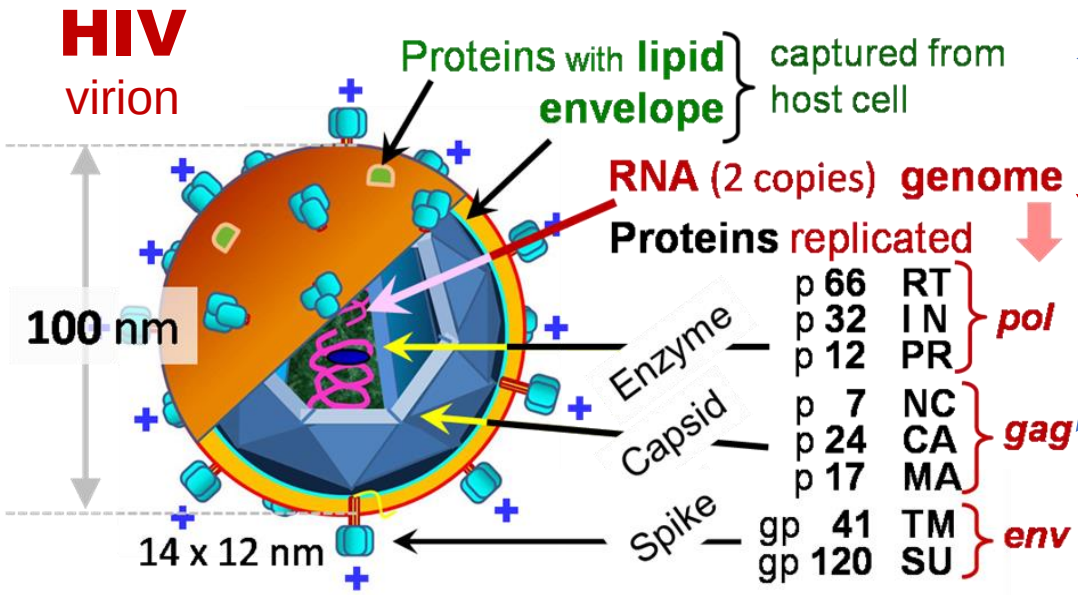
Molecular evolution of biological forms of Life

*Covalently **polymer**ized chains & networks* → to "**Great**"

flexible, but stable self-organization

Extracellular Viral Particles =
max compressed inter-bio-polymeric complexes

Bio Polymer Basis of Cells:



- Lipides → *-methylene motifs*
- Proteins → *-peptides (amides)*
- Hydrocarbons → *-saccharides (ethers)*
- Nucleic Acids → *-nucleotide (esters)*

Membranes

Structuring & Functionali-zation

Genome

Comments

- *The unique compact concentrates of these vital biopolymers, without small molecules ballast, represents extracellular viral particles, the virions. ……They are in fact the maximally compressed inter-bio-polymeric nano-complexes .*

ANTIVIRAL DRUG DESIGN

1. FUNDAMENTALLY PREDICTABLE BASIC PRINCIPLES

1.1. Small and Macro Molecules In view for counter intervention in Viral Life Cycle

Small Size ≤ ≈ 1 nm	Nano Scale ≥ 2 - 500 nm
The Sub-nano sites of:*	The Nano objects:

Targets ↓
Stages

Extracellular Viral Particles (Virions) — I

- Virions' surface local points
- **Virions' surface full scale**

Virions Entry into Cells, and Uncoating — II

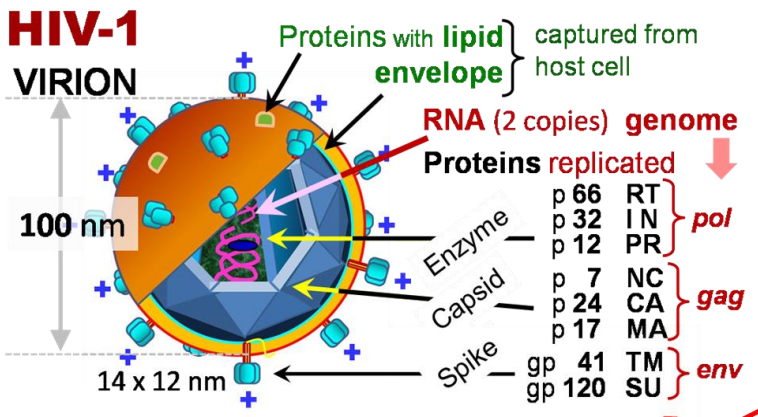
- Virion Spikes*
- Cell Receptors*
- Passage of Ion Channels
- Virion **Spikes**
- Cell **Receptors**
- Cell **membrane Raft –domains**

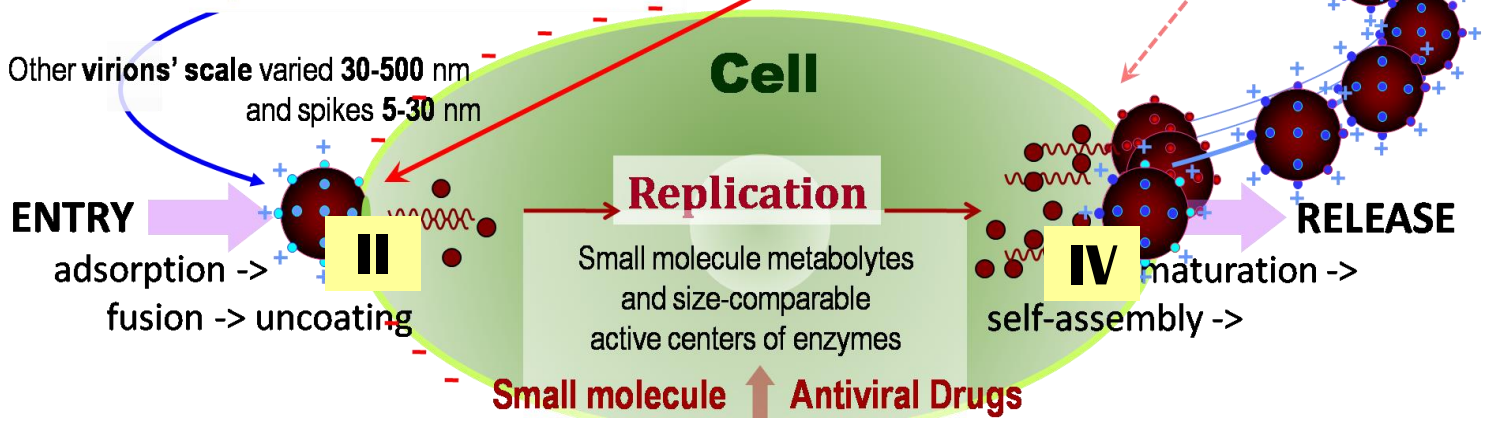
Intracell Replication of Viral Species — III

- **Metabolites**
- **Enzyme Centers**
- Nucleic Acids & complexes

Virions Assenmbly, Maturation, Release — IV

- Pre Assembling points
- Assembling pre-virion nano-units
- Cell membrane Raft –domains





Comments

● This fact is very important in view for any therapeutic counter intervention in a viral life cycle, which could be divided conditionally into 4 stages: I – extracellular Virions, II – Entry into Cell, III – Intracellular replication, and IV – assembly, maturation and release of new virions. ● Only the III stage involves small molecules as metabolites for biosynthesis, While other stages dominantly supported by biopolymeric macromolecules and their nano- complexes
Therefore, the stages I, II, and IV can and should be natural priority for adequate neutralization by exactly macromolecular scale drugs, that we named as "PolyAntivirals". Just that is our general strategy for development of the PolyAntivirals.

Some Basic Principles/Criteria

toward

Poly-ANTIVIRALS

Design – Practical Synthesis

Comments

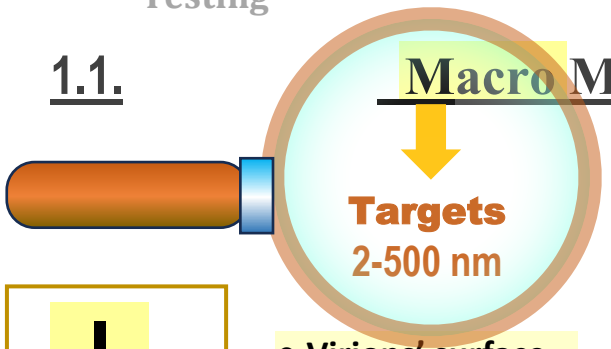
- *The first task is formulation and implementation of same relevant principles and criteria for stepwise design and practical synthesis such products*

Basic Design
Model. Synth.
Testing

ANTIVIRAL DRUG DESIGN

1. FUNDAMENTALLY PREDICTABLE BASIC PRINCIPLES

1.1. Macro Molecules In view for counter intervention in Viral Life Cycle



I Virions
- Virions' surface (incl. **Spikes**)

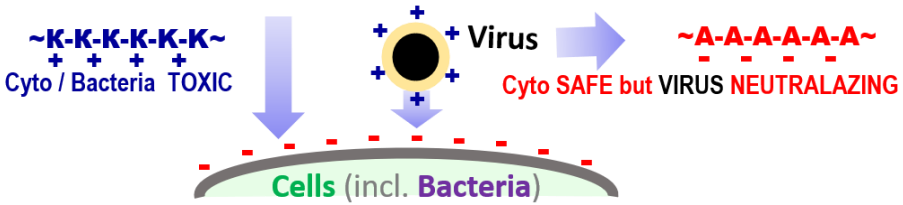
II V. Entry
- Virion **Spikes**
- Cell **Receptors**
- Cell **membrane Raft –domains**
- **Fusion** Mediators

III Replication
- Nucleic Acids & complexes

IV Assembly
- Assembling pre-virion nano-units
- Cell membrane Raft –domains

1.2. Relevant Criteria for Macromolecular (Poly)Antivirals Synthesis

- **Solubility** in aqua-based physiological media → **hydrophilic O / N groups**
- **Charge selectivity** to Virions in competition with Cell's Receptors → **Poly Anions** $^{n-}$



Comments
The 1st is– solubility in aqua media, 2nd – Charge regulated selectivity toward the positively charged virions, used Coulomb forges to be attracted by negatively charged cell's receptors. Exactly the polyanionic polymers may be most effective interceptors of virions in competition with cells, suppressing an adsorption of viruses on cells.

ANTIVIRAL DRUG DESIGN

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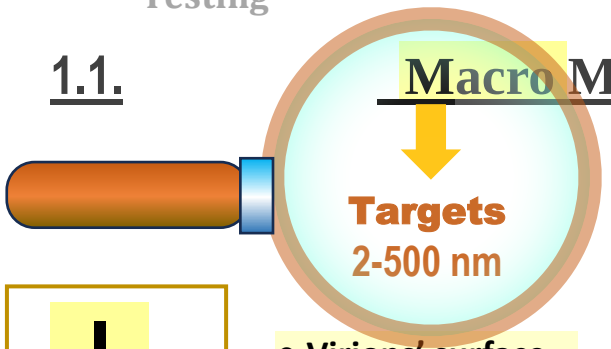

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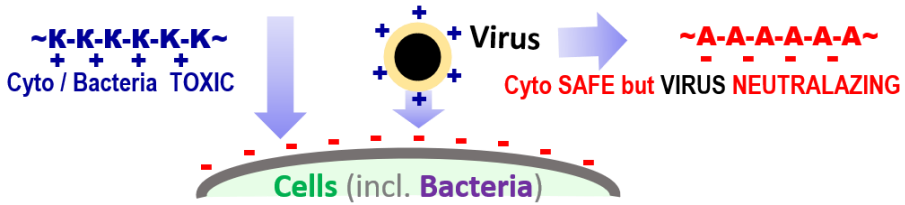
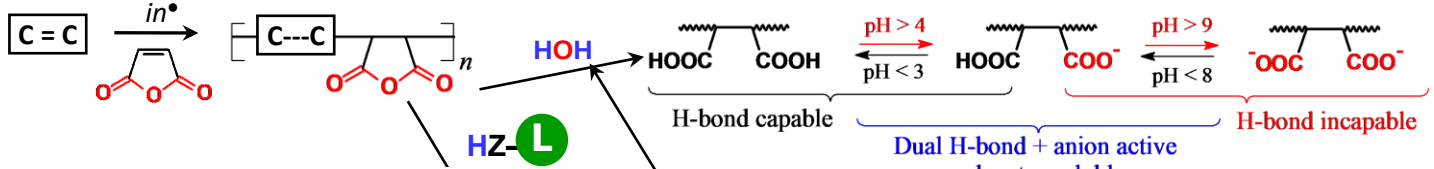
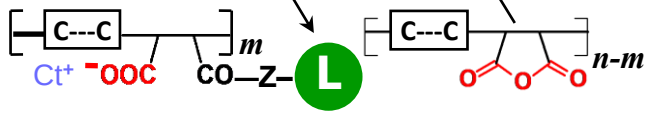


- **Ability to bind Targets via combinations of ionic + H-bonds simultaneously**



- **Modifiability for said Ligands**



Comments

● The bio motivated criteria should be completed by chemical requirements for Ability to bind Targets double effective - using both ionic and hydrogen bonds simultaneously. The most suitable can be intrachain-inserted fragments of succinic acid, that easy obtained from copolymers of maleic anhydride via hydrolysis. Moreover, the anhydride centers are excellent points for covalent linkage of desired ligands in side positions of polymeric chain through aminolysis and/or esterification

Basic Design
Model. Synth.
Testing

ANTIVIRAL DRUG DESIGN

1. FUNDAMENTALLY PREDICTABLE BASIC PRINCIPLES

1.1. Macro Molecules In view for counter intervention in Viral Life Cycle

Stages → **Targets** 2-500 nm

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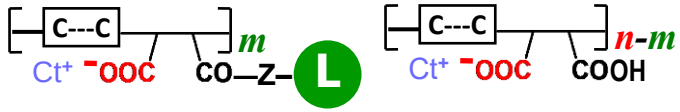
Comments

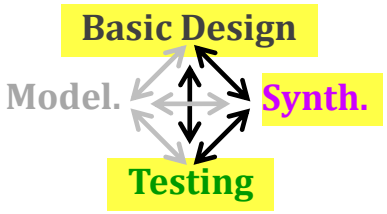
1.2. Relevant Criteria for Macromolecular (Poly)Antivirals Synthesis

Resulted Variant of some Basic Formulation for Synthetically Allowed Poly-Antivirals



Required Combination of Properties	Structural Determinants: Polymerization degree *n*	Succinic Units Ionizable H-bondable $Ct^+ {}^-OOC / \leftrightarrow \backslash COOH$	Co-monomer residue C---C	Side Chain Ligands –Z–L *m/n*
• Nano-competency	Determinant			
• Aqua-Solubility	Co-factor	Determinant	Co-factor	Co-factor
• Bio-Selectivity	Nano-Trigger	Det. Vector	Co-factor	Modulator
• Non-Toxicity	Variator	Determinant	Co-factor	Co-factor
• Anti-Viral Efficiency	Variator	Determinant	Co-factor	Modulator
Immune mediated	Variator	Determinant	Co-factor	Co-factor
Directly Targeted	Nano-Trigger	Co-Vector	Co-factor	Modulator

• *These leads us to the resulted variant of Basic Formulation of candidate for Polyantivirals. Here we have understandable set of macromolecular structure's determinants allows us to regulate their desired properties: Nano-competency, Aqua-solubility, Charge-dependent Bio selectivity, as well: Non-toxicity and Antiviral efficiency, which could be conducted through immune modulation and/or be directly targeted to virus objects in view for above mentioned priority within stages I, II and IV*



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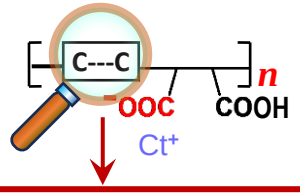
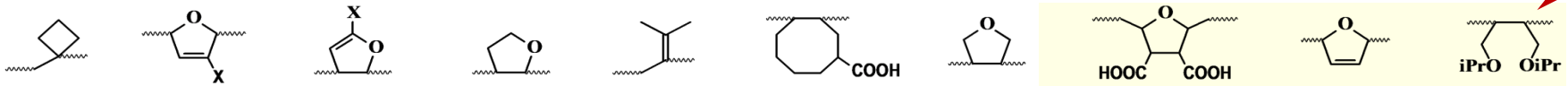
Non Toxicity = *f* (-C---C-)



Increasing the **LD_{50}** (mg/kg) = *decreasing the toxicity*

In vivo, intraperitoneally (i.p.)



90 < 196 ≈ 170-300 < 386 ≈ >400 < 1230 < 1415 < 1600 < >2000 ≈ >2000

Comments

- The next is history of pilot synthesis and selection of most prospective candidates in accordance with criteria of Non-toxicity & (next slide)

Basic Design
Model. Synth.
Testing

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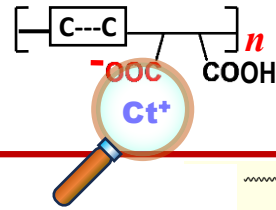
Non Toxicity = *f*(Ct⁺)



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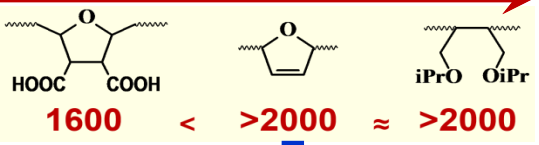

Ct⁺ =	Cu^{++}	Ni^{++}	Zn^{++}	K^{+}	Ba^{++}	H^{+}	$Pt^{***++}(NH_3)_2$	$Pd^{++}(NH_3)_2$	Sr^{++}	Li^{+}	NH_4^{+}	Ca^{++}	Na^{+}	
%	25	25	25	50	25	100	25	25	25	50	50	25	50	
LD_{50} =	90	190	470	> 1000	1100	1600	1700	2000	> 2000	> 2000	> 2000	> 2000	> 2000	*mg/kg*

Comments

Next slide

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Model. Synth.
Testing

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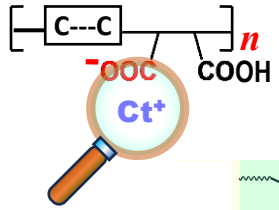

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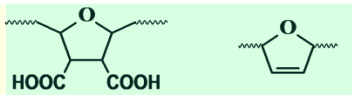

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Anti-Viral Efficiency *Immune mediated*

IFN =	≤ 10	≤ 10	≤ 80	≤ 320	≤ 80	≤ 80	≤ 10	≤ 40	≤ 40	≤ 40	≤ 10	≤ 80	≤ 320	*mg/kg*
Ig =	---	---	60	310	160	280	170	---	60	---	---	190	360	*mg/kg*

Comments

And Antiviral potency, at least, of an immune mediated mode

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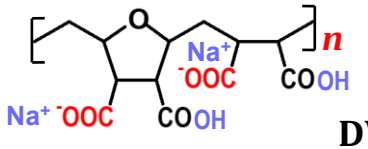
Leaders for Non Toxicity + *immune stimulation:*



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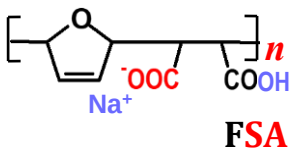

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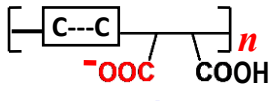

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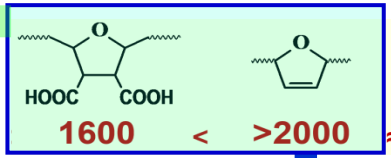

≈ >2000

Ct^+ =	Cu^{++}	Ni^{++}	Zn^{++}	K^+	Ba^{++}	H^+	$Pt^{++(NH_3)_2}$ ***	$Pd^{++(NH_3)_2}$	Sr^{++}	Li^+	NH_4^+	Ca^{++}	Na^+	
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Anti-Viral Efficiency														*Immune mediated*
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Comments

- Finely we come to the displayed two copolymeric structures

Basic Design
Model. Synth. Testing

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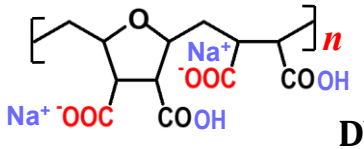

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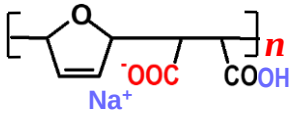
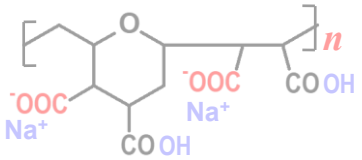
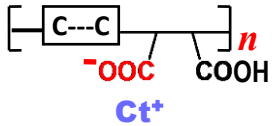


FSA





In vivo, intraperitoneally (i.p.)

in vivo, Protection, %		
TBV	**RbV**	**EEEV**
65(-)	55(82)	65(95)

In vivo evaluations were performed under the **lethally hard conditions** up to **200 LD_{50}** of Viruses (in brackets – for combined: **PolyAntivirals + Vaccine**)

Anti-Viral Efficiency *Immune mediated*

Comments

• *and following bio evaluations in vivo revealed highly significant capacity of these polyanionic compound protecting mace or rats against lethal doses of neuroviral infections.*

Immune mediated Potency

+

Direct

Anti-Viral Targeting

Amplification

Comments

The next step of the Polyantivirals development was oriented to combining the immune mediated potency with an additional capacity for direct anti-viral targeting impacts

Basic Design
Model. Synth.
Testing

ANTIVIRAL DRUG DESIGN

1. FUNDAMENTALLY PREDICTABLE BASIC PRINCIPLES

1.1. Macro Molecules In view for counter intervention in Viral Life Cycle

Stages → **Targets** 2-500 nm

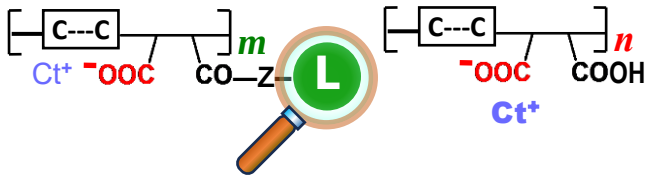
Stages	Targets 2-500 nm
I Virions	• **Virions'** surface (incl. **Spikes**)
II V. Entry	• Virion **Spikes** • Cell **Receptors** • Cell **membrane Raft –domains** • **Fusion** Mediators
III Replication	• Nucleic Acids & complexes
IV Assembly	• Assembling pre-virion nano-units • Cell membrane Raft –domains

1.2. Relevant Criteria for Macromolecular (Poly)Antivirals Synthesis

Resulted Variant of some Basic Formulation for Synthetically Allowed Poly-Antivirals

• **NEXT GENERATIONS**

The **L**-co-SAR-programmed directly against Viral Targets



In vivo, intraperitoneally (i.p.)

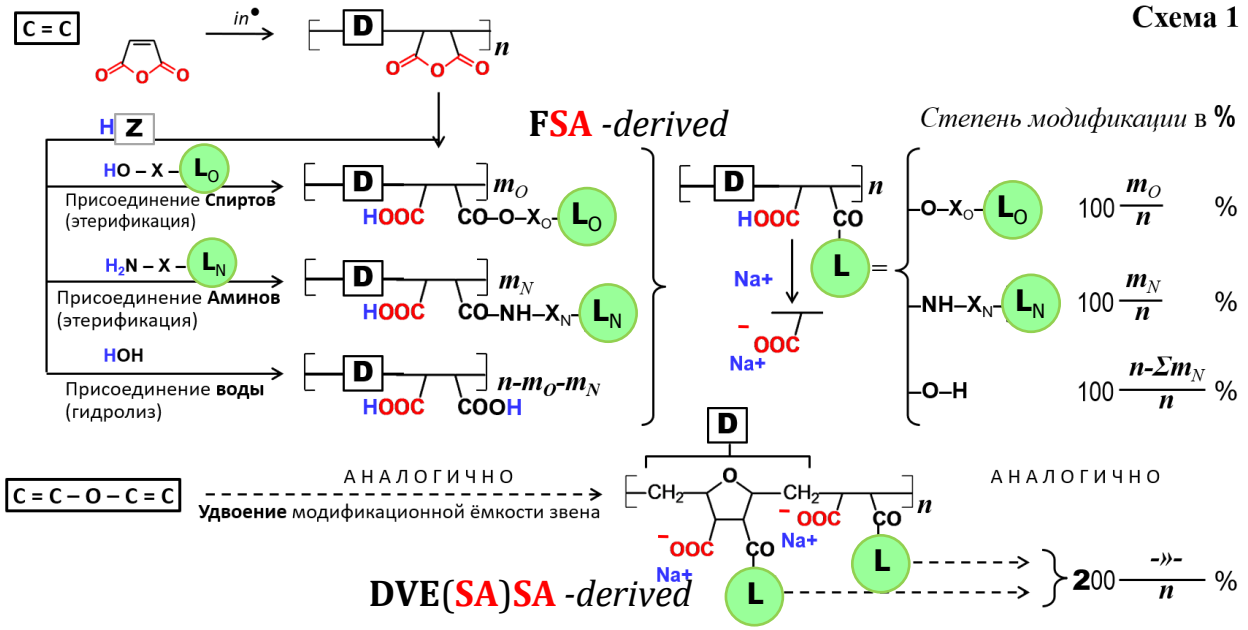


Схема 1

in vivo, Protection, %		
TBV	**RbV**	**EEEV**
65(-)	55(82)	65(95)

In vivo evaluations were performed under the **lethally hard conditions** up to **200 LD_{50}** of Viruses (in brackets – for combined: **PolyAntivirals + Vaccine**)

Comments

This task was taken into realization via chain's side positions modification by desired combinations of ligand-expecting species, even if they are not active in small molecule forms. • We propose an ability of they activation to detectable levels of purposed bio activity due to a rational cointegration together on the prepared platforms of polymeric chains. • Similarly macromolecular programming the protein and nucleic acid biopolymeric chains by certain combinations of side-groups6 we hope to find novel artificial combinations of so called "synthetic" polymers which could programmed these polymers toward virus-specific targets

Basic Design

Model. Synth. Testing

ANTIVIRAL DRUG DESIGN

1. FUNDAMENTALLY PREDICTABLE BASIC PRINCIPLES

1.1. Macro Molecules In view for counter intervention in Viral Life Cycle

Stages → **Targets** 2-500 nm

I Virions

- Virions' surface (incl. **Spikes**) ← 1, 2

II V. Entry

- Virion **Spikes** ← 1, 2
- Cell **Receptors** ⊂ 1,2
- Cell **membrane Raft –domains** ← 5
- **Fusion** Mediators ← 3,4

III Replication

- Nucleic Acids & complexes ⊂ 1,2

IV Assembly

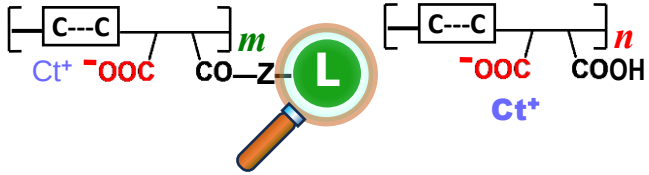
- Assembling pre-virion nano-units ⊂ 6
- Cell membrane Raft –domains ← 5

1.2. Relevant Criteria for Macromolecular (Poly)Antivirals Synthesis

Resulted Variant of some Basic Formulation for Synthetically Allowed Poly-Antivirals

Next Generations

The **L**-co-SAR-programmed directly against Viral Targets



In vivo, intraperitoneally (i.p.)

№	–Z–L		m/n	*in vitro*, SI = CC_{50}/IC_{50}			*in vivo*, Protection, %		
				HIV	Infl.	CMV	TBV	RbV	EEEV
1	No Side Ligands	Small Molecules are not Effective	0	10-100	≤ 30	≤ 350	65(-)	55(82)	65(95)
2	-Z-SO_3^-	Polymer based generations	≤ 0.80	>680	→10000	7500	*In vivo* evaluations were performed under the **lethally hard conditions** up to **200 LD_{50}** of Viruses (in brackets – for combined: **PolyAntivirals + Vaccine**)		
3	-Z-**Nb**		0.1-0.3	>3300	>2140	240			
4	-Z-**Ad**		0.1-0.3	>1100	→10000	25			
5	-Z-**Chol**		≤ 0.03	>220	5400	-			
6	-Z-**Pept** Cell Receptors		≤ 0.02	→10000	-	-			
7	-Z-**Pept** Viral (HIV, MA)		≤ 0.01	+	← Test-Samples are completed for bio evaluations				

Comments

● And today we have, at least, seven original generations that possess many-folds more higher and widen antiviral activity in comparison with known small molecule prototypes. . The correspondent indexes of selectivity for inhibition of HIV, Influenza, Cytomegalo viruses, as examples, are shown in the Table.. The markers to the left indicate the most expected virus-specific targets for the each generation in correspondence with stages of a viral life cycle.

Modeling

the interactions between

Poly-ANTIVIRALS (of 1-4 generations)

and **Viral Fusion mediated Proteins**

gp41 (**HIV**), **HA2** (**Influenza**), **Gp2** (**Ebola**)

…

Comments

Of cause, some of that polymeric compounds should be investigated in details applying modern possibilities of computer-aided modeling

Basic Design

Model. Synth. Testing

ANTIVIRAL DRUG DESIGN

2. MODELING the POLY-ANTIVIRALS ↔ VIRAL TARGETS

2.1. Macro Molecular Products synthesized within the generations 1, 2, 3, 4

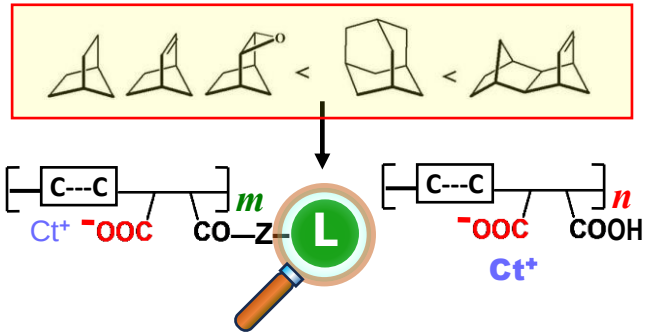
Stages | **Targets 2-500 nm**

I Virions
- Virions' surface (incl. Spikes) ← 1, 2

II V. Entry
- Virion Spikes ← 1, 2
- Cell Receptors ↔ 1,2
- Cell membrane Raft –domains ← 5
- **Fusion** Mediators ← **3,4**

III Replication
- Nucleic Acids & complexes ↔ 1,2

IV Assembly
- Assembling pre-virion nano-unit
- Cell membrane Raft –domains



Next Generations

The **L**-co-SAR-programmed directly against Viral Targets

№	–Z–**L**	*m*/*n*	*in vitro*, **SI** = CC_{50}/IC_{50}			*in vivo*, Protection, %		
			HIV	**Infl.**	**CMV**	**TBV**	**RbV**	**EEEV**
1	No Side Ligands	0	10-100	≤ 30	≤ 350	65(-)	55(82)	65(95)
2	-Z-SO_3^-	≤ 0.80	>680	→10000	7500			
3	-Z-**Nb**	0.1-0.3	>3300	>2140	240			
4	-Z-**Ad**	0.1-0.3	>1100	→10000	25			

Strongly **effective** ● **Antiviral protection** + ● **Drug resistance prevention**
fundamentally predicted
by virtue of the
● **Polymer capacity for multipoint covering** the **viral Nano-Targets**

Comments

● *First of all, there are generations 3 and 4 where the norbornane (terpenoid related) and adamantane-derived side ligands has been used, in comparison with 1 and 2 generations*

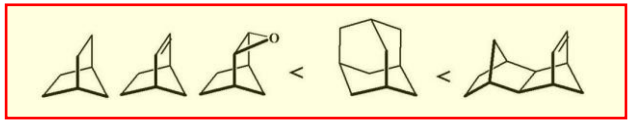
ANTIVIRAL DRUG DESIGN

2. MODELING the POLY-ANTIVIRALS ↔ VIRAL TARGETS

2.1. Small and Macro Molecular Products synthesized within the generations 1, 2, 3, 4

Stage II
Virus Entry

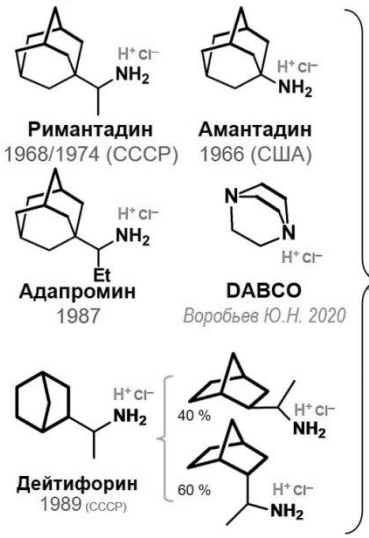
L

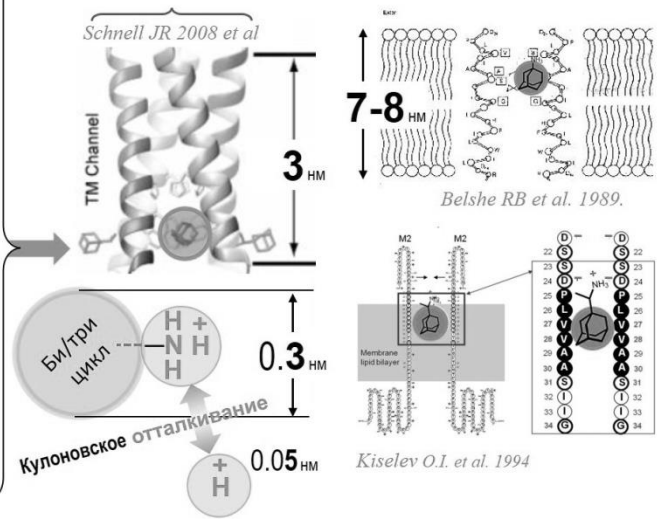


Amantadine, Rimantadine, Deitiforin, … are well known to be a fairly good **inhibitors of some Influenza type A viruses,**

but without any significant protection against other viruses

Amino derivatives of Adamantane (**Ad**), Norbornane (**Nb**) ➡ **Virus of Influenza type A** block the very small gate of ion (proton) channel between 4 nano-scale molecules M2





Objectively:
the **small** size → the **highly limited effectiveness & applicability**

- within the **only size adequate - very specific targets**, which can be not typical for other viruses
- because of easily allowed **Drug Resistance** – by simplest (one point) mutations of virus
- in virtue of an enhanced **Permeability** through **bio-protective barriers** → resulted in hardly controllable **risks of toxicity**

Comments

● The small molecule prototypes such as rimantadine and similar are well known to be a fairly good inhibitors of some Influenza type A viruses, but without any significant protection against other viruses. ● However, considered here approach to the 'Polyantivirals' implies novel possibilities for powerful amplification of the small molecules' potency due to their rational cointegration into the polyanionic macromolecules,

Basic Design

Model. Synth. Testing

ANTIVIRAL DRUG DESIGN

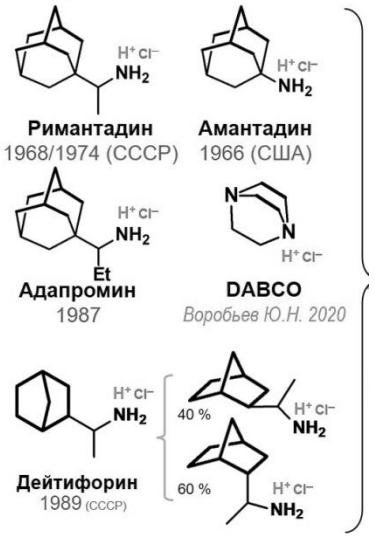
2. MODELING the POLY-ANTIVIRALS ↔ VIRAL TARGETS

2.1. Small and Macro Molecular Products synthesized within the generations 1, 2, 3, 4

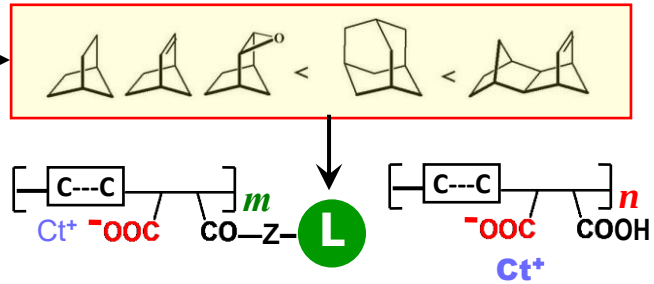
Stage II
Virus Entry

Rimantadine + many variations

Amino derivatives of
Adamantane (**Ad**), Norbornane (**Nb**)



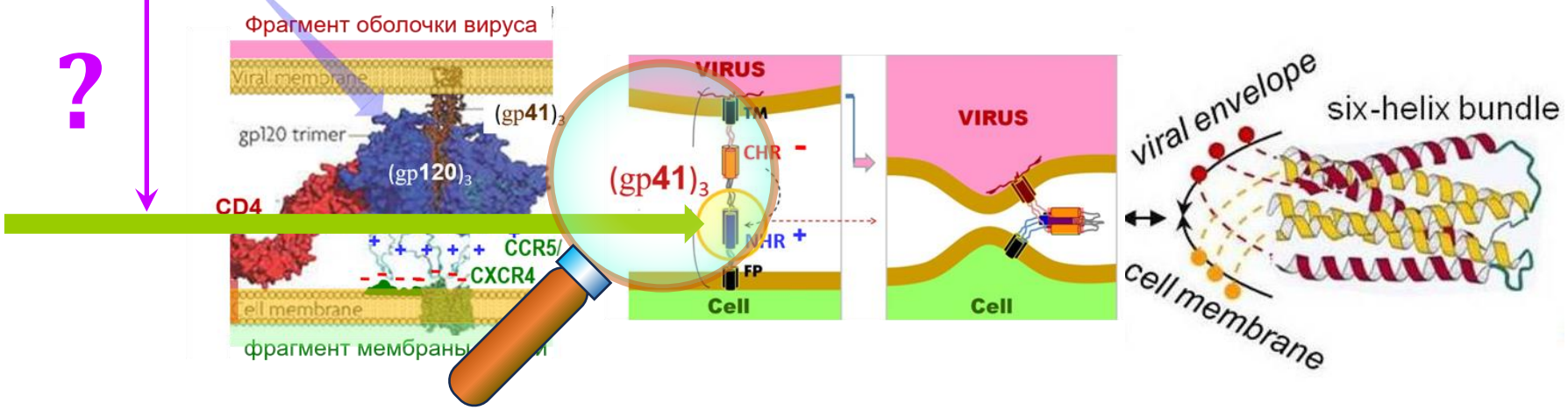
HZ--- L



Poly-Antivirals, *Generations* **3** *and* **4**

HIV-1
Stage II Entry,
Sub-Step **Fusion** *of Vir. Envelope with Cell Membrane mediated by glycoprotein* $(gp41)_3$ **=** *nano*-**Target?**

?



Comments

● That has been first demonstrated experimentally by our research group in relation to rimantadine resistant viruses of Influenza and HIV ● Particularly, the gp41, being key mediator of HIV fusion, was found could be the most probable nano-target of anti-HIV protection by these Polyantivirals.. Extraction from literature data includes modelling works, and analysis these data lead us to NHR region of gp41, as a most probable target

ANTIVIRAL DRUG DESIGN

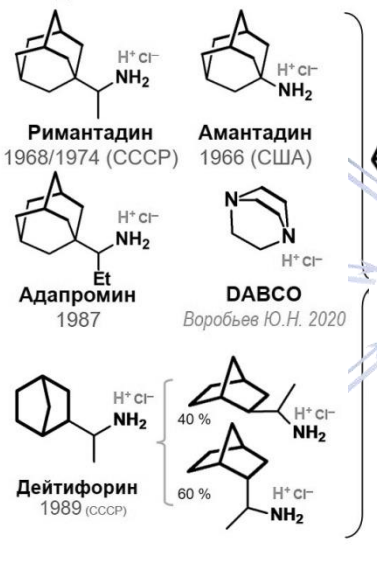
2. MODELING the POLY-ANTIVIRALS ↔ VIRAL TARGETS

2.1. Small and Macro Molecular Products synthesized within the generations 1, 2, 3, 4

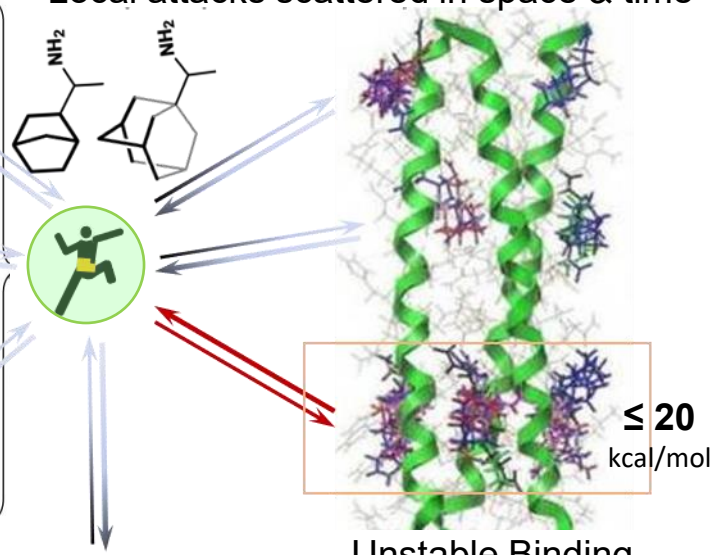
Stage II
Virus Entry

Rimantadine + many variations

Amino derivatives of
Adamantane (**Ad**), Norbornane (**Nb**)



Local attacks scattered in space & time

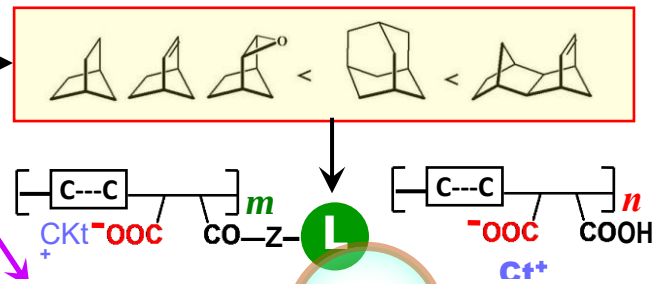


Unstable Binding

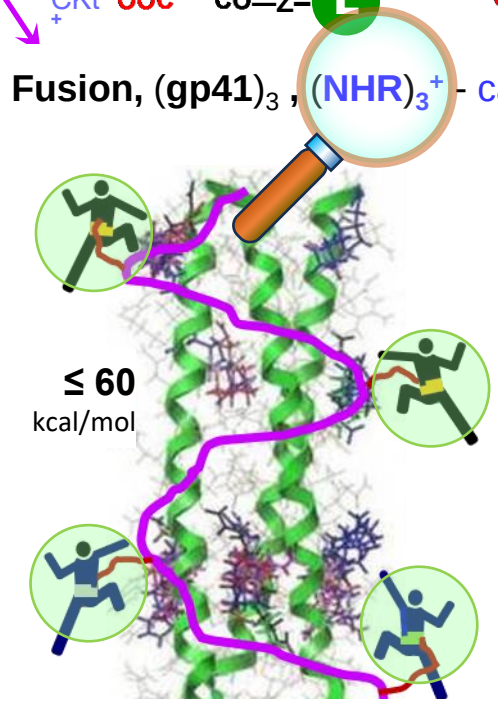
HZ--- L

Poly-Antivirals, *Generations* **3** *and* **4**

DOCKING



HIV-1, Stage II Entry, Fusion, $(gp41)_3$, $(NHR)_3^+$ - cationic domain = *nano*-Target?



Binding **strongly Stabilized** by Polymeric Chain

Polymer chain – combines small precursors together, supporting:

- **multi-point cooperative attacks**
- **mutual reinforcing in space & time**
- Polymer **Charge-selective** orientation toward the **cationic Target**

Chain flexibility allows ligand-cooperating **adaptation** to the **Target**

Comments

• The small molecule carbocycles inefficiency against HIV fusion is well explained by the Docking modeling, The binding energies are to slow to provide a stable blocking. The observed multiple binding-permitted sites allows to conclude that these small molecules capable of only local attacks, scattered in space and time. But they incapable working together in mutual coordination against the target. • However the required possibility can be achieved hypothetically on basis of integrated polymeric chains

Basic Design

Model. Synth. Testing

ANTIVIRAL DRUG DESIGN

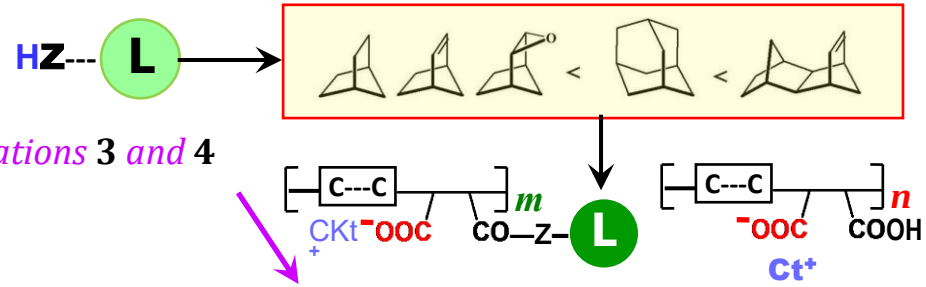
2. MODELING the POLY-ANTIVIRALS ↔ VIRAL TARGETS

2.1. Small and Macro Molecular Products synthesized within the generations 1, 2, 3, 4

Stage II Virus Entry

Vladimir B. Tsvetkov, *Alexander V. Serbin, et al.*

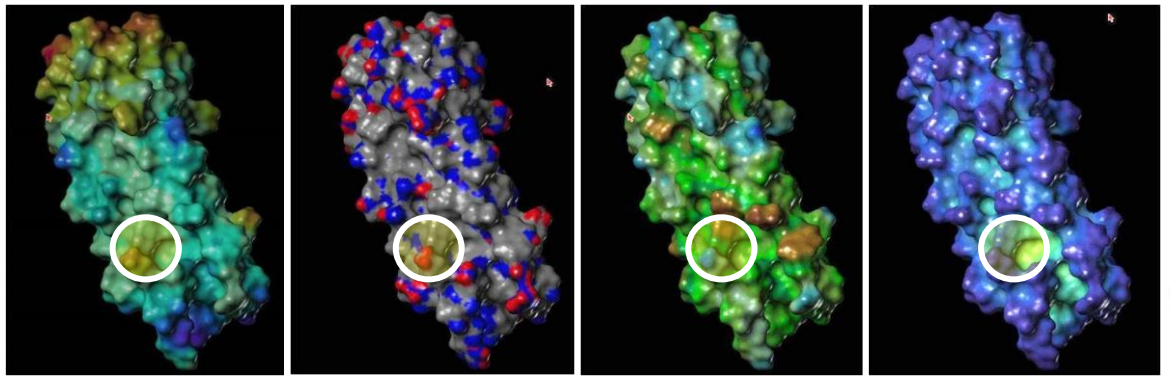
Биотехнология – 2012. – № 1. – С. 72-89:
Applied Biochem Microbiol – 2012. - N 9. – P. 723-739.
J Comp-Aided Mol Design – 2012 – 26(12):1369-1388
J Comp-Aided Mol Design – 2014 – 28(6):647-673;

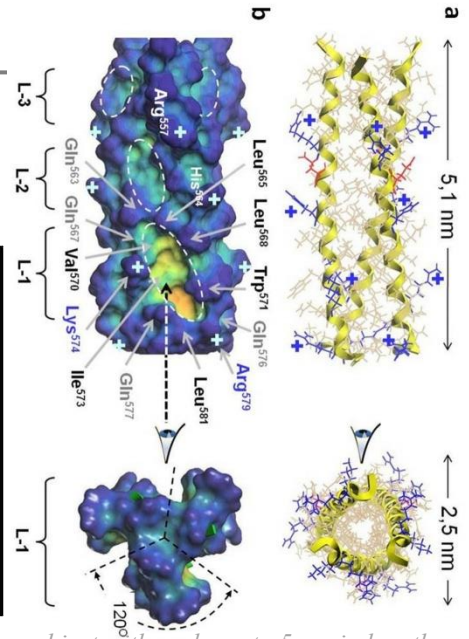


DOCKING

HIV-1, Stage II Entry, Fusion, $(gp41)_3$, $(NHR)_3^+$ - cationic domain = *nano*-Target?

Electrostatic Potential (EP) | H-bonding Sites (HB) | Lipophilic Potential (LP) | Cavity Depth (CD)





Comments

• *The Docking and MD exploration undertaken in collaboration with Vladimir Tsvetkov has been launched from pre-investigation of the Target parameters. Particularly it is typical nano-object with scale up to 5 nm in length, enriched by positive charged amino acids potentially sensitive to polyanionic chains*

Basic Design

Model. Synth. Testing

ANTIVIRAL DRUG DESIGN

2. MODELING the POLY-ANTIVIRALS ↔ VIRAL TARGETS

2.1. Small and Macro Molecular Products synthesized within the generations 1, 2, 3, 4

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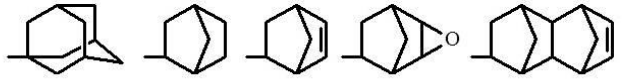
J Comp-Aided Mol Design – 2012 – 26(12):1369-1388
J Comp-Aided Mol Design – 2014 – 28(6):647-673;

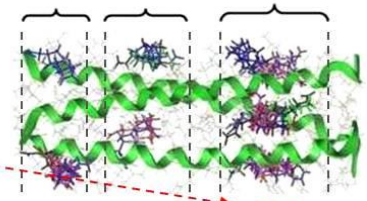
Step 1 Separate backbone unit or pendant anchor (small molecule) models, e.g. :

X = Y-Anc -Anc =

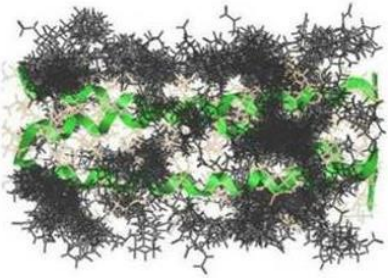


- 16.6 - 15.1 - 16.8 - 18.7 kcal/mol

(1)

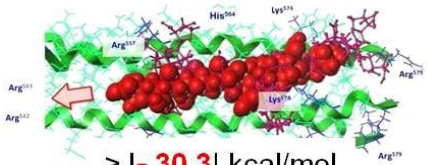


DOCKING



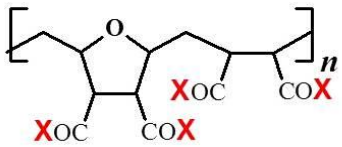
Step 2 Polymeric chain motifs

L1 L2 L3

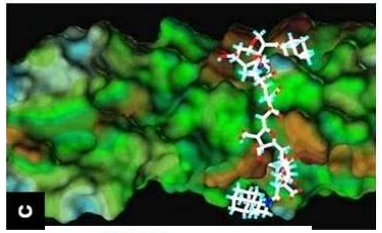


≥ |- 30.3| kcal/mol

(2)

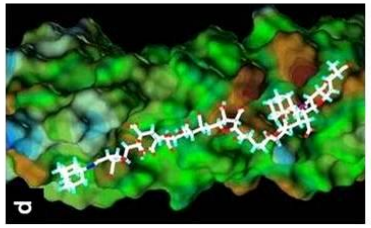


(3)

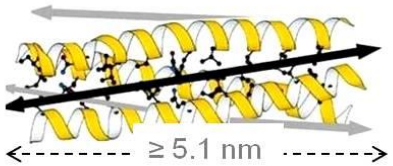


≥ |- 58.0| kcal/mol

(4)

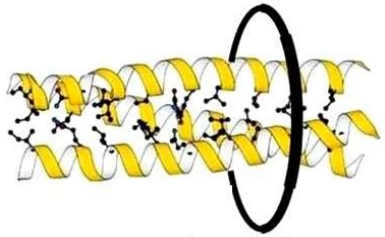


≥ |- 70.6| kcal/mol



minimum ***n*** ≥ 3-4

optimum ***n*** = 5-6



minimum ***n*** ≥ 4, + 2 Anc

optimum ***n*** = 9-12, + 3 Anc

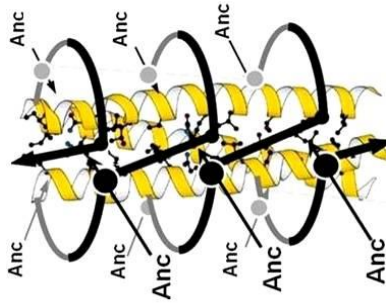
(5)

Step 3 Extrapolation toward

1) ***n*** → 30-50

2) effective Anc ≥ 9 (≥ 6-8% from all X)

Predicted ΔG_{min} ≤ - 200 kcal/mol



Comments

● *Then docking of small size structural fragment from backbone of polymeric chain, as well side-ligands and linkers were performed with following stepwise elongation of models toward bigger parts of polymeric antiviral molecule till the scale that permitted by docking program applied. Further the data obtained were used for extrapolations to scale comparable with original polymer compound.*

Basic Design

Model. Synth. Testing

ANTIVIRAL DRUG DESIGN

2. MODELING the POLY-ANTIVIRALS ↔ VIRAL TARGETS

2.1. Small and Macro Molecular Products synthesized within the generations 1, 2, 3, 4

Stage II Virus Entry

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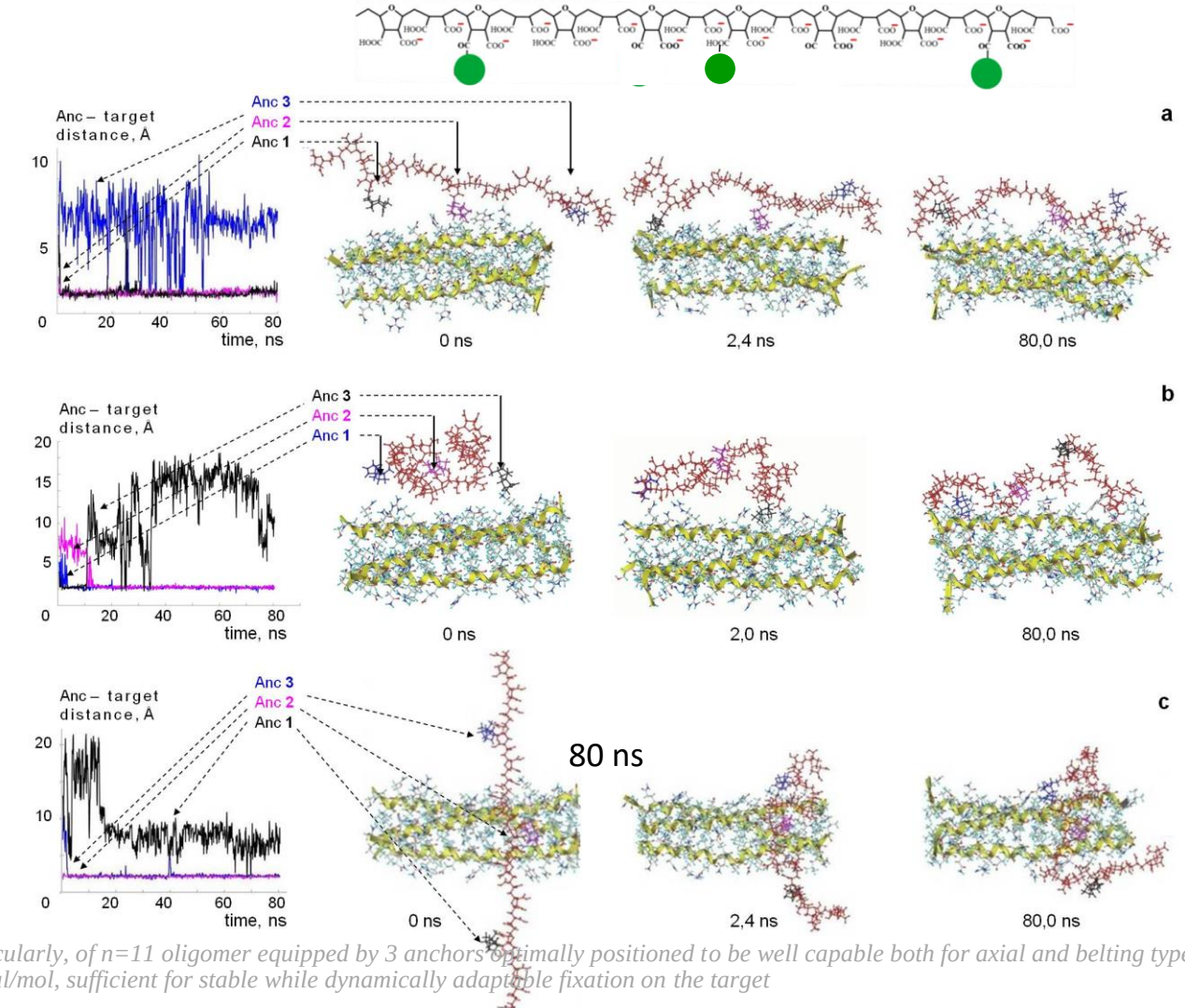


DOCKING
+ MOLECULAR DYNAMICS

- **63.0** ± 9.7 *kcal/mol*

- **59.1** ±12.5 *kcal/mol*

- **61.8** ±14.5 *kcal/mol*

Comments

- *The studies were completed by molecular dynamics, particularly, of n=11 oligomer equipped by 3 anchors optimally positioned to be well capable both for axial and belting types binding*

This model demonstrated good binding energy nearly 60 kcal/mol, sufficient for stable while dynamically adaptable fixation on the target

Basic Design

Model. Synth. Testing

ANTIVIRAL DRUG DESIGN

2. MODELING the POLY-ANTIVIRALS ↔ VIRAL TARGETS

2.1. Small and Macro Molecular Products synthesized within the generations 1, 2, 3, 4

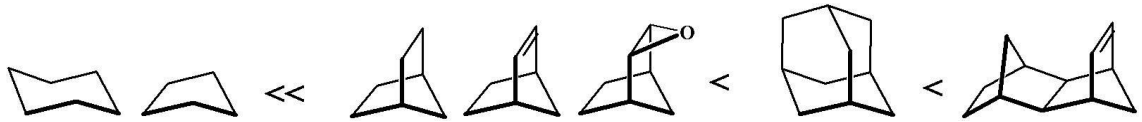
Stage II Virus Entry

Small Molecules

HZ--- L

ΔE kcal/mol

Antiviral SI



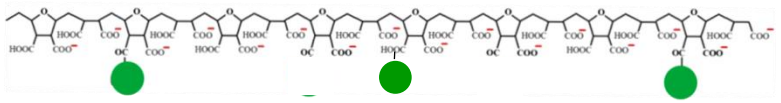
≤ [-12.7] ≤ [-13.8]---[-15.6] ≤ [-16.7] ≤ [-18.4]

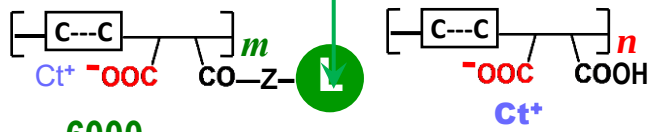
DOCKING + MD

Binding Energy

No detectable and statistically significant anti-HIV activity

Poly-Antivirals





Antiviral SI: < 10 → 900 → 1100 → 6000

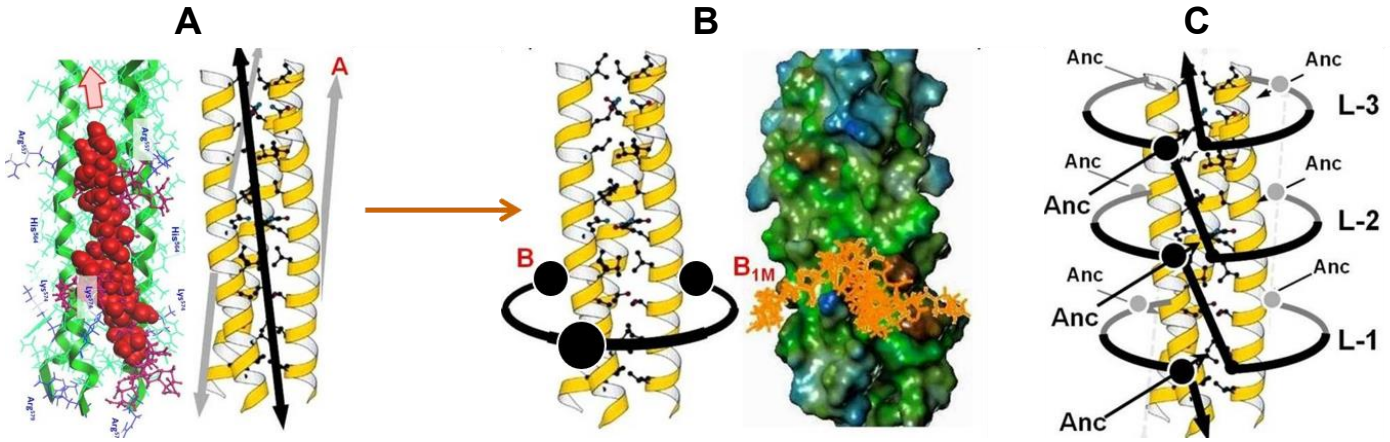
ΔE kcal/mol: ≥ [-(50 → 70)], if *n* ≥ 9-12 and *m* ≥ 3

→ ≥ [- 200 …], when *n* ≥ 30-35 and *m* ≥ 9

Binding Energy

Vladimir B. Tsvetkov, *Alexander V. Serbin, et al.*

Биотехнология – 2012. – № 1. – С. 72-89:
Applied Biochem Microbiol – 2012. - N 9. – P. 723-739.
J Comp-Aided Mol Design – 2012 – 26(12):1369-1388
J Comp-Aided Mol Design – 2014 – 28(6):647-673;



Binding Mode Regulation:

A – *Axial* *n* ≥ 4-6, *m* → 0

B – *Belting* *n* ≈ 4-12 *m* ≈ 2-3

C - *Combined* *n* ≥ 30-50 *m* ≥ 9

Comments

- *The results obtained are in well correlation with experimentally detected anti-HIV-1 activity in vitro*

Finally, the tree modes of the targe binding were found (axial, belting, combined) in dependance on degree of polymerization and in comparison with grade of side modification by hydrophobic carbocyclic ligands (anchors) and their configuration

Polymeric Chain Synthesis

Molecular Mass – Size

regulation

Comments

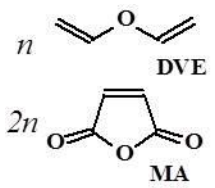
- *In view of important role of the polymerization degree, related to molecular mass, the next task of special modeling was oriented toward the problem of the mass control under practical synthesis of precursors for polymeric chains*

ANTIVIRAL DRUG DESIGN

3. POLY-ANTIVIRALS SYNTHESIS CONTROL FOR CHAIN SIZE

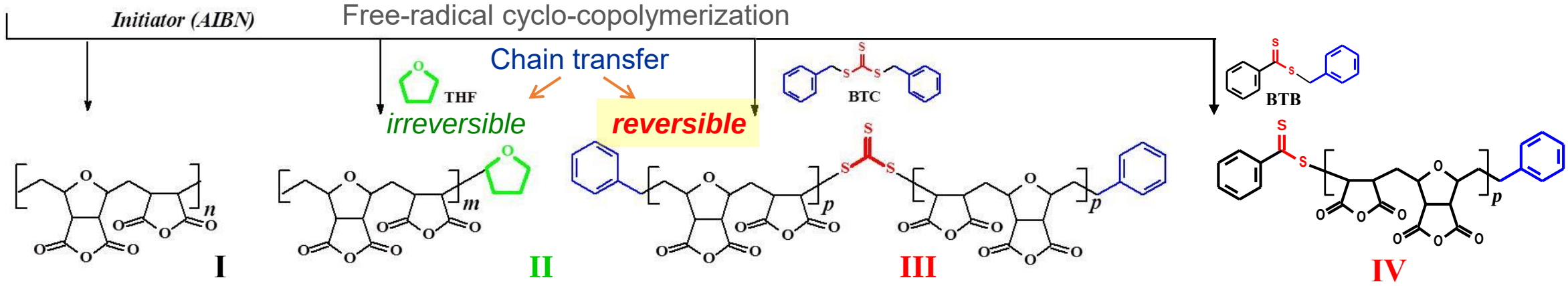
3.1. Providing the MM and MMD of Polymeric Basis required for the purposed bioactivity

The widely used methods for control of MM and MMD required in **practical synthesis**:



(**MM**) – Molecular Mass and their distribution (**MMD**)

n – degree of polymerization ⇔ the Polymeric Chain's length / size



Comments

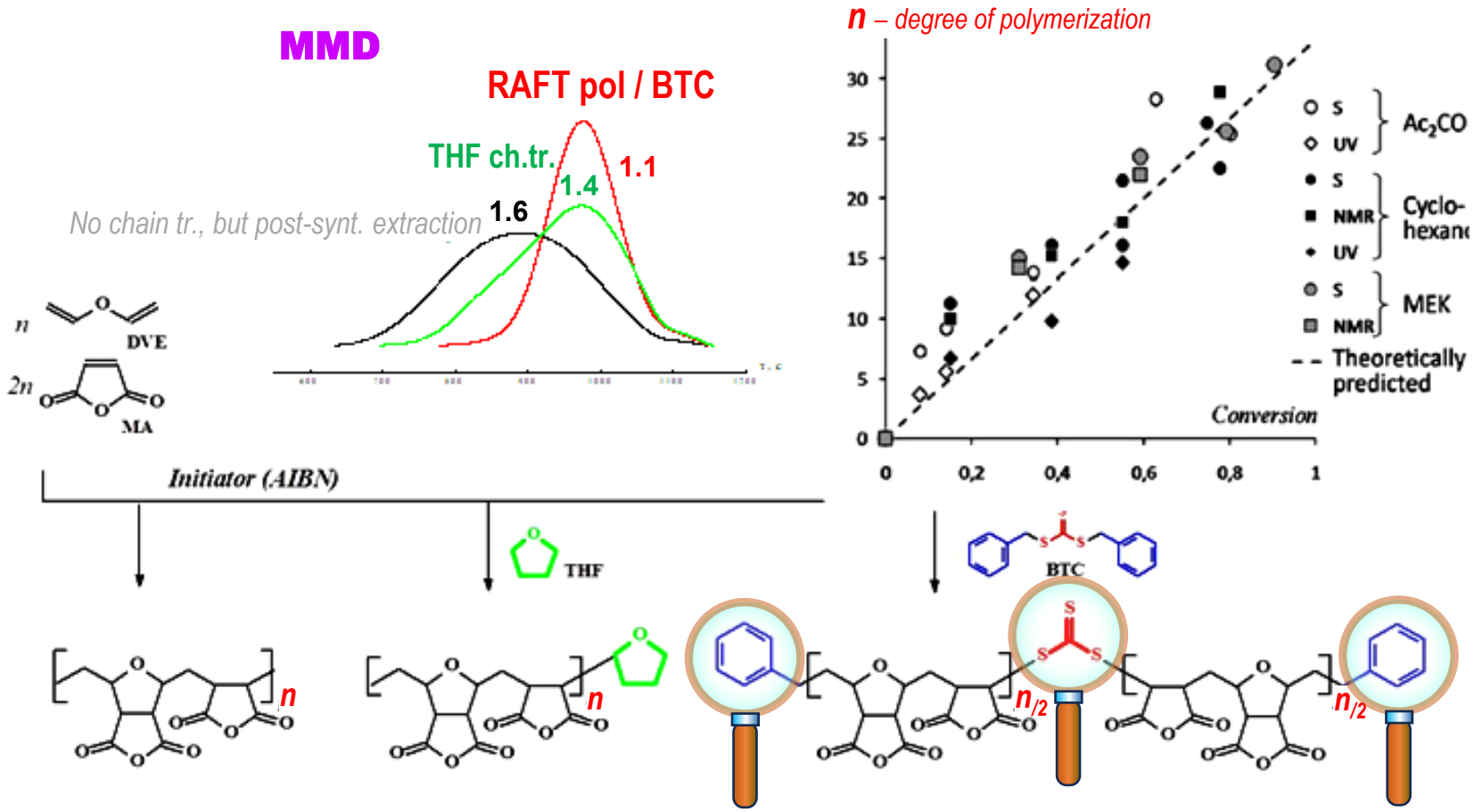
Serbin A., Karaseva E., Chernikova E., et. al . ***Graft and RAFT Reactive Macro Reagents: …*** Macromol Symp, ***2010***, 296 (1):80-91
Serbin A. V., Karaseva E. N., Dunaeva I. V., et al ***Controlled Free-Radical Copolymerization …*** Polym Sci, B, ***2011***, 53 (3–4):116–124...

for regulation of polymeric chains propagation during the polymerization commonly chain transfer agent of irreversible or reversible modes are used

ANTIVIRAL DRUG DESIGN

3. POLY-ANTIVIRALS SYNTHESIS CONTROL FOR CHAIN SIZE

3.1. Providing the MM and MMD of Polymeric Basis required for the purposed bioactivity



Comments

- *In studied case the best MM-controlling results were observed for reversible three thiocarbonate RAFT-agent*

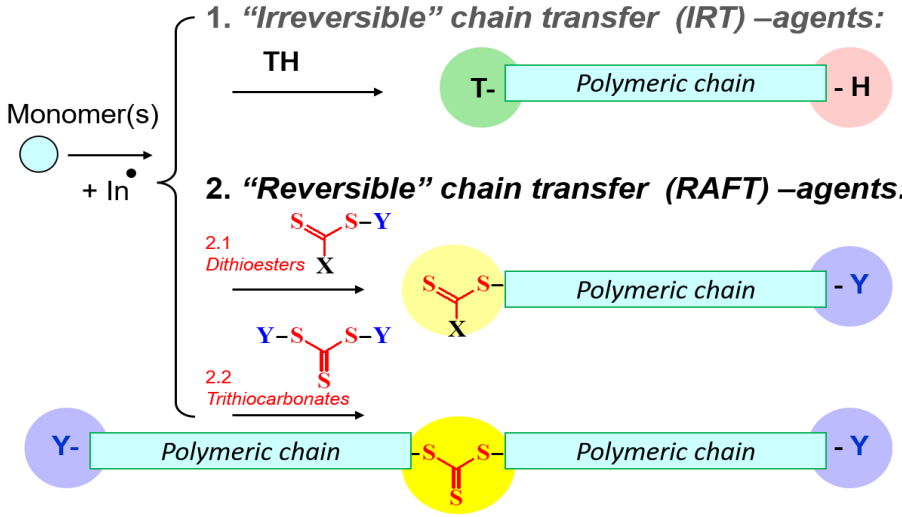
However this method have one by-effect: inserting the threethiocarbonate residue in center of chain and the benzene cycles – in both tails of the chain

ANTIVIRAL DRUG DESIGN

3. POLY-ANTIVIRALS SYNTHESIS CONTROL FOR CHAIN SIZE

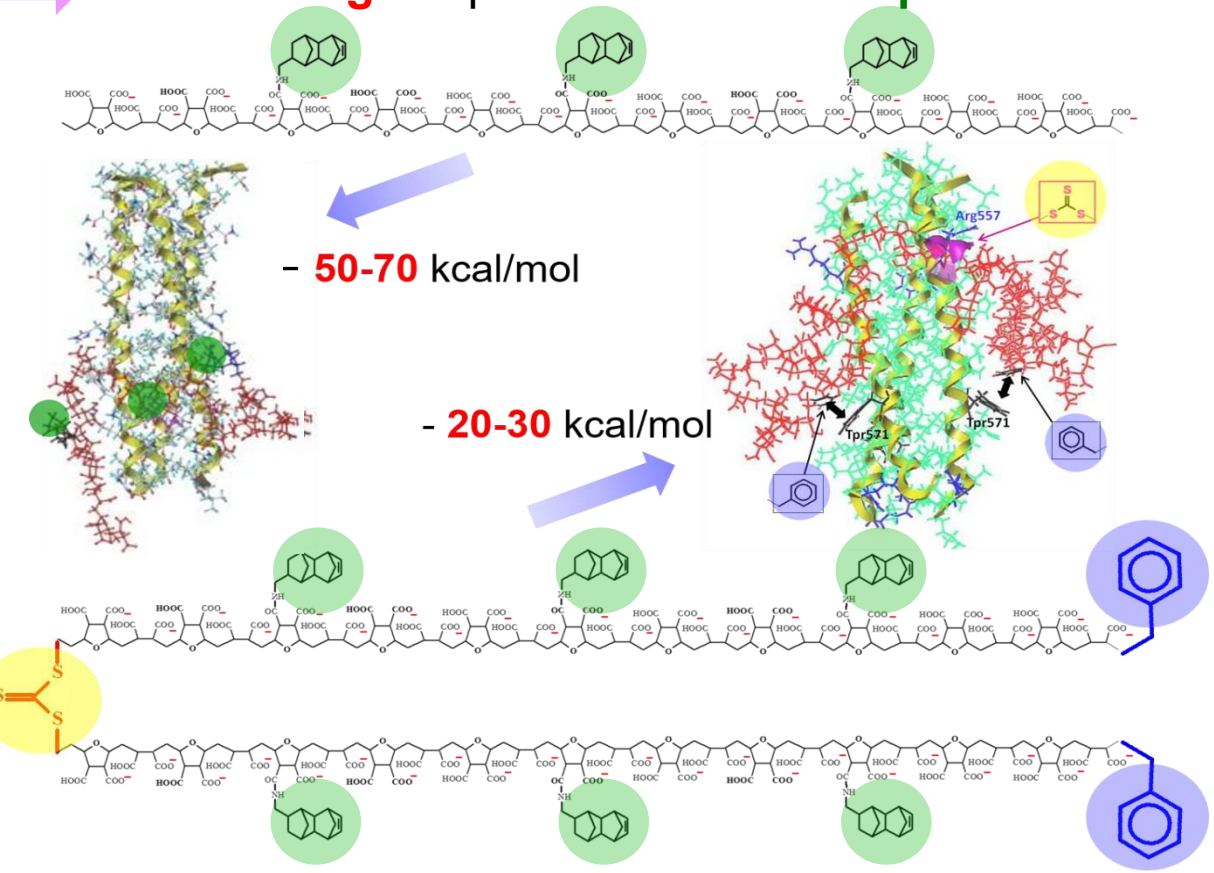
3.1. Providing the MM and MMD of Polymeric Basis required for the purposed bioactivity

The control required for **Practical Synthesis**:



Modeling the possible **bio consequences:**

DOCKING + MD



Reverse corrections for the **Synthesis methodology**

Comments

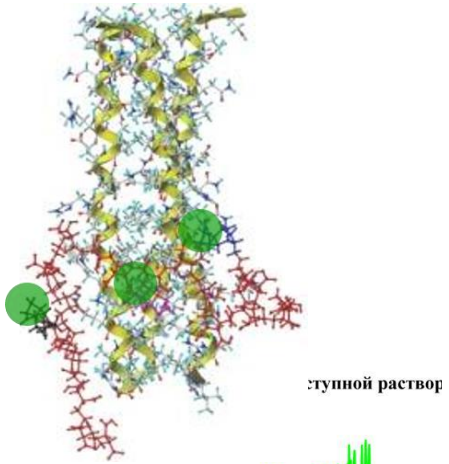
- *So prior usage these methods we need estimate the possible bio consequences*
- *The MD shown significant decreasing the binding energy crucially required for purposed antivoiral activity.*

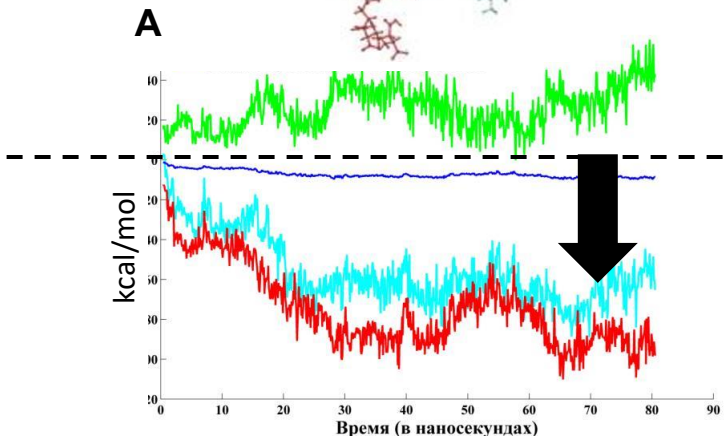
Therefore it indicates the necessity to find reverse corrections of the practical synthesis methodology to prevent or remove the undesired micro insertions within polymeric chain

ANTIVIRAL DRUG DESIGN

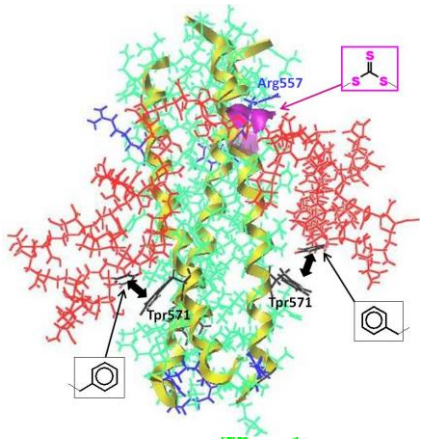
3. POLY-ANTIVIRALS SYNTHESIS CONTROL FOR CHAIN SIZE

3.1. Providing the MM and MMD of Polymeric Basis required for the purposed bioactivity

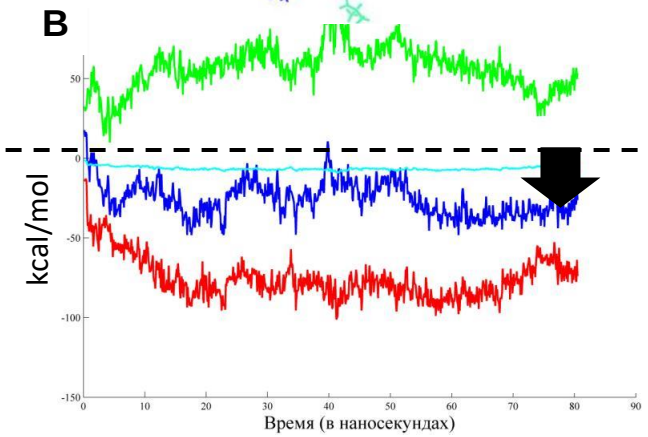




With RAFT residues



+ MD



Coulomb + hydration

Sum

van-der-Waals

Sum = |-50-70| kcal/mol

Sum = |-20-30| kcal/mol

Comments

No comment, illustration only

Polymeric Chain Synthesis

Isomerism

regulation

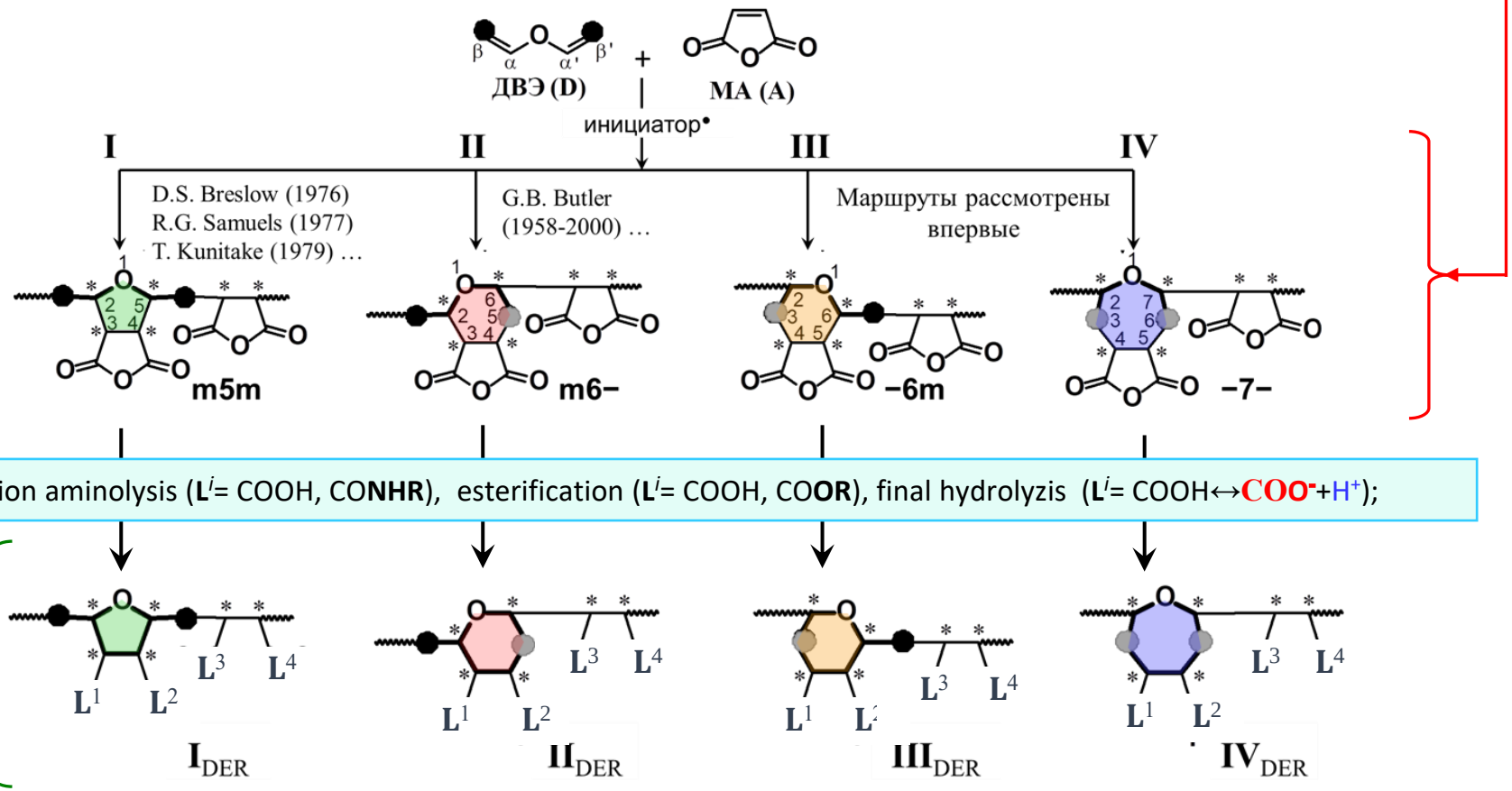
Comments

The second unique problem of the practical synthesis appeared as polymeric chain isomerism

3.2. Clearing mechanisms and conditions of Synthesis for chain isomers (↔ bio activity?)

4 routs · 2^6 stereo isomers = **256** isomeric variants of chin backbone units **?**

Synthesis of the Parent Polymeric backbone, [-**DVE(MA)-MA-**]$_n$ which is reactive for the following conversions toward Poly-ANTIVIRALS



BIO ACTIVE
Poly-ANTIVIRAL GENERATIONS
[**1,2,3,4,5,6,7, p**resented above]

Comments

Alternating radical cyclo copolymerization of DVE with MA hypothetically could assume up to 256 variations of isomerism. Of course, some of them are predictable preferable. But no reliable information in this regard was found

ANTIVIRAL DRUG DESIGN

3. POLY-ANTIVIRALS SYNTHESIS CONTROL FOR CHAIN ISOMERISM

3.2. Clearing mechanisms and conditions of Synthesis for chain isomers (↔ bio activity?)

Boris D. Bolshchikov
Alexander V. Serbin, et al.

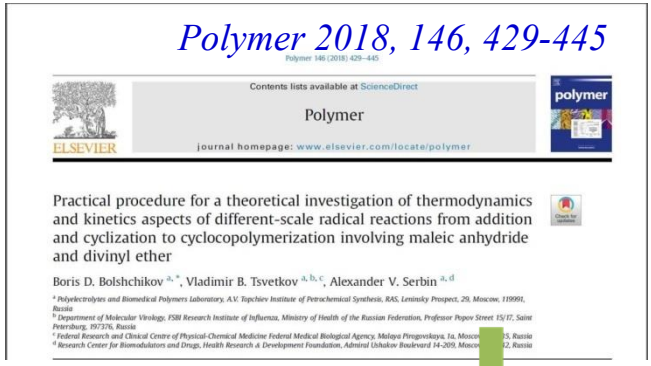
Polymer. 2018. 146, 429-445.
Biomed Chem (Russia). 2019, 65 (2) 133-151J
Macromolecular Chemistry and Physics. 2019, V. 220, Issue 23, 1900389, p. 1-20

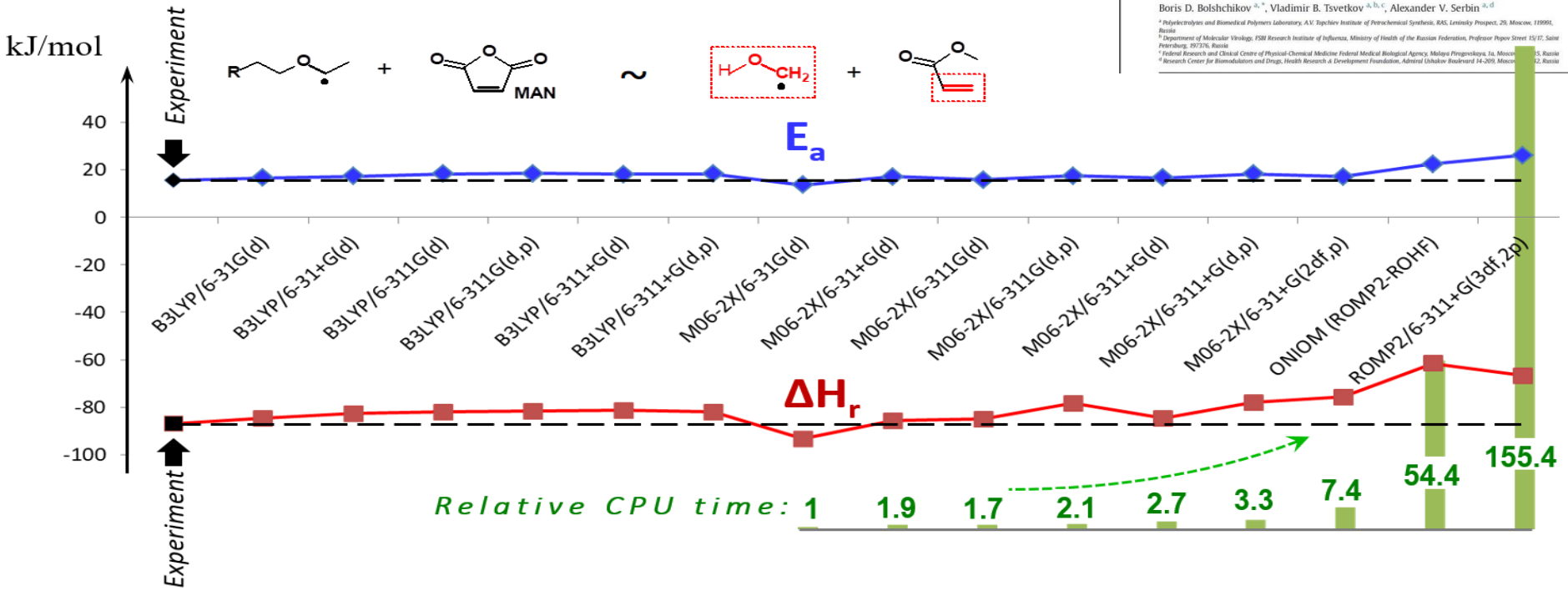
Quantum chemical investigation of chain isomerism regulation

Methods

Approbation and selection of known Methods in search for
- CPU-time saving, but
- precisely adequate to estimation of the E_a and ΔH_r

in reference to experimental data about related reactions





Comments

- *Then a special quantum chemical studies in combination with kinetics modeling were performed in collaboration with Boris Bolshchikov*

3.2. Clearing mechanisms and conditions of Synthesis for chain isomers (↔ bio activity?)

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Alexander V. Serbin, et al.

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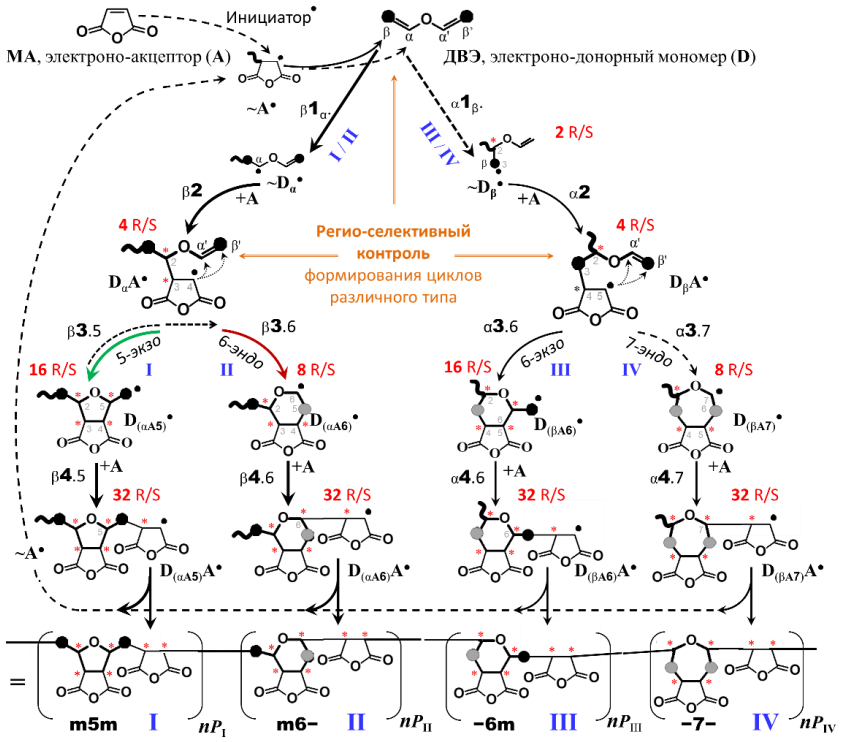
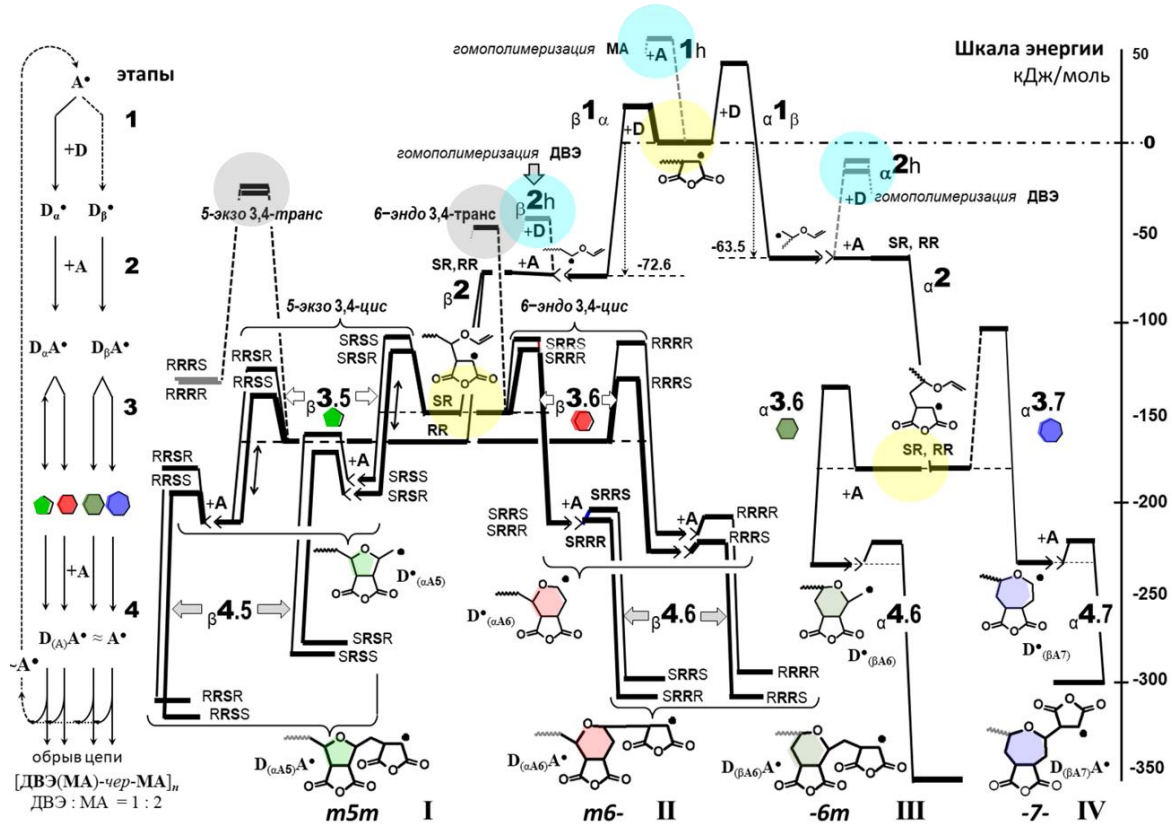
Quantum chemical investigation of chain isomerism regulation

Stepwise sub-Reactions Map



где $P_I + P_{II} + P_{III} + P_{IV} \le 1$ – сумма парциальных вероятностей образования в цепи ДВЭМА изомерных продуцентов I, II, III и IV маршрутов

Stepwise sub-Reactions' energy (the E_a and ΔH_r) Map



Comments

- *All considerable routes of sub reactions and activation energies and enthalpies were estimated, mapped and analyzed.*

ANTIVIRAL DRUG DESIGN

3. POLY-ANTIVIRALS SYNTHESIS CONTROL FOR CHAIN ISOMERISM

3.2. Clearing mechanisms and conditions of Synthesis for chain isomers (↔ bio activity?)

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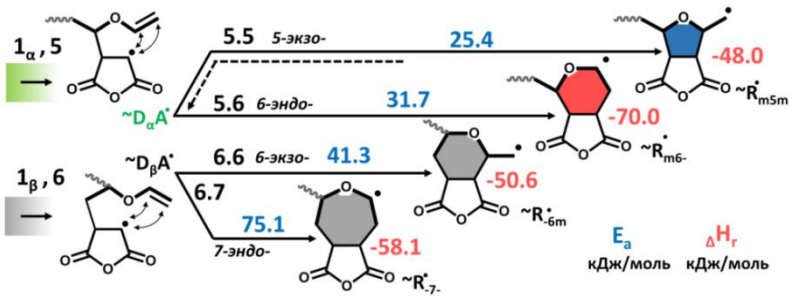
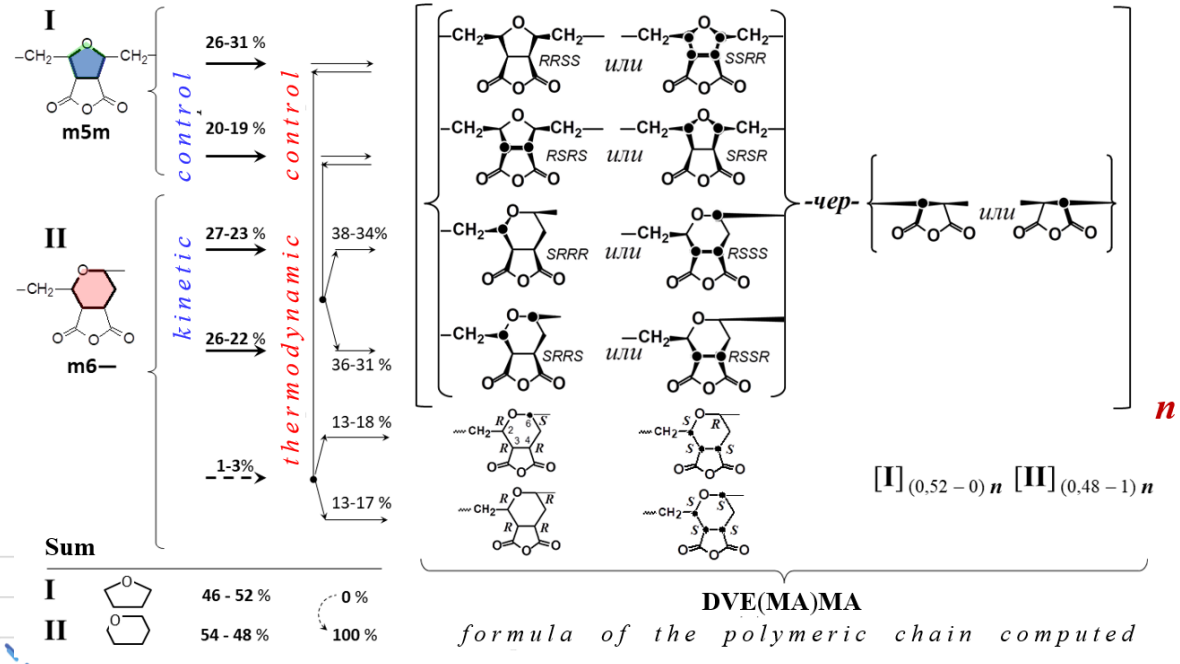
2021 Ph.D. Dissertation

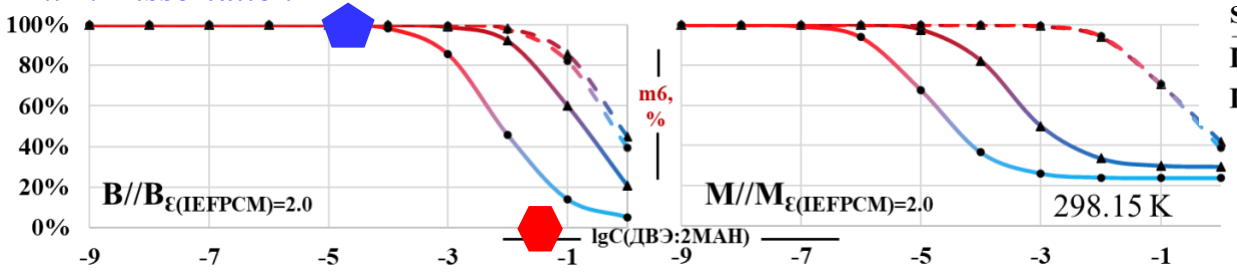
Quantum chemical investigation of chain isomerism regulation

+ Kinetics Modeling





= *f (concentrations); as well as of other factors*



Comments

● Crucial points and factors of kinetic and thermodynamic control of isomerism, as well as quantitative estimations of isomeric variations in polymeric chain were determined. The computational prognosis for possible variations of special experimental conditions allowing switching isomerism from furan-related cyclization toward pyran-related alternative were found and formulated in practical recommendations.

ANTIVIRAL DRUG DESIGN

3. POLY-ANTIVIRALS SYNTHESIS CONTROL FOR CHAIN ISOMERISM

3.2. Clearing mechanisms and conditions of Synthesis for chain isomers (↔ bio activity?)

Boris D. Bolshchikov
Alexander V. Serbin, et al.

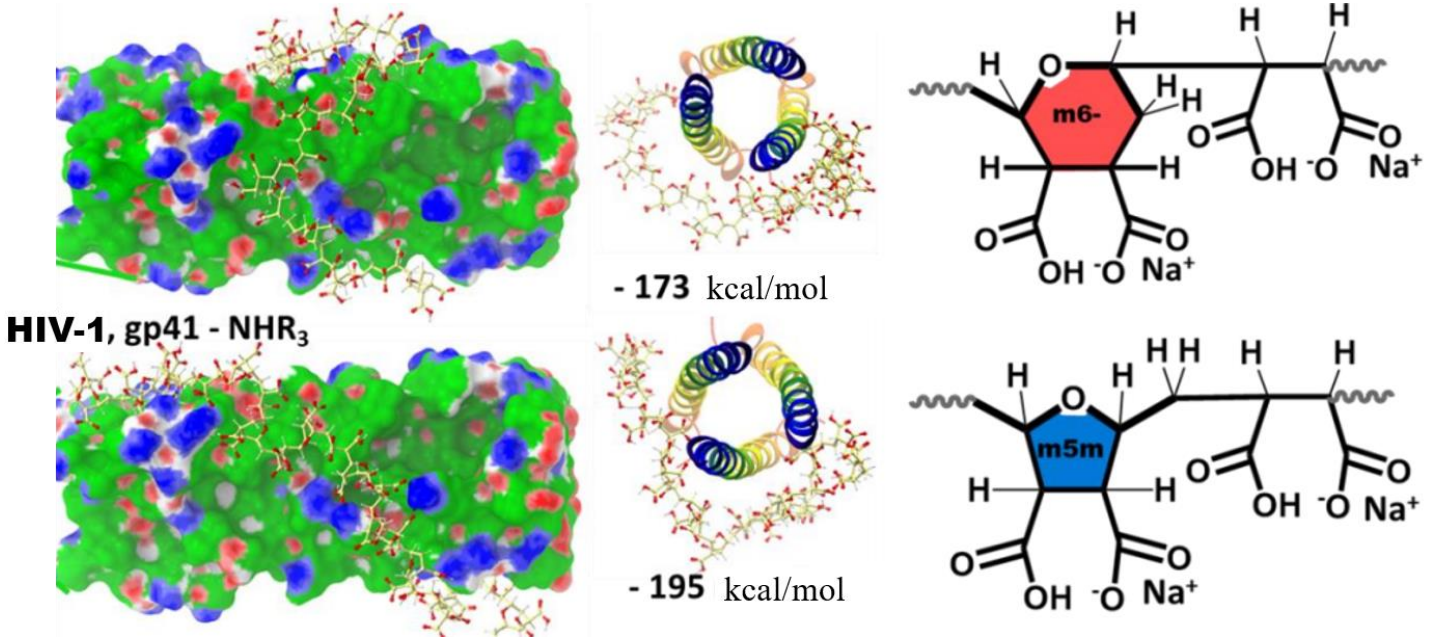
Polymer. 2018. 146, 429-445.
Biomed Chem (Russia). 2019, 65 (2) 133-151J
Macromolecular Chemistry and Physics. 2019, V. 220, Issue 23, 1900389, p. 1-20

2021 Ph.D. Dissertation

Quantum chemical investigation of chain isomerism regulation

DOCKING + MD

● *Pyranose-like cyclo- isomerism =* ***Polysaccharide – related mimicry***



⬟ *Furanose-like cyclo- isomerism =* ***Nucleic Acids – related mimicry***

Comments In parallel, the different capacity to bind the viral target depending on furan / pyran related isomeric content was found
An ability to regulate proportions between pyranose and furanose like intrachain mimicry is very interesting from bio functional aspect of view.
● The firs variant may imitates polysaccharide chains, while ● second one – the nucleic acid backbone. ● The last opportunity can be favorable factor for an enhanced IFN inducing activity, at least, but ● pyranose related similarity – for imitation of some virus-responsible cell receptors.

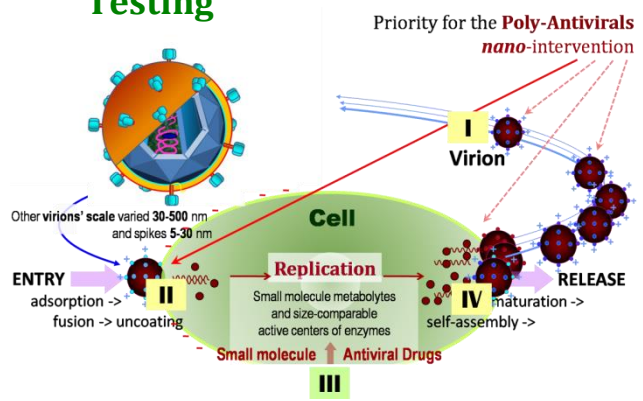
Current Results
&
Prospects

Comments
● And finally Current results & Prospects

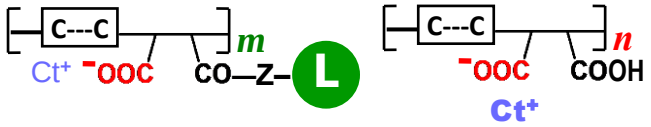
ANTIVIRAL DRUG DESIGN

Basic Design

Model. Synth. Testing



Poly-Antivirals



I Virions

II V. Entry

- **Virions' surface** (incl. **Spikes**) ← 1 ← 2
- Virion **Spikes** ← 1 ← 2
- Cell **Receptors** ↩ 1,2
- Cell **membrane Raft –domains** ← 5
- **Fusion** Mediators ← 3,4

III Replication

- Nucleic Acids & complexes ↩ 1,2

IV Assembly

- Assembling pre-virion nano-units ↩ 6
- Cell membrane Raft –domains ← 5

№	–Z– L		*m*/*n*	*in vitro*, **SI** = CC_{50}/IC_{50}			*in vivo*, Protection, %		
				HIV	**Infl.**	**CMV**	**TBV**	**RbV**	**EEEV**
1	No Side Ligands	Small Molecules are not Effective	0	10-100	≤ 30	≤ 350	65(-)	55(82)	65(95)
2	-Z-SO_3^-	Polymer based generations	≤ 0.80	>680	→10000	7500			
3	-Z-**Nb**		0.1-0.3	>3300	>2140	240			
4	-Z-**Ad**		0.1-0.3	>1100	→10000	25			
5	-Z-**Chol**		≤ 0.03	>220	5400	-			
6	-Z-**Pept** Cell Receptors		≤ 0.02	→10000	-	-			
7	-Z-**Pept** Viral (HIV, MA)		≤ 0.01	+	← Test-Samples are completed for bio evaluations				

In vivo evaluations were performed under the **lethally hard conditions** up to **200 LD_{50}** of Viruses (in brackets – for combined: **PolyAntivirals + Vaccine**)

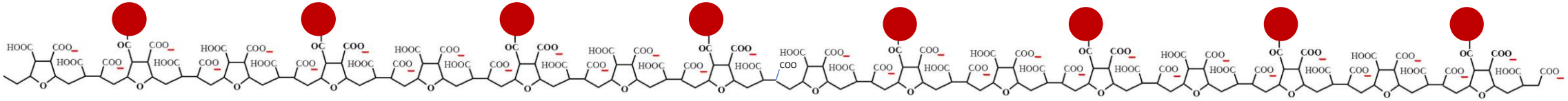
Comments

The set of novel high effective Polyantivirals was designed, synthesized, successfully tested and partially modeled with great use for theory and practice of antiviral drug development

Some other part of polyantiviral generations needs future studies basing on modeling techniques

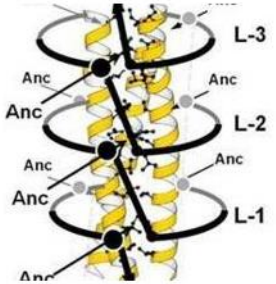
ANTIVIRAL DRUG DESIGN

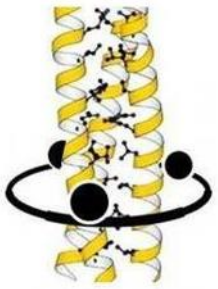
Poly-Antivirals

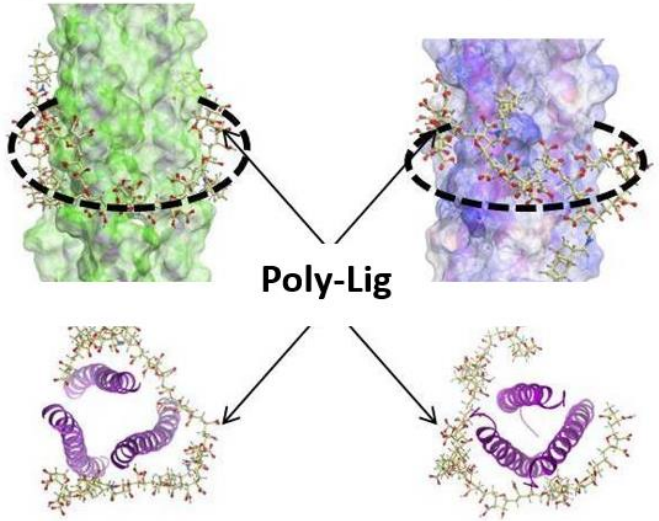


SI = 40–300 ⇨ **20–10 000** ⇨ **???** ⇨ **???**

HIV → Influenza → Ebola → CORONA







Comments

- *Current groundwork opens wide horizon for future advancing, including inhibition of other danger viruses*

Especially concerning the viruses with similar biomolecular mechanisms of entry into cells, where viruses can be stopped at the very initial stage

Basic Design

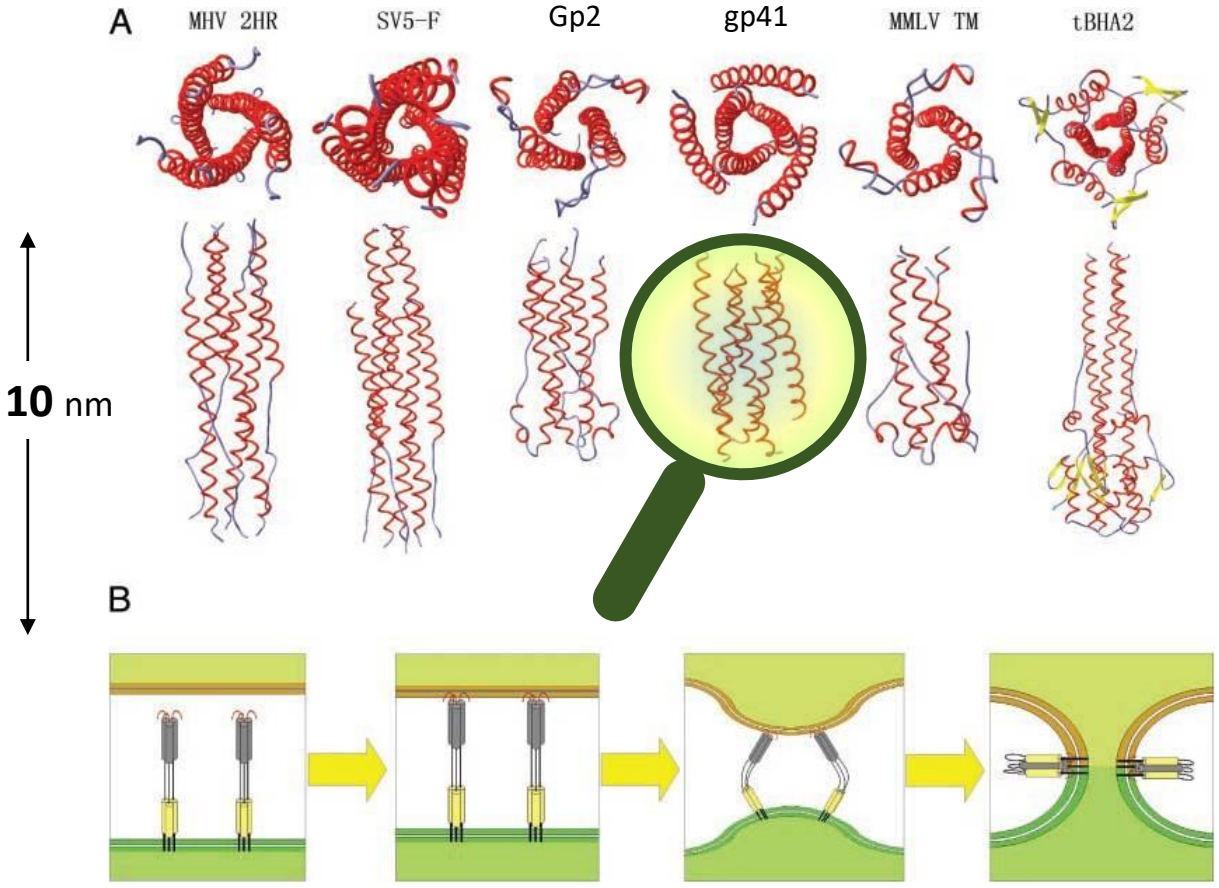
Model. Synth. Testing

ANTIVIRAL DRUG DESIGN

Ebola **HIV** **Influenza** **COVID** **… Hepatitis B …**

Gp2 gp41 HA2 spike spike

… etc. …



Xu Y **2004** Str…

Eckert DM **2001** Mec…

Fan X **2020** Cryo…

Comments

- *Current groundwork opens wide horizon for future advancing, including inhibition of other danger viruses*

Especially concerning the viruses with similar biomolecular mechanisms of entry into cells, where viruses can be stopped at the very initial stage

Thank you for your attention