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# **COMPUTER-ASSISTED DISCOVERY OF ANTI-INFECTIVE AGENTS**

**Vladimir Poroikov**

**Institute of Biomedical Chemistry  
of Rus. Acad. Med. Sci., Moscow, Russia**

# Congratulations to the 15<sup>th</sup> Anniversary of ISTC !

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Biomedical  
researches with  
postgenomic  
nanotechnologies

Postgenomic  
technologies  
Nanobiotechnology  
and nanomedicine  
Journal "Biomed-  
ical chemistry"  
Sections of interna-  
tional communities:  
.QSAR .RHUPO

Institute  
Research  
Developments  
Joint Projects  
Departments  
Education  
Links

[Intranet](#)

[EVENTS](#)

Human Proteom Project - preparation phase.

#### News

Our Institute took part in an exhibition prepared for exit session of presidium of the State Council of the Russian Federation, devoted to development of innovative technologies...  
[Read more](#)

From 2008 the new section "Nanoproteomics" is introduced in Proteomics journal by Institute's director Alexander Archakov.

Proteomics 2007, 7, 1029-1032

4402

#### EDITORIAL

Introducing Nanoproteomics, a new section in PROTEOMICS

**W**hat is (post) proteomics? According to the most general concept, proteomics is a scientific discipline that studies the structure, function, and interactions of proteins in a cell or organism. The goal is to identify and characterize all the proteins in a system, and to understand how they interact with each other and with the environment. This is a complex task, as the number of proteins in a cell is estimated to be between 10,000 and 20,000. The first step in proteomics is to identify the proteins in a sample. This can be done using a variety of techniques, including mass spectrometry, 2D gel electrophoresis, and protein microarrays. Once the proteins are identified, the next step is to study their function and interactions. This can be done using a variety of techniques, including X-ray crystallography, NMR spectroscopy, and protein-protein interaction assays. The final step in proteomics is to integrate the data from all these techniques to build a comprehensive model of the proteome. This model can then be used to study the role of the proteome in various biological processes, such as disease and drug response.



Alexander Archakov

[Read more](#)

The Opening of Systems biology Laboratory was on **December 4, 2007** at the Institute of biomedical chemistry. The laboratory is aimed to conduct highly productive research...  
[Read more](#)

[News archive](#)

# Main Directions of Research

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## 1. Postgenomic Technologies:

- Gen-, transcript-, prote-, metabol- OMICS;
- Bioinformatics;
- Systems / Cell Biology.

## 2. Nanobiotechnologies:

- To the reverse Avogadro number ( $10^{-24}$  M);
- Molecular detectors for medical diagnostics;
- Phospholipid system for drug delivery.

## 3. Computer-Aided Drug Design:

- Development of software and databases for CADD.
- Computer-aided search for new targets and ligands.

## 4. «Traditional» biochemistry.

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## Personnel:

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**235 people (156 researchers),**

**including:**

**3 – Full Members of Rus. Acad. Med. Sci.;**

**1 – Corresponding Member of Rus. Acad. Med. Sci.;**

**11 - Professors;**

**31 – Dr. Sci.;**

**72 – Ph.D.**

**59 (>35%) - <35 y.o.**

**Annually ~20 Ph.D. and graduate students.**

**12 requests for training from developing countries in 2008.**

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# Modern Equipment for Postgenomic Studies





## **Grants and Programs**

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- **Multidisciplinary Program «Proteomics for medicine and biotechnology».**
  - **Federal Targeted Program «Research and development according to the priorities for development of scientific-technological complex on 2007-1012».**
  - **Russian Foundation of Basic Research.**
  - **Programs and grants of Moscow Government.**
  - **Grants of ISTC, IFTI, Welcome Trust, Royal Society, CRDF, INTAS, etc.**
  - **Contracts and agreements with Russian and International companies.**
-

## Educational-Research Course «Bioinformatics and Computer-Aided Drug Discovery»

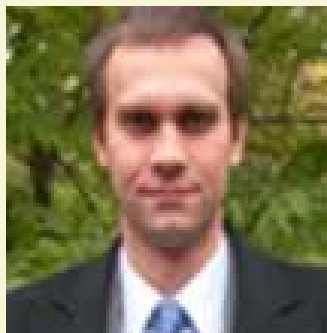
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# Department for Bioinformatics:

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**Bioinformatics Technologies**  
(Head – Andrey Lisitsa, Dr.Sc.)



**Molecular Graphics Based Drug Design**  
(Head – Alexander Veselovsky, Dr.Sc.)

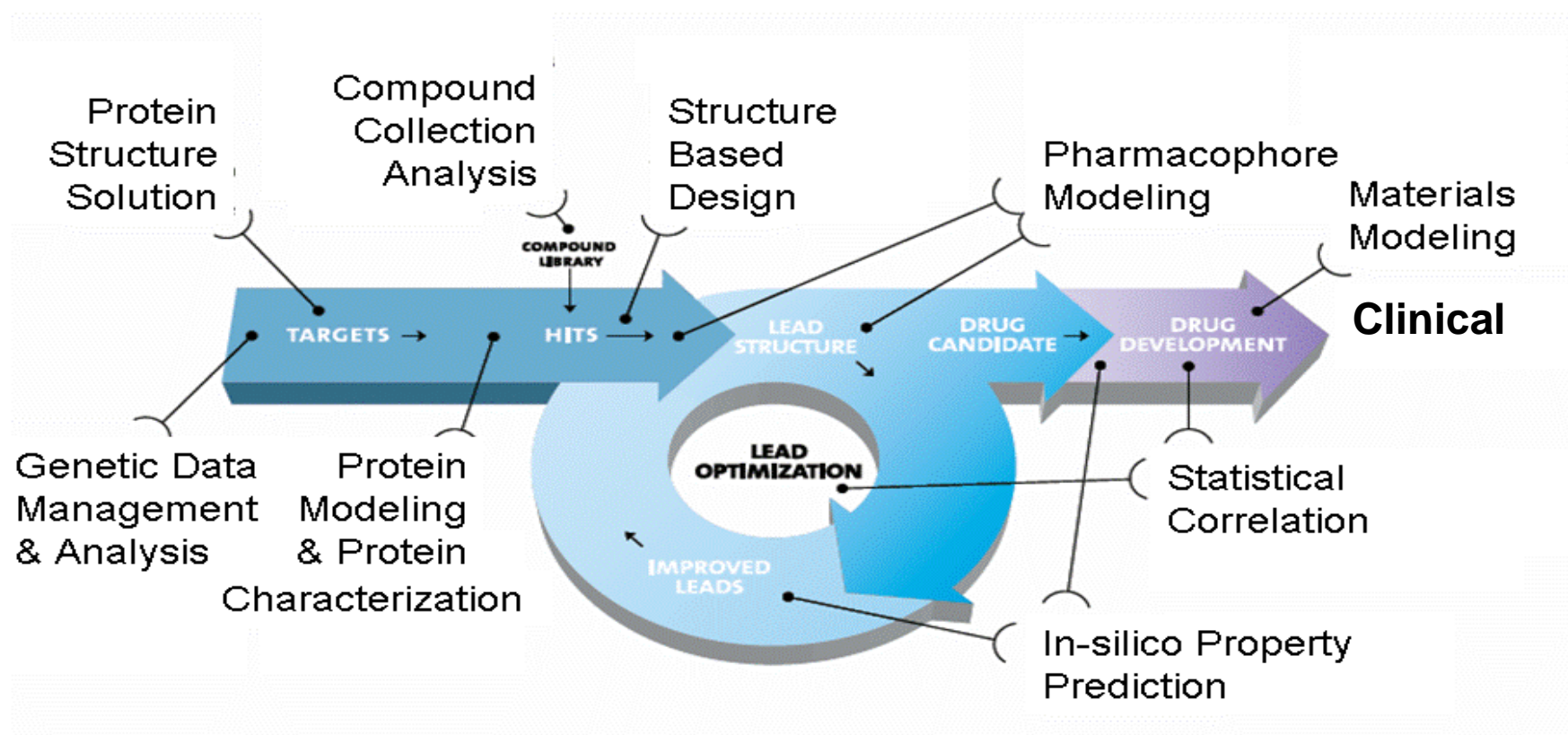
**Structure-Function Based Drug Design**  
(Head – Vladimir Poroikov, Prof. Dr.)

**High-Performance Computations**  
(Head – Vladlen Skvortsov, Ph.D.)

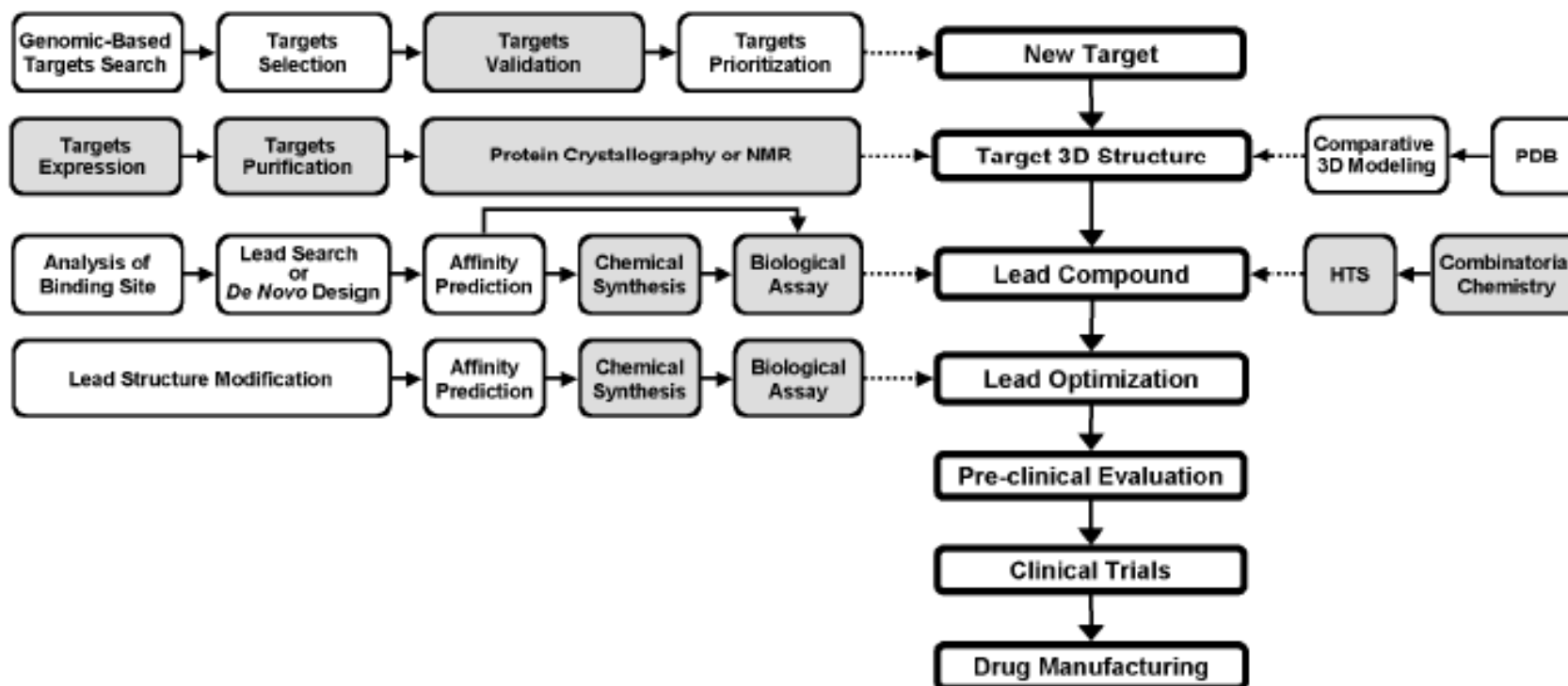
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# Drug Targets to Drug Candidates



## General Platform “From Genomes to Drugs”



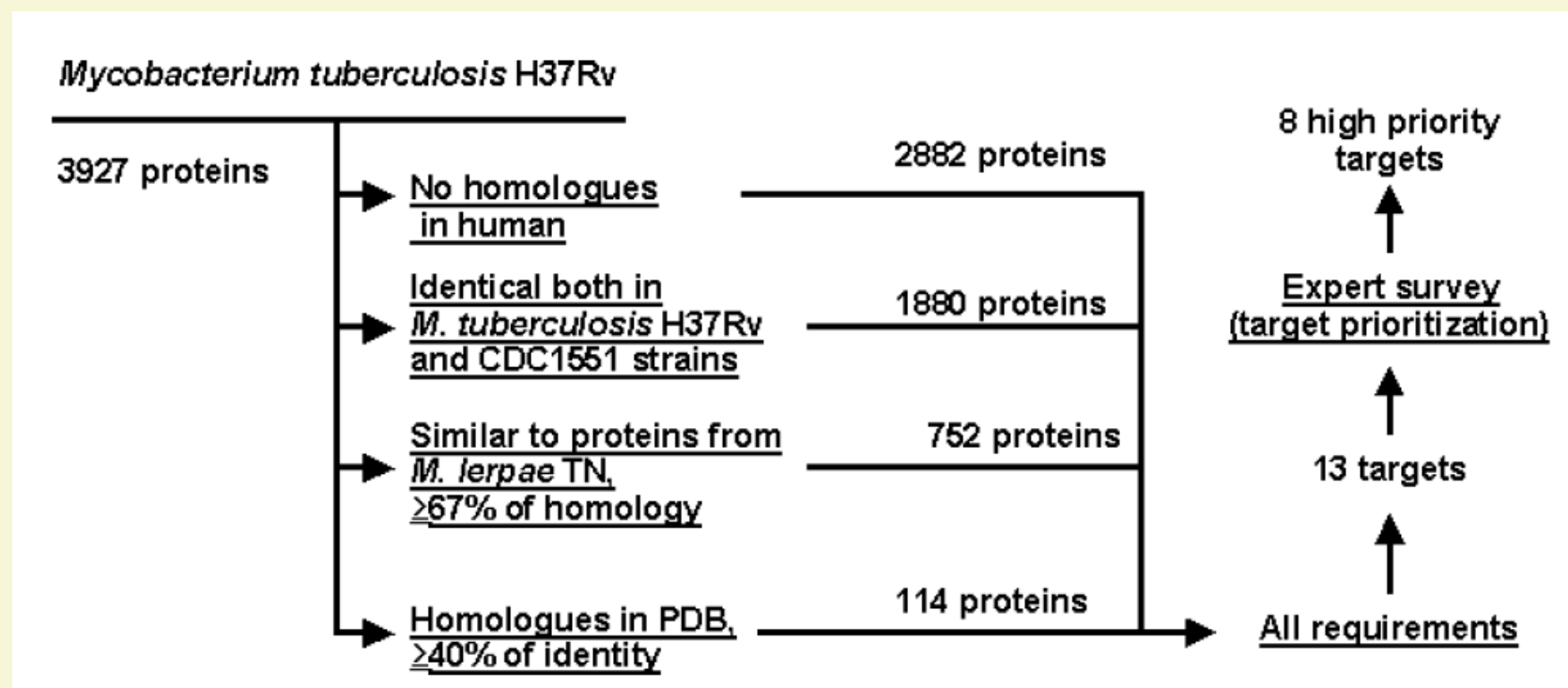
Ivanov A., Veselovsky A., Dubanov A., Skvortsov V. Bioinformatics Platform Development. From Gene to lead Compound. Methods Mol. Biol., 2006, 316, 389-431.

## Requirements to “Ideal” Antimicrobial Targets & Agents

Drug	Target
Biomedical requirements	
Effective suppression of growth and reproduction of micro-organism	Important for growth and reproduction
Lethality to pathogen	Essential for survival
Definite antimicrobial spectrum	Occurs in all target microbial species and strains
Selectivity: minimal host toxicity	Absent in host (human)
Selectivity: minimal alteration of normal microflora	Absent in host's (human) symbiont bacteria
Low risk of resistance	Conserved in all target strains
Technological requirements	
Target-based CADD	Available 3D structure
Definite mechanism of action	Known function
CADD, computer-aided drug discovery.	

Ivanov A., Veselovsky A., Dubanov A., Skvortsov V. Bioinformatics Platform Development. From Gene to lead Compound. Methods Mol. Biol., 2006, 316, 389-431.

## Search for New Antimycobacterial Targets



## Targets Identified in Mycobacterium Tuberculosis

Target no.	Gene	Target protein
1.	<i>infA</i>	Translation initiation factor IF-1
2.	<i>hupB</i>	Histone-like protein
3.	<i>rpoA</i>	DNA-directed RNA polymerase (transcriptase) alpha chain
4.	<i>rpsD</i>	30S ribosomal protein S4
5.	<i>rpsE</i>	30S ribosomal protein S5
6.	<i>rpsH</i>	30S ribosomal protein S8
7.	<i>bfrA</i>	Bacterioferritin
* 8.	<i>kdtB</i>	Phosphopantetheine adenylyltransferase
9.	<i>glcB</i>	Malate synthase G
10.	<i>purE</i>	Phosphoribosylaminoimidazole carboxylase catalytic subunit
11.	<i>ruvA</i>	Holliday junction DNA helicase
12.	<i>trpB</i>	Tryptophan synthase beta chain
* 13.	<i>mscL</i>	Large-conductance mechanosensitive channel

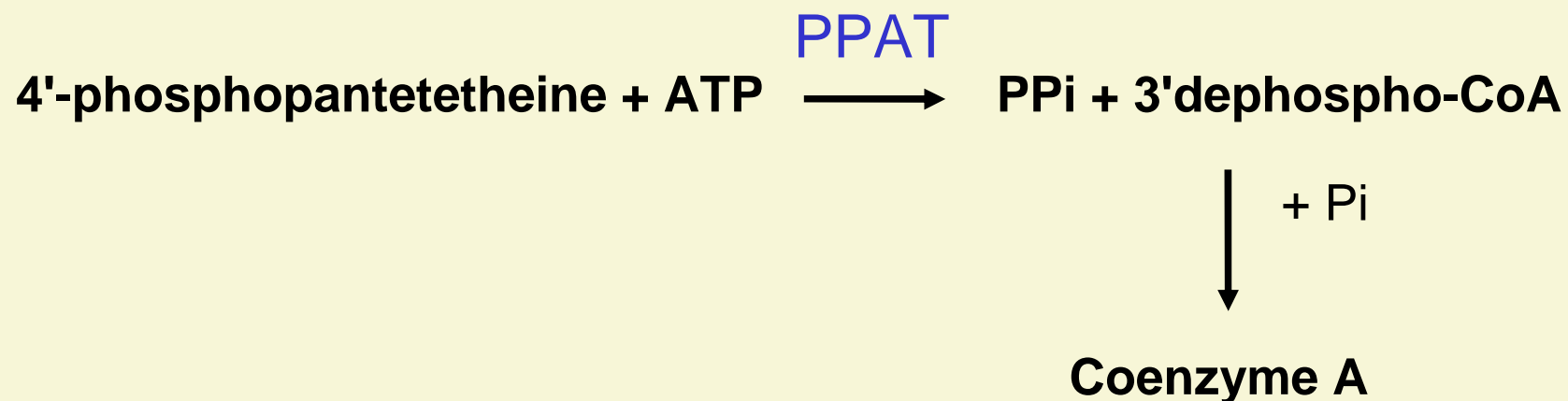
Freiberg C, Wieland B, Spaltmann F, Ehlert K, Broetz H, Labischinski H. Identification of novel essential Escherichia coli genes conserved among pathogenic bacteria. J Mol Microbiol Biotechnol. 2001, 3(3):483-489.

Thanassi JA, Hartman-Neumann SL, Dougherty TJ, Dougherty BA, Pucci MJ. Identification of 113 conserved essential genes using a high-throughput gene disruption system in Streptococcus pneumoniae. Nucleic Acids Res. 2002, 30(14):3152-3162.



## Phosphopantetheine Adenylyltransferase (PPAT) in Bacteria

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Penultimate and rate-limited enzyme of bacterial coenzyme A biosynthesis.

## 3D Structure Determination of PPAT

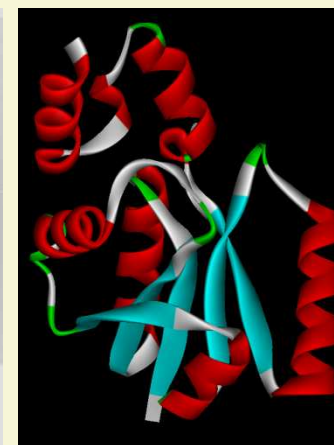
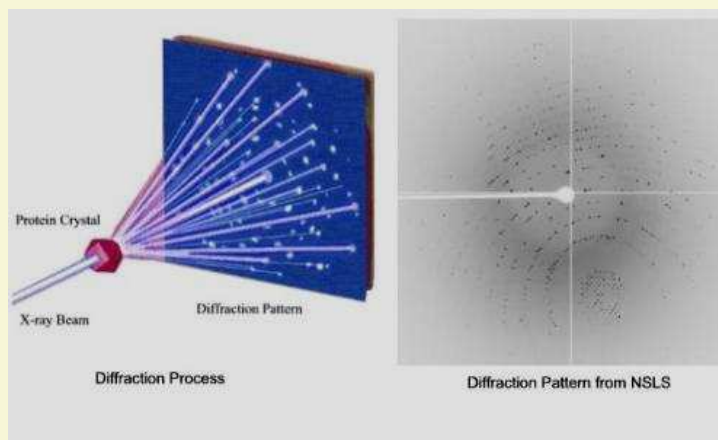
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**Expression, extraction and purification.**

**Institute of Bioorganic Chemistry of Rus. Acad. Sci.**

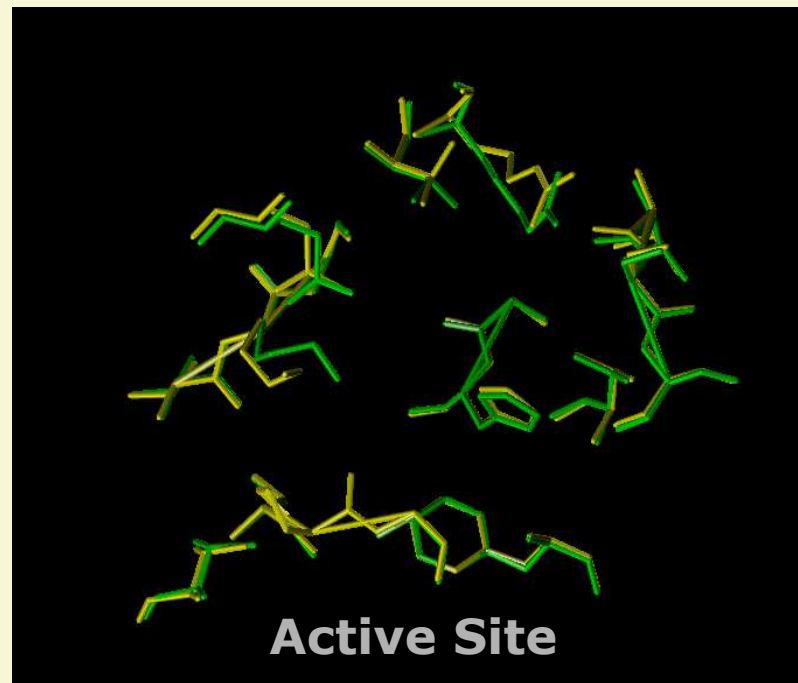
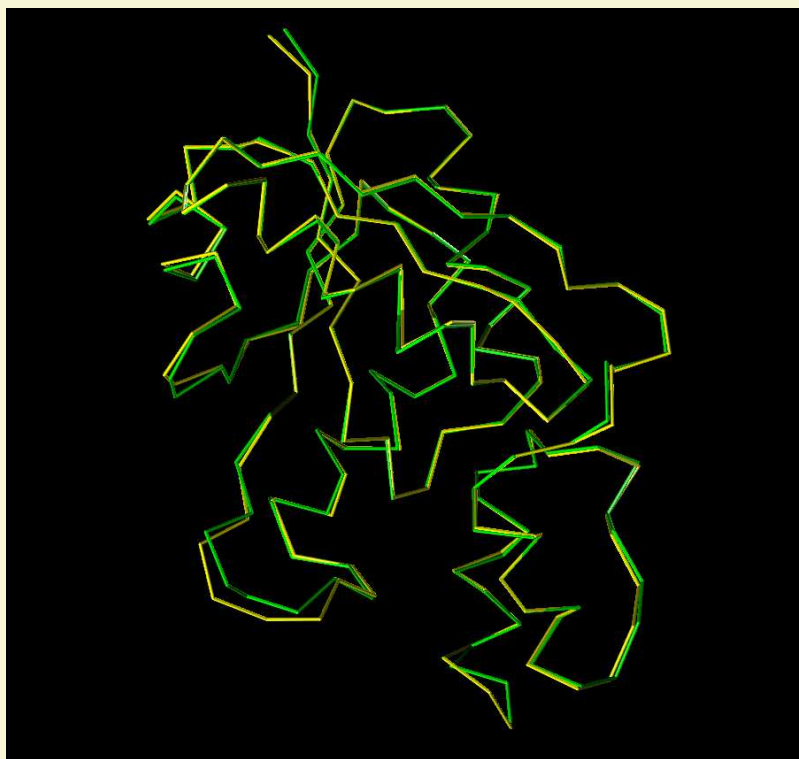
**Crystal growth, X-ray structure determination.**

**Institute of Crystallography of Rus. Acad. Sci.**



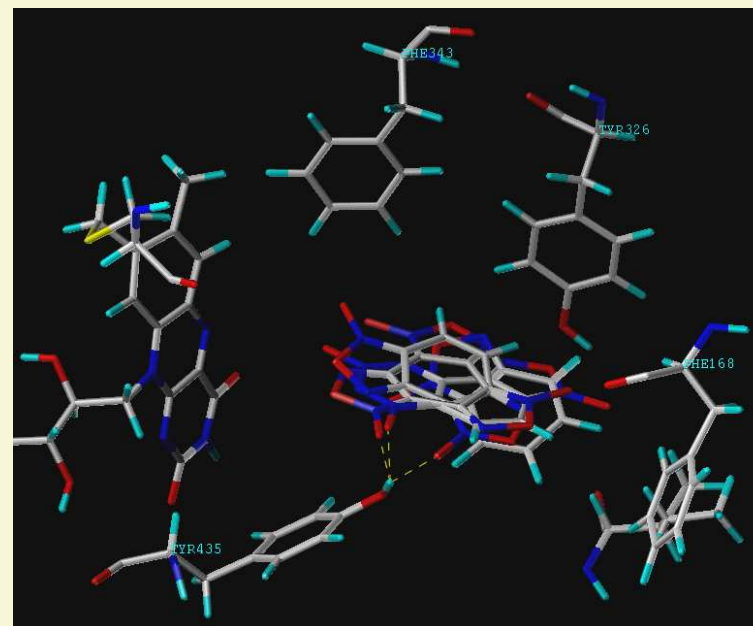
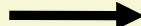
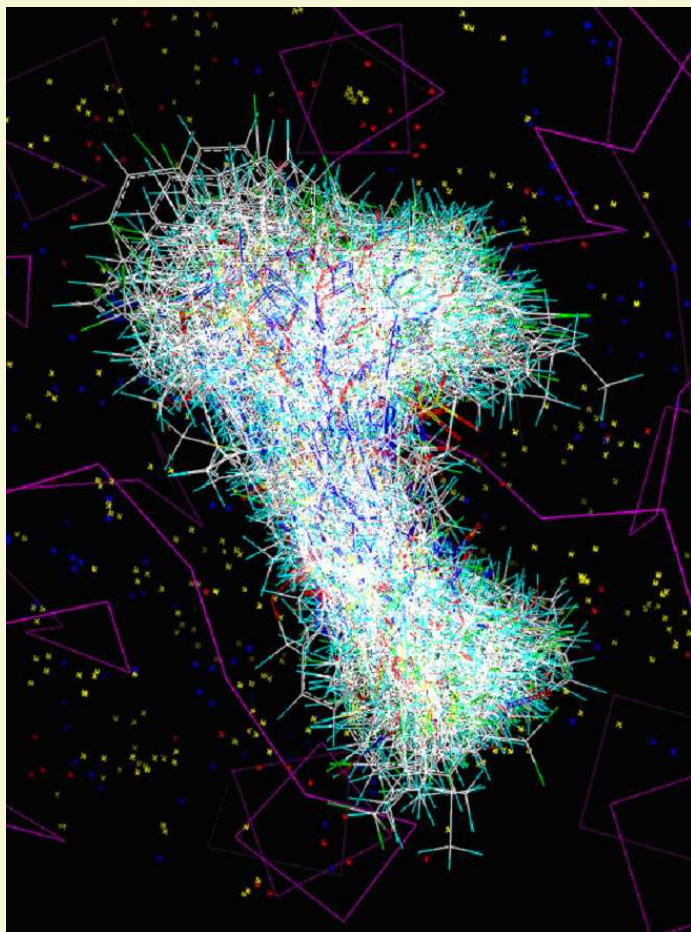
## Comparison of 3D Structure of PPAT

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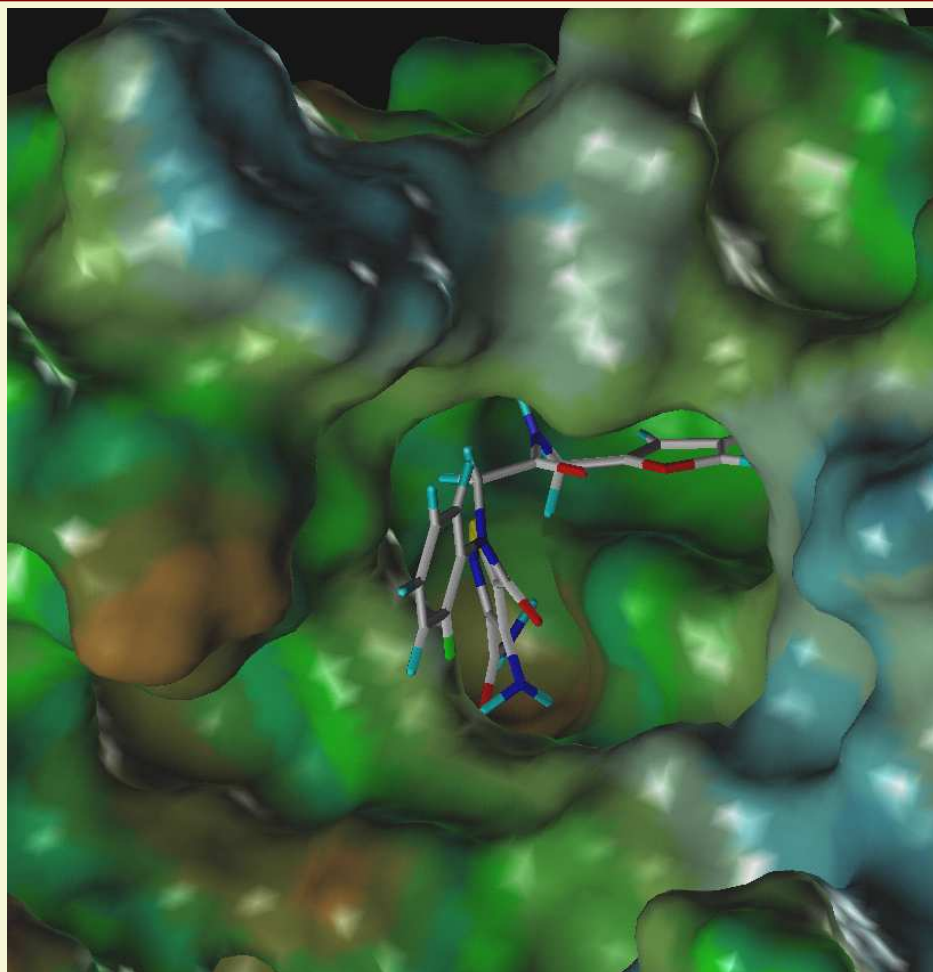
Green – original structure (1.6 Å); Yellow – 1TFU.pdb (1.99 Å)

# Virtual Screening of Ligands by Docking



## Docking of Ligands to PPAT Active Site

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## Biological Activity Testing in Vitro with BIACORE 3000

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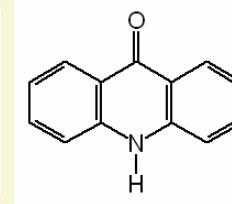
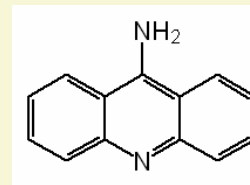
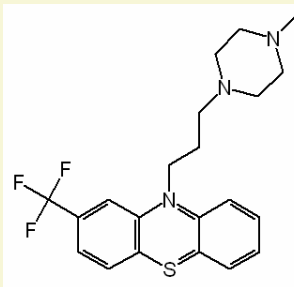
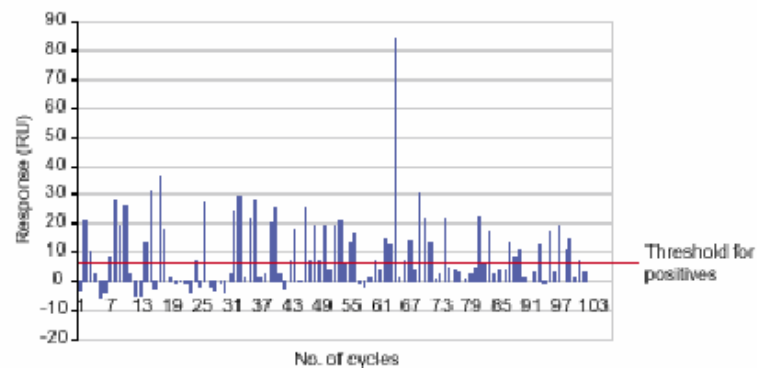


### Advantages:

- High sensitivity.
  - Small amount of sample.
  - Fast analysis.
  - Good performance.
  - Different optical chips.
-



# First Hits Active Against PPAT Are Identified



## **To overcome the resistance:**

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- **Search for inhibitors of protein-protein interactions (multisubunit proteins, protein complexes).**
- **Analysis of M.tuberculosis interactome.**
- **Analysis of host-pathogen interactions.**
- **Search for ligands acting on multiple targets.**

## Search for New Hits Among the Available Samples

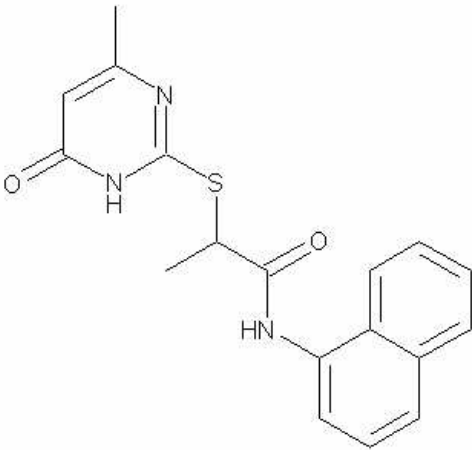
ISIS/Base - [DVS\_U\_DB.DB/TEMP]

File Edit Options Object Database Search List Window Help

Forms Query Browse Update <Root> 25700 of 50000  
Search Domain: All

**ChemBridge Corporation**  
16981 Via Tazon, Suite G, San Diego, CA. 92127, USA  
Phone: (858)451-7400; Fax: (858)451-7401  
e-mail: sales@chembridge.com; web: www.chembridge.com

Program: **Diverset™**

ID	7654404	Formula	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S
		MW	339.42
		RB	4
		cLogP	2.40
		tPSA	74.85
		Hacc	3
		Hdon	2
		LogSw	-4.07
		Supplier	ChemBridge
© 2003, ChemBridge Corporation			

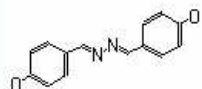


Pa &gt; Pi

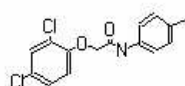


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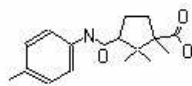
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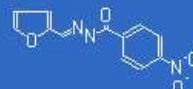
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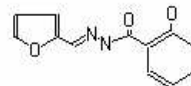
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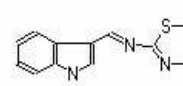
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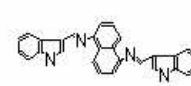
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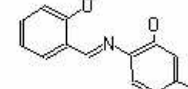
5105020



5105025



5105183



Save TXT Save SD Clipboard Exclude

Pa &gt; Pi Sort

Pa Pi &lt;ID&gt;

0.922	0.002	5280532
0.915	0.002	5301427
0.912	0.002	5306380
0.911	0.002	5366392
0.909	0.002	5321608
0.907	0.002	5104999
0.905	0.002	5310376
0.904	0.002	5210283
0.903	0.002	5348877
0.903	0.002	5310066
0.902	0.002	5230331
0.901	0.002	5273034

Pa Pi Types of Activities Pa-Pi descending

0.973	0.002	Carcinogenic, female mice
0.964	0.001	Antituberculosic
0.954	0.003	Carcinogenic, male mice
0.907	0.002	Antimycobacterial
0.907	0.003	Mutagenic
0.881	0.003	Carcinogenic, group 3
0.858	0.003	Carcinogenic, female rats
0.843	0.007	Non mutagenic, Salmonella
0.837	0.003	Mutagenic, Salmonella
0.804	0.004	Carcinogenic
0.755	0.005	Carcinogenic, male rats
0.747	0.040	Thermopain inhibitor
0.707	0.006	Antiviral (Picornavirus)
0.713	0.013	Phosphatidylserine decarboxylase inhibitor
0.737	0.053	Emetic
0.720	0.055	Chymosin inhibitor
0.720	0.055	Saccharopepsin inhibitor
0.720	0.055	Acrocyllindropepsin inhibitor
0.668	0.005	Antiinfective
0.689	0.047	Phosphatase inhibitor
0.628	0.010	Antiprotozoal
0.619	0.002	Catalase stimulant
0.613	0.005	Carcinogenic, group 2B
0.636	0.035	Antianemic
0.597	0.005	Maillard reaction inhibitor
0.593	0.006	Antiprotozoal (Amoeba)
0.667	0.096	Ubiquinol-cytochrome-c reductase inhibitor
0.575	0.022	Antiviral (Poxvirus)
0.555	0.021	Radioprotector
0.608	0.080	Fibrinolytic
0.611	0.089	Polyporopepsin inhibitor

Substance used for the treatment of Mycobacterium Tuberculosis infection.

Effect Mechanisms Toxicity Metabolism Transport Gene Expression

0.707	0.006	Antiviral (Picornavirus)
0.668	0.005	Antiinfective
0.636	0.035	Antianemic
0.628	0.010	Antiprotozoal
0.499	0.022	Antiprotozoal (Trypanosoma)
0.593	0.006	Antiprotozoal (Amoeba)
0.488	0.004	Antiprotozoal (Coccidia)
0.608	0.080	Fibrinolytic
0.575	0.022	Antiviral (Poxvirus)
0.555	0.021	Radioprotector
0.543	0.107	Cardioprotectant
0.524	0.082	Antineoplastic (gastric cancer)
0.501	0.061	Amyotrophic lateral sclerosis treatment
0.494	0.200	Sialagogue
0.455	0.016	Antiparasitic
0.460	0.008	Anthelmintic
0.535	0.024	Anthelmintic (Nematodes)
0.446	0.212	Antineoplastic (lung cancer)
0.440	0.036	Cytostatic
0.439	0.016	Antibacterial
0.907	0.002	Antimycobacterial
0.964	0.001	Antituberculosic
0.436	0.255	Antineoplastic (ovarian cancer)
0.433	0.055	Antineoplastic (hematological cancer)
0.417	0.025	Antiviral (Adenovirus)
0.403	0.260	Antineoplastic (lymphoma)

Pa &gt; 0.900 antimycobacterial

Drug-likeness &gt; 0

New Descriptors &gt;= 0

Pa &gt; 0.900 Antituberculosic

Pa &gt; 0.900 Antimycobacterial

# Search for Multitargeted Antibacterial Agents

PharmaExpert

File Tools View Help

Pa > Pi

7 from 863

Prediction & Interpretation - G:\ACTUALDATABASES\CHEMBRIDGE-JUNE-2009\dvs-u-db\_SA-40.SDF

5104875 5104952 5104970 5104999

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Pa > Pi Sort

Pa	Pi	<ID>
0.922	0.002	5280532
0.915	0.002	5301427
0.912	0.002	5306380
0.911	0.002	5366992
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0.668	0.005	Antinfective
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0.597	0.005	Maillard reaction inhibitor
0.593	0.006	Antiprotozoal (Amoeba)
0.667	0.096	Ubiquinol-cytochrome-c reductase inhibitor
0.575	0.022	Antiviral (Poxvirus)
0.555	0.021	Radioprotector
0.608	0.080	Fibrinolytic
0.611	0.089	Polyporopepsin inhibitor

Substance used for the treatment of Mycobacterium Tuberculosis infection.

Pa > 0.900 antimycobacterial

Pa > 0.900 Antituberculosic

Pa > 0.900 Antimycobacterial

Multitargeted actions

Effects Number of targets

Antibacterial 3 Run Load Save

Aspartate carbamoyltransferase inhibitor  
Cell wall synthesis inhibitor  
CMP-KDO synthase inhibitor  
Diaminopimelate epimerase inhibitor  
Dihydrofolate reductase inhibitor  
Dihydroorotate dehydrogenase inhibitor  
DNA directed RNA polymerase inhibitor  
Enoyl-acyl-carrier-protein reductase (NADH) inhibitor  
Lanosterol 14 alpha demethylase inhibitor  
Membrane integrity antagonist  
Membrane permeability inhibitor  
Oxidizing agent  
Para amino benzoic acid antagonist  
Peptide deformylase inhibitor  
Phosphoenolpyruvate-protein phosphotransferase inhibitor  
Protein 30S ribosomal subunit inhibitor  
Protein 50S ribosomal subunit inhibitor  
Protein synthesis inhibitor  
Pyruvate synthase inhibitor  
Serine-type D-Ala-D-Ala carboxypeptidase inhibitor  
Topoisomerase I inhibitor  
Topoisomerase II inhibitor  
Tumour necrosis factor alpha antagonist

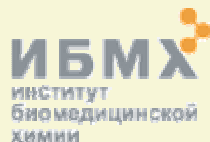
No	Pa	Number	Activity type	Activity type	Activity type
48	0.627	7	Membrane permeability inhibitor	Topoisomerase I inhibitor	
49	0.490	8	Membrane permeability inhibitor	Topoisomerase II inhibitor	
50	0.752	33	Oxidizing agent	Phosphoenolpyruvate-protein phosphotransferase int	
51	0.458	1	Oxidizing agent	Protein synthesis inhibitor	
52	0.408	1	Oxidizing agent	Topoisomerase I inhibitor	
53	0.509	3	Phosphoenolpyruvate-protein phosphotransferase int	Protein synthesis inhibitor	
54	0.408	1	Phosphoenolpyruvate-protein phosphotransferase int	Topoisomerase I inhibitor	
55	0.634	18	(R)-Pantolactone dehydrogenase (flavin) inhibitor	Aminoacyl-tRNA synthetase inhibitor	Membrane integrity antagonist
56	0.771	27	(R)-Pantolactone dehydrogenase (flavin) inhibitor	Aminoacyl-tRNA synthetase inhibitor	Membrane permeability inhibitor
57	0.533	1	(R)-Pantolactone dehydrogenase (flavin) inhibitor	Aminoacyl-tRNA synthetase inhibitor	Phosphoenolpyruvate-protein phosphotrans
58	0.417	1	(R)-Pantolactone dehydrogenase (flavin) inhibitor	Aminoacyl-tRNA synthetase inhibitor	Protein synthesis inhibitor
59	0.474	1	(R)-Pantolactone dehydrogenase (flavin) inhibitor	Aminoacyl-tRNA synthetase inhibitor	Topoisomerase II inhibitor
60	0.589	4	(R)-Pantolactone dehydrogenase (flavin) inhibitor	Diaminopimelate epimerase inhibitor	Membrane permeability inhibitor
61	0.639	22	(R)-Pantolactone dehydrogenase (flavin) inhibitor	Dihydroorotate dehydrogenase inhibitor	Membrane integrity antagonist
62	0.755	68	(R)-Pantolactone dehydrogenase (flavin) inhibitor	Dihydroorotate dehydrogenase inhibitor	Membrane permeability inhibitor
63	0.447	1	(R)-Pantolactone dehydrogenase (flavin) inhibitor	Dihydroorotate dehydrogenase inhibitor	Phosphoenolpyruvate-protein phosphotrans
64	0.598	17	(R)-Pantolactone dehydrogenase (flavin) inhibitor	DNA directed RNA polymerase inhibitor	Membrane integrity antagonist
65	0.782	65	(R)-Pantolactone dehydrogenase (flavin) inhibitor	DNA directed RNA polymerase inhibitor	Membrane permeability inhibitor
66	0.406	1	(R)-Pantolactone dehydrogenase (flavin) inhibitor	DNA directed RNA polymerase inhibitor	Oxidizing agent
67	0.507	3	(R)-Pantolactone dehydrogenase (flavin) inhibitor	DNA directed RNA polymerase inhibitor	Phosphoenolpyruvate-protein phosphotrans
68	0.581	3	(R)-Pantolactone dehydrogenase (flavin) inhibitor	Enoyl-acyl-carrier-protein reductase (NADH) inhibitor	Membrane integrity antagonist

## **Computer-Aided Discovery of New HIV-1 Integrase Inhibitors ISTC/BTEP/BII Project # 3197/111/Q-257**

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The purpose of the project is to find new efficient inhibitors of HIV-1 integrase on the basis of the latest technologies in bioinformatics and computer-aided drug discovery.

Duration: April 1, 2005 – March 31, 2008





# Participating Institutions

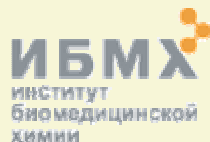
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Institute of Biomedical Chemistry of RAMS (IBMC),  
Moscow (leading organization – computer-aided drug  
discovery)

Institute of Organic Chemistry of RAS (IOC), Moscow  
(chemical synthesis of potential compounds)

Institute of Physical-Chemical Biology of MSU (IPCB),  
Moscow (testing of potential compounds *in vitro*)

National Cancer Institute, NIH, Frederick, MD  
(molecular modelling, testing in cell culture)



## Background and Experience: IBMC

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Computer-aided finding and optimization of new pharmaceuticals:

- development of methods & programs;
- applications.

(Vladimir Poroikov team)



Lagunin A.A., Gomazkov O.A., Filimonov D.A., et al. (2003). *J. Med. Chem.*, **46** (15), 3326-3332.

Geronikaki A., Dearden J., Filimonov D., et al. (2004). *J. Med. Chem.*, **47** (11), 2870-2876.

Akimov D.V., Filimonov D.A., Prikazchikova T.T., Gottikh M.B., Poroikov V.V. (2005). **51** (3), 335-340.

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## Background and Experience: IOC

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Development of methods of organic synthesis and preparation of chemical compounds; synthesis of compounds from very different chemical classes.

(Svyatoslav A. Shevelev team)



Shevelev S.A. and Dalinger I.L. (1998) *Russ. J. Org. Chem*, **34**(8), 1071-1080.

Shevelev S.A., et al (2002) In: *Combustion of Energetic Materials*, (Eds.)

K.K. Kuo, L.T. DeLuca, Begell House, Inc., NY, USA, 62-70.

## Background and Experience: IPCB

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Study of molecular mechanisms of viral integration, development of assays and testing of HIV-1 integrase inhibitors.

(Marina B. Gottikh team)



Isolation and purification of natural compounds from marine worms Polychaeta as a source for new biologically active substances.

(Ludmila A. Elyakova group)

## Background and Experience: NCI-Frederick, NIH, USA

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Molecular modelling of HIV-1 full-length integrase 3D structure and its inhibitors; computer-aided search for new HIV-1 integrase inhibitors.

(Marc C. Nicklaus team)



Cell-based assaying of HIV-1 integrase inhibitors.

(Vinay K. Pathak team)

## Tasks Specified by the Workplan

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1. Computer prediction of HIV-1 integrase inhibitors.
  2. Isolation and determination of the structure of peptide integrase inhibitors from marine worm Polychaeta.
  3. Molecular modeling of HIV-1 integrase interaction with inhibitors.
  4. Development of methods, synthesis and preparation of potential HIV-1 integrase inhibitors.
  5. Experimental testing of hits identified by computer methods and preparations obtained from marine worm Polychaeta.
  6. Computer-aided optimization of structure & properties of HIV-1 integrase inhibitors.
  7. Experimental testing of the most prospective compounds in HIV infected cell cultures.
  8. Preparation of reports, publications, and materials for IP protection.
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## The Main Results (04/01/2005 – 03/31/2008)

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- A database with information about known HIV-1 integrase inhibitors was created, our computer system was trained using new data that increased the accuracy of prediction.
  - Computer experiments performed with virtual compound databases provided the basis for selection of the most prospective hits.
  - 227 compounds were selected as hits, synthesized by IOC or purchased from different vendors.
  - Most of compounds were tested in enzyme assays *in vitro* on inhibition of 3' processing or/and strand transfer.
  - 39 compounds were identified as HIV-1 integrase inhibiting agents ( $IC_{50} < 100 \mu M$ ).
  - The most active compounds have  $IC_{50}$  values in the micromolar and sub-micromolar range;
  - The discovered compounds belong to the chemical series, in which HIV-1 integrase inhibiting activity had never been found before; thus, these compounds can be considered as New Chemical Entities (NCEs).
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## Extending of the project – BII # Q-257

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To increase the IP value, it is necessary to design, synthesize and test more derivatives from this chemical series, as well as to investigate in more details their mechanism of binding.

The tasks of this project, which is considered as the “with-cost” extension of the currently ongoing ISTC/BTEP project # 3197/111, are specified below.

1. Rational computer-aided design of new derivatives from the discovered chemical series with putative HIV-1 integrase inhibiting activity.
  2. Development of methods, synthesis and preparation of potential HIV-1 integrase inhibitors.
  3. Experimental study of HIV-1 integrase inhibiting activity and their mechanism of binding in in vitro and cellular culture assays.
  4. Preparation of reports, publications, and materials for IP protection.
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## The main results (04/01/2008 – 12/31/2008)

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- Sixteen new derivatives were synthesized and seventeen compounds were tested on the HIV-1 integrase inhibiting activity in *in vitro* enzymatic assays. Seven compounds were found to be active in micromolar range. Based on the structure of active compounds discovered in the framework of the project, a few samples were purchased by NCI from ChemNavigator and tested for their HIV-1 integrase inhibiting activity in *in vitro* enzymatic assays. Three compounds appeared to be active in micromolar range.
- Mechanism of action of HIV-1 integrase inhibitors from this chemical class was studied, It was concluded that this class of compounds: (1) inhibits 3'-processing as they act with an almost the same activity on both reactions catalyzed by HIV-1 integrase; (2) binds to the active center of the HIV-integrase and impedes its interaction with the DNA substrate.

## Summary (I)

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- Computer-assisted methods were applied by IBMC for finding and optimization of potential HIV-1 integrase inhibitors. In the framework of the project 162 new chemical compounds were synthesized by IOC and 81 commercially available samples were purchased from different vendors for testing on HIV-1 integrase inhibiting activity.
- All these compounds were tested by IPCB on the HIV-1 integrase inhibiting activity in *in vitro* enzymatic assays (3'-processing and/or strand transfer reaction). Taking into account that for active compounds some repeated studies were executed, the total number of tests equals to about 460.
- Thirty six chemical compounds were found to be inhibitors of 3'-processing and thirty one compounds – inhibitors of strand transfer reaction in concentrations less than 100  $\mu\text{M}$ .

## Summary (II)

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- **IC<sub>50</sub> values of the most potent compounds were no more than 10  $\mu$ M for 10 molecules (3'-processing inhibition) and 15 molecules (ST inhibition). The majority of the discovered compounds belong to the chemical series, in which HIV-1 integrase inhibiting activity had never been found before, and can be considered as New Chemical Entities (NCEs).**
  - **To provide more detailed information about the mechanism of binding for this class of compounds additional experiments were executed by IPCB. It was concluded that this class of compounds: (1) inhibits 3'-processing as they act with an almost the same activity on both reactions catalyzed by HIV-1 integrase; (2) binds to the active center of the HIV-integrase and impedes its interaction with the DNA substrate.**
  - **Ten the most potent compounds were prepared in necessary quantities and tested by NCI in HIV-1 infected cell culture assays. This class of compounds was confirmed to be active against HIV-1 infected cell culture. Their EC<sub>50</sub>, CC<sub>50</sub> and SI values were determined. In the best cases (IOCh-18-48, IOCh-18-131) the selectivity index value appeared to be about 3, which is rather low for further development of this class of compounds as a potential drugs.**
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# Acknowledgements

## IBMC

Alexander Archakov  
Alexander Veselovsky  
Alexis Ivanov  
Vladlen Skvortsov  
Boris Sobolev  
Dmitry Filimonov  
Andrey Lisitsa  
Tamara Fedoronchuk  
Dmitry Druzhilovsky  
Dmitry Filimonov  
Tatyana Gloriovova  
Alexey Lagunin  
Alexander Shkrob

## IOC

Svyatoslav Shevelev & Associates

## IPCB

Marina Gottikh & Associates

## NCI/NIH

Marc Nicklaus & Associates

## ISTC

Nelly Smirnova  
Ekaterina Manukhina  
Natalya Savinova  
Albert Gozal  
Zarina Azimova  
**and many others**

**For the financial support: Russian Academy of Medical Science; Russian Space Agency; ISTC/BTEP/BII # 3197/111/Q-257, ISTC # 3777; FP6 # LSHB-037590, FP7 # 200787; RFBR 05-07-90123, 06-03-08077 and 09-04-01281.**



**We are open for new collaborative projects:**

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