UNIQUE COLLECTION OF THE COMPOUNDS STORED WITHIN PLIVA COMPOUNDS LIBRARY

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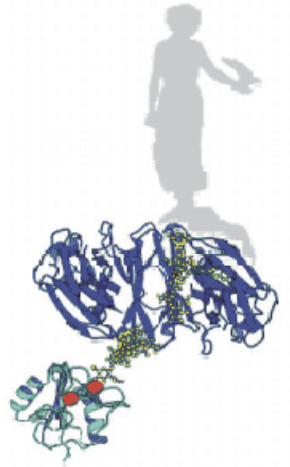


INTRODUCTION

In the 1990s, several new technologies with its laboratory automation and miniaturization changed the drug discovery process in the pharmaceutical industries: Combinatorial Chemistry (CC) and High Throughput Screening (HTS), as well as Genomics and Proteomics, as a complimentary techniques revolutionized the field of drug discovery. Screening of collections of diverse chemical libraries or structurally related compounds increased the possibility of finding new and valuable drugs in short times and at reasonable costs. The impact of these new technologies should be greatly enhanced by synergies with ongoing parallel developments in medicinal synthetic chemistry, analytics, bioinformatics and computing (compound logistics). Regarding to these facts, strategic interest of all bigger Pharma Industries is to have own Compound Library, as a "key to success". Therefore, in the year 2000. PLIVA formed HTS Unit, with HTS Compounds Library within this Unit. We started collecting old "historical" PLIVA's compounds as well as all newly synthesized high quality drug-like compounds from our R&D laboratories. HTS is performing screening of these compounds on different targets, with the aim to improve the drug discovery process (cost/time saving) and to generate quality valuable hits and leads.

DEPOSITORY, EQUIPMENT AND MAINTAINANCE

Compound Library in PLIVA is stored under GLP conditions (room 24 hours controlled temperature and humidity, in and out documentation). Compounds are deposited in specially designed containers (Figure 1) at 20°C, or in refrigerators at +4°C, -20°C and/or -80°C, depending on sample stability. Samples are bar-coded and placed at different formats: vials, microtitar plates or deep-well microtitar plates. In new Research Institute building all samples stored at room temperature will undergo N_2 pressure, to minimize decomposition of samples.

Figure 1: PLIVA Compounds Library

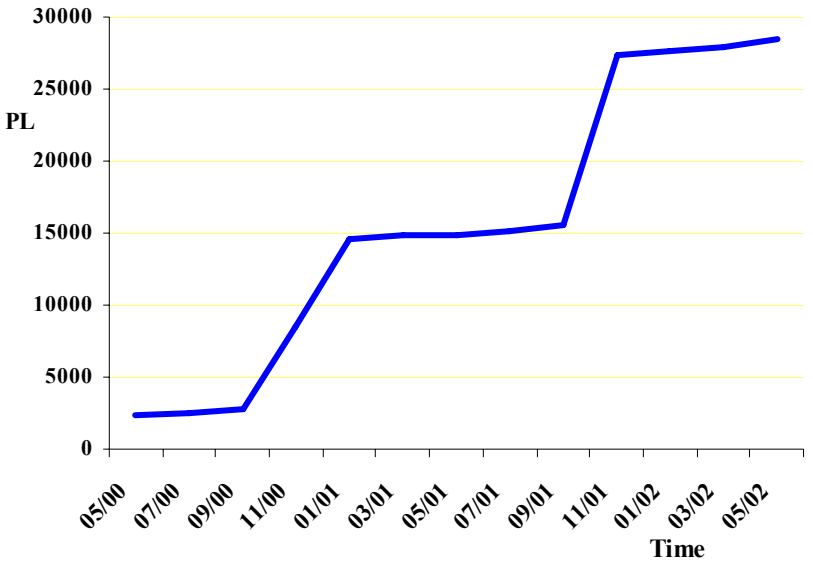


Figure 2: PLIVA Compound Library - increment over time

PLIVA Depository consists over 25.000 small organic compounds produced by PLIVA R&D laboratories, or acquired from different commercial companies or Universities inside or outside Croatia (Figure 2). The Library consists of many different structural classes and some of them are produced by original synthetic techniques. With the 80 years experience in synthetic medicinal chemistry, PLIVA is developing unique techniques for the synthesis of “New Chemical Entities” from new patentable scaffolds.

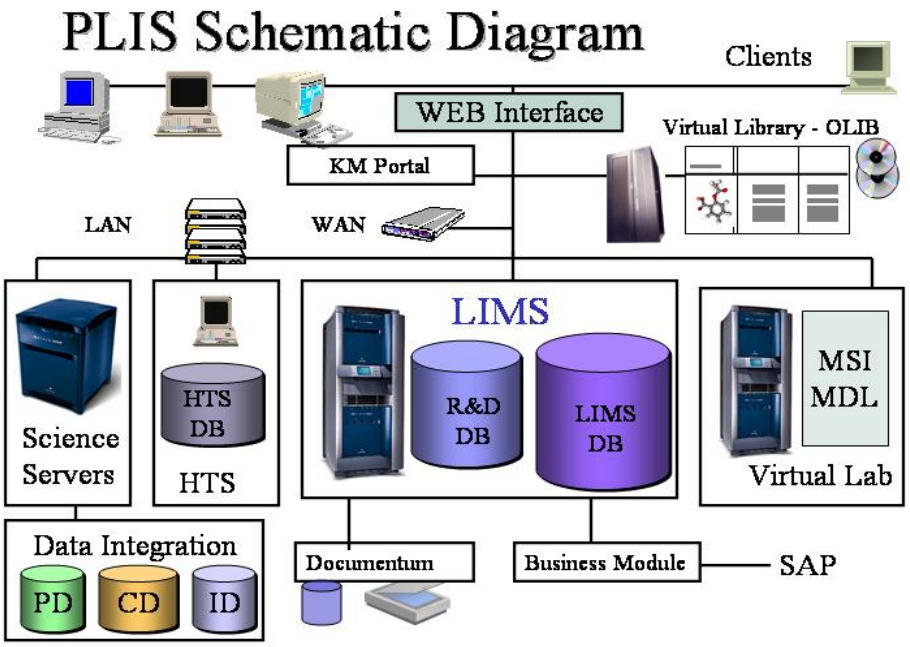
There are several types of collaboration between various institutions and PLIVA, and therefore compounds in PLIVA Compounds Library are from various sources (Figure 3). Commercial synthetic companies produces very large number of compounds, mostly using combinatorial chemistry approach, and this HTS compounds collections are fully available (cherry picking, patentable). On the other side, Universities and scientific or academic institutions have smaller number of available compounds, but these are more interesting compounds, regarding the fact that most of them are new chemical entities. With these institutions PLIVA has specific collaboration contracts to buy some smaller amount of compounds, and if some of them show interesting activity, chemists or institutions who synthesized these compounds have some benefits (they are inventors).

Figure 3: Sources of compounds in PLIVA Depository

HTS in PLIVA Research is requesting a top quality and high purity for the compounds we acquire from outside. Compounds undergo rigorous analysis before becoming recorded as PL compounds (unique PLIVA's code). The compounds in PLIVA are characterised mostly by HPLC/MS and H^1NMR. Amounts of compounds we are collecting in PLIVA Compounds Library are sufficient to perform screening on many selected targets (microorganisms, enzymes, cell-lines…).

SOFTWARE AND HARDWARE SUPPORT

PLIVA R&D has multifunctional and good organized Central Database on SQL server and/or UNIX server (ISIS Host, MDL-platform). Complete R&D Database is part of the LIMS (Oracle server) and this is central depository of chemistry, biology, analytics, pharmacology, microbiology, biotechnology and all other data produced in R&D (Figure 4). Central part of this Database is ChemClient®, software developed by PLIVA-Research Information Center. ChemClient is a tool for successful handling with all chemical compounds synthesized in PLIVA or acquired from outside.



Hardware delivered, installed, configured and operational!

UNIX (IRIX) Machines – File and Application Servers cluster with 24 RISC CPUs, 16 GB RAM and 3 TB of storage.

NT Cluster with 24 CPUs, 12 GB RAM and 1TB of storage.

Figure 4: PLIVA Informatic Software and Hardware System

CHARACTERISTICS OF PLIVA COMPOUNDS LIBRARY

The main requirement for hit and lead generation is often to maximize the range of structural types within the library with the expectation that a broad range of activities will result. The advent of rational drug design (RDD) gave us the power to design candidate drugs based on the physical properties of their targets. Synthesizing large libraries of compounds is not cheap. Depending on the cost of reagents, a very large library of potential ligands may have to be reduced to one percent of its size before synthesis. Ideally, chemical diversity should be maximized while minimizing the cost of reagents. Therefore, in PLIVA medicinal chemistry laboratories we are working on specific structural classes, and we are trying to achieve maximal diversity within these classes. Concerning the compounds acquired from outside, we are trying to receive as many as possible diverse "drug-like" structural classes, in order to be as powerful as possible in High Throughput Screening of whole PLIVA Compounds Library on present and future targets, producing hits and leads for future research programs.

Most of the compounds in our collection follow the "Lipinski Rule of Five". These are rules defined by Lipinski, which describes the characteristics of chemical compounds with a stronger prospect of becoming potential drug candidates relative to other molecules. But, although majority of drugs on the market have no Rule of Five violations (or maximal one violation), we in PLIVA have strong examples of the specific structural classes of the compounds who does not undergo these rules: Macrolides have very specific shape and size, and they are not fit in these rules at all (Table 1).

Lipinski 'RULE OF FIVE'	PLIVA Compounds Library (average results)	Example of Azythromycin
Molecular weight < 500	Molecular weight = 379,69	Molecular weight = 749,00
LogP < 5	ALogP = 3,23	LogP = 4,1
H-bond donors < 5	H-bond donors = 1,66	H-bond donors = 5
H-bond acceptors < 10	H-bond acceptors = 5,45	H-bond acceptors = 14
Rotatable bonds < 5	Rotatable bonds = 5,66	Rotatable bonds = 12

Table 1: Comparison of Lipinski Rule of Five with the compounds in PLIVA Compounds Library

We took azythromycin ("Sumamed") as an example for comparison with standard Lipinski Rule of Five. PLIVA's azythromycin, as a representative of macrolides is one of the best and most powerful known antibiotic. We can see here from Table 1 that azythromycin have even 4 of 5 violations of Lipinski Rule of Five. That's example why the rules are not absolute and should not be used to immediately eliminate compounds from consideration.

When we look to whole PLIVA R&D Database structures, we can see clearly from average results for Lipinski Rule of Five that our Compounds Library has drug-like characteristics and overlap the chemistry space occupied by drugs, which has been reached the market (Table 1; Figure 5-6).

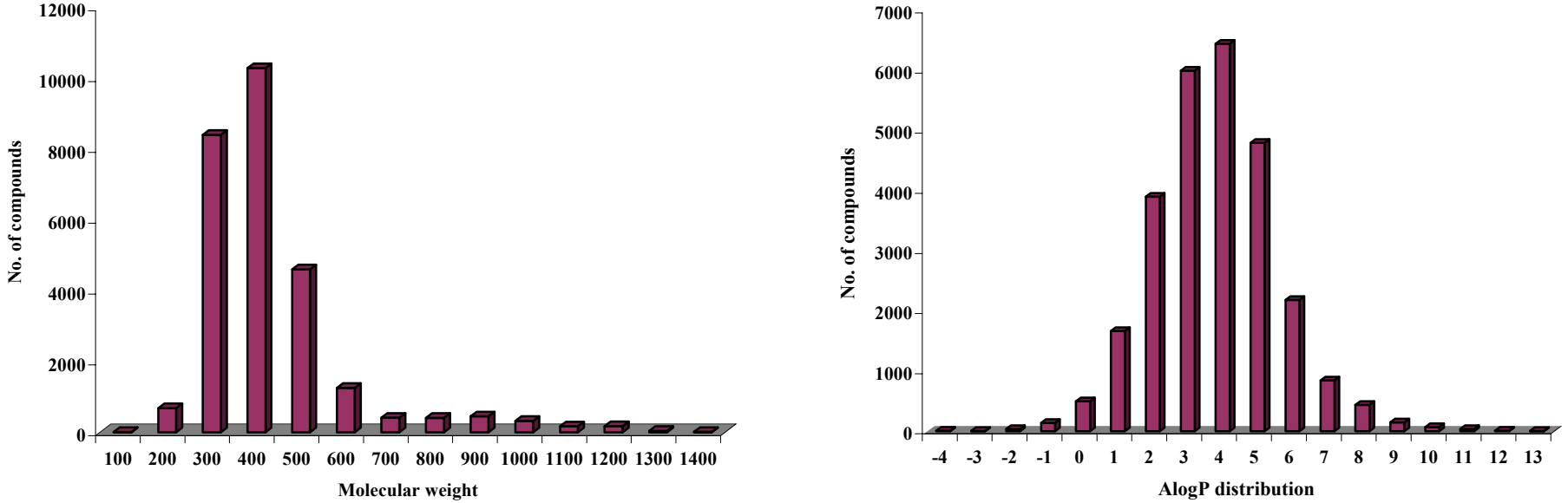


Figure 5: Molecular weight and AlogP distribution of compounds in PLIVA Database calculated with Cerius[2]
(data generated by I. Bašic)

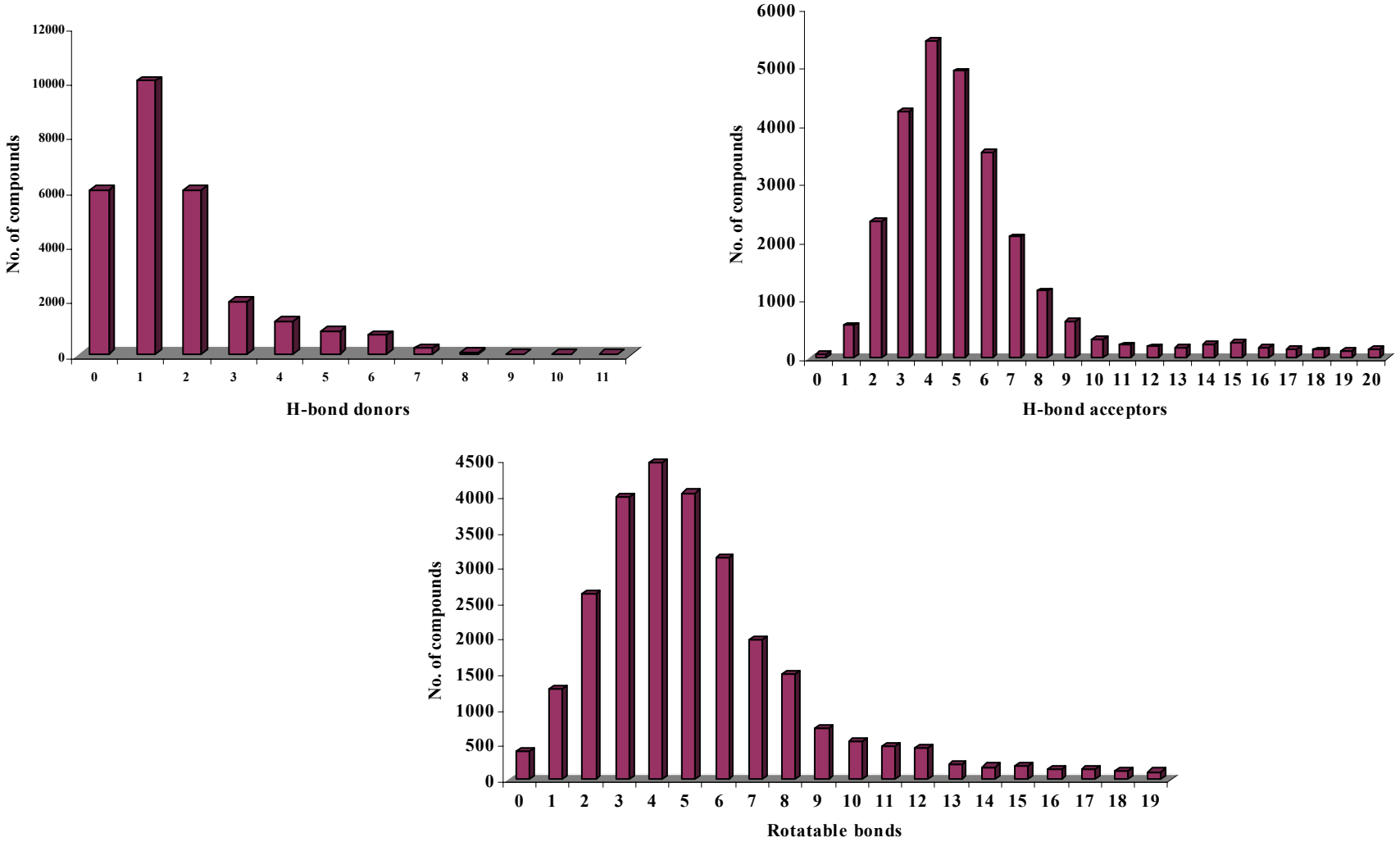


Figure 6: H-bond donors, H-bond acceptors and rotatable bonds distribution of compounds in PLIVA Database calculated with Cerius[2]
(data generated by I. Bašic)