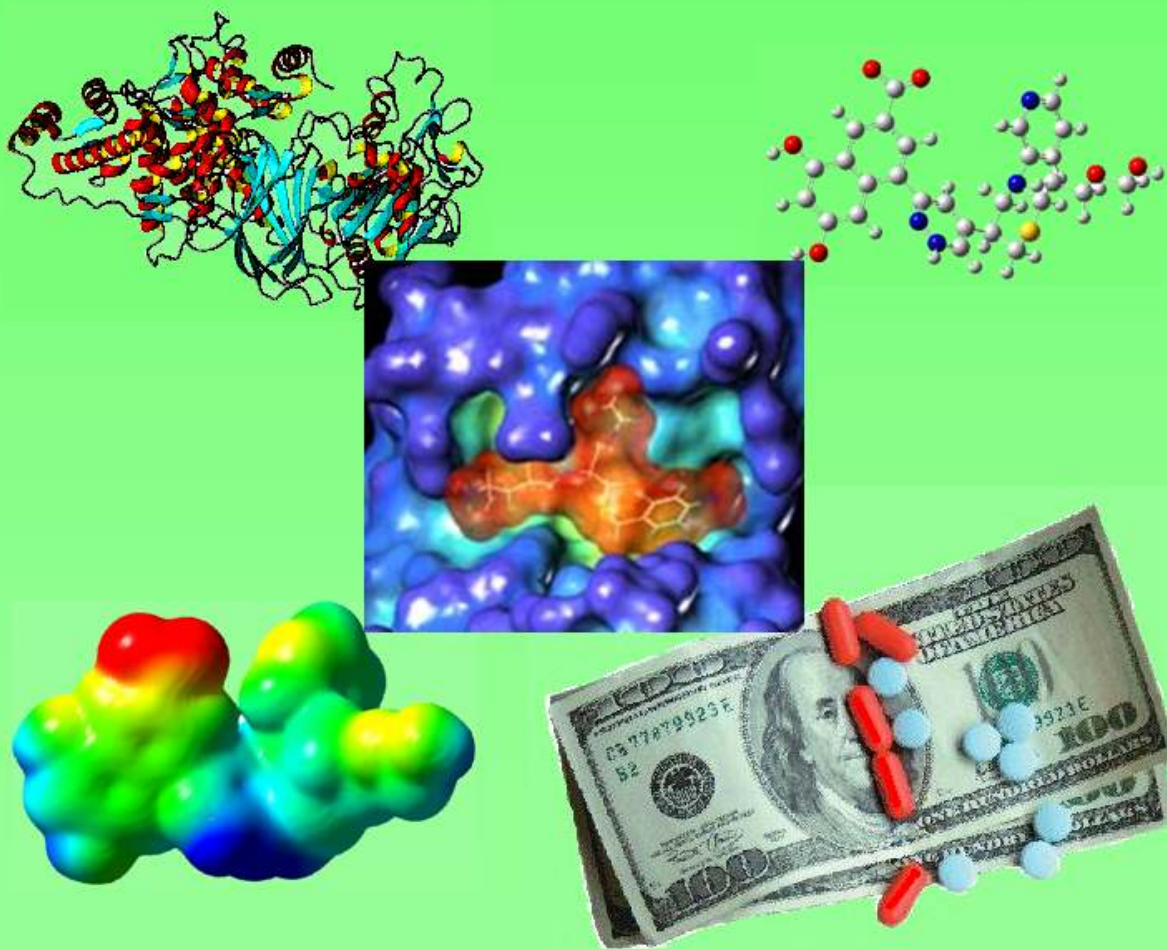


The Future of the Drug Discovery Process and the New Renaissance of the Pharmaceutical Industry

An economical and scientific study



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The Future of the Drug Discovery Process and the Fate of the Pharmaceutical Industry

“We can’t solve problems
by using the same thinking we used when we created them”
Albert Einstein

Executive Summary

In accordance with the structure of *Scientific Revolutions* the Pharmaceutical Industry ran into “dead-end streets” several times during its modern history. Such problematic periods were followed by a new *Renaissance* which was due to a new mode of thinking, the application of a new philosophy, amounting to nothing less than a characteristic *Paradigm-shift*. The acceptance of the paradigm-shift, and the application of its associated new technology, resulted in a corresponding *Breakthrough*, at every time. We may assign, to these happenings, approximately, the following years, with ± 5 year tolerance: 1890s, 1920s, 1950s, 1980s, thus, these breakthroughs occurred in roughly 30 years of intervals. Clearly, we are facing a new *Breakthrough*, in the near future, perhaps in 2010 or soon thereafter.

Those who will act as midwives for the birth of the new technology can take advantage of the emerging new *Molecular Revolution*. In essence, their advanced knowledge will allow them to apply the new technology before anybody else does, thus, they can become leaders of a multi-trillion-dollar Pharmaceutical Industry

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1 Current Predicaments

1.1 Economic Success of the Pharmaceutical Industry in the 20th Century

The pharmaceutical research is continuously changing and a renewing area due to the novel chemical, pharmaceutical, and biological findings. The economic performance of the Pharmaceutical Industry during the 2 decade long period of 1994-2013 is shown in **Figure 1**. The various phases of pharmaceutical research are illustrated in **Figure 2**.

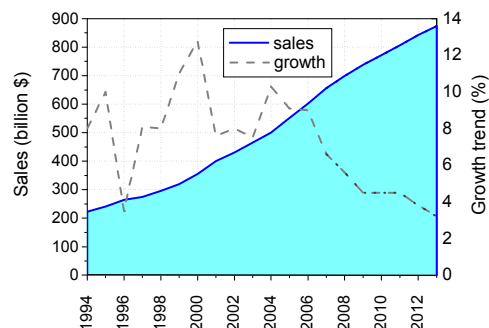


Figure 1. Global sales and growth trends of drugs. Data for the period 2007-2013 was predicted, by Wood Mackenzie.

In the beginning, which may be dated back to ancient times, the drug industry dealt with the various collections of different herbs and other living organism. The active ingredients were extracted from these mixtures, producing multi-component products *e.g.* solutions, creams *etc.* Later, the development of the isolation techniques initiated the isolation of different compounds in a very pure form, in order to concentrate the active component, and in that way, the bio-absorption and bioavailability could be improved. After that, the rapidly developing chemical science determined the pharmaceutical research, and certain chemical modifications were carried out on the isolated active compounds, to increase their biological activity and pharmaceutical property.

A classical example is the case of Aspirin. In ancient Greece, Aristoteles recommended that pregnant women should chew the bark of a willow tree in order to reduce pain during delivery. It was not until the end of 19th Century that Bayer synthesized and subsequently marketed the Aspirin. The first prescriptions for Aspirin were given in 1899. A marketing of Aspirin and the appearance of the 1st synthetic drug (Salvarsan-606) are still regarded nowadays as the golden age of the Pharmaceutical Industry, **Breakthrough 1**.

We may consider the discovery of sulfonamides, penicillines as **Breakthrough**

During the past few decades, practically all the easily isolable active ingredients were studied and modified in a wide range. At that time, soon after World War-II, the revolution in the chemical science (total and retro-synthetic approaches) could reform the drug research (**Breakthrough 3**), because a large number of the synthesized compounds showed a certain biological effect. The parallel developing fine-chemical industry provided a large variety of chemical building blocks. A success story of **Breakthrough 3** is the anti-hypertension angiotensine converting enzyme (ACE) inhibitors (captopril, enalapril, lisinopril, etc.) which were designed on the structural basis of viper venom. However, the randomly and accidentally

studied biological effect, without the deep biochemical background, these trials were very ineffective. The new breakthrough (**Breakthrough 4**), happened in the 1980's, involved the complete change in the way of thinking and the strategy of the pharmaceutical research. The High Throughput Screening (HTS) in combination with the combinatorial chemistry extended extremely the palette of the available chemical structures up to millions. Moreover, a parallel development that occurred in genetic engineering was able to provide in sufficient amount and in satisfactory quality the biological targets (proteins, receptors) for *in vitro* testing. Now, at the dawn of the 21st Century, we are facing a period that may well be characterized as **Breakthrough 5**, due to the golden age of computational chemistry.

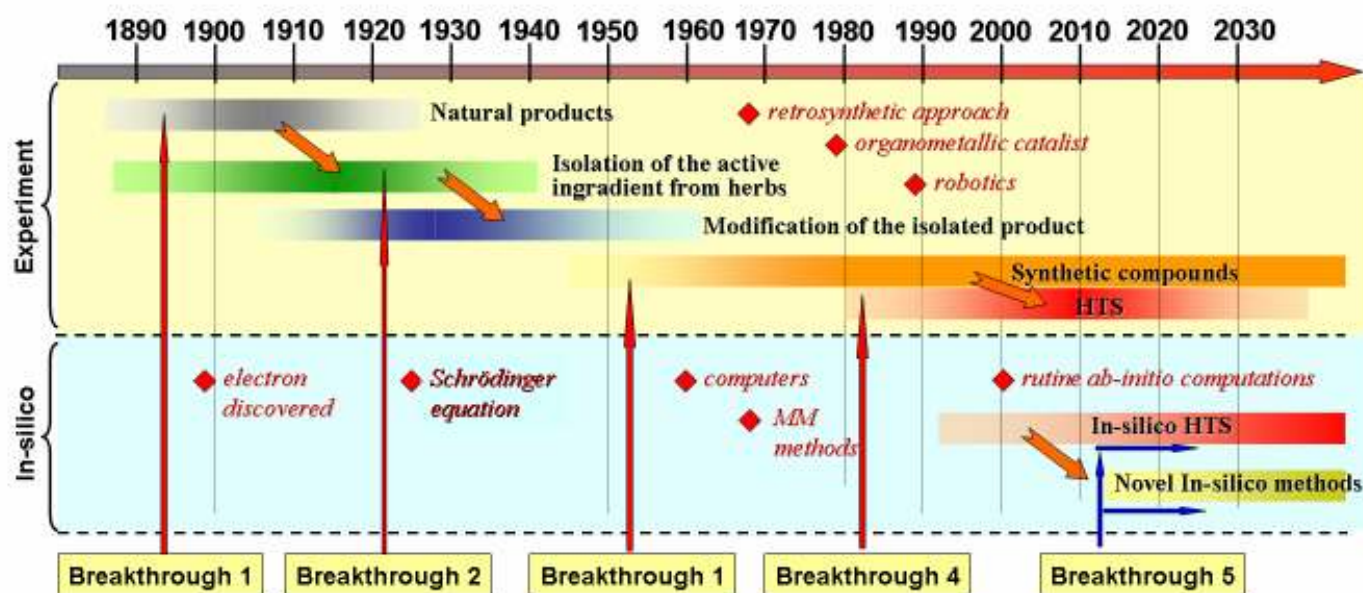


Figure 2. Historical milestones and strategies in the pharmaceutical research. HTS = High Throughput Screening

The years before a given breakthrough the Pharmaceutical Industry had problems that appeared insurmountable. Yet, within a relatively short time, usually within a period that was less than a decade, some solutions were found that lead to a **Breakthrough** moving the Pharmaceutical Industry to a new Renaissance. These phenomena are summarized in **Table 1** for the last three Breakthroughs. All of these historic happenings are well within the “anatomy” of *Scientific Revolutions*.

Table 1 Problems of the Pharmaceutical Industry before a given Breakthrough and Solutions that had the potential to save the Pharmaceutical industry and channel it toward a new Renaissance.

Breakthrough	PROBLEMS	SOLUTION
	Isolation period	Synthetic chemistry
3	1. all, easily isolable compounds had been studied, 2. there was no new concept,	1. the chemical science extended the palette of the available compounds. 2. the systematic structural scanning bring the change of the concept.
	Synthetic chemistry	HTS
4	1. random testing 2. no biological background 3. relatively narrow range for chemical structures	1. systematic search 2. deep biological background, in vitro testing, genetic engineering, 3. the combinatorial aspects extended dramatically the number of organic compounds
	HTS	In silico methods
5	1. most of the chemical backbone are patented, therefore the freedom is narrow, 2. the performance of the classical synthetic methods are exhausted	1. the modification of natural products having larger molecular mass (> 500 Da) will extend the chemical palette 2. the novel organo- and organometallic- catalyst will need to be applied in larger extent to achieve sophisticated molecular engineering

1.2 Economic Doom of the Pharmaceutical Industry at the Dawn of the 21st Century

It is known that the pharmaceutical industry is in crisis now. The diagnostics of the crisis are the mergers and takeovers, which are due to the insufficiency of current pharmaceutical R&D. The economical and technological factors are summarized in the following points:

1. On the one hand, the research expenses are increasing continuously (presently ~ \$1 billion/single drug) and ,on the other hand, the Pharmaceutical Industry must continuously fulfill the more and ever stricter official requirements. Thus, while the operational costs are increasing, the number of patents and the number of drug products are stagnant. This causes a dramatic decrease in the overall profit. This unfavorable trend raises the financial risk associated with research, therefore the large companies do not increase the research expenditure at the degree as it would be necessary. This is illustrated in **Figure 3**.

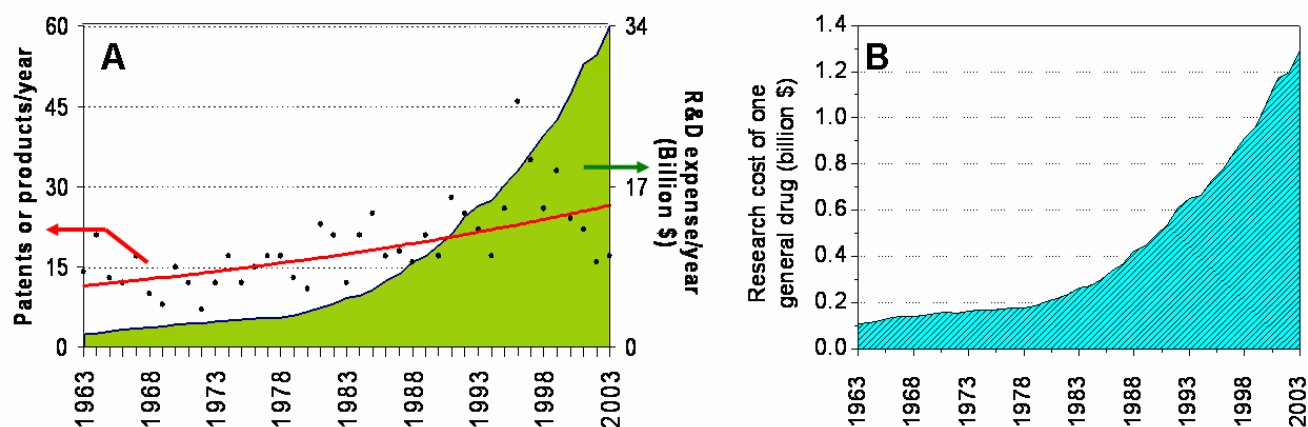


Figure 3. A: R&D Expenses of the Pharmaceutical Industry and the Number of Drug-related patents as a function of time. B: Average Research Cost of a Drug Development as a function of time.

2. In addition, beside the disadvantageous industrial background, governments are continuously lowering health care expenses worldwide, pressuring the pharmaceutical industry to cut the prices of drugs (e.g. turn to generic drug production). For these reasons, the pharmaceutical companies find themselves “between a rock and a hard place” or inside of pincers (Figure 4), which problem usually manifests itself in increasingly frequent takeovers and merges in the industrial sector.



Figure 4. The current squeeze on Drug Research

1.3 The 20th Century R&D Philosophy is not a viable concept in the 21st Century

The present R&D activity is continuously slowing, due to the following factors:

1. Most of the simple chemical backbones (around 500 Dalton) are already patented and only the sophisticated larger structures (above 500 Da) could provide sufficient chemical freedom and variability for the drug research. These larger molecules have not been investigated as yet since the overall process for larger molecules is more difficult.
2. The present drug substances have relatively low molecular mass structures (around 500 Da), compared to the usual natural ligands of the receptors (1500–50000 Da or even larger), therefore these small molecules can never exhibit as high activity and selectivity on the target receptor, than the natural

counterparts. This is due to the significantly less possible interactions between the ligands and the protein (3–7 interactions, see **Figure 5**), than the natural ligands or products having larger and more complex chemical structure (10–30 interactions).

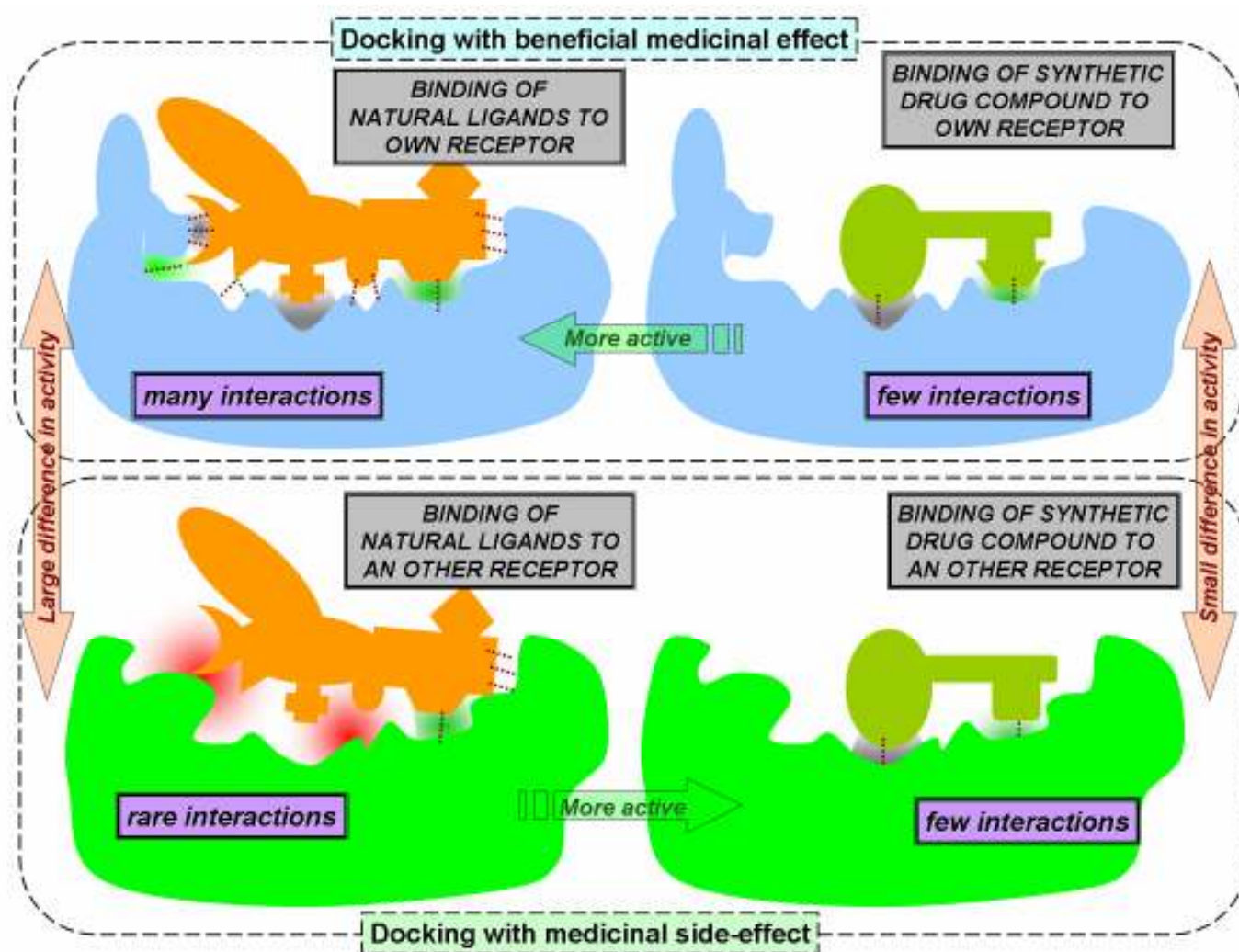


Figure 5. Schematic representation of binding pattern between a natural ligand and a smaller, drug-type molecule.

3. The *in-vitro* experiments require a good and very reliable biological testing protocol, however, many biological target can not adjust properly, which lead to many false positive and false negative results.

4. The common theoretical approach based on the experimental HTS screening, namely millions of chemical structures are tried to dock into the active site and the results scored according to several aspects. After a crude selection, some refinements are carried out to tighten the palette of the compounds. At the end, usually, numerous basic skeletons are found (hits) to be appropriate to continue the research. This virtual

screening (**Figure 6**) is an indirect method, because one may find the correct structure from some indirect information. During this procedure, many false positive and false negative as well as positive correct hits are found, which means that lots of promising structures are dropped, meanwhile many wrong structures are studied to waste the research time and resource.

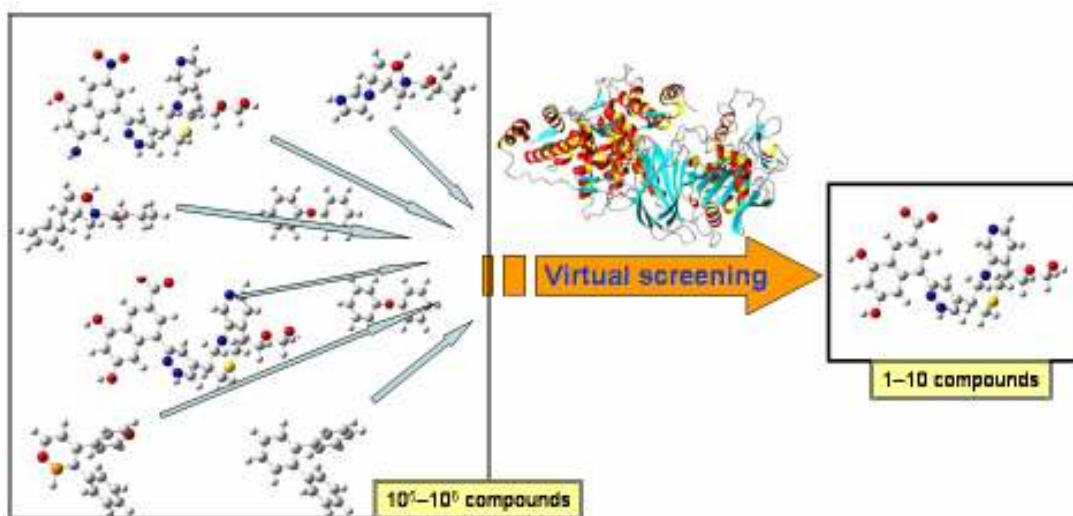


Figure 6. Schematic view of the philosophy of the Virtual Screening.

2. New Directions

2.1 Beyond the 500 Dalton Limit; Larger Molecules show greater selectivity

The palette of the chemical structure should be extended toward the natural products, having molecular mass far above the 500 Dalton limit, defined by C. A. Lipinski ten years ago. As can be seen (**Figure 7**) the collection of the natural products (The examples shown in **Figure 7** are taken from the *Journal of Natural Products* of the American Chemical Society), exhibit excellent bioactivity, bioavailability, pharmaceutical properties (metabolism, transportation, etc.), in spite of their large molecular mass (500–2000 Da). Consequently, this Lipinski rule should be neglected or its impact should be reduced in the future. Usually, not only their chemical activities are thousands of times better (pmolar), than the currently used small drug substances (nmolar), but the selectivity between the target receptor and other possible biological targets are, at many a times, million-fold better. Their higher activity may decrease the daily dose (lower toxicity) and their better selectivity may lowers the risk of the therapeutic side effect. Moreover, due to their natural origin usually they have a sufficient metabolism procedure, which is also a key point during the research. The chemically modified version of these compounds may well be the future drugs.

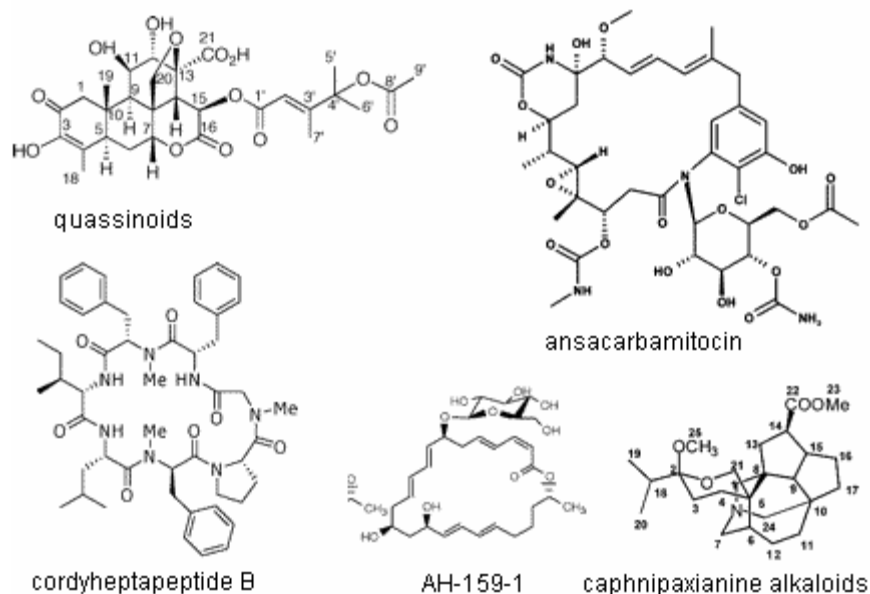


Figure 7. Selected natural products from the recent issue of the *Journals of Natural Products* (ACS).

2.2 Learning from Nature: “how to do it”

If Nature can design molecular structures *intelligently* so can we, but first we have to learn the secret of Nature. The following points are only preliminary illustrations for the magnitude of the task

1. It is known that most of the biological ligands and inhibitors have an auto-activating system, which increases dramatically their biological activity, due conformational changes, which should be considered and applied in the drug design to reach better effect. These compounds may call as *intelligent molecules*.
2. The synthesis of large, intelligent multi-interacting compounds, copied from natural products, however, requires the intensive application of the modern organo- and organometallic catalyst, due to their sophisticated structure. In the near future, not only the reaction route will have to be scouted and optimized, but the structure of the organocatalyst will need to be modified in order to achieve a certain multi-step reaction.
3. Both the design of a drug and the sophisticated level of chemical synthesis of that drug require a considerably more intensive application of the *in-silico* methods that has ever been achieved up until this very day. This is also predictable not only for the docking procedure, but for the modeling of the way of working of the intelligent drug and catalyst optimization for the different chemical reaction steps.

3. New Philosophy

What may be the solution? It may be the introduction of new more efficient techniques, which can decrease the research cost and the time requirement. Clearly sophisticated molecular computations can be the solution!

3.1 The Emergence of “ Systems Biology”

The following three quotations clearly illustrates that we are experiencing a paradigm shift in biological research that is governed by a new philosophy of science. This new approach is called “Systems Biology”.

1. *“System biology is the science of discovering, modeling, understanding and ultimately engineering at the molecular level the dynamic relationships between biological molecules that define living organisms.”*

2. *“The reductionist approach has successfully identified most of the components and many of the interactions but, unfortunately, offers no convincing concepts or methods to understand how system properties emerge...the pluralism of causes and effects in biological networks is better addressed by observing, through quantitative measures, multiple components simultaneously and by rigorous data integration with mathematical models”*

3. *“Systems biology...is about putting together rather than taking apart, integration rather than reduction. It requires that we develop ways of thinking about integration that are as rigorous as our reductionist programmes, but different....It means changing our philosophy, in the full sense of the term”.*

Undoubtedly this will be followed by a paradigm shift in pharmaceutical research that may properly be termed as “Systems Pharmaceutical Science”. However, the prerequisite for such a change is that first of all we develop “Systems Chemistry” since the Drug Discovery Process is based on the combination of Biology and Chemistry. Such conditions and capabilities are discussed in the subsequent sections.

3.2 The Emergence of Accurate Quantum Predictions, leading to “Systems Chemistry”

The interaction between the ligand and the target protein is usually very complex (**Figure 8**), but in its detailed it is rarely studied. We believe that the deep and quantitative understanding of these various interactions is necessary to know the way of a ligand-target complex is working. For this reason, some

quantitative scale have been defined, by the Authors, to describe, not only qualitatively but quantitatively well the different chemical interactions, such as Aromaticity, Amidity, Carbonility, Stericity, Hydrogen-bonding and the like. These methodologies will lead to more detailed understanding of the certain chemical and biochemical reaction as well.

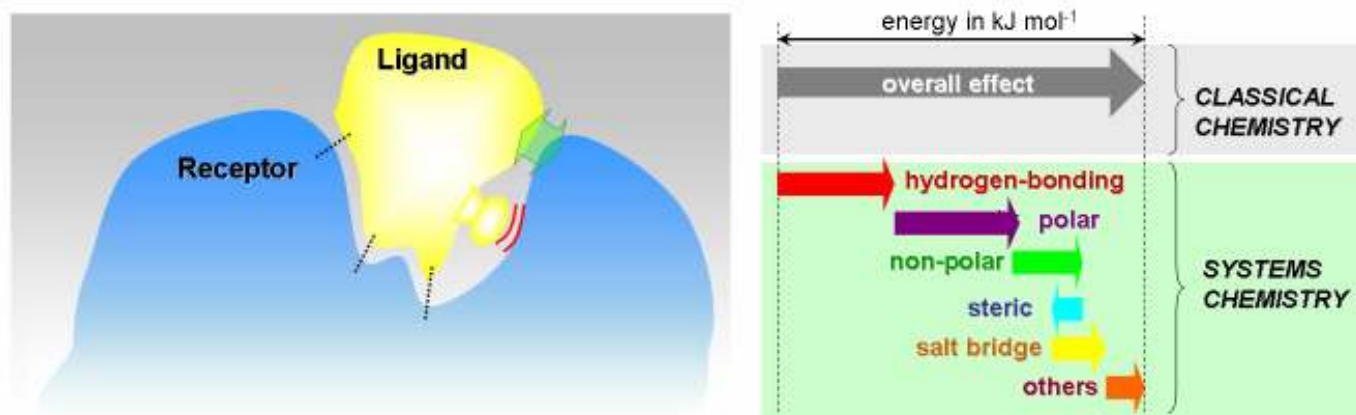


Figure 8 A schematic illustration of what “Classical Chemistry” and what “Systems Chemistry” sees in a Receptor/Ligand complex

3.3 The Quest for Intelligent Catalyst Design to produce the new types of Drugs

As was mentioned before, in the near future the organic or organo-metallic catalysts will need to be optimized in addition to the reaction routes, due to the increasing complexity of the target compounds. The catalyst optimization is not feasible without strong theoretical background. Consequently, in the early phase of the research, such an appropriate software should be developed.

The more sophisticated structures (**Figure 9**) more and more frequently require the organo- and organometallic catalyst, which are a significant bottleneck of the present production.

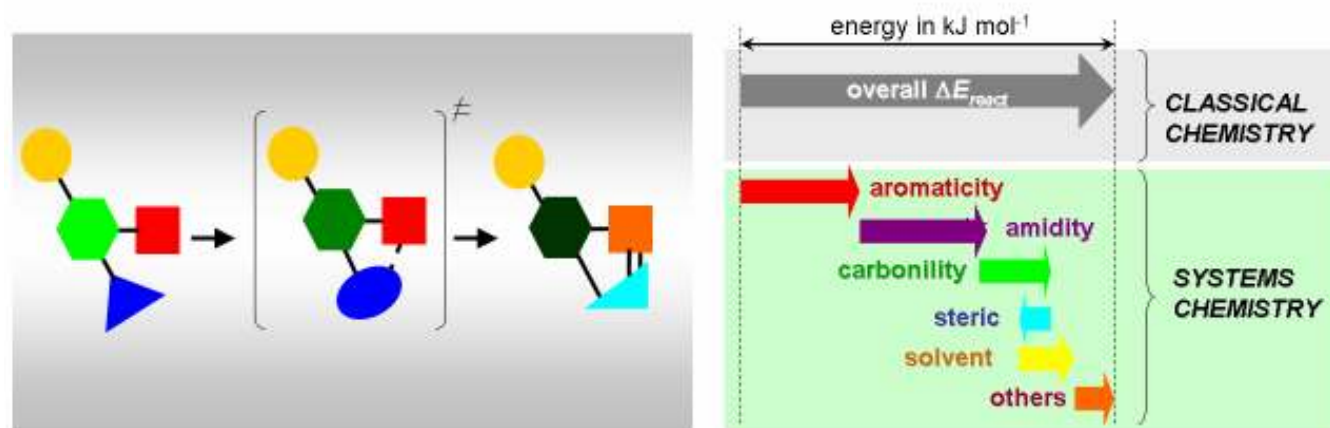


Figure 9 A schematic illustration of what “Classical Chemistry” and what “Systems Chemistry” sees in a synthetic reaction process or in a metabolic reaction process of a drug molecule

3.4 The need for “Systems Pharmaceutical Science”

In our opinion, this screening should be changed to a more reliable and direct theoretical method. In this procedure (**Figure 10**) the active hole is filled with a media, which indicate the negative molecular volume and the fingerprint of this hole and should be proportional to the volume of the predictable active molecule (see the purple irregular form). Later, the electrostatic interactions, hydrogen bonding donors and acceptors, that perturb the form obtained, coloring its surface by a code of possible polar, non-polar, electrostatic, hydrogen-bonding interactions. Finally, this irregular, colorful form could be brought to correspond to a few exact chemical entities, which may be one of the lead compounds of the research.

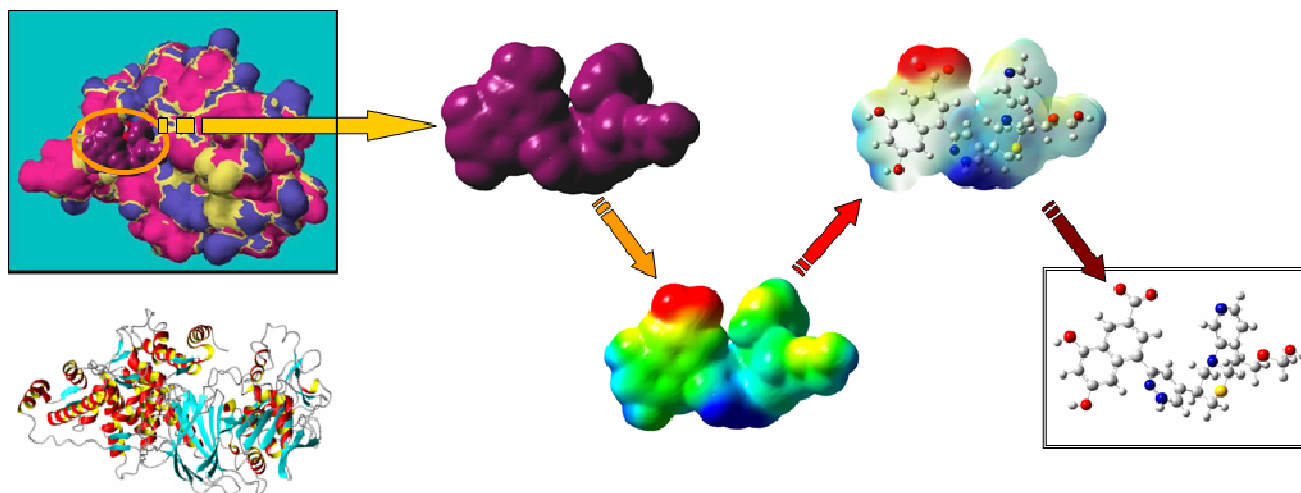


Figure 10. Novel direct theoretical prediction.

However, both the indirect (Figure 6) and the direct (Figure 10) processes require the initial 3D-structure of the biological target, but such an information available presently only for a few of them. When the 3D-structure is not available, the homology modeling may result an appropriate structure for the study.

4. Intelligent software

4.1 A "Total System" Approach

The total system approach, always represent the most general philosophy. Biotechnology, Drug Discovery, Drug Synthesis has to be merged with all existing chemical as well as biological knowledge and know-how together with completely new concepts.

In Figure 11, a possible future perspective is outlined, where hypothetically, a very efficient computational background (hardware and software) are introduced into the research, shortening the time required for the research and development, compared to the present situation. According to this hypothetical, but viable prediction, the time shortening may be 4 years, decreasing the average research time from 12 to 8 years.

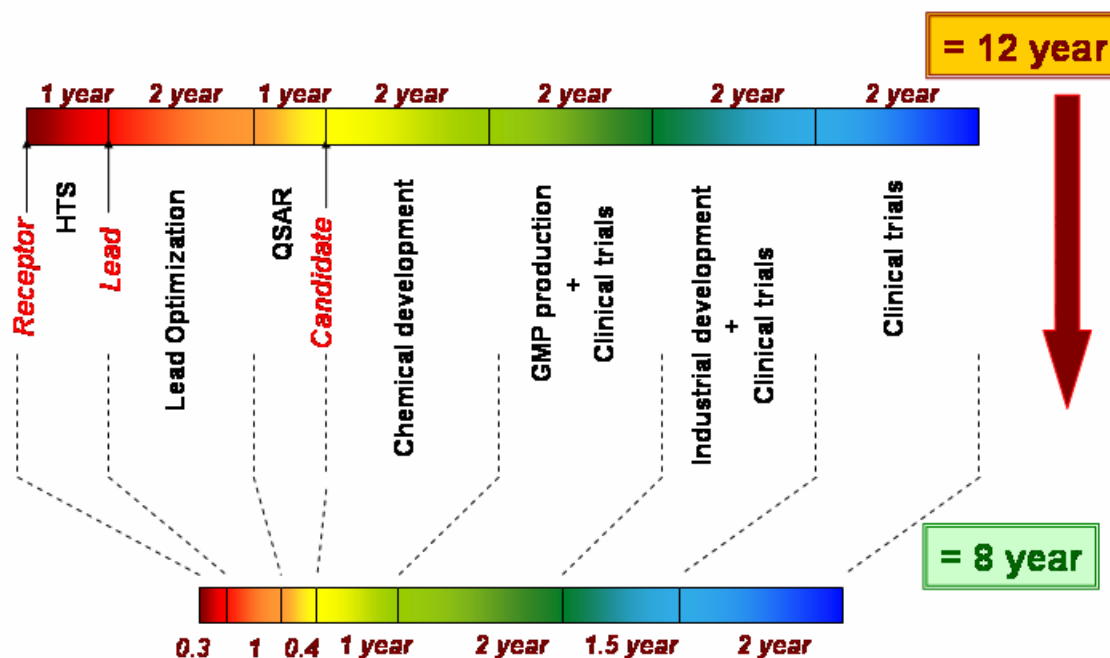


Figure 11. A possible reduction of time-requirement (from 12 to 8 years) of the Drug Development Process

4.2 A Flow-Chart, illustrating the Software System to be developed

The required software to be constructed within the “Total System” approach is illustrated schematically in **Figure 12**. The final software will combine the best existing experimental and theoretical techniques, developed during the 20th Century, with the new concepts necessary for the advancement of the 21st Century.

This flowchart (**Figure 12**) represents an absolutely automated system, where the input is the genetic information with some homology information or the exact 3D structure of the biological target (enzyme, receptor). After some self-fine-tuning in the *Discovery* phase, the output may be a candidate molecule (with high biological activity and selectivity) for the *Development* phase with a synthetic plan utilizing pre-designed catalysts.

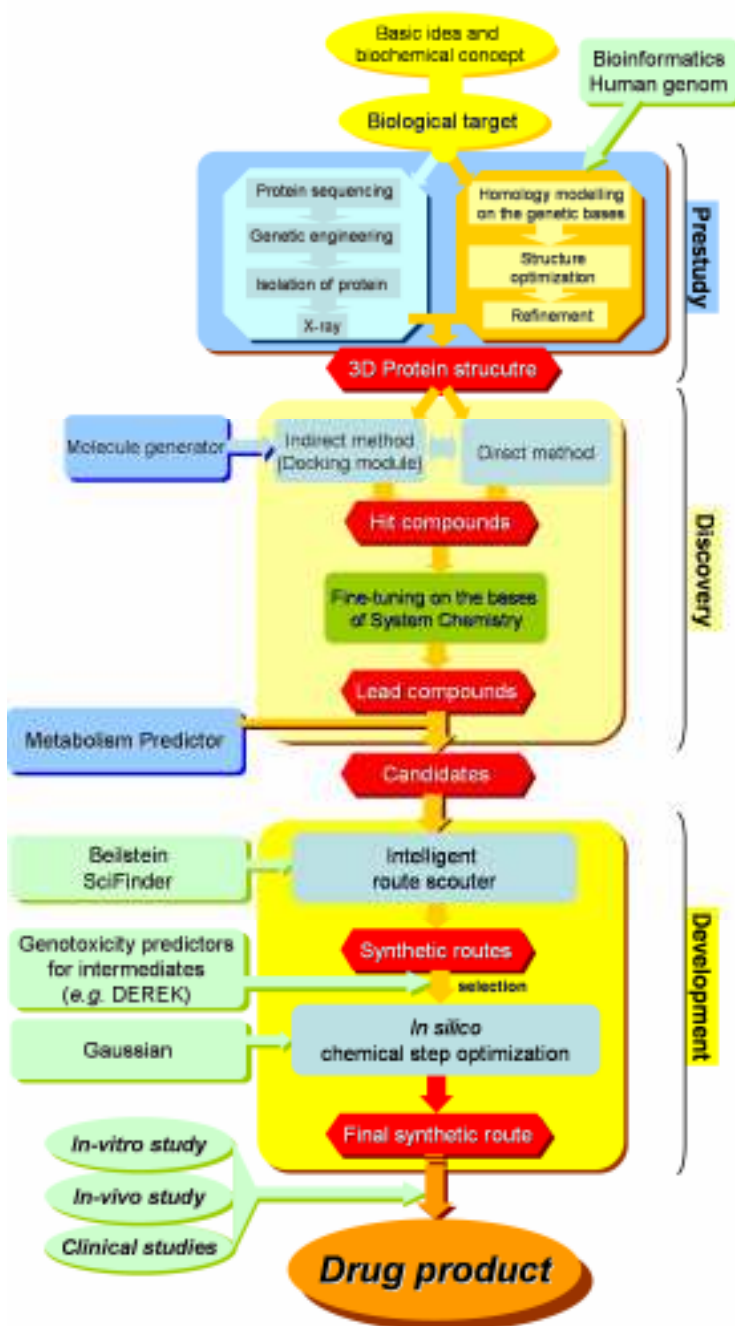


Figure 12 A schematic flow-chart of the Automatic Drug Discovery Software based on the *Total System* approach.

5. Anticipated Results

5.1 An unprecedented revival of the Pharmaceutical Industry

A dramatic reduction of research cost and an appreciable reduction of drug development time will make major change in the operational philosophy of the Pharmaceutical Industry, while at this time business considerations are coming first due to the research expenses. After the introduction of the new technology, health considerations could come to focus of attention. In the near future, the population of the developed part of the world will use even more kind of drugs day by day, practically for all small health problems. Due to the increasing longevity more and more old-age diseases will appear, requiring more and more drugs. However, to avoid the cross-reactions between the daily dosing of ten or even twenty different types of drugs, their selectivity should be improved. If not fewer than 100, but more than 1000 drugs will succeed to pass through all the phases of clinical trials, the pharmaceutical company would focus of health since the profit will be virtually guaranteed from such a large number of new drugs introduced to the market annually. This would amount to the Pharmaceutical Industry nothing less than a new Renaissance.

5.2 An ultimate financial reward on the initial R&D investment

The progressivity of the economy of the Pharmaceutical Industry is shown schematically in Figure 13. Each step that occurs after a new technology introduced, at paradigm-shift, this higher than the previous step. The insert at the upper left hand corner of Figure 13 shown a quantitative extrapolation from the current 0.6 trillion dollar volume to 30 trillion dollar sale. This is clearly a 50-fold increase of business activity.

The software developed could be used by a single pharmaceutical company that wishes to be the leader or the software may be sold, with annual additional improvement, to any one of the pharmaceutical companies. In each way, the return of the R&D investment in the software development would be very rewarding, to say the least.

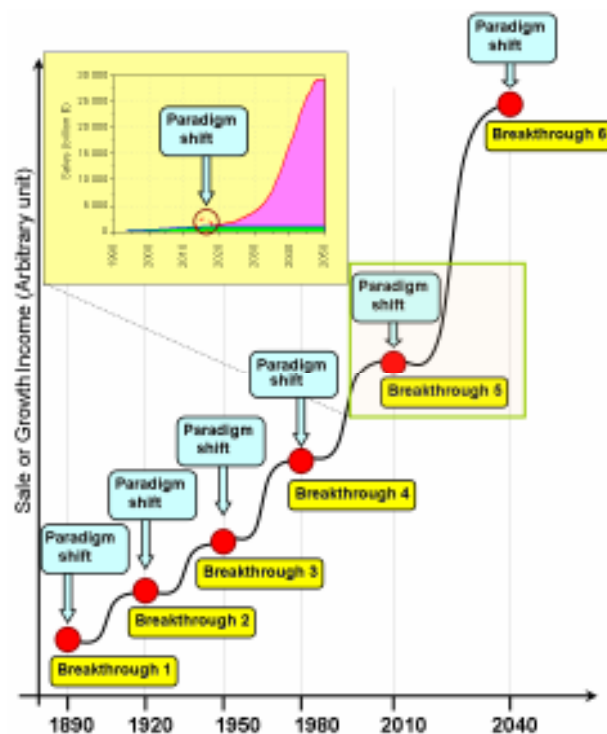


Figure 13. A schematic illustration of the stepwise increase of the Pharmaceutical Industry. At each of the steps the paradigm-shift results in the introduction of a new technology in the research and development.