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AI Integrated Theoretical/Organic Chemistry is Set to Revolutionize the Future of Education and De Novo Drug Discovery

Soykan Agar[1,*], Ilgaz Tokay[2], Barbaros Akkurt[3], Erkan Gokoluk[1], M. Berk Akbulut[1], Berin Damla Ozler[1], Muzaffer Elmas[4]

[1]AGAR *In Silico* Drug Design Center, Department of Biochemistry, Faculty of Pharmacy, Kocaeli Health and Technology University, Izmit, Türkiye
[2]Coordination of Foreign Language, Okan University, Istanbul, Türkiye
[3]Department of Chemistry, Faculty of Science and Letters, Istanbul Technical University, Istanbul, Türkiye
[4]Rector of University, Former Dean of Faculty of Pharmacy, Kocaeli Health and Technology University, Izmit, Türkiye
*Corresponding author: soykan.agar@kocaelisaglik.edu.tr

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Abstract This article discusses the rapidly expanding artificial intelligence (AI) tools combined with theoretical and organic chemistry software to point out the fact that near future is being reborn with a new education system and research system in drug discovery. The integration of AI into the field of chemistry and pharmacy has expanded rapidly in recent years. There has been a significant surge in both journal articles and patents, particularly from 2015 onward. Analyzing the distribution of these publications across various pharmaceutical and chemical research domains reveal that theoretical chemistry, organic chemistry and biochemistry have embraced AI most extensively, showing the highest growth rates. Utilizing such new software tools in educational research centers and academia, students and scholars can learn and apply much more long-durational and larger techniques in shorter times to yield massive results for the sake of humankind's future with no diseases. This new type of educational and research-oriented technique integrating the control and check mechanism of AI is being used today for the design of new drugs which are essential for the longevity. The utilization of AI with *in-silico* studies and education increases the ability to stop diseases with a logarithmic increase while the old-fashioned ways of chemistry will be no more in the near future. Overall, this research paper offers a comprehensive overview of AI's advancement in pharmaceutical and chemical area and sheds light on its potential future trajectories.

Keywords: *artificial intelligence, AI, theoretical chemistry, organic chemistry, biochemistry, de novo drug design, university education*

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1. Introduction

1.1. The Educational System in Chemistry is Altering with the Use of AI

Throughout history, education has always been a face-to-face activity. Examining the term education's root, we find that it comes from the same root as the Turkish words maarif, tedrisat, training, and etiquette. But a lot of terms come forth, including developing, fostering, educating, bending, and applying from this root [1].

There are numerous ways to describe education, but at its most fundamental, it is the constant application of information, skills, and understanding gained by experience to an individual's behavior, whether they are in or out of school [2]. This definition demonstrates that encountering others involves the exchange of information, either directly or indirectly. In addition to being done in person, this action can be completed virtually.

Given the historical evolution of education, the fast-advancing state of technology has allowed for several advancements in the process up to this point. The usage of technology-based tools like computers, tablets, smart boards, and other devices in education is growing quickly as a result of this process of creation and setup. Reason and logic have emerged as a result of the fast growth of creativity, knowledge, skills, adaptation, and science from the hunter-gatherer to the agricultural to the industrial to the information to the exponential ages [3,4].

Mechanization and industrialization in education during the 20th century resulted in the factory model of divided education, strained relationships, little regard for social

knowledge, and deterioration of values. With the proliferation of technology in education, artificial intelligence evolved in the twenty-first century. Thanks to the combination of reason and intelligence with technology, technical solutions have brought the field of applied sciences, especially chemistry, which has an important place in education with new formulas to the chaos arising from problems, to a more advanced dimension. By saving time and space, educators have joined the online education network for many people at the same time. Today, the necessity of education without going to school has increased the demand for technology. Thus, the constant increase in the need for technology reveals an exponential change. As a result, there is a rapid transition from the Information Age to the Exponential Age with the combination of the biological with the digital, physical and cyber [5].

When technology is advancing at a rapid pace, there are several advantages in every sector, including schooling. The school environment in which education is implemented is impacted by the in-person learning process just as much as the instructor and student. The teacher and the student are both learning from this interaction, and it becomes clear that merely imparting knowledge is insufficient when looking at the classroom setting in which the course will be taught. Learning is thus directly impacted by the manner and content of information transmission. Even if in-person instruction is still the norm nowadays, there are still plenty of choices available for those who cannot attend classes or who choose to continue their education for other reasons. With the advancement of computers and the internet, using technological tools are growing in popularity. Obviously, with the rapid development of technology together with artificial intelligence machines are far more capable than people because of technology. Additionally, one option whose use is expanding quickly is artificial intelligence (AI) technology. Artificial intelligence is a scientific field that aims to replicate human intellect and learning capabilities in robots and computers, enabling them to accomplish intricate tasks. AI provides breakthroughs that simulate human behavior and thought processes in a variety of industries, including entertainment, banking, transportation, and health [6]. With several application fields, including data analysis, natural language processing, image recognition, and autonomous systems, this technology is crucial in today's digital world [7].

The use of AI in chemistry has grown significantly in the last several years, both in terms of industrial applications and research [8]. AI makes it simple to predict complicated chemical processes, analyze massive data sets, and find novel materials and medications [9]. More speed and accuracy may be achieved when modeling molecular structures and reaction processes, particularly with the use of machine learning methods. Thus, by increasing the efficiency of experimental procedures, researchers may save expenses and lessen their negative effects on the environment.

Thus, by increasing the efficiency of experimental procedures, researchers may save expenses and lessen their negative effects on the environment. Furthermore, the chemical industry's competitiveness and sustainability are raised by the opportunities presented by AI, modeling, and optimization. Chemistry research and development procedures are accelerated and made more efficient by artificial intelligence [10]. AI is having an impact on a wide range of fields, including materials research, medicine development, chemical prediction, molecule discovery, and creative problem solving. Thanks to AI's data analysis and modeling tools, chemists may find new things faster and for less money, which advances science [11]. The chemical industry is improving efficiency while simultaneously contributing to environmental and economic sustainability.

Education in chemistry is greatly enhanced by the application of AI, which gives students access to a more thorough and personalized learning experience. By offering information that is adaptive to students' learning levels and speeds, AI-based educational platforms and tools assist maximize students' learning processes [12]. Students may do risk-free and affordable sophisticated chemical experiments with virtual laboratories and simulations. Students receive immediate feedback from AI-powered instructors and assistance tools, which aids in their understanding of the material. These technology developments have made teaching chemistry simpler and more engaging while also enhancing students' ability to solve problems and think analytically [13]. Teachers and students can benefit from more productive and efficient learning opportunities through the use of artificial intelligence in chemistry education through a variety of applications. Here are some examples:

Labster: This platform, which provides virtual lab simulations, enables students to do experiments that they would not be able to carry out in actual lab settings in a safe and economical manner. Labster uses AI-powered simulations to help students become more proficient experimenters [14].

Socratic: Designed by Google, this application leverages artificial intelligence to assist learners in comprehending and resolving chemical and other scientific topics. If students take pictures of their queries or write them down, they can receive answers and explanations right away [15].

ChemTutor: During chemistry lectures, students may receive individualized help from this AI-powered instructional application. By customizing questions and course materials to each student's learning style and speed, it helps them grasp topics more fully [16].

ALEKS (Assessment and Learning in Knowledge Spaces): This adaptive learning platform, which is used in several areas, including chemistry, makes use of artificial intelligence to determine what students do not know and to provide them with individualized learning routes [17].

1.2. The Benefits of AI Integrated Drug Design

The use of AI in chemistry has seen a significant rise in recent years, particularly reflected in the growing number of publications. AI implementations dramatically reduced design and experimental efforts in the last years. This growth in the power of AI isn't consistent across all fields. For instance, AI's integration is more advanced in life sciences, organic chemistry, theoretical chemistry and analytical chemistry, where it has likely moved beyond

the "peak of inflated expectations" and the "trough of disillusionment." The effectiveness of AI in a specific area is closely tied to the availability and quality of data, and the potential to extract meaningful insights from it. AI is particularly valuable in uncovering new insights that traditional methods might miss and in handling large, complex datasets, making it especially useful in fields like organic chemistry, analytical chemistry and biochemistry, where large amounts of data are available, particularly for studying macromolecules with complex structure-property relationships. These successes in data-rich fields are now being mirrored in other areas of chemistry. The surge in AI-related publications involving small molecules is largely driven by its application in drug discovery. An analysis of the types of substances discussed in these publications shows a strong focus on nucleic acid and peptide sequences, indicating AI's significant role in biochemistry. The way AI is being applied in biochemical and pharmaceutical research is also reflected in the distribution of substance roles within these studies. Several factors have contributed to the increased use of AI in chemistry since 2015. The availability of software and hardware necessary for AI has lowered the barriers to its use, and there has been a proliferation of data sets suitable for AI analysis. Additionally, many researchers have become adept at generating and handling data for AI applications. Between 2000 and 2020, there has been a notable increase in the co-occurrence of AI with specific research areas in publications, showing how AI has been integrated into various aspects of chemical research. As a result, many AI methods have been successfully adapted for use in chemistry, with some fields even seeing AI become a routine tool. However, in areas like organic synthetic and theoretical chemistry, AI has yet to make a significant impact and it is expected that improvements in AI technology, coupled with interdisciplinary research, will eventually bring these fields to a great breakthrough in discovering new science and education models [18,19,20,21,22].

The fundamental concept in AI health sciences such as pharmacy, medicine, genetic engineering, medical biochemistry will possess the following elements in the near future; The discovery of new drugs (de novo drug design) [23]. This is being made possible through the use of artificial intelligence and simulation software. This can only be achieved through the combination of advanced knowledge and great grasp in organic chemistry for drug design.

The actual efficacy of a molecule designed with the organic chemistry/pharmaceutical chemistry knowledge is now anticipated not only through laboratory experiments but also by simulating its interactions with cells beforehand (Figure 1). A pharmacist/pharmaceutical engineer/medical doctor with a strong foundation, possessing a profound understanding of organic chemistry and AI simulation use, can significantly influence the world of pharmaceuticals [24].

In the modern world of artificial intelligence technologies, machine learning, and computational simulation software, the “organic pharmaceutical chemistry de novo drug design” has expanded its variety of tools to battle the spread of cancer to a point where it will be even wiped out from the earth once and for all shortly soon. To be able to achieve such a difficult task, medical doctors, genetic engineers, pharmacists, and biologists need to upgrade the methodologies of designing and producing antineoplastic drugs. In this matter, rather than the conventional ways of drug design for production that were taking at least 15 years for FDA approval, now brand-new computational simulation tools integrated with AI shortened this period to 5 - 6 years since large compound databases both can be virtually screened with AI integration as well as it helps functional group alterations for the simulations. In the past, with conventional ways, an FDA approved drug design takes 10 to 15 years and a total amount of money 2 - 5 billion dollars minimum [25,26]. New modern techniques including AI machine learning and simulation studies are being used to shorten the possible de novo drug design period where as much as side effects and counter-indications can be eliminated.

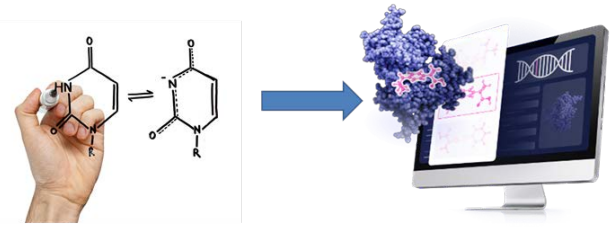

Figure 1. *De novo* drug design from scratch using AI integrated tools combined with theoretical/organic chemistry software

1.3. The Relationship Between Drug Discovery and AI

Big data analysis with AI software, allows the correct chemical functional groups for the drugs to be found. While doing so, high yield drugs will be able to synthesized faster than ever before while being environmentally green with the high precision target indications. Our article discusses a potential application of artificial intelligence to *in silico* studies. It is relevant to university education and encompasses a broad area. There are software programs that we use to enhance the speed of estimating the correct functional groups 10-fold using the versions of Schrodinger 2013-4, Autodock Vina 1.1.2, and Dock.AI [27,28,29,30]. We published 14 research papers and 3 patents within the last 6 months with these such novel techniques since AI also further helps in the estimations of correct new functional groups on drug candidate chemical structures just like an experienced organic/pharmaceutical chemistry professor.

Also another tool in pace enhancing in the drug discovery is a software called “AIDDISON” owned by Merck KGaA is available for solving the AI Drug Discovery-centered problems. It combines the power of artificial intelligence, machine learning, and computer-aided drug design. It is a unified platform for efficient and effective ligand-based and structure-based drug design. It has an integration tool for virtual screening and it supports methods for lead discovery and lead optimization [30].

Synthetic organic chemistry encompasses several areas of chemistry, especially drug discovery. Performing complex chemical syntheses requires expert knowledge, including many years of study and hands-on laboratory

practice. AI, empowered by enhanced computing power, data availability and algorithms, seems to overturn the limited success in the past [31,32]. A review article by Almeida et al. delineates the recent impact of AI on some synthetic organic chemical reactions and selects some examples from the existing literature [33]. This example gives a lucid knowledge that AI is an indispensable tool for computational organic chemistry and pharmaceutical chemistry, against efforts that do not use AI at all.

Machine learning (ML) methods of AI supply a number of tools that can improve discovery and decision making for well-specified questions with abundant data having high-quality. Applying ML is possible in all stages of drug discovery, with examples of target validation, identification of prognostic biomarkers and analysis of digital pathology data in clinical trials [34].

Deep learning models of AI are sometimes notoriously hard to debug, and they require high cost of computation. In some time, these drawbacks will be resolved. Nevertheless, AI (neural networks, deep learning models and such) are able to "learn" given the training time and adequate samples [35]. It is also interesting to note that drug discovery systems usually began to use AI tools rather than conventional hands-on drug discovery methods.

A review article by Yang et al. comprehensively describes ML techniques and of their applications in medicinal chemistry. The basic principles, and some application notes of the various ML algorithms are noted, and the current state of AI-assisted pharmaceutical discovery, namely, structure- and ligand-based virtual screening, *de novo* drug design, physicochemical and pharmacokinetic predictions of properties, drug repurposing, and related aspects are discussed. They conclude by mentioning of several challenges and limitations of the conventional old methods, with a view to potential future directions for AI-assisted drug discovery and design [36]. This example also shows that a study deprived of AI is not available or even preferred.

Chemists perform experiments and gather data and the knowledge is expanded. When the data are collected and analyzed, chemists increase the understanding of chemistry. With the invent of cheminformatics, it began to use AI and the process gained more momentum [37].

AI is effective for data mining based on the vast amount of pharmacological data and the process of machine learning. AI has been used in *de novo* drug design, activity scoring, virtual screening and *in-silico* evaluation in the properties (ADMET[1]) of a drug molecule. It is normal to observe that many pharmaceutical companies work closely with companies specialized on AI for faster progress in the field of drug development, along with the healthcare system [38].

When pharmaceutical industry discovered new drugs over the past 100 years, the practice of medicine has dramatically changed and it has a certain impact on our culture. For many years, drug discovery had been a target- and mechanism-agnostic approach and based on ethnobotanical knowledge with serendipity. When modern molecular biology methods are discovered and human genome knowledge has been displayed, drug discovery has been converted into a hypothesis-driven target-based approach, along with important environmental changes in the pharmaceutical industry. Academia, regulatory agencies, and pharmaceutical industry all contribute to drug discovery and basic science is translated into new medical treatments (for medical needs not seen before) and pharmaceutical companies must recruit many scientists working in the many branches of therapeutic sciences, disciplines, and technologies [39]. The synergism between experiments and computational approaches on the selection and optimization of bioactive compounds makes it important to integrate advanced technologies in drug discovery [40].

Phenotypic assays are useful in the improvement of drug discovery and they speed up the selection of the required molecules. Phenotypic drug discovery (PDD) uses biological systems for new drug screening. Drugs with new mechanisms are presented well by PDD but poorly qualified leads, overloaded pipelines, and advancement of leads with undesirable mechanisms failing at stages that are more expensive. Hit triage, prioritization, elimination of hits with unsuitable mechanisms, and supporting clinical strategies of pathway-based frameworks of decision. If the mentioned approaches are used with increased pace, better decisions are possible, better leads are produced faster, and PDD is adopted greatly [41]. There is an urgent need to develop drug discovery strategies, but PDD's capabilities and culture of pharmaceutical industry are surrounded by very strong challenges [42].

Mullin discusses the relationship between high-throughput screening (HTS) and drug discovery, this relationship helped medicinal chemists a lot. The researcher's ingenuity and intellectual capacity is replaced with HTS. Authorities on the subject have come to an agreement that combinatorial chemistry plays an important role to build a library of compounds from the workplace and also HTS is needed, at some point, in the progress of drug discovery [43].

Drug discovery is involved in target discovery and validation, along with lead identification by HTS and lead optimization by medicinal chemical efforts. Follow-up pre-clinical evaluation includes the following elements: Analysis in animal models of compound efficacy, pharmacology (well-known ADME analysis), followed by toxicological studies, specificity, and drug interaction studies. Drug design in academy can focus on rare occasions like third-word and rare diseases, and "chemical genetics" in which the research team develops research reagents like high-affinity inhibitors for pharmacological "gene knockout" in animal models. As an example for academic drug discovery program, small molecule inhibitors and activators of cystic fibrosis transmembrane conductance regulator; new compounds emerged for physiologic research and clinical development [44].

A review article by Duarte et al. delineates the current situation in computational strategies for target discovery, drug discovery and drug delivery and methods about how they could be integrated. The items needed in these fields and how the databases and computational tools are developed continuously will have a certain effect on the improvement of those areas [45].

A book chapter by Weeber introduces an algorithmic description of the system in question and presents a

[1] Absorption, distribution, metabolism, excretion, toxicity.

potential drug discovery effort. He finishes by discussing the current and future status of literature-based discovery in the biomedical research domain [46].

1.4. The Significance of Drug Design Centers in Academia

In silico AI studies allow many probabilities of molecule bindings to be tested before going into the wet-lab experiments. Thus, it saves time for finding the right drug molecule. Such in silico simulation centers take less physical space compared to ones in wet-labs. It is easy to be set up from the scratch, and the cost comes solely from the maintenance of supercomputers. In silico centers (Figure 2) have nearly zero cost for maintenance. However, wet-labs require constant chemical and biological purchases [47].

When the *in-silico* drug simulations decrease the chemical and pharmaceutical synthesis expenditures, computational drug design simulation studies (*de novo* drug design) can span hundreds of chemical structures to find out the correct drug formula fitting for the right indication to the target/receptor molecule inhibiting the diseases or symptoms [48].

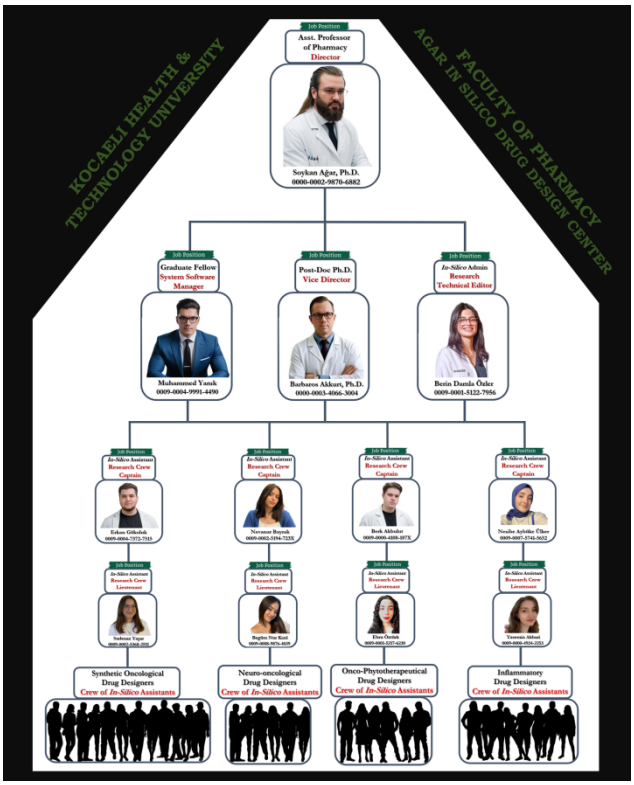

Figure 2. The Educational and Applied AI integrated De novo Drug Discovery Research Group Hierarchy in ‘’AGAR In Silico Drug Design Center’’ within the Faculty of Pharmacy at Kocaeli Health and Technology University

Our educational and research-oriented center’s scope is on the discovery of the binding mechanisms of *de novo* drugs that will cause the apoptosis of cancerous cells. Gene silencing factors, nucleotide regioselectivity factors and DNA domain selector factors depending on the alteration of functional groups on the designed drugs are untouched fields that should be revealed. Therefore, since the spread of cancer in humans increase day by day quite rapidly, the anti-neoplastic drug design has become one of the major research areas in computational chemistry & medicinal chemistry [49].

1.5. Molecular Docking and Molecular Dynamics Software are Now Under the Control of AI Tools

In the field of medicinal chemistry & oncological research, intertwined with artificial intelligence integration, the pursuit of innovative organic-pharmaceutical drug design has emerged as a cornerstone strategy (Figure 3) [50]. This extends beyond exclusively, targeting DNAs and encompasses a comprehensive approach toward the intricate pathways, as well as the molecular targets of RNAs and proteins.

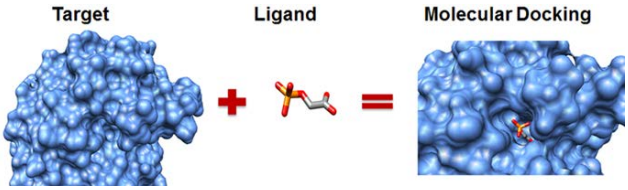

Figure 3. Molecular Docking is the key to find drug candidates for target molecules of diseases

In the current landscape, pharmaceutical companies find themselves in the midst of an era marked by the excessive production of chemotherapeutic drugs, predominantly composed of non-targeted molecules. More academic collaborations can solve this. Yet, within the annals of scientific history, certain cancer-suppressing drugs designed to target specific elements have been synthesized and utilized, albeit with elusive underlying mechanisms. The pharmaceutical landscape is adorned with FDA-approved anti-neoplastic drugs, but their mechanisms remain in mystery [51].

Unlocking the cell biological intricacies and effects of these drugs could potentially catapult their capabilities to unprecedented heights. Delving into the uncharted territory of understanding which molecular domains engage with cancerous cell DNA, elucidating the binding modes, and comprehending the stabilization mechanisms can provide invaluable insights for future drug designs. Central to this exploration are chemotherapeutic DNA damaging agents; compact cytostatic molecules that frequently bind and unpair the double-stranded DNA. Often, the most efficient ones are the cancerous DNA intercalators [52].

This binding induces modifications in structural and nano-mechanical properties, disrupting the proliferation process of cancer cells and triggering apoptosis. Cytotoxic drugs, revered for their varied interference with cell division, seek to inhibit this process with the ultimate goal of eliminating cancer within the host. The trajectory of pharmaceutical drug discovery in the oncological arena has steadily evolved, aiming to silence cancerous DNAs by either inhibiting their protein expression or irreversibly dismantling their DNA structure. In the realm of DNA-targeted drug designs, this lofty objective is realized through gene silencing employing groove-binding methodologies, shutting down DNA via external phosphodiester binding, or obliterating helical strands

through intercalation. The theoretical foundations of these approaches necessitate empirical validation through multi-spectroscopic experimental methodologies (such as FTIR, NMR, absorption spectroscopy etc. as in Figure 4) [53] and cell line inhibitions within in vitro experiments, and go further with in vivo, ex vivo, and human phase studies.

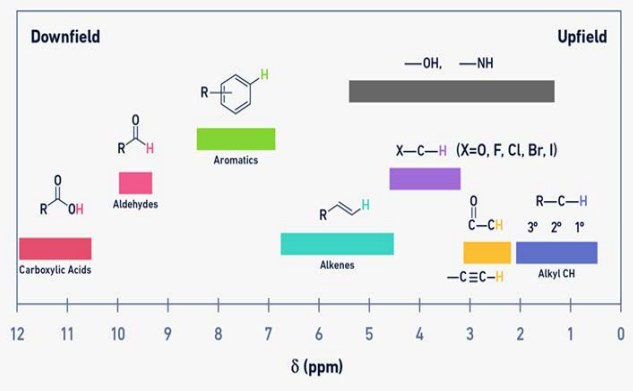

Figure 4. Drug candidate characterization using theoretical ^{1}H NMR tools

This imperative step bridges the gap between theoretical computations and practical applications, unraveling the hidden mechanisms of drugs and providing a comprehensive understanding of their capabilities. As part of this ongoing pursuit, pharmaceutical chemical databases become meticulously curated to encapsulate the properties of studied drugs [54].

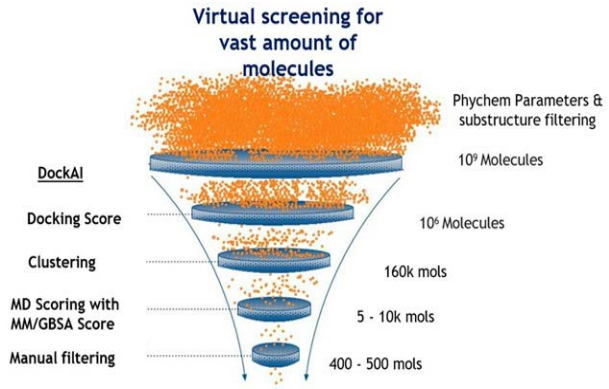

Figure 5. Virtual Screening to create a library of efficient drug molecules using AI integration

This virtually scanned molecules create a huge library (Figure 5) [55] that have affinities towards the target molecules of interest. The inception of a new chemical structure on paper, devoid of laboratory synthesis or experimental validations, prompts the need for predictive assessments concerning its indications, toxicity, and binding mechanisms on the target molecule with specific regioselectivity. The ability to foresee the preferred functional groups of target molecules and their strong bonds, as well as the prediction of repeating amino acids or nucleotides and their frequency, plays a pivotal role in shaping the trajectory of drug design and development. [40].

The intricate intersection of medicinal chemistry, oncological research, and artificial intelligence heralds a new era of pharmaceutical innovation. The necessity of the great knowledge of advanced organic and theoretical chemistry is essential. The pursuit of targeted drug design, grounded in a deep understanding of the organic chemistry of molecular interactions, promises to revolutionize cancer or any other type of disease treatment paradigms, ushering in an era where drugs are not only efficacious but also precisely tailored to combat the complexities of the disease.

With such good supercomputers at hand, virtually scanning new molecules utilizing integrated AI and new Post-MD methods, one can find accurate and precise drug-like molecules easily within minutes/hours per each run. Since the drug design center was established last year, within its first 6 - 7 weeks as soon as the supercomputers were provided to for the *in-silico* lab, we have been finding tens of new efficient molecules that can suppress pancreatic cancer, prostate cancer, head cancer, fatty liver disease (NASH) [56-64] etc. Thus, we have created a massive library of virtual molecules that works efficiently without toxic effects within in vitro & in vivo wet-lab results. So with the assistants of ‘’AGAR In Silico Research Center’’, we started writing many research papers and applied for patents for each molecule and methodology immediately which they were all accepted by prestigious high impact factored journals.

Then our educational research center was accepted to COST Action (European Cooperation in Science and Technology) in the oncological research working group. All of these new discoveries had nearly 95 to 99% accuracy compared to the cell line wet-lab studies. Why? Because computational simulation drug design software has come to a great point where it can estimate the reality of the biological systems very efficiently with the most updated software and forcefield computations.

Any information that are computed via simulations with molecular docking, molecular dynamics and AI software, decreases time and money spent in *in vitro*, *in vivo*, and human phase clinical stages (Figure 6). Especially very high accurate drug molecules computed in the *in-silico* stages shorten the production of any molecule drastically.

In a hit discovery, which is simply a process of finding efficient molecules that can suppress the diseased cell’s target molecule, among billions of molecules, the AI based virtual screening begins until good docking results can be obtained. Then AI goes on predicting results by altering the functional groups of those good results and re-runs the estimation tests. If all goes well with Molecular Dynamics as well, great hit molecules are yielded and ready for organic synthesis and in vitro characterizations.

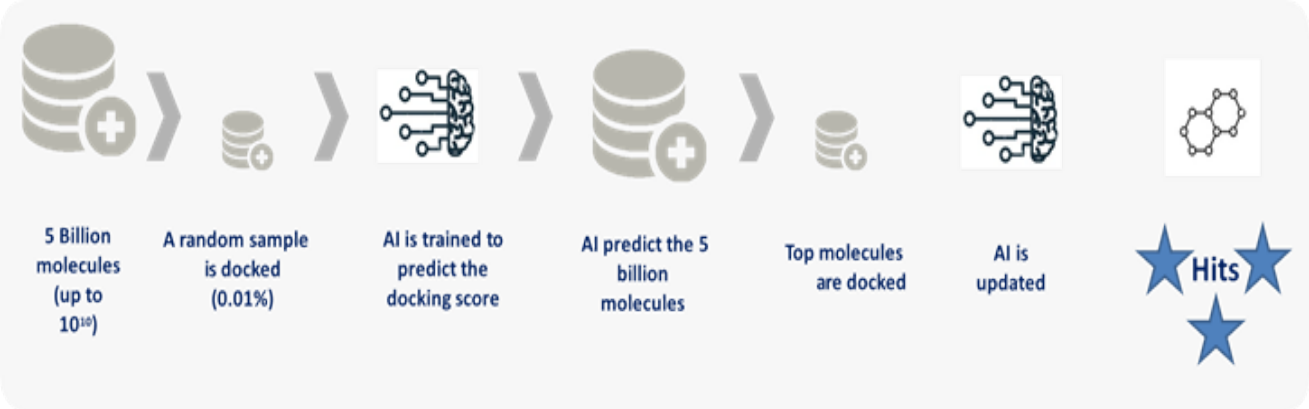

Figure 6. Hit Discovery with AI integration to find the correct molecules suppressing the diseases of interest

2. Conclusion

The future of drug discovery, especially in fields like oncological research, lies in precise targeting of target molecules whatever their origins are. In oncological AI simulations, there is no more cancer type classifications, solely the classification of target molecules and their structures are studied. This emphasizes the great change and the significance of AI integrated computational studies. Our ongoing studies have revealed promising insights into various drugs, contributing valuable data to our organic pharmaceutical chemistry database, particularly in understanding the roles of functional groups.

By scrutinizing the affinity, the binding score, the mode of binding, and the nucleotide regioselectivity of different functional groups in drugs, we were able to draw meaningful comparisons and contrasts. This analysis involves examining the overlapping outcomes from computational simulations, AI software, and multi-spectroscopic analyses.

Through this comprehensive approach, it becomes possible to anticipate both the new effects & repurposing effects of de novo designed drugs. The goal is always to create medications that are not only efficient & enduring but also have reduced toxicity & a specific regioselective focus on their target.

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