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Critical Examination of Synthetic Compounds and Drug Efficacy

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Abstract:

Synthetic compounds has revolutionized the field of pharmacology and drug development, enabling researchers to precisely create, modify, and optimize drugs that may not be attainable through natural product isolation. This paper explores the critical role of synthetic compounds in drug development and their impact on drug efficacy.

Drug discovery is a complex process aimed at identifying chemical compounds with therapeutic potential, particularly for addressing unmet medical needs in life-threatening diseases lacking effective treatments. However, this journey is fraught with challenges, including high attrition rates and significant time and financial investments. To mitigate these challenges, well-thought-out strategies are essential, especially when exploring new drug targets or therapeutic areas. A working definition of a "drug" within the context of drug discovery is presented, emphasizing chemically defined entities subjected to rigorous testing and validation, distinct from recreational or herbal substances.

The role of synthetic compounds in drug discovery is crucial, with chemists aiming to balance in vitro potency, selectivity, oral bioavailability, and safety. An example highlights the importance of addressing hERG channel inhibition while preserving other critical attributes. To enhance the drug discovery process, three key recommendations are offered. First, an integrated approach that coordinates in vitro and in vivo testing can provide a more robust foundation for lead compound selection. Second, appointing a dedicated drug champion with deep institutional knowledge can guide drug development teams effectively.

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Lastly, passing on the tacit knowledge of experienced chemists to the next generation is crucial for sustaining the art of successful drug discovery.

The development of synthetic compounds has played a pivotal role in modern medicine, leading to the discovery of numerous pharmaceutical drugs that have revolutionized healthcare. This research paper critically examines the relationship between synthetic compounds and drug efficacy, aiming to shed light on the complexities, challenges, and innovations in drug development. We explore the synthetic compounds' role in drug discovery, their impact on drug efficacy, the factors affecting drug efficacy, and future prospects in the field.

Keywords: synthetic compounds, drug efficacy, drug discovery, pharmacokinetics, pharmacodynamics, personalized medicine, drug repurposing, green chemistry, innovation, regulatory challenges, resistance, tolerance, patient compliance, biological variability.

1. INTRODUCTION

The introduction of synthetic compounds has been a cornerstone in the field of pharmacology and drug development. Synthetic compounds have allowed researchers to create, modify, and optimize drugs with a precision that is often unattainable through natural product isolation. This paper examines the critical aspects of this relationship, considering the significance of synthetic compounds in drug development, and their impact on drug efficacy.

Drug discovery is the intricate process of identifying chemical compounds with the potential to become therapeutic agents. One primary objective of drug discovery endeavors is to uncover novel molecular entities capable of addressing unmet medical needs, particularly in the context of diseases lacking effective treatments and presenting life-threatening consequences. Currently, the spectrum of marketed drugs is relatively narrow, predominantly encompassing those targeted at G-protein coupled receptors, nuclear receptors, and ion channels, which together make up roughly 50% of available drugs. However, branching into new classes of drug targets is a considerable challenge, demanding careful target selection, especially when exploring less-explored avenues.

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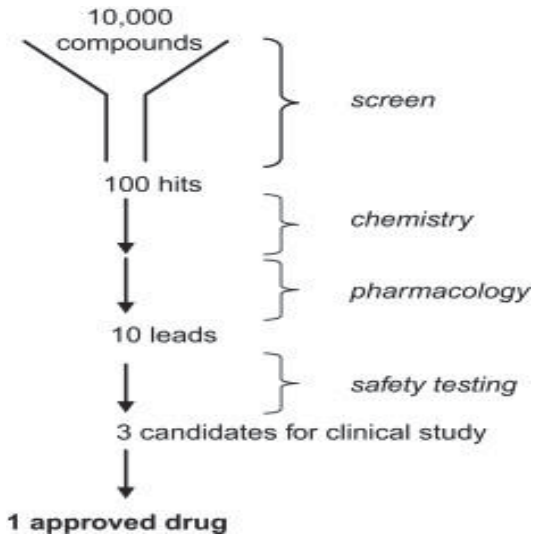
Conventional pharmaceutical research and development face substantial attrition rates. To bring a single drug to market, researchers may conduct over 100 screens, sifting through thousands of compounds. The lead compound discovery phase is both time-consuming, taking more than 5 years, and expensive, costing upwards of $200 million, excluding the subsequent development phase's expenses. Even when promising lead compounds are identified, unforeseen issues during development, such as toxicity, inadequate in vivo efficacy, market viability, and suboptimal biopharmaceutical properties, can lead to failure. Synthetic complexity, low potency, and ambiguous toxicological data can further slow development. Hence, it is imperative to implement well-thought-out strategies for drug discovery, particularly when exploring new drug targets or therapeutic areas.

Drug discovery strives to find solutions for unmet medical needs, but the road from initial screening to market is laden with challenges and costs. Therefore, carefully designed approaches are essential, especially when entering uncharted territory in drug development.



2. LITERATURE REVIEW

In 2001, Syam Kumar et al. introduced a novel method for spiro pyrrolidinyl oxindole alkaloid synthesis, involving iodide-induced rearrangement of [(N-aziridino methyl thio) methylene] oxindoles. Grigg et al. (2002) later demonstrated a spiro-oxindole creation via intramolecular Heck reaction and Ag(I)-catalyzed imine-azomethine ylide-cycloaddition.

In 2004, Feldman et al. described diastereoselective pummerer-based oxidative cyclization, yielding spirocyclic butyrolactone oxindoles from tryptophan derivatives. Miyake et al. (2004) introduced a new stereoselective intramolecular iminium ion spirocyclization for elacomine and isoelacomine synthesis. Nair et al. (2005) reported the formation of spirooxadiazolines using zwitterionic intermediates from dialkyl azodicarboxylate and triphenylphosphine with N-substituted isatins.

Zhu et al. (2007) employed a one-pot method in water, combining isatin, activated methylene reagent, and 1,3-dicarbonyl chemicals to synthesize physiologically relevant spiro-oxindoles. The isomerized bromo derivative of Baylis-Hillman adducts of isatin, as reported by Shanmugam et al. (2006), could undergo reductive cyclization with NaBH4 to yield functionalized diastereomeric 3-spiro cyclopropane-2-indolones. The versatile spiroannulated oxindole derivatives, a key structural unit in natural chemicals, were synthesized by Nair et al. (2006) using enols and 1,2-dicarbonyl compounds.

Shanthi. G et al. (2007) presented a one-pot three-component synthesis method for generating new spirooxindoles using conventional and solvent-free microwave irradiation.

Redkin et al. (2007) achieved the synthesis of 4,3'-spiro[(6-amino-5-R-3-methyl-2H,4H-pyrano[2,3-c] pyrazolo]-2'-oxindoles through a three-component condensation of isatins with 3-methylpyrazol-5-one and corresponding methylene active nitriles in the presence of basic catalysts.

Elinson, M.N. et al. (2007) reported the functionalized 5, 6, 7, 8-tetrahydro-4H-chromene system obtained through an efficient electrochemistry-induced catalytic multicomponent transformation of cyclic 1,3-diketones, isatin, and malononitrile in alcohols in the presence of NaBr as an electrolyte.

Gnanamani Shanthi, et al. (2010) utilized L-proline as a catalyst for a three-component synthesis, successfully producing new pyrazolo phthalazinyl spiro-oxindoles.

A straightforward one-pot synthesis of functionalized spiro-oxindoles via the vinylogous aldol reaction of vinyl malononitriles with isatin derivatives in aqueous media was reported.

Joseph J. Badillo et al. (2011) discovered a regio and stereoselective cyclization between isatins and 5-methoxy oxazoles, yielding spiro [3, 3'-Oxindoleoxazolines] using catalytic titanium (IV) chloride.

Hydrozonoyl halides reacted with exocyclic 4-aryliden-2-methyl imidazolin-5-one in benzene, facilitated by triethylamine, leading to the production of spiro compounds. They exhibited significantly improved antibacterial activity compared to a conventional medication.

Zhibin Huang et al. (2012) described a series of new dispiro-oxindole derivatives through the condensation of isatin and -amino acid with the dipolarophile 5-benzylidene-1,3-dimethylpyrimidine-2,4,6-trione in a single pot.

Chunhui Dai et al. (2012) synthesized spiro-oxindole (1, 3) oxazino derivatives from N-substituted isatins and 1,3-dicarbonyl compounds using a pyridine derivative, achieving good to outstanding yields. These compounds offer a diverse chemical landscape for further exploration, demonstrated through Diels-Alder reactions.

The existing literature provides a comprehensive overview of various synthetic methods for spiro-oxindole compound synthesis. However, a critical analysis of their comparative efficacy, scope, and limitations, as well as their potential applications in drug development, remains unaddressed.

3. A WORKING DEFINITION

In the context of drug discovery, defining the term "drug" is paramount, as it encompasses a wide array of substances and disciplines. Historically, the word "drug" originated from the Old English word "dryge," signifying the preparation of herbs into dried powders for medicinal purposes. However, the modern interpretation of a drug is a single chemical entity, often with accompanying excipients, intended for use in human or veterinary medicine, whether by prescription or as over-the-counter products. This definition excludes recreational or abused substances and herbals, focusing on substances subjected to rigorous testing, validation, and marketing. The interdisciplinary nature of drug development, leading to a substance being administered as a medicinal product, underscores the complexity and challenges involved in this process. This chapter primarily concentrates on small molecule

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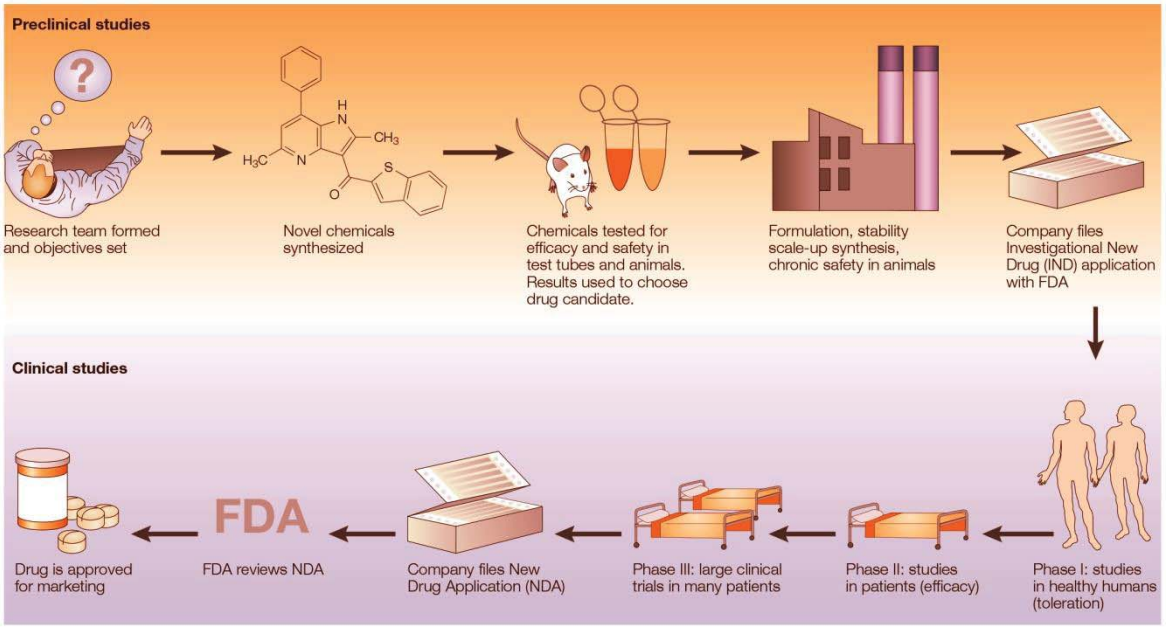
agents, differentiating them from biopolymers and vaccines, which require distinct development methods. In summary, a drug, within this context, is a chemically defined entity marketed for medicinal use, aligning with contemporary medical and pharmaceutical standards.



The drug discovery process commences with the recognition of a medical requirement, encompassing an evaluation of the existing treatments, if any. This assessment, in conjunction with an understanding of the current knowledge related to the target disease, leads to the formulation of hypotheses on how to enhance therapy. These hypotheses entail potential improvements in terms of efficacy, safety, or mechanistic novelty to advance the approach to treating patients with the targeted disease. Based on these hypotheses, specific objectives are established for the project. Subsequently, the process involves the evaluation of selected chemicals in appropriate biological tests.

Critical milestones in this process encompass the identification of relevant biological activity, referred to as a 'hit,' for a structurally novel compound in vitro. This is followed by the discovery of a related compound with in vivo activity demonstrated in an appropriate animal model. The next stage involves the optimization of this activity through the creation of structurally analogous compounds. Ultimately, one compound is chosen as the drug development candidate.

The selected drug candidate then undergoes mandatory toxicological testing in animals, in accordance with legal requirements. If the compound successfully passes all these tests, all the research data accumulated throughout the process are collated and submitted as an Investigational New Drug Application (IND) to the Food and Drug Administration (FDA) in the United States, or a comparable regulatory agency in other countries. This submission occurs before initiating clinical trials.

In the clinical phase, the drug candidate undergoes a stepwise evaluation, beginning with an assessment of toleration in normal human volunteers (Phase I). Subsequent phases involve evaluating efficacy and determining the optimal dosage range in patients (Phase II), followed by extensive trials involving thousands of eligible patients to establish a robust database of efficacy and safety. For the small percentage of drug candidates (approximately 4-7%) that successfully navigate this series of development trials, a New Drug Application (NDA) is filed. This NDA includes all the research data accumulated to date and undergoes a comprehensive review by experts at the FDA. Only upon receiving their approval can the new drug be made available to healthcare professionals and their patients for the intended treatment of the targeted disease.

4. BACKGROUND

The project that produced the novel anti-arthritic and anti-inflammatory agent piroxicam (Feldene; Pfizer) began in 1962 and led to the product launching into key European markets in 1980. A detailed history of this 18-year process, including the failures and setbacks along the way, has been described elsewhere, so only a brief outline will be given here.

- **Discovery of Piroxicam (1962–1980)**

The journey that led to the development of the anti-arthritic and anti-inflammatory drug, piroxicam (Feldene; Pfizer), began in 1962 and culminated with its launch in key European markets in 1980. A two-person research team, initially inexperienced in inflammation research, embarked on this ambitious project. They observed that existing anti-inflammatory drugs were predominantly carboxylic acids, necessitating frequent dosing and causing potential toxicity. To address these issues, the team set stringent project objectives over the

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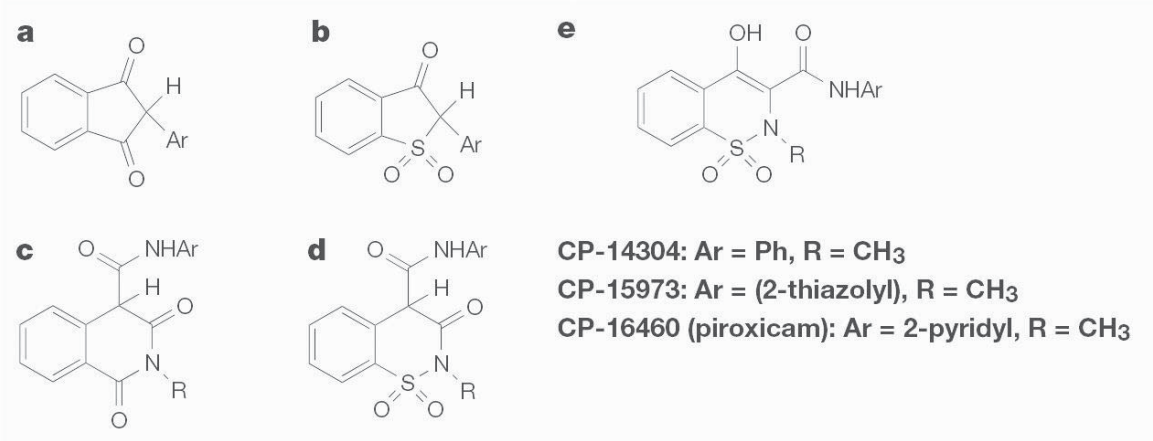
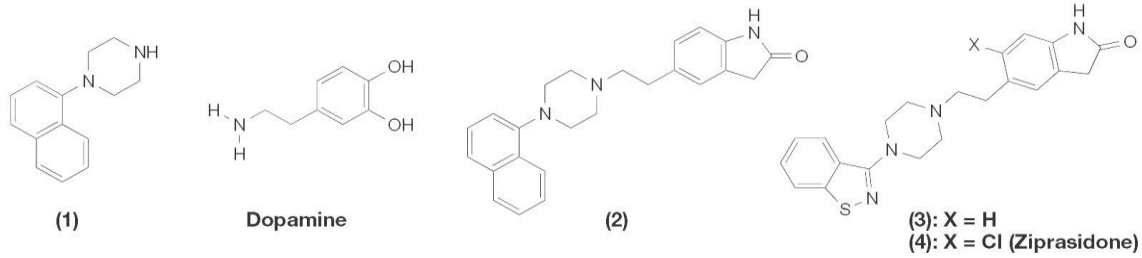
18-year span: the search for a structurally unique, non-carboxylic acid compound, high potency, reduced metabolism, and exceptional safety for long-term use in arthritic patients.



Despite several failures, the team synthesized numerous compounds with potential. The introduction of a carboxamide function eventually led to the discovery of piroxicam. Extensive clinical trials confirmed its efficacy and safety, and the drug offered 24-hour symptom control with just one daily 20-mg dose, gaining widespread patient acceptance. After 1992, generic brands of piroxicam dominated the market as major protective patents expired.

- **Discovery of Ziprasidone (1984–2001)**

Ziprasidone (Geodon; Pfizer) was launched in 2001 as a treatment for schizophrenia. The project relied on disease-relevant animal models and in vitro receptor-binding assays, striving for improved antipsychotic drugs over existing treatments. The use of animal models dating back to the discovery of chlorpromazine in the 1950s and receptor-based pharmacology in the 1980s contributed to the search for ziprasidone. Researchers focused on developing agents with a favorable D2/5-HT2 receptor ratio, seeking to reduce motor side effects.



The search for ziprasidone began with the synthesis of a compound that combined features of serotonin and dopamine receptors. Extensive testing and fine-tuning of the structure–activity relationship led to the discovery of ziprasidone. Despite a 5-year discovery phase and 9 years of clinical testing, the drug finally received FDA approval after a 3-year period addressing regulatory requirements. Ziprasidone's efficacy and safety have been validated through extensive clinical testing and years of patient use, offering relief to those suffering from schizophrenia.

5. THE ROLE OF SYNTHETIC COMPOUNDS IN DRUG DISCOVERY

Inventing and developing a new medicine is a protracted, intricate, expensive, and exceedingly precarious undertaking, unlike any other in the business world. Research and development (R&D) behind most of today's pharmaceuticals necessitates a daunting 12-24 years, spanning from the project's inception to the drug's market launch (Fig. 1). Moreover, numerous costly, long-term research endeavors culminate in failure to yield a marketable medicine. The price tag for this arduous journey has surged to an estimated US $1.4 billion for a solitary novel drug. These financial resources predominantly originate from private pharmaceutical firms that sponsor the research. During the research ('R') phase, only a modest fraction of the scientific hypotheses generate viable drug candidates for development. In the drug development ('D') stage, statistics reveal that only about 1 in 15-25 drug candidates surmount the rigorous safety and efficacy testing, both in animals and humans, essential for market entry. For the select few that do succeed in reaching the market, some may fail to recoup their developmental costs due to intense market competition, and merely about one in three emerge as major commercial successes. Clearly, this is a high-stakes, long-term, and hazardous endeavor, yet the potential to improve the lives of countless patients suffering from serious illnesses remains an unwavering motivator. At virtually every juncture, from project inception to discovery, development, and pre-marketing preparations, modern medicinal chemists play an integral role.

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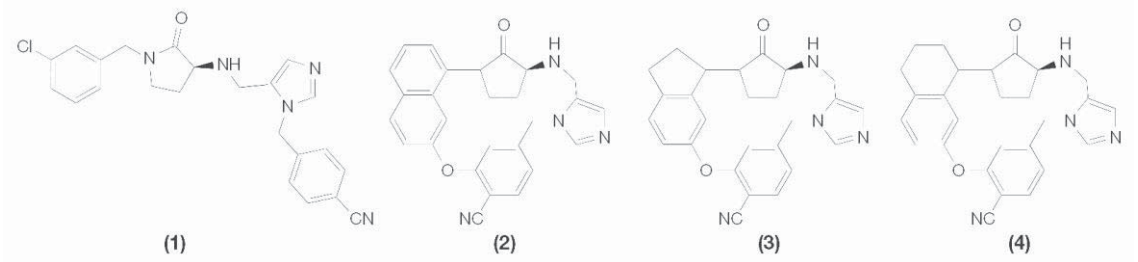
6. IMPACT OF SYNTHETIC COMPOUNDS ON DRUG EFFICACY

The data table presented in the figure showcases information about a set of chemical compounds, highlighting the criteria that the Merck research group employed to assess these compounds. Compound 1 demonstrates substantial in vitro activity for the primary endpoint, which is the inhibition of farnesyl transferase (FTase), with the corresponding IC50 values provided. It also exhibits selectivity against geranylgeranyl transferase type I (GGTase), a crucial factor for cell viability, and the respective IC50 values are also included. Despite showing excellent oral bioavailability (F) at 81%, Compound 1 inhibits the hERG channel, characterized by an inflection point for binding to the hERG channel through radioligand displacement assay (hERG IP) at 440 nM. Additionally, it leads to QT prolongation in dogs at a dose that is considered unacceptable.



FTase	1.9 nM	3.5 nM	0.15 nM	0.020 nM
GGTase	3.4 µM	650 nM	18 µM	390 nM
Func 1	0.52 nM	3.8 nM	0.22 nM	0.054 nM
Func 2	N/A	48/130 nM	3.0/3.0 nM	0.18/0.25 nM
hERG IP	440 nM	10.5 µM	80 nM	7 µM
CLp	5.8	1.1	2.1	7.3
F (%)	81	68	N/A	N/A
P450	1.0 µM	8.0 µM	6.6 µM	N/A

To address the issue of hERG channel inhibition while maintaining in vitro potency, selectivity, and oral bioavailability, the Merck group pursued macrocyclization, resulting in the development of Compound 2. Furthermore, the X-ray crystal structure data of Compound 2 bound to FTase sheds light on how the enzyme accommodates this structural change, thereby aiding in further drug design. The introduction of increased flexibility by saturating one of the rings of the naphthyl core in Compound 2 led to the creation of Compound 3 and Compound 4, both of which significantly enhance in vitro potency.

However, Compound 3 exhibited a drawback, being excessively potent at hERG (80 nM), while Compound 4 faced rapid clearance (as indicated by the rate of plasma clearance in dogs, CLp = 7.3 ml per minute per kilogram). Consequently, despite being the least potent compound within the set, Compound 2 emerged as the most suitable choice for further development in the context of structure-activity relationship optimization, primarily due to its favorable pharmacokinetic and safety characteristics.

This example underscores why modern chemists often prefer to initiate their research with compounds that possess superior pharmacokinetic and selectivity properties, subsequently focusing on enhancing potency for the primary in vitro endpoint. (Func 1: Cell-based radiotracer assay for FTase inhibition; Func 2: Cell-based assay for the inhibition of FTase substrate derivatization, assessed in the absence and presence of human serum; N/A: Information not available; P450: IC50 value for inhibiting human P450 3A4.)

7. CONCLUSION

The complex and lengthy journey of drug discovery is a high-stakes endeavor with a significant impact on healthcare and patient well-being. It begins with the identification of a medical need, followed by a meticulous process that involves extensive research, testing, and regulatory scrutiny. The definition of a "drug" in this context is crucial, emphasizing chemically defined entities subject to rigorous testing and validation, distinct from recreational or herbal substances.

Two case studies, the development of piroxicam and ziprasidone, illustrate the challenges and dedication required in bringing novel pharmaceuticals to market. The arduous 18-year journey that led to piroxicam's launch highlighted the importance of setting stringent objectives and rigorous clinical testing, resulting in a medication that offered a significant advancement in the treatment of arthritis and inflammation. Similarly, the discovery of ziprasidone for schizophrenia treatment showcases the essential role of animal models and receptor-based pharmacology in refining drug candidates over several years, ultimately providing relief to patients.

The role of synthetic compounds in drug discovery is pivotal, with chemists continually striving to balance in vitro potency, selectivity, oral bioavailability, and safety. The example of optimizing compounds to address hERG channel inhibition while preserving other essential attributes underscores the importance of early focus on pharmacokinetic properties.

To enhance the drug discovery process, three key recommendations are put forth. First, a more integrated approach, coordinating in vitro and in vivo testing, can provide a stronger foundation for lead compound selection. Second, the appointment of a dedicated drug champion with deep institutional knowledge can help guide drug development teams and address challenges effectively. Finally, passing on the tacit knowledge of experienced chemists to the next generation is crucial for sustaining the art of successful drug discovery.

In a world where the cost and time associated with bringing a new drug to market are substantial, these recommendations aim to improve the efficiency of the drug discovery process, ultimately benefiting patients by delivering safer and more effective treatments. As the pharmaceutical industry evolves, the pursuit of innovative drugs remains unwavering, driven by the potential to positively impact the lives of those suffering from serious illnesses.

REFERENCE

- Ahmad, Z., Makaya, N. H., & Grosset, J. (2011). History of drug discovery: Early evaluation studies and lessons learnt from them. In Antituberculosis chemotherapy (Vol. 40, pp. 2-9). Karger Publishers.
- Coura, J. R., & De Castro, S. L. (2002). A critical review on Chagas disease chemotherapy. Memórias do Instituto Oswaldo Cruz, 97, 3-24.
- Drews, J. (2000). Drug discovery: a historical perspective. science, 287(5460), 1960-1964.
- Elinson, Michail N., Ilovaisky, Alexey I., Dorofeev, Alexander S., Merkulova, Valentina M., Stepanov, Nikita O., Miloserdov, Fedor M., Ogibin, Yuri N., Nikishin, Gennady I. ane Tetrahedron (2007). Electrocatalytic multicomponent transformation of cyclic 1,3-diketones, isatins, and malononitrile: facile and convenient way to functionalize spirocyclic (5,6,7,8-tetrahydro-4H-chromene)-4,3′-oxindole system. N. D. Zelinsky Institute of Organic Chemistry, Leninsky prospect 47, 119991 Moscow, Russia
- Li H, Qiu Y, Guo C, Han M, Zhou Y, Feng Y, Luo S, Tong Y, Zheng G, Zhu S. (2019). Pyrroloindoline cyclization in tryptophan-containing cyclodipeptides mediated by an unprecedented indole C3 methyltransferase from Streptomyces sp. HPH0547. Chem Commun (Camb). 2019 Jul 25;55(58):8390-8393. doi: 10.1039/c9cc03745d. Epub 2019 Jul 1. PMID: 31257394.
- Manouchehr Mamaghani & Roghayeh Hossein Nia (2021) A Review on the Recent Multicomponent Synthesis of Pyranopyrazoles, Polycyclic Aromatic Compounds, 41:2, 223-291, DOI: 10.1080/10406638.2019.1584576
- Newman, D. J., Cragg, G. M., & Snader, K. M. (2000). The influence of natural products upon drug discovery. Natural product reports, 17(3), 215-234.
- Pina, A. S., Hussain, A., & Roque, A. C. A. (2010). An historical overview of drug discovery. Ligand-Macromolecular Interactions in Drug Discovery: Methods and Protocols, 3-12.
- Schedler, D. J. (2006). Drug discovery: a history (sneader, walter).

- Shanthi, G., Subbulakshmi, G., & Perumal, P. T. (2007). A new InCl3-catalyzed, facile and efficient method for the synthesis of spirooxindoles under conventional and solvent-free microwave conditions. Tetrahedron, 63(9), 2057-2063.
- Sneader, W. (2005). Drug discovery: a history. John Wiley & Sons.
- Syam Kumar UK, Ila H, Junjappa H. (2001). A new route to spiropyrrolidinyl-oxindole alkaloids via iodide ion induced rearrangement of [(N-aziridinomethylthio) methylene]-2-oxindoles. Org Lett. 2001 Dec 27;3(26):4193-6. doi: 10.1021/ol016824i. PMID: 11784175.
- Vadivel V, Ganesan R, Kannaiyan V, Vellikannu E, Vijayakumar T. (2019). Synthesis of Substituted Isatins from the MBH Adduct of 1,5,6-Trisubstituted Isatins Using (2,4-Dinitrophenyl) hydrazine and K-10 Clay Explored as Protection-Deprotection Chemistry. ACS Omega. 2019 May 31;4(5):9563-9568. doi: 10.1021/acsomega.9b01002. PMID: 31460047; PMCID: PMC6648401.
- Zhao, C., Rakesh, K. P., Ravidar, L., Fang, W. Y., & Qin, H. L. (2019). Pharmaceutical and medicinal significance of sulfur (SVI)-Containing motifs for drug discovery: A critical review. European journal of medicinal chemistry, 162, 679-734.