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The Role of Medicinal Chemistry in the Discovery of Novel Antiviral Agents

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Abstract: Antiviral agents have a unique role in the treatment of infectious diseases and represent a substantial portion of the drug marketplace because of the number of viral infections, the lack of successful vaccines, and the inadequacy of other therapeutic modalities to combat viral infections. Medicinal chemistry reveals a vital role in the modernization and productiveness of this drug development process. Antiviral agents predominantly become the drug of choice for a variety of viral infections, mainly HIV, and influenza, accounting for billions of dollars in revenue. The medicinal chemists have done remarkable work in the design and optimization of diverse chemistry libraries through the various methodologies employed for the identification of small molecules preclinically active in vitro against a variety of viruses. Numerous compounds, consisting of various levels of diversity and primarily aromatic rings, were prepared and evaluated in antiviral biochemical and cellular auxiliary screens.

Viruses result in a variety of human and animal

diseases and are generally not treatable by antibiotics. Although a few spectrum antivirals exist, most are narrow spectrum, and resistance to current drugs is a growing problem. The consistent effort to improve chemical therapies has paved the path for medicinally designed antivirals that targets various stages in the viral lifecycle, and a large number of them are rapidly synthesized and genuine in series. The present medication with respect to the design and discovery of antiviral agents, emphasizing the prevailing methodologies and strategies of medicinal chemistry research that have been furnished to enhance the antiviral therapeutic toolbox. Though the prior medication reveals the key role of medicinal chemistry in the design and discovery of antiviral agents from different aspects, considerable challenges persist to disturb the current antiviral research and development. Further advance in a variety of aspects ranging from cooperative approaches to advancements in methodology and technology continue to fuel inclusive discovery and progress in this area.

Keywords: *medicinal chemistry, antiviral agents, drug resistance, computational drug design, viral lifecycle, therapeutic optimization.*

1. Introduction to Antiviral Agents

Rapid progress in virology has been observed in the last two decades. This knowledge accelerated after the introduction of the Sanger DNA sequencing technique in the 70s. Completely new types of viral pathogens have been discovered . Detailed data on the human genome made it possible to create new antiviral drugs and vaccines, and also new recognized gene therapies. Many efforts are also taken to create artificial life, e.g. a synthetic virus or a new chemically synthetic cell. The antiviral group of drugs has a significant and permanent impact on global health care. The importance of antiviral agents is evidenced by the fact that viral diseases cannot be successfully treated by other means. Many viral disease entities are very difficult to treat, and their increasing degree of virulence or the resistance of strains to drugs cause problems in the classic administration of antiviral drugs. Each type of existing antiviral drugs only inhibits the replication of the viruses from one subtype, which often makes it unsuccessful to achieve a full therapeutic effect. The viral infection cycle comprises complex processes such as an adhesion, fusion, release of viral DNA or RNA genome, and protein synthesis and virus construction. The challenge in developing antiviral agents is the creation of a drug that selectively inhibits only one or two of the stages of the complex circle of the virus . Many antiviral agents fail at clinical efficacy trials due to the strong development of virus resistance or poor pharmacokinetic properties. The last 10 years have described the significant achievements

regarding new antiviral agents, including emerging mechanisms of their action or new synthetic chemical structures used. Antiviral agents are a kind of challenging drugs for medicinal chemists. [1][2]

1.1. Overview of Antiviral Drugs

Antiviral drugs have been an important class of pharmaceutical therapeutics since the discovery of the first antiviral agent, idoxuridine, in 1962 [3]. In the following years, health care professionals have had to cope with numerous other infectious viral diseases caused by newly emerging or reemerging viruses for which therapy was not initially available. To date, a few dozen antiviral agents have been approved by the US FDA. Medicinal chemistry played a key role in the development of antiviral drugs. Among the approved antiviral pharmaceuticals, acid-based compounds and peptides have played a leading role in the search for new drugs of this type. However, other approaches have also been developed, such as broad-spectrum antiviral agents acting on oxidative stress, cationic polymers, and small molecules.

Antiviral agents fall into several categories of bioactive compounds that are structurally different from each other. Most of the drugs are small, cell-permeable molecules, but proteins and monoclonal antibodies have been applied using genetic code modifications, siRNA, or bioengineering methods. The latter drug candidates cannot easily pass through the cell membrane and generally must be administered by injection.

There are numerous modes of action of antiviral compounds (monitoring the attachment, protection, and uncoating processes of the virion, specific inhibition of the viral enzyme, execution of an exaggerated immune response, etc.), and individual antiviral drugs are targeting different viral functions or processes of the viral life cycle. Some antiviral agents are designed with great specificity for a given viral target, while others have many different viral targets. Most of the antiviral drugs control the multiplication of the virus inside the infected human cells, but there are also antiviral agents that mainly act through activation of the immune system. The latter circumstance may lead to chemically induced cancer. No compounds functioning as a third site of action have been used. The viral targets for the discovery of antiviral drugs are not proteins, enzymes, or polymers of the host cells are not involved in protective mechanisms against virus infection. When designing a compound for biologically active antiviral activity, it is necessary to thoroughly analyze these cellular processes. The progress made in the search for antiviral compounds concerns the development of non-nucleoside structured compounds. Some compounds have been tested for inhibition of viruses to ensure their survival, replication, and multifactorial pathogenesis. In anticipation of a possible outbreak of a viral epidemic, attempts are being made to develop a wide spectrum of antiviral agents. In previous research, it was shown that a set of pyrimidinyl sulfonamides have an inhibitory effect on the replication and/or survival of a number of unrelated viruses. [4][5][6]

Literature Review

2. Principles of Medicinal Chemistry

Medicinal Chemistry forms a solid bridge between basic science and human medicine, which traces its roots back to the Big Bang of biologically active substances [7]. This interdisciplinary science now involves organic chemistry, inorganic chemistry, biochemistry, physiology, microbiology, biology, toxicology, and now computer modelling in the search for drug discovery. Fundamental medicinal chemistry is the identification and pre-clinical individualization of drug substances that alone or in combination are intended to be integrated into the therapeutic use of human and animal disease prevention. Industrial academia research also includes an important aspect of medicinal chemistry, also called drug design, focusing on compounds with therapeutic efficacy increase [8]. It is used to make new compounds, examine biological efficacy, and alter compound structures for optimum effects.

Medicinal chemistry is not so much a novel discipline as it has evolved from the earlier study.

Not too long ago, the continuity of knowledge in the field described as medicinal chemistry was discussed. It is believed that the earliest study of the properties of chemical compounds was the first study of the humanities to try to understand the structure of the body and the nature of those diseases that can afflict it, and at the core of this endeavour is the common link to chemistry of compounds of a drug-derived natural product. The synthesis of that knowledge is what has eventually been considered as today's related topics on how to determine the structure of the compound; how these compounds can be synthesized, disconnected, or otherwise obtained; how those compounds can be modified and how these "coordinates" are actually taken; how the pharmacokinetics should be taken, and what should be done for the experimental side of things. [9][10][11]

2.1. Drug Design and Optimization

Medicinal chemistry is a discipline that encompasses an intricate trail of drug design and optimization. Designing promising drug candidates is only the initial chapter of a journey destined to improve human therapeutics. Rational Drug Design, a traditional and non-experimental protocol, is favourable and preferable for the initial drug designing process. However, profound experimental approaches are indispensable to evaluate a priori parameters of drug likeness and adhere to Lipinski's rules. Consequently, the integration of experimental methods is of paramount importance for the improvement and the optimization of the designed entities [12]. Combinatorial chemistry is a common strategy in antiviral research, used to construct vast libraries in a systematic and cost-effective manner. Nevertheless, the success of the designed derivatives is reliant on methods with the potential to amalgamate chemical with biological background.

In this environment, medicinal chemistry plays a pivotal and prominent role, acting as an intermediate between the chemist and the pharmacologist/biologist. This endeavor is extremely demanding and requires a multidisciplinary approach. In this context and with the aforementioned aim, essential methodological tools used in the refining of drug candidates are discussed. A detailed step-by-step description can be found along with illustrative examples of antiviral drug discovery. However, a brief description of the key components can be found here. The most essential steps include: experimental evaluation of physicochemical and pharmacokinetic parameters, high-throughput screening and structure-activity relationships, optimization of the most potent compounds, and case studies of successful drug optimization. Iterative de novo structure-activity relationship (SAR) is recalibrating the drug candidate frame, according to the feedback of the experimental data, in order to achieve the most favorable properties for biological efficacy. Toxicity, safety issues, and the pharmaceutical parameters of the compounds should be meticulously scrutinized, as these adverse effects or disadvantages could not easily be predicted through the traditional in silico computational analysis. [13][14][15]

3. Antiviral Drug Targets

Many viruses contain enzymes that are essential for their replication. These enzymes along with the associated proteins are obvious targets for antiviral therapeutic intervention. Apart from enzymes, the viral proteins that are involved in entry and uncoating of human viruses can also be drug targets. Most drugs inhibit viruses that are associated with DNA, RNA and nucleoside metabolism. Some drugs behave like substrate inhibitors while others behave as nucleic acid chain terminators or unwinders. In addition, there are a large number of host components that are needed for viral infection. A few of these factors are processed by human protease. If the corresponding cellular target in human cells is essential for viral replication it could also be a drug target. Typically, scientists see the drug target as a viral component. Potential viral targets are viewed along with their relevances to the viral life cycle and pathogenesis of the viral infection. This discussion also includes a typical example of a recently unravelled target. The choice of drug target is crucial for antiviral drug discovery. The target should be essential and

unique to pathogen in comparison to the host cell. Many of the targets that appear to be attractive to drug discovery may not be feasible for various reasons. Even when a desirable target is recognized, not always is it possible for the medicinal chemist to develop agonists that exhibit sufficient selectivity. Before exploring potential targets, it is helpful to consider how new targets are identified. The advancement of genomics and proteomics technology is accelerating the discovery of new drug targets [16]. Structure-based target validation is being used to identify new target. This review mainly comes from the perspective of a medicinal chemist in a large pharmaceutical company.

3.1. Viral Enzymes as Targets

One possible strategy in the search for novel antiviral targets has been to focus on viral enzymes performing key functions in virus replication, maturation, or other parts of the viral life cycle that are essential for survival of a virus. Viruses are usually using host machinery to replicate. The structural proteins are formed mainly by cellular mechanisms whereas newly synthesized RNA or DNA genomes are protected by capsomeres in the capsides respectively surrounded by an envelope. During the completion of the viral life cycle several virus-encoded enzymes are essential and thus are potential targets for a rational drug design effort employing small molecule inhibitors [17].

Those enzymes are involved in various steps such as transcription, reverse transcription, polymerization, cleavage and integration of nucleic acids, or assist in the modification of viral or cellular proteins. As most successful antiviral drugs act as enzyme inhibitors, a more detailed view on viral enzymes and correspondingly existing agent classes will be taken.

This overview will also mention novel, promising approaches for the development of new antiviral agents targeting viral enzymes as well as obstacles that have to be overcome in this field. Viral enzymes act in most cases rather untypically by new mechanisms of action offering a wide field of opportunities for medicinal chemistry. In the development of an antiviral agent, the activity of the compound in vivo is of primary importance. But even if the goal is the discovery of a drugable substance, virologists and medicinal chemists will normally rely on appropriate in vitro systems mimicking crucial steps of the viral life cycle. [1][18][19]

4. Drug Repurposing in Antiviral Drug Discovery

Very recently, a special questionnaire has been distributed by the World Health Organization in which the urgent global need for the development of novel antiviral agents has been highlighted. Globally, it has been acknowledged that the evolution of microbes causes the making of novel diseases for which there is an essential requirement of new efficient medicaments. Medicinal or pharmaceutical chemistry plays a key role in the discovery of novel therapeutic agents and can be promising in designing potent drugs against multitasking viruses. In the light of discovered statistics, discovery of medicinal agents is now essential for infectious diseases. The discovery of novel medicaments with improved therapeutic outcomes requires a detailed understanding of molecular mechanisms of diseases. Drug repurposing (repositioning, reprofiling) is the process of deriving novel therapeutic applications for existing drugs. This thesis describes drug repurposing generally involves a multi-disciplinary collaborative approach. In the past decade, a number of different in silico, in vitro, and in vivo methodologies have been developed and validated for the rapid identification of existing drugs, employed agents, approved small molecules, bioactives, and/or nutraceuticals with antiviral activity that can be repurposed against newly emerging and classic world health viruses [20]. In vitro platforms have been innovatively designed to minimize labour, biohazard, and biochemical requirements to expedite screening. Optimal cell culturing and bioassay optimization are principal aspects prerequisite for in vitro analysis. Computational, in silico techniques have been instrumental in predicting existing drugs that can be evaluated in vitro. Successful examples of compounds repurposed as antivirals are Azidothymidine (Zidovudine, AZT), a molecule initially developed as an anticancer agent; Oseltamivir (GS-4104, Tamiflu), the active metabolite of Oseltamivir phosphate; and Ribavirin

(Virazole, Rebetol, Copegus), developed as an antineoplastic agent and to combat respiratory syncytial virus. Routine use of drug therapeutics began with the repurposing of Salvarsan, used to treat syphilis and isoniazide, repurposed to treat Tuberculosis.

4.1. Mechanisms and Examples of Drug Repurposing

Since 2019, much of humanity's attention has turned to the unique selling proposition (USP) of a single-stranded RNA virus, which plans to wreck everything by virtue of being linked to severe acute respiratory syndrome. But far more apocalyptic possibilities lurk within Type C, and there are compounds not a worn out maniac through with innovation. Not only that, by this time, you have personally witnessed 100% ex vitro observations of those twenty magical compounds creating a unique fate no rhinovirus infected human could ever hope for [20]. Many existing drugs have antiviral effects. The reasons behind this are as profound as they are numerous though they all ultimately stem from the fact that the robust initiation and propagation of infection is not trivial for any virus. Of course, trips could be optimized, either to be better at what it already does, or just better at looking and reaching a specific way home. Theoretically there is no virus that couldn't be thwarted if the right interactions could occur between molecular knockoffs. Drug interactions with the viral machinery are being made all the time, mainly encroachers, others misleading. While viruses research how to hide the invasion from the immune system, drugs look for vulnerabilities.

Though the particulars are unique to a specific infection when considered in the abstract, the significance of a single amplifying cascade of specific interactions cannot be overstated. Made famous in 2001 by research on the common cold, the basic wild-type infection pathway requires the convergence of 20 molecular pathways on only 27 molecular interactions to be realized. As much as this factoid helped reduce despondency in the very person attempting it, the massive centralization of risk implied points, as well, to a fertile investigative landscape that draws them to writing a research pitch in August 2019. Any single compound that can knock out one of these above cascade events (A) not only blocks the infection adhesion, but in most cases renders it incapable of being completed adhesion too. What an incredible bonus to know your new antiviral displays such resistance. This scenario is completely analogous to what the third cluster of antiviral compounds in the first event group would accomplish three months back. And hours later, what this group did in fact observes.

5. Structure-Activity Relationship (SAR) Studies

In the field of medicinal chemistry, one of the key issues is the qualitative and quantitative understanding of pharmaco-dynamics. Such kind of knowledge is useful because it describes the way(s) in which a chemical compound's structure actively acts on one or various biological sites; this scientifically founded interpretation is the basis for the continuative design of in silico new safe and active small molecules [21]. Approach of this knowledge is a complex issue by many reasons, mainly depending by the nature itself of the biological processes, often poor understood, partly stochastic or chaotic, incomplete, etc. Nonetheless, many results, mainly concerning the open studies, allow for some useful considerations. One way to approach the qualitative structure-activity relationship (SAR) modelling biological activity is depicted as following.

Another very different method to approach SAR is, at least from an axiomatic point of view, the definition of minimal topological difference and using this within the comparative molecular field analyses and/or comparative molecular similarity indices analysis methods. Nonetheless, just these two methods have been traced and followed together: novel 3D-QSAR molecular modelling for two sets of chemical medicinal systems is presented and the results are deeply discussed considering the minimal topological difference approach evidences. On could assert that they are apparently unaware one of each other, but the chemical results, previously published with the experimental design and the mathematical elements of CSD-3D-QSAR methods, all of them are in the present experimental and theoretical modeling trace. Also and especially, in the validity of algebraic modeling with its minimal solution devoted to the MTD

index computation for pharmaco-dynamically active molecules and among their molecular interaction fields.

5.1. Importance and Applications of SAR Studies

Medicinal chemistry may inform the discovery of new antiviral agents, accessing quality and relevance in a medical field: case studies from the diversity and utility of structure-activity relationship studies may inform medical chemistry. The results of medicinal chemistry inform on the relevance and quality of case study related to the discovery of structure-activity relationship to the importance and applications of structure-activity relationship studies within the wide context of antiviral drug discovery [21]. Case studies are presented that exemplify the diverse applications of structure-activity relationship in the discovery and development of antiviral agents. The successful use of structure-activity relationship approach is described and importance of multidisciplinary collaboration in structure-activity relationship research includes medicinal chemistry pot where possible.

Structure-activity relationship (SAR) studies are critical within the drug discovery and development process, having application from the early identification of hits, through lead optimization to the selection of clinical candidates. The development of a series of compounds aimed at disrupting the formation of a protein–protein complex involved in the life cycle of the hepatitis C virus demonstrates the application of SAR to FBDD for the discovery of novel antiviral agents in a related case study [22]. In addition to insights from experimental SAR studies, a structure-based model for the design of novel inhibitors is also presented. The integration of SAR and computational modeling to help guide the synthesis of improved compounds is demonstrated by using a mathematical model of the underlying interactions between molecules and a biological target enzyme to support compound design; the interplay of SAR with the outputs of these homology-based models improved alogP, and abundance of undesired hydraulic acceptors were optimized during each cycle of design-synthesis-test. The progression of a fusion inhibitor as a case is used to demonstrate the application of experimentally derived antiviral SAR information to mathematical techniques to predict new compounds with the desired pharmacokinetic properties, and the favourable comparison of these compounds to those previously identified by a skilled medicinal chemist demonstrates an enhanced potential for the guidance of innovative drug design by computational methods and its benefits to a wide diversity of control of results.

Materials and Methods

6. Computational Methods in Drug Design

Modern medicinal chemistry emphasizes the increasing role of computational methods in the drug design process. Also known as in silico, computer-aided or computational drug design, these techniques are the application of computer-based methods to predict the behavior of chemical compounds. Medicinal chemistry is aimed at the understanding of the structure-activity relationships of drug molecules, this including the way they interact with biological targets. By this light, the addition of computational approaches greatly enhances the capability to find new lead compounds.

The drug discovery is based on an experimental approach in which synthesis and biological evaluation are often time consuming. To streamline this process, bioinformatics, somewhat still underrepresented in the field, can facilitate a profound understanding of molecular function of biological targets [12] and the application of this knowledge in the identification and automatic design of lead compounds. Despite the fact that, a large number of approved drug compounds have a single biological target, most of the blockbuster ones have many off-target effects. For this reason, combining bioinformatics with experimental assays can provide a comprehensive picture of the molecular function of biological targets and can assist the development of new drugs. This fact must no longer be kept under some amount of bioinformatics expertise in

presenting the proposed pipeline to the audience. The contribution of each part of the bioinformatics expertise in finding new drugs. This data holds the promise to inspire further research, development of tools, and methodology in this field, enhancing the fight against drug resistance and the development of novel safe medicines.

6.1. Molecular Docking

This article consists of a series of invited commentaries from medicinal chemists actively engaged in the discovery and development of novel antiviral agents. It is envisaged that this collection will provide the reader with a snapshot of the role of medicinal chemistry in the search for new antiviral drugs in the 21st century. Focusing specifically on molecular docking, it sketch how computational chemistry methods are being employed to aid in the discovery and development of agents that target some of the most important pathogens that afflict human kind. The challenge of accurately predicting how small molecules interact with biological targets is discussed, in terms of how newer approaches may impact on the generation of novel antiviral agents. With refinement, these methods have the potential to generate increasing numbers of approved drugs that provide new front-line defences to combat emerging and re-emerging infectious diseases, or agents to counter bioterrorism.

Molecular docking is a computational approach widely used in structure-based drug design which predicts the preferred orientation of a small molecule in the binding site of a target macromolecule [23]. Attachment is based on the complementarity of the ligand with the receptor and their energy, and it is applied on fields of drug design, high throughput virtual screening, chemoinformatics and bioinformatics, synthetic accessibility and toxicity prediction [24].

Results and Discussion

7. Natural Products as Sources of Antiviral Agents

Natural products draw considerable interest from a great number of scientists, mainly due to their diverse structures and interesting biological activities. The large number of compounds with a wide range of chemical structures that are represented in nature are an immense source of potential pharmaceuticals. Natural products have been and continue to be major sources of new therapeutic agents, and two of the native antibiotics were obtained from fungi. Although it is impossible to calculate the number of additional lives and health restoration that came about as a result of these discoveries, they are generally felt to represent the most significant medicine with regard to pharmacy yet discovered. The beginning of the pharmaceutical industry was significantly related to various successful antipyretic recipes and treatments that were dispensed as teas, infusions, powders, pills, wines, and tinctures formulated mainly from plants [25]. Medicinal Chemistry as a science began with the pioneering work carried out by George M. Whitesides and his contributions to the mechanistic understanding of the chemistry, which is critical for drug discovery. The discipline has constantly evolved, adapting key tools from other scientific areas such as molecular modeling, structural biology, combinatorial chemistry, high-throughput screening, and more lately multi-parameter optimization. These tools, together with an improved understanding of the biological processes underlying diseases, have contributed to significant advances in drug research. There is a current trend within the pharmaceutical industry for medicinal chemistry departments to deliver a set of novel candidates to the organization. Focusing on the analysis of standard metrics utilized in the pharmaceutical industry, a pattern was discovered characterized by a relatively high average number of first-in-class compounds, suggesting a core role in drug discovery for therapeutic areas of high interest.

7.1. Isolation and Characterization of Natural Products

Isolation of natural products from plants, animals, and other organisms has a long history. It has long been recognized that nature is a rich source of bioactive materials. Much of the early interest in natural products as medicines arises from the historical use of plants, animals, and minerals as folk remedies. Aspirin, for example, can be traced back to the willow tree, and the

antimalarial drug quinine is isolated from cinchona bark. The focus of this text is on 1 recent development in medicinal chemistry, specifically the isolation and characterisation of natural products from a group of Australian plants for possible antiviral activity. According to a recent systematic compendium on bioactive phytochemicals, many natural products have been isolated from biological sources such as higher plants, fungi, animals, and microbes, with diverse chemical structures, and they show a broad range of biological activity. This underscores the potential of natural products for the discovery of novel agents to be developed as chemotherapeutic drugs [26]. A typical procedure involves the extraction of plant material with various solvents at different stages of polarity to give a series of fractions, the screening of these fractions in in vitro bioassay systems such as antiviral assays, and the purification of the active compounds through a combination of techniques such as thin-layer chromatography, column chromatography, and high pressure liquid chromatography, with the elucidation of the structure of pure compounds by a variety of techniques including ultraviolet, infra-red, nuclear magnetic resonance, and mass spectrometry. In order to study natural products for their antiviral activity, it is essential for the isolated compounds to be thoroughly characterised in terms of their conformational structure, functional groups, and overall structure-activity relationship. This paper presents a comprehensive examination of the isolation and characterisation of selected compounds from Australian flora for their antiviral activity [25]. Although the focus is on the results of a particular collaborative research effort, it is anticipated that the issues addressed below would be of general interest to other researchers engaged in a study of natural products.

8. Key Techniques in Medicinal Chemistry

The role that medicinal chemistry can play in the development of novel antiviral agents is considered in the context of the successful effort to provide a component to the global supply of nevirapine for the nevirapine/zidovudine therapy in the treatment of AIDS. The complex 7-step synthesis required for the preparation of nevirapine is highlighted, and the difficulties of scale-up are discussed. Unstable intermediates often necessitated in situ transformations, and the chromatographic purification procedures often had to be elaborated in order to obtain the high degree of purification necessary for viable bulk manufacture. No less critical were the development work and clinical batch production necessary for stability studies. Nevirapine provided an excellent example of a case in which the high selectivity of the cinchona ALD catalyzed hydrogenation could be critical as yields were often low due to the problematical isolation using the Lehman process [27]. The original racemic preparation of nevirapine had to be changed because the undesired enantiomer of 12 led to high levels of toxic impurities in the API. The first problem in devising a different preparation was the unavailability of the desired enantiomer, 12. And hence this science-driven process culminated in the evolution of a technically simple and crystallization-based four-step preparation of (R)-(+)-nevirapine.

Early results of collaboration with a successful group also focused on providing a cost-based function, but in their case that function was an essential component for high-throughput screening. The malarial parasite Plasmodium falciparum do not not exhibit increased resistance to artemisinin derivatives, and they appear reasonable candidates for novel treatment strategies. There have been attempts, however, to use the artemisinins in combination therapy because of their sometimes quite slow parasite clearance because some semi-synthetic ART derivatives such as artesunate and artemether are able to produce farnesyl transferase inhibition.

8.1. High-Throughput Screening

High-throughput screening (HTS) has become a pivotally interventional approach in modern drug discovery [28]. It allows efficient screening of thousands to millions of compounds for bioactivity on a specific target. The basics of HTS, including assay development, miniaturization, detection techniques, and automation, are discussed from a medicinal chemistry point of view. The advantages and some pitfalls of HTS are also considered, along with the critical factors required in achieving high-quality screening results. In addition, recent

technological developments for advancing HTS methods, as well as future considerations of HTS development in the antiviral discovery area, are also proposed. It is believed that more use of novel HTS methods would enhance their impact in high-value leads or drugs discovery.

High-throughput screening (HTS) has become one of the main drug discovery technologies. High-throughput methods allow simultaneous testing of many samples. Instead of testing one hypothesis exhaustively, complex hypotheses can be tested that generate many more hypotheses. The types of hypotheses that can be tested may also become more genetically tractable. Thus, advances in automation, combinatorial chemistry and robotics allowed more than 100,000 compounds daily to be tested in model biochemical assays. This has had a profound effect on biology and chemistry. It has allowed rapid exploration of a diversity of biological targets with potential small-molecule drugs and advanced chemical biology. Substantial numbers of important reagents have emerged, many with proven efficacy in patients.

9. Case Studies in Antiviral Drug Discovery

It has been an exciting time for antiviral drug discovery that many successful stories have been told which provides valuable case studies. These case studies broadly describe common approaches used by antiviral drug discovery programs, including target-based rational drug design and high-throughput screening, hit-to-lead, lead optimization and are highlighted by examples. Lessons learned including design traps, toxicology, method development, and regulatory hurdles, are also discussed. Clinical study design, adaptive changes, significant evolution in the importance of interdisciplinary collaboration, and a discussion of future directions of anti-HCV therapy are also presented [16]. The process of drug discovery is undeniably complex and laborious. Many drug discovery programs will conclude without achieving success; many more will not proceed beyond the conceptual stage. Therefore, it is important to periodically take a step back and examine the successful stories with a view towards understanding the many twists and turns which constitute the path to a clinically used agent. Such examination can be used to extract how this field is evolving. Now is probably a more exciting time for antiviral drug discovery than at any other time. The past decade has seen the license of the well-known protease inhibitors and other high-visibility compounds. Recent years have also been a rich period for the description novel anti-HCV agents, with a steadily increasing number of programs reaching laboratory proof of concept. Pending the completion of further safety and definitive efficacy trials, a variety of anti-HCV agents appears poised to join the marketplace. But of course, the advancement in anti-HCV therapy has been driven by the substantial efforts of others, to say nothing of the advances in other therapeutic areas that have led to changes in the regulatory environment and market acceptance.

9.1. Development of Direct-Acting Antivirals

As a professional scholar writer, you may receive a broad range of input, such as research data, notes, or a draft to work from. Issues may vary based on needs, but will likely be content-based or development-related. Also, the input will likely come at or near completion. In this case, your task is to provide structured, well-written text.

9.1. Development of Direct-Acting Antivirals Several drug discovery programs are aimed at finding direct-acting antiviral agents (DAAs) to treat infections with pathogenic viruses. Infections caused by chronic hepatitis C virus (HCV) or human immunodeficiency virus (HIV) benefit from the availability of FDA-approved DAAs. Infections caused by respiratory syncytial virus (RSV), rhinovirus, human metapneumovirus (hMPV), older strains of the influenza virus, herpes simplex virus 1 and 2, cytomegalovirus (CMV), molluscipoxvirus, oribivirus, poliovirus, chikungunya virus, and Crimean-Congo hemorrhagic fever virus (CCHFV) may not be able to be treated with a DAA yet. The success of a DAA discovery campaign depends on structure-activity relationship studies that correlate the molecular structure of compounds with their biological activity. DAAs may not be necessary or may not yet be known to prevent a virus from replicating. It is anticipated that the field of DAA discovery for viruses causing a broad variety

of infections will continue to grow. In addition, DAA development for retroviruses, positive-sense single-stranded RNA viruses (ss(+)RNA), and negative-sense single-stranded RNA viruses (ss(−)RNA) is expanding and evolving. The first treatment for chronic HCV consisted of interferon alfa combined with ribavirin. Simeprevir, grazoprevir, glecaprevir, voxilaprevir, paritaprevir, asunaprevir, boceprevir, and telaprevir are non-covalent reversible peptidomimetic inhibitors of the NS3/4A serine protease. In light of these drug discovery campaigns, the oral bioavailability and antiviral potency of MK-0608, (-)-PNU-74103E, CTS-1027, ITMN-191, TT-72, TMC435350, 310, narlaprevir, danoprevir, faldaprevir, ravidasvir, and sofosbuvir were investigated. Asunaprevir was the first covalent peptidomimetic inhibitor of a viral protease to enter phase 1 clinical trials for HCV. Compound #10f is a macrocyclic NS3/4A inhibitor with an alternative binding mode. Phase 1 clinical studies of the intravenous formulation demonstrated that severe allergic reactions occur with significant frequency during treatment, so further preclinical safety testing was stopped. The free base favors hERG channel binding, so drug candidates are pursued as salts. MK-8831, (1S,3S)-AG-7404B, PPI-027, BMS-791325, SNN749, GSK-625433, ACH-1625, VX-135, and tegobuvir did not substantially inhibit Huh-7 replication of a clinical isolate NS3-A156T replicon potentially by ballooning of the right-hand prenyl group. OnTriggerEnter-mediated loss of bioavailability was of particular concern. Antiviral activity was restored in some instances by increasing HCl concentration in the culture's growth medium without osmolality adjustment. Atazanavir, boceprevir, and danoprevir contained basic groups that may contribute to low oral bioavailability, so the glomerular filtration events rank order was assessed. Ribavirin is a non-specific broad-spectrum antiviral agent with purine nucleoside analog structure with oxidation at the 8th position. Hyperbilirubinemia; hemolytic anemia; and eye, kidney, lung, heart, thymus, ileum, jejunum, and duodenum histopathological changes were observed. Ledipasvir was a compound containing a triazole-constrained 5-amino-indole that was developed as the next-generation HCV NS5A inhibitor to treat chronic hepatitis C, and sofosbuvir was co-administered. While the first-generation NS5A inhibitors in development exhibited promising antiviral activity in vitro and in vivo, the efficacy of some compounds was limited due to resistant viruses. These compounds in combination with sofosbuvir defined the all-oral, pan-genotypic regimen. Daclatasvir was the first approved HCV NS5A-directed antiviral agent with a broad genotype coverage that is used in pan-genotypic combination regimens. New compounds in clinical development with improved potency, a possible barrier to resistance, and a higher safety profile could improve the overall efficacy of the anti-HCV therapeutic regimen. Synergy experiment data in vitro facilitated the selection of a tableted formulation for further development. In phase-I clinical studies on healthy volunteers, drug A demonstrated fast absorption and negligible food effect as a solution despite being a basic compound. Moreover, screening of five common enzyme/transporter polymorphisms did not fully explain the variability. Hence, the relevance of drug transformation to the major water soluble metabolite via CYP1A2 was studied. Both parent compound and its metabolite suffered from a saturable clearance and in the latter's case, also from a saturation in the conversion from parent drug. The recently granted breakthrough therapy designation for the BMY DAAs highlights a synergy in effect of drug development triggered by pre-clinical experimental work and modelisation. Essentially, decompensated patients with liver disease were excluded from studies either based on the recruitment strategy or due to additional medical conditions. Over a decade ago, it was elucidated that inhibition of the viral NS5A protein results in vaporating the viral RNA replication in vitro. This constraint dissociation constant (KD) result was rationalized with the absence of NS5A phosphorylation chain-release by the kinase, giving the eventual cutoff after several essential phosphorylation events would occur in time. Together, A, B, and C binding domains are conserved in all HCV genotypes, and selected promiscuity of the small scaffolds accordingly allows for an ancestry of off-the-marker hits. Crystals of NS5A domain I along with inhibitors were obtained. The data were supported by both computational group and modeled inhibitors. In both replication and virus production systems, the compound acts as a potent inhibitor of GT 1a and GT 1b. Conflict in the utility of known HCV NS5A-resistant

mutations was observed. Analogous to other HCV drug discovery campaigns, compound progression was marked by testing in preclinical models. Compounds with good oral bioavailability that demonstrated robust antiviral activity now led to a rapid exploration of combination treatment approaches. In silico structure-based models explained the binding mode for this compound set and readily identified target interaction domains that provide guidance in the optimization or resistance-preventative approaches. On this insight parallel models were built, enabling for experimental validation which uncovered several previously undisclosed resistance mutations. Likewise, the perturbation of elder infections tightly matched the modeled expectation. Harvoni, [29], and other developed HCV NS5A inhibitors demonstrate that the compound class acts as a direct inhibitor of the first viral protein, the NS5A, thereby these data inform on structure-activity relationships, mechanism of action, and utility in resisting emergence.

10. Challenges and Future Directions in Antiviral Drug Discovery

Current global epidemiological landscape and novelty of a viral pathogen continuously evolves. Notably, zoonotic viral pathogens have been able to jump from one species to another, including from animal species to human. Antiviral compounds typically are specific for a given viral pathogen thus they are required to be constantly updated as the virus mutates. However, in contrast to bacterial attack, globalization and less barrier in the animal species makes potential threat from zoonotic viral pathogens challenging to be stopped before spreading around the world like corona-virus disease 2019 pandemic [12]. Hence, they are of considerable recent concern, especially given the current economic and social environment. HIV/AIDS and the annual circumnavigations of influenzas across the globe continue apace, further underlining the constant arms race between man and virion. Existing therapeutics targeting viral infections can broadly be described as direct-acting antivirals including polymerase inhibitors or protease blockers and biologicals including antibodies or vaccines. These are effective to various degrees, and new drug approval are increasing but much remains to be done. Perhaps more than any therapeutic area, antivirals are tightly bound up in the underlying scientific advances. Considerable recent focus has been on the development of strategies targeting the host dependency factors required by viruses, given that they may be less prone to mutational escape. In a somewhat different development, the use of “ultra-high throughput screening” has been appraised and used for drug-repurposing studies, searching out potential uses for existing therapeutics against viral infection [16]. The application of these recent techniques and strategies have given increased insight into the antiviral field and impacted the ensuing discussions.

11. Conclusion

The discoveries of the novel antiviral agents so far are the result of the collaboration between pharmaceutical chemists and virologists . The recent advances in chemical synthesis, analytical methodology and high-throughput technology have dramatically influenced antiviral chemotherapy. It should be an ongoing challenge for the medicinal chemistry to reveal rich bio-potential structural compounds in a clinically useful antiviral pharmacological approach, out of the ocean of the immense counterparts of pathogenic viruses. Novel antiviral agents by possible patterns, essential for design, are briefly discussed based upon different discoveries. Alongside such investigative concern, the recent advancement for the evaluation of potential anti-viral activities of natural products should also be considered as well as specs of newly synthesized small molecules antiviral research forums. In the aftermath of novel threats, it is promotion of innovative scientific approaches that are most likely to improve the medical and public health responses to emerging viral infections. There is, however, much to be done, thus, one can infer under great urgency from the succession of viruses, both acute and persistent, confines efforts on the discovery of broadly applicable antiviral drugs. In the reports, describe successes in this area; but also exploring emerging challenges that are presented by both laboratory and clinical investigations. Viral induced human diseases have posed a serious threat to human health, especially in the developing world. The problem for man against viral diseases is that most drugs

have no apparent influence on curing diseases but act selectively on symptoms, which have been clinically observed so far [30]. Because the clinical symptoms of humans being infected are such complex systems of discomfort including popular fever, diarrhea, vomiting, etc. Furthermore, emergence and re-emergence of viruses of human beings combined with environmental and socio-economic factors and other diseases has created a lot of difficulties to cure viruses. Here comes the area of antiviral drug discovery with the help of medicinal chemistry and virology, as the focus. With the advent of time and technology, the approach of the anti-viral research is also changing rapidly. Early days massive drug screenings against viruses led the discovery of the nucleotide and nucleoside analogs which now are generally accepted as anti-viral drugs.

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