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OLD DRUGS IN NEW THERAPEUTIC INDICATIONS – THE CASE OF CHLOROQUINE

ZNANE LEKI W NOWYCH WSKAZANIACH TERAPEUTYCZNYCH – PRZYPADEK CHLOROCHINY

Summary: *Drug reposition is a viable strategy of pharmaceutical R & D, considerably reducing risk, cost and time needed for drug registration and implementation. Chloroquine, designed already in 1930 as a synthetic replacement for scarcely available alkaloid quinine, a traditional malaria treatment, was recently proposed as an antiviral substance, with putative efficacy in some cases of SARS COVID infections. This unexpected connection has revived interest in drug repositioning at large and in particular in the context of identifying antiviral preparations, critically needed in time of COVID-19 pandemia. The paper recounts the story of development of synthetic antmalarials and describes modern chemoinformatics tools, which can efficiently assist synthetic chemists in planning and executing both: drug repositioning and API manufacturing.*

Keywords: *drug repositioning; antivirals; antimalarials; Chematica; artificial intelligence*

Streszczenie: *Zastosowanie znanych leków w nowych wskazaniach terapeutycznych (repozycjonowanie leków) jest obecnie akceptowane jako skrócona ścieżka do rejestracji i autoryzacji rynkowej nowego specyfiku. Przykładem takiej drogi znanej substancji do leku o nowym zastosowaniu jest historia chlorochiny, zaprojektowanej w latach 30-tych ubiegłego wieku w charakterze zastępstwa trudnodostępnej substancji pochodzenia naturalnego – chininy, skutecznej w leczeniu malarii. Według dostępnych danych chlorochina może się okazać przez długi czas pandemii jedynym specyfikiem o działaniu terapeutycznym w infekcjach wirusowych SARS COVID. W artykule przedstawiono rolę nowoczesnych narzędzi chemoinformatycznych, takich jak Chematica, we wspomaganiu zarówno procesu repozycjonowania leków, jak i syntezy chemicznej substancji o zastosowaniach farmaceutycznych i medycznych.*

Słowa kluczowe: *repozycjonowanie leków, substancje o działaniu przeciwwirusowym, leki przeciwmalaryczne, Chematica, zastosowania sztucznej inteligencji w chemii i farmacji*

Introduction

Progress in pharmaceutical industry depends on continuous technical innovation often originating in academic environment, subsequently absorbed by global business organizations, and always limited by ethical issues prescribed by pharmaceutical law regulations. Since the costs of radical innovation in drug research and development are exorbitant, concerns regarding R&D efficiency tend to dominate the sector's development strategies. In a reasonable attempt to re-evaluate pharmaceutical industry's assets and resources, factors such as structural diversity of drug candidates, their availability from either natural or synthetic origins, or the ability to boost the discovery process by modern IT tools all come into consideration. Unfortunately, new molecules and corresponding new chemical entities require long times and massive investment to progress through all segments of drug design and development pipeline and, hopefully to obtain marketing authorization as a new drug. Modern pharmacology, based on systems biology and equipped withan array of omics technologies, such as genomics, proteomics and metabolomics, recognizes ability of small molecule ligands to engage in variety of noncovalent interactions. Specificity of drug pharmacodynamics appears more like an idealization than biological reality, in which multiple interactions with variety of macromolecular targets may be operative. Practical observations in medicinal applications of available chemicals – ranging from natural products abundant in and utilized by ethnopharmacology to the targets of contemporary, sophisticated multistep syntheses of the newest API substances–indicate clearly that therapeutical assignment of a given medicine can evolve in time considerably, as new knowledge accumulates. Consequently, drugs are sometimes dropped from lists of applied medicines but also shifted between therapeutical categories and regimens. In this context, it is always judicious to consider new medical interventions for the privileged compounds already registered as drugs [1-3].

Drug repositioning as a new trend in pharmaceutical industry

Efficient pharmaceuticals are vigorously sought in most therapeutic areas, though the need is particularly pressing for rare and infectious diseases. For example, ca. 6,800 rare diseases and conditions exist, for which ca. 300 approved drugs are applied, but the most of the ailments have no assigned pharmaceutical treatment. In the area of infectious diseases, new medicines are also urgently needed in view of microbial pathogens' genetic plasticity and their frequent mutations resulting in acquired drug resistance. At any rate, continuous progress in research on drug molecular targets and mechanisms of their action can change our perception of drug profile and its applicability, and even evoke a switch in its therapeutical indication. Aspirin, which functioned for ca. seven decades as a popular antipyretic, has finally had its pharmacological role assigned as an anti-inflammatory inhibitor of cyclooxygenases, responsible for synthesis of prostaglandins [4]. Some examples of more radical changes in specifications and applications of known drugs, described in current literature as repositioning, repurposing, redirecting, or reprofiling, are summarized in Table 1 below. The seminal paper in which drug reposition ideology was outlined [1] compared the traditional ***de novo*** drug discovery and development process with some of the abbreviated repositioning procedures: It concluded that considerable reduction of time and risk is possible on the way of known drug substances towards registration and market under new therapeutical indication. Obviously, a drug candidate being repositioned has typically already completed some phases of development like ADMET and formulation studies. Repositioning can sometimes take rather unexpected and dramatic turns. As a case in point, a once popular sedative thalidomide was

Table 1. Examples of drugs for which an alternate therapeutic indication was approved by registration

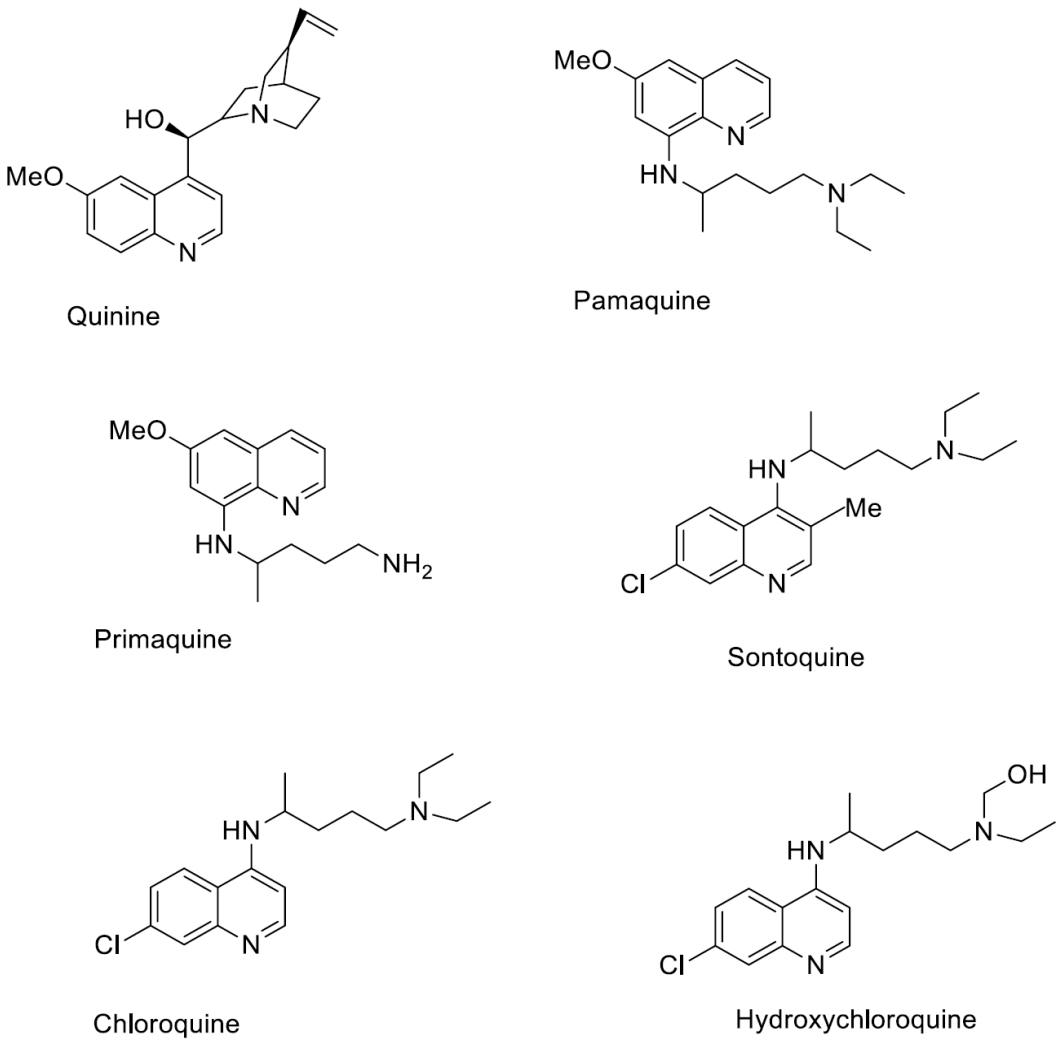
Drug name	Primary indication	Alternative indication
Amantadine	influenza	Parkinson's disease
Amphotericin	antifungal	leishmaniasis
Aspirin	antipyretic	antiplatelet COX inhibitor
Atomoxetine	depression	ADHD
Bimatoprost	glaucoma	eyelash hair growth
Bromocriptine	Parkinson's disease	diabetes
Bupropion	depression	smoking cessation
Celecoxib	osteoarthritis	colon and breast cancer
Chloropromazine	general sedative	tranquilizer
Chloroquine	antiparasitic	antiviral
Colchicine	gout	recurrent pericarditis
Colesevelam	hyperlipidemia	diabetes type 2
Dapsone	leprosy	malaria
Disulfiram	alcoholism	melanoma
Doxepin	depression	antipruritic
Eflornithine	depression	ADHD
Finasteride	benign prostatic hyperplasia	hair loss
Gabapentin	epilepsy	neuropathy
Galantamine	anaesthesia	Alzheimer's disease
Gemcitabine	antiviral	anticancer
Methotrexate	anticancer	psoriasis
Minoxidil	hypertension	hair loss
Naltrexone	opioid addiction	alcohol withdrawal
Nortriptyline	depression	neuropathy
Premetrexed	mesothelioma	lung cancer
Raloxifene	contraceptive	osteoporosis
Ropinirole	hypertension	Parkinson's disease
Sildenafil	angina	male erectile dysfunction
Thalidomide	sedation	leprosy
Topiramate	epilepsy	obesity
Tretinoin	acne	leucemia
Zidovudine	cancer	HIV/AIDS

withdrawn from the market as a cause of skeletal birth defects in at least 15 000 children, but it later made a successful comeback as a TNFα inhibitor with indication for treating condition named erythema nodosumlaprosum (ENL), one of typical inflammatory developments in leprosy. Further studies of thalidomide revealed its anti-angiogenic activity, prompting its widespread off-label use for the treatment of primary multiple myeloma cancer. Thalidomide example shows clearly that drug repositioning may be a viable therapeutic and also a business option [1-3]. Present repositioning efforts are generally based on registered ***drug libraries*** such as SCREEN-WELL (FDA; Enzo Life Sciences); LOPAC (Sigma Aldrich); Spectrum Collection (Microsource); UCFS Small Molecule Discovery Center Library, or the NIH Chemical Collection Library and Chemical Genomics Center. These small collections (FDA approved drugs list contains less than 2 000 compounds) are often supplemented by drug candidates under investigation, in advanced phases of clinical trials [5]. As a result, three different groups of API compounds are pursued as candidates for repositioning: currently used drugs with valid registrations, drugs discontinued for any reason, and drug candidates in clinical trials with ongoing investigation of the mechanism of action. Recent bibliometric review of drug repurposing activity, based on PubMed (MEDLINE) data revealed a relationship between 35,580 individual chemical entities and 4,333 diseases or medical conditions. Based on PubMed article count listing many thousands of papers for each: drug – disease – article axis [6], it has been estimated that for many established medicines - including prednisolone, dexamethasone, ascorbic acid, cyclosporine, aspirin, hydrocortisone, metothrexate, vit. E, propranolol, doxycycline, indomethacin, etc. – the count of diseases examined is in the hundreds. In recent years, much of repurposing effort based on theoretical and computational approaches has focused on antiviral drugs, in connection with recurring Ebola, Denga and Zika viral epidemics. These trends likely reflect advancing research of viral proteins, and the reasoning that broad spectrum antiviral agents are good first-line candidates for clinical trials and experimental treatments of newly emerging pathogens [7].

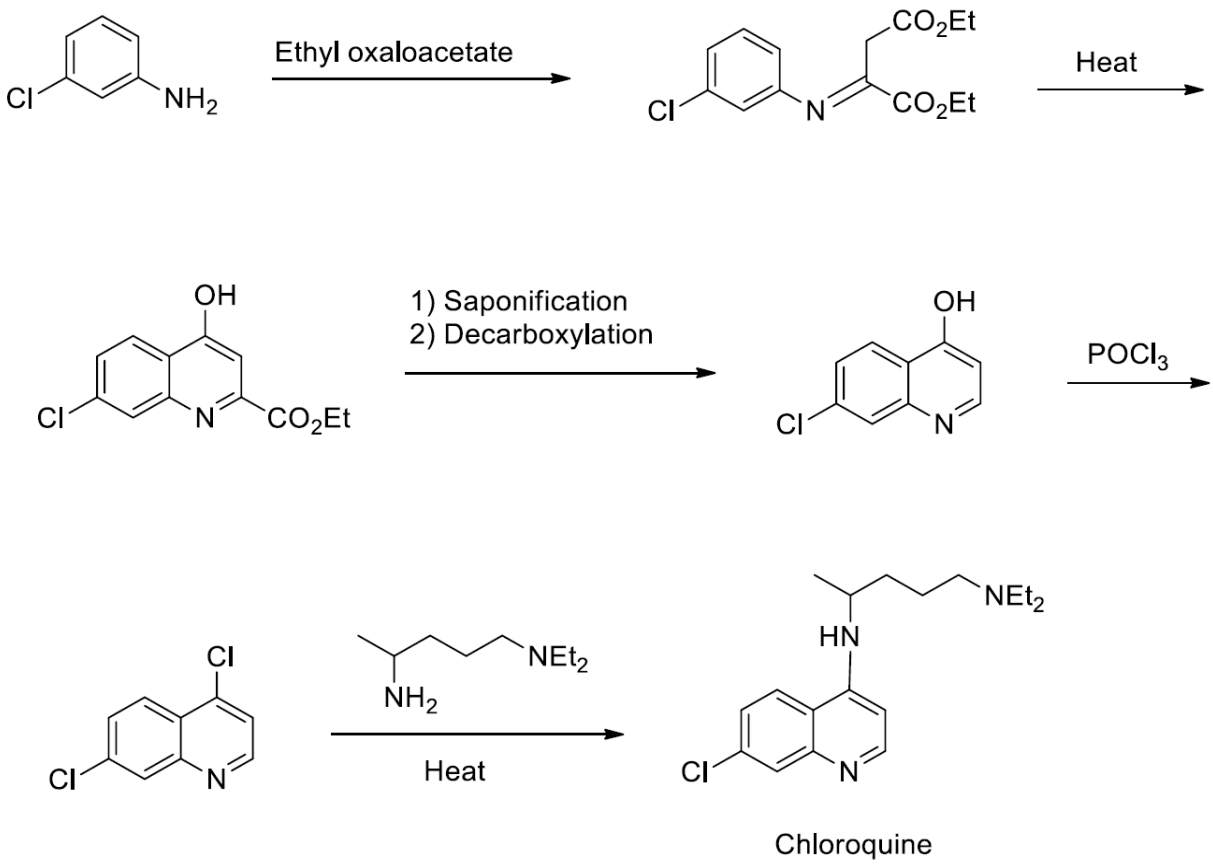
Development of synthetic antimalarials

Malaria is one of the most devastating diseases, affecting more than 400 million people with current worldwide mortality estimates between 1.5 and 2.7 mln per annum. The condition is known since the antiquity and its treatment has left many records in ethnopharmacology as well as in early history of

Fig. 1. Structures of alkaloid quinine and antimalarial aminoquinolines



Scheme 1. The first synthesis of chloroquine



modern medicine. For centuries, ***Cinchona*** tree (indigenous to South America) bark extracts were considered an effective treatment against malaria, which prompted the search for its active principle. Alkaloid quinine was isolated in 1820 by P. Pelletier and J. Caventou and it became principal antimalarial agent for the next century. Natural tree bark sources were initially monopolized in their native habitats but were later successfully transplanted, principally to Java island [4]. The isolated active compound defied practical chemical synthesis because of its complicated structure and stereochemistry (academic formal synthesis of quinine was completed by R. B. Woodward and W. von Eggers Doering in 1944 but it was never scaled up), which resulted in dramatic shortages of antimalarial drug substance, suffered by allied forces practically throughout the entire second world war. The need for effective synthetic replacement of quinine mobilized considerable research effort in German Bayer company, which later became I. G. Farben, with many thousands of new heterocyclic compounds synthesized and tested in relatively short time. In 1928, the structure of quinoline derivative antimalarial drug pamaquine, backed by some active, patented analogs (sontoquine, chloroquine) was announced in Germany and parallel research started in Britain, led by Robert Robinson in University College London and subsequently continued by Robert Elderfield at Columbia University in New York [8,9]. Eventually, competition between isomeric aminoquinoline derivatives active as anti-plasmodium agents was resolved by indicating chloroquine, with basic substitutent placed in position 4- as the drug of choice for the eradication of a relatively benign form of malaria caused by ***Plasmodium vivax*** parasite transmitted by mosquitoes [10,11].

New indications for chloroquine

Recently, the subject of drug repurposing for viral infectious diseases attracted considerable attention in connection with some epidemic events, and, most recently, in the context of the ongoing Covid-19 pandemia. Emergence of highly pathogenic severe acute respiratory syndrome (SARSCoV) in China in 2002/2003 was responsible for an epidemic with over 8000 infected people and ca. 10% mortality (www.cdc.gov). During the Middle East Respiratory Syndrome outbreak in 2013, caused by a coronavirus called MERS-CoV, attempts for repurposing known drugs were made, targeting the pathogen jointly with SARS-CoV-2 [13]. A library of 290 compounds was screened for antiviral activity, from which 27 promising candidates were selected, among them well known antiparasitic drugs such as chloroquine, hydroxychloroquine and mefloquine. The present Covid-19 outbreak took place in Wuhan, China at the end of last

year. WHO released the official name of 2019-nCoV as SARS-CoV-2. In January 2020, the first whole-genome sequence of SARSCoV-2 was published, which helped to develop tests for selection of infected patients. Several viral proteins have been identified (SARS main protease; coronavirus spike protein; nucleocapsid protein) some of which are suitable as targets for drug development [14]. In Poland, where chloroquine phosphate is available as preparation Arechine, indicated for malaria, additional marketing authorization for SARS-CoV-2 was acquired at the beginning of 2020 by its manufacturer: Adamed; the drug is recommended exclusively for hospital use. Ultimately a vaccine is likely to be the first specific treatment for the virus but its development must take several months at best. At present, the vintage antimalarial chloroquine appears to be a viable candidate for repositioning as an antiviral agent. Although conclusing evidence for its efficacy is still lacking, there are some encouraging though preliminary reports advocating its use for the treatment of SARS-CoV-2 infection, at a dose 500 mg of phosphate or 300 mg free base, to be taken 3 times a day, orally, for no more than ten days [15]. Interestingly, if this regimen becomes approved more widely, it will pose a considerable challenge to current API manufacturing capacity.

Availability of active pharmaceutical ingredients and pharmaceutical intermediates

We have recently pointed out that general availability of medicines can no longer be taken for granted, as a result of shifting practically all API manufacturing industry to Asian countries [16]. Not surprisingly, the drug availability crisis worsened with the emergence of the Covid-19 pandemic. In view of rather poor prognosis for quick elaboration of an efficient antiviral vaccine and even less likely perspective for a discovery of a new drug targeting one of essential viral proteins, the quest for alternative solutions to the global health danger becomes a matter of great importance and urgency. In particular, repurposing the abovementioned antimalarial chloroquine may be one option for a supportive remedy in anti-Covid-19 treatment. It should be pointed out that successful drug repositioning cases completed thus far resulted from rather serendipitous preclinical pharmacology observations, whereas contemporary chemoinformatics has at its disposal uniquely powerful tools for rational investigation of issues related to multitarget pharmacology. In connection with the case of chloroquine , two practical chemoinformatic topics come to focus. First is the matter of systemic support to the „pencil-assisted" design of synthetic pathways, practiced by organic chemists for more than a century. Recently, original achievement of Polish chemists – the so-called **Chematica** software platform for autonomous, computer – driven planning and optimization of multistep syntheses – has been described, expanded and validated, also experimentally, for a variety of targets important to medicinal chemistry and pharmaceutical industry [17-20]. A very important feature of **Chematica** is its integrated approach to the questions of plausibility and availability: chemical (chemical reaction knowledge-base), legal (IP surrounding intermediate and target molecules, based on compound and reaction databases), and economical (commercial data for starting materials and/or intermediates). Thus, even for such simple molecule as chloroquine, with a rather apparent synthetic scheme (Scheme 1), multiple manufacturing pathways can be generated in order to manage a crisis situation generated by incidental unavailability of a raw material or a manufacturing site. Such synthetic planning has, in fact, been recently performed as is described in ***https://chemrxiv.org/articles/Computer-Assisted_Planning_of_Hydroxychloroquine_s_Syntheses_Commencing_from_Inexpensive_Substrates_and_Bypassing_Patented_Routes_/12026439***. The second topic concerns rational approach to repositioning, based on achievements of artificial intelligence (AI) as applied to chemoinformatics methods in medicinal chemistry. The **Allchemy** team, also originating from Poland but operating mostly on the US market, has been developing sophisticated algorithms, based on recently elaborated molecular similarity tools, which allow the use of „big data" for the selection of appropriate lead compounds („parent molecules" exhibiting desired biological activity), from which progeny of novel candidates with already known structures can be obtained promptly. Interested readers can read about this approach at ***https://chemrxiv.org/articles/Suggestions_for_second-pass_anti-COVID-19_drugs_based_on_the_Artificial_Intelligence_measures_of_molecular_similarity_shape_and_pharmacophore_distribution_/12084690***. Evidently, this pragmatic solution can bypass the need for drug target identification, which makes it particularly useful when the time factor is decisive. In a broader context, these and similar advances illustrate aptly that chemistry can – and perhaps should –be perceived as a system, composed of millions of structures and comparable number of chemical reactions. As outlined above, new methods based on AI are being elaborated, which allow to manage such system as a network of molecular objects with an array of defined properties and their possible logical or chemical transformations, fit for coding in formal languages suitable for computer programs, but also for more traditional forms of scientific communication, like graph schemes, supplemented with 2D and 3D chemical formulae. While these tools are now primarily scientific, their industrial application is imminent as already demonstrated in present quest for new means to fight the SARS-CoV-2 pandemia.

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