In Silico Study of Antimalarial Agents & Their Derivatives Against SARS-Cov-2 & Rheumatoid Arthritis: The New Face of Innovation

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Article History: Received: 03/09/22 **Revised:** 19/11/22 **Accepted:** 21/12/22

Abstract-

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-caused COVID-19 pandemic has spread globally. On the other hand, Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. The goals of treatment are to reduce pain, decrease inflammation, and improve a person's overall functioning. Disease-modifying antirheumatic drugs (DMARDs), such as hydroxychloroquine and methotrexate, may be used to try to slow the progression of disease. Despite the production of different treatments, finding potent drug compounds to control RA, and COVID-19 is still a challenging task. The main objective of this work drug repurposing & design new molecule candidates more quickly by using computational techniques effective towards COVID-19 [Interleukin-2 (3qb1), Mitogen-activated protein kinase 1 (4qp3), Tyrosine-protein kinase JAK2 (4z32), Prostaglandin G/H synthase 2 (5f1a)] & RA [Spike glycoprotein (6cs2), 3C-like proteinase (6lu7), Spike glycoprotein (6vxx)]. In this simple & elegance studies revealed efficacy of 14 marketed antimalarials & 5 proposed molecules were targeted against Interleukin-2 (3qb1), Mitogen-activated protein kinase 1 (4qp3), Tyrosine-protein kinase JAK2 (4z32), Prostaglandin G/H synthase 2 (5f1a), Spike glycoprotein (6cs2), 3C-like proteinase (6lu7), Spike glycoprotein (6vxx). After accessing all docking results, it can be observed that the proposed molecule H-2 may have the better docking affinity compared to marketed best antimalarial drugs.The present work will further enable researchers to understand how in-silico designing tools may help to expedite new drug discovery process in a minimum cost.

Keywords: COVID-19, Rheumatoid arthritis, Drug Repurposing, Docking, Antimalarial drugs.

DOI: 10.31838/ecb/2023.12.4.291

Introduction

Drug Repurposing (DR), is the process of redeveloping an existing drug for licensed use in a different therapeutic indication or indicationsand/ or via a different drug delivery route. It is also known as drug repositioning, drug re-tasking, drug reprofiling, drug rescuing, drug recycling, drug redirection, and therapeutic switching. It can be defined as a process of identification of new pharmacological indications from old/existing/failed/investigational/already marketed/FDA approved drugs/pro-drugs, and the application of the newly developed drugs to the treatment of diseases other than the drug's original/intended therapeutic use. It involves establishing new therapeutic uses for already known drugs, including approved, discontinued, abandoned and experimental drugs. DRUG REPURPOSING, is the process of redeveloping an existing drug for licensed use in a different therapeutic indication or indications [1] and/ or via a different drug delivery route. In contrast, off- label use (OLU) describes a drug being used in a fashion that is not covered by the current license, eg, using higher doses, paediatric use or for another illness.[2] One fifth of the prescriptions in the US may be for OLU;[3] however, there is an increased risk of adverse events because OLU drugs are not fully investigated in controlled clinical studies. Traditional drug discovery is a time-consuming, laborious, highly expensive and high-risk process. The novel approach of drug repositioning has the potential to be employed over traditional drug discovery program by mitigating the high monetary cost, longer duration of development and increased risk of failure. It confers reduced risk of failure where a failure rate of ~45% is associated due to safety or toxicity issues in traditional drug discovery program with additional benefit of saving up to 5–7 years in average drug development time. In recent years, the drug repositioning strategy has gained considerable momentum with about one-third of the new drug approvals correspond to repurposed drugs which currently generate around 25% of the annual revenue for the pharmaceutical industry. It has been accounted that approximately 30% of the US Food and Drug Administration (FDA) approved drugs and biologics (vaccines) are repositioned drugs. According to recent estimates, pharmaceutical industries have significantly placed the market for repurposed drugs at $24.4 billion in 2015 with projected growth up to $31.3 billion in 2020. The first example of drug repositioning was an accidental discovery / serendipitous observation in the 1920s. After about a century of development, more approaches were developed for accelerating the process of drug repositioning. Some most successful and best-known drugs that have been emerged out of the DR approach are sildenafil, minoxidil, aspirin, valproic acid, methotrexate etc. For example, sildenafil originally developed for the treatment of hypertension and angina pectoris has currently been used to treat erectile dysfunction.

Drug repurposing can often be an integral part of a company's lifecycle management (LCM) strategy, for example, the development of age-appropriate dosage forms as product line extensions (PLEs). It can also be in response to an unmet clinical need, often driven by extensive OLU. [4] It is often undertaken because it is less risky, with lower costs and shorter European Pharmaceutical Review timelines. [5] Repurposed drugs have been estimated to require only three to four years to reach pivotal clinical trials [6] and the estimated cost is $1.6 billion compared with $12 billion for a new molecular entity (NME). [7,8] Many drugs

have been extensively assessed from a repurposing perspective; for example, prednisolone has been evaluated in over 1,340 therapeutic disorders. [9] Repurposing is often utilised when treating rare, orphan or neglected diseases, [5,8] or during pandemics, where there is an urgent need to find a rapid treatment. [10] New methods have now been developed, based in particular on data mining, to identify new candidates for drug repositioning. Many start-ups are entirely focused on developing this concept, a thesis has been devoted to Drug Repurposing, Rescue, and Repositioning, this dissertation provides a brief overview of repurposing and particularly evokes its most recent scientific basis as well as the new tools, and especially the computational ones, used to render it more efficient.

However, the repositioning strategy of using approved therapeutics for new therapeutic indications has demonstrated success particularly through prior serendipitous observations. The discovery of drugs by this approach is certainly advantageous as depicted above over traditional drug discovery program as described below. For example, sildenafil (Viagra), a phosphodiesterase-5 (PDE5) inhibitor initially developed for coronary artery disease (angina) by Pfizer (1985) has been repurposed for the treatment of erectile dysfunction. It potentially reduced the development cost at shorter development time. Metformin (Glucophage), an oral anti-diabetic medication used widely in type 2 diabetes mellitus has been developed as a cancer therapeutic which is currently under phase II/phase III clinical trials.

Drug repositioning has several advantages in comparison with traditional approaches to drug discovery. When comparing with traditional drug discovery program, a significant reduction of the time spent in R&D can be observed. In traditional approach, it is estimated that 10–16 years are spent for the development of a new drug, while in DR the estimated time is between 3 and 12 years. It only costs $1.6 billion to develop a new drug using a drug repositioning strategy, while the drug development through traditional strategy costs around $12 billion.

Moreover, researchers only need 1–2 years to identify new drug targets and about an average of 8 years to develop a repositioned drug. A repositioned drug does not require the initial 6–9 years typically required for the development of new drugs by traditional process, but instead enters directly to preclinical testing and clinical trials, thus reducing the overall risk, time and cost of development. Reports suggest that repurposed drugs require approximately 3–12 years for gaining approval from FDA and/or European Medicines Agency (EMA) and at reduced 50–60% cost. At the beginning of a repositioning project, a range of pre-clinical (pharmacological, toxicological, etc.), and clinical efficacy and safety information is already available, as the candidate drug has already undergone through the early stages of drug development such as structural optimization, preclinical and/or clinical trials, in addition to the possibility of the candidate drug being an approved drug, having its clinical efficacy and safety profile. In this way, there is a reduction of the risks associated with failures in the early stages of development, which are high in traditional approaches, as well as a significant reduction of cost with the possible increase in clinical safety and therefore, high success rate.

Due to the availability of previously collected pharmacokinetic, toxicological, clinical and safety data at the start of a repurposing development project, the advantages that are encountered with drug repurposing over traditional drug discovery approach are reduced time of development, lower cost of development and reduced risks of failure in the clinical development.

It has been estimated that the time required for development of a repositioned drug varies

from 3 to 12 years (which is about 10–17 years in traditional discovery program) with substantially lower costs, which ensures the repositioning company's significant savings in terms of time and capital. The average cost required to bring a new drug to market is USD 1.24 billion by traditional drug development process, whereas in drug repurposing it costs around ≤60% expenditure of traditional drug discovery. Some other advantages are as follow. The primary focus of traditional discovery program is to discover drugs to treat chronic and complex diseases, whereas by drug repositioning approach, development of drugs for rapidly emerging and re-emerging infectious diseases, difficult to treat diseases and neglected diseases (NTDs) are focused. Due to the availability of bioinformatics or cheminformatics approaches, huge omics (proteomics, transcriptomics, metabolomics, genomics etc.) data and database resources, disease targeted-based repositioning methods can be used to explore the unknown mechanisms of action (such as unknown targets for drugs, unknown drug–drug similarities, new biomarkers for diseases etc.) of known/existing drugs.

Minoxidil was transformed from an antihypertensive vasodilator anti hair loss drug. As an antihypertensive vasodilator, minoxidil has the property of widening blood vessels and opening potassium channels, which allows more oxygen, blood, and nutrients to the hair follicles and this pharmacological action helps its use in the treatment of male pattern baldness (androgenic alopecia). On the other hand, in the off-target profile, the pharmacological mechanism is unknown. Drugs and drugs candidates act on new targets, out of the original scope, for new therapeutic indications. Therefore, both the targets and the indications are new. Aspirin (Colsprin) is good example of the off-target profile. Aspirin has been traditionally used as NSAID in the treatment of various pain and inflammatory disorders. It also suppresses blood coagulation (clot formation) by inhibiting the normal functioning of platelets (antiplatelet drug). It is, therefore, used in the treatment of heart attacks and strokes. Another new use of aspirin in the treatment of prostate cancer has also been reported

In contrast, in silico repositioning carries out virtual screening of public databases of huge drug/chemical libraries using computational biology and bioinformatics/cheminformatics tools. In this approach, the identification of potential bioactive molecules is achieved based upon the molecular interaction between drug molecule and protein target.

In particular, medicinal chemistry in its most common practice focusing on small organic molecules encompasses synthetic organic chemistry and aspects of natural products and computational chemistry in close combination with chemical biology, enzymology and structural biology, together aiming at the discovery and development of new therapeutic agents. Practically speaking, it involves chemical aspects of identification, and then systematic, thorough synthetic alteration of new chemical entities to make them suitable for therapeutic use. It includes synthetic and computational aspects of the study of existing drugs and agents in development in relation to their bioactivities (biological activities and properties), i.e., understanding their structure-activity relationships (SAR). Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for purpose of medicinal products.

However, once hits or leads have been co-crystallized with their targets and exact binding conformations have been established, docking of analogues can be facilitated by the application of algorithms that model compound modification on pre-defined core fragments

of leads. At the very least automated analogue design and evaluation makes it possible to quickly eliminate molecules that are too large or do not satisfy binding constraints and shifts focused towards more promising candidates. Combining docking and designing of analogue libraries provides a particularly promising route to lead optimization for COVID -19 & Rheumatoid Arthritis.

COVID 19 (SARS-COV-2)

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Symptoms of COVID-19 are variable, but often include fever, [11] cough, headache, [12] fatigue, breathing difficulties, and loss of smell and taste. [13-16]

Symptoms may begin one to fourteen days after exposure to the virus. At least a third of people who are infected do not develop noticeable symptoms. [17] Of those people who develop noticeable symptoms enough to be classed as patients, most (81%) develop mild to moderate symptoms (up to mild pneumonia), while 14% develop severe symptoms (dyspnea, hypoxia, or more than 50% lung involvement on imaging), and 5% suffer critical symptoms (respiratory failure, shock, or multiorgan dysfunction). [18] Older people are at a higher risk of developing severe symptoms. Some people continue to experience a range of effects (long COVID) for months after recovery, and damage to organs has been observed. Work is underway to develop drugs that inhibit the virus (and several vaccines for it have been approved and distributed in various countries, which have since initiated mass vaccination campaigns), the primary treatment is symptomatic. Management involves the treatment of symptoms, supportive care, isolation, and experimental measures.

Methods

Protease and ligands download

At first, the drug molecules were fetched from the literature. The 3-dimensional (3D) structure of the compounds was download from the PubChem chemical database (http://pubchem.ncbi.nlm.nih.gov). The crystallographic structures of proteins [Interleukin-2 (3qb1), Mitogen-activated protein kinase 1 (4qp3), Tyrosine-protein kinase JAK2 (4z32), Prostaglandin G/H synthase 2 (5f1a)] & RA [Spike glycoprotein (6cs2), 3C-like proteinase (6lu7), Spike glycoprotein (6vxx)]. were obtained from a protein data bank (http://www.rcsb.org).

Evaluation of Lipinski's parameters-

The potential effective of antimalarial drugs was evaluated using the Lipinski parameter to inhibit the activity of COVID-19 main protease. Items such as Molecular weight (MW), high lipophilicity, hydrogen bonds donor, hydrogen bonds acceptor, and Molar refractivity were considered for the compounds (table 1). Analysis of Bioactive Scores has also been noted in table 2.

Table 1: Analysis of Lipinski rule of 5 for titlecompounds

Compound	miLogP	TPSA	natoms	MW	nON	nOHNH	nviolations	nrotb	Volume

Hydroxychloroquine	4.00	48.38	23	335.88	4	2	0	9	321.38
Chloroquine	5.00	28.16	22	319.88	3	1	1	8	313.12
Amodiaquine	6.21	35.49	25	354.88	3	2	1	6	329.71
Mepacrine	6.56	37.39	28	399.97	4	1	1	9	382.66
Quinine	3.06	45.59	24	324.42	4	1	0	4	310.79
Proguanil	2.05	83.78	17	253.74	5	5	0	6	229.33
Pyrimethamine	2.84	77.83	17	248.72	4	4	0	2	216.62
Trimethoprim	0.99	105.53	21	290.32	7	4	0	5	263.15
Primaquine	2.10	60.18	19	259.35	4	3	0	6	256.91
Sulfadoxine	0.36	116.44	21	310.33	8	3	0	5	253.35
Sulfamethopyrazine	0.38	107.21	19	280.31	7	3	0	4	227.81
Dapsone	0.93	86.19	17	248.31	4	4	0	2	209.46
Artemisinin	3.63	4.77	20	280.36	4	0	0	0	266.04
Halofantrine	7.48	23.47	33	502.45	2	1	2	11	441.77

Table 2: Analysis of Bioactive Scores of title Compounds

Compound Name	**GPCR Ligand**	**Ion channel modular**	**Kinase inhibitor**	**Nuclear receptor ligand**	**Protease inhibitor**	**Enzyme inhibitor**
Hydroxychloroquine	0.35	0.30	0.44	-0.12	0.12	0.15
Chloroquine	0.32	0.32	0.38	-0.19	0.05	0.11
Amodiaquine	0.11	0.03	0.27	-0.23	-0.07	0.04
Mepacrine	0.18	0.17	0.10	-0.22	-0.05	0.09
Quinine	0.39	0.37	-0.05	0.10	0.18	0.11
Proguanil	-0.05	0.31	-0.77	-1.18	-0.09	0.06
Pyrimethamine	0.31	0.07	0.38	-0.61	-0.14	0.66
Trimethoprim	0.17	-0.14	0.51	-0.47	-0.15	0.52

Primaquine	0.20	0.22	0.23	-0.35	0.04	0.15
Sulfadoxine	0.26	-0.21	0.16	-0.62	-0.18	0.10
Sulfamethopyrazine	-0.04	-0.26	0.03	-0.53	-0.14	0.08
Dapsone	-0.15	0.08	-0.30	-0.62	-0.19	0.17
Artemisinin	-0.06	0.02	-0.66	0.19	-0.13	0.48
Halofantrine	0.37	0.11	0.05	0.39	0.06	0.34

Docking

In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example scoring functions. Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized. [19]

For our present study we used bioinformatics tools, biological databases like PDB (Protein Data Bank) & software like Hex Version 5.1, CHEM SKETCH. Hex is an interactive molecular graphics program for calculating &displaying feasible docking modes of pairs of protein & DNA molecules. Hex can also calculate Protein-Ligand Docking, assuming the ligand is rigid, & it can superpose pairs of molecules using only knowledge of their 3D shapes. It uses Spherical Polar Fourier (SPF) correlations to accelerate the calculations & it's one of the few docking programs which has built in graphics to view the result.

RASMOL (Raster Display of Molecules) is a molecular graphics program intended for the structural visualization of proteins, nucleic acids & small biomolecules. The program reads in molecular coordinate files & interactively displays the molecule on the screen in variety of representations & color schemes.

Docking of antimalarial drug molecules with arthritic targets [3qb1, 4qp3, 4z32, 5f1a, 6cs2, 6lu7, 6vxx]

The docking scores of the drugs have been noted in the following section (Table 3, 4, 5, 6,7, 8, 9).

Table 3: Molecular docking score of the Anti-malarial compounds with 3qb1 receptor

Sl.No.	PDB(3qb1) with compound	Docking Score (Kcal)
1	Hydroxychloroquine	-274.14

2	Chloroquine	-272.41
3	Amodiaquine	-299.80
4	Mepacrine	-319.45
5	Quinine	-283.85
6	Proguanil	-228.84
7	Pyrimethamine	-200.68
8	Trimethoprim	-247.46
9	Primaquine	-242.89
10	Sulfadoxine	-259.25
11	Sulfamethopyrazine	-238.95
12	Dapsone	-228.97
13	Artemisinin	-232.62
14	Halofantrine	-327.43

Table 4: Molecular docking score of the Anti-malarial compounds with 4qp3 receptor

Sl.No.	PDB(4qp3) with compound	Docking Score
1	Hydroxychloroquine	-127.90
2	Chloroquine	-121.43
3	Amodiaquine	-142.78
4	Mepacrine	-152.51
5	Quinine	-94.30
6	Proguanil	-105.98
7	Pyrimethamine	-69.06
8	Trimethoprim	-84.16
9	Primaquine	-80.18
10	Sulfadoxine	-101.52
11	Sulfamethopyrazine	-107.91
12	Dapsone	-90.85

13	Artemisinin	-61.14
14	Halofantrine	-150.43

Table No. 5: Molecular docking score of the Anti-malarial compounds with 4z32 receptor

Sl.No.	PDB(4z32) with compound	Docking Score
1	Hydroxychloroquine	-175.66
2	Chloroquine	-161.48
3	Amodiaquine	-215.43
4	Mepacrine	-223.68
5	Quinine	-242.72
6	Proguanil	-168.32
7	Pyrimethamine	-158.29
8	Trimethoprim	-185.87
9	Primaquine	-204.00
10	Sulfadoxine	-167.38
11	Sulfamethopyrazine	-174.08
12	Dapsone	-158.53
13	Artemisinin	-163.16
14	Halofantrine	-247.04

Table No. 6: Molecular docking score of the antimalarial compounds with 5f1a receptor

Sl.No.	PDB(5f1a) with compound	Docking Score
1	Hydroxychloroquine	-61.68
2	Chloroquine	-50.26
3	Amodiaquine	-52.90
4	Mepacrine	-74.46
5	Quinine	-58.55
6	Proguanil	-54.58
7	Pyrimethamine	-51.32
8	Trimethoprim	-45.83
9	Primaquine	-51.43
10	Sulfadoxine	-42.13
11	Sulfamethopyrazine	-44.96
12	Dapsone	-36.98
13	Artemisinin	-54.81
14	Halofantrine	-52.96

Table No. 7: Molecular docking score of the antimalarial compounds with 6cs2 receptor

Sl.No.	PDB(6cs2) with compound	Docking Score
1	Hydroxychloroquine	-30.41
2	Chloroquine	-36.45
3	Amodiaquine	0.00
4	Mepacrine	-28.22
5	Quinine	-37.68
6	Proguanil	-34.77
7	Pyrimethamine	0.00
8	Trimethoprim	0.00
9	Primaquine	0.00
10	Sulfadoxine	0.00
11	Sulfamethopyrazine	-34.18
12	Dapsone	-27.52
13	Artemisinin	0.00
14	Halofantrine	0.00

Table No. 8: Molecular docking score of the antimalarial compounds with 6lu7 receptor

Sl.No.	PDB(6lu7) with compound	Docking Score
1	Hydroxychloroquine	-255.47
2	Chloroquine	-247.84
3	Amodiaquine	-263.26
4	Mepacrine	-273.09
5	Quinine	-277.35
6	Proguanil	-213.93
7	Pyrimethamine	-193.58

8	Trimethoprim	-248.73
9	Primaquine	-224.78
10	Sulfadoxine	-225.51
11	Sulfamethopyrazine	-223.87
12	Dapsone	-198.29
13	Artemisinin	-202.14
14	Halofantrine	-202.14

Table No. 9: Molecular docking score of the antimalarial compounds with 6vxx receptor

Sl.No.	PDB(6vxx) with compound	Docking Score
1	Hydroxychloroquine	0.00
2	Chloroquine	0.00
3	Amodiaquine	-29.33
4	Mepacrine	-31.16
5	Quinine	-31.72
6	Proguanil	-26.43
7	Pyrimethamine	0.00
8	Trimethoprim	0.00
9	Primaquine	0.00
10	Sulfadoxine	-36.27
11	Sulfamethopyrazine	-32.84
12	Dapsone	-32.80
13	Artemisinin	0.00
14	Halofantrine	0.00

Docking study of the activity against SARS-CoV-2 infection activity:
The docking scores of the drugs have been noted in the following section (table 10, 11, 12 respectively).

Table No. 10 : Molecular docking score of the Anti-malarial compounds with 6cs2 receptor

Sl.No.	PDB(6cs2) with compound	Docking Score

1	Hydroxychloroquine	-30.41
2	Chloroquine	-36.45
3	Amodiaquine	0.00
4	Mepacrine	-28.22
5	Quinine	-37.68
6	Proguanil	-34.77
7	Pyrimethamine	0.00
8	Trimethoprim	0.00
9	Primaquine	0.00
10	Sulfadoxine	0.00
11	Sulfamethopyrazine	-34.18
12	Dapsone	-27.52
13	Artemisinin	0.00
14	Halofantrine	0.00

Table No. 11: Molecular docking score of the Anti-malarial compounds with 6lu7 receptor

Sl.No.	PDB(6lu7) with compound	Docking Score
1	Hydroxychloroquine	-255.47
2	Chloroquine	-247.84
3	Amodiaquine	-263.26
4	Mepacrine	-273.09
5	Quinine	-277.35
6	Proguanil	-213.93
7	Pyrimethamine	-193.58
8	Trimethoprim	-248.73
9	Primaquine	-224.78
10	Sulfadoxine	-225.51
11	Sulfamethopyrazine	-223.87
12	Dapsone	-198.29

13	Artemisinin	-202.14
14	Halofantrine	-202.14

Table No. 12: Molecular docking score of the Anti-malarial compounds with 6vxx receptor

Sl.No.	PDB(6vxx) with compound	Docking Score
1	Hydroxychloroquine	0.00
2	Chloroquine	0.00
3	Amodiaquine	-29.33
4	Mepacrine	-31.16
5	Quinine	-31.72
6	Proguanil	-26.43
7	Pyrimethamine	0.00
8	Trimethoprim	0.00
9	Primaquine	0.00
10	Sulfadoxine	-36.27
11	Sulfamethopyrazine	-32.84
12	Dapsone	-32.80
13	Artemisinin	0.00
14	Halofantrine	0.00

PROPOSED FUTURE MOLECULE EFFECTIVE AGAINST RA & COVID-19

ADME Characteristics of all the above 14 molecules were calculated by using Med-Chem Designer Software. Molecules which follow Lipinski rule were further docked by using HEX version 5.1 docking software and others were rejected. The proposed molecules were as following (table 13, 14)

HC-1: Hydroxychloroquine derivative -1; HC-2: Hydroxychloroquine derivative-2; C-1: Chloroquine derivative -1; Q-1: Quinine derivative -1; Q-2: Quinine derivative -2.

Table No. 13: Analysis of Lipinski rule of 5 for proposed molecules

Compound	miLogP	TPSA	natom s	MW	nON	nOHNH	nviolations	nrotb	Volume

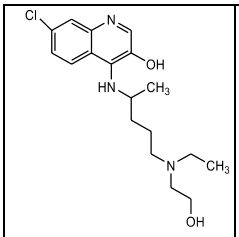
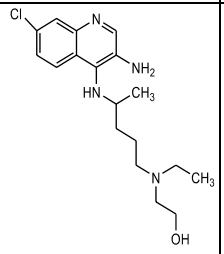
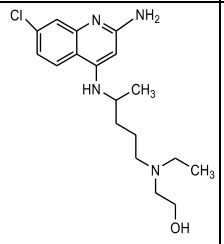
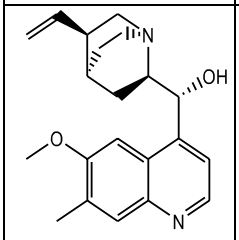
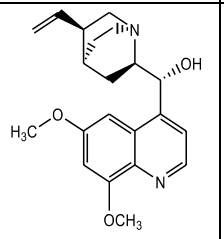
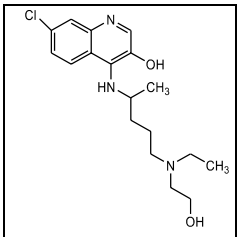
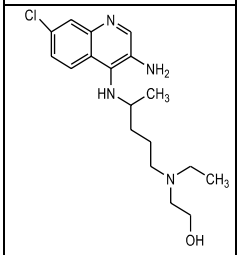
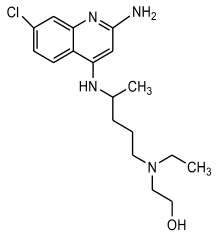
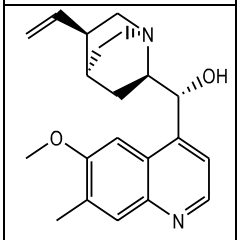
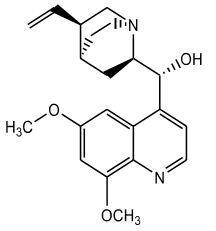
 HC-1	3.92	68.61	24	351.88	5	3	0	9	329.40
 HC-2	3.63	74.41	24	350.89	5	4	0	9	332.67
 C-1	4.83	54.18	23	334.89	4	3	0	8	324.41
 Q-1	3.44	45.59	25	338.45	4	1	0	4	327.35
 Q-2	3.04	54.83	26	354.45	5	1	0	5	336.34

Table No. 14: Bioactive Scores of proposed molecules

Compound Name	GPCR Ligand	Ion channel modular	Kinase inhibitor	Nuclear receptor ligand	Proteas e inhibito r	Enzyme inhibitor

 HC-1	0.36	0.24	0.37	-0.00	0.08	0.15
 HC-2	0.25	0.18	0.34	-0.20	0.09	0.09
 C-1	0.41	0.33	0.47	-0.59	0.04	0.17
 Q-1	0.33	0.31	-0.05	0.12	0.13	0.07
 Q-2	0.39	0.29	-0.07	0.09	0.15	0.13

Docking study of the arthritic activity:

The molecular docking score of the proposed compounds with different receptors have been noted in table 15-21.

Table No. 15: Molecular docking score of the proposed compounds with 3qb1 receptor

Sl.No.	PDB(3qb1) with compound	Docking Score
1	H-1	-284.21
2	H-2	-292.17

3	C-1	-297.67
4	Q-1	-292.65
5	Q-2	-277.50

Table No.16: Molecular docking score of the proposed compounds with 4qp3 receptor

Sl.No.	PDB(4QP3) with compound	Docking Score
1	H-1	-147.48
2	H-2	-164.03
3	C-1	-131.95
4	Q-1	-90.83
5	Q-2	-86.24

Table No.17: Molecular docking score of the proposed compounds with 4z32 receptor

Sl.No.	PDB(4Z32) with compound	Docking Score
1	H-1	-179.66
2	H-2	-197.68
3	C-1	-172.72
4	Q-1	-223.02
5	Q-2	-209.10

Table No.18: Molecular docking score of the proposed compounds with 5f1a receptor

Sl.No.	PDB(5f1a) with compound	Docking Score
1	H-1	-63.75
2	H-2	-50.04
3	C-1	-46.24
4	Q-1	-55.56
5	Q-2	-72.32

Table No.19: Molecular docking score of the proposed compounds with 6cs2 receptor

Sl.No.	PDB(6cs2) with compound	Docking Score
1	H-1	0.00
2	H-2	-59.13
3	C-1	-30.25
4	Q-1	-29.85
5	Q-2	-39.42

Table No.20: Molecular docking score of the proposed compounds with 6lu7 receptor

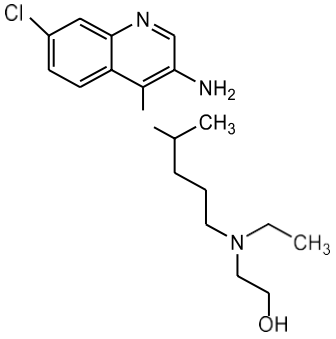
Sl.No.	PDB(6lu7) with compound	Docking Score
1	H-1	-256.90
2	H-2	-289.34
3	C-1	-252.26
4	Q-1	-276.86
5	Q-2	-255.32

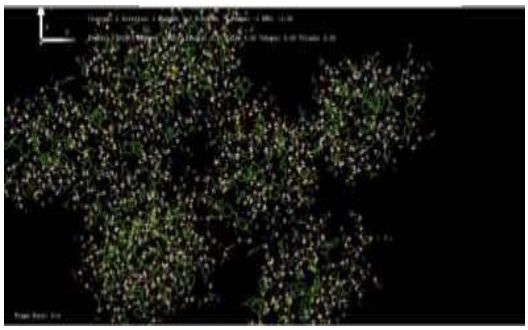
Table No.21: Molecular docking score of the proposed compounds with 6vxx receptor

Sl.No.	PDB(6vxx) with compound	Docking Score
1	H-1	0.00
2	H-2	-52.48
3	C-1	28.96
4	Q-1	-37.51
5	Q-2	-27.04

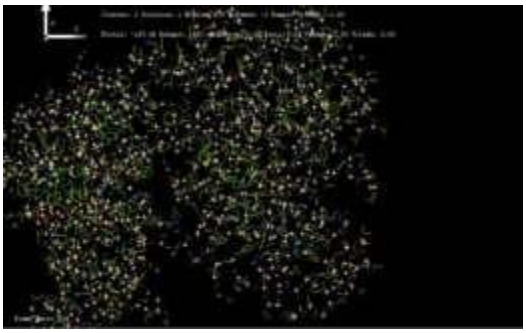
Result and Discussion

After docking of 5 proposed molecules with 4 PDBs (i.e; 3qb1, 4qp3, 4z32, 5f1a) of rheumatoid arthritis, structure H-2 gives best result.

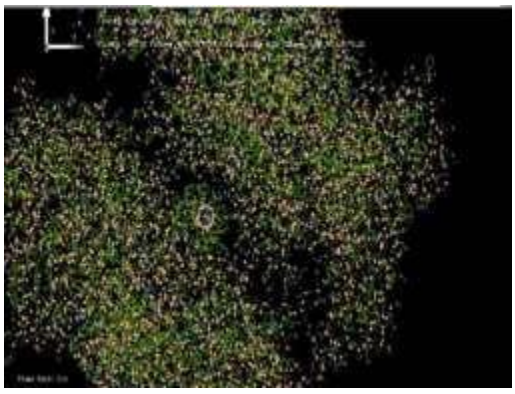
Best Proposed Structure	PDB	Docking Score
	3qb1	-292.17
	4qp3	-164.02
	4z32	-197.68
	5f1a	-50.04



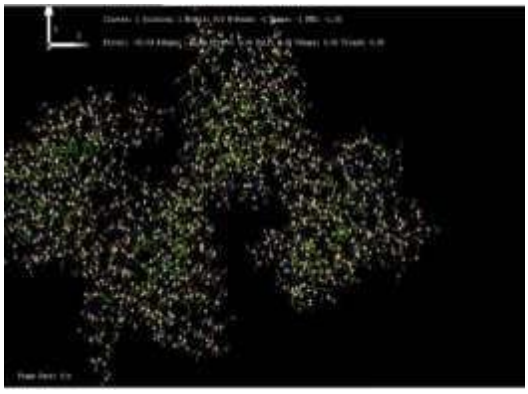
Docking of HC-2 with 3qp1 receptor



Docking of HC-2 with 4qp3 receptor

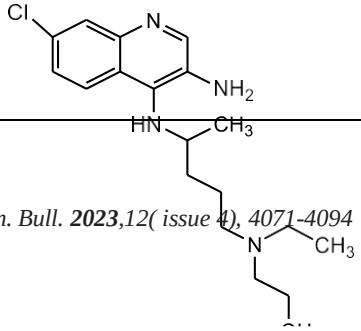


Docking of HC-2 with 4z32 receptor

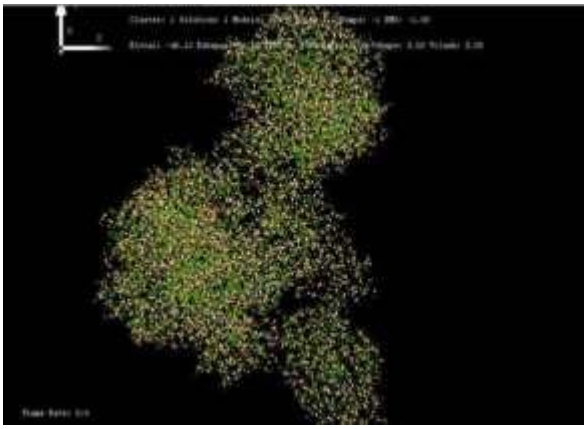


Docking of HC-2 with 5f1a receptor

After docking of 5 proposed molecules with 3 PDBs (i.e; 6cs2, 6lu7, 6vxx) of SARS-CoV-2, structure H-2 gives best result (figure 1).

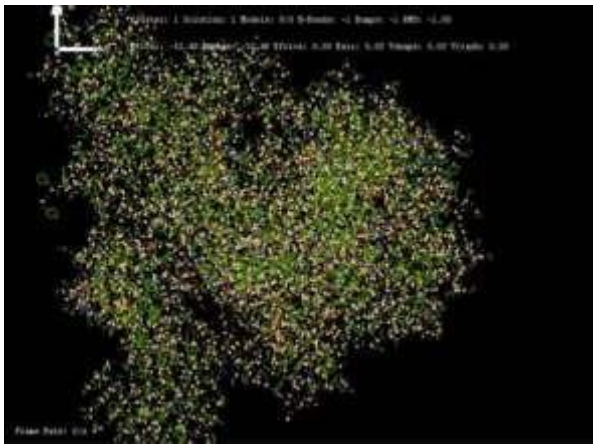
Best Proposed Structure	PDB	Docking Score
	6cs2	-46.10

	6lu7	-273.62
	6vxx	-52.48



Docking of HC-2 with 6cs2 receptor

Docking of HC-2 with 6lu7 receptor



Docking of HC-2 with 6vxx receptor

Figure 1. Docking figure of HC-2 compound.

Conclusion and Future Prospects

Drug repurposing (DR) is also known as drug repositioning, drug re- tasking, drug reprofiling, drug rescuing, drug recycling, drug redirection, and therapeutic switching. It can be defined as a process of identification of new pharmacological indications from old/existing/failed/investigational/already marketed/FDA approved drugs/pro-drugs, and the application of the newly developed drugs to the treatment of diseases other than the drug's original/intended therapeutic use. It involves establishing new therapeutic uses for already known drugs, including approved, discontinued, abandoned and experimental drugs. DRUG

Repurposing is the process of redeveloping an existing drug for licensed use in adifferent therapeutic indication or indications and/ or via a different drug delivery route.

The novel approach of drug repositioning has the potential to be employed over traditional drug discovery program by mitigating the high monetary cost, longer duration of development and increased risk of failure. It confers reduced risk of failure where a failure rate of ~45% is associated due to safety or toxicity issues in traditional drug discovery program with additional benefit of saving up to 5–7 years in average drug development time.

Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints.[15] It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest.[15] Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body. The disease may also affect other parts of the body, including skin, eyes, lungs, heart, nerves and blood. The goals of treatment are to reduce pain, decrease inflammation, and improve a person's overall functioning. Disease-modifying anti-rheumatic drugs (DMARDs), such as hydroxychloroquine and methotrexate,may be used to try to slow the progression of disease.

Corona virus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Symptoms of COVID-19 are variable, but often include fever, cough, headache, fatigue, breathing difficulties, and loss of smell and taste. Work is underway to develop drugs that inhibit the virus (and several vaccines for it have been approved and distributed in various countries, which have since initiated mass vaccination campaigns), the primary treatment is symptomatic. Management involves the treatment of symptoms, supportive care, isolation, and experimental measures.

There are two main strategies of DR, viz., on-target and off target. In on- target DR, the known pharmacological mechanism of a drug molecule is applied to a new therapeutic indication. In this strategy, the biological target of the drug molecule is same, but the disease is different.

Drug repositioning has two alternative and complementary approaches, one is experiment-based approach and the other is in silico-based approach.

The methodologies adopted in DR can be divided into three broad groups depending on the quantity and quality of the pharmacological, toxicological and biological activity information available. These are mainly (i) drug-oriented, (ii) target-oriented, and (iii) disease/therapy-oriented.

Hydroxychloroquine, an FDA-approved prescription drug used for malaria, has been suggested as a possible treatment or preventive for COVID-19 based on demonstrated antiviral or immune system activity also prescribed to patient suffering from RA. Hence, we focus on all types of antimalarial drugs to check which antimalarial drug shows more activity towards RA & Covid-19.

For this purpose, 4 protein binding sites along with their PDB ID to check the RA activity & 3 protein binding sites along with their PDB ID to check the covid-19 activity are selected.

The target proteins & their PDB IDs are:

1. RA Protein (PDB ID) - Interleukin-2 (3qb1)

Mitogen-activated protein kinase 1 (4qp3) Tyrosine-protein kinase JAK2 (4z32) Prostaglandin G/H synthase 2 (5f1a)

2. COVID Protein (PDB ID) – Spike glycoprotein (6cs2)

3C-like proteinase (6lu7) Spike glycoprotein (6vxx)

New antimalarial agents in such initiatives may be derived as novel compounds or modifications of existing drugs which may show high efficacy & efficiency towards RA & Covid-19.

This investigation was to determine the comparative efficacy & docking affinity of commonly used Antimalarials, reported molecules & my proposed molecules on targeting 3D model 3qb1, 4qp3, 4z32, 5f1a, 6cs2, 6lu7, 6vxx structure, using in silico techniques by different computational drug designing Sources and softwares i.e., RCSB PROTEIN DATA BANK, MED CHEM DESIGNER, CHEM SKETCH, HEX 5.1, ARGUS LAB, MDL MOL FILE, BROOKHAVEN PDB FILE, etc.

After energy minimization of 3D structure of Interleukin-2 (3qb1), Mitogen-activated protein kinase 1 (4qp3), Tyrosine-protein kinase JAK2 (4z32), Prostaglandin G/H synthase 2 (5f1a), Spike glycoprotein (6cs2), 3C-like proteinase (6lu7), Spike glycoprotein (6vxx) those were docked with Energy minimized marketed Antimalarials, reported molecules & proposed molecules by using docking software HEX5.1The inhibitors binding efficacy & affinities were determined using HEX docking scoring (Etotal negative value) fitness function. The application on computational science (In silico drug designing) to pharmaceutical research is a discipline, which is phenomenal.

In this simple & elegance studies revealed efficacy of 14 marketed antimalarials & 5 proposed molecules were targeted against Interleukin-2 (3qb1), Mitogen-activated protein kinase 1 (4qp3), Tyrosine-protein kinase JAK2 (4z32), Prostaglandin G/H synthase 2 (5f1a), Spike glycoprotein (6cs2), 3C-like proteinase (6lu7), Spike glycoprotein (6vxx). After accessing all docking results, it can be observed that the proposed molecule H-2 may have the better docking affinity (Total:-292.17, -164.02, -197.68, -50.04, -46.10, -273.62, -52.48 values against PDB ID 3qb1, 4qp3, 4z32, 5f1a, 6cs2, 6lu7, 6vxx respectively) compared to marketed best antimalarial (i.e., hydroxychloroquine, chloroquine, quinine) .

Finally, it can be concluded from these reported studies, molecule like hydroxychloroquine & their derivatives may be a new class of potent drugs for treatment of RA & Covid-19. Moreover, further exploration for detailed mechanism of action of these compounds is required to be investigated before declaring them as safe as well as potent therapeutic agents. However, data reported in this work may be a helpful guide for the medicinal chemists and the researchers who are working in this area.

Acknowledgement

All authors are thankful to Institute of Pharmacy and Technology, Salipur.

Conflict of Interest

Not Applicable.

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