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ROYAL SOCIETY OF CHEMISTRY

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Direct synthesis, characterization, *in vitro* and *in silico* studies of simple chalcones as potential antimicrobial and antileishmanial agents

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Chalcone represents a vital biosynthetic scaffold owing to its numerous therapeutic effects. The present study was intended to synthesize 17 chalcone derivatives (**3a–q**) by direct coupling of substituted acetophenones and benzaldehyde. The target chalcones were characterized by spectroscopic analyses followed by their *in vitro* antimicrobial, and antileishmanial investigations with reference to standard drugs. The majority of the chalcones displayed good to excellent biological activities. Chalcone **3q** (1000 µg ml^{-1}) exhibited the most potent antibacterial effect with its zone of inhibition values of 30, 33 and 34 mm versus *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* respectively. The results also confirmed chalcone **3q** to be the most potent versus *Leishmania major* with the lowest IC_{50} value of 0.59 ± 0.12 µg ml^{-1}. Chalcone **3i** (500 µg ml^{-1}) was noticed to be the most potent antifungal agent with its zone of inhibition being 29 mm against *Candida albicans*. Computational studies of chalcones **3i** and **3q** supported the preliminary *in vivo* results. The existence of the amino moiety and bromine atom on ring-A and methoxy moieties on ring-B caused better biological effects of

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Research article

In silico evaluation of favipiravir-associated potential new drugs against polymerase enzyme of SARS-CoV-2

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ARTICLE INFO

Keywords:
SARS-CoV-2
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ABSTRACT

Millions of lives have been lost to the deadly SARS-CoV-2 virus. Vaccines and antiviral drugs are essential scientific tools in combating viral infections. This *in silico* study focused on the RdRp inhibitor favipiravir, exploring new analogs by substituting the fluorine atom on the pyrazine ring with both homocyclic and heterocyclic moieties. Initially, ADME and toxicity properties were assessed using SwissADME and ProTox-II online tools. Ligands **L6** and **L7** exhibited high bioavailability and drug-likeness compared to favipiravir. Subsequently, all new analogs were docked into the RdRp active site using AutoDock Vina, demonstrating high affinity compared to favipiravir. Based on optimal ADMET profiles and docking scores, ligands **L4**, **L6**, and **L7** underwent 200 ns MDS using the CHAARM 36 force field in NAMD software to validate docking results. Various trajectory analyses, including RMSD, RMSF, histograms, total number of contacts, and ligand properties, were conducted to gain insights into the interaction patterns between ligands and RdRp. All protein-ligand complexes exhibited greater stability than favipiravir throughout simulations period. This theoretical study suggests that ligands **L6** and **L7** could serve as lead candidates for RdRp inhibition. Cell-Based SARS-CoV-2 RdRp Activity Assay is recommended to validate these *in silico* findings.

1. Introduction

Coronaviruses induce respiratory infections in mammals such as bats, masked palm civets, and camels, as well as in avian species

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ORIGINAL PAPER

In silico evaluation of the potential anticancer effects of Viscosine and Quercetin 7-rutinoside: inhibition of DEAD-box RNA helicase DDX3X and b-cell lymphoma-extra large (Bcl-XL) activity

Soma Khan[1] · Khalid Khan[1] · Tanzeel Shah[2] · Haroon ur Rashid[3] · Nasir Ahmad[1] · Akhtar Muhammad[1] · Muhammad Zahoor[4] · Muhammad Naveed Umar[5] · Riaz Ullah[6] · Zafar Iqbal[7]

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Abstract

Globally, cancer is the second leading cause of mortality, surpassed only by cardiovascular disorders. Among its various types, Non-Small Cell Lung Cancer (NSCLC) poses a significant global health risk. Chemotherapy is the most common therapeutic approach for treating cancer. However, chemotherapeutic drugs can cause serious toxicity by reducing the survival of both tumor and normal cells, thereby diminishing the survival chances of patients. Natural products extracted from medicinal plants serve as effective anticancer agents with minimal side effects. Among natural compounds, flavonoids have been reported as effective anticancer agents. In this study, two flavonoids, viscosine and quercetin 7-rutinoside, were evaluated for their antitumor potential using in silico models. These flavonoids were tested for their inhibitory activity against DEAD-box RNA helicase DDX3X (referred to as DDX3) and B-cell lymphoma-extra-large (Bcl-XL) enzymes through molecular docking and dynamic simulation analyses. The docking analysis revealed low docking scores and binding energies for both viscosine and quercetin 7-rutinoside. The overall docking results revealed that the selected flavonoids exhibited a favorable binding affinity for DDX3 and Bcl-$\mathbf{X_L}$. They bind firmly to the key active sites and remain stably within the pocket regions of DDX3 and Bcl-$\mathbf{X_L}$, thereby inhibiting their activity. This data was further supported by the RMSF and RMSD analyses. The preliminary molecular docking and simulation analyses confirm the promising inhibitory effects of viscosine and quercetin 7-rutinoside against DDX3 and Bcl-$\mathbf{X_L}$. Therefore, these flavonoids could serve as potential antitumor drug candidates in the future. However, further experimental studies are needed to validate their potential for clinical trials.

Keywords Flavonoids · Viscosine · Quercetin 7-rutinoside · Chemotherapy · DDX3X · Bcl-$\mathbf{X_L}$ apoptosis

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Advances in liposomes loaded with photoresponse materials for cancer therapy

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Photoresponsive nanomaterials
Delivery system
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ABSTRACT

Cancer treatment is presently a significant challenge in the medical domain, wherein the primary modalities of intervention include chemotherapy, radiation therapy and surgery. However, these therapeutic modalities carry side effects. Photothermal therapy (PTT) and photodynamic therapy (PDT) have emerged as promising modalities for the treatment of tumors in recent years. Phototherapy is a therapeutic approach that involves the exposure of materials to specific wavelengths of light, which can subsequently be converted into either heat or Reactive Oxygen Species (ROS) to effectively eradicate cancer cells. Due to the hydrophobicity and lack of targeting of many photoresponsive materials, the use of nano-carriers for their transportation has been extensively explored. Among these nanocarriers, liposomes have been identified as an effective drug delivery system due to their controllability and availability in the biomedical field. By binding photoresponsive materials to liposomes, it is possible to reduce the cytotoxicity of the material and regulate drug release and accumulation at the tumor site. This article provides a comprehensive review of the progress made in cancer therapy using photoresponsive materials loaded onto liposomes. Additionally, the article discusses the potential synergistic treatment through the combination of phototherapy with chemo/immuno/gene therapy using liposomes.

1. Introduction

Cancer remains a major health crisis affecting mankind. Over the next 20 years, the number of cancer cases worldwide is projected to increase by approximately 50% [1]. While chemotherapy (CT), radiation therapy (RT) and surgical treatment are commonly used to treat cancer, these methods often come with side effects. Long-term monotherapy with chemotherapy drugs is often limited by therapeutic efficacy, drug resistance, metastasis, and adverse side effects [2]. Radiation therapy can damage normal cells, leading to side effects such as secondary cancers, blisters, and other skin problems [3–5]. Surgical treatment is both risky and traumatic for the patient, and it is also prone to complications [6]. However, due to the unclear etiology of certain tumors, it is difficult to cure completely. Moreover, the proliferation of malignant tumors can lead to disturbances in normal physiological functions of the body, such as the inability of the immune system to initiate normal immune processes to suppress tumor growth. Tumor drug resistance is perhaps the greatest challenge in the treatment of late-stage cancer. The reasons leading to tumor drug resistance can be divided into the following aspect: tumor heterogeneity, undruggable

Abbreviations: CT, chemotherapy; RT, radiation therapy; PTT, photothermal therapy; PDT, photodynamic therapy; EPR, enhanced permeabilityand retention; PTCAs, photothermal conversion agents; PEG, polyethylene glycol; UV, unilamellar vesicles; LUV, large unilamellar vesicles; GUV, giant unilamellar vesicles; MLV, multilamellar vesicles; ROS, reactive oxygen species; LDDS, Liposomal drug delivery systems; VEGF, vascular endothelial growth factor; NIR, Near Infrared; PTAs, photothermal agents; ICG, Indocyanine green; PA, photoacoustic; LSPR, local surface plasmon resonance; NPs, nanoparticles; GA, gambogic acid; HSP90, heat shock protein 90; CNTs, carbon nanotubes; GO, graphene oxide; CDs, carbon dots; RGO, graphene oxide.; DOX, Doxorubicin; PL, peptide lipid; SL, sucrose laurate; SiRNAs, small interfering RNAs; PSs, photosensitizers; ACQ, aggregation-induced quenching; BP, bis-pyrene; TME, tumor microenvironment; CAT, catalase; GSH, glutathione; TAMs, Tumor-associated macrophages; TAAs, tumor-associated antigens; IERL, immune-enhancing liposome; UCNPs, upconversion nanoparticles; ITH, intratumor heterogeneity; ILPCR, immunoliposome polymerase chain reaction; ILPCR, immunoliposome polymerase chain reaction.; CSCs, cancer stem cells.

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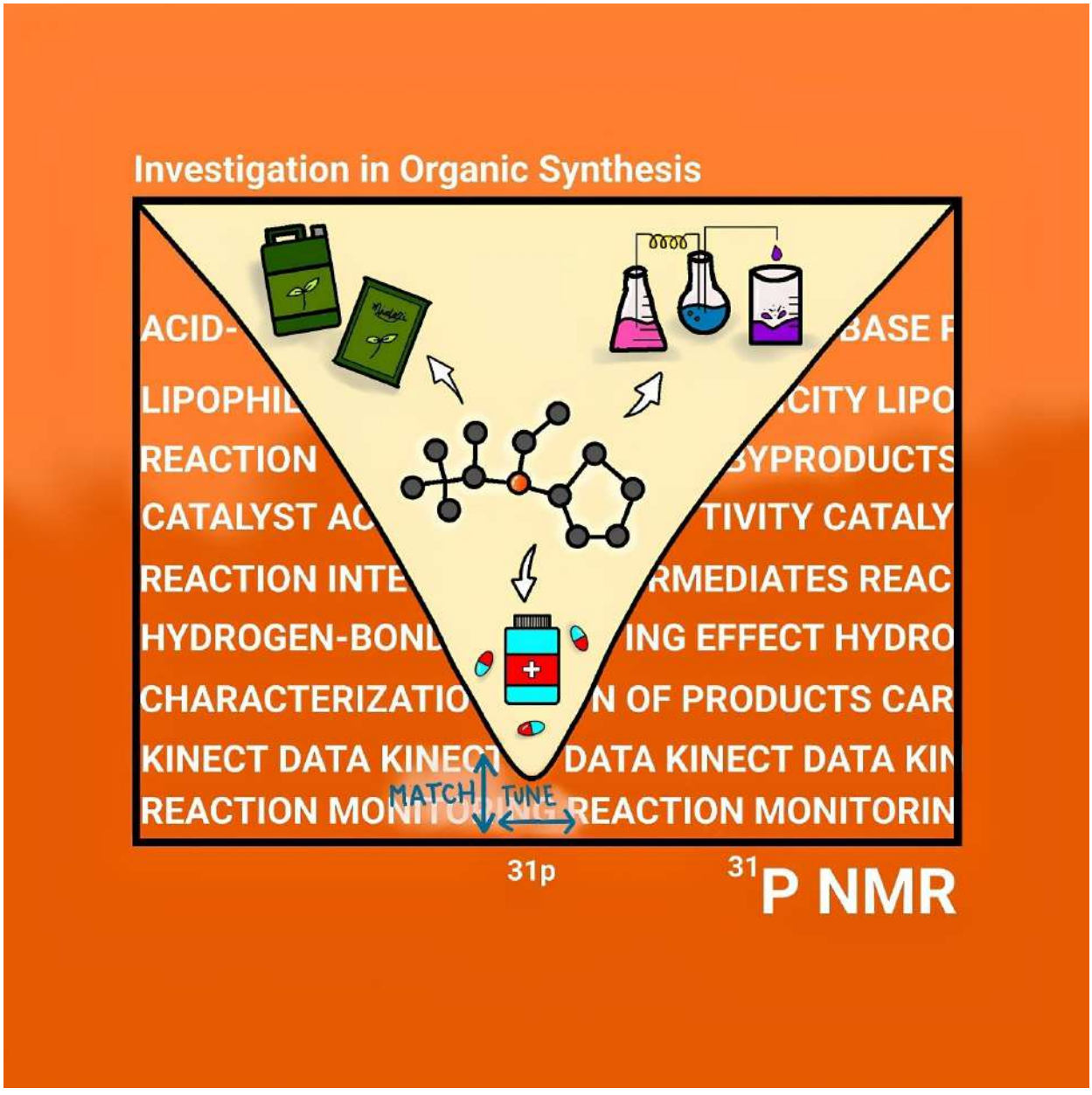
THE CHEMICAL RECORD

^{31}P Nuclear Magnetic Resonance Spectroscopy for Monitoring Organic Reactions and Organic Compounds

João Marcos Anghinoni, Irum, Haroon Ur Rashid, Eder João Lenardão,* and Márcio Santos Silva*[a]



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Research Article

Muhammad Kashif, Sumaira Naz, Muhammad Zahoor*, Syed Wadood Ali Shah, Jalal Uddin, Muhammad Esa, Haroon ur Rashid, Riaz Ullah, Amal Alotaibi

Antioxidant and antidiabetic potentials of methoxy-substituted Schiff bases using *in vitro*, *in vivo*, and molecular simulation approaches

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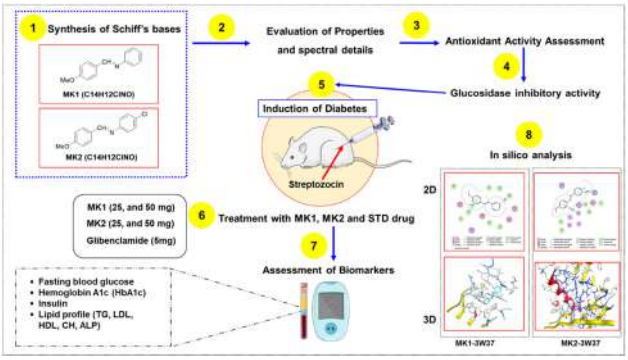
received June 1, 2024; accepted August 27, 2024

Abstract: The current study attempted to synthesize methoxy-substituted Schiff's bases, namely MK1 and MK2, and evaluate their antidiabetic effects using *in vitro*, *in vivo*, and molecular docking studies. Experimental animals (rat model) received the synthetic compounds, MK1 and MK2, orally in doses of 25 and 50 mg/kg body weight, respectively. When comparing compound MK2 at the tested doses to glibenclamide on day 28, the diabetic rats' blood glucose levels were nearly normal (139.02 and 121.23 mg/dL at 25 and 50 mg/kg body weight doses). The IC_{50} for MK1 against α-glucosidase inhibitory potential was found to be 281.29 μg/mL, while for MK2, it is reported to be 204.69 μg/mL. Furthermore, the acute toxicity, lipid profile, and its effect on blood biochemical parameters were also examined. In addition, through *in silico* analysis, the binding of MK1 and MK2 was elucidated with α-glucosidase enzyme, showcasing its antidiabetic mechanism at molecular levels. The *in silico* studies also predicted the two compounds to be inactive toward the human hERGs cardiac potassium channel, which indicates no potential risk of cardiac toxicity. Overall, the toxicity predictions suggest that compounds MK1 and MK2 are non-toxic and non-carcinogenic.



Graphical abstract

Keywords: Schiff's bases, antidiabetic potential, diabetes, glibenclamide

1 Introduction

Diabetes mellitus (DM), one of the metabolic illnesses, is characterized by a persistent increase in the level of blood glucose [1]. This is associated with the interruption of the metabolism of carbohydrates, proteins, and lipids. This variation in metabolism arises due to the low amount of insulin production from the pancreas or because the body does not use the insulin produced [2]. It ranks among the top ten causes of adult mortality, accounting for an estimated four million deaths globally in 2023 [3]. The biomarkers of diabetes include fasting blood sugar, hemoglobin A1c (HbA1c), insulin, β-cell function markers (e.g., HOMA-B), triglycerides (TG), lipid profile, and inflammatory

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Research Article

Gulab Said, Waqas Ahmad, Muhammad Tariq Jan, Muhammad Zahoor*, Azmat Ullah, Riaz Ullah, Muhammad Naveed Umar, Zafar Iqbal and Haroon ur Rashid

Removal of metaldehyde pesticide from aquatic media using modified cellulose obtained from *Populus nigra* plant, as potential adsorbent

https://doi.org/10.1515/pac-2024-0234

Abstract: In this study modified cellulose based adsorbent was prepared from *Populus nigra* plant, and used for elimination of metaldehyde (herbicide) from model waste water. The adsorbent was characterized through analytical technique such as FTIR, SEM, EDX and XRD for structural adsorption related parameters. The results of SEM showed the suitability of the material to be used as adsorbent and FTIR showed successful crosslinking of polyvinyl alcohol into cellulose structure. In order to get maximum reclamation benefits from adsorbent it was subjected to a number of tests evaluating the effect of metaldehyde concentration, sorbent dose, contact time, initial pH of solution and temperature. The maximum removal of 70 % was achieved under conditions of 80 mg/L metaldehyde concentration, 60 min contact time, pH of 8, 0.08 g sorbent dosage, and room temperature (25 °C). The Langmuir isotherm model with correlation coefficients of 0.9855 and maximum adsorption capacity recorded was 8.32 mg/g, while excellent agreement was shown by kinetic data with pseudo second order kinetic model with R^2 = 0.9876. Thermodynamic study indicated enthalpy change ($\Delta H°$ = –129 kJ/mol) to be negative, entropy change ($\Delta S°$ = 161.7 j/mol) positive, and the Gibbs free energy (ΔG) as negative showing that the process to be exothermic and feasible/spontaneous with an increase of randomness at solid liquid interface. The finding indicated that modified cellulose could be used as an efficient adsorbent for removal of metaldehyde from model waste water. However, further validation with other pollutants will be helpful in checking reproducibility of the present findings.

Keywords: Acetylated cellulose; isothermal study; kinetic study; metaldehyde; polyvinyl alcohol; *Populus nigra*.

Introduction

The increase in demand of food due to increasing world population have led to increased agriculture activities which in turn have increased the use of herbicides globally. There are different types of herbicides used to increase crops production. However, many of these herbicides are persistent and remains intact in different

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Research Article

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Homology modeling and molecular docking study of corticotrophin-releasing hormone: An approach to treat stress-related diseases

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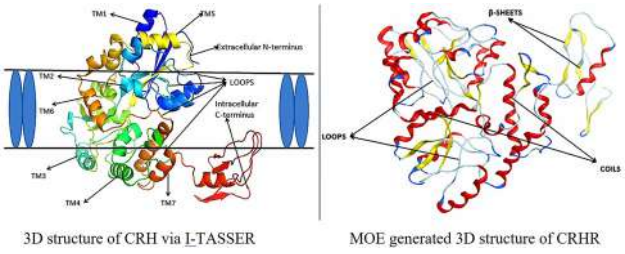
Abstract: Corticotropin-releasing hormone receptors (CRHRs), also termed corticotropin-releasing factor receptors, are linked to G-protein-coupled receptor class. Corticotropin-releasing hormone (CRH) is medically significant in stress, immune response, gastrointestinal motility, and eating patterns. It serves as a releasing hormone and is encoded by the CRH gene. It has been established that there are two subtypes of CRHRs: CRH1-R and CRH2-R. These receptors, representing types 1 and 2, respectively, play a crucial role in regulating biological functions triggered by CRH. To treat stress-related gut abnormalities and stress-related disorders, regulation and optimization of CRH1-R and CRH2-R have turned into a novel idea. The three-dimensional (3D) structure of CRH is not completely recognized, and it is believed that the peptide key unit is helical and both the ultimate edges are relatively unsaturated. We can envisage its 3D structure from the amino acid order of a model protein by homology modeling procedures using Molecular Operating Environment and the Iterative Threading Assembly Refinement program. The assessment and authentication of the 3D structure were performed with RAMPAGE and ERRATE online servers. Utilizing the 3D structure of the target protein and predictions of its active site assists us in the development of new drug candidates aimed at treating disorders associated with stress. CRHR was docked with 19 CP376395 analogs acting as antagonists.



Graphical abstract

Keywords: homology modeling, molecular docking, corticotrophin, adenylate cyclase, nucleotides

1 Introduction

G-protein-coupled receptors (GPCRs) facilitate most of our biological feedback to neurotransmitters, hormones, and environmental stimulants, and so they possess a significant potential to act as therapeutic targets for a variety of diseases. [1]. The structure of GPCRs is usually comprised of seven α-helical transmembrane (TM) domains, an intracellular C-terminus, and an extracellular N-terminus [2,3]. Hydrophobic seven TM helical central core domain is linked by three intracellular and three extracellular loops. In extracellular loops 1 and 2, two cysteine residues are conserved to form a disulfide bridge, which is important for the stabilization and packing of a restricted number of conformations of seven TMs [4,5]. They are included in the cell membranes of a wide range of organisms including invertebrates, microorganisms, plants, and mammals [6,7]. All types of GPCRs share a common membrane topology, the

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Nasir Ahmad, Khalid Khan*, Haroon ur Rashid*, Sher Wali Khan, Muhammad Naveed Umar, Naila Gulfam, Muhammad Zahoor*, Riaz Ullah and Essam A. Ali

Homology modeling and molecular docking study of metabotropic glutamate receptor 5 variant F: an attempt to develop drugs for treating CNS diseases

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Abstract: G protein-coupled receptors (GPCRs) constitute the largest protein family involved in signal transduction and are the main targets for drug delivery. The metabotropic glutamate receptors (mGluRs) are class C of GPCRs that contribute to the modulation of glutamatergic neurotransmission which regulates vital physiological processes and is recognized as a potential therapeutic target throughout the central nervous system. Intracellular C-terminal domains of mGluR are the main targets for proteins regulating these receptors and are also involved in alternative splicing, regulation by phosphorylation, and modulatory protein-protein interactions. Class C of GPCRs exist as dimers and is mediated by interactions

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ARTICLE

Molecular Mechanisms of Buzhong Yiqi Decoction in the Treatment of Gastric Cancer: A Network Pharmacology, Molecular Docking, and In Vitro Experimental Analysis

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Keywords: Buzhong Yiqi decoction | experimental verification | gastric cancer | molecular docking | molecular mechanisms | network pharmacology

ABSTRACT

Gastric cancer (GC) is the most common type of cancer of the digestive system with high morbidity and mortality. Chemotherapy and targeted therapy are used to treat patients with advanced GC. However, side effects and drug resistance to the two modalities remain the main challenges. The Buzhong Yiqi decoction (BZYQD), a classical traditional Chinese medicine formula, has been reported for the treatment of various types of cancers. However, the underlying pharmacological mechanism has not been fully elucidated. Therefore, this study integrated network pharmacology, molecular docking, cancer public databases, and cell experiments to explore the potential bioactive compounds and BZYQD's mechanism of action against GC. A total of 245 targets of BZYQD, 5291 GC-related targets, and 186 were identified as their common targets through the database. Network analysis confirmed AKT1, TP53, TNF, and EGFR to be the core targets, while the main compounds observed were quercetin, kaempferol, and β-Sitosterol. The core signaling pathways included PI3K-AKT, MAPK, TNF, and IL-17. Molecular docking revealed good binding activity for the main compounds and core targets. Based on the database's validation of core targets, a large number of core genes were verified to be consistent with this study. Quercetin, kaempferol, and β-Sitosterol were found to significantly reduce the growth of GC cells in the MTT experiment. The current study revealed that BZYQD may inhibit GC progression by interfering with core targets such as AKT1, TP53, TNF, EGFR, and MAPK3, and by regulating the activity of PI3K-AKT, MAPK, TNF, and IL-17 signaling pathways.

1 | Introduction

Gastric cancer (GC) is one of the most prevalent malignancies and the world's fourth-leading cause of cancer-related deaths. The occurrence and progression of GC are influenced by several factors, including family genetic history, irregular diet, excessive alcohol consumption, and Helicobacter pylori infection. Current statistics indicate that morbidity and mortality rates are elevated in many countries [1]. Additionally, GC stands as the second-leading cause of cancer morbidity and mortality in China. In comparison to the developed countries, China exhibits higher 5-year incidence (27.6/100,000) and mortality/incidence ratio (0.845) rates. Furthermore, the incidence of early-onset gastric cancer (EOGC) in the young

Panke Zeng and Xinyu Wu shared the first authorship.

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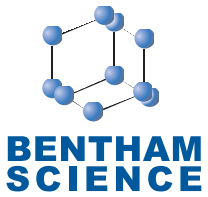

Recent Advances on the Antimicrobial Activities of Schiff Bases and their Metal Complexes: An Updated Overview

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Abstract: Schiff bases represent a valuable class of organic compounds, synthesized *via* condensation of primary amines with ketones or aldehydes. They are renowned for possessing innumerable applications in agricultural chemistry, organic synthesis, chemical and biological sensing, coating, polymer and resin industries, catalysis, coordination chemistry, and drug designing. Schiff bases contain imine or azomethine (-C=N-) functional groups which are important pharmacophores for the design and synthesis of lead bioactive compounds. In medicinal chemistry, Schiff bases have attracted immense attention due to their diverse biological activities. This review aims to encompass the recent developments on the antimicrobial activities of Schiff bases. The article summarizes the antibacterial, antifungal, antiviral, antimalarial, and antileishmanial activities of Schiff bases reported since 2011.

Keywords: Schiff base, antimicrobial activity, imine, azomethine, antibacterial, antifungal, antiviral, antimalarial.

1. INTRODUCTION

Schiff bases are a class of nitrogenous organic compounds that have a general structure R-CH=N-R', where R and R' can be an alkyl or aryl group, linear or cyclic, which can be substituted in many ways [1-3] They can be considered a subclass of imines, being secondary ketamines (when both R and R' are different from H) and secondary aldimines (when R or R' is an H atom), depending on the presented structure [1, 2, 4, 5].

In the literature, they are considered synonyms for imines (>C=N-) and azomethines (or secondary aldimines, -HC=N-), as they are also known [1, 4-8]. They received this name because of Hugo Schiff (1834-1915), an Italian-German chemist laureated with the Nobel Prize and brother of the physiologist Moritz Schiff [1, 2, 4]. Hugo Schiff also discovered other imines, in addition to studying aldehydes, which led to the development of the Schiff reagent, for the identification of these compounds, which consists of a colorless solution containing an indicator produced by the reaction between pararosaniline with sulfite in an acid medium [5, 6].

The formation reaction of a Schiff base is presented according to the Schiff methodology (Fig. **1**). They can be synthesized from an aliphatic or aromatic primary amine (of the type R-NH_2 or Ar-NH_2), with an active

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Integrating network pharmacology and experimental verification to investigate the pharmacological mechanisms of Buzhong Yiqi decoction in the treatment of non-small cell lung cancer

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Abstract

Among all types of cancers, non-small cell lung cancer (NSCLC) exhibits the highest mortality rate with a five-year survival rate below 17% for patients. The Buzhong Yiqi decoction (BZYQD), traditional Chinese medicine (TCM) formula, has been reported to exhibit clinical efficacy in the treatment of NSCLC. Nevertheless, the underlying molecular mechanism remains elusive. This study aimed to assess the mechanistic actions exerted by BZYQD against NSCLC using network pharmacological analysis and experimental validation. The public databases were searched for active compounds in BZYQD, their potential targets, and NSCLC-related targets. The protein–protein interaction (PPI) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed to predict the core targets and signaling pathways of BZYQD against NSCLC. After screening, this study validated the results of predictions through in vitro experiments and public databases. We found 192 common targets between BZYQD and NSCLC. KEGG analysis showed that the anti-NSCLC effects of BZYQD were mediated through the PI3K-AKT signaling pathway. The results of in vitro experiment indicated that BZYQD could inhibit cell viability and proliferation of A549 and H1299 cells apart from inducing cell apoptosis. In addition, western blot results substantiated that BZYQD could treat NSCLC by inhibiting the activation of the PI3K-AKT signaling pathway. The current study investigated the pharmacological mechanism of BZYQD against NSCLC via network pharmacology and in vitro analyses. Overall, the results revealed that BZYQD could be a promising therapeutic agent for the treatment of NSCLC in the future. Still, more experimental investigations are needed to confirm the applicability of BZYQD for clinical trials.

KEYWORDS

Buzhong Yiqi decoction, experimental verification, network pharmacology, non-small cell lung cancer, PI3K-AKT signaling pathway

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Homology Modeling of Alpha-Glucosidase from *Candida albicans*: Sequence Analysis and Structural Validation Studies *in silico*

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The alpha-glucosidase enzyme of *Candida albicans* plays a vital role in the pathogenesis of candidiasis, a serious fatal disease in immune-compromised patients. The unavailability of the three-dimensional crystallographic structure of this enzyme creates a hindrance in developing novel and potent inhibitors. Here, an attempt has been made to design a stable three-dimensional conformer of alpha-glucosidase through *in silico* analysis which may be helpful for the designing of effective drugs. For this purpose, the oligo-1-6-glucosidase enzyme is used as a template for homology modeling of the alpha-glucosidase structure by Molecular Operating Environment 2011-12 software. The generated model was validated through ERRAT and Ramachandran tools, whereas its stability was studied through the molecular dynamics simulation technique. The obtained results indicate that model of alpha-glucosidase has stable secondary and tertiary arrangements. This finding may spur new directions for the rational designing and development of new antifungal inhibitors. Nevertheless, additional experimental investigations and validation are needed to confirm the *in silico* results of this study.

Keywords: alpha-glucosidase, candidiasis, homology modeling, simulations

Introduction

The infections associated with the fungus have been enhanced at a large scale which leads to the enhancement of the mortality rate in humans. The species of *Candida* are mostly human pathogens responsible for infections of deep tissues and mucosa. The species of candida are related to the microbiota of a patient mucosal oral cavity vagina and gastrointestinal tract;[1] and cause different diseases ranging from an overgrowth of mucocutaneous to the infections of blood[2] which include candidemia a major disease that causes death. Candidiasis is included among the infections of *Candida* species.[3] *Candida* infection may present as angular cheilitis, acute pseudomembranous, acute atrophic, chronic atrophic, or chronic hyperplastic candidiasis. There are many reasons like diabetes, malignancies, and weak immunity which strengthen oropharyngeal candidiasis. Denture stomatitis and oropharyngeal candidiasis are caused by *Candida albicans*. The occult esophageal infection and oral fungal disease are linked with each other while the past study of odynophagia warned medical scientists about the development of systemic candidiasis.[4] Normally, healthy humans also carry the above-mentioned fungus but they caused disease in human immunodeficiency virus (HIV) patients because they have weak immunity. The composition of the genus involved a diverse group that included 17 different *Candida* species which cause infection in humans about 90% of infections are caused by *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*,

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Research Article

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Synthesis, characterization, *in silico* and *in vitro* studies of novel glycoconjugates as potential antibacterial, antifungal, and antileishmanial agents

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Abstract: In the present work, several new glycoconjugates (**8a–e**) were generated from glycopyranosyl-α-trichloroacetimidates (sugar-OTCA) as glycosyl donors and dimethyl-L-tartrate as an aglycone acceptor in good to excellent yields. In the synthetic protocol, various monosaccharides were transformed into pentaacetylated derivatives and then into glycopyranosyl-α-trichloroacetimidates. Afterward, the sugar-OTCA was reacted with dimethyl-L-tartrate using Schmidt's trichloroacetimidate protocol to give the desired products. The newly synthesized glycoconjugates were characterized by FT-IR, ^{1}H, and ^{13}C-NMR spectroscopic analytical methods. All the target compounds (**8a–e**) were tested *in vitro* against various strains of bacteria and fungi at different concentrations. The results revealed that the target compounds had encouraging antibacterial and antifungal potential. The antileishmanial activity of the target compounds against Leishmania tropica promastigotes was also investigated. The *in vitro* results were further supported by the *in silico* docking study that indicated minimum values of the docking scores and binding energies for the resulting complexes obtained by the favorable interactions between the target compounds (**8a–e**) and the selected strains of bacteria and fungi. The docking results proposed promising antibacterial and antifungal activities of the target compounds (**8a–e**) against the selected bacterial and fungal species.

Keywords: glycoconjugates, glycopyranosyl-α-trichloroacetimidates, glycosylation, antimicrobial, antileishmanial, molecular docking

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1 Introduction

Carbohydrates (biomolecules) are often found attached to other biomolecules that constitute glycoconjugates. Glycolipids and glycoproteins are normally found on cell surfaces that act as receptors for cell–cell determination and are involved in cell growth, repair adhesion, migration, and tumor metastasis in cancer [1]. Vaccination is one of the most cost-effective ways and a key strategy for controlling various infectious diseases

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Biological investigations of *Aspergillus ficuum* via in vivo, in vitro and in silico analyses

Zafar Ali Shah[1], Khalid Khan[1]✉, Tanzeel Shah[2], Nasir Ahmad[1], Akhtar Muhammad[1] & Haroon ur Rashid[3,4]✉

Serious human health impacts have been observed worldwide due to several life-threatening diseases such as cancer, candidiasis, hepatic coma, and gastritis etc. Exploration of nature for the treatment of such fatal diseases is an area of immense interest for the scientific community. Based on this idea, the genus *Aspergillus* was selected to discover its hidden therapeutic potential. The genus *Aspergillus* is known to possess several biologically active compounds. The current research aimed to assess the biological and pharmacological potency of the extracts of less-studied *Aspergillus ficuum* (FCBP-DNA-1266) (*A. ficuum*) employing experimental and bioinformatics approaches. The disc diffusion method was used for the antifungal investigation, and the MTT assay was performed to assess the anticancer effects. Mice were employed as an in vivo *model* to evaluate the antispasmodic effects. A standard spectrophotometric technique was applied to gauge the urease inhibitory activity. The antifungal studies indicate that both n-hexane and ethyl acetate extracts were significantly active against *Candida albicans* (*C. albicans*) with their zone of inhibitions (ZOI) values reported as 19 ± 1.06 mm and 25 ± 0.55 mm, respectively at a dose of 30 µg.mL^{-1}. In vitro cytotoxicity assay against HeLa, fibroblast 3T3, prostate PC3, and breast MCF-7 cancer cell lines was performed. The ethyl acetate extract of *A. ficuum* was found to be significantly active against MCF-7 with its IC_{50} value of 43.88 µg.mL^{-1}. However, no substantial effects on the percent cell death of HeLa cancer cell lines were observed. In addition, the *A. ficuum* extracts also inhibited the urease enzyme compared to standard thiourea. The antispasmodic activity of *A. ficuum* extract was assessed by an in vivo model and the results demonstrated promising activity at 150 mg.kg^{-1}. Molecular docking results also supported the antifungal, anticancer, and antiurease potency of *A. ficuum* extract. Overall, the results display promising aspects of *A. ficuum* extract as a future pharmacological source.

New drugs are needed due to certain factors such as globalization, the aging population, and microbial resistance to existing medicines. Only a small number of biologically active compounds are currently used in prescription drugs[1]. Scientists are currently investigating emerging diseases to gain a better understanding of them and find their potential cures using various natural and chemical formulations. However, there are still many areas that remain unexplored due to insufficient knowledge and techniques. To find new bioactive compounds that can be used for medicinal, agricultural, and industrial purposes, researchers are focusing on isolating such compounds from new species of fungi[2].

In recent times, researchers have isolated several metabolites from fungi, including anthraquinones, alkaloids, terpenes, steroids, flavonoids, and cyclic peptides. Some secondary metabolites produced by various fungi have been found to exhibit potent biological activities such as antifungal, antitumor, anti-inflammatory antibacterial, antiparasitic, and antiviral properties. The chemical diversity of fungal secondary metabolites provides a significant advantage for the development of new drugs[3,4].

Anofinic acid, a potent active metabolite produced by *Aspergillus tubingensis*, has shown strong antimicrobial activity against a variety of hazardous bacteria in addition to its potent activity against various carcinoma cells, including Hep-G2, MCF-7, and HCT-116[2]. Sorbicillinoids possess the capability to be used as pharmaceutical and agrochemical agents due to their antiviral, antimicrobial, and anticancer effects besides their use as food

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Evaluation of potential bacterial protease inhibitor properties of selected hydroxyquinoline derivatives: an *in silico* docking and molecular dynamics simulation approach

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ABSTRACT

Antimicrobial drug resistance (AMR) is a severe global threat to public health. The increasing emergence of drug-resistant bacteria requires the discovery of novel antibacterial agents. Quinoline derivatives have previously been reported to exhibit antimalarial, antiviral, antitumor, antiulcer, antioxidant and, most interestingly, antibacterial properties. In this study, we evaluated the binding affinity of three newly designed hydroxyquinolines derived from sulfanilamide (**1**), 4-amino benzoic acid (**2**) and sulfanilic acid (**3**) towards five bacterial protein targets (PDB ID: 1JIJ, 3VOB, 1ZI0, 6F86, 4CJN). The three derivatives were designed considering the amino acid residues identified at the active site of each protein involved in the binding of each co-crystallized ligand and drug-likeness properties. The ligands displayed binding energy values with the target proteins ranging from −2.17 to −8.45 kcal/mol. Compounds (**1**) and (**3**) showed the best binding scores towards 1ZI0/3VOB and 1JIJ/4CJN, respectively, which may serve as new antibiotic scaffolds. Our *in silico* results suggest that sulfanilamide (**1**) or sulfanilic acid (**3**) hydroxyquinoline derivatives have the potential to be developed as bacterial inhibitors, particularly MRSA inhibitors. But before that, it must go through the proper preclinical and clinical trials for further scientific validation. Further experimental studies are warranted to explore the antibacterial potential of these compounds through preclinical and clinical studies.

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Antibacterial agents; hydroxyquinolines; molecular docking; ADMET; drug-likeness; *in silico*

Introduction

Infections remain one of the major threats to human health, and combatting infectious diseases has become a challenge worldwide (M. S. Hossain et al., 2021; S. Hossain et al., 2021; Sharma et al., 2018; Urbi et al., 2021). The human and economic costs of infections caused by bacteria, in particular, are a growing cause of concern (Muthukumar et al., 2019). Several bacterial pathogens have developed resistance to antibiotics, including strains identified as multi- or extensively-drug-resistant (El Faydy et al., 2017; Karuniawati et al., 2021). The Gram-positive bacterium Methicillin-resistant *Staphylococcus aureus* (MRSA) can cause skin, soft tissue, bone, joint infections, endocarditis and septicemia is a typical example of a drug-resistant microorganism (Qiu et al., 2001; Solomon & Oliver, 2014; Tjampakasari et al., 2021). Gram-negative bacteria also cause significant morbidity and mortality worldwide; several strains have also become drug-resistant (Breijyeh et al., 2020).

Staphylococcus aureus infections are a global concern due to their high rate of developing antimicrobial resistance (AMR), limiting therapeutic options and healthcare-associated infections. The all-cause mortality rate, particularly from *S. aureus* bacteremia in the developed countries, reached up to 20–30%, with even over 50% rates in some less- and average-developing countries (Nakajima et al., 1978). The leading cause of AMR development is either one of them: (i) alteration of target, (ii) inactivation of antibiotic, (iii) bypass antibiotic and (iv) restricted antibiotic accumulation. Additionally, this process accelerated because of the misuse and overuse of antibiotics and poor infection prevention and control (Karuniawati et al., 2021; WHO, 2020). There are multiple enzymes involved in the development of AMR. For example,

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RESEARCH

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Insights into metabolic and pharmacological profiling of *Aspergillus ficuum* through bioinformatics and experimental techniques

Zafar Ali Shah[1,2], Khalid Khan[1*], Haroon Ur Rashid[3], Tanzeel Shah[4], Mariusz Jaremko[5*] and Zafar Iqbal[2]

Abstract

Background: Recently, numerous novel bioactive fungal metabolites have been identified that possess broad therapeutic activities including anti-inflammatory, antibiotic, antioxidant, and antitumor. The fungal mycochemicals as well as extracts have increased the interest of the scientific community in drug discovery research through a combination approach such as, molecular metabolic, pharmacological and computational techniques. Therefore, the natural fungus *Aspergillus ficuum* (*A. ficuum*) (FCBP-DNA-1266) was selected for metabolic and pharmacological profiling in this study.

Results: The metabolic profile of *A. ficuum* was explored for the first time and revealed the presence of bioactive compounds such as choline sulfate, noruron, hydroxyvittatine, aurasperone D, cetrimonium, kurilensoside, heneicosane, nonadecane and eicosane. Similarly, a pharmacological screen of *A. ficuum* was performed for the first time in *in vivo* and *in vitro* models. Interestingly, both the ethyl acetate and n-hexane fractions of *A. ficuum* were found to be more active against *Bacillus subtilis* among five tested bacteria with their zone of inhibition (ZOI) values of 21.00 mm ±1.00 and 23.00 mm ±1.00, at a concentration of 150 μgmL^{-1} respectively. Similarly, a significant decrease ($P<0.001$) and ($P<0.01$) in paw edema was observed in *A. ficuum*-treated animals at doses of 50 and 150 $mgkg^{-1}$, respectively, reflecting its potent anti-inflammatory effect. Furthermore, the docking results supported the antibacterial and anti-inflammatory effects of *A. ficuum*. In addition, the crude extract demonstrated no acute toxicity and the highest percent radical scavenging was recorded for both n-hexane and ethyl acetate extracts.

Conclusion: The metabolic profile of *A. ficuum* indicated the presence of biological relevant compounds. *A. ficuum* extract exhibited potent antibacterial and anti-inflammatory effects supported by docking results. Furthermore, *A. ficuum* extract demonstrated the highest percentage of radical scavenging activity along with no acute toxicity.

Keywords: Metabolic Profiling, Pharmacological screening, Molecular docking, *Aspergillus ficuum*

Introduction

Human life is under threat worldwide as mortality increases in developing countries. The spread and development of infectious diseases and drug-resistant pathogens has stimulated the search for new pharmaceutical agents [1]. The development of novel bioactive drugs is not only required against microbial resistance but also very important to overcome degenerative diseases. As a

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Research

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Synthesis of novel silica encapsulated spiropyran-based thermochromic materials

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A series of novel spiropyrans were synthesized through the condensation of substituted 3,3-dimethyl-2-methyleneindoline with different nitro-substituted *o*-hydroxy aromatic aldehydes. Indoles were initially substituted with a variety of alkanes and esters moieties. The substituted 3,3-dimethyl-2-methyleneindoline was then reacted with nitro-substituted *o*-hydroxy aromatic aldehydes to yield the respective spiropyrans. The synthesized novel spiropyrans were encapsulated in silica nano-shells to protect them from the effect of moisture and pH. The thermochromic behaviour of novel spiropyrans was studied by UV-visible spectroscopy. The thermally induced isomerization of spiropyran derivatives was carried out in a water/ethanol mixture. The thermal isomerization of spiro-heterocyclic (colourless form) to merocyanine (MC) (coloured form) was a discontinuous process and was observed in a temperature range of 5–60°C via UV-visible spectrometer. The absorption process occurs reversibly regardless of the heating/cooling sequence. The spiropyran derivatives, therefore, have a potential application for colorimetric temperature indication.

1. Introduction

The phenomenon of thermochromism has been known since 1926 when the reversible colour change was observed with temperature [1]. Therefore, thermochromism can be defined as the reversible thermo-transformation of chemical species between two forms

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Molecular docking and dynamic simulations of Cefixime, Etoposide and Nebrodenside A against the pathogenic proteins of SARS-CoV-2

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ABSTRACT

The catastrophe of the coronavirus continues from one part of the world to another, and hardly a country is left without its devastations. Millions of people were infected and several hundred thousand died of the COVID-19 pandemic across the world. There is no clear targeted drug therapy available for the treatment of the patients. The discovery of vaccines is not enough to curtail its spread and disastrous implications. An instantly qualifying approach is needed to utilize the current drugs and isolated compounds. The purpose of this work is to determine potent inhibitors against the target proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For this purpose, molecular docking study of pathogenic spike glycoproteins (S), nucleocapsid phosphoprotein (N), an envelope protein (E), two drugs i.e., cefixime, etoposide, and a previously isolated compound nebrodenside A is performed. Promising results were obtained via complimentary analysis of molecular dynamics (MD) simulations performed for the complexes of three proteins with etoposide drug. Minimum values were recorded for the docking scores and binding energies of the complexes. These results were further supported by the RMSD, RMSF data for the stability of proteins and ligands. Additionally, ligand properties and ligand-protein contacts were also explained with histograms of every simulation trajectory. The computational studies confirmed that cefixime, etoposide, and nebrodenoside A can be used as potent inhibitors of COVID-19. Nevertheless, additional experimental investigations and validation of the selected candidates are mandatory to confirm their applicability for clinical trials.

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Introduction

Coronavirus disease 2019 (COVID-19) is a contagious disease triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was discovered in Wuhan, China, and has since outspread around the world like a pandemic, causing more than 150.6 million infections and about 32 hundred thousand deaths as of May 8, 2021 [1,2]. The World Health Organization called the disorder COVID-19 (coronavirus disease 2019). Genome sequencing reveals high similarity between SARS-CoV-2 and bat coronaviruses (CoV) especially beta-CoV and RaTG13 viruses that cause human diseases such as the Middle East respiratory syndrome (MERS) and the Severe acute respiratory syndrome (SARS) and to a smaller extent HCoV-OC43 and HCoV-HKU1 [3,4]. The nucleocapsid protein, spike (S) protein, envelope (E) protein, membrane (M) protein, and coronavirus key protease participate actively in gene formulation and break polyproteins into replication-associated proteins. They are all encoded in the genome of the new coronavirus (SARS-COV-2) [5]. The SARS-CoV-2 genome, like that of other coronaviruses, encrypt spike (S) glycoproteins, which project from the exterior of grown-up virions. The S glycoprotein is required for virus adhesion, incorporation, and infection of the host cell. The S glycoprotein's external spot makes it a straightforward target for the host immune feedbacks, making it a principal target for compensating the antibodies. The S protein is the subject of several vaccination campaigns and treatments due to its critical role in viral infection and innate immunity [6,7]. The nucleocapsid phosphoprotein (N) is a multifunctional and immunogenic virulence and pathogenicity determinant whose primary roles are oligomerization and packing

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catalysts

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Article

Conditions Optimization and Physiochemical Analysis of Oil Obtained by Catalytic Pyrolysis of Scrap Tube Rubber Using MgO as Catalyst

Riaz Muhammad [1,2,*], Yousaf Ali [1], Younes Messaddeq [3], Haroon ur Rashid [4], Marco Antonio Utrera Martines [4], Muhammad Naveed Umar [5], Sher Wali Khan [6] and Ali Riaz [1,3]

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Abstract: Motor vehicles scrap tires and tube rubbers generate a large amount of waste with different characteristics and compositions, contaminating the environment when not properly disposed. Waste inner tube rubber (isobutylene isoprene) representing a threat to the environment can be used as valuable source of energy. Waste inner tube rubber was pyrolyzed thermally under atmospheric pressure both with and without catalyst. Parameters of temperature, time, and catalyst weight were optimized for catalytic and thermal pyrolysis of isobutylene-isoprene rubber into liquid fuel, using MgO as catalyst. It was found that one-hour heating time at 350 °C using 2 g catalyst (MgO) constitutes a suitable parameter for the maximum conversion of scrap inner tube rubber into oil. The oil obtained was characterized by physical and chemical tests. Among the physical tests, Density, specific gravity, viscosity, kinematic viscosity, analine point and flash point were determined according to IP and ASTM standard valves. The physical tests indicate the presence of aromatic and olefinic hydrocarbons. Among the chemical tests, the phenol test, bromine number, bromine water test, and $KMnO_4$ tests were conducted. The chemical tests are also the support of physical tests conducted. The physical and chemical tests indicate that the oil obtained is a mixture of kerosene, diesel, and light oil and could be used for fuel purposes.

Keywords: pyrolysis; scrap rubber; liquid fuel; magnesium oxide; catalysis

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1. Introduction

Human lifestyle is improving rapidly, resulting in the increased demand for high-end freeways and highways, consequently increasing the demand for motor vehicles around the world. The rapid expansion of automobile business has therefore brought up some environmental drawbacks where handlings of waste tires/tubes are one of the fast-growing issues [1]. European Tyre & Rubber Manufacturers' Association (ETRMA) statistics reported that 1400 million tires are being produced, generating 17 million tons of used tires/tube waste every year [2].

Millions of tires/tubes are either thrown away or buried all over the world which is considered a threat to the ecosystem. As per a concise study, there would be 5000 million tires discarded annually by the year 2030 [3]. These scrap tire/tube rubber due to their

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Research developments in the syntheses, anti-inflammatory activities and structure–activity relationships of pyrimidines†

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Pyrimidines are aromatic heterocyclic compounds that contain two nitrogen atoms at positions 1 and 3 of the six-membered ring. Numerous natural and synthetic pyrimidines are known to exist. They display a range of pharmacological effects including antioxidants, antibacterial, antiviral, antifungal, antituberculosis, and anti-inflammatory. This review sums up recent developments in the synthesis, anti-inflammatory effects, and structure–activity relationships (SARs) of pyrimidine derivatives. Numerous methods for the synthesis of pyrimidines are described. Anti-inflammatory effects of pyrimidines are attributed to their inhibitory response *versus* the expression and activities of certain vital inflammatory mediators namely prostaglandin E_2, inducible nitric oxide synthase, tumor necrosis factor-α, nuclear factor κB, leukotrienes, and some interleukins. Literature studies reveal that a large number of pyrimidines exhibit potent anti-inflammatory effects. SARs of numerous pyrimidines have been discussed in detail. Several possible research guidelines and suggestions for the development of new pyrimidines as anti-inflammatory agents are also given. Detailed SAR analysis and prospects together provide clues for the synthesis of novel pyrimidine analogs possessing enhanced anti-inflammatory activities with minimum toxicity.

1. Introduction

The word inflammation is derived from the Latin "flamma" meaning flame. It is normal feedback of the body to safeguard tissues against disease or infection. The inflammatory reaction initiates with the generation and discharge of chemical agents from the cells in the diseased, infected, or wounded tissue. Inflamed tissues produce extra signals that use leukocytes (white blood cells) at the position of inflammation. Leukocytes damage any infective or harmful agent and eliminate cellular residues from damaged tissue. This inflammatory reaction generally stimulates the curing process. However, an uncontrolled inflammatory response may become detrimental.[1,2] Inflammation represents a portion of the body's immune response. An inflammatory reaction is liable for curing wounds, infections, and any damage to the tissues. Numerous feedbacks produced by the defense mechanism as a response to a physical injury or an infection result in inflammation.[3] Acute inflammation grows rapidly and turns out to be severe in a brief time. Its symptoms continue for a few days but may last for several weeks under certain circumstances. Common indications of acute inflammation include swelling, redness, pain, immovability, and heat. Acute inflammation can be caused by certain conditions and diseases including acute bronchitis, abrasion or cut on the skin, achy throat from flu or cold, infected ingrown toenail, acute appendicitis, sinusitis, tonsillitis, dermatitis, infective meningitis, high-intensity exercise, and physical trauma.[4,5] Chronic inflammation persists for a prolonged duration (for several months and even years) in which active inflammation, tissue damage, and repair occur concurrently. Usually, the extent and effects of chronic inflammation differ with the source of the injury and the efficiency of the body to heal and control the damage. Chronic inflammation is characterized by typical symptoms such as body pain, fever, rash, weight gain or weight loss, fatigue, joint pain, and mouth sores. Chronic inflammation may lead to the progression of certain diseases namely diabetes, cancer, cardiovascular diseases, rheumatoid arthritis, allergies, chronic obstructive pulmonary disease (COPD), tuberculosis, asthma, hepatitis, periodontitis, and chronic peptic ulcer.[1,6] Fig. 1 indicates the health

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RESEARCH ARTICLE

Discovery of Biomarkers in Hepatocellular Carcinoma Metastasis Using Bioinformatic Analysis

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Abstract: ***Background*:** Liver cancer is one of the most deadly malignancies worldwide. Tumor metastasis is the main cause of liver cancer-related death. So far, the mechanism of liver cancer metastasis is far away from fully elucidated. In this study, we aimed to discover key regulators involved in liver cancer metastasis by data mining.

***Methods*:** Two different types of data, including mRNA microarray (GSE6222 and GSE6764) and miRNA microarray (GSE67138), were analyzed. A total of 83 intersectant differently expressed genes (DEGs) with the same expression pattern in GSE6222 and GSE6764 were identified. One hundred and thirty-one differently expressed miRNAs (DEMs) were identified in GSE 67138. Furthermore, a total of 26 pairs of miRNA-target, including 18 DEMs and 13 DEGs were identified as critical miRNA-target axis *via* miRNA-target gene interaction analysis.

***Results and Conclusion*:** Among the 18 DEMs and 13 DEGs, 10 miRNAs and 10 target genes are significantly correlated with patients' survival ($p < 0.05$). Our results and methods might be interesting for data mining and helpful for further experimental functional validation.

Keywords: Bioinformatic analysis, biomarkers, hepatocellular carcinoma, metastasis, liver cancer, key genes.

1. INTRODUCTION

Liver cancer is one of the most prevalent malignancies, which is the fourth common cause of mortality worldwide [1]. Liver cancer presents a heavy burden for many countries due to its high aggressiveness and poor survival. Tumor metastasis is the leading cause of liver cancer-related death [2]. Presently, the mechanism of HCC metastasis has not been fully elucidated. Thus, in-depth understanding of HCC metastasis can be useful in clinical settings for prognosis and treatment.

Aberrant expressions of gene and dysregulated signaling pathways are key hallmarks of cancer. It has been reported that cancer cells may benefit from undesirable changes in microRNAs (miRNAs) [3]. It is well-recognized that miRNAs play a vital role in the cancer metastasis by negatively regulating their target genes [4]. Han reported that miR-532-3p could regulate KIFC1 to promote metastasis in HCC [5]. Xu reported miR-876-5p could inhibit HCC metastasis by targeting BCORL1 [6]. These results implied that the characterization of dysregulated miRNAs and their target genes could uncover potential metastasis biomarkers of HCC.

In recent years, with the rapid development in high-throughput technologies, gene microarray appears to be an effective method for quickly detecting differentially expressed genes (DEGs) between tumor and normal samples [7]. A large number of data have been generated and stored in public platforms, such as the Gene Expression Omnibus (GEO) profiles, which could be accessed for free [8]. Although prognostic biomarkers of HCC have been identified by analyzing datasets from GEO [9], results are always inconsistent due to sample heterogeneity, leading to unreliable results. To get reliable results, an integrated bioinformatics analysis of different types of data could be applied. In the present study, two gene microarray and one miRNA microarray datasets were retrieved and analyzed with R software (version 3.4.4) and Bioconductor packages (http://www.bioconductor.org/) to produce DEGs and DEMs. Then, miRNet and Kaplan-Meier Plotter online databases were used to construct miRNA-protein interactions and predict potential miRNAs-targets pairs in HCC (Fig. **1**). Our results and method might be interesting for data mining and helpful for further experimental functional validation.

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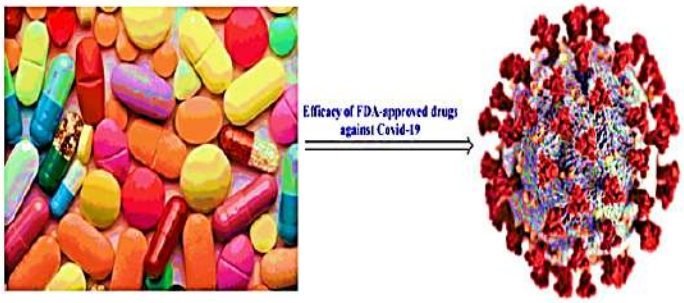
Potential Drug Candidates in Clinical Trials for the Treatment of Covid-19: An Updated Overview

Osmar Ignacio Ayala Cáceres †, Fernanda Timóteo †, Kristiane Fanti Del Pino Santos, Rafael Rodrigo Piva Vasconcelos, Marco Antonio Utrera Martines, Juliana Jorge*, and Haroon ur Rashid*

The coronavirus (SARS-CoV-2) emerged in December 2019 in Wuhan, China and by the end of April 2020, it spread to more than 200 countries worldwide. Particularly the USA, Brazil, Spain, Italy, France, Germany, UK, Turkey, Iran, and Russia were the most affected countries till December 2020. Currently, most of the researchers are in a continuous struggle to develop a vaccine or new drugs to combat Covid-19. There are more than 30 drug candidates including Western medicines, natural products, and traditional Chinese medicines, that have shown to exhibit some efficacy against this highly infectious virus. This review encompasses the potential efficacy of some key drugs recently tested against Covid-19. With the rapid spread of Covid-19 reaching a new level every day, there is an immediate need to find safe and effective measures to diagnose, treat, mitigate, and combat the disease. Looking at the alarming dimensions that the disease is acquiring, treatment strategies among the different drug systems are being investigated. Currently, clinical management includes infection prevention, control measures, and supportive care, including supplemental oxygen and mechanical ventilation when indicated. The pharmaceutical interventions evaluated for the treatment of Covid-19 include human immunoglobulin, interferons, chloroquine, hydroxychloroquine, arbidol, remdesivir, oseltamivir, favipiravir, carrimycin, methylprednisolone, bevacizumab, thalidomide, vitamin C, pyrodfenidone, darthviravir, bromexistone, ryrexavir, lopinavir, xiyanping, and traditional Chinese medicine. But still, the researchers are struggling to discover the most effective drug for the treatment of the current pandemic of Covid-19.

Graphical abstract



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EMODIN-CONTAINING MCM-41 TYPE MESOPOROUS SILICA NANOPARTICLE DRUG DELIVERY SYSTEM

I. M. D. dos Santos[1], S. P. Pereira[1], A. V. Mezacasa[1], O. I. A. Caceres[1], F. Timoteo[1], A. S. Lopes[1], K. F. del Pino[1], A. P. Duarte[1], T. F. M. Cardoso[2], G. R. de Castro[3], H. U. Rashid[1], and M. A. U. Martines[1]

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With the aim of developing drug delivery systems, it was shown that nanoparticles of mesoporous silica molecular sieve MCM-41 with average size 100-150 nm and specific surface 655 m^2/g could include 202 mg of emodin per one gram of the carrier and release more than 85% of this compound at pH 8 during 48 h.

Keywords: *Emodin, anthraquinone, mesoporous silica nanoparticles, drug controlled release system, ultraviolet-visible*

Emodin (Fig. 1), also known as 1,3,8-trihydroxy-6-methyl-anthraquinone, a natural compound extracted from herbaceous plants such as *Reynoutria japonica* and *Rheum officinale,* has been widely used as a traditional medicine in some regions of Asia [1]. It has been reported to possess biological activities such as antibacterial, anti-inflammatory, immunosuppressive, vasodilator, laxative, and antineoplastic [2, 3].

One major drawback of emodin as a biological agent is its low solubility in water [1]. The biological system consists of different types of barriers with hydrophobic or hydrophilic characteristics. The biodistribution of a drug in an organism is related to its capability to pass through tissues containing aqueous and lipidic environments. The majority of drugs are organic and generally have poor water solubility, which in turn interferes with their biodistribution and affects the efficiency of cell delivery [4].

In this perspective, substantial efforts have been made to discover more efficient and suitable liberation system, so that drugs can reach their targets in the estimated time and thus can ensure the desired effects only. Therefore, in pursuit of some potential strategies to promote a long-lasting release of insoluble-water drugs, emodin has been used as a model drug for research on controlled liberation systems (CLS) [5, 6].

The research field of CLS is in focus among the scientific community and is proliferating, with nanotechnology playing a pivotal role in this expansion [7].

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Anti-cancer potential of sophoridine and its derivatives: Recent progress and future perspectives

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ABSTRACT

Cancer is the second leading cause of mortality and has resulted in about 9.6 million deaths around the world in 2018. Cancer-caused deaths are expected to be 11.5 million by 2030 all over the world. Because of the fatal nature of cancer, substantial efforts are made all over the world to combat it. Phytoconstituents such as certain alkaloids, saponins, tannins, polyphenols, and terpenoids exhibit anticancer effects. Sophoridine is a tetracyclic quinolizidine alkaloid isolated from the stem and leaves of medicinal plants *Sophora alopecuroides L.,* and *Euchresta japonica Benth,* and roots of *Sophora alopecuroides Ait.* Chinese Food and Drug Administration (CFDA) approved sophoridine as an antitumor agent in 2005. This review covers the antitumor activities of sophoridine and its derivatives. The efficacy of sophoridine analogs is expressed with respect to their half-maximal inhibitory concentration (IC_{50} values). Structure-activity relationship (SAR) study for most of the sophoridine derivatives has been explained. Moreover, the current market of anticancer drugs and its expected growth are discussed. Prospects provide suggestions and clues for novel sophoridine-based anticancer agents with enhanced expected efficacy and minimum toxicity.

1. Introduction

Cancer represents the uncontrolled division of abnormal body cells. Cancer cells attack or reach to the adjacent healthy tissues of the body via the bloodstream and lymphatic systems, causing malignant tumors. On the contrary, cells in benign tumors neither invade the neighboring tissues nor spread to other body parts. Nearly 90% of cancer-related mortalities are triggered by tumor dispersion, a phenomenon termed as metastasis. (Fig. 1) [1,2] DNA damage is reckoned to be the primary cause of cancer growth. It produces mutations and epimutations, which then lead to cancer progression through the process of natural selection. (Fig. 2) [3] Cancer is the second-highest cause of deaths in the world, only excelled by cardiovascular ailments [4].

According to a recent press release of the International Agency for Research on Cancer (IARC), 18.1 million new cancer cases, and 9.6 million cancer- caused deaths were reported worldwide in 2018 [5]. According to a report from the World Health Organization (WHO), over 70% of the cancer-related mortalities happened in developing countries. Cancer-related deaths will increase and are expected to reach an approximate number of 11.5 million by 2030 all over the world. Major risk factors for cancer include alcohol consumption, smoking, dietary aspects (comprising inadequate vegetables and fruits consumption), obesity, lack of physical activity, exposure to ionizing and non-ionizing radiations, and exposure to toxins, chronic infections from helicobacter pylori, human papillomavirus (HPV), hepatitis B virus (HBV), and hepatitis C virus (HCV) [6].

Approximately 100 kinds of cancer have been recognized, which are characteristically named for the organs or tissues where they arise. Statistics show that prostate and breast cancers are the two principal kinds of cancer identified in males and females, respectively [1,7]. In modern medicine, surgery, radiotherapy, and systemic therapy (such as chemotherapy, immunotherapy, hormonal therapy, and targeted therapy) represent the key modalities applied to treat different types of cancer [8,9]. Owing to the deadly nature of cancer, considerable efforts are made worldwide to combat it by the exploration of novel antitumor agents, which has resulted in a noteworthy success. US Food and Drug Administration (FDA) recommended approximately 150 antitumor drugs from 1949 to 2014. Depending on their mode of action, these drugs have been classified into two sets (a) 61 cytotoxic drugs and (b) 89 target-oriented drugs [10–13]. Selected FDA approved drugs are

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New modification strategy of matrine as Hsp90 inhibitors based on its specific L conformation for cancer treatment

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ABSTRACT

The similarity of spatial structure between radicicol and matrine urged us to perform conformation modification of matrine, followed by L-shaped matrine derivatives, **6**, **12**, **21a-h** and **22a-h** were originally designed, synthesized and evaluated for Hsp90^{N} inhibitors as anticancer agents. TSA (Thermal Shift Assay) results indicated that **21e**, **22a-c** and **22e-g** exhibited strong binding force against Hsp90^{N} with|ΔTm| > 3, meanwhile, MTT assay also revealed these compounds displayed potent anticancer activity with IC_{50} values below 25 μM against HepG2, HeLa and MDA-MB-231 cells lines. Then, compound **22g** with a high ΔTm = 10.92 was chosen as a representative to perform further mechanism study. It can induce cell apoptosis, arrest the cell cycle at the S phase and decrease the expression level of Hsp90 in Hela cell. These results originally provided targeted modification strategy for matrine derivatives to serve as Hsp90 inhibitors for cancer therapy.

1. Introduction

Matrine (Fig. 2**d**), a quinolizidine natural product extracted from *Sophora flavescens* (Kushen),[1–4] was approved by Chinese FDA in 1995 for cancer treatment. Currently, matrine has been widely used to adjuvant treatment of liver cancer, lung carcinoma and gastric cancer with low side effects for many years in China.[5,6] Although large-scale application of matrine with reference to its use for the treatment of cancer was confirmed,[7–11] its activity is moderate, which might be caused by its speculated features such as broad binding sites but low specificity. Thus, enhancing the sensibility and specificity against anticancer targets of matrine attracted our attention. On the other hand, matrine possess many advantages such as high solubility, good safety profiles and a special chemical scaffold, suggesting that it is an ideal lead compound for further modifications and optimizations to treat cancer.

Recently, our group also conducted a comprehensive literature review (Fig. 1) on modification strategy of matrine.[12] As illustrated in Fig. 1, lots of matrine derivatives have been synthesized through various modifications on different positions of matrine. However, up to now, research on targeted design for matrine derivatives is still not be involved which caused blindness for their development. Different from traditional cytotoxic chemotherapy, targeted therapy has many advantages, such as high specificity, good efficacy and low toxicity. Inspired by above suggestions, targeted design for matrine might be an effective strategy to discover anticancer candidates of matrine derivatives.

Interestingly, the specific L-shaped conformation of matrine is similar with radicicol (Fig. 2). Besides, radicicol serves as a Hsp90^{N} inhibitor and its molecular mechanism has been thoroughly studied, which provided possibility for structural modification of matrine derivatives to target Hsp90^{N} based on radicicol conformation analysis. Moreover, the overexpressed characteristics in tumor cells and the prospect of stalling a number of oncogenes by inhibiting a single protein have made Hsp90 an attractive target for cancer therapy.[13–15] Thus, by targeted design and inhibiting the activity of Hsp90, it might be an effective strategy for matrine modifications to treat cancer.

2. Drug design

Radicicol, as the Hsp90^{N} inhibitor, its mechanism involves a competition with ATP at *N*-terminal ATP-binding pocket of Hsp90, resulting

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SYNTHESIS AND CHARACTERIZATION OF GADOLINIUM-BASED NANOCRYSTALS FOR THEIR POTENTIAL APPLICATION AS TRIMODAL IMAGING CONTRAST AGENTS

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ABSTRACT

Lanthanide-doped gadolinium nanomaterials have attracted considerable attention due to their promising applications in biological imaging. Sodium gadolinium fluoride (β-$NaGdF_4$) nanomaterials act as perfect host for doping of luminescent lanthanide ions. Due to heavy nature of gadolinium, it can strongly absorb X-ray radiations. Therefore, Gd-based nanomaterials are applied as contrast agents for X-ray tomography (CT). Presence of seven unpaired electrons in Gd^{+3} ion, its large magnetic moment and long electronic relaxation time makes it an ideal candidate to enhance water proton relaxation rates. These characteristics make Gd-based nanomaterial useful for their potential application as MRI contrast agents. In this work, sodium gadolinium fluoride is doped with ytterbium and erbium to produce β-$NaGdF_4$:Yb/Er as core nanocrystals. They are subsequently coated with sodium gadolinium fluoride doped with neodymium (β-$NaGdF_4$:Nd) to produce β-$NaGdF_4$:Yb/Er@β-$NaGdF_4$:Nd core-shell nanocrystals. Powder X-ray diffraction (XRD) results indicated that β-$NaGdF_4$ (host), β-$NaGdF_4$:Yb/Er (core) and β-$NaGdF_4$:Yb/Er@β-$NaGdF_4$:Nd (core-shell) nanocrystals all exist in hexagonal crystalline phase. While Dynamic Light Scattering (DLS) results indicated that the particle size of the synthesized nanocrystals was in range of 12 to 27 nm. FTIR results confirmed that the synthesized nanocrystals were stabilized by oleic acid. Nanocrystals reported in this work are expected to be useful trimodal contrast agents for photoluminescence, X-ray tomography and Magnetic Resonance Imaging (MRI).

Keywords: lanthanide, nanocrystals, trimodal, gadolinium, contrast agents.

INTRODUCTION

Recently, rapid research developments in the field of medicine and life science have also driven the biomedical research. This emerging and growing research field comprises of a number of bioassay approaches such as X-ray Computed Tomography (also called Computed Tomography, CT), Single-Photon Emission Computed Tomography (SPECT) [1-4], Positron Emission Tomography (PET) [5, 6] and Magnetic Resonance Imaging (MRI) [7-9]. These tomographic imaging methods have high penetration power. Therefore, they play a key role in biomedical imaging. However, these techniques have some unavoidable drawbacks such as limited spatial resolution, long scan acquisition time and application of strong ionizing radiations (except for MRI) [10-13]. Furthermore, these modalities differ from each other in spatial and temporal resolution, imaging depths, anatomical and molecular details and the necessary material properties of contrast agents essential to improve the quality of images in terms of their visibility. In many cases, it is beneficial to use several complimentary imaging techniques for rapid and precise diagnosis. Since majority of these imaging modalities apply exogenous contrast agents to improve the signal-to-noise ratio, therefore, the development of multimodal contrast agents is highly desirable to obtain images of better quality. Such agents have proved more useful for patient care.

Moreover, they also reduce the cost and increase the safety by restricting the number of contrast agents administration needed for imaging purposes [14]. The idea of designing multimodal contrast agents provides the prospective to integrate the benefits of different modalities while at the same time overcoming the shortcomings of one another [15, 16]. In addition, multimodal contrast agents can be very useful for the technical development of emerging imaging techniques [17-19]. Current research indicate that nanomaterial-based multimodal imaging probes have been developed for accurate imaging and diagnosis while applying different imaging modalities Recently, lanthanide metal ions doped with upconverting (Excitation at lower energy than emission) nanomaterial have been investigated for their potential applications in biomedical imaging. Such nanomaterials possess high photostability and show neither photobleaching nor photoblinking [20]. Additionally, upconverting nanomaterials are excited by near-infrared (NIR) radiations which ensure optical imaging of deeper tissues with significantly controlled autofluorescence, and create enhanced image contrast [21-23]. β-$NaGdF_4$ host nanomaterial doped with lanthanide ions combination of Yb^{3+}, Er^{3+} or Yb^{3+}, Tm^{3+} have exhibited significant upconversion luminescence [24]. Gadolinium is a heavy metal of high atomic number which strongly absorbs X-rays. Its trivalent ion (Gd^{3+}) causes enhancement of water proton relaxation rate due to maximum number (seven) of unpaired electrons (among all lanthanide ions), a long electronic relaxation time (~10^{-9} s) and a large magnetic moment (7.9 BM). These properties make Gadolinium the best candidate for applications as luminescence, CT and MRI contrast agents [11, 25, 26]. Upconverting nanomaterial based multimodal contrast agents can serve for fluorescence imaging, CT and MRI modalities. Such contrast agents possess the advantages of high sensitivity (fluorescence imaging) as well as the potential of high spatial resolution imaging (of MRI and CT techniques) [27]. This work reports the synthesis of β-$NaGdF_4$ nanocrystals doped with Yb^{3+} and Er^{3+} ($NaGDF_4$:Yb/Er). They were synthesized as core nanocrystals and were subsequently coated with a shell of $NaGdF_4$:Nd^{3+} (Core-shell nanocrystals).

EXPERIMENTAL

Chemicals: Gadolinium Oxide (99.9%), Ytterbium(III) acetate hydrate (99.99%), Erbium Oxide (99.9%), Neodymium(III) acetate hydrate (99.9%), Sodium hydroxide (≥ 97%), 1-octadecene (90%), oleic acid (90%), Ammonium fluoride (≥ 99.9%), Acetic Acid glacial (≥ 99.85%) and cyclohexane were purchased from Sigma-Aldrich. All chemicals were used without any further purification.

Synthesis of Gadolinium acetate hydrate

Gadolinium acetate hydrate was prepared following the procedure reported by Dühnen and Haase for the synthesis of gadolinium trifluoroacetate (Gd-TFA) [28]. Gd_2O_3 (3.63 g, 10 mmol) was added to a solution of 80 mmol of concentrated acetic acid (4.6 mL) and 12.4 mL of distilled water. The solution was heated under reflux (at ca. 90 °C) for 60 min to dissolve the Gd_2O_3 completely. After removing excess acetic acid and water with a rotary evaporator at 50 °C, Gadolinium acetate hydrate was obtained as a white powder. Subsequently the powder was dried at 60 °C for 17 h.

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