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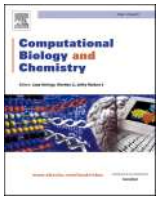

Synthesis, *In Vitro*, and *In Silico* studies of imide derivatives of phthalic anhydride as potential antimicrobial agents

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ABSTRACT

This study reports the synthesis and assessment of a series of imide derivatives of phthalic anhydride (phthalimides) for their potential antimicrobial activities. Phthalic acid was first converted into phthalic anhydride using acetic anhydride, which was then reacted with various *L*-amino acids to obtain phthalimides in high yields. Compounds HUPB, HUPC, HUPF, and HUPH exhibited promising antimicrobial activity, with HUPF and HUPH being the most potent. **HUPF** exhibited significant antimicrobial activity, showing inhibition zones of 24 mm versus *Staphylococcus aureus* (at 2000 μg/mL), 17 mm versus *Escherichia coli* (at 2000 μg/mL), and 18 mm against *Candida albicans* (at 1000 μg/mL). The minimum inhibitory concentrations (MICs) were 16 μg/mL, 24 μg/mL, and 24 μg/mL for *S. aureus*, *E. coli*, and *C. albicans*, respectively. **HUPH** demonstrated strong antimicrobial activity, exhibiting inhibition zones of 23 mm versus *S. aureus*, 19 mm versus *E. coli*, and 20 mm versus *C. albicans*, with corresponding MICs of 20 μg/mL, 28 μg/mL, and 20 μg/mL, respectively. Molecular docking reinforced these results, demonstrating effective bindings for HUPF and HUPH, suggesting their potential as antimicrobial agents. Both compounds adhered to Lipinski's Rule of Five, signifying decent oral bioavailability, gastrointestinal absorption (≥0.55), and no PAINS (pan-assay interference compounds) alerts. Density functional theory (DFT) calculations revealed that HUPF and HUPH possess narrow HOMO-LUMO energy gaps and elevated dipole moments, indicating high chemical reactivity, and strong polarity, which further support their enhanced antimicrobial potential. These results highlight the therapeutic potential of the two compounds for further development as novel antimicrobial agents.

1. Introduction

The emergence of multidrug-resistant (MDR) microbial pathogens has become a worldwide health concern, dictating the urgent development of novel antimicrobial drugs. Traditional antibiotics and antifungal medication are increasingly ineffective against resistant strains, leading to higher morbidity and mortality rates worldwide. Neglecting drug-resistant bacteria is expected to lead to a high rise in fatal infections and elevate the threat of getting difficult-to-treat infections in hospitals. Consequently, there is a demanding need to discover new antimicrobial compounds, both synthetic and natural. In this context, the design and synthesis of new chemical entities with potent antimicrobial potential have gained significant attention in medicinal chemistry (Prestinaci et al., 2015; Salam et al., 2023). As antimicrobial resistance becomes an increasingly challenging issue in modern medicine, scientists across the globe are working thoroughly to discover new antimicrobial agents. Chemical synthesis is fundamental to antimicrobial drug discovery, as it allows for the design, modification, and optimization of molecular assemblies with therapeutic promise (Wright et al., 2014).

Phthalic anhydride is an important industrial chemical with diverse applications. Its various derivatives play a vital role in the synthesis of numerous essential compounds. Phthalic anhydride is a crucial component in the production of plasticizers, unsaturated polyesters, and

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RESEARCH ARTICLE

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Synthesis, *in vitro* and *in-silico* evaluation of amide derivatives as prospective antimicrobial and antileishmanial agents

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ABSTRACT

This study focused on the synthesis, antimicrobial, and antileishmanial evaluation of seven amide derivatives (**AL-1** to **AL-7**). The target compounds were synthesized from *L*-cysteine methyl ester and various substituted aromatic and aliphatic carboxylic acids. The final products were characterized using physical and spectro-analytical techniques (FT-IR, ^{1}H NMR). The derivatives were evaluated for their antimicrobial activity at various concentrations. Experimental studies revealed that compounds **AL-5** and **AL-6** were the most potent against *Staphylococcus aureus* and *Escherichia coli*, exhibiting 18 mm and 21 mm inhibition zones, respectively, at a concentration of 2000 µg/mL. Additionally, **AL-5** and **AL-6** showed significant activity against *Candida albicans*, with 20 mm and 23 mm inhibition zones, respectively, at a concentration of 1000 µg/mL. The compounds also exhibited moderate to good activity against *Leishmania tropica*. Compounds **AL-2, AL-4, AL-5**, and **AL-6** demonstrated good activity, with IC_{50} values of 0.68 ± 0.09, 0.68 ± 0.16, 0.66 ± 0.08, and 0.68 ± 0.12 µg/mL, respectively. Molecular docking, *in silico* Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) analysis, and Density Functional Theory (DFT) studies were conducted on the most potent compounds (**AL-5** and **AL-6**) to validate and support their experimental antimicrobial and antileishmanial potential.

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KEYWORDS
Amide; DCC; antimicrobial; antileishmanial; molecular docking

1. Introduction

Infectious diseases caused by fungi, bacteria, and protozoa pose a significant global public health risk, affecting diverse geographical regions [1]. Fungal infections range from superficial mucocutaneous conditions to severe invasive diseases, particularly in immunocompromised individuals [2]. Human fungal infections have historically received little research attention despite causing over 1.5 million deaths annually. Over the past decade, our understanding of the pathophysiology of these infections has significantly advanced, primarily due to key discoveries about both host and pathogen factors that influence the severity and characteristics of these diseases [3]. A sophisticated strategy is essential for effectively managing the complexities of fungal infections, as they are closely linked to host immunity [4]. Bacteria are ubiquitous microorganisms capable of causing a wide range of diseases, from minor skin infections to severe, potentially life-threatening conditions such as sepsis and pneumonia [5,6]. The growing threat of bacterial resistance to antibiotics highlights the urgent need for innovative therapeutic approaches [7]. The emergence of multidrug-resistant Gram-positive and Gram-negative bacteria has been linked to severe infectious diseases worldwide [8]. Despite the availability of numerous antimicrobial agents with diverse modes of action, bacterial infections remain a global health concern due to the limited efficacy and potential adverse effects of existing treatments [9]. Leishmaniasis is classified as a neglected tropical disease (NTD) and ranks as the second deadliest parasitic infection worldwide after malaria. It is transmitted to humans through the bite of sand flies, primarily from the *Lutzomyia* and *Phlebotomus* genera. Despite ongoing efforts, leishmaniasis remains a significant public health challenge. Each year, global reports estimate between 700,000 and 1 million new cases of leishmaniasis. Treatment remains a significant challenge, as many patients rely on drugs with severe side effects. The presence of over 20 *Leishmania* parasite species further complicates the implementation of standardized treatment protocols across different regions. Consequently, there is an urgent need for new therapeutic alternatives to combat leishmaniasis [10].

Amides are important organic compounds that serve various applications. The amide bond stability is crucial for synthetic chemists. Certain amide derivatives display biological properties, including antihistamine, anticancer, antibacterial, and antifungal activities [11]. Failing to address drug-resistant bacteria is expected to cause a significant rise in fatal infections and have increased the risk of contracting

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Isolation, characterization, antidiabetic and antityrosinase potentials of compounds isolated from *Anabasis Articulata*

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ABSTRACT

Herein, we report the isolation, characterization, in silico evaluation and biological potentials of four compounds (**1–4**) isolated from *A. Articulata*. All compounds (isoleteolin (**2**), hyperoside (**3**) and quercitrin (**4**)) demonstrated antioxidant properties; notably, quercetin (**1**) exhibited exceptional free-radical scavenging activity (87.75 % DPPH and 85.75 % ABTS at 1000 μg/mL) with an IC_{50} value of 62 μg/mL, and 35 μg/mL, respectively against the tested radicals. The antidiabetic potential was revealed through the inhibition of α-glucosidase and α-amylase. All 4 compounds exhibited α-glucosidase activity (IC_{50} =32–110 μg/mL) and α-amylase (30–59 μg/mL), among them quercetin showed maximum inhibition of 89.92 % at 1000 μg/mL against α-glucosidase with an IC_{50} value of 32 μg/mL, and 85.98 % inhibition at 1000 μg/mL against α-amylase with an IC_{50} value of 30 μg/mL. Next, along with quercetin, all compounds displayed dose-dependent behaviour in tyrosinase inhibition with IC_{50} values ranging from 4.14–75.99 μM, whereas Lineweaver Burk and Dixon plots, displayed that quercetin with potent inhibition exhibited a competitive mode of inhibition. Further, in silico analyses validated the enzymatic binding affinity of quercetin with docking scores against α-glucosidase (-5.37 kcal/mol), α-amylase (-5.82 kcal/mol), and tyrosinase (-5.37 kcal/mol), respectively. ADMET study revealed that quercetin possesses adequate water solubility, high bioavailability, and low toxicity. These results imply that quercetin has a great deal of promise as a treatment for diabetes, hyperpigmentation disorders, and oxidative stress.

1. Introduction

Throughout human history, the use of natural products derived from plants has been documented on a trial-and-error basis, leading to the discovery of herbal cures and traditional medicine systems. The main source of information on the utilization of remedies derived from medicinal plants was human experimentation over hundreds of years, whether via trials or untimely deaths in an attempt to develop treatments that may be used to heal a variety of ailments (Rausch et al., 2024). The majority of early drug compounds emerged based on traditional medical procedures, which were then investigated further in terms of pharmacology, chemistry, and clinical outcomes. Perhaps the most well-known example to date is aspirin, an anti-inflammatory drug, from salicin, a naturally occurring substance that was extracted from the willow tree (Mahdi et al., 2006). Research on *Papaver somniferum* L. led to the separation of several alkaloids, including morphine, an essential drug that was originally described in 1803 (Duarte, 2005). The understanding of complementary and alternative herbal products used in

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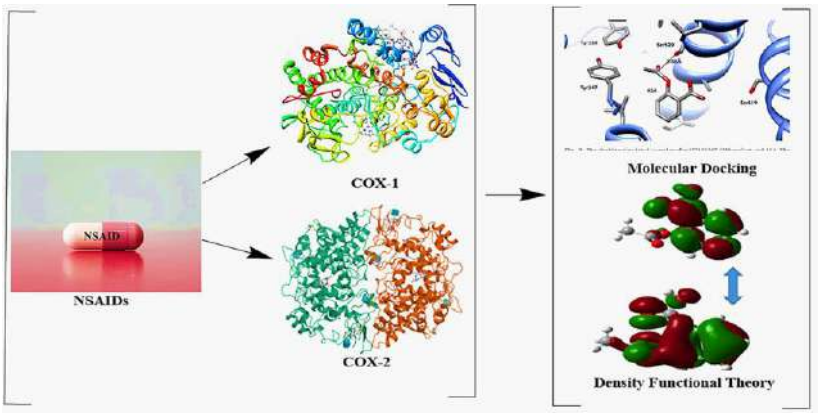
Density Functional Theory and Molecular Docking Investigation of Selected NSAIDs against COX-1 and COX-2 Enzymes: Study of Correlation Between Computational and Experimental Results

Ateeq Ullah Jan[a], Khalid Khan* [a], Tanzeel Shah [b], Nasir Ahmad [a], and Haroon ur Rashid [c]

Research has been conducted to align computational and experimental results, enhancing the understanding of phenomena affordably and quickly. This study investigated the reliability of docking results for selected nonsteroidal anti-inflammatory drugs (NSAIDs) against cyclooxygenase (COX) proteins, compared to experimental findings from the literature. COX proteins causing inflammation were obtained from a protein data bank and prepared for docking analysis using Molecular Operating Environment (MOE) software. NSAIDs were also selected from the literature and docked to COX protein active sites, with binding affinities recorded. Density functional theory (DFT) analysis, using Becke's three-parameter hybrid model and Lee-Yang-Parr (B3LYP) approach, validated the docking results by examining the molecular properties of NSAIDs. Experimental IC_{50} data for COX inhibition by NSAIDs were compared with computational results, supported by DFT analysis. The study confirmed that computational results align with experimental data, supporting their use in drug development.

Graphical abstract



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1. Introduction

Keeping in view the time, resources, and pharmacological importance of a molecule during the process of drug discovery and development, scientists evaluate a large number of compounds following a wide range of criteria using diverse computer models, to guide the decision of which compound to synthesize, test, and promote, with the ultimate goal of identifying those with the best potential to become a medicine that works for patients. Among all computational

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Investigating the Inhibitory Mechanism of *para*-Sulfonato-calix[4]arenes against Polymerase and Helicase of SARS-CoV-2: Molecular Docking and Dynamics Simulation Studies

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The coronavirus disease (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a profound impact on global health and socio-economic conditions. To date, various vaccines have been administered worldwide in an effort to curb the spread of the virus. Despite vaccination efforts, there have been complications. Existing antiviral drugs have shown limited effectiveness, prompting the use of computational methods to understand the dynamics of the virus and develop suitable treatments. The current study focuses on using biocompatible *para*-sulfonato-calix[4]arenes to dock against two key proteins of SARS-CoV-2, namely ribonucleic acid (RNA)-dependent RNA polymerase, and helicase. Docking results indicate a strong binding affinity of these compounds to the target proteins, with higher scores compared to commonly used medications. Molecular dynamics (MD) simulation validates the docking results, showing stable protein-ligand complexes over time. The compounds are also screened for absorption, distribution, metabolism, and excretion properties and toxicity, suggesting their potential as lead candidates for inhibiting the virus's key proteins. However, further *in vivo* and *in vitro* studies are recommended to confirm these findings.

Keywords: coronavirus, helicase, *para*-sulfonato-calix[4]arenes, molecular docking, MD simulations

Introduction

A novel coronavirus emerged in Wuhan City, China, in December 2019.[1,2] This new virus, responsible for severe respiratory syndrome, quickly spread globally. Consequently, the World Health Organization (WHO) declared a Public Health Emergency of International Concern on January 30, 2020.[3,4] As of WHO's report in 2024,[5] the deadly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected 0.776 billion people worldwide and caused 7.1 million deaths. Moreover, it has had a significant adverse impact on the global economy. SARS-CoV-2 belongs to the Coronaviridae family and β-coronavirus genus. Other viruses within this genus, such as severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), human coronavirus OC43 (HCoV-OC43), and human coronavirus HKU1 (HCoV-HKU1), can also infect humans.[6-8] The SARS-CoV-2 genome consists of a positive-sense single stranded RNA with a size varies

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Research

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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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A R T I C L E I N F O

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A B S T R A C T

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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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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Review

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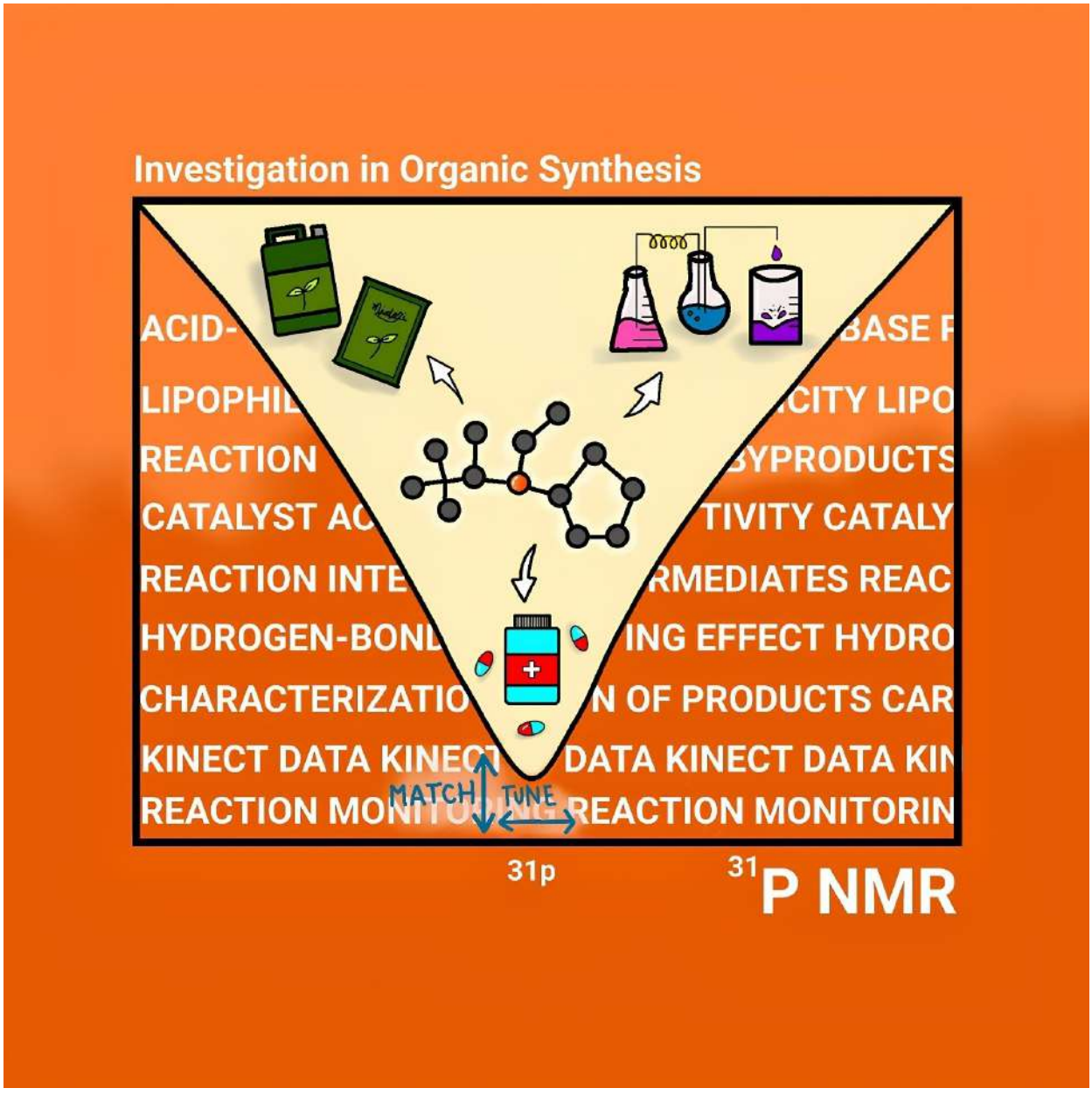
THE CHEMICAL RECORD

^{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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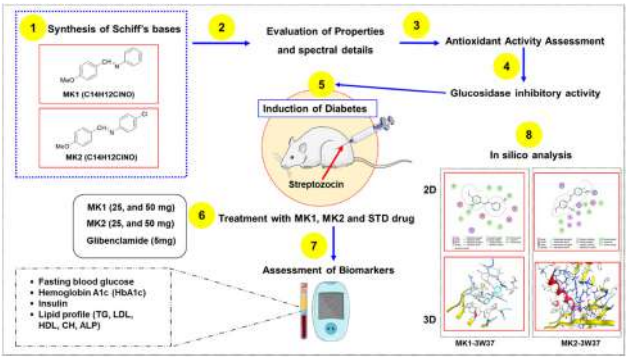
Abstract: The current study attempted to synthesize methoxy-substituted Schiff's bases, namely MK1 and MK2, and evaluate their antidiabetic effects using *in vitro*, *in vivo*, and molecular docking studies. Experimental animals (rat model) received the synthetic compounds, MK1 and MK2, orally in doses 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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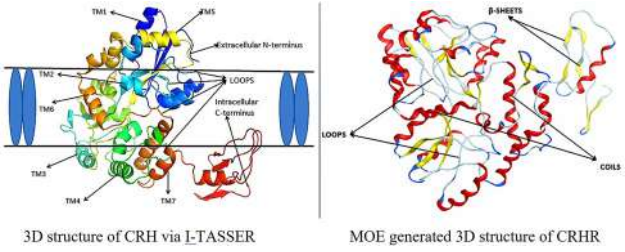
Abstract: Corticotropin-releasing hormone receptors (CRHRs), also termed corticotropin-releasing factor receptors, are linked to G-protein-coupled receptor class. Corticotropin-releasing hormone (CRH) is medically significant in stress, immune response, gastrointestinal motility, and eating patterns. 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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REVIEW ARTICLE

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

Juliana Jorge[1,#], Kristiane Fanti Del Pino Santos[1,#], Fernanda Timóteo[1], Rafael Rodrigo Piva Vasconcelos[1], Osmar Ignacio Ayala Cáceres[1], Isis Juliane Arantes Granja[2], David Monteiro de Souza Jr.[1], Tiago Elias Allievi Frizon[3], Giancarlo Di Vaccari Botteselle[4], Antonio Luiz Braga[5], Sumbal Saba[2,*], Haroon ur Rashid[1,5,*] and Jamal Rafique[1,2,*]

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ARTICLE HISTORY

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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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RESEARCH ARTICLE

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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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Cefixime

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

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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†

Haroon ur Rashid,[ab] Marco Antonio Utrera Martines,*[a] Adriana Pereira Duarte,[a] Juliana Jorge,[a] Shagufta Rasool,[b] Riaz Muhammad,[b] Nasir Ahmad[c] and Muhammad Naveed Umar*[d]

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.

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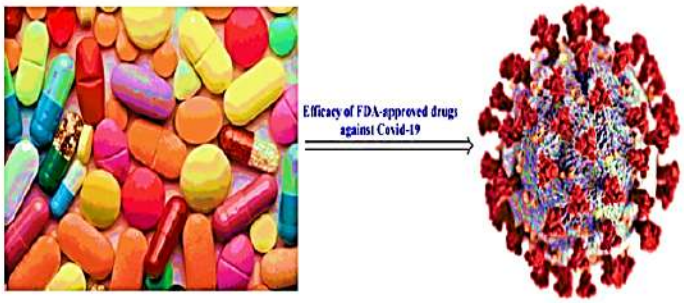
Potential Drug Candidates in Clinical Trials for the Treatment of Covid-19: An Updated Overview

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]

UDC 544.23.022

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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SYNTHESIS AND CHARACTERIZATION OF POLY(ACRYLIC ACID-CO-ACRYLAMIDE)-SAWDUST COMPOSITE FOR THE ADSORPTIVE REMOVAL OF Cd(II) AND Pb(II) FROM AQUEOUS SOLUTIONS

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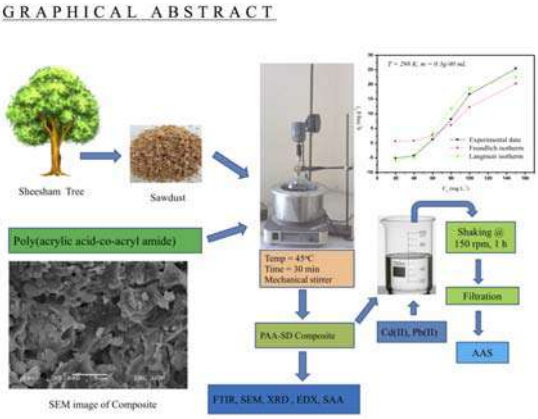
A novel poly(acrylic acid-co-acrylamide)/sawdust composite was synthesized by copolymerization of partially neutralized acrylic acid and acrylamide with sawdust using N,N-methylenebisacrylamide as a crosslinker and potassium persulfate/sodium sulphite as initiators. The composite was characterized by FTIR, XRD, SEM, EDX and BET techniques. The adsorption of Cd(II) and Pb(II) ions on composite in aqueous solution was studied in batch experiments optimizing reaction parameters like initial concentration, contact time, pH and temperature. The adsorption kinetics followed pseudo second order kinetic model. Adsorption isotherms were applied to the experimental data which fitted well with Langmuir and Freundlich isotherms. The maximum adsorption capacities (q_m) (from Langmuir model) of the prepared composite at 25 ^oC, were 28.57 mg g^{-1} and 32.25 mg g^{-1} for Cd(II) and Pb(II) ions, respectively. Activation energy data (12.148 kJ mol^{-1} and 7.165 kJ mol^{-1} Cd(II) and Pb(II), respectively) indicated physiosorption. Results of thermodynamic parameters like ΔG^o, ΔH^o and ΔS^o for both Cd(II) and Pb(II) ions suggested the spontaneity and endothermic nature of the process. The newly synthesized composite attributed to its cost effective and environment friendly nature and ease of synthesis, could be deemed as a potential candidate for the removal of Cd(II) and Pb(II) ions from waste-water.

GRAPHICAL ABSTRACT



INTRODUCTION

Heavy metal pollution is a serious environmental problem of global concern caused by rapid growth in industrialization. They are generally hazardous, non-biodegradable and persistent in nature.[1] They cause serious detrimental effects on biotic as well as abiotic segments of ecosystem including health hazards in human and plants.[2] These metals include Pb, Cd, Cr, As etc.[3] Metal plating, lead acid batteries, printing, glass and ceramic industries, lead mining, phosphate fertilizers, forest fires, electronics, and automobile emission are the major sources of lead (Pb) pollution.[4] Pb has been reported with problems like brain and kidney dysfunction, miscarriage, under developed fetus, disruption of nervous system and infertility.[5] Severe exposure to Pb causes abortion, sterility, neo-natal deaths and stillbirths.[6] The world health organization (WHO) drinking water standard for Pb is 0.01 mg/L.[7] Similar to Pb, cadmium (Cd) is

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

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Design, synthesis, and biological evaluation of matrine derivatives possessing piperazine moiety as antitumor agents

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Abstract

Using matrine (1) as the lead compound, a series of new piperazinyl matrine derivatives were designed, synthesized and evaluated for their antitumor activities in vitro and in vivo. Structure activity relationship (SAR) analysis indicated that introduction of substituted piperazine on matrine might significantly enhance the antiproliferative activity. Moreover, types of substituents of piperazine exhibited great different effects on the antiproliferative activity of target compounds against Bel-7402 and RKO cell lines. The in vivo antitumor assay results revealed that some of the target derivatives possessed better therapeutic efficacy than matrine and low toxicity. More importantly, among the newly synthesized compounds, **M16** and **M26** possessed strong antitumor activity against the two cell lines. Moreover, six of the synthesized compounds **M1**, **M3**, **M7**, **M10**, **M11** and **M17** proved to be of much better therapeutic efficacy than matrine via in vivo antitumor assay. The study provides a theoretical basis for further structural optimizations and discovery of the antitumor pathways of this kind of compounds.

Keywords Piperazine · Matrine · Antiproliferative activity · Cisplatin

Introduction

Malignant tumors continue to be a serious threat to human health. Currently, radiotherapy, chemotherapy and surgery are the major clinical techniques used to treat cancer. However, these techniques are extremely painful and cause serious side effects to the patients (Hamdy 2012). As a traditional means, tumor treatment through traditional Chinese medicine has attained significant attention due to their improved efficacy and low side effects. Matrine (1, Fig. 1), isolated from the natural herb-Sophora, has attracted considerable attention because of its broad-spectrum biological activities, including antitumor, anti-inflammatory, antiviral and anti-nociceptive effects (Zhang et al. 2010; Aghvami et al. 2018; Dai et al. 2009). Moreover, it has a flexible structure and good safety profiles. However, matrine has not been widely used in clinics as antitumor agent, but it has served as an adjuvant therapy in combination with chemotherapeutic or targeted anticancer agents in clinical cancer treatment, such as with cisplatin (Zhang et al. 2015) and sorafenib (Lin et al. 2014). Low bioavailability and moderate antitumor activity limited its application in tumor treatment. Thus, it is highly desirable to develop matrine derivatives in order to discover more effective drug candidates.

Piperazine scaffold has been recognized as one of the privileged structures in drug discovery and is widely distributed in biologically active compounds applied in a number of different therapeutic areas, including antitumor, antifungal, antidepressant, and antiviral (Solomon et al. 2010; Kimura et al. 2004; Shapiro et al. 1995; Yang et al. 2005).

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Design, synthesis and evaluation of novel (S)-tryptamine derivatives containing an allyl group and an aryl sulfonamide unit as anticancer agents

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ARTICLE INFO

Keywords:
Tryptamine
Aryl sulfonamide
Cell cycle arrest
Anticancer

ABSTRACT

A series of (S)-tryptamine derivatives containing an allyl group and an aryl sulfonamide unit were designed, synthesized and evaluated for their potential application as anticancer agents. The structures of the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and ESI-MS spectral analyses. The target compounds were evaluated for their *in vitro* cytotoxicity against HepG2, HeLa, CNE1 and A549 human cancer cell lines. Some of the synthesized compounds showed moderate to good anticancer activities against four selected cancer cell lines, among of which 6ag was found to be the most active analogue possessing IC_{50} values 16.5–18.7 μM. Further mechanism studies revealed that compound 6ag could significantly induce HepG2 cell cycle arrest at G1 phase, promote cell apoptosis, and inhibit the colony formation as well.

Cancer has become one of the most serious threats against human health and life all over the world, and its mortality rate surpasses heart diseases.[1] Nowadays, the progress of cancer treatment still relies on chemotherapy in which antitumor drugs play an important role.[2] Although researchers made much efforts to develop new drugs to cure cancer, still millions of cancer caused deaths are reported globally.[3] Therefore, it remained a tremendous challenge for scientists to search for effective and unexplored anticancer agents with valid potency against tumor cells.

Tryptamine, a bicyclic heterocycle, is the most important and best-characterized member of the indoleamine family. Tryptamine scaffold is regarded as a privileged structure, due to its broad applications for designing medicinal agents. The tryptamine and its analogues have been reported to exhibit diverse pharmacological activities (Fig. 1), such as anti-migraine,[4,5] antibacterial[6] and antitumour[2,7]. Owning to its multiples pharmacological activities, tryptamine has been considered as the common functional group in a set of compounds termed collectively substituted tryptamines.

D-tryptophan (Fig. 2), a non-protein amino acid derived from Tryptamine, possesses special physiological properties due to its optical activity, which can serve as sweetener, feed additive and plant growth substance etc. in various fields. Especially in pharmaceuticals, it is an essential synthetic precursor for anticancer agents and immunosuppressants.[8] The above suggestions urged us to perform modifications based on D-tryptophan, maintaining the chirality and tryptamine scaffold. On the other hand, the S-allylcysteine (Fig. 2) is identified as a potent compound from garlic, and is reported to have anticancer effect.[9,10]. An obvious characteristic is the similarity of chiral center between D-tryptophan and S-allylcysteine. It was also discovered that the biochemical transformation of the allyl sulfur compounds in the cell and their adducts with thiol functional groups of proteins, could be considered relevant events to uncover the anticancer properties of the allyl sulfur compounds.[11] Moreover, lack of allyl group can cause the biological activity of S-allylcysteine lose.[12] Thus, with the chirality and tryptamine structure of D-tryptophan unchanged, allyl group was primarily introduced into the D-tryptophan, forming another analogous scaffold of S-allylcysteine, which was expected to exhibit anticancer synergies.

Further, in considering the significant biological effect of chirality in medicinal chemistry, the degree of selectivity was altered followed by modification on amino position. On the other hand, sulfonamide moiety is a core part of many clinical drugs which have broad spectrum applications in the fields of medicine, pharmacology and pharmaceutics such as antibacterial, antiviral, anti-inflammatory, protease inhibitor,

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Design, synthesis and evaluation of novel sophoridinic imine derivatives containing conjugated planar structure as potent anticancer agents

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ARTICLE INFO

Keywords:
Sophoridine
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Camptothecin
Schiff base
Antitumor activity

ABSTRACT

Based on our previous study and the binding mode of camptothecin with Topo I, a series of novel sophoridine imine derivatives containing conjugated planar structure were designed, synthesized and tested for their *in vitro* anticancer activity. The results showed that most of the derivatives displayed potent activity. In particular, compounds **10b** exhibited excellent anti-proliferative activities with IC_{50} 5.7 μM and 8.5 μM against HepG-2 and HeLa cell lines, respectively. Molecular docking studies revealed that the introduction of conjugated planar structure could form π-π stacking interaction with DNA, leading to the improvement of biological activity. Its mode of action was to inhibit the activity of DNA Topo I, followed by the G0/G1 phase arrest. This work provides a theoretical basis for structural optimizations and exploring anticancer pathways of this kind of compound and **10b** could emerge as promising lead compounds for the development of novel Topo I inhibitors.

1. Introduction

Cancer continues to be a serious threat to human health.[1] Presently, chemotherapy is the main modality for cancer therapy.[2] Although it can effectively control the spread and metastasis of tumors, there still exists new issues, such as low selectivity, side effects. Thus, the targeted therapy has received more widespread attention.[3,4] With the target of topoisomerase for designing new drugs via traditional Chinese medicine, it could inhibit the DNA replication selectively, kill tumor cells intensively and reduce untoward effects.[5,6,7,8]

Sophoridine, a kind of monomer alkaloid purified from *Sophora alopecuroides* L., has been widely used to treat live cancer, gastric cancer and lung cancer in China for decades with low side-effects.[9] The mechanism of action of Sophoridine is to inhibit the DNA topoisomerase I (Topo I) activity, induce cell cycle arrest at the G0/G1 phase, and cause apoptotic cell death.[10,11] But the moderate antitumor activity of sophoridine limits its use as a drug for clinical applications. Furthermore, various druggable advantages of sophoridine, such as special chemical scaffold, flexible structure, high solubility, and good safety profiles, also provoked our strong interest for further modifications and optimizations.

The structure-activity relationship study (SAR) of sohporidine as anticancer agent was carried out via the modifications at 14-position in our laboratory, and SAR results revealed that introduction of the plannar aromatic group could enhance the anticancer activity by improving the binding affinity with the base-pairs of DNA through π-π stacking interaction.[12] Herein, we hypothesize that similar modifications at nearby position might also be valuable for improving anticancer activity. In addition, C═N functional group, as the necessary component of Schiff base, is present in a number of bioactive molecules, and is recognized as a key building block for the synthesis of small-molecules with potential pharmaceutical activities such as antibacterial,[13,14] antihypertensive,[15] anti-inflammatory[16,17] and anticancer,[18–20] etc. Besides, some researchers demonstrated that the D-ring was not necessary for activity.[21] In consideration of above conditions, our present study was focused on the modification at 15-position of sophoridine involving the transformation of C═O to C═N group, followed by the introduction of a variety of aromatic rings. The strategy adopted for the synthesis target compounds, is depicted in Fig. 1.

Camptothecin (CPT), another cytotoxic quinoline alkaloid, is a potent anticancer agent, especially for leukemia and solid tumors.[22,23] Currently, it's one of the most widely studied anticancer agents among

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Boosting the hydrodesulfurization of dibenzothiophene efficiency of Mn decorated (Co/Ni)-Mo/Al_2O_3 catalysts at mild temperature and pressure by coupling with phosphonium based ionic liquids

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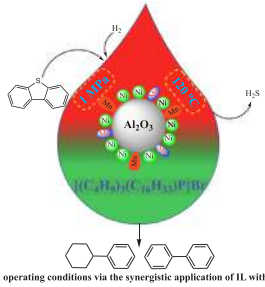
HIGHLIGHTS

- Mn-Co-Mo/Al_2O_3 or Mn-Ni-Mo/Al_2O_3 catalysts were prepared by incipient impregnation.
- HDS of DBT was conducted over Mn-Ni-Mo/Al_2O_3 coupled with PILs at 120 °C and 1 MPa.
- Mn-Ni-Mo/Al_2O_3 coupled PIL achieved DBT conversion to 84% at 120 °C and 3 MPa.
- Better H_2 transport and IL-π electrons interaction resulted in higher HDS activity.
- GC-MS confirmed DDS and HYD routes for the catalyst-IL coupled HDS reaction.

GRAPHICAL ABSTRACT



HDS of DBT at mild operating conditions via the synergistic application of IL with Mn-Ni-Mo/Al2O3 catalyst

ARTICLE INFO

Keywords:
Catalytic hydrodesulfurization
Coupled application of Mn-Ni-Mo/Al_2O_3 with phosphonium based IL
Mild operating condition
Dibenzothiophene
XPS and BET characterization
GC-MS

ABSTRACT

Hydrodesulfurization (HDS) of fuel oils is the most viable and commercially acceptable approach operated under harsh operating conditions. To avoid harsh reaction conditions, this study is designed on the HDS of dibenzothiophene (DBT) under the combined effect of five types of Phosphonium based ionic liquids (PILs) i.e. $[C_4H_9)_3(C_{14}H_{29})P]Br$, $[(C_8H_{17})(C_4H_9)_3P]Br$ $[(C_4H_9)_4P]Cl$, $[BMIM]PF_6$ and $[C_4H_9)_3(C_{16}H_{33})P]Br$ with 5 wt% Mn promoted (Co or Ni)-Mo/Al_2O_3 catalysts at extremely ambient temperature and pressure. Catalysts were prepared by wet impregnation technique followed by their sulfidation (30% CS_2 in cyclohexane) and textural characterization via SEM, BET, PXRD and XPS techniques. Catalytic activity results indicated that DBT conversion was boosted from 24% (by mere Mn-Ni-Mo/Al_2O_3) to 84% (by Mn-Ni-Mo/Al_2O_3 coupled with 10 g of $[(C_4H_9)_3(C_{16}H_{33})P]Br$) at 3 MPa H_2 pressure, 120 °C and 4 h reaction time. Among the five types of PILs, the enhancement in HDS activity combined with solid catalyst was found dependent on the type and length of cation chain. The enhanced DBT conversion caused by Mn-Ni-Mo/Al_2O_3 solid catalyst coupled with IL was envisioned to be due the synergy between hydrogenation reaction (by the former) and extractive desulfurization (by the later) with an overall HDS activity order of: Mn-Ni-Mo/Al_2O_3 > Mn-Co-Mo/Al_2O_3 > Ni-Mo/Al_2O_3 > Co-Mo/Al_2O_3. HDS products were analyzed by GC-MS and possible reaction route was anticipated. This study successfully discovered and elaborated of boosting of HDS of DBT at extremely mild operation conditions under the

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Review article

Promising anti-inflammatory effects of chalcones via inhibition of cyclooxygenase, prostaglandin E_2, inducible NO synthase and nuclear factor κb activities

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ARTICLE INFO

Keywords:
Chalcone
Inflammation
Cyclooxygenase
Inhibition
Cardamonin

ABSTRACT

Chalcones (1, 3-Diphenyl-2-propen-1-one) consist of a three carbon α, β-unsaturated carbonyl system and act as precursors for the biosynthesis of flavonoids in plants. However, laboratory synthesis of various chalcones has also been reported. Both natural and synthetic chalcones are known to exhibit a variety of pharmacological activities such as anti-inflammatory, antitumor, antibacterial, antifungal, antimalarial and antituberculosis. These promising activities, ease of synthesis and simple chemical structure have awarded chalcones considerable attraction. This review focuses on the anti-inflammatory effects of chalcones, caused by their inhibitory action primarily against the activities and expressions of four key inflammatory mediators viz., cyclooxygenase, prostaglandin E_2, inducible NO synthase, and nuclear factor κB. Various methodologies for the synthesis of chalcones have been discussed. The potency of recently synthesized chalcones is given in terms of their IC_{50} values. Structure-Activity Relationships (SARs) of a variety of chalcone derivatives have been discussed. Computational methods were applied to calculate the ideal orientation of a typical chalcone scaffold against three enzymes, namely, cyclooxygenase-1, cyclooxygenase-2 and inducible NO synthase for the formation of stable complexes. The global market of anti-inflammatory drugs and its expected growth (from 2018 to 2026) have been discussed. SAR analysis, docking studies, and future prospects all together provide useful clues for the synthesis of novel chalcones of improved anti-inflammatory activities.

1. Introduction

Leukocytes or white blood cells are involved in counteracting foreign substances, microorganisms, and infectious diseases and therefore, constitute a key component of the host immune system. However, they can also generate cellular impairment in host tissues in inflammatory disorders via degranulation and production of reactive species [1–3]. Inflammation is a defensive strategy in higher organisms in which the immune system identifies impaired cells, irritants, pathogens, and other harmful stimuli, and initiates the curing process [4]. Inflammation constitutes part of the body's immune feedback. An inflammatory response is responsible for healing infections, injuries, and any impairment to the tissues. A number of physical responses initiated by the immune system as a reaction to a physical injury or an infection cause inflammation [5]. Acute inflammation initiates quickly and becomes intense in a short period. Symptoms last for several days but may continue for a few weeks in some conditions. Acute inflammation is characterized by pain, redness, immobility, swelling, and heat. Acute bronchitis, infected ingrown toenail, a sore throat from a cold or flu, a scratch or cut on the skin, high-intensity exercise, acute appendicitis, dermatitis, tonsillitis, infective meningitis, sinusitis, and physical trauma are the conditions and diseases which can cause acute

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; COX, cyclooxygenase; NOS, nitric oxide synthase; CAM, cell adhesion molecules; LOX, lipooxygenase; PGs, prostaglandins; PGE_2, prostaglandin E_2; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; LOX, lysyl oxidase; mPGES-1, microsomal prostaglandin E synthase-1; LPS, Lipopolysaccharide; TNF-α, tumor necrosis factor-α; NO, nitric oxide; nNOS, neural NO Synthase; eNOS, endothelium NO synthase; ERK, extracellular signal-regulated kinase; IFN-g, interferon-g; IκBα, the inhibitor of kappa B; IL-1, interleukin-1; EMSA, electrophoretic mobility shift assay; IKK, inhibitor κB kinase; IκB, inhibitor κB; RANKL, receptor activator of NF-κB ligand; TRAP, tartrate-resistant acid phosphatase

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molecules

MDPI

Article

Characteristics and Kinetics of Rosin Pentaerythritol Ester via Oxidation Process under Ultraviolet Irradiation

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Abstract: A self-designed reaction device was used as a promising equipment to investigate the oxidation characteristics and kinetics of rosin pentaerythritol ester (RPE) under UV irradiation. Photo-oxidation kinetics and the initial quantum yield (Φ) of RPE were calculated. The initial oxidation product of the photo-oxidation reaction—peroxide was analyzed by iodimetry. The peroxide concentration is related to the light intensity (I) and the temperature (T), and the increasing T and I would destabilize the RPE by accelerating peroxide forming. Photo-oxidation of RPE follows the pseudo first-order reaction kinetics. The relationship between activation energy and logarithm of light intensity (ln I) is linear, and it is expressed as Ea = −4.937ln I + 45.565. Φ was calculated by the photo-oxidation kinetics, and the average value of Φ was 7.19% in the light intensity range of 200–800 μW cm^{-2}. This research can provide fundamental information for application of RPE, and help obtain a better understanding of the stability of rosin esters.

Keywords: rosin pentaerythritol ester; photo-oxidation; kinetics; UV

1. Introduction

Rosin is a significant and renewable natural product produced by the resin of some conifers, such as pine trees. It is a non-volatile transparent or translucent solid and plays an important role in daily life. The main components of rosin include abietic acid and a few other resin acids [1]. The carboxylic group of rosin can be coupled to different alcohols such as pentaerythritol, methanol, ethylene-glycol, and glycerol via esterification, and rosin esters are some of the most common rosin derivatives [2,3]. China's annual production of gum rosin is about 400,000 tons, accounting for 60% of the world's total production. In 2017, the output of rosin ester products in China was about 100,000 tons [4].

Rosin pentaerythritol ester (RPE) is a common modified rosin product obtained by esterification of rosin acid and pentaerythritol, and its molecular structure is shown in Figure 1. RPE is widely used in paper, food, inks and coatings, as well as in adhesive industries [5–9]. Lee et al. [10] used RPE as an additive to polyvinylidene fluoride binders and it effectively improved the lithium-titanium oxide (LTO) electrochemical performance. Kumooka et al. [11] reported the addition of the rosin pentaerythritol ester, causing improvement in the cohesive strength of the adhesive. Sangjun et al. [12] prepared a pressure-sensitive adhesive (PSA) using RPE as tackifier, which promised sustainability and high adhesion properties.

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Review article

Research advances on anticancer activities of matrine and its derivatives: An updated overview

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ABSTRACT

Cancer is the second leading cause of mortality, only overcome by cardiovascular diseases, and has caused more than 8.7 million deaths in 2015 all over the world. This figure is expected to rise to about 13.1 million by 2030. In order to prevent or cure this fatal illness, substantial efforts have been devoted to develop and discover new anticancer drugs with same or better antitumor activity but lesser toxicity. Matrine is an alkaloid isolated from *Sophora flavescens* Ait. For decades, matrine and its derivatives have been studied as antineoplastic agents which predominantly work by inhibiting proliferation and inducing apoptosis of cancer cells. The mechanism responsible for the anticancer activity of matrine can be recognized via up-regulating or down-regulating expression of the cancer related molecules, eventually causing tumor cell death. This review summarizes research developments of matrine and its derivatives as anticancer agents. A few possible research directions, suggestions and clues for future work on the development of novel matrine-based anticancer agents with improved expected activities and lesser toxicity have also been provided.

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Full Length Article

Ultra-fast and highly efficient catalytic oxidative desulfurization of dibenzothiophene at ambient temperature over low Mn loaded Co-Mo/Al_2O_3 and Ni-Mo/Al_2O_3 catalysts using NaClO as oxidant

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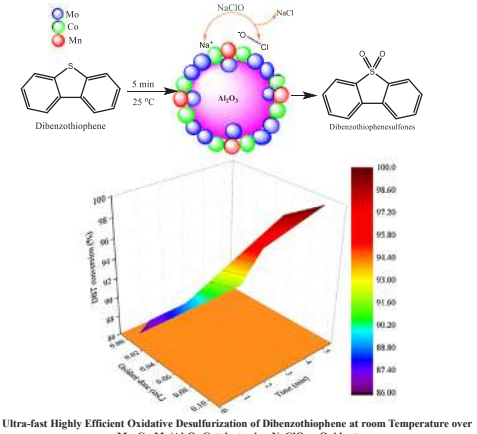
GRAPHICAL ABSTRACT



Ultra-fast Highly Efficient Oxidative Desulfurization of Dibenzothiophene at room Temperature over Mn-Co-Mo/Al_2O_3 Catalyst using NaClO as Oxidant

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Keywords:
Oxidative desulfurization
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ABSTRACT

This study reports the ultra-fast and highly efficient oxidative desulfurization (ODS) of dibenzothiophene (DBT) at room temperature over low Mn (0.5 wt%) incorporated Co-Mo/Al_2O_3 and Ni-Mo/Al_2O_3 catalysts using NaClO as oxidant. The effect of disparate operating parameters i.e. mode of catalyst preparation, DBT initial concentration, reaction time, temperature, catalyst and oxidant dose, oxidant type and reaction pH on oxidation process was investigated. Results revealed that remarkably high and ultra-fast A DBT conversion of 100% was achieved within 5 min utilizing 15 mL sample of 2000 ppm (347 ppm sulfur), 0.1 mL of 0.138 M NaClO (O/S-6.6 mol/mol), 0.1 g Mn-Co-Mo/Al_2O_3 catalyst at pH 12, and 25 °C reaction temperature. A reaction mechanism for the highly efficient ODS activity of Mn promoted catalysts accredited to the synergistic effect of Mn active phase and high oxidizing power of NaClO was proposed. An overall ODS catalytic activity order of: Mn–Co–Mo/Al_2O_3 > Mn–Ni–Mo/Al_2O_3 > Co–Mo/Al_2O_3 > Ni-Mo/Al_2O_3 > Mo/Al_2O_3 was observed. Discernment of the

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Research paper

Novel indolo-sophoridinic scaffold as Topo I inhibitors: Design, synthesis and biological evaluation as anticancer agents

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ABSTRACT

Based on the mechanism of action, novel scaffolds as Topo I inhibitors bearing indole and sophoridinine were designed. Preliminary docking study revealed that some molecules among the designed series possessed promising Topo I inhibitor properties. Subsequently, thirty new compounds were synthesized and characterized by ^{1}H NMR, ^{13}C NMR, and Mass spectral analyses. The compounds were then screened for their antiproliferative and enzymatic inhibitory activities. The results affirmed the consistency between docking and activities and the rationality of the design strategy. Furthermore, compound **10b** was chosen as a representative compound to test its anticancer effects *in vitro* and *in vivo*. The results showed that **10b** caused prominent S phase cell cycle arrest and significantly suppressed tumor growth in HepG2 cell derived mouse model. These findings present a promising series of lead molecules which can serve as potential Topo I inhibitors for the treatment of cancer and a theoretical basis for structural modifications.

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1. Introduction

DNA topoisomerase I (Topo I) is an essential and ubiquitous enzyme that cleaves a single DNA strand to relax supercoiled DNA for replication, transcription, recombination, and chromatin remodeling [1–3]. Topo I is over-expressed in many cancer types and can promote cancer cell proliferation [4–7]. Thus, Topo I is recognized as important target in cancer therapy and anticancer drug design. Therefore, developing new Topo I inhibitors has become a hotspot research in medicinal chemistry.

Presently, the studies on Topo I inhibitors have focused on alkaloids, among which camptothecins are the primary Topo I inhibitors. Despite of their potent anticancer activity, many limitations could be well-defined in all of the camptothecins [8,9]. In addition to their dose-limiting toxicity, camptothecins are inactivated within minutes at physiological PH due to their transformation to camptothecin carboxylate by lactone E ring opening [10–12]. Thus, development of Topo I inhibitors with new scaffold can be expected to overcome these shortcomings. Indolocarbazoles, indenoisoquinolines, and dibenzonaphthyridinones represent a class of non-camptothecins compounds which have been reported to possess the most extensive applications as Topo I inhibitors (Fig. 1) [13–17].

An evident feature of the above poisons is their planar heterocyclic ring structure containing nitrogen. A comparative analysis of three different ternary structures obtained via X-ray crystal structure models indicates that camptothecin, indolocarbazole, and indenoisoquinoline compounds are bound to the topoisomerase I-DNA complex, and further reveals some prominent resemblance on the mode of action of the Topo I poisons. The characteristic structures of these poisons allow them to intercalate into DNA and form stacking interactions with base pairs by mimicking a DNA base pair. It is vital to mention that most of the solvent accessible part of every compound is protected by DNA (57%–70%) due to intercalation binding mode, which further supports the idea that stacking interactions may be the primary binding interaction for these Topo I poisons [18] (Fig. 2). Thus, it is necessary to design new drug

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Research paper

Design, synthesis, biological evaluation and structure-activity relationship of sophoridine derivatives bearing pyrrole or indole scaffold as potential antitumor agents

Zheng Li [a, 1], Mengyang Luo [a, 1], Bin Cai [c, 1], Haroon-Ur-Rashid [a], Mengtian Huang [a], Jun Jiang [a], Lisheng Wang [b, **], Lichuan Wu [b, *]

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ABSTRACT

Taking sophoridine as a lead compound, 58 sophoridine derivatives were designed, synthesized and evaluated for their antiproliferative activity in the HepG2 cancer cell line. Among the 58 compounds, 33 compounds showed potent antiproliferative activity with IC_{50} less than 10 μM. Compound **5w** showed the most potent anti-proliferative activity in the HepG2 cancer cell line. Thus, we further extended our characterization of the antiproliferative activity of **5w** in six cancer cell lines (HepG2, SMMC-7721, Hela, CNE1, CNE2 and MCF7). The representative compound **5w** displayed robust anti-proliferative activities in all the tested cell lines with IC_{50} values in range of 0.93–1.89 μM which were much lower than that of sophoridine. Here, we report the structure–activity relationships (SAR) in a sophoridine series of compounds, which indicated that introduction of N-benzyl indole group on the 14-carbon atom of sophoridine can significantly enhance the antiproliferative activity. By molecular docking and enzymatic assay, compound **5w** was found to be able to inhibit the activity of DNA Topo I. Furthermore, apoptosis assay displayed that compound **5w** could significantly induce the apoptosis of HepG2 cells in a dose-dependent manner by activating caspase-3, increasing expression of cleaved caspase-3 and reducing the ratio of Bcl-2/Bax. The *in vivo* antitumor assay demonstrated that **5w** suppressed the growth of HepG2 xenografts in nude mice without any obvious side effects.

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1. Introduction

Sophoridine is one of the main active ingredients of the Chinese traditional medicine *FufangKushen injection* [1–3] which was approved by CFDA (Chinese Food & Drug Administration) in 1995 as an adjuvant to treat non-small cell lung cancer (NSCLC), liver cancer and gastric cancer in combination with other anticancer agents [3–7]. As a single agent, sophoridine was approved by CFDA to cure cancer patients with malignant trophoblastic tumors in 2005 [8]. It has been reported that sophoridine displayed anticancer activity via inhibiting DNA topo I activity and arresting the cell cycle at G0/G1 phase, resulting in cell apoptosis [9–11]. Owing to its multiple drug like properties, such as special scaffold, simple structure and high solubility, sophoridine has been considered as an ideal lead compound for further structural modifications and optimizations.

In our previous study, we found that introduction of aromatic methylene group at 14 position of sophoridine skeleton could obviously increase its anticancer activity [12]. While some synthetic derivatives of sophoridine with an open D ring have exhibited favorable antiproliferative activity [8,13,14], no derivatives with four intact rings and prominent cytotoxic activities ($IC_{50} < 10$ μM) have been reported. It provoked our strong interest to further develop structural modifications and optimizations in an effort to discover a novel class of anticancer candidates with a 4-ring scaffold. The introduction of nitrogen-containing heterocycle is a ubiquitous strategy towards the structure modification of natural products as nitrogen atom can influence the interaction between the molecule and its target [15]. In particular, pyrrole or

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Hydrodesulfurization of dibenzothiophene using Pd-promoted Co–Mo/Al_2O_3 and Ni–Mo/Al_2O_3 catalysts coupled with ionic liquids at ambient operating conditions†

Yaseen Muhammad,[ab] Ata Ur Rahman,[b] Haroon Ur Rashid,[a] Maria Sahibzada,[c] Sidra Subhan[ab] and Zhangfa Tong *[a]

Sulfur compounds in fuel oils are a major source of atmospheric pollution. This study is focused on the hydrodesulfurization (HDS) of dibenzothiophene (DBT) *via* the coupled application of 0.5 wt% Pd-loaded Co–Mo/Al_2O_3 and Ni–Mo/Al_2O_3 catalysts with ionic liquids (ILs) at ambient temperature (120 °C) and pressure (1 MPa H_2). The enhanced HDS activity of the solid catalysts coupled with [BMIM]BF_4, $[(CH_3)_4N]Cl$, [EMIM]$AlCl_4$, and $[(n\text{-}C_8H_{17})(C_4H_9)_3P]Br$ was credited to the synergism between hydrogenation by the former and extractive desulfurization and better H_2 transport by the latter, which was confirmed by DFT simulation. The Pd-loaded catalysts ranked highest by activity *i.e.* Pd–Ni–Mo/Al_2O_3 > Pd–Co–Mo/Al_2O_3 > Ni–Mo/Al_2O_3 > Co–Mo/Al_2O_3. With mild experimental conditions of 1 MPa H_2 pressure and 120 °C temperature and an oil : IL ratio of 10 : 3.3, DBT conversion was enhanced from 21% (by blank Ni–Mo/Al_2O_3) to 70% by Pd–Ni–Mo/Al_2O_3 coupled with $[(n\text{-}C_8H_{17})(C_4H_9)_3P]Br$. The interaction of polarizable delocalized bonds (in DBT) and van der Waals forces influenced the higher solubility in ILs and hence led to higher DBT conversion. The IL was recycled four times with minimal loss of activity. Fresh and spent catalysts were characterized by FESEM, ICP-MS, EDX, XRD, XPS and BET surface area techniques. GC-MS analysis revealed biphenyl as the major HDS product. This study presents a considerable advance to the classical HDS processes in terms of mild operating conditions, cost-effectiveness, and simplified mechanization, and hence can be envisaged as an alternative approach for fuel oil processing.

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1. Introduction

Organosulfur compounds leading to the production of deleterious and hazardous sulfur oxides, *i.e.* SO_x, from the combustion of fuel oils has led to the permissible limits of sulfur becoming much more stringent over the years.[1] Among the many desulfurization approaches, such as oxidative desulfurization,[2] biodesulfurization[3] and extractive desulfurization,[4] hydrodesulfurization (HDS) ranks higher, attributed to its diverse nature, high practicability and efficiency.[5] HDS generally utilizes a Co or Ni sulfide phase added to Mo impregnated over Al_2O_3-supported catalysts.[6–8] Furthermore, incorporation of a third promoter metal, *i.e.* Pt, Pd, and Ir, can further enhance the HDS activity of classical catalysts.[5,9,10] Despite its efficient and versatile nature, HDS suffers from complex mechanization, poor safety and harsh temperature (380–400 °C) and pressure (8 MPa) operating conditions.[11–13] Similarly, expensive catalytic promoters like Pt, Pd, and Ir further add to the uncontrolled process costs. Thus, an HDS process operated at mild temperature and pressure over a low-cost catalyst without compromising on the process efficiency could offer an alternative route for fuel oil processing.

Apart from HDS, a newer approach to fuel oil desulfurization research is extraction using ionic liquids (ILs).[14,15] Aspects such as ease of synthesis, high recycling ability, low volatility, high thermal stability and environmental friendliness are credited for the widespread application of ILs.[16] However, few studies on the integrated application of ILs with solid catalysts have been reported in hydrogenation reactions,[17] which emphasizes that ILs coupled with solid catalysts should be tested for HDS of fuel oils.

In previous work, we reported 52% dibenzothiophene (DBT) conversion in a HDS process with a mild operating temperature and pressure by the coupled application of selected ILs with Ce–Ni–Mo/Al_2O_3 catalysts.[18] However, to further improve the efficiency of solid catalyst-coupled ILs HDS processes, more exploration is required for new types of catalysts and ILs.

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, and biological evaluation of thiomatrine derivatives as potential anticancer agents

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Abstract

A series of new thiomatrine derivatives was designed and synthesized for their potential application as anticancer agents. The structure of these compounds was characterized by ^{1}H-NMR, ^{13}C-NMR, and ESI-MS spectral analyses. Single crystals of compound 3k were obtained by recrystallization and the structure was further confirmed by X-ray diffraction determination. All the target compounds were evaluated for their in vitro cytotoxicity against human cancer cell lines A549 and HepG2. Among these compounds, the derivative 3aa displayed the most significant anticancer activity against four cancer cell lines with IC_{50} values in range of 7.8–11.4 μM, indicating much better activity than the parent compound (matrine). The cell cycle analysis revealed that compound 3aa could cause cell cycle arrest of SMMC-7721 and CNE2 cells at G2/M phase. Furthermore, the Annexin V-FITC/PI dual staining assay revealed that compound 3aa could significantly induce the apoptosis of SMMC-7721 and CNE2 cells in a dose-dependent manner. Western blot analysis revealed that compound 3aa could induce apoptosis by activating caspase-3, increasing expression of cleaved caspase-3 and reducing the ratio of Bcl-2/Bax.

Keywords Thiomatrine derivatives · Anticancer · Cell cycle · Apoptosis · Crystal structure

Introduction

Matrine (Fig. 1) is one of the main active ingredients in Fufang Kushen injection. In combination with other anticancer agents such as vinorelbine, taxol and cisplatin, matrine was also approved by CFDA in 1995 as an adjuvant to treat non-small cell lung cancer, liver cancer and gastric cancer. (Zhong and Wu 2006; Sun et al. 2012; Sun et al. 2011; Wang et al. 2014; Wei et al. 2011; Liu et al. 2012; Qi et al. 2013; Tian et al. 2007) Owing to its advantage properties, such as special scaffold, good safety profles and high solubility, matrine has been considered as an ideal lead compound for further structural modifications and optimizations. (Peng-Yi et al. 2012; Li et al. 2004; Ye et al. 2007) It has been found that matrine displayed potent anticancer activity and induced apoptosis in cancer cells via down-regulation of Bcl-2, upregulation of Bax and suppression of β-catenin/survivin pathway. (Yong et al. 2015; Liu et al. 2010; Li et al. 2015; Li et al. 2010; Zhou et al. 2015; Wang et al. 2015)

The structure of matrine consists of a 15-carbon skeleton which has an available site for chemical modification at C-14 position. In our previous study, we selected matrine as a lead compound and successfully identified that introduction of double bond and aromatic ring at 14 site of matrine skeleton could largely increase its anticancer activity. (Wang et al. 2012; Xie et al. 2014; Wu et al. 2011) The representative compound **YF18** (Fig. 1), 14-napthylmethylene matrine, exhibited a significantly enhanced anticancer

These authors contributed equally: Zheng Li and Lichuan Wu

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Research Article

Synthesis, Characterization, X-Ray Crystallography, and Antileishmanial Activities of *N*-Linked and *O*-Linked Glycopyranosides

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Novel *N*-linked **5a–e** and *O*-linked glycopyranosides **7a–e** were synthesized in high yield from commercially available L-tartaric acid containing two asymmetric centers and C_2 axis of symmetry. The compound L-tartaric acid was completely protected and then partially hydrolyzed to get the monoester, which upon treatment with different amino and hydroxyl derivatives of glycopyranoses gave the desired amides and esters. The synthesized derivatives were purified by chromatography and characterized by spectroanalytical techniques. The structure of compound **7c** in the series was supported by X-ray analysis. Leishmanicidal activities of compounds **5a–e** and **7a–e** were investigated which showed moderate to good activities.

1. Introduction

Leishmania has long been known to human beings especially in African and Indian populations since the mid eighteenth century [1–3]. In 1903, Leishman and Donovan discovered the protozoan in spleen tissues of patients in India, which is now known as *Leishmania donovani* [4, 5]. Nicolle and Comte reported infection by *Leishmania* in dogs in 1908 [6]. Leishmaniasis is a vector-borne disease carried by sand fly and caused by protozoa of the genus *Leishmania*. Recent reports confirm that people in about 88 countries are affected by *Leishmania* and 350 million are at risk, and more or less 2 million new cases are reported each year [7]. In spite of the socioeconomical significance of this tropical infectious disease, the discovery of new potential drugs against it is underway [8, 9].

Glycolipid and glycoprotein oligosaccharides present on cell surfaces are known to play an important role in various biological processes, that is, cellular recognition, adhesion, tumor metastasis, and cell growth regulation [10]. One major class of glycoprotein oligosaccharides consists of *N*-oligosaccharides linked to asparagine by an amide bond [11, 12]. Amides are usually prepared by thermolysis of carboxylic acids with amines, by coupling of carboxylic acids and amines in the presence of a coupling reagent [13] or by prior conversion of the carboxylic acid into a more electrophilic derivative [14]. The concept to add a chiral aglycone moiety such as tartaric acid to prepare glycosides is an active area

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Design, synthesis and biological evaluation of matrine derivatives as potential anticancer agents

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ABSTRACT

Using matrine (**1**) as the lead compound, a series of new 14-(*N*-substituted-2-pyrrolemethylene) matrine and 14-(*N*-substituted-indolemethylene) matrine derivatives was designed and synthesized for their potential application as anticancer agents. The structure of these compounds was characterized by ^{1}H NMR, ^{13}C NMR and ESI-MS spectral analyses. The target compounds were evaluated for their in vitro cytotoxicity against three human cancer cell lines (SMMC-7721, A549 and CNE2). The results revealed that compound **A6** and **B21** displayed the most significant anticancer activity against three cancer cell lines with IC_{50} values in range of 3.42–8.05 μM, which showed better activity than the parent compound (Matrine) and positive control Cisplatin. Furthermore, the Annexin V-FITC/PI dual staining assay revealed that compound **A6** and **B21** could significantly induce the apoptosis of SMMC-7721 and CNE2 cells in a dose-dependent manner. The cell cycle analysis also revealed that compound **A6** could cause cell cycle arrest of SMMC-7721 and CNE2 cells at G2/M phase.

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Matrine (Fig. 1) is one of the main active ingredients in Fufang-Kushen injection. In combination with other anticancer agents such as vinorelbine, taxol and cisplatin, matrine was also approved by CFDA in 1995 as an adjuvant to treat non-small cell lung cancer (NSCLC), liver cancer and gastric cancer.[1–8] It has been found that matrine displayed potent anticancer activity and induced apoptosis in cancer cells via downregulation of Bcl-2, upregulation of Bax and suppression of β-catenin/survivin pathway.[9–14]

Owing to its multiple drug like properties, such as special scaffold, simple structure and high solubility, matrine has been considered as an ideal lead compound for further structural modifications and optimizations.[15–17]

In our previous study, we selected matrine as a lead compound and successfully identified that introduction of double bond and aromatic ring at 14 site of matrine skeleton could largely increase its anticancer activity.[18–20] The representative compound **YF18** (Fig. 1), 14-napthylmethylene matrine, exhibited a significantly enhanced anticancer activity in three human lung cancer cell lines i.e. A549, H1975 and 95D, with IC_{50} ranging from 10 to 15 μM. Thus, compound YF18 showed much better anticancer activity than matrine.[20]

Moreover, the introduction of nitrogen-containing heterocycle is a ubiquitous strategy towards the structure modification of natural products as nitrogen atom can influence the interaction between the molecule and its target.[21] It is also reported that an *N*-substituted pyrrole scaffold (Fig. 1) is essential to enhance anticancer activity of several natural products, such as lukianol A and lamellarin O.[22] And it is well-known that a *N*-benzyl indole scaffolds possess various biological activities and continues to be a pervasive structural feature of many pharmacologically active compounds, such as a newly discovered anticancer agent Indibulin.[23] Based on this idea, it provoked our strong interest to introduce *N*-substituted pyrrole and indole group into 14 site of matrine in order to discover a novel class of anticancer candidates (Fig. 1).

Therefore, a variety of *N*-substituted pyrroles and indole were introduced on the 14 site of matrine skeleton which resulted in designing two series of new matrine derivatives. These derivatives were synthesized, and biologically evaluated for their anticancer activities. In this study, structure–activity relationship (**SAR**) was first conducted to focus on the variations of the *N*-substitution of pyrrole, while keeping the 14-(2-pyrrolemethylene) matrine

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Ultrasonic-assisted reductive extraction of matrine from sophorae tonkinesis and its purification by macroporous resin column chromatography

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ABSTRACT

In this work, ultrasonic-assisted reductive extraction of matrine from Sophorae tonkinesis was studied for the first time. During this process, sodium metabisulfite was added as a reducing agent in order to covert maximum amount of oxymatrine, sophocarpine, and oxysophocarpine to matrine. After optimization by response surface methodology, the extraction yield of matrine was found to be 2.03%, much higher than the yield obtained through traditional extraction method. After filtration, H103-macroporous adsorption resin column chromatography, concentration, and recrystallization, matrine with 98.2% purity was obtained.

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Introduction

Sophorae tonkinesis is a herb, widely distributed in southwest China. It has been extensively used for a long time as a traditional Chinese medicine to relieve inflammations. It contains quinolizidine alkaloids as its principal constituents which possess pharmacological effects such as analgesic, anti-inflammatory, antipyretic, antitumor, and remarkable antiviral activities.[1] Two major alkaloids namely oxymatrine and matrine, extracted from Sophorae tonkinesis have been reported to exhibit antihepatitis B virus (HBV) activity as well.[2]

Extraction is an effective method for obtaining bioactive substances from medicinal plants. Compared with the traditional extraction such as water bath heating extraction, ethanol refluxing extraction, and Soxhlet extraction, ultrasound assisted extraction (UAE) is an environment-friendly technique and has been used to increase the extraction rate of biologically active substances from natural products. Furthermore, it plays an important role in disruption of cell walls, reduction of particle size, and enhancement of mass transfer to the cell contents as a result of cavitation bubble collapse.[3] Compared to traditional extraction process, ultrasonic extraction is an economical alternative for obtaining expensive raw materials and is, therefore, the need of sustainable industrial development.[4] Response surface methodology (RSM) can save time and labor, and reduce the number of experimental trials when interactions of multiple factors need to be evaluated.[5] The Box-Behnken design (BBD), one of the most common models of RSM, is widely used to optimize extraction conditions.[6] In addition, many methods namely silica gel, polyamide column chromatography, high-speed counter-current chromatography, molecular imprinting technology, and preparative high performance liquid chromatography (Pre-HPLC), have previously been reported for the preparative separation and purification of matrine.[7–9] However, the above-mentioned techniques have disadvantages, like small-scale operation and complicated procedures. Recently, macroporous adsorption resin chromatography (MARC) has been successfully used for the separation of various bioactive molecules due to its easy operation, high adsorption capacity, good stability, low fluid resistance, and repeated use.[10–12] Ultrasonic-assisted reductive extraction (URAE) and MARC were combined together to establish a green and efficient method for simultaneous extraction and purification of matrine from Sophorae tonkinesis in this work.

Materials and methods

Materials and reagents

Sophorae tonkinesis were purchased in Nanning, Guangxi province. Anhydrous ethyl alcohol, Petroleum ether, Sodium metabisulfite, Sodium hydroxide, and sulfuric acid were of analytical grade and purchased from West long science co., Ltd (Guangxi, China). The reference substance of matrine was obtained from Mansite Biological Technology Co., Ltd. (Chengdu, China). All other

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Research Article

Tuning of Activated Carbon for Solvent-Free Oxidation of Cyclohexane

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Activated carbon (AC) was prepared from carbonization of phosphoric acid soaked peanut shell at 380°C under inert atmosphere followed by activation with hydrogen peroxide. The AC was characterized by SEM, EDX, FTIR, TGA, and BET surface area and pore size analyzer. The potential of AC as a catalyst for solvent-free oxidation of cyclohexane to cyclohexanol and cyclohexanone (the mixture is known as KA oil) in the presence of molecular oxygen at moderate temperature was investigated in a self-designed double-walled three-necked batch reactor. The effect of different reaction parameters/additive was optimized. The maximum productivity value (2.14 $mmol g^{-1} h^{-1}$, without base, and 4.85 $mmol g^{-1} h^{-1}$, with 0.2 mmol NaOH) of the desired product was achieved under optimal reaction parameters: vol 12.5 mL, cat 0.4 g, time 14 h, oxygen flow 40 mL/min (pO_2 760 Torr), stirring 1100 rpm, and temp 75°C. The AC shows recyclability for multiple runs without any significant loss in activity. Thus, the AC can be an efficient catalyst, due to low cost, ease of synthesis, easy recovery, nonleaching, and recyclability for multiple uses for the solvent-free oxidation of cyclohexane.

1. Introduction

Activated carbon (AC) was reported as an effective catalyst for the first time in the beginning of 19th century [1]. In early nineteenth century, AC was prepared commonly by thermal activation method from different agricultural raw materials and investigated as a catalyst for the degradation of hydrogen peroxide. The catalytic activity of the AC for the decomposition of hydrogen peroxide was very good but persisted only for short duration. The most probable reason for the vanishing of catalytic activity being used for decomposition of hydrogen peroxide may be deactivation of oxygenated groups on the surface of activated carbon [2, 3]. The major issue related to durability of AC was successfully addressed by researchers in recent decades. Through physical, physicothermal, chemical, and chemothermal activation, the AC was tuned to show a good catalytic activity [4] in production of phosgene, sulphur halides, hydrogenation, polymerization, halogenation [5–7], removal of SO_2 and NOx [8, 9], and oxidation of benzyl alcohol [10]. This performance of AC was attributed to its porosity, active sites, and high surface area. Thus, by controlling these parameters, AC can be tuned as an effective catalyst for a selected organic transformation.

The oxidation of cyclohexane to cyclohexanol and cyclohexanone (KA oil) has paramount importance due to their applications in the synthesis of Nylon-6,6 and Nylon-6, as solvent lacquers, varnishes and shellacs, and as homogenizer

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Research Article

Transport of Zn (II) by TDDA-Polypropylene Supported Liquid Membranes and Recovery from Waste Discharge Liquor of Galvanizing Plant of Zn (II)

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The facilitated passage of Zn (II) across flat sheet supported liquid membrane saturated with TDDA (tri-n-dodecylamine) in xylene membrane phase has been investigated. The effect of acid and metal ion concentration in the feed solution, the carrier concentration in membrane phase, stripping agent concentration in stripping phase, and coions on the extraction of Zn (II) was investigated. The stoichiometry of the extracted species, that is, complex, was investigated on slope analysis method and it was found that the complex $(LH)_2{\cdot}Zn(Cl_2)$ is responsible for transport of Zn (II). A mathematical model was developed for transport of Zn (II), and the predicted results strongly agree with experimental ones. The mechanism of transport was determined by coupled coion transport mechanism with H^+ and Cl^- coupled ions. The optimized SLM was effectively used for elimination of Zn (II) from waste discharge liquor of galvanizing plant of Zn (II).

1. Introduction

Over the past few decades, the prompt boost in the utilization of heavy metals has increased the flux of metallic ingredients into soils and natural water resources. The presence of even small amount of heavy metals in the environment is hazardous as the majority of them are harmful and persistent [1]. The zinc concentration in the earth crust is about 70 ppm. Zinc and its compounds have many applications and are used in galvanization, alloys, catalysts, wood preservation, vulcanization for rubber, photographic paper, ceramics, fertilizers, textiles, batteries, pigments and as dietary supplements and in medicines [2, 3].

About two billion people suffer from zinc deficiency in the developing countries and this thus causes various disorders in them. In minors, zinc deficiency is responsible for growth retardation, infection susceptibility, delayed sexual maturation, and diarrhea. These disorders lead to the deaths of about 800,000 children throughout the world every year.

Excess of zinc in the human body has been associated with system dysfunction which in turn can affect growth and reproduction. The presence of free zinc ion in solution has been reported to be very toxic for vertebrates, invertebrates, and plants [4–6]. Due to its toxic effect, large scale applications, and increasing demand for pure zinc, it is necessary to remove and separate zinc from industrial effluents.

Traditional techniques of recovery for metal ions, such as adsorption [7, 8], solvent extraction [9–12], precipitation [13], and ion exchange [14]. have normally low efficiency, require high capital and operating cost, and produce secondary pollution complications [15]. Among novel techniques suggested for transport of metal ions, supported liquid membrane is one of the promising methods. The technique comprises the applications of solvent extraction (high selectivity and

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Article

Oxidative desulfurization of dibenzothiophene over Fe promoted Co–Mo/Al_2O_3 and Ni–Mo/Al_2O_3 catalysts using hydrogen peroxide and formic acid as oxidants

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ABSTRACT

This work reports the enhancing effect of a highly cost effective and efficient metal, Fe, incorporation to Co or Ni based Mo/Al_2O_3 catalysts in the oxidative desulfurization (ODS) of dibenzothiophene (DBT) using H_2O_2 and formic acid as oxidants. The influence of operating parameters *i.e.* reaction time, catalyst dose, reaction temperature and oxidant amount on oxidation process was investigated. Results revealed that 99% DBT conversion was achieved at 60 °C and 150 min reaction time over Fe–Ni–Mo/Al_2O_3. Fe tremendously enhanced the ODS activity of Co or Ni based Mo/Al_2O_3 catalysts following the activity order: Fe–Ni–Mo/Al_2O_3 > Fe–Co–Mo/Al_2O_3 > Ni–Mo/Al_2O_3 > Co–Mo/Al_2O_3, while H_2O_2 exhibited higher oxidation activity than formic acid over all catalyst systems. Insight about the surface morphology and textural properties of fresh and spent catalysts were achieved using scanning electron microscopy (SEM), X-ray diffraction (XRD), energy dispersive X-ray (EDX) analysis, Atomic Absorption Spectroscopy (AAS) and BET surface area analysis, which helped in the interpretation of experimental data. The present study can be deemed as an effective approach on industrial level for ODS of fuel oils crediting to its high efficiency, low process/catalyst cost, safety and mild operating condition.
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1. Introduction

Fossil fuels are contributing more than 82% of energy all over the globe, of which, 50% comes from fuel oils and hence petroleum is still the primary source to fulfill these needs [1]. Fuel oils are generally contaminated with organosulfur compounds comprising of thiols, aromatic sulfides, mercaptanes and benzothiophenes (BTs), where BTs contribute about 85% [2,3]. These organosulfur ring compounds exist in non-substituted *i.e.* BT, dibenzothiophenes (DBT), as well as alkyl derivatives *i.e.* 4-methyldibenzothiophene (4-MDBT) and 4,6-dimethyldibenzothiophene (4,6-DMDBT) [4]. These sulfur (S) compounds adversely affect the quality of petroleum products by decreasing the API gravity and calorific value as well as contribute to environmental pollution by getting converted into SO_x during combustion. Moreover, S species also lead to particulates production resulting in black exhaust fumes [5], causing impairment of pipelines, acid rain and poisoning of catalysts in oil refineries [6].

Worldwide oil refineries are now producing low S fuel oils (less than 50 ppm) to meet new regulation mandate [7] which is a challenging job. Several reports following different approaches are available in literature to cope with these challenges including hydrodesulfurization (HDS) [8,9], biodesulfurization (BDS) [10], adsorptive desulfurization [11], oxidative desulfurization (ODS) [12,13], and extraction through ionic liquids (ILs) *etc.* [14,15]. HDS, operated at high temperature and pressure in the presence of excess hydrogen over a suitable catalyst, is quite effective for cyclic and aliphatic S containing hydrocarbons but less attractive towards BT and DBT [16]. Also harsh operating conditions in HDS cause higher consumption of hydrogen and decrease of catalyst life resulting in higher costs [17]. Similarly, the use of other approaches like BDS is hindered by low versatility of types of enzymes, slow reaction rates and low miscibility of the reactants [18]. On the contrary, ODS is an interesting and conventional process characterized by mild temperature and pressure operation in the presence of a suitable catalyst and oxidant *i.e.* ozone, perchlorate, potassium permanganate, nitric acid, nitrogen oxides, *ter*-butyl hydroperoxide and hydrogen peroxide where H_2O_2 has been reported with good activity [19]. In addition to oxidant selection, various catalytic systems such as polyoxometalates, molybdates supported on alumina, tungsten, vanadium and titanium supported catalysts have been reported elsewhere [20]. A positive point of this approach is that the most refractory S containing compounds *i.e.* DBT and its derivatives show high reactivity [21] and are easily oxidized to highly polarized sulfones, which can be subsequently removed by distillation and solvent extraction [22].

Mo supported over alumina has been the choice of researcher for the ODS of DBT over the years with high activity. For example, Cedeno-Caero, *et al.* reported enhanced desulfurization activity using Al_2O_3

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molecules

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Article

Novel α, β-Unsaturated Sophoridinic Derivatives: Design, Synthesis, Molecular Docking and Anti-Cancer Activities

Yiming Xu [1,†], Lichuan Wu [2,3,†], Hang Dai [4], Mingyan Gao [4], Haroon Ur Rashid [1,5], Haodong Wang [1], Peng Xie [1], Xu Liu [1], Jun Jiang [1,*] and Lisheng Wang [1,*]

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Abstract: Using sophoridine **1** and chalcone **3** as the lead compounds, a series of novel α, β-unsaturated sophoridinic derivatives were designed, synthesized, and evaluated for their in vitro cytotoxicity. Structure-activity relationship (SAR) analysis indicated that introduction of α, β-unsaturated ketone moiety and heterocyclic group might significantly enhance anticancer activity. Among the compounds, **2f** and **2m** exhibited potential effects against HepG-2 and CNE-2 human cancer cell lines. Furthermore, molecular docking studies were performed to understand possible docking sites of the molecules on the target proteins and the mode of binding. This work provides a theoretical basis for structural optimizations and exploring anticancer pathways of this kind of compound.

Keywords: sophoridine; chalcone; derivatives; anticancer activity; molecular docking

1. Introduction

Traditional herbs contain numerous biologically active natural compounds. Such compounds have been reported to possess remarkable therapeutic value with slight harmful effects. Their therapeutic efficacy offers a useful platform for developing new standard drugs. Sophoridine is a quinolizidine monomeric alkaloid isolated from traditional Chinese herbs. It is found in leaves and stem of Leguminous plants *Sophora alopecuroides* L., *Euchresta japonica* Benth., and the roots of *Sophora alopecuroides* Ait. Evidence suggests that sophoridine has remarkable pharmacological effects including anti-inflammatory, anti-viral, and anti-cancer effects. Sophoridine has been used to treat malignant tumors for decades in china [1–7]. It exhibits the potential therapeutic efficacy against gastric, colon and lung cancer. The mechanism of action of sophoridine is to inhibit DNA topoisomerase I (Topo I) activity and induce cell cycle arrest at the G0/G1 phase and then cause apoptotic cell death [8]. Compared to other DNA topo I inhibitors, such as 10-hydroxycamptothecin (HCPT) and topotecan, sophoridine has many advantages such as a special chemical scaffold, flexibility structure, high solubility, and good safety profiles [9]. However, the moderate antitumor activities of sophoridine

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Artigo

FACILE SYNTHESIS, CHARACTERIZATION AND DFT CALCULATIONS OF 2-ACETYL PYRIDINE DERIVATIVES

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Deprotonation of 2-acetylpyridine was carried out in the presence of NaH as a phase transfer catalyst instead of NaOH to minimize side products formation. The products were then treated with two equivalents of alkyl/aryl halide to synthesize a variety of acetyl pyridine derivatives. The compounds were structurally characterized by ^{1}H- and ^{13}C-NMR spectroscopy in solution state. Structure of compound **2** was also confirmed in solid state by X-ray diffraction. Electronic properties such as Mulliken charges, frontier molecular orbitals (HOMO-LUMO), ionization energy (IE), electron affinity (EA), global hardness (η), Chemical Potential (μ) and Global electrophilicity (ω) of some compounds were investigated by the same theory using B3LYP-6-311G basis set.

Keywords: 2-acetylpyridine; phase transfer catalyst; NMR studies; X-ray structure; DFT calculations.

INTRODUCTION

The pyridine as nucleus can be found in numerous natural products as well as in synthetic compounds and play a key role in chemistry of biological and non-biological systems.[1]Nitrogen containing heterocyclic compounds have anti-allergic,[2] anti-microbial,[3-10] anti-bacterial, anti-fungal,[11,12] anti-inflammatory,[13,14] and anti-cancer[15,16] activities. Many ligands derived from pyridine containing precursors are capable to couple with metals, the resulted complexes exhibit anti-tumor activities.[17] Among metals, Cu (II) and Co(III) complexes with pyridine derivatives efficiently interact with DNA[18] and can bind the two strands of DNA in an effective manner. Pyridine containing compounds and its metal complexes get much attention in the field of catalysis i.e. asymmetric synthesis[19] atom transfer radical polymerization[20] oligomerization[21] polymerization[22] and transfer hydrogenation of carbonyl compounds.[23] In this work an easy and facile substitution on $-CH_3$ group of the 2-acetylpyridine was carried out. The reaction was found to be equally effective with aryl and alkyl groups, formation of ether as byproduct or other side reactions were not observed. NaH instead of KOH/NaOH was used for the deprotonation of CH_3 group of 2-acetyl pyridine. In case of KOH/NaOH unexpectedly ether is formed as major product exactly as in Williamson's synthesis.[24] All the desired compounds were obtained in very good quantity, they were purified by using purification techniques and were structurally characterized with the help of ^{1}H- and ^{13}C-NMR spectroscopy. Structure of compound 1 was confirmed in solid state by X-ray diffraction. Structural data of compound 2 and electronic properties of compounds 1-3 were calculated by DFT. Experimental and theoretical data of compounds are discussed.

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EXPERIMENTAL

General

All manipulations were performed in Schlenk-type glassware. Carefully dried toluene and oven-dried glassware were used throughout. The 2-acetyl pyridine (Sigma Aldrich), 18-Crown-6-ether (TCI Japan), Sodium hydride (Alpha Aesar), 1-(bromomethyl)-4-methylbenzene (TCI, Japan), 2-(bromomethyl)naphthalene (TCI, Japan), iodomethane (Alpha Aesar) were commercial products and were used as received. The NMR spectra for compounds 1-3 were recorded in $CDCl_3$ using AVANCE AV-300 spectrophotometer, chemical shifts are given relative to Me_4Si [δ^{1}H ($CHCl_3$) = 7.23; δ ^{13}C($CDCl_3$) = 77.0; Chemical shifts are given to ±0.1 for both ^{1}H and ^{13}C-NMR. Crystal structure of compound 2 was determined by STOE-IPDS II equipped with low temperature unit. Structural solutions and refinements were accomplished by using SIR 97,[19] SHELXL97,[20] and WinGX.[21]

Melting point uncorrected was determined by melting point apparatus model SMP 10, England. All quantum-chemical calculations were carried out using the Gaussian 03 program package. Optimized geometries at the B3LYP/6-311+G level of theory were found to be minima by the absence of imaginary frequencies.[25-30]

Synthesis of 2-Methyl-1-(pyridine-2-yl)propane-1-one, 1

Following the literature procedure[31,32] with modification, a 250 mL round bottom flask was charged with 29 mmol L^{-1} (3.53 g, 2 mL) of 2-Acetylpyridine in 58 mL dry toluene. After some time 3 equivalents, 2.1 g of Sodium hydride and 0.2 mol% of 18-crown-6-ether were added and the mixture was stirred for 20 minutes followed by addition of 2 equivalents (3.5 mL) of iodomethane. The reaction mixture was kept stirring for 3 h at 23±1 °C. The reaction mixture was washed with ethyl acetate several times. The solvent and other readily volatile materials were evaporated. The final product was purified with the help of column chromatography and was obtained

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Topical Perspectives

Molecular modeling, simulation and docking study of ebola virus glycoprotein

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ABSTRACT

Ebola virus (EBOV) is a filamentous, enveloped, non-segmented, negative-strand ribonucleic acid (RNA) virus which belongs to family Filoviridae. Ebola virus includes different glycoproteins each of which plays their roles in different aspects of viral life cycle. In this study secreted glycoprotein (Q7T9E0) of Ebola virus was acquired from Uniprot. The formation of alpha helix and beta sheets of secondary structures were predicted through online servers. Higher flexibility and disordered regions of proteins were determined through RONN, GLOBPLOT and DISSEMBLE. Three dimensional (3D) structure of the protein was built through homology modeling techniques and MOE software. The validation and evaluation of the refined models were determined with two stereochemical tests i-e RAMPAGE and ERRAT servers. Further docking studies of given protein was performed with different derivatives of two antiviral drugs dronedarone and amiodarone through MOE. Docking score and binding affinity of respective derivatives demonstrate that these might be used as protein receptors.

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1. Introduction

Ebola virus first discovered in 1976 is responsible to cause hemorrhagic fever in humans and non-human primates. Its fatality rate is nearly from 25 to 90% [1]. Ebola, Marburg and Cueva-virus are the three infectious viruses with a common ancestor of the family Filoviridae to humans [2]. Ebola virus includes different glycoproteins each of which plays their roles in different aspects of viral life cycle. Each gene product has distinct biochemical and biological properties [3,4]. The fourth gene, GP is formed by a process known as glycosylation in which carbohydrate are linked covalently to the polypeptide chain [5]. sGP is a nonstructural protein with a single frame and has total 364–372 residues. Towards the N-terminal 295 residues which also include the signal sequence are similar with full length GP. It differs in the length of C-terminal sequences [3,6].

Literature study revealed that there are no crystal structures of Secreted glycoprotein available which are a key requirement for the active site finding and for further the designing of receptors. So, their 3D structures were architected by homology modeling. Molecular dynamics simulation study of the obtained homology models were simulated with the help of MOE. The structure helped us to find the active sites. Further Molecular docking analysis helped us in designing novel inhibitors and drugs in treating Ebola virus disease.

2. Materials and methods

2.1. Protein sequence selection/ransom

The primary sequences of sGP of Ebola virus with accession no Q7T9E0 was acquired from the Uniprot in FASTA format. In (PDB) available at (www.rcsb.org.pdb) [7] the protein 3 dimensional structure was not found. So, their 3 dimensional structures were architected through homology modeling.

2.2. Prediction of secondary structures

The secondary structure elements were analyzed by online servers. They were as follows PREDATOR [8], PHD [9], GOR4 [10], DPM [11], HNN, Discrimination of protein secondary structure

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molecules

MDPI

Article

Inclusion Complexes of a New Family of Non-Ionic Amphiphilic Dendrocalix[4]arene and Poorly Water-Soluble Drugs Naproxen and Ibuprofen

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Abstract: The inclusion complexes of a new family of nonionic amphiphilic calix[4]arenes with the anti-inflammatory hydrophobic drugs naproxen (NAP) and ibuprofen (IBP) were investigated. The effects of the alkyl chain's length and the inner core of calix[4]arenes on the interaction of the two drugs with the calix[4]arenes were explored. The inclusion complexes of Amphiphiles **1a–c** with NAP and IBP increased the solubility of these drugs in aqueous media. The interaction of **1a–c** with the drugs in aqueous media was investigated through fluorescence, molecular modeling, and ^{1}H-NMR analysis. TEM studies further supported the formation of inclusion complexes. The length of lipophilic alkyl chains and the intrinsic cyclic nature of cailx[4]arene derivatives **1a–c** were found to have a significant impact on the solubility of NAP and IBP in pure water.

Keywords: amphiphilic calix[4]arene; naproxen; ibuprofen; solubility; inclusion complexes

1. Introduction

Naproxen (NAP), (+)-(*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid, and ibuprofen (IBP), (*RS*)-2-(4-(2-methylpropyl)phenyl)propanoic acid (Scheme 1), are two commercial non-steroid anti-inflammatory drugs (NSAIDs) that are used with increasing frequency as an analgesic and antipyretic; they are prescribed for the treatment of rheumatoid arthritis, osteoarthritis, dysmenorrhea, and other medical conditions [1]. Owing to the poor solubility of NAP and IBP [2], several systems, i.e., chitosan [3], cyclodextrin derivatives [4], and cosolvent systems [5–8], have been developed to enhance the solubility of drugs in aqueous media in order to help in its better distribution inside the human body [9].

Calix[4]arenes consist of a framework of four phenolic units which are linked together by methylene moieties [10]. These calix[4]arenes are highly attractive to the scientific community due their preparation methods, their suitability as a potential drug carriers, and the ease with which they can cross biomembranes [10]. They have lower side effects and low immunogenicity; as a result, they are encouraging drug carriers in the biomedicine field [11–14].

Mostly, ionic amphiphilic calixarenes have been employed in the pharmaceutical field as a drug carrier due to their unique biophysical and biochemical properties where they have the ability to take hydrophobic drugs by forming chemical inclusion bodies [15–17]. Only in a few cases, however, have non-ionic amphiphilic calixarenes been reported as drug carriers [18]. Here, we report a new family of

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Research Article

Photooxidation of Toluene: Correlation of Noble Metal Loading on Titania and Activation Energy

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A series of platinum and palladium supported on titania catalysts were prepared by wet impregnation method with the Pt or Pd loading varying in the range of 0.1–1.2 weight percent. The catalysts were characterized by SEM, EDX, XRF, XRD, FT-IR, and BET surface area analysis. The catalysts were tested for their efficiency in the liquid phase solvent-free photooxidation of toluene to benzyl alcohol and benzaldehyde in the presence of molecular oxygen. The effect of noble metal contents on the activation energy was studied. Activation energy was found to be in a reciprocal relation to the platinum or palladium content of the catalyst. The percent conversion of toluene was observed to increase in response to an increase in the metal loading on titania. The apparent quantum yield, however, was independent of the platinum or palladium content of the catalyst.

1. Introduction

Photocatalysis is based on the consumption of solar energy and has been extensively considered to be the approach of green chemistry. There are many applications of titanium dioxide such as scratch-resistant optical coating paint pigments, which can also show high activity to photooxidation reaction, in which the researchers are beginning to exploit the field [1]. TiO_2 is a well-known and most applicable photocatalyst; it provides a best agreement between aqueous media and catalytic activity. It has been broadly studied due to its outstanding properties such as thermal stability, nontoxicity, low cost, availability, chemical inertness, and oxidizing ability of organic compounds [2–5]. Below 390 nm, titania can be activated by UV radiations. Absorption of light results in charge production and consequently activity is increased. Photocatalytic reactions of TiO_2 have attracted much attention of the researchers in the field of organic synthesis [6–8]. The photocatalytic activity of titania depends on its crystalline phase. TiO_2 (anatase) was thoroughly investigated as a photocatalyst for the oxidation of cyclohexane and cyclohexanol. The photocatalytic activity of titania can be enhanced by incorporating metal ions. A variety of methods such as precipitation, doping, and impregnation are used to introduce metal ions into titania [9–11].

Recently, the effects of noble metals such as platinum, gold, palladium, and rhodium on the photocatalytic activity of titania have been extensively studied [12–15]. It has been found that the addition of these noble metals substantially improves the photocatalytic activity of titania. This effect may be attributed to shutting and storing of photogenerated electrons from the titania to acceptor. Platinum loading especially effectuates a remarkable enhancement in the photocatalytic activity of titania through the formation of Schottky barrier at the Pt or Pd/TiO_2 interface [16]. However, many parameters can alter the enhancing effect of noble metal

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Research Article

Potent Heterogeneous Catalyst for Low Temperature Selective Oxidation of Cyclohexanol by Molecular Oxygen

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Platinum supported on zirconium dioxide catalyst was prepared by standard method and characterized by SEM, EDX, XRD, BET surface area and pore size analyzer, and FT-IR. The catalyst was screened for its catalytic activity in a model reaction, selective oxidation of cyclohexanol. The only one major product, cyclohexanone 31%, with 99.8% selectivity was obtained. Experimental data was analyzed through different kinetic models and we deduced that the reaction follows Langmuir-Hinshelwood mechanism. The apparent activation energy for the model reaction was calculated as 45 kJ/mole. The catalyst was regenerated several times with same efficiency.

1. Introduction

The oxidation reaction involving the conversion of alcohol with molecular oxygen to the corresponding carbonyl compounds has vital role in laboratory as well as in chemical industries [1, 2]. It provides a green rout for the production of fine chemicals [3]. Cyclohexanone is quite important intermediate in the synthesis of caprolactam which is used in the production of nylon 6 and nylon 6,6. It is used as a solvent in a coating process, as well as a plasticizer, food additive, and pharmaceutical. Besides this some other applications of cyclohexanone are being as raw materials in the production of insecticides and herbicides [4–6]. Due to the importance of this catalytic conversion the researchers are interested in developing such a pathway which is nontoxic and simple with low cost and high % yield.

Commonly, different kinds of methods are known for the large scale production of cyclohexanone by the conversion of cyclohexanol [7, 8]. Nevertheless, the new methods are gaining much attention of the researchers, because of the importance of the desired products. Formally, the researchers made efforts for the catalytic transformation of alcohol to the corresponding product, by the use of strong oxidants such as manganese, chromium complexes, mineral acids, tert-butyl hydroperoxide, ruthenium oxide, selenium dioxide, hydrogen peroxide, nitric acid, permanganates, and molecular oxygen. These reagents are toxic, corrosive, expensive, and unstable in normal condition and may produce by-products [9–11]. Hence, to overcome these problems it is required to change the conventional route of oxidation heterogeneous catalyst (noble metal catalyst by solid support) and molecular oxygen as an oxidant which are much cleaner technologies [12]. In the heterogeneous system, we can recover and reuse the catalyst.

The Ru hydroxyapatite, Pd hydroxyapatite, and Ru/Al_2O_3 are reported heterogeneous catalysts in the literature [13]. However, these catalysts work only at elevated reaction condition which is undesirable. Parentis et al. reported the oxidation of cyclohexanol in the presence of chromium supported on silica by tert-butyl hydroperoxide as an oxidant; approximately 40% conversions were achieved but the oxidant is very toxic. Various gold based heterogeneous catalysts have been reported such as Au supported on CeO_2, Au-Pd on titanium dioxide, and $Au/Ga_3Al_3O_9$ but these catalysts require high reaction temperature [14–17].

Currently, a zirconium dioxide is used as catalyst and catalyst support and gains much attention, because of its high

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Review article

Cyclen-based Gd^{3+} complexes as MRI contrast agents: Relaxivity enhancement and ligand design

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ABSTRACT

Magnetic Resonance Imaging (MRI) is a noninvasive radiology technique used to examine the internal organs of human body. It is useful for the diagnosis of structural abnormalities in the body. Contrast agents are used to increase the sensitivity of this technique. 1,4,7,10-Tetraazacyclododecane (cyclen) is a macrocyclic tetraamine. Its derivatives act as useful ligands to produce stable complexes with Gd^{3+} ion. Such chelates are investigated as MRI contrast agents. Free Gd^{3+} ion is extremely toxic for in vivo use. Upon complexation with a cyclen-based ligand, it is trapped in the preformed central cavity of the ligand resulting in the formation of a highly stable Gd^{3+}-chelate. Better kinetic and thermodynamic stability of cyclen-based MRI contrast agents decrease their potential toxicity for in vivo use. Consequently, such agents have proved to be safest for clinical applications. Relaxivity is the most important parameter used to measure the effectiveness of a contrast agent. A number of factors influence this parameter. This article elucidates detailed strategies to increase relaxivity of cyclen-based MRI contrast agents. 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (DO3A) are two key ligands derived from cyclen. They also act as building blocks for the synthesis of novel ligands. A few important methodologies for the synthesis of DOTA and DO3A derivatives are described. Moreover, the coordination geometry of chelates formed by these ligands and their derivatives is discussed as well. Novel ligands can be developed by the appropriate derivatization of DOTA and DO3A. Gd^{3+}-chelates of such ligands prove to be useful MRI contrast agents of enhanced relaxivity, greater stability, better clearance, lesser toxicity and higher water solubility.

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SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 1,3-BIS[(*S*)PHENYLETHYL]IMIDAZOLIDINE-2-THIONE

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Original article submitted May 13, 2015.

Enantiomerically and diastereomerically pure thiourea derivative (compound **I**) has been synthesized in two steps starting from (*S*)-1-phenylethanamine and 1,2-dibromoethane. Compound **I** was screened for various biochemical parameters including blood glucose level, serum total cholesterol level, serum bilirubin and triglyceride levels, serum glutamate pyruvate transaminase (SGPT) and alkaline phosphatase (ALP) activity in New Zealand White (NZW) rabbits. Compound **I** was also screened for brine shrimp cytotoxicity, antileishmanial and antioxidant activity. Acute toxicity tests in NZW rabbits were performed and the results showed that compound **I** was safe up to 2 mg/mL/kg rabbit body weight. For the blood parameters, it was found that compound **I** caused slightly reduced blood glucose level, increased blood serum bilirubin, ALP and SGPT levels, and caused no changes in cholesterol and triglyceride levels. Thus, results show that compound **I** possesses good cytotoxic, poor antileishmanial activity, and no prominent antioxidant activity.

Keywords: antileishmanial activity; antioxidant; brine shrimp cytotoxicity; blood parameters; cytotoxicity; thiourea derivative.

INTRODUCTION

Thioureas are important compounds that are building blocks in the synthesis of heterocycles. Their extensive applications have gained much attention in various fields [1]. Scientifically, it has also been proved that thioureas and their derivatives exhibit important biological activities such as antioxidant [2] antibacterial, antiviral, HDL-elevating, analgesic, anti-HIV [3 – 6], antitumor [7], antithyroid, antitubercular, antifungal, diuretic, hypnotic, insecticidal, herbicidal [8], algaecidal [9], rodenticidal, anti-helmintic, and plant-growth regulator [10].

Various natural products have urea and/or thiourea as important functional groups [11]. In particular, thiourea derivative has been isolated from the leaves of *Pyricuiria oryzae* Cav. rice [12]. Most of methods used for the extraction of bioactive constituents are tedious, time consuming, and require large amount of solvents [13], therefore, synthetic molecules replace natural extracts on industrial level. Synthetic chemistry made a great progress in the 20th century which helped humankind in the treatment and prevention of many diseases [14].

It has been previously reported that thiourea and its derivatives possess good antidiabetic activity [15]. Diabetes mellitus is a major degenerative disease in which body cannot produce adequate amount of insulin or cannot properly use insulin [16]. In either case, the augment level of glucose in the blood represents hyperglycemic state and, if this state persists for longer time, may irreversibly damage kidneys, nervous system, eyes, and heart [17]. Currently, two drugs – sulfonylureas and biguanides – are available in the market that can be consumed orally for hypoglycemic activity. However, a number of adverse effects are associated with these drugs, including vomiting, nausea, and increased appetite [18, 19]. So, new drugs with hypoglycemic potential having little adverse effects are still a challenge for scientists [20 – 22].

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Efficient Aerobic Oxidation of Cyclohexane to KA Oil Catalyzed by Pt-Sn supported on MWCNTs

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Abstract. Pt-Sn supported on MWCNTs were synthesized and characterized by SEM, EDX, XRD, XRF and surface area and pore size analyzer. The catalyst was used for the partial oxidation of cyclohexane in a Parr type reactor. It was found that Pt-Sn supported on MWCNTs can act as an efficient catalyst for the partial oxidation of cyclohexane into cyclohexanol and cyclohexanone, generating both in a high yield under mild reaction conditions.

Keywords. Cyclohexane; oxidation; cyclohexanol; cyclohexanone.

1. Introduction

The selective oxidation of cyclohexane to KA oil (cyclohexanone and cyclohexanol) is a process of significant industrial importance because KA oil is used as a raw material for the manufacture of nylon 6 and nylon 6, 6.[1] Conventionally, the oxidation of cyclohexanol to KA oil is catalyzed by soluble cobalt or manganese salts where they act as homogeneous catalysts. The reaction is carried out at 140–180°C and 0.8–2MPa in air for 15–60 min.[1] This process gives 70–85% selectivity. However, the cyclohexane conversion ratio is usually limited to less than 6% to prevent further oxidation of the target KA-oil. A number of alternative processes that employ heterogeneous catalysts have been proposed for the selective cyclohexane conversion without a significant decrease in the selectivity for KA-oil. Catalysts consisting of gold nanoparticles supported on zeolites can convert cyclohexane to KA-oil at 150°C in a 1 MPa; O_2 atmosphere for 2–6 h with a 6–19% conversion ratio and 92–100% selectivity, in the absence of free-radical scavengers.[2–4] Gold nanoparticles embedded in amorphous silica ($Au/Si0_2$) has been reported as a catalyst for the conversion of cyclohexane with a high catalytic activity and selectivity of 22.7% and 80.6%, respectively. However, the process requires toxic and explosive tert-butyl hydro peroxide (TBHP) as radical initiator.[5] Size-controlled Au clusters on hydroxyapatite have exhibited a cyclohexane conversion ratio of 6.7–14.9% with an efficient selectivity for KA-oil at 150°C under 1 MPa O_2 for 24 h, but the addition of a small amount of TBHP is also essential in this case to initiate the reaction.[6]

Mesoporous chromium iron terepthalates have been demonstrated to efficiently catalyze the oxidation of cyclohexane.[7] The Cr-MIL-101/TBHP system has been reported to produce KA oil with 92% selectivity at a 25% cyclohexane conversion ratio, while Fe-MIL-101/TBHP/O_2 has been reported to yield a mixture of cyclohexyl hydroperoxide, cyclohexanol and cyclohexanone with 99% total selectivity (49% selectivity for KA-oil) and a conversion ratio of about 38% at 70°C in air (1 atm) in 8 h. However, in this case too, the addition of TBHP is essential. Fe-filled carbon nanotubes have yielded a cyclohexane conversion ratio of about 37% at 125°C and 1.5 MPa; O_2 for 8 h, but the selectivity for KA-oil was about 30% due to over-oxidation.[8]

This scenario has promoted to develop catalysts for the oxidation of cyclohexane that can generate high conversion ratio with high selectivity for KA oil in a liquid phase reaction. We have previously reported zirconia and zirconia supported noble metals as catalysts for the oxidation of cyclohexane under moderate conditions.[9]

In the current study, we have designed an advanced catalyst that is beautifully tailored for the oxidation of cyclohexane to KA-oil in the liquid phase without requiring radical initiators or free-radical scavengers. In this catalyst, platinum acts as the main oxidizing agent

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Artigo

KINETIC STUDY OF SELECTIVE GAS-PHASE OXIDATION OF ISOPROPANOL TO ACETONE USING MONOCLINIC ZrO_2 AS A CATALYST

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Zirconia was prepared by a precipitation method and calcined at 723 K, 1023 K, and 1253 K in order to obtain monoclinic zirconia. The prepared zirconia was characterized by XRD, SEM, EDX, surface area and pore size analyzer, and particle size analyzer. Monoclinic ZrO_2 as a catalyst was used for the gas-phase oxidation of isopropanol to acetone in a Pyrex-glass-flow-type reactor with a temperature range of 443 K - 473 K. It was found that monoclinic ZrO_2 shows remarkable catalytic activity (68%) and selectivity (100%) for the oxidation of isopropanol to acetone. This kinetic study reveals that the oxidation of isopropanol to acetone follows the L–H mechanism.

Keywords: zirconia; oxidation; gas phase; isopropanol.

INTRODUCTION

The industrial significance of the oxy-functionalization of alcohols results from the fact that the products of the process are valuable precursors in the manufacture of many drugs, vitamins and fragrances, etc.[1] For example, cyclohexanone and adipic acid, which are the oxidation products of cyclohexanol, have been widely used in the manufacture of nylon-6, nylon-6, 6, plasticizers, food additives, insecticides and herbicides, etc.[2] Keeping in view the immense significance of oxidation of alcohols to aldehydes and ketones, researchers are endeavoring to develop simple and eco-friendly methods for the chemical transformation under question.

Generally, homogeneous catalysts like soluble salts and transition metal complexes in combination with oxidants like O_2, H_2O_2 or RO_2H have been used for the liquid phase oxidation of alcohols. But several problems have been encountered in these homogeneous catalytic oxidation reactions, such as, the separation of the catalyst, its recovery and recycling from the reaction mixture.[3] Therefore, it is a worthwhile effort to replace homogeneous catalysts with heterogeneous counterparts. The development of heterogeneous catalysts for the oxidation of alcohols is a field of intensive research. Several different heterogeneous catalysts for the oxy-functionalization of alcohols have been reported. For example, Ilyas *et al*. have demonstrated the efficiency of Y_2O_3/ZrO_2 in the dehydrogenation of cyclohexanol to cyclohexanone.[4] Sugunan *et al*. have studied the catalytic activity of ZrO_2-Y_2O_3 in the oxidation of cyclohexanol.[5] Venkathatathri and coworkers have employed Mn-MCM-41 molecular sieves in the selective gas phase oxidation of cyclohexanol.[6] Muhler and coworkers have reported the oxidation of isopropanol with oxygen using Au/TiO_2 as a catalyst.[7] Hutchings reported that TiO2 supported Au-Pd alloy nanocrystals give significantly enhanced activity for the oxidation of alcohol using oxygen as oxidant.[8] Hutchings and coworkers have also explored the catalytic efficiency of zeolite supported Au and Au-Pd catalysts for the oxidation of benzyl alcohol with molecular oxygen.[9] Stucky and coworkers have utilized gold nanoparticles in the solvent free selective aerobic oxidation of alcohols.[10] Many other similar examples of attempts for carrying out the oxidation of alcohols with heterogeneous catalysts can be found in the literature.[5-10]

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ZrO_2 is of considerable interest for researchers working to develop heterogeneous catalytic systems for various applications. A lot of research work has been devoted to the application of ZrO_2 as a catalyst support in various oxidative reactions such as oxidative carbonylation of methanol to dimethyl carbonate,[11] combustion of trace amounts of methane under exhaust gas condition,[12] oxidative dehydrogenation of propane,[13,14] and oxidation of CO,[15] etc. We have also reported the efficiency of ZrO_2 as a support for Pt catalyst in the aerobic oxidation of toluene.[16] A study of literature reveals that though ZrO_2 has been an efficient support for a number of oxidation reactions but there is a lack of sufficient literature on the use of ZrO_2 as a catalyst in these reactions. We were thus motivated to study the activity of ZrO_2 in the oxidation of alcohols. The oxidation of isopropanol was chosen as a model reaction as it is widely used as a probe reaction to explore the activity and selectivity of various catalysts in oxidative dehydrogenation and dehydration reactions.

To the best of our knowledge, ZrO_2 has not been thoroughly studied in the aspect of its catalytic activity in the gas phase oxidation of isopropanol. In this paper, we report the catalytic activity of ZrO_2 in the gas phase oxidation of isopropanol to acetone, using oxygen as the oxidant.

EXPERIMENTAL

General

All chemicals used in the study were of high purity grade and were used without further purification. Gases like nitrogen, oxygen and hydrogen were supplied by BOC Pakistan and further purified by specific filters.

Preparation of zirconia

Zirconia was prepared from its precursor compound (Octa-hydrated zirconium oxychloride) by ammonolysis, i.e. aqueous ammonia was added drop wise to 0.5 mol L^{-1} solution of zirconyl chloride over a time span of approximately 4 h. White precipitate of zirconium hydroxide was obtained at pH 9. The precipitate was washed and dried overnight in oven at 383 K. The dried sample was pulverized, meshed (100-150 mesh) and calcined at a desired temperature in a temperature controlled furnace at 723 K, 1023 K and 1253 K.

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SYNTHESIS AND EVALUATION OF ANALGESIC, ANTI-INFLAMMATORY AND ANTI-BACTERIAL ACTIVITY OF SYNTHETIC PORPHYRIN DERIVATIVES

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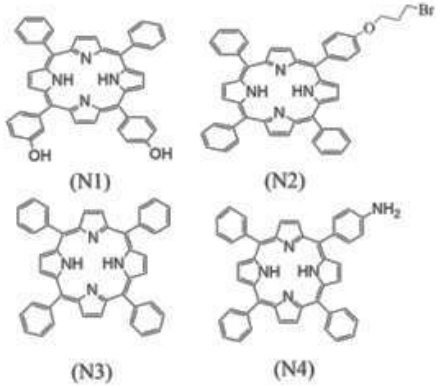
In this work porphyrins compounds (N1-N4) were synthesized from monohydroxy tetraphenylporphyrin, and then characterized on the basis of their chemical properties and spectral data. They were further tested for their potential analgesic and anti-inflammatory activities in acetic acid induced writhing test in mice and carrageenan induced paw edema in rats. The compounds were also evaluated for antibacterial activity in disc diffusion method. Compounds N1, N2 and N4 showed significant analgesic and anti-inflammatory activity at 10 and 30 mg/kg (b.w), comparable to the standard reference drugs. Furthermore, all the tested compounds possessed significant anti-bacterial activity against both gram positive and gram negative bacteria. The analgesic, anti-inflammatory and anti-bacterial activities of the tested compounds were found comparable to reference drugs. These compounds can serve as precursors for the development of clinically useful analgesics, anti-inflammatory and anti-bacterial agents.



INTRODUCTION

Porphyrins (derived from Greek πορφυροσ means "purple, scarlet") are very important class of naturally occurring molecules. Many biological molecules work with prosthetic groups basically consisting of these units. Heme, a component of hemoglobin which transports oxygen to animal tissues and chlorophylls of chloroplasts responsible for the process of photosynthesis in plants, both have active sites essentially made of porphyrin core.[1] Porphyrins play vital role in biological systems and they also have useful applications in material science and medicine. Infectious diseases have shown exponential growth recently. The problem is becoming more complex due to the emergence of resistance to current anti-bacterial therapy.[2] Infections are caused by microorganisms and are usually accompanied by pain and inflammation which is the response of the organism towards the pathogen. Although inflammation is a protective response of the body and constitutes a form of innate immunity but chronic inflammation causes a number of serious disorders such as hay fever, periodontitis, atherosclerosis rheumatoid arthritis, and even cancer (e.g. gallbladder carcinoma). Thus there is an urgent need to develop new anti-bacterial agents

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ORIGINAL PAPER

Synthesis and characterization of monoaryl esters of L-tartaric acid and their process for fries rearrangement

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Abstract Chiral protected monoaryl esters (**2a–2h**) were synthesized from monoester of L-tartaric acid, having two asymmetric centers and C2 axis of symmetry. L-tartaric acid was protected and partially hydrolyzed to give the corresponding monoester. Monoester upon treatment with different substituted phenols gave desired monoaryl esters (**2a–2h**). Fries rearrangement of monoaryl esters was then tried under various conditions by using different Lewis acids. All the compounds were purified and characterized by using spectroscopic techniques like IR, ^{1}H-NMR, ^{13}C-NMR, HRMS-ESI, and elemental analysis. The structure of compound **2e** was obtained by X-ray crystallography.

Keywords L-Tartaric acid · Protection · Monoaryl esters · Fries rearrangement

Introduction

Tartaric acid is an important optically active compound. It has been used to study the stereochemistry. The different derivatives of tartaric acid have wide applications in the synthesis of numerous chiral building blocks [1–3]. In addition, it is also used as a precursor of chiral ligands, auxiliaries, and resolving agents [4–8]. Among the derivatives of tartaric acid, its dialkyl esters are most frequently used, not only for the preparation of other tartaric acid derivatives but also in asymmetric catalysis, for example, as chiral ligands in the Sharpless asymmetric epoxidation [9, 10], kinetic resolution of racemic allyl alcohols [11, 12], asymmetric synthesis of sulfoxides by the Kagan-Modena method [13–16], asymmetric Simmons-Smith reaction [17–20], asymmetric allylation [21–23], asymmetric allylboration developed by Roush [24, 25], and homoallenylboration of aldehydes developed by Brown [26].

Keeping in view the importance of L-tartaric acid derivatives, we planned to synthesize some new chiral substrates of potential value for synthetic and biological applications.

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Experimental

Materials and methods

All chemicals were of highest purity available and used as supplied. Dry solvents like methanol, dichloromethane, chloroform, and *n*-hexane were obtained by distillation using standard procedures or by passage through a column of anhydrous alumina using equipment from anhydrous engineering (University of Bristol, UK) based on the Grubbs' design. Reactions were carried out under anhydrous conditions using three-way stopcock and rubber septa.

All reactions were monitored by TLC on Kieselgel 60 F254 (Merck), and ethyl acetate/*n*-Hexane and methanol/chloroform were used as eluents.

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CATALYST ROLE IN CHEMICAL VAPOR DEPOSITION (CVD) PROCESS: A REVIEW

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Abstract. The article describes significant role of catalyst in the deposition of various materials on different substrates surface via Chemical vapor deposition (CVD) process. CVD is a complex process of depositing thin coatings on a substrate surface via chemical reactions of gaseous materials. It is a useful process to produce materials of high purity, density and strength. It has emerged as a novel manufacturing technique in industrial sectors such as semiconductor and ceramic industries. Catalyst Enhanced Chemical Vapor Deposition (CECVD) is an enhancement method, used for the synthesis of nanomaterials on thermally sensitive substrates in the presence of appropriate metal catalysts. Such catalysts not only ensure the deposition to be carried out at considerably low temperature but they also produce films of high purity. The article provides the published data about nanomaterials synthesis by CECVD process. Catalytic chemical vapor deposition (CCVD) is another efficient and low-cost method for the mass production of highly pure carbon nanotubes (CNTs). In this process, CNTs are produced by the catalytic decomposition of hydrocarbon vapors. Cobalt, Iron, Nickel and their alloys are the most widely used catalysts in CNTs production through CVD process. This idea has been explained in detail with appropriate examples from recent literature.

1. INTRODUCTION

Chemical Vapor Deposition (CVD) is a synthesis process in which the chemical components react in the vapor phase close to or on a hot substrate. Activation of the substrate is usually performed by heating, radiation or plasma This process produces a solid deposit. The deposition consists of either homogenous gas phase reactions taking place in the gas phase or heterogeneous chemical reactions which take place on/in close proximity of a hot surface resulting in the formation of powders or coatings respectively. The technique is systematically elucidated in Fig. 1. Materials with different properties can be produced by changing the substrate temperature, composition of the reaction gas mixture, total pressure gas flow, and experimental conditions, etc. [1,2]. For structural component applications, deposition usually occurs at a temperature of about 1000 °C. Reactive processes differentiate CVD from physical vapor deposition (PVD) processes such as physical evaporation, sputtering and sublimation processes [3].

Volatilization of a solid or liquid feed produces the gaseous compound containing the deposit material. A carrier gas (usually Hydrogen or Nitrogen) is then used to transport gaseous materials to hot

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SYNTHESIS AND RELAXIVITY MEASUREMENT OF CYCLEN BASED MAGNETIC RESONANCE IMAGING (MRI) CONTRAST AGENT**

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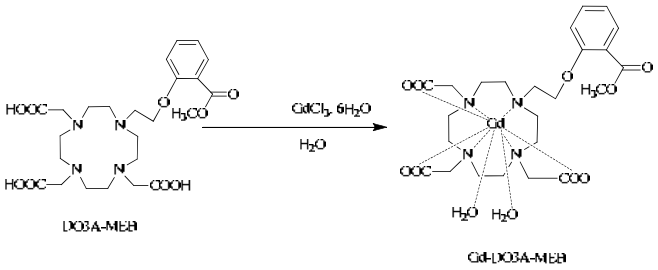
1, 4, 7, 10-teraazacyclododecane (cyclen) is a key macrocycle used for the synthesis of Magnetic Resonance Imaging (MRI) contrast agents. Substituting the hydrogen atoms (attached to the nitrogen atoms in the ring) of cyclen with suitable groups produce stable ligands. These ligands on complexation with Ln^{3+} ions lead to the formation of useful chelates. Cyclen is widely synthesized via Richman and Atkins method. Cyclen based ligand 1,4,7-*tris*(carboxymethyl)-10-(methyl,2-ethoxybenzoate)-1,4,7,10-tetraazacyclododecane (DO3A-MEB) was synthesized in this work. It was subsequently coupled with Gd^{3+} ion to afford its stable complex. Relaxivity of the complex was measured by inversion recovery (IR) method and it was compared with that of the commonly used MRI contrast agent Gd-DTPA. Longitudinal relaxivity measurements indicated 128 % enhancement compared to Gd-DTPA.



DO3A-MEB Gd-DO3A-MEB

INTRODUCTION

1, 4, 7, 10-Teraazacyclododecane (cyclen) is a macrocycle, the aza analogue of the crown ether. The most important application of cyclen is the development of Magnetic Resonance Imaging (MRI) contrast agents by its derivatization followed by complexation with Ln^{3+} ions. Diagnostic and therapeutic pharmaceutical agents are developed by the proper substitution of its ring nitrogen atoms. In stable cyclen based-macrocyclic chelates three or four of the ring nitrogen atoms carry a pendant, ionizable metal coordinating group such as phosphonic or carboxylic acid group. As lanthanide ions are in +3 state, the complexation of cyclen-based ligands containing three acid groups with suitable lanthanide ions results in the formation of neutral chelates. This effect is of specific importance because various side effects of contrast agents depend on the hypertonicity. Neutral complexes of lanthanide ions also show small contribution to the overall osmolality of the composition. Such neutral complexes (with low osmolality) decrease the pain and tissue sloughing during the injection. Therefore, cyclen is considered as a crucial intermediate for the synthesis of suitable macrocyclic chelating agents.[1-3] For imaging purposes, various cyclen-based chelates are used as contrast agents. These chelates serve as carriers for the paramagnetic metal ions (gadolinium and dysprosium) and thus ensure their appropriate biodistribution and elimination.[4]

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** Supplementary material on http: //web.icf.ro/rrch or http: //revroum.lew.ro

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Adsorption of methyl orange using self-assembled porous microspheres of poly(*o*-chloroaniline)

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Abstract−Self-assembled hollow microspheres poly(*o*-chloroaniline) (POC) have been synthesized by simple oxidative polymerization of *o*-chloroaniline using camphor-sulfonic acid (CSA) as dopant acid and ammonium persulfate (APS) as oxidant. The POC microspheres were characterized by means of FTIR, XRD and SEM analysis. Adsorption characteristics of POC spheres were studied by using methyl orange (MO) as adsorbate. It was found that adsorption of MO by POC was better described by pseudo-second-order kinetics than any other kinetic model, such as the pseudo-first-order and intra-particle diffusion models. Langmuir adsorption isotherm model was the best to fit experimental data. The results showed that hollow microspheres of POC can be used as novel and low-cost adsorbent for removal of organic dye from waste water.

Keywords: Adsorption, Methyl Orange, Hollow Microspheres, Poly(*o*-chloroaniline)

INTRODUCTION

Hollow microspheres of conducting polymers have attracted much attention for their unique physical and chemical properties [1-3]. During the last decade, hollow micro or nanospheres have shown promising applications in fields of controlled drug release, stationary phases for separation, chemical sensor and biosensors, and microencapsulation [4-6]. These versatile applications made it an interesting and important subject in the field of material science [7-9]. Hollow microspheres are generally synthesized by using spherical particle as templates [10,11]. Self-assembly method, using 'soft templates' such as micelles, attracts much attention for producing hollow micro or nanospheres of conducting polymers. This approach is inexpensive and simple as it does not involve the required pre- and post-synthesis procedures to prepare and remove the 'hard' templates [12,13]. Wan et al. prepared hollow microspheres of polyaniline (PANI) by self-assembly method with salicylic acid and naphthalene-2-sulphonic acid as dopants [14,15]. Travas-Sejdic reported self-assembly of hollow microspheres of poly(*o*-methoxyaniline) with *p*-toluene sulfonic acid and poly(methyl vinyl etheraltmaleic acid) as dopant acids, and found that the size and morphology of the hollow spheres were dependent on the weight ratio of dopant acid to monomer [16,17]. Hollow spheres of PANI can also be produced from 'alkali-guided' synthesis in which ammonium persulfate (APS) was used to oxidize aniline in alkaline medium of sodium hydroxide or ammonium hydroxide [18].

Dyes are a subject of much interest as they are extensively used in industries such as plastics, paper, leather, cosmetic and textile. The presence of dyes in wastewaters from these industries may pose a potential eco-toxic hazard. Therefore, removing dyes from wastewaters is very important [19-23]. Several techniques such as chemical oxidation, ion-exchange, precipitation, coagulation, filtration and adsorption are used for removal of dyes from wastewaters. Among these, adsorption has the advantage of recycling and reuse of adsorbents [24,25]. For this purpose, several adsorbent materials have been reported such as banana peels, orange peels, activated carbon, neem leaf powder, modified sporopollenin, saw-dust, deoiled soya and rice-husk [26-32]. Similarly, characteristics and photocatalytic degradation [33] and removal of methyl orange [34] using TiO_2 with different composite films have been reported. Azo dye removal from aqueous solution by organic-inorganic hybrid dodecanoic acid modified layered Mg-Al hydrotalcite has also been studied [35]. Moreover, conducting polymers have been used in adsorption of dyes from wastewaters [36,37]. It is well known that PANI emeraldine salt contains a large number of amine and imine functional groups with considerable quantities of positive charges, which render it as an ideal candidate for removal of anionic dyes from waste water [36,37]. Mahanta et al. reported that the adsorption of dye depended on the nature of dopant used to synthesize PANI, and Guo et al. reported that the morphology of PANI also affects the adsorption dye [37]. However, the PANI derivatives have not been studied for adsorption of dye. Herein, we report the synthesis of a hollow microspheres of poly(*o*-chloroaniline) (POC) in aqueous medium by using APS as oxidant, and diaminodiphenylamine (DDPA) as an aniline

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SOLVENT DEGRADATION IN CO_2 CAPTURE PROCESS FROM POWER PLANT FLUE GAS

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UDC 544.478

The chemical absorption of CO_2 by monoethanolamine for CO_2 separation from other gases produced by burning fossil fuels in power plants was considered. The factors that influence the process of decomposition of monoethanolamine were studied. It was shown that addition of piperazine to the system reduces the decomposition rate of monoethanolamine during CO_2 absorption from the flue gases, which are formed in an oxidizing atmosphere.

***Key words**: solvent degradation, flue gas, monoethanolamine, diethanolamine, oligomerization.*

Flue gas from power plants is responsible for more than 1/3 of the US emissions, and for about 7% of the world's carbon dioxide (CO_2) emissions. CO_2 constitutes ~15% of flue gas from conventional fossil fuel combustion processes; therefore, it is important to separate CO_2 from other flue gas components prior to storage because it is too expensive to compress and store the total flue gas output from a power plant.

The most widely used method for the capture and separation of CO_2 on an industrial scale is chemical absorption by scrubbing using an aqueous solution of monoethanolamine (MEA), or blended with secondary amine, diethanolamine (DEA), or tertiary amine, methyldiethanolamine (MDEA), as a solvent. In this method, the amine solution, e.g., MEA, absorbs CO_2 through chemical reaction in an absorber column (Eq. 1). Heating the CO_2-rich amine in a separate stripper column can drive off the CO_2 absorbed by MEA because the reaction is reversible. The MEA is then recycled back in the process.

$$RNH_2 + CO_2 + H_2O \leftrightarrows RNH_3^+ \cdot HCO_3^- . \quad (1)$$

However, the main problem in a chemical absorption using MEA is the degradation of the solvent during irreversible side reactions with CO_2 and other flue gas components, which makes the process complicated. Typically coal-fired power-plant flue gas is composed of 14% CO_2, 5% O_2, 81% N_2, 300-3000 ppm SO_x, 100-1000 ppm NO_x, and 1000-10000 mg/m^3 fly ash particulate, etc. [1]. Fly ash is fine particulates in flue gas that consist of inorganic oxides such as SiO_2, Al_2O_3, Fe_2O_3, CaO, MgO, Na_2O, K_2O, and P_2O_5. A typical composition of flue gas from a natural gas turbine contains 4% CO_2, 15% O_2, 81% N_2, 1 ppm SO_x, 100-500 ppm NO_x, and ~10 mg /m^3 particulate matter. Because of the complexity of the flue gas composition, MEA degradation by coal-fired flue gas is a complicated process.

To achieve an economical and efficient process of CO_2 absorption, it is essential to have a solvent that is stable under a wide range of conditions. However, the amine solvent undergoes degradation when exposed to coal-fired power-plant flue gas.

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SYNTHESIS AND RELAXIVITY MEASUREMENT OF PORPHYRIN-BASED MAGNETIC RESONANCE IMAGING (MRI) CONTRAST AGENTS

Haroon-Ur-Rashid,[1] M. N. Umar,[2] K. Khan,[3] M. N. Anjum,[4] and M. Yaseen[1]

UDC 541.6:541.49:546.48

Magnetic Resonance Imaging (MRI) has become a prominent imaging technique in medicine. MRI contrast agents are used to increase the sensitivity of this technique. Recently, a new method for cancer treatment with a less side effect called photodynamic therapy (PDT) has been introduced. In this method cancer tissues are selectively destroyed without injuring the surrounding healthy cells. However, for the successful use of this method, the selection of an appropriate photosensitizer is important. Hence, diagnosis-treat union of MRI and PDT will be significantly promoted if a new family of bi-functional agents is found, which would combine the effects of a contrast agent in MRI and of a photosensitizer in PDT. It will bring great improvement to the cancer diagnosis and treatment. Porphyrins have proved to be useful photosensitizing agents in PDT due to their promising photophysical efficiency and a less side effect. This work briefly describes the research development of porphyrins as a photosensitizer applied in PDT, and also highlights the recent progress in the research on bi-functional agents of MRI-PDT. Diethylenetriamine pentaacetic acid (DTPA) units are incorporated at a meso-position of the porphyrin ring to synthesize new bi-functional agents of MRI-PDT with sufficient water solubility and high relaxation potency. Gd^{3+} complexes are prepared by the reaction of the high molecular weight porphyrin-based ligand with $GdCl_3 \cdot 6H_2O$. The longitudinal relaxivity measurement indicates 154% and 251% enhancement compared to that of the widely used MRI contrast agent Gd–DTPA. These results indicate that the two complexes could possibly be used as bi-functional agents of MRI-PDT.

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Keywords: contrast agent, porphyrin, relaxivity, gadolinium, ligand.

INTRODUCTION

Magnetic resonance imaging (MRI) is a noninvasive imaging modality used in modern clinical diagnosis to visualize a detailed internal structure and the limited function of the body. It is based on the detection of NMR signals emitted by protons of water and fat molecules in the body in a magnetic field. A magnetic field is applied to the region of interest which is then modulated by radio waves. The nuclear energy states of protons interact with the incident radio waves.

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LANTHANIDE(III) CHELATES AS MRI CONTRAST AGENTS: A BRIEF DESCRIPTION

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Magnetic resonance imaging (MRI) has become a prominent imaging technique in medicine. Gadolinium-based contrast agents are extensively used to enhance the contrast between normal and diseased tissues through MRI scans. The article illustrates the paramount significance of such contrast agents in MRI applications. Clinically approved contrast agents as well as those in trial period are discussed. Important parameters, i.e. hydration number, rotational correlation time, and mean residence lifetime, influencing the relaxivity (sensitivity) of such agents are described in detail. Various approaches towards relaxivity enhancement are discussed with appropriate examples from the recent literature. A decrease in the Gd-water proton distance results in significant relaxivity enhancement. A comprehensive classification and explanation of Gd^{3+}-based contrast agents are presented. Each class is explained with suitable examples. The stability of contrast agents is dependent on their chemical structure. Future contrast agents need to be tissue specific of high relaxivity, low toxicity, and lower administered dose for *in vivo* use.
Keywords: magnetic resonance imaging (MRI), gadolinium, relaxivity, nuclear relaxation, mean residence lifetime, contrast agents, hydration number, nephrogenic systemic fibrosis (NSF).

INTRODUCTION

Magnetic resonance imaging (MRI) is a noninvasive imaging modality used in modern clinical diagnosis to visualize a detailed internal structure and the limited function of the body. It is based on the detection of NMR signals emitted by protons of water and fat molecules in the body in a magnetic field. A magnetic field is applied to the region of interest, which is then modulated by radio waves. The nuclear energy states of protons interact with the incident radio waves. The radio frequency emission by tissue that follows the absorption of photons can be exploited to produce images [1-3]. In this method, three-dimensional images of the body parts are obtained in thin slices [4]. Paul C. Lauterbur and Sir Peter Mansfield won the Nobel Prize in 2003 for their work on MRI [5]. It is a useful medical technique for the diagnosis and monitoring of malignant tumors, cerebral abnormalities, multiple sclerosis, infarcted artery, and lesions. The key advantage of MRI is that it is safer for the patients than other imaging techniques such as X-rays where highly ionizing radiations are used for this purpose. Compared to computed tomography (CT), MRI provides much greater contrast between the different soft tissues of the body. In modern medicine, MRI has emerged as one of the most powerful techniques for the diagnosis and treatment of human diseases [6, 7].

The main challenge to this technique is, however, its low sensitivity. For clinical purposes hydrogen atoms of water molecules are considered, which are found in tissues at ~90 M. In order to improve the sensitivity of images obtained and

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Advances in the Development of Methane Bromination

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Summary: The bromination reactions of Methane were studied and majority of the work done so far was outlined, as these reactions have gained immense importance for years in the industrial sector. Thermodynamically, Bromine (Br) is the most suitable species for halogenation of methane. Bromination of methane proceeds via a radical chain mechanism which involves radical intermediates. The mechanism consists of three key steps i.e. Initiation, propagation and termination. It results in the formation of methyl bromide and hydrogen bromide. Hydrogen bromide has been found to inhibit the bromination of methane. However, it has no influence on the bromination of methyl bromide. Bromination of methane can occur both thermally as well as photochemically, following the same free radical chain mechanism. It is a gently exothermic reaction. Studies of the transition state showed that the symmetry for such reaction is of C_{3v} type. Monobromination reaction is hard to control. Supported Lewis acid halides-oxyhalides were found to be suitable as catalysts for monobromination of methane. Catalytic bromination gave more than 90 %.conversions with selectivity in methyl bromide. Oxidative bromination of methane occurs when $FePO_4/SiO_2$ or BaO/SiO_2 are used as catalyst.

Introduction

The global reserves of natural gas are more than that of petroleum [1, 2]. Methane is the major constituent of natural gas, a mixture consists of about 80 % CH_4, 15 % ethane (C_2H_6) and 5 % other hydrocarbons, such as propane (C_3H_8) and butane (C_4H_{10})., Methane can mainly be converted to higher hydrocarbon liquid fuels. However, due to the strong C–H bonds of CH_4 (439 kJ/mol), it is hard to convert it to chemicals of better use [3, 4]. A major part of the literature and organic chemistry textbooks report pyrolytic and free-radical reactions for the conversion of methane into substituted derivatives and higher hydrocarbons. The oldest method for the halgenation of alkanes by substitution reaction was reported by Dumas in 1840. Natural gas conversion by halogenation was proposed in 1980's by Olah [5-7] and Benson [8, 9]. In this method, hydrogen atom is extracted from methane producing methyl halide under relatively mild conditions. Then methyl halide is condensed to produce higher hydrocarbons or is oxygenated providing an alternative route for commercial methane conversion into hydrocarbons through syn-gas route.

At present, chlorination is the key method for the halogenation of methane. However, low methane conversion rate, low target production selectivity and the difficulty of converting chlorinated methane to other higher hydrocarbons are the major shortcomings of this process. [10-14]. On the other hand, the bromination of methane is rarely reported in the literature. In this paper, recent progresses in the development of methane bromination were reviewed. The emphasis was focused on eight sections: (1) overall reaction mechanism (2) the transition state (TS) for the bromination of methane (3) reaction kinetics (4) HBr effect (5) Effect of O_2 (6) production of dibromomethane (7) bromination with chlorine and (8) bromination with catalyst

Overall Reaction Mechanism

The process of methane bromination, both in the gas and liquid phases, proceeds by a free-radical chain mechanism and requires photolytic or thermal initiation. There are three stages:

Initiation

This step is the initial, homolytic cleavage of bromine to form two bromine atoms that are free radicals. Ultraviolet light or heat provides energy for this step. (Equation 1)

Propagation

A bromine free radical abstracts a hydrogen atom from methane to form a methyl free radical and HBr. As the methyl free radical is highly reactive, it in turn abstracts a bromine atom from another molecule of Br_2 to form methyl bromide product and another bromine free radical. Thus the formation of only a few bromine free radicals cause self-perpetuating or chain reaction. (Equations 2-4).

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