近 5 年药物化学硕士研究生以第一作者发表论文

论文均为中科院一区，安徽中医药大学为第一单位

导师为学位点成员和通讯作者

1. Based on BODIPY fluorescent probe for detecting NO in tumour cells, zebrafish and rice roots under abiotic stresses. *Sensors and Actuators B: Chemical*, 2024, 418, 136244. (IF: 8.0).
2. A lysosomal targeted fluorescent probe based on BODIPY for monitoring NO in living cells and zebrafish imaging. *Sensors and Actuators B: Chemical*, 2023, 383, 133592. (IF: 8.0).
3. Discovery of novel brain-penetrant GluN2B NMDAR antagonists via pharmacophore-merging strategy as anti-stroke therapeutic agents. *European Journal of Medicinal Chemistry*, 2022,227:113876. (IF: 6.0)
4. Identification and optimization of nitrophenolic analogues as dopamine metabolic enzyme inhibitors for the treatment of Parkinson’s disease. *Bioorganic Chemistry*, 2024, 148, 107488. (IF: 4.5).
5. Site-Selective C−H Arylation of 2-Pyridones via Pd/NBE Cooperative Catalysis. *ACS Catal.* 2024, 14, 7762−7770. (IF: 11.3).
6. Photoinduced [3+2] Cycloaddition of Alkyl-Acceptor Diazoalkanes: Diversity-Oriented Synthesis of Pyrazolines Containing a Quaternary Center. *Org. Lett.* 2024, 26, 4031-4036. (IF: 4.9).
7. Design, Synthesis, and Biological Evaluation of Pierardine Derivatives as Novel Brain-Penetrant and In Vivo Potent NMDAR-GluN2B Antagonists for Ischemic Stroke Treatment. *Journal of Medicinal Chemistry*, 2024, 67, 3358-3384. (IF: 6.8).
8. Ionic liquid ultrasound-assisted hydrodistillation high efficiency extraction of turmeric (Curcuma longa L.) essential oil and study of its extraction mechanism. *Separation and Purification Technology*, 2025, 359, 130504. (IF: 8.2).
9. Unraveling hydrogen bond interactions between ketoconazole and imidazolium-based ionic liquids: An experimental and theoretical study. *Journal of Molecular liquids*, 2024, 395, 123883. (IF: 5.3).
10. Directly Suppressing MYC Function with Novel Alkynyl-Substituted Phenylpyrazole Derivatives that Induce Protein Degradation and Perturb MYC/MAX Interaction. *Journal of Medicinal Chemistry*, 2024, 67, 11751-11768. (IF: 6.8).
11. Exploitation of Proximity-Mediated Effects in Drug Discovery: An Update of Recent Research Highlights in Perturbing Pathogenic Proteins and Correlated

Issues. *Journal of Medicinal Chemistry*, 2023, 66, 10122-10149. (IF: 6.8).

12. Discovery of selective HDAC6 inhibitors capped by flavonoid or flavonoid-analogous moieties as anti-cancer therapeutics simultaneously harboring anti-proliferative and immunomodulatory activities. *Bioorganic Chemistry*, 2022, 129, 106146. (IF: 5.1).
13. SAR study culminates in a series of HDAC6 selective inhibitors featuring Schisandrin C-analogous Cap as potential immunomodulatory agents for cancer therapy. *Bioorganic Chemistry*, 2022, 127, 105992. (IF: 5.1).
14. Superdispersed spherical fullerenol and lamellar graphene oxide synergize to enhance the antiwear properties of water-based lubricants: Mathematical model and mechanism investigation. *Wear*, 2024, 554-555, 205481. (IF: 5.3,).
15. Natural product of angelica essential oil developed as a stable Pickering emulsion for joint interface lubrication. *Colloids and Surfaces B: Biointerfaces*, 2024, 240, 113993. (IF: 5.4).
16. A one-pot stepwise approach to axially chiral quinoline-3-carbaldehydes enabled by iminium–allenamine cascade catalysis. *Org. Chem. Front.*, 2021, 8, 605-612. (IF: 4.6).
17. Catalytic Asymmetric Reductive Amination for Axially Chiral Aryl Aldehydes via Desymmetrization/Kinetic Resolution Cascade. *Org. Lett.*, 2024, 26, 7161-7165. (IF: 4.9).
18. Electrodialysis with ultrafiltration membrane for efficient isolation of oxymatrine from simulated eluent of traditional Chinese medicine. *Desalination*, 2024, 592, 118058. (IF: 8.4).
19. Bipolar membrane electrodialysis for efficient production of ferulic acid in alcohol/water mixed solvent. *Separation and Purification Technology*, 2024, 341, 126876. (IF: 8.2).
20. Enantioselective Photoredox- and Cu-Catalyzed Cyanoalkylation of Styrenes via Deoxygenation of Alkoxyl Radicals with Organophosphorus Compounds(III). *Org. Lett.*, 2025, 27, 1750-1756. (IF: 4.9).

近 5 年药物化学研究生学位点成员授权发明专利

安徽中医药大学为第一申请人，学位点成员为第一发明人

1. 一种蜂胶挥发油包覆物及其制备的牙膏的制备方法；王虎传；ZL202210869796.9；2023 年 12 月 22 日.
2. 一类 NO 供体型 HDAC 抑制剂、组合物及其用途；方方；ZL202310293220.7；2024 年 8 月 2 日.
3. 含四氢异喹啉类结构 HDAC 抑制剂、组合物及其用途；方方；ZL202210901388.7；2023 年 12 月 22 日.
4. 一类 PI3Kδ抑制剂及其用途；马晓东；ZL201910709742.4；2021 年 7 月 23 日.
5. 一类 HDAC 抑制剂及其用途；马晓东；ZL201910992789.6；2021 年 7 月 2 日.
6. 一类 mTOR/HDAC 双重抑制剂及其应用；马晓东；ZL202010682309.9；2021 年 6 月 11 日.
7. 1-氰基咪唑并吡啶类化合物及其合成方法；冯承涛；ZL202110830659.X9；2021 年 7 月 22 日.
8. 苯并噁唑啉酮衍生物及其制备方法和用途；李家明；ZL202211450288.3；2024 年 12 月 6 日.
9. 一类查尔酮芳氧乙酰胺化合物、制备方法及应用；李家明；ZL201610639939.1；2022 年 2 月 1 日.
10. 一类石斛生物碱衍生物、制备方法和医药用途；李家明；ZL201811248817.5；2022 年 8 月 23 日.

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Based on BODIPY fluorescent probe for detecting NO in tumour cells, zebrafish and rice roots under abiotic stresses

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ABSTRACT

As a ubiquitous signaling molecule in organisms and plants, NO plays an important role in their physiological and pathological processes. To date, numerous fluorescent probes have been successfully developed for the detection of NO. However, there are still limitations in the ability to simultaneously detect fluctuations of NO in *vivo* and plants. In this study, we have developed a fluorescent probe (BZD) specifically probe that reacts with NO under aerobic conditions, leading to a disruption of the photoinduced electron transfer (PeT) process from the secondary amine to the core of BODIPY. This disruption results in the emission of a distinct fluorescent signal. The tests showed that BZD had the advantages of low detection limit (28.4 nM), fast detection time (60 s), and successfully demonstrated good imaging ability in cell, zebrafish. Moreover, the probe was used to detect the changes in NO content in rice roots under abiotic stresses, such as heavy metals and salt stress for the first time. Thus, BZD has significant potential to analyze and detect NO in animal cells and insights into the role of NO in plant signaling.

1. Introduction

Nitric oxide (NO), a ubiquitous signaling molecule, is involved in various physiological processes in plants and animals. The endogenous NO production in the human body is mainly generated from L-arginine via the synthesis of nitric oxide synthase (NOS) [1]. NO participates in a series of essential processes such as immunomodulation, regulation of inflammation, effective promotion of vasodilation, and energy metabolism [2–6]. In plants, NO is produced by both enzymatic and non-enzymatic pathways, with the main enzymatic reactions being through nitric oxide synthase-like (NOS-like) and nitrate reductase (NR) [7,8]. Although the pathway of NO production in plants is controversial, it has been found that endogenous production of appropriate levels of NO can effectively promote and regulate physiological processes such as seed germination, growth, and development, stomatal motility, delayed maturation and senescence of tissues, programmed cell death, and antistress responses in plants [9–16]. Abnormal NO levels in organisms are often closely associated with disease, therefore the detection of NO level content is important for the diagnosis and prevention of disease.

Traditional protocols for the detection of NO in animals and plants include laser photoacoustics [17], enzymatic methods [18], the hemoglobin method [19], ozone-based chemiluminescence [20], amperometric methods with NO-specific electrodes [21], etc. However, these methods are difficult to achieve the expected results due to the disadvantages of cumbersome operation, poor biocompatibility, and limitations of the detection methods. The rise of nanomaterials and small molecule sensors is gradually becoming an important research direction [22–24]. Fluorescent probe detection has gradually become a critical detection tool owing to its good sensitivity, photostability, and specificity. In the past, there were two main types of probes for NO detection: a fluorescent probe based on *o*-phenylenediamines, first developed by Nagano's group [25], and a fluorescent probe for metal complexes, developed by Lippard's group [26]. However, classical detection methods like *o*-phenylenediamine can sometimes cause disturbances in spectral detection due to the influence of ascorbic acid and dehydroascorbic acid [27]. As the level of research continues to improve, probes for detecting NO are gradually diversifying. These include reaction with NO to generate diazo cyclic detection [28], arylation of

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A lysosomal targeted fluorescent probe based on BODIPY for monitoring NO in living cells and zebrafish imaging

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ABSTRACT

Nitric oxide (NO), as a special biological small molecule, plays an important role in physiology and pathology. Studies have revealed a strong correlation between human illness and the amount of NO in lysosomes. In this research, we synthesized a BODIPY-based fluorescent probe BML that can be localized in the lysosome to detect NO. The secondary amine in the BML structure can be *N*-nitrosation reaction with NO in the lysosome, preventing the initial photo-induced electron transfer (PET) process and leading to the creation of the highly luminescent BML-NO. The reaction mechanism was proved in the high-resolution mass spectrometry and DFT simulation calculations. Additionally, BML was discovered to have some evident benefits, such as fast detection time (3.5 min), low detection limit (LOD = 10.3 nM), and the resistance to interference and acidity, which are essential for the detection of NO in lysosomes. Furthermore, the BML was effectively employed to detect endogenous and exogenous nitric oxide in living cells and zebrafish.

1. Introduction

As an ancient signaling molecule, nitric oxide (NO) is involved in the normal physiological regulation of the body to keep it in a healthy dynamic balance and is a signaling molecule on which mammals depend for their survival [1]. According to studies, lung fibrosis, Alzheimer's disease etc. can cause abnormal subcellular NO levels during the pathogenesis, and the accumulation of excess NO in organelles results in organelle dysfunction, and then in cell death [2–7]. Premature detection of changes in the distribution and concentration of NO in organelles is essential for the earlier diagnosis and prevention of these diseases [8,9]. However, traditional NO detection techniques are poorly biocompatible, cumbersome and costly, hardly achieving the expected results [10–12]. In recent years, fluorescent probes have gradually become an irreplaceable detection tool for studying bioactive molecules due to their high sensitivity, high selectivity and excellent biocompatibility [13].

The classical detection methods in the design of fluorescent probes for the detection of NO fall into two main categories. One is the electron-rich *o*-phenylenediamine as a reaction site for NO by the Nagano group [14]. The other is the category of transition metal complexes, pioneered by the Lippard group [15]. However, electron-rich groups such as *o*-phenylenediamine are susceptible to interference by bio reductants (DHA, AA, MGO) in the cell [16,17]. Moreover, they are greatly affected by pH and not suitable for detection in lysosomes [18]. Therefore, fluorescent probes including secondary amine nitrosation reactions in aromatic groups [19–21], Hantzschester aromatization [22,23], the formation of Se-NO bonds [24,25], reduction of aromatic primary amines [26] and the formation of a diazo ring from *o*-amino-3-′-dimethylaminophenyl aromatics [27], have been developed to address these issues during recent years of research [28]. However, as an important organelle for cellular metabolism, the complex acidic environment of lysosomes easily interferes by protonating the probe for

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Research paper

Target identification, and optimization of dioxygenated amide derivatives as potent antibacterial agents with FabH inhibitory activity

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ABSTRACT

The enzyme FabH plays a critical role in the initial step of fatty acid biosynthesis, which is vital for the survival of bacteria. As a result, FabH has emerged as an appealing target for the development of novel antibacterial agents. In this study, employing the chemical proteomics method, we validated the previously identified skeleton amide derivatives bearing dioxygenated rings, potentially formed through metabolic processes. Building upon the proteomics findings, we then synthesized and evaluated 32 compounds containing *N*-heterocyclic amides for their antimicrobial activity for future optimizing the deoxygenated amides. Several compounds demonstrated potent antimicrobial properties with low toxicity, particularly compound **25**, which exhibited remarkable potential as an agent with an MIC range of 1.25–3.13 μg/mL against the tested bacterial strains and an IC_{50} of 2.0 μM against *E. coli*-derived FabH. Furthermore, we evaluated nine analogues with relatively low MIC values through cytotoxicity and hemolytic activity assessments, Lipinski's rule-of-five criteria, and in silico ADMET predictions to ascertain their druggability potential. Notably, a detailed docking simulation was performed to investigate the binding interactions of compound **25** within the binding pocket of *E. coli* FabH, which encouragingly revealed strong binding interactions. Based on our findings, compound **25** emerges as the optimal candidate for in vivo therapy aimed at treating infected skin defects. Remarkably, the application of compound **25** demonstrated a significant reduction in the duration of wound infection and notably accelerated the healing process of infected wounds, achieving an impressive 94 % healing rate by day 10.

1. Introduction

Despite the fact that multiple antibiotics are readily accessible and often used to treat bacterial infections. The conflict between humans and bacterial pathogens has persisted for centuries and will do so for the calculable future [1]. A rise in the number of bacteria that are resistant to antibiotics is being fueled by the widespread misuse of antibiotics. Generic antibiotics have become ineffective against harmful bacteria, and pan-resistant microorganisms have been linked to diseases that cannot be cured by conventional medicine [2]. According to the latest report of WHO, bacteria in hospitals, that commonly cause bloodstream infections, such as *Klebsiella pneumoniae* and *Proteus mirabilis*, exhibit high levels of drug resistance (over 50 %). More than 60 % of the *Neisseria gonorrhoeae* isolates, which cause prevalent sexually transmitted diseases, are resistant to ciprofloxacin. As the most prevalent bacteria that cause urinary tract infections, more than 20 % *Escherichia coli* isolates are resistant to first-line medications like ampicillin and cotrimoxazole, as well as second-line treatment agents like fluoroquinolones. The treatment of common bacterial infections is growing extremely complicated and resistant [3]. In addition to controlling the abuse and misuse of antimicrobials, exploring novel pharmacological targets for the development of new antimicrobial agents is of strategic importance in addressing the antibiotic resistance dilemma [4–6].

The fatty acid synthesis of bacteria (FAS II), which plays an essential

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Discovery of novel brain-penetrant GluN2B NMDAR antagonists via pharmacophore-merging strategy as anti-stroke therapeutic agents

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ABSTRACT

In this work, a novel structural series of brain-penetrant GluN2B NMDAR antagonists were designed, synthesized and biologically evaluated as anti-stroke therapeutic agents via merging the structures of NBP and known GluN2B ligands. Approximately half of them exhibited superior neuroprotective activity to NBP against NMDA-induced neurotoxicity in hippocampal neurons at 10 μM, and compound 45e and 45f exerted equipotent activity to ifenprodil, an approved GluN2B- selective NMDAR antagonist. In particular, 45e, with the most potent neuroprotective activity throughout this series, displayed dramatically enhanced activity (K_i = 3.26 nM) compared to ifenprodil (K_i = 14.80 nM) in Radioligand Competitive Binding Assay, and remarkable inhibition (IC_{50} = 79.32 nM) against GluN1/GluN2B receptor-mediated current in Patch Clamp Assay. Meanwhile, 45e and its enantiomers exhibited low inhibition rate against the current mediated by other investigated receptors at the concentration of 10 μM, indicating their favorable selectivity for GluN1/GluN2B. In the rat model of middle cerebral artery ischemia (MCAO), 45e exerted comparable therapeutic efficacy to ifenprodil at the same dosage. In addition to the attractive in *vitro* and *in vivo* potency, 45e displayed a favorable bioavailability (F = 63.37%) and an excellent brain exposure. In further repeated dose toxicity experiments, compound 45e demonstrated an acceptable safety profile. With the above merits, 45e is worthy of further functional investigation as a novel anti-stroke therapeutic agent.

1. Introduction

Stroke has ranked as the 2nd leading cause of mortality and the 3rd most common cause of disability worldwide, consuming 4% of total health care costs annually and posing a huge burden on the health care system [1]. Among two predominant types of stroke, termed as ischemic and hemorrhagic strokes, the former comprises approximately 87% of all strokes [2]. The primary pathological process of ischemic strokes include brain edema, apoptosis, oxidative stress, energy failure, high-frequency amino acid neurotoxins, and intracellular calcium overload [3]. After cerebral ischemia, a sequence of cascade reactions is initiated, such as the release of excitotoxic amino acids, the stagnation of energy metabolism, the generation of free radicals, and the release of inflammatory factors, resulting in severe damage to structure and function of nerve cells [4,5].

Excitotoxicity, one of the most well-established pathogenic mechanisms underlying ischemic brain injury, is triggered by the interaction of the crucial excitatory neurotransmitter Glutamate (Glu) with ionotropic glutamate receptors (iGluRs). iGluRs are divided into three subtypes, known as *N*-methyl-*D*-aspartate receptors (NMDARs), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPARs) and kainite receptors [6]. Accumulating evidence has supported the involvement of NMDAR-mediated excitotoxicity with neurodegenerative diseases. In particular, the Glu-induced activation of NMDARs harboring GluN2B subunits is responsible for the excitotoxicity, rendering GluN2B-selective NMDAR antagonists as potential drug for battling neurodegenerative diseases, including stroke, Alzheimer and Parkinson [7–9]. Non-selective NMDAR antagonists, such as MK-801(1, Fig. 1)

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Identification and optimization of nitrophenolic analogues as dopamine metabolic enzyme inhibitors for the treatment of Parkinson's disease

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Dopamine metabolizing enzymes
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ABSTRACT

Progressive loss of dopaminergic neurons leads to the depletion of the striatal neurotransmitter dopamine, which is the main cause of Parkinson's disease (PD) motor symptoms. Simultaneous inhibition of the two key dopamine metabolic enzymes, catechol-*O*-methyltransferase (COMT) and monoamine oxidase B (MAO-B), could potentially be a breakthrough in achieving clinical efficacy. Representative compound **C12** exhibits good COMT inhibitory activity (IC_{50} = 0.37 μM), metal chelation ability, and BBB permeability. Furthermore, results from *in vivo* biological activity evaluations indicate that **C12** can improve dopamine levels and ameliorate MPTP-induced PD symptoms in mice. Preliminary *in vivo* and *in vitro* study results highlight the potential of compound **C12** in PD treatment.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that manifests clinically through motor symptoms like resting tremor, bradykinesia, muscle stiffness, and impaired gait. It also presents non-motor symptoms, including cognitive decline, depression, constipation, and disrupted sleep [1–3]. The pathological hallmarks of PD encompass extensive dopaminergic neuron death (over 50 %) in the substantia nigra pars compacta, widespread degeneration of pigmented neurons, a marked decrease (more than 80 %) in striatal dopamine levels, abnormal α-synuclein aggregation, and Lewy bodies within the cytoplasm of surviving substantia nigra neurons [4–7].

Dopaminergic neurons regulate essential physiological functions such as behavior, cognition, movement, and the neuroendocrine response [8]. The progressive loss of dopaminergic neurons leads to a depletion of dopamine in the striatum, a primary contributor to PD's motor symptoms [9]. Considering dopamine's critical role in alleviating PD motor symptoms, clinicians use dopamine supplementation therapy to enhance dopamine levels in the CNS by targeting specific aspects of its biosynthesis, transport, metabolism, or receptor function [10]. The therapy primarily utilizes drugs such as levodopa [11,12], dopamine receptor agonist [13,14], monoamine oxidase B (MAO-B) inhibitors [15,16], catechol-*O*-methyltransferase inhibitors (COMT) [17,18] and adenosine A2 receptor antagonists [19,20].

COMT and MAO are the main enzymes responsible for dopamine metabolism. COMT can methylate dopamine into 3-methoxytyramine (3-MT), while MAO can oxidize and deaminate dopamine into 3,4-dihydroxyphenylacetaldehyde (DOPAA), resulting in the production of ammonia and hydrogen peroxide [21,22]. Dopamine is ultimately metabolized into homovanillic acid (HVA), with the involvement of enzymes like acetaldehyde dehydrogenase (ALDH) and aromatic L-amino acid decarboxylase (AADC) (Fig. 1). Additionally, levodopa can also undergo metabolism by COMT, resulting in the formation of the inactive 3-*O*-Methyldopa (3-OMD). Taking into account the involvement of COMT and MAO-B in the metabolism of dopamine and levodopa, the development of COMT/MAO dual inhibitors to hinder dopamine metabolism pathways could potentially lead to synergistic effects and benefits, such as delaying drug resistance and improving effectiveness [23,24].

Herein, we present the results of the chemical optimization and

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Site-Selective C−H Arylation of 2-Pyridones via Pd/NBE Cooperative Catalysis

Ziyi Sun,[‖] Zibin Jiang,[‖] Fengya He, Chenyue Li, Hujie Xiong, Dan Yang, Hui Miao, Qinglin Li,* Jinxiang Ye,* and Chenggui Wu*

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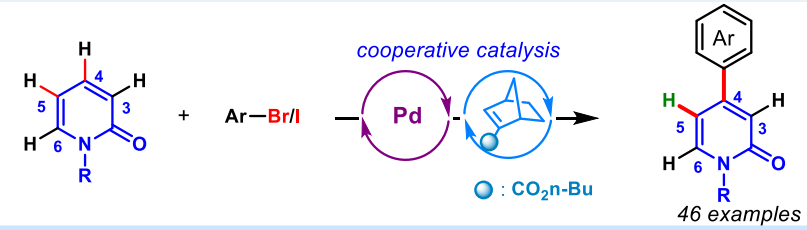

ABSTRACT: The 4-aryl-2-pyridone scaffold is considered to be a privileged pharmacophore. Diversity-oriented synthesis of its derivatives is a pressing demand within the field of medicinal chemistry. Herein, we report a site-selective C−H arylation of 2-pyridones via palladium/norbornene cooperative catalysis. The success of this research is based on the nucleophilicity and metalation properties exhibited by the C5 position in 2-pyridones, an activated norbornene that was employed to capture the C5-palladation intermediate and transfer it to the C4 position, resulting in a highly specific C−H arylation of 2-pyridones at the C4 position. This methodology showcases remarkable compatibility with readily available 2-pyridones and aryl bromides, enabling the efficient synthesis of a diverse range of functional 4-aryl-2-pyridone scaffolds (46 examples) with notable site selectivity, which will be very useful in drug discovery. Furthermore, this approach was successfully utilized for the economically viable synthesis of the perlolidine analogues. Density functional theory calculations revealed a preference for C−H bond activation at the C5 position in 2-pyridones. In addition, the insights into the mechanism suggest that oxidative addition and reductive elimination of aryl bromides are crucial steps in the conversion.

KEYWORDS: *cooperative catalysis, C−H activation, arylation, selectivity, 2-pyridone*

INTRODUCTION

2-Pyridone is a highly utilized and essential constituent that is commonly found in numerous natural products and bioactive compounds,[1] including (+)-hosieine A, ciclopirox, (+)-lycopodin A, huperzine A, milrinone, and camptothecin. Additionally, 2-pyridone also serves as a pivotal ligand in the development of transition-metal catalytic systems.[2] As a result, the exploration of techniques for the synthesis of diverse derivatives of 2-pyridone has attracted significant attention from both synthetic organic chemists and medicinal chemists. Diverse elegant methods have been developed for the functionalization of 2-pyridone in the past few decades. However, precise site-selective functionalization has not been fully realized.

The transition-metal-catalyzed site-selective C−H functionalization of 2-pyridones has emerged as a potent approach, supplementing the conventional techniques such as intrinsic electrophilic substitutions,[3] pyridine hydrolysis,[4] and de novo constructions of acyclic precursors.[5] This approach demonstrates superior cost-effectiveness and versatility in contrast to traditional methodologies.[6] However, the unique characteristics of 2-pyridones, such as the presence of four potential reactive C−H bonds, resonance configurations, and notable electronic biases, result in varying reactivities at each location, presenting difficulties in attaining site selectivity.[6a] C−H functionalization,[6] O−H functionalization,[7] and N−H functionalization[8] are all involved in site-selective reactions. Previous studies have successfully achieved C−H functional-

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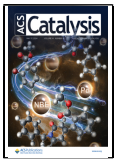

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OL | Organic Letters

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Photoinduced [3+2] Cycloaddition of Alkyl−Acceptor Diazoalkanes: Diversity-Oriented Synthesis of Pyrazolines Containing a Quaternary Center

Fengya He, Ziyi Sun, Yiwei Xu, Jingwen Yu, Wenyong Li,* Hui Miao,* and Chenggui Wu*

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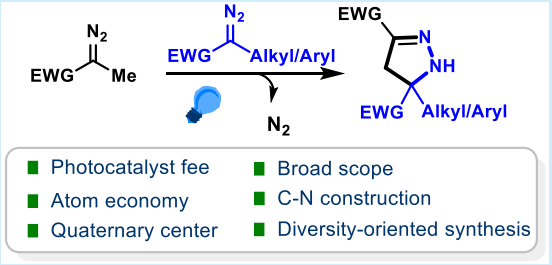
ABSTRACT: We present a new [3+2] cycloaddition reaction between alkyl−acceptor diazoalkanes under visible light irradiation. By employing easily accessible alkyl−acceptor-type diazoalkanes or their precursor hydrazones as both 1,3-dipoles and dipolarophiles, a diverse range of pyrazoline derivatives featuring a quaternary center have been efficiently synthesized in a predictable manner, with excellent functional group tolerance and good yields. Furthermore, scale-up experiments and downstream transformations of the product were also detailed.



Pyrazoline, an important heterocycle that widely exists in numerous biologically active molecules and pharmaceuticals, exhibits several properties such as antimicrobial, antitumor, anti-inflammatory, antiviral, antimalarial, and antituberculosis activity.[1] Accordingly, significant research endeavors have been dedicated to their synthesis, and remarkable advances have been achieved in their construction, such as catalytic [3+2][2] and [4+1][3] cycloadditions, cyclocondensations,[4] and 5-exo annulations.[5] Despite the advancements made, a significant demand for more practical and efficient synthetic methods for constructing pyrazolines with a quaternary center remains (Figure 1A).

Diazoalkanes are organic building blocks for constructing C−C and C−X bonds, which have garnered much attention from synthetic and pharmaceutical chemists.[6] Classic reactions, including cyclopropanation, rearrangement, and C−H or X−H insertions, commonly entail the formation of metal carbene and free carbene intermediates.[7−9] Recently, the development of photocatalysis as a new stratagem has largely expanded this classic reactivity toward radical reactivity.[9] In addition, diazoalkanes, as ambiphilic reagents, can react with electrophiles to yield diazonium ions or with nucleophiles to yield azo compounds (Figure 1B).[10] As such, diazoalkanes serve as practical 1,3-dipoles to react with dipolarophiles for constructing five-membered nitrogen heterocycles.[11,12] For example, olefins as dipolarophiles can react with diazoalkanes to assemble pyrazoline rings (Figure 1C).[11] This strategy is powerful for the diversity-oriented synthesis of pyrazoline derivatives. However, the protocol is confined to olefin dipolarophiles, and the 1,3-dipoles are restricted to acceptor-only or donor−acceptor-type diazoalkanes. To extend the scope of diazoalkanes, Zhang et al. have recently expanded the scope to the donor−donor-type diazoalkanes generated from *N*-tosylhydrazones.[13]

Generally, diazoalkanes undergo self-polymerization, including the information about azoic compounds and olefin side products, which challenge many kinds of reactions engaged by diazoalkanes.[14] Thus, restraining these undesired reactions to improve the reaction efficiency or utilizing the undesired products for facile diversity-oriented synthesis of nitrogen heterocycles remains a challenge. Inspired by previous studies, we conceived a novel approach utilizing alkyl−acceptor-type diazoalkanes as both 1,3-dipoles and dipolarophiles to undergo formal intermolecular [3+2] cycloaddition for the diversity-oriented synthesis of pyrazolines with the release of nitrogen (Figure 1D). If successful, the reaction will immensely enrich the diversity of pyrazoline structures and provide an economical and efficient synthetic method for the synthesis of pyrazolines containing a quaternary center.

Our investigation started with benzyl 2-diazopropanoate (**1a**) as the reactant to optimize the reaction conditions. After an extensive survey of the reaction parameters (for details, see Tables S1−S4), the optimized conditions were identified: a 20:1 mixture of solvents PhCl and DCE,[15] Et_3N, and irradiation for 24 h with blue LEDs (15 W, 455 nm) (Table 1). To our delight, pyrazoline **2a** was obtained in 84% isolated yield (entry 1). Control experiments were subsequently

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Design, Synthesis, and Biological Evaluation of *Pierardine* Derivatives as Novel Brain-Penetrant and *In Vivo* Potent NMDAR-GluN2B Antagonists for Ischemic Stroke Treatment

Gaofeng Lin,[▽] Qinlong Xu,[▽] Jiaming Li,* Zhaoxing Chu, Xiaodong Ma, Qihua Zhu, Yan Zhao, Jiajia Mo, Wenfeng Ye, Li Shao, Tao Fang, Minghan He, Shaoyun Yue, and Mingqi Dai

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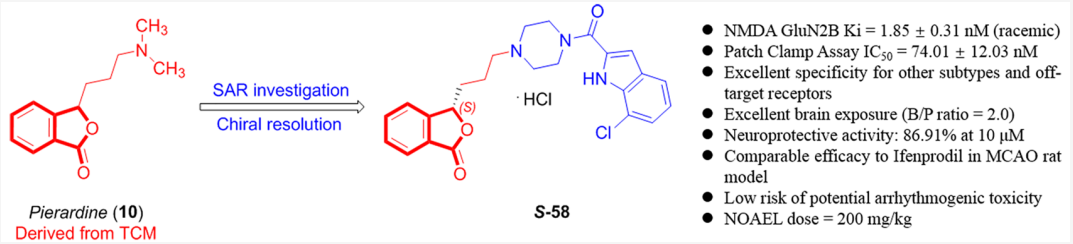

ABSTRACT: A series of structurally novel GluN2B NMDAR antagonists were designed, synthesized, and biologically evaluated as anti-stroke therapeutics by optimizing the chemical structure of *Pierardine*, the active ingredient of traditional Chinese medicine *Dendrobium aphyllum (Roxb.) C. E. Fischer* identified via *in silico* screening. The systematic structure−activity relationship study led to the discovery of **58** with promising NMDAR-GluN2B binding affinity and antagonistic activity. Of the two enantiomers, ***S*-58** exhibited significant inhibition (IC_{50} = 74.01 ± 12.03 nM) against a GluN1/GluN2B receptor-mediated current in a patch clamp assay. In addition, it displayed favorable specificity over other subtypes and off-target receptors. *In vivo*, ***S*-58** exerted therapeutic efficacy comparable to that of the approved GluN2B NMDAR antagonist ifenprodil and excellent safety profiles. In addition to the attractive *in vitro* and *in vivo* potency, ***S*-58** exhibited excellent brain exposure. In light of these merits, ***S*-58** has been advanced to further preclinical investigation as a potential anti-stroke candidate.

INTRODUCTION

Stroke, as a leading cause of mortality and a major contributor to neurological disability, poses an increasing burden on the global health service.[1,2] Characterized by permanent post-stroke brain damage, it commonly results from a sudden rupture or blockage of a blood vessel in the brain. Cerebral ischemia-induced ischemic stroke (IS) accounts for 80% of all strokes[3,4] and is associated with complicated pathogenesis, including brain edema, cell apoptosis, oxidative stress, energy failure, a high level of amino acid neurotoxins, and intracellular calcium overload.[5−7] A series of cascade reactions are triggered after cerebral ischemia, such as the release of excitotoxic amino acids, the stagnation of energy metabolism, the production of free radicals, and the release of inflammatory factors, thereby leading to the death of nerve cells.[8−11]

In the central nervous system (CNS), glutamate, as the primary excitatory neurotransmitter mediating rapid synaptic transmission, is responsible for neurotoxicity under pathological conditions. This specific neurotoxicity provoked by glutamate, termed excitotoxicity, serves as a critical link between ischemia and neuronal death in stroke.[12] Over the past few decades, large numbers of studies have demonstrated that excitotoxicity plays an essential role in the pathogenesis of stroke.[13] In general, glutamatergic receptors can be divided into two categories: ionotropic receptors (iGluRs) and metabotropic receptors (mGluRs).[14] The former consists of *N*-methyl-D-aspartate receptors (NMDARs), kainate receptors (KARs), and 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)-propanoic acid receptors (AMPARs).[15] Among these, NMDARs are regarded as the predominant contributor to glutamate-mediated excitotoxicity.[13,14] After stroke, an excessive amount of glutamate is released, and the agonism of NMDARs induces an imbalance of Ca^{2+} within the neuron, ultimately activating a series of signaling cascades involved with neuronal cell death.[13]

NMDARs are heterotetrameric complexes assembled from two obligatory NR1 subunits and variable NR2 subunits. Because of their distinct biophysical, pharmacological, and

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Ionic liquid ultrasound-assisted hydrodistillation high efficiency extraction of turmeric (*Curcuma longa L.*) essential oil and study of its extraction mechanism

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ABSTRACT

The optimal conditions for extracting turmeric essential oil (CEO) using ionic liquid ultrasound-assisted hydrodistillation (IL-U-HD) were determined in this study. In this context, the CEO extraction yield reached 6.88 %, significantly higher than that of hydrodistillation (HD), ultrasound-assisted hydrodistillation (U-HD), and ionic liquid-assisted hydrodistillation (IL-HD). The extraction kinetics, GC–MS compositional analysis, cell viability, and antioxidant properties of the extracted CEO indicate enhanced cell viability and antioxidant properties when extracted by IL-U-HD. Additionally, the compositional fractions exhibited an increase while improving extraction efficiency by 22 % compared to HD. To explore the efficient extraction mechanism at the molecular level, cellobiose and *ar*-turmerone were established as model molecules representing the primary constituents of the plant cell wall and CEO, respectively. Their interaction with ILs was investigated using quantum chemical calculations (QC) and wavefunction analysis. The results revealed that [EMIM][Tf_2N] formed hydrogen bond (HB) interactions with cellobiose and exhibited strong van der Waals (vdW) interactions as well as HB interactions with *ar*-turmerone, leading to a significant enhancement in CEO extraction.

1. Introduction

Volatile oils, also known as essential oils, are a category of oily liquids derived from plants, which possess volatile characteristics and can be extracted through steam distillation and are insoluble in water [1,2]. Due to their distinct biological characteristics, essential oils derived from fragrant plants (such as flowers, roots, bark, leaves, seeds, pericarp, fruits, wood, and the entire plant) find extensive applications in various domains including medicine, food industry and cosmetics [3–5].

Turmeric (*Curcuma longa L.*) is the dried rhizome of Curcuma longa, a plant in the ginger family. It is a commonly used traditional Chinese medicine with the effects of moving qi, dispersing wind and activating blood circulation, as well as relieving menstruation and pain. Turmeric contains more chemical constituents, and turmeric essential oil (CEO) is one of its main constituents, with broad-spectrum antibacterial, antioxidant, anti-inflammatory, cough, asthma and other effects [6–9]. The CEO also exhibits anti-tumorigenic, hypolipidemic, immunoregulatory, and anti-fibrotic properties, making it highly versatile for applications in diverse sectors including food processing, pharmaceuticals, personal care products, among others [10].

The most commonly used extraction techniques for CEO are hydrodistillation and organic solvent extraction [11]. Although the hydrodistillation method is easy to operate, simple equipment, low production cost, inadequate process control can result in a diminished yield of essential oil. And the hydrodistillation method is not applicable to thermally unstable essential oil components [12]. The traditional organic solvent extraction method exists in the organic solvent residue, environmental pollution, low extraction efficiency and other problems, and the extraction method usually extracts the fat-soluble components of the herbs such as resins in the herbs, which results in the CEO containing more impurities. In addition, the organic solvent extraction method is not easy to extract Chinese herbal essential oil on an industrial scale, and is only used to extract small amounts of essential oil in the laboratory. Therefore, new extraction methods are urgently needed to obtain high yields of essential oils.

Ultrasound-assisted extraction is commonly employed for obtaining

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Unraveling hydrogen bond interactions between ketoconazole and imidazolium-based ionic liquids: An experimental and theoretical study

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ABSTRACT

The solubility and solvation mechanism of the Biopharmaceutical Classification System class II insoluble drug, ketoconazole (KCZ), were investigated in eight different types of imidazolium-based ionic liquids (ILs). An in vitro cytotoxicity test was conducted on Human immortalized keratinocytes cells to evaluate the potential toxicity of these ILs. The results showed no cytotoxicity for any of the imidazolium-based ILs tested. The solubility of KCZ was then examined in the eight imidazolium-based ILs at temperatures ranging from 298.15 K to 338.15 K. The findings revealed that the solubility of KCZ followed a specific order among the imidazolium-based ILs tested. The imidazolium-based IL [BMIM][Tf_2N] exhibited the highest solubility of KCZ, followed by [HMIM][PF_6], [EMIM][Tf_2N], [BMIM][TfO], [BMIM][PF_6], [EMIM][TfO], [BMIM][BF_4], and [EMIM][BF_4] in decreasing order. To understand the interaction mechanism between the imidazolium-based ILs and KCZ, the cations, anions and KCZ were analyzed using σ-profiles computed from both the COSMO-RS model and quantum chemical calculations. The results indicated that KCZ had strong hydrogen bond (HB) acceptors, particularly the oxygen atom of the carbonyl group and the nitrogen atom of the imidazole ring. These HB acceptors contributed to the formation of stronger HBs with the hydrogen atoms of cations compared to the oxygen atoms of the anions. The trend of HB strength followed $[Emim]^+ > [Bmim]^+ > [Hmim]^+ > [Tf_2N]^- > [TfO]^- > [PF_6]^- > [BF_4]^-$. Based on these findings, it can be concluded that [BMIM][Tf_2N], which has a strong HB donor cation and a strong HB acceptor anion, displayed the most effective dissolution of KCZ.

1. Introduction

Ketoconazole (KCZ) is a commonly used broad-spectrum antimycotic drug for treating various fungal infections [1]. Its antimicrobial activity is primarily achieved by inhibiting the biosynthesis of fungal ergosterol and altering the composition of lipid compounds in the cell membrane. KCZ belongs to Biopharmaceutical Classification System (BCS) class II, characterized by low water solubility and high permeability [2]. The limited water solubility of KCZ (40 μg/mL) along with its high octanol–water partition coefficient (log P = 4.31) hampers its effective transdermal delivery for the treatment of localized skin fungal infections [3]. Hence, enhancing the solubility of KCZ is important.

Various methods have been developed to increase the water solubility of KCZ, including the use of co-solvents, solid dispersion, inclusion, crystallization, salifying, and surfactants [4–6]. For instance, the co-crystallization of KCZ with fumaric and adipic acids demonstrated a significant increase in water solubility, by up to 100 times [7]. However, the stability of the co-crystallization product was found to be poor, limiting its storage time at 40℃/75 % relative humidity to a few months. Additionally, co-crystallization has limited applicability to certain insoluble weak acid or weak base drugs. Another approach is the use of co-solvents, such as mixtures of PEG200, PEG400, or PEG600 with water, which have shown potential in enhancing the solubility of KCZ. However, limited information is available regarding the potential toxic side effects of this method [8]. The complexation of KCZ with β-cyclodextrin (β-CD) has also been investigated as a solubility enhancement strategy. However, the inclusion method only showed a marginal improvement in solubility, reaching a maximum of 0.303 mg/mL [9]. Despite these methods, they still suffer from limitations such as low bioavailability, unstable absorption, uncertain biosafety and low

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Directly Suppressing MYC Function with Novel Alkynyl-Substituted Phenylpyrazole Derivatives that Induce Protein Degradation and Perturb MYC/MAX Interaction

Can Zhao,[⊥] Fang Zhao,[⊥] Liuqing Yang,[⊥] Yang Wang,* Henian Wang, Fang Fang, Haojie Zuo, Zhi Li, Ge He, Wenhu Zhan,* and Xiaodong Ma*

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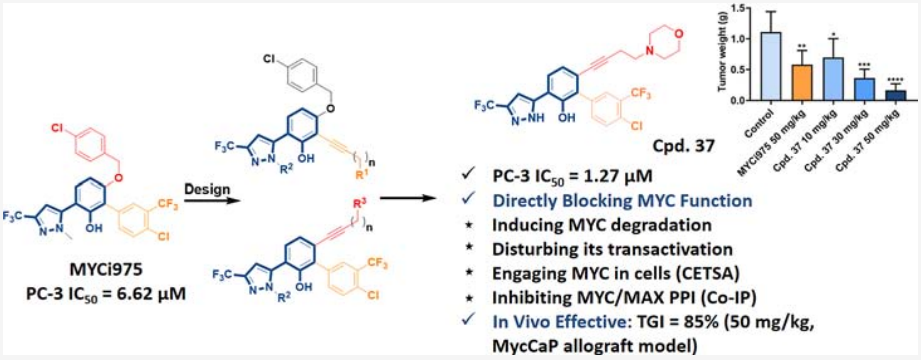

ABSTRACT: Despite being a highly sought-after therapeutic target for human malignancies, myelocytomatosis viral oncogene homologue (MYC) has been considered intractable due to its intrinsically disordered nature, making the discovery of in vivo effective inhibitors that directly block its function challenging. Herein, we report structurally novel alkynyl-substituted phenylpyrazole derivatives directly perturbing MYC function. Among them, compound **37** exhibited superior antiproliferative activities to those of MYCi975 against multiple malignant cell lines. It induced dose-dependent MYC degradation in cells with degradation observed at the concentration as low as 1.0 μM. Meanwhile, its direct suppression of MYC function was confirmed by the capability to inhibit the binding of MYC/MYC-associated protein X (MAX) heterodimer to DNA consensus sequence, induce MYC thermal instability, and disturb MYC/MAX interaction. Moreover, **37** demonstrated enhanced therapeutic efficacy over MYCi975 in a mouse allograft model of prostate cancer. Overall, **37** deserves further development for exploring MYC-targeting cancer therapeutics.

1. INTRODUCTION

Myelocytomatosis viral oncogene homologue (MYC), the nuclear transcription factor discovered approximately 40 years ago, has emerged as one of the most appealing anticancer targets, attributed to its ubiquitous dysfunction in the majority of human malignancies.[1−3] As a master regulator orchestrating a network of pro-cancer proteins, MYC oncogene is implicated in almost all hallmarks of cancer,[4−6] including cellular proliferation,[7] metabolism,[8] angiogenesis, cross-talk with the tumor microenvironment,[9] and chemo-resistance.[10] Despite its crucial and nonredundant role in cancer development and maintenance, MYC has long been considered as "undruggable".[1,11−13] First, MYC, an intrinsically disordered protein (IDP), is devoid of well-defined and ligandable pockets accessible to pharmacological interrogation. Second, due to its central role in a wide array of cellular processes,[14,15] the development of therapeutics suppressing MYC function is further challenged by potential undesirable side effects on normal proliferating cells. Unlike other common oncogenes sparking tumorigenesis through direct mutation, MYC function is deregulated by increased expression in response to upstream tumorigenic signals, making it impractical to target cancer-specific MYC mutant.[16−18]

The concern regarding the safety has been relieved by a wealth of researches that demonstrate the druggability of MYC inactivation. Although the overabundance and aberrant expression of MYC are frequently observed in cancer, MYC is tightly regulated under quiescent and physiological

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Journal of Medicinal Chemistry

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Perspective

Exploitation of Proximity-Mediated Effects in Drug Discovery: An Update of Recent Research Highlights in Perturbing Pathogenic Proteins and Correlated Issues

Can Zhao,[‖] Henian Wang,[‖] Wenhu Zhan, Xiaoqing Lv,[*] and Xiaodong Ma[*]

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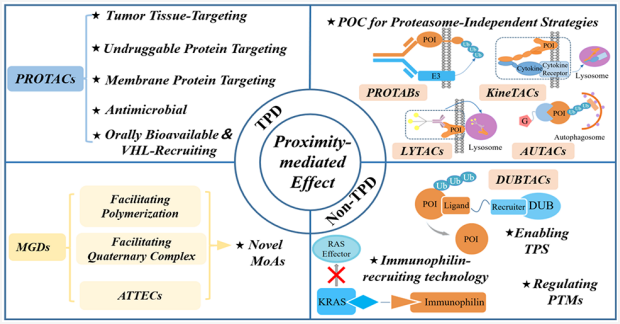
ABSTRACT: The utilization of proximity-mediated effects to perturb pathogenic proteins of interest (POIs) has emerged as a powerful strategic alternative to conventional drug design approaches based on target occupancy. Over the past three years, the burgeoning field of targeted protein degradation (TPD) has witnessed the expansion of degradable POIs to membrane-associated, extracellular, proteasome-resistant, and even microbial proteins. Beyond TPD, researchers have achieved the proximity-mediated targeted protein stabilization, the recruitment of intracellular immunophilins to disturb undruggable targets, and the nonphysiological post-translational modifications of POIs. All of these strides provide new avenues for innovative drug discovery aimed at battling human malignancies and other major diseases. This perspective presents recent research highlights and discusses correlated issues in developing therapeutic modalities that exploit proximity-mediated effects to modulate pathogenic proteins, thereby guiding future academic and industrial efforts in this field.



SIGNIFICANCE

- The newly developed drug design approaches exploiting proximity-mediated effects have exerted significant impact on innovative drug discovery.
- This perspective presents recent research highlights in the field of TPD, including PROTAC, MGD, and proteasome-independent TPD strategies.
- Meanwhile, it highlights the strides made in non-TPD strategies that exploit proximity-mediated effects.
- The perspective discusses the unsolved issues and future directions in these fields for guiding the academic and industrial efforts.

1. INTRODUCTION

With the continuous evolution of small-molecule drugs and biological medicines, and the emergence of cell therapy and gene therapy,[1] innovative drug discovery has entered a new era. Undoubtedly, biological therapeutic modalities and genome editing approaches, including small interfering RNAs (siRNAs), antisense oligonucleotides (ASOs), short hairpin RNAs (shRNAs), and CRISPR-based agents, have offered avenues to harness the targets that are not amenable to pharmacological intervention using conventional small-molecule approaches (Figure 1). However, the development of these modalities is accompanied by several intractable challenges, such as high investment, inconvenient delivery, and restricted tissue distribution.

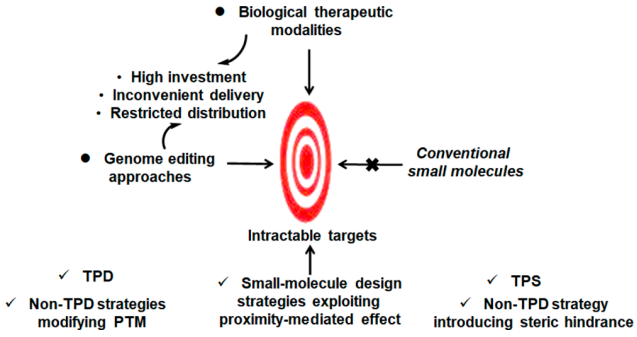


Figure 1. An outline of strategic advances in tackling targets categorized as intractable in conventional drug discovery (targeted protein degradation, TPD; targeted protein stabilization, TPS; post-translational modification, PTM).

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Discovery of selective HDAC6 inhibitors capped by flavonoid or flavonoid-analogous moieties as anti-cancer therapeutics simultaneously harboring anti-proliferative and immunomodulatory activities

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Anti-proliferative
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ABSTRACT

Specific HDAC6 inhibitors (HDAC6is) simultaneously harboring anti-proliferative and immunomodulatory properties may prohibit tumor progression *via* intrinsic and immune driven effects. Herein, built upon the structurally novel lead TFH-7, structure–activity relationship study culminated in the identification of azaflavone-capped compound **20**, which exhibited comparable HDAC6 inhibitory activity (IC_{50} = 8.5 nM) to that of Tubastatin A, a highly selective HDAC6i, as well as favorable subtype specificity. Importantly, concurrent with its impressive anti-proliferative efficacy against several solid tumor cell lines, **20** remarkably alleviated the transduction of immune-related STAT3 signaling and attenuated the expression of immunosuppressive checkpoint PD-L1 at submicromolar concentration, highlighting the immunomodulatory properties. Moreover, consistent with its favorable subtype selectivity, **20** displayed low cytotoxicity against normal human umbilical vein endothelial cells, revealing a promising safety profile. Following the intravenous administration, it demonstrated acceptable elimination half-life and exposure in Sprague-Dawley rats. Hence, the extensive functional investigation or structural modification of **20** is valuable.

1. Introduction

The medicinal potential of histone deacetylases (HDACs) as anti-cancer target has been verified by the successive approval of five HDAC inhibitors (HDACis) for battling hematopoietic malignancies [1–3]. Nonetheless, the development of HDACis has encountered major challenge in achieving therapeutic activity against solid tumors with acceptable tolerance [4,5]. As well-established epigenetic modulators of gene expression, HDACs promote the reversible cleavage of the acetyl groups at histone lysine residue, thereafter influencing nucleosome structure [6–8]. Composed of eighteen members, HDACs can be divided into four classes. Among these, class I (HDAC1, 2, 3, and 8), II (IIa HDAC4, 5, 7, and 9; IIb 6 and 10) and class IV (HDAC11) are Zn^{2+}-dependent, while class III, also termed as Sirtuins (SIRT 1-7), is NAD^{+}-dependent [9]. Attributed to the pan-inhibition against HDAC isoforms or the concomitant suppression of several subtypes, the presently marketed HDACis suffer from a modest therapeutic window. Additionally, the untoward reactions, including hematological toxicity, fatigue, nausea, and laboratory abnormalities, hamper their extensive application as therapeutic weapons against solid tumors [4,10]. Hence, their approved indications are presently confined to a minor subset of lymphoma or myeloma [11,12].

With the preferred substrates covering a broad spectrum of non-histones, exemplified by α-tubulin, heat shock factor-1 (HSF-1), heat

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SAR study culminates in a series of HDAC6 selective inhibitors featuring Schisandrin C-analogous Cap as potential immunomodulatory agents for cancer therapy

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Keywords:
HDAC6 inhibitors
Traditional Chinese medicine monomer
Selectivity
Immunomodulatory
Oral bioavailability
Human malignance

ABSTRACT

HDAC6 inhibitors (HDAC6is) represent an emerging therapeutic option for triggering anti-cancer immune response. In this work, a novel series of HDAC6is, derived from an in-house analog of the traditional Chinese medicine monomer Schisandrin C, were designed and synthesized for SAR study. Throughout the 29 target compounds, **24a**, **24b** and **24h** exerted single-digit nanomolar enzymatic activity and remarkably elevated subtype selectivity compared to the clinically investigated HDAC6i Ricolinostat (Selectivity index = 3.3). In A549 tumor cells, **24h**, as the representative in this series (IC_{50} = 7.7 nM; selectivity index = 31.4), was capable of reversing IL-6-mediated PD-L1 upregulation, highlighting its immunomodulatory capability. Importantly, unlike numerous other hydroxamate-based HDACis, **24h** displayed an acceptable oral bioavailability in Sprague-Dawley rats, along with high plasma exposure, long elimination half-life and slow clearance. With the aforementioned attractive performance, **24h** deserves further *in vivo* investigation as an immunomodulatory therapeutic agent for batting human malignance.

1. Introduction

The histone acetylation state plays a prominent role in epigenetic modulation of gene expression via altering nuclear chromatin structure [1,2]. Under physiological conditions, the equilibrium of histone acetylation was governed by histone deacetylases (HDACs) and histone acetyltransferases (HATs) upon the reversible cleavage or attachment of the acetyl groups at lysine residues [3]. HDAC superfamily, comprising eighteen members, is divided into four classes based on the phylogenetic analysis: Zn^{2+}-dependent class I (HDAC1, 2, 3 and 8), II (IIa HDAC4, 5, 7 and 9; IIb 6 and 10), IV (HDAC11) HDACs, and NAD^{+}-dependent class III HDACs, also termed as Sirtuins (SIRT1-7) [4,5]. Owing to the canonical role of HDACs, especially class I isotypes, in modifying DNA-histone state and transcriptional silencing of tumor suppressor genes, HDAC has emerged as a reasonable target in the exploration of epigenetic cancer therapies [6,7]. With the massive pharmaceutical investment, five HDAC inhibitors (HDACis) have been successively marketed as therapeutics for a limited subset of hematological malignancies [8,9]. However, the narrow therapeutic window and profound side-effects, due to the lack of subtype specificity, pose a considerable obstacle to their widespread application. Hence, the pursuit of surrogates with subtype selectivity and efficacy against solid tumors represents a major challenge encountering HDACi discovery [10–12].

Throughout HDAC superfamily, the predominantly cytoplasm-

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Superdispersed spherical fullerenol and lamellar graphene oxide synergize to enhance the antiwear properties of water-based lubricants: Mathematical model and mechanism investigation

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ARTICLE INFO

Keywords:
Water-based lubricant
Carbon-based nanomaterials
Tribological property
Antiwear mechanism

ABSTRACT

The development of high-performance water-based lubricating additives with excellent properties has been the focus of research recently. Herein, carbon-based nanomaterials made of spherical fullerenol and lamellar graphene oxide (GO) were explored as water-based lubricating additives to enhance tribological properties via the response surface method systematically. The antiwear mechanisms of the carbon-based nanomaterials were revealed through simultaneous wear surface characterizations and molecular dynamics simulations. Results showed that the spherical fullerenol and lamellar GO had superdispersion stability in the water-based lubricants. Fullerenol and GO could play a superior synergistic role to considerably enhance the antiwear properties of the water-based lubricants. Particularly, the wear rate decreased by almost 93 % when the water-based lubricant was supplemented with fullerenol and GO (0.1 wt% each) at the load of 1.5 N and sliding speed of 30 mm/s. The antiwear mechanisms indicated that an excellent antiwear effect was produced by the stable tribofilms containing GO and fullerenol, which combined with hydration layers synergistically exerting a bearing capacity.

1. Introduction

Lubricants are crucial in reducing friction and guaranteeing the precision of workpiece machining [1,2]. With the improvement of sustainable development and environmental protection awareness, the research on water-based lubricants with environmental friendliness, low cost, and high safety has been promoted [3]. However, the properties of water-based lubricants are poor because of their low viscosity and high surface tension [4,5]. Therefore, advanced additives are needed to enhance the tribological properties of practical water-based lubricants [6,7]. Nano-lubricants are highly efficient methods because they reduce resource consumption and increase mechanical effectiveness [8,9]. Many studies have used nanomaterials as additives to enhance lubricants' tribological properties because of their excellent physical and chemical characteristics [10]. Carbon-based nanomaterials have recently received much attention in the area of lubricants because of their low contamination, high chemical stability and excellent load-bearing ability [11].

Graphene oxide (GO) and fullerene are archetypal delegates of lamellar and spherical carbon-based nanomaterials. GO contains many functional groups with oxygen, such as hydroxyl, carboxyl, and epoxy, enabling it to disperse in water stably [12,13]. Researchers have found that GO has excellent mechanical properties and reduces wear at the friction interface effectively [14,15]. Su et al. studied the tribological properties of GO and onion-like carbon as water-based lubricants, and discovered that GO is an effective water-based lubricating additive [16]. Song et al. proved that GO, as a nanoaddition, prevents direct contact between friction pairs through adhesion, thereby helping reduce friction and wear in water-based lubricants [17]. These results indicate that GO can be used as an excellent additive for water-based lubricants.

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Natural product of angelica essential oil developed as a stable Pickering emulsion for joint interface lubrication

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ARTICLE INFO

Keywords:
Angelica essential oil
Pickering emulsion
Biological lubricant
Lubrication mechanism

ABSTRACT

Development of high-performance joint injection lubricants has become the focus in the field of osteoarthritis treatment. Herein, natural product of angelica essential oil combined with the graphene oxide were prepared to the stable Pickering emulsion as a biological lubricant. The tribological properties of the Pickering emulsion under different friction conditions were studied. The lubricating mechanism was revealed and the biological activities were evaluated. Results showed that the prepared Pickering emulsion displayed superior lubrication property at the Ti6Al4V biological material interface. The maximum friction reduction and anti-wear abilities of the Pickering emulsion were improved by 36% and 50% compared to water, respectively. This was primarily due to the action of the double-layer lubrication films composed of the graphene oxide and angelica essential oil molecules. It was worth noting that the friction reduction effect of the Pickering emulsion at the natural cartilage interface was higher about 19% than that of HA used in clinic for OA commonly. In addition, the Pickering emulsion also displayed antioxidant activity and cell biocompatibility, showing a good clinical application prospect in the future.

1. Introduction

Osteoarthritis (OA) is a familiar chronic degenerative disease affecting the joints [1]. Latest data showed that about 240 million people suffered from OA in the world [2]. Biomechanical behavior of the joint interface is highly correlated with the onset of OA [3]. Studies have indicated that the diseased articular cartilage is unable to secrete sufficient synovial fluid, resulting in its self-lubricating dysfunction. This causes the interface cartilage to be damaged by frictional force, which triggers a cascade of joint inflammatory factors [4–6]. Hyaluronic acid (HA) injected solution is often applied to improve the joint interface lubricating properties for early OA in clinics [7,8]. However, it does not display satisfactory lubricating properties in long-terms of clinical effects. Therefore, the development of high-performance joint injection lubricants has become the focus in the field of OA treatment.

Angelica essential oil is a natural anti-inflammatory and antioxidant derived from the natural product of *Angelica sinensis*. It had shown good therapeutic effect on joint diseases. Zhou et al. reported that ligustilide as the main active component of angelica essential oil could inhibit chondrocyte apoptosis and articular cartilage degeneration through suppressing JNK and p38 MAPK pathways [9]. Zhu et al. found that the ligustilide could also improve the various antioxidant genes' expression and restrain the production of ROS, thus alleviating the cell damage induced by ROS [10]. In addition, natural plant essential oils have certain lubricating properties [11,12], which makes angelica essential oil has a good prospect as a novel injection drug for OA. However, the poor water solubility, poor stability and low bioavailability of angelica essential oil inhibits its clinical use as a joint cavity injection solution.

Recently, emulsion as a novel joint cavity injection has drawn wide focus on the area of OA treatment due to its excellent packaging function and lubrication property [13]. Wang et al. used W/W emulsions to serve as composite synovial fluids for the treatment of OA, they found that the emulsions had excellent lubrication properties at the joint interface [14]. The nano emulsions containing peppermint and rosemary essential oils prepared by Mohammadifar et al. were discovered to be efficient in treating OA [15]. Saeedi et al. [16] developed an oil-in-water emulsion containing non-steroidal anti-inflammatory drugs for the treatment of OA. These show the potential of emulsions as a novel intra-articular injection for treating OA.

Pickering emulsions as a stable emulsion system stabilized with solid

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A one-pot stepwise approach to axially chiral quinoline-3-carbaldehydes enabled by iminium–allenamine cascade catalysis†

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An unprecedented atroposelective annulation between 2-(tosylamino)aryl ketones and 2-alkynals for the construction of N-heterobiaryl atropisomers is achieved. The reaction involves a Michael/aldol cascade reaction catalyzed by a chiral secondary amine organocatalyst followed by acid promoted aromatization, providing a wide spectrum of axially chiral 4-arylquinoline-3-carbaldehydes in a one-pot fashion in good to high yields (up to 96%) and with excellent enantiocontrol (up to 99% ee). The power of the approach is also demonstrated by versatile transformations towards other functional N-heterobiaryl atropisomers.

Axially chiral (hetero)biaryl scaffolds hold a special place in many research domains, including drug discovery, catalyst design and materials science.[1–3] Therefore, extensive efforts have been devoted to the development of efficient catalytic asymmetric methods for their construction over the past few decades. A myriad of structurally unique (hetero)biaryl atropisomers have been designed and prepared in a highly atroposelective manner.[4] Among them, axially chiral hexatomic N-heterobiaryls are particularly appealing synthetic targets due to their growing application in medicinal chemistry and asymmetric catalysis. For example, the quinoline-based biaryl BI 224436 was found to be a potent HIV integrase inhibitor.[5] QUINAP, one of the most frequently used P,N-type chiral ligands, features an atropisomeric isoquinoline backbone (Fig. 1, left).[6]

Generally, current catalytic approaches to axially chiral hexatomic N-heterobiaryls involve cross-coupling,[7] (dynamic) kinetic resolution/asymmetric transformation,[8,9] desymmetrization[10] and stereoselective arene formation.[11–13] Compared with relatively mature metal catalysis, only a limited number of methods using organocatalysis have been disclosed. Notably, a conceptually new tactic, combining organocatalytic asymmetric heteroannulation with central-to-axial chirality conversion, has emerged as a versatile and flexible means to access complex N-heterobiaryl atropisomers since the pioneering report by Rodriguez, Bugaut, and Bressy *et al.* in 2016.[12a] Motivated by the "privileged" status of quinoline and its derivatives,[14] we and the group of Jiang have recently achieved the preparation of stereochemically stable 4-arylquinoline and 9-aryltetrahydroacridine atropisomers *via* the chiral phosphoric acid promoted atroposelective Friedländer reaction successively (Fig. 1, right).[12c–e] However, there is much room for improvement in our developed methodologies. A relatively high reaction temperature was required in these protocols. Besides, the enantiocontrol was very sensitive to the axial rotation resistance group, thereby leading to a limited substrate scope. Consequently, the development of new and efficient organocatalytic approaches to axially chiral quinoline-containing heterobiaryls with excellent tolerance of functional groups under mild reaction conditions is still a challenging and meaningful task.

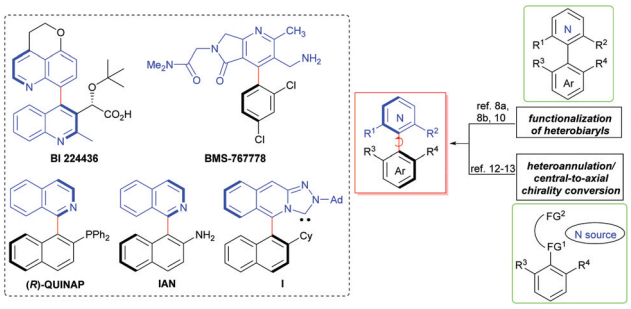

Fig. 1 Selected examples of atropisomeric pharmaceuticals and ligands containing a six-membered N-heteroaromatic ring and an overview of state-of-the-art organocatalytic approaches to axially chiral hexatomic N-heterobiaryls.

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†Electronic supplementary information (ESI) available. CCDC 2021435. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0qo01339k

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Catalytic Asymmetric Reductive Amination for Axially Chiral Aryl Aldehydes via Desymmetrization/Kinetic Resolution Cascade

Yi Wang,[#] Rui-Ping Song,[#] Xin-Yue Li, Wen-Li Chen, Yu Tian, Shu-Hui Zhang, You-Dong Shao, and Dao-Juan Cheng*

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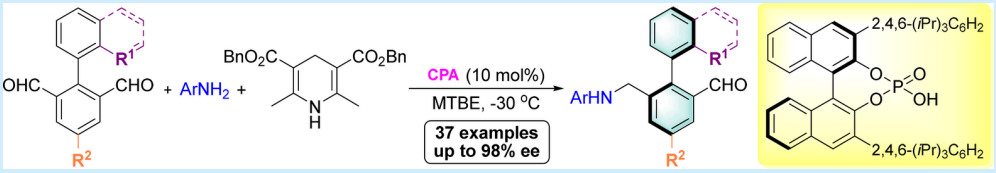
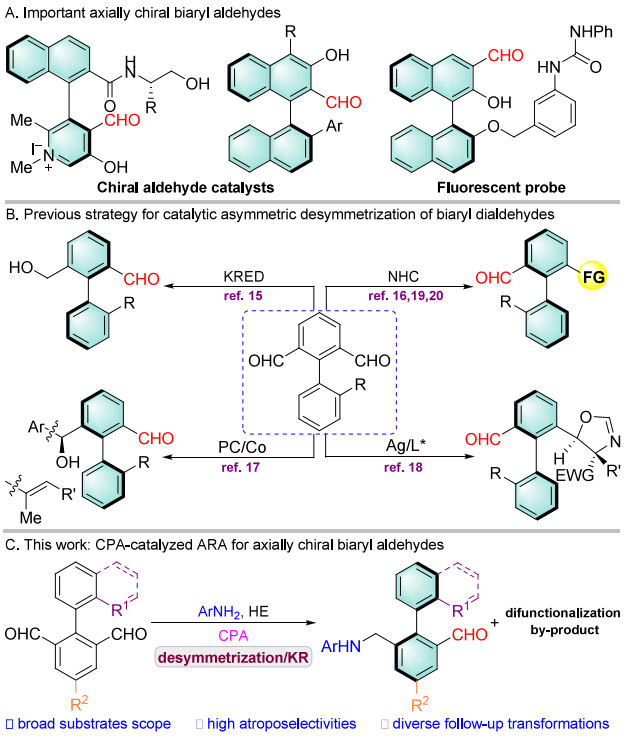


ABSTRACT: Herein we present an efficient chiral phosphoric-acid-catalyzed atropoenantioselective asymmetric reductive amination of biaryl dialdehydes. The process involves desymmetrization and the following kinetic resolution, with a wide range of axially chiral aryl aldehydes obtained with high optical purities.

Enantioselective construction of axial chirality has garnered considerable attention due to its widespread applications in a range of research domains, including drug discovery, catalyst design, material science, and so on.[1,2] Axially chiral aryl aldehydes are particularly appealing synthetic targets, serving as efficient chiral catalysts for activation of amines[3] as demonstrated by Guo,[4] Zhao,[5] and others,[6] as well as probes for fluorescent recognition of amino acids.[7] They are also valuable precursors to produce structurally diverse atropisomeric scaffolds (Scheme 1A).

Current catalytic asymmetric approaches to axially chiral aryl aldehydes involve transition metal-catalyzed cross-coupling/C−H activation[8,9] and organocatalyst-controlled arene formation.[10] Wang and co-workers reported an impressive atroposelective [8 + 2] cycloaddition for the synthesis of 4-formyl-3-arylindolizines.[11] Research from Wang et al.,[12] our laboratory,[13] and Wang, Wang et al.[14] have shown that the aza-Michael/aldol reaction of alkynes with 2-(tosylamino)aryl ketones/aldehydes could deliver axially chiral aryl-quinoline aldehydes. Besides, desymmetrization of prochiral dialdehydes has opened a new avenue to access biaryl carbaldehyde atropisomers (Scheme 1B) since the contribution by Clayde, Turner et al. using enzymatic catalysis in 2014.[15] In 2022, Zhang, Zheng and co-workers developed a pioneering N-heterocyclic carbene (NHC) mediated esterification of biaryl dialdehydes proceeding through desymmetrization and following kinetic resolution (KR).[16] Later on, the same group and Xiao, Cheng et al. independently applied photoinduced cobalt-catalyzed asymmetric reductive coupling of biaryl dialdehydes with aryl iodides or alkynes to the simultaneous construction of axial and central chirality.[17] Liao, Qian et al. described a desymmetric [3 + 2] cycloaddition of activated isocyanides with biaryl dialdehydes under silver catalysis.[18] Recently,

Scheme 1. Background and Project Proposal



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Electrodialysis with ultrafiltration membrane for efficient isolation of oxymatrine from simulated eluent of traditional Chinese medicine

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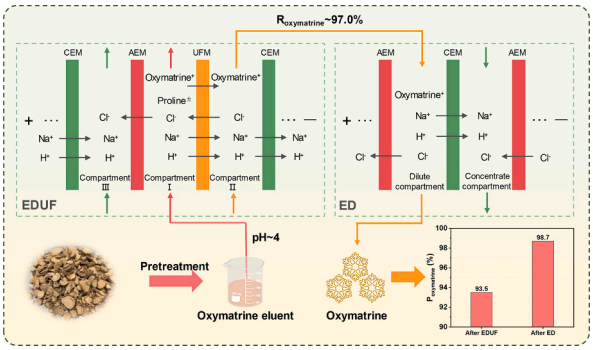
HIGHLIGHTS

- Positively charge oxymatrine was successfully isolated by EDUF from the simulated eluent.
- High recovery ratio of oxymatrine (97.0 %) can be reached by EDUF.
- Purity of oxymatrine can be increased to 98.7 % by ED desalination.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Electrodialysis
Ultrafiltration membrane
Oxymatrine
Traditional Chinese medicine
Separation mechanism

ABSTRACT

Precise screening of bioactive molecules from traditional Chinese medicine (TCM) is increasingly important in the development of TCM as well as drug discovery, however, it remains a challenge due to the low separation efficiency of the target substance. In this study, a specially designed electrodialysis with ultrafiltration membrane (EDUF) was proposed to isolate positively charged oxymatrine from the simulated eluent of TCM that contains oxymatrine, proline and NaCl. Results indicate that the oxymatrine^{+} can be efficiently isolated by EDUF with a low diffusion of proline ($J_{proline}$). The current density was optimized at 10–15 mA/cm^2 to obtain a high recovery ratio of oxymatrine ($R_{oxymatrine}$) and low energy consumption. Moreover, a low feed concentration was recommended for the efficient isolation of oxymatrine due to a low $J_{proline}$ and high $R_{oxymatrine}$. Furthermore, the $R_{oxymatrine}$ can be increased to a high value of 97.0 % through a continuous operation of EDUF, and the purity of oxymatrine can be increased to 98.7 % by electrodialysis desalination. Therefore, the EDUF process exhibits a great potential in isolating positively charged oxymatrine from the simulated eluent of TCM.

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Bipolar membrane electrodialysis for efficient production of ferulic acid in alcohol/water mixed solvent

Xixi Ma [a], Wenlong Liu [a], Chuanrun Li [a,b,*], Yiwei Dong [a], Rong Zhou [a], Zhiguo Dong [a], Jinfeng He [a,b], Li Sun [a,b,*], Haiyang Yan [a,b,*]

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Editor: Gaohong He

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Bipolar membrane electrodialysis
Ferulic acid production
Alcohol/water mixed solvent
Ion transport mechanism

ABSTRACT

In this study, bipolar membrane electrodialysis (BMED) was proposed to produce ferulic acid, as a kind of poorly water-soluble organic acids, in the alcohol/water mixed solvent system. Among the mixed solvents of EtOH/H_2O, n-PrOH/H_2O, and i-PrOH/H_2O, high solubilities of both ferulic acid and sodium ferulate were achieved in the solvent of 50 v/v% n-PrOH/H_2O. Meanwhile, the ionization of the produced ferulic acid was relatively low in the above system due to a feasible pK_a of ferulic acid, resulting in a high purity of the product. Furthermore, a low current density of 10 mA/cm^2 was recommended for the BMED process due to the stable membrane performance (no obvious membrane fouling observed) and low energy consumption. Moreover, the ionization of ferulic acid can be further lowered due to the solvation effects at a high feed concentration (0.5 mol/L, nearly saturated concentration). The low ionization of ferulic acid means that the migration of H^+ ions instead of Na^+ ions through cation exchange membrane can be suppressed efficiently, resulting in a high concentration of the product. Under the optimized parameters, the purity of ferulic acid, the current efficiency and energy consumption were 99.5%, 99.4%, and 0.30 kWh/kg ferulic acid, respectively. Also, the process economy estimation shows a low total process cost of 0.49 $/kg ferulic acid. Therefore, the BMED process exhibits an excellent economic competitiveness for efficient production of ferulic acid.

1. Introduction

Ferulic acid, as a kind of phenolic acid, is widely existed in wheat, grains, vegetables, traditional Chinese medicines (e.g. angelica and rhizoma ligustici chuanxiong) and etc [1]. To date, it is found that the ferulic acid has significant biological activities, including antioxidant, antithrombotic, anticancer and hypolipidemic [2–4]. Thus, it has been used widely in pharmaceutical, food and cosmetic industries. The most common methods to produce ferulic acid are enzymatic hydrolysis, alkaline hydrolysis and tissue culture, in which the alkaline hydrolysis is used predominately [5]. As well known, wheat bran contains abundant ferulic acid. Zhao et al [5] reported an extraction process to recover ferulic acid from the wheat bran, which was carried out in 0.25 mol/L NaOH at a mixed solvent system of 50 v/v% ethanol–water. Then, the ferulic acid with a purity of 84.5% can be obtained after the ultrafiltration, nanofiltration, acidification, and crystallization processes as shown in Fig S2. In addition, Dupoiron et al [6] reported a novel process associating cation exchange, electrodialysis (ED), weak anion exchange, acidification and crystallization for the recovery of ferulic acid from a model wheat bran enzymatic hydrolysate. Specifically, cationic impurities in the model solution can be removed in cation exchange process, then the obtained solution was further desalinated by ED. After that, the anionic impurities in ED dilute can be purified by weak anion exchange that was eluted by NaOH. Subsequently, the eluent (sodium ferulate) was acidified by H_2SO_4 to convert sodium ferulate to ferulic acid, and the ferulic acid can be recovered by crystallization process. In this process, the purity of ferulic acid can be increased to 90%-95%. However, large amounts of fresh acid and base need to be consumed in weak anion exchange and acidification processes, increasing the running cost. Besides, the high-salinity wastewater that was produced in the acidification process should be treated rather than discharged. Therefore, a green and efficient process was expected to produce ferulic acid, especially for the conversion of ferulic acid from sodium ferulate.

Bipolar membrane (BPM) is a polymeric membrane with a sandwich

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Enantioselective Photoredox- and Cu-Catalyzed Cyanoalkylation of Styrenes via Deoxygenation of Alkoxyl Radicals with Organophosphorus Compounds(III)

Hongzhou Yu,[▽] Xiang Yu,[▽] Xingyu Li, Wanqing Kou, Fang Fang,* and Guoyu Zhang*

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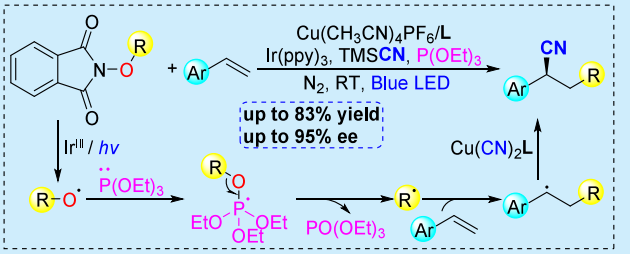
ABSTRACT: The enantioselective cyanoalkylation of styrenes by a cooperative photoredox and copper catalysis system has been established, providing straightforward access to structurally diverse enantioenriched alkyl nitriles in good yields with excellent enantioselectivities under mild conditions via deoxygenation of alkoxyl radicals with organophosphorus compounds(III). In addition, the reaction features a wide substrate scope and good functional group tolerance, and the resultant alkyl nitriles could be easily converted into a series of chiral carboxylic acids, amides, esters, etc.



The alkoxyl radical is a highly reactive species that has been recognized as an important intermediate in organic chemistry and biological chemistry.[1−3] Traditional methods of the generation of alkoxyl radicals are mainly realized by some unstable alkoxyl precursors or harsh conditions, such as peroxides,[4] Barton nitrite esters,[5] and *N*-alkoxylpyridine-2-thiones[6] are widely used as alkoxyl radical precursors. Recently, because of the development of photocatalytic reactions, a series of stable precursors or alcohols could be transformed into alkoxyl radicals under mild conditions,[7−10] such as generation of alkoxyl radicals from O−I bonds,[11−16] electron donor−acceptor (EDA) complex-enabled O−N bond cleavage,[17−20] generation of alkoxyl radicals via proton-coupled electron transfer (PCET),[21−25] and generation of alkoxyl radicals via ligand-to-metal charge transfer (LMCT).[26−30] Thus, for the promotion of vigorous development in this field, its related reaction mainly focuses on the following three types: alkoxyl radical-mediated hydrogen atom transfer,[31−33] alkoxyl radical-mediated C=C bond addition,[34−38] and alkoxyl radical-mediated C−C bond scission.[39,40] Despite the fact that the photocatalytic reaction promoted the development of alkoxyl radical research, C−O bonds of alkoxyl radicals remain difficult to break.

To the best of our knowledge, the strategy of deoxygenation of alkoxyl radicals to alkyl radicals with organophosphorus compounds(III) has been reported many years ago.[41] However, there is a little research in this field (Scheme 1a). For example, in 1956, Hoffmann and co-workers reported the desulfurization of mercaptans with trialkyl phosphites at increased temperatures or in the presence of light.[42] In 1959, Rabmowitz's group further reported the reaction of trialkyl phosphites with thiyl and alkoxyl radicals.[43] Soon thereafter, this laboratory continued to further extend the reaction.[44] Until 2018, Schmidt's group used this strategy of deoxygenation again to develop an intermolecular anti-Markovnikov hydroamination of alkenes.[45] In 2019, Tang's group realized the alkylation of allyl/alkenyl sulfones by deoxygenation of alkoxyl radicals.[46] In addition, there are no related reports on asymmetric reactions through the strategy of deoxygenation of alkoxyl radicals to alkyl radicals with organophosphorus compounds(III).

In recent years, the transition-metal-catalyzed asymmetric difunctionalization of alkenes has developed rapidly.[47−49] For example, Liu's group reported work realizing enantioselective copper-catalyzed cyanation/arylation/alkynylation of alkenes,[50−54] Bao's group reported iron-catalyzed asymmetric azidation of alkenes,[55] Nevado's group reported Ni-catalyzed asymmetric intermolecular dicarbofunctionalization of alkenes,[56] etc.[57−62]

Inspired by these elegant reports on asymmetric radical reactions and the strategy of deoxygenation of alkoxyl radicals to alkyl radicals by organophosphorus compounds(III), we proposed a photoredox- and copper-catalyzed asymmetric cyanoalkylation reaction of styrenes using alkyl *N*-hydroxyphthalimide ethers as alkylation reagents via deoxygenation of alkoxyl radicals. Although similar asymmetric cyanoalkylation reactions have been reported,[63,64] as previously reported related alkylating reagents mainly come from alkyl halides and alkyl *N*-hydroxyphthalimide esters, which seriously limits

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发明专利证书

发 明 名 称：一种蜂胶挥发油包覆物及其制备的牙膏的制备方法

发　明　人：王虎传;徐亚;彭成军;李传润;韦邦昌;沙梦蝶

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证书号第7254240号

专利公告信息

发明专利证书

发明名称：一类NO供体型HDAC抑制剂、组合物及其用途

专利权人：安徽中医药大学

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发 明 人：方方;高鑫;马晓东;韩京晶;柴化怡

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申请日时申请人：安徽中医药大学

申请日时发明人：方方;高鑫;马晓东;韩京晶;柴化怡

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证书号第6578746号

发明专利证书

发 明 名 称：含四氢异喹啉类结构的HDAC抑制剂、组合物及其用途

发 明 人：方方;高鑫;韩维维;马晓东;田诗意;范思琪;汪洋

专 利 号：ZL 2022 1 0901388.7

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证书号第4565444号

发明专利证书

发明名称：一类PI3Kδ抑制剂及其用途

发明人：马晓东;李家明;桂双英;方方;李丰;许勤龙;陶强强
陈雨晴;孟畅;乔韬

专利号：ZL 2019 1 0709742.4

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其他事项参见续页

证书号第4523345号

发明专利证书

发明名称：一类HDAC抑制剂及其用途

发 明 人：马晓东;王昊;方方;陶强强;彭成军;孙松;王虎传;胡海霞

专 利 号：ZL 2019 1 0992789.6

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专利权人：安徽中医药大学

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证书号第4479277号

发明专利证书

发明名称：一类mTOR/HDAC双重抑制剂及其应用

发明人：马晓东;彭成军;张明明;李传润;陶强强;王虎传;胡孟奇
董宁

专利号：ZL 2020 1 0682309.9

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证书号第5507791号

发明专利证书

发明名称：1-氰基咪唑并[1,5-a]吡啶类化合物及其合成方法

发明人：冯承涛;杨晴;严小童

专利号：ZL 2021 1 0830659.X

专利申请日：2021年07月22日

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证书号第7582656号

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发明专利证书

发明名称：苯并噁唑啉酮衍生物及其制备方法和用途

专利权人：安徽中医药大学;合肥医工医药股份有限公司
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申请日时发明人：李家明;许勤龙;林高峰;崔恩静;杜乐;钱诗虎;王宏伟
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发明专利证书

发明名称：一类查尔酮芳氧乙酰胺化合物、制备方法及其应用

发明人：李家明;何广卫;储昭兴;黄伟军;刘为中;朱盼虎;张阳
左健;刘会财;王玉骏

专利号：ZL 2016 1 0639939.1

专利申请日：2016年08月05日

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证书号第5402536号

发明专利证书

发明名称：一类石斛生物碱衍生物、制备方法和医药用途

发明人：李家明;何广卫;胡孟奇;储昭兴;许勤龙;王玉峻;杨雨
刘万东;高慄繁;莫佳佳

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专利申请日：2018年10月25日

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