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Structural, dielectric and magnetic characteristics of Mn-substituted $Bi_{0.80}Nd_{0.20}FeO_3$ multiferroics

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Abstract
Recently, investigations have been focused on modified $BiFeO_3$ multiferroics for obtaining improved physical properties. Keeping this in view, multiferroics having composition $Bi_{0.80}Nd_{0.20}Fe_{1-x}Mn_xO_3$ ($x=0.01$, 0.03 and 0.05) have been synthesized using solid-state reaction method. The crystal structure was examined by X-ray diffraction technique and Rietveld refinement. All unit cells were described by a combination of rhombohedral (R3c) and orthorhombic (Pbnm) phase. Increasing Mn content results in phase transformation with increasing orthorhombic character and major contribution by rhombohedral symmetry for all samples. Dielectric measurements carried out by impedance/gain phase analyzer in the frequency range from 10 Hz to 1 MHz. Dielectric constant (ε') and loss tangent ($\tan\delta$) show dispersion in the lower frequency range. The characteristics of the Nyquist plot confirmed the non-Debye type of relaxation processes with negative temperature coefficient behaviour of resistance (NTCR) in the ceramics. A strong variation in impedance is observed with Mn content also confirmed by conductivity analysis. The variation of 's' with temperature described that conduction mechanism is overlapping of large polaron tunnelling for $x=0.01$, 0.03 and for $x\mp0.05$ the appropriate mechanism is small polaron tunnelling. Magnetic measurements indicate the change in ferromagnetic character which might be due to a small change in structural parameters and maximum remanent magnetization is $M_r=0.023$ emu/g and coercive field is $H_c=0.760$ kOe for $x=0.05$. These prepared materials with improved multiferroic properties may lead to many technical applications, such as sensors, transducers and memory devices, etc.

Keywords Multiferroics · Perovskite · Phase transition · Rietveld refinement · Dielectric properties

1 Introduction

The best approaches to create novel materials with rich functional properties can be achieved by combining two or more physical properties, viz., electrical, magnetism and elasticity, in a single material [1]. Among various types of materials, multiferroics possess such characteristics. Multiferroics have a combination of ferromagnetic, ferroelectric and ferroelastic orders in a single material and gained importance due to their fascinating properties [2, 3]. Along with multiferroic materials, nano-sized materials have been drawing attention in such potential applications [4–6]. These types of multifunctional properties can be attained by either naturally occurring multiple ferroic orders or preparing composite using two separate single ferroic order materials [7, 8]. These materials have an additional property known as magneto-electric coupling (M–E coupling) in which magnetization can be controlled by applying an electric field and vice versa [9, 10]. This magnetoelectric effect contributes to an additional degree of freedom that supports rich functional properties in multiferroic materials [4]. On the basis of origin of these ferroic orderings, multiferroic materials can be divided in two categories, such as: (1) Intrinsic multiferroics and (2) Artificial multiferroics. Intrinsic multiferroics are those natural materials that possess two ferroic orders in a single-phase material. The main drawbacks of such single-phase/intrinsic multiferroic materials are that they possess

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REVIEW

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A minireview of 1,2,3-triazole hybrids with O-heterocycles as leads in medicinal chemistry

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Abstract

Over the past few decades, the dynamic progress in the synthesis and screening of heterocyclic compounds against varibus targets has made a significant contribution in the field of medicinal chemistry. Among the wide array of heterocyclic compounds, triazole moiety has attracted the attention of researchers owing to its vast therapeutic potential and easy preparation via copper and ruthenium-catalyzed azide-alkyne cycloaddition reactions. Triazole skeletons are found as major structural components in a different class of drugs possessing diverse pharmacological profiles including anti-cancer, anti-bacterial, anti-fungal, anti-viral, anti-oxidant, anti-inflammatory, anti-diabetic, anti-tubercular, and anti-depressant among various others. Furthermore, in the past few years, a significantly large number of triazole hybrids were synthesized with various heterocyclic moieties in order to gain the added advantage of the improved pharmacological profile, overcoming the multiple drug resistance and reduced toxicity from molecular hybridization. Among these synthesized triazole hybrids, many compounds are available commercially and used for treating different infections/disorders like tazobactam and cefatrizine as potent anti-bacterial agents while isavuconazole and ravuconazole as anti-fungal activities to name a few. In this review, we will summarize the biological activities of various 1,2,3-triazole hybrids with copious oxygen-containing heterocycles as lead compounds in medicinal chemistry. This review will be very helpful for researchers working in the field of molecular modeling, drug design and development, and medicinal chemistry.

KEYWORDS

1,2,3-triazole, biological activities, hybrid compounds, oxygen heterocycles, structure-activity relationship

1 | INTRODUCTION

In order to grapple with the diseases originating from various microbes (bacterial/viral/others), their mutated forms and resistant strains as well as from various bodily malfunctions and mutated genes in humans/other organisms, there remains the continuous need for biologically potent chemical entities capable of treating these disorders. Heterocyclic compounds form the backbone of medicinal chemistry. The great breakthroughs in the synthesis of various complex heterocyclic skeletons have made possible, the task of creating the libraries of unique heterocyclic compounds. Furthermore, the screening of these huge numbers of heterocyclic

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Review

Recent Developments in Nanocatalyzed Green Synthetic Protocols of Biologically Potent Diverse O-Heterocycles—A Review

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Abstract: The dynamic growth in green organic synthetic methodologies for diverse heterocyclic scaffolds has substantially contributed to the field of medicinal chemistry over the last few decades. The use of hybrid metal nanocatalysts (NCs) is one such benign strategy for ensuring the advancement of modern synthetic chemistry by adhering to the principles of green chemistry, which call for a sustainable catalytic system that converts reacting species into profitable chemicals at a faster rate and tends to reduce waste generation. The metal nanoparticles (NPs) enhance the exposed surface area of the catalytic active sites, thereby making it easier for reactants and metal NCs to have an effective interaction. Several review articles have been published on the preparation of metal NCs and their uses for various catalytic heterocyclic transformations. This review will summarize different metal NCs for the efficient green synthesis of various O-heterocycles. Furthermore, the review will provide a concise overview of the role of metal NCs in the synthesis of O-heterocycles and will be extremely useful to researchers working on developing novel green and simple synthetic pathways to various O-heterocyclic-derived molecules.

Keywords: nanocatalyst; green chemistry; chalcone; coumarin; furan; oxazole; pyran

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1. Introduction

Chemistry is an undeniably important part of our daily lives, and its advancements have been developed to provide people with access to innovative medicines for healthier living conditions. Several heterocycle scaffolds have been found to be pharmaceutically active for applications in the development and formulation of new drugs [1]. Heterocycles are found in both natural and synthesized biologically active compounds [2]. Despite incidents [3] such as the clioquinol tragedy, the thalidomide tragedy, and others, the importance of heterocycles in drug discovery continues to rise due to their selectively pharmacophore binding potential. The heterocyclic skeleton can be found in a large number of commercially accessible Food and Drug Administration (FDA)-approved synthesized

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ARTICLE

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Design, synthesis, biological evaluation, and molecular docking studies of some novel *N,N*-dimethylaminopropoxy-substituted aurones

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Abstract

In continuation of our ongoing research on the discovery of novel and potentially bioactive aurones, we have designed and synthesized some novel *N,N*-dimethylaminopropoxy-substituted pyrazole-based aurones **10(a-l)**. These pyrazole-benzofuranone hybrid compounds were characterized by using their IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry data. Compound **10c** was used as a model to further explicate the structure of tilted compounds by means of ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMQC, ^{1}H-^{13}C HMBC, ^{1}H-^{1}H TOCSY, ^{1}H-^{1}H NOSEY, DEPT-45°, DEPT-90°, and DEPT-135° NMR spectra. The comparative molecular docking study of *N,N*-dimethylaminopropoxy-substituted pyrazole-based aurones and standard drugs (Ampicillin and Chloramphenicol) against *Bacillus subtilis* (PDB: 6tzp) active site was performed to determine the binding interactions, binding energy, and orientation of the molecules at the active site of the target protein. Out of these synthesized compounds, five best analogs (**10b**, **10f**, **10h**, **10k**, and **10l**) of docking results were also evaluated for their in vitro antibacterial potential against *Bacillus subtilis* to validate the docking results.

1 | INTRODUCTION

Aurone, that is, 2-benzylidenebenzofuran-3(2*H*)-one, is a ubiquitous family of compounds having a benzofuranone heterocyclic ring connected to phenyl moiety via a carbon–carbon exocyclic double bond. These fascinating scaffolds are secondary plant metabolites and are liable for imparting pigmentation in flowers, fruits, and other colored portions of the plants [1]. Aurones are the active ingredients of various conventional remedies like *Vaccinium oxycoccos* (European cranberry), *Glycyrrhiza glabra* (Licorice), and *Ceanothus americanus* (New Jersey tea) [2]. Even though aurones have very confined existence in nature, they constitute a blazing class of pharmacologically effectual skeletons, which exhibit prodigious range of biological accent [3] including anticancer [4], antioxidant [5], antiparasitic [6], antiobesity [7], tyrosinase inhibition [8], cathepsin B inhibition [9], antihormonal [7], antileishmanial [10], antiquorum sensing [11], anti-Alzheimer [12], and antiinflammatory [13] activities. Some of the eminent aurones are cephalocerone, hemiltron, hispidol, and maritimetin, where Cephalocerone, extracted from the plant of *Cephalocereus senilis*, showed antibacterial activity [14]; hamiltrone, isolated from plant *Uvaria hamiltonii* displays DNA strand scission activity [15]; hispidol obtained from soybean *Glycine max* exhibits antifungal activity [16]; and maritimetin present in genus *Coreopsis* depicted anticarcinogen and antioxidant activities [7,17]. Figure 1.

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Synthesis of propynyloxy substituted some novel aurones as potent cathepsin B inhibitors

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ABSTRACT

A two-step synthesis was designed to develop a novel series of 6-propynyloxyaurones, **2(a-r)**. The synthesized aurone derivatives were characterized by their IR, NMR, and mass spectrometry data. The present study proposes these aurones as anti-inflammatory and anti-Alzheimer candidates on the basis of their cathepsin B inhibitory activities. Anti-cathepsin B activity of some of the synthesized aurones was found, either equivalent to or higher than the reference drugs, aspirin and curcumin at submicromolar concentrations. Among the studied compounds, **2e, 2i, 2n, 2q**, and **2r** exhibited much higher activity in comparison to the standard drugs. The molecular docking study also highlighted compound **2r** for its greater anti-cathepsin B activity among all the designed aurones.

Specifications Table

Subject area	*Organic Chemistry*
Compounds	*Aurones*
Data category	*Spectral, Synthesis, Molecular docking*
Data acquisition format	*NMR, IR, Mass spectra*
Data type	*Analysis*
Procedure	*Brief description of the procedure (e.g., transformation, simulation, etc.)*
Data accessibility	*A series of novel aurones were synthesized and characterized by spectral data and further evaluated for their biological activity.*

1. Rationale

Cathepsin B, the most abundantly expressed mammalian lysosomal protease, involved in intracellular protein catabolism, has emerged out as a potential drug target for a number of diseases [1]. The elevated level of cathepsin B has been found responsible for several pathological conditions, which include inflammation [2,3], cancer [4–6], neurological disorders such as Alzheimer's [3,7] and cardiac disorders [8] among various others. Elevated levels of cathepsins have been found vis-à-vis decreased levels of intracellular inhibitors [9] thereby generating the need for development of novel cathepsin B inhibitors.

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Recent Advances in Synthesis and Biological Assessment of Quinoline-Oxygen Heterocycle Hybrids

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The exploration of hybrid molecules for targeting various diseases represents a highly promising approach which has showcased significant momentum worldwide, in the last two decades. Diversely substituted quinoline scaffolds present in naturally occurring bioactive compounds, signify their role in various biological processes and stimulated the research developments around it, for diverse therapeutic applications. With the ongoing search for suitable pharmacophores, the quinoline derivatives have emerged as versatile compounds possessing significant and broad spectrum of biological activities. Further, conjugation of quinoline with other bioactive heterocycles containing oxygen yielded hybrid organic frameworks with improved therapeutic profile leading to an emerging paradigm and tremendous growth in the contemporary drug discovery regime. The synthesis of these hybrid skeletons with high efficiency still remains the most strenuous task and a lot of research work is being performed in this direction. In the present article, we have reviewed the synthetic protocols leading to quinoline-oxygen heterocycle hybrids and also highlighted the systematic and biological assessment of developed pharmacophores.

1. Introduction

In order to combat the increasing number of viral and microbial infections and other diseases, there is an intensive demand for developing the innovative formulations with suitable pharmacophores which could be synthesized using novel and highly efficient synthetic strategies. The requirement for newer therapeutic moieties further amplifies with the increasing cases of side-effects and drug resistance. The chemotherapeutic response of these heterocyclic moieties is generated by their affinity to serve as ligands towards various biological receptors. The therapeutic response of these heterocyclic moieties is significantly influenced by the presence of different substituents through the changes in electronic structure and binding affinity. Quinoline i.e. benzo[b]pyridine or 1-azanapthalene is an ubiquitous heterocyclic moiety found in numerous biologically active natural products serving as anti-malarial,[1] anti-plasmodial,[2] anti-cancer,[3] anti-inflammatory,[4] anti-tubercular,[5] anti-biotic,[6] tyrokinase PDGF-RTK,[7] anti-fungal,[8] analgesic,[9] cardiovascular[10] activities among various others. Some of the well known drugs having quinoline skeleton involve: quinine, chloroquine, primaquine, amodiaquine etc. as antimalarial; moxifloxacin, ciprofloxacin as anti-tubercular agents,[11] pyrvinium as anthelmintic agent[12] ; and cinchocaine as an anesthetic,[13] and various others (Figure 1). Owing to the high medicinal value and good solubility in most of the organic solvents as well as partial solubility in water, many research groups are elaborating the research work related to synthesis and bioactivity evaluation of quinoline based skeletons with an aim to exploit their inherent properties.[14]

Further, in order to gain the benefits from molecular hybridization, a modern strategy for drug design in medicinal chemistry, the conjugation of quinoline scaffolds with other oxygen based bioactive heterocyclic compounds has gained much attention in the last few years. The molecular hybridization involves the chemical conjugation fusion of two or more pharmacophores with specific structural domains into a hybrid skeleton with significant enhancement expectation of improved therapeutic profile. These hybrid molecules possessing diverse skeletons not only provide increased efficacy and safety but also help in overcoming the resistance on account of multiple modes of action as well as binding with multiple targets.[15] Among the various oxygen containing heterocycles, furans and pyrans have gathered enormous attention as versatile and fruitful organic compounds with impressive medicinal history. These vital oxygen heterocyclic compounds have reflected interesting pharmacological behaviors such as anti-hyperglycemic,[16] analgesic,[17] anti-tumor and kinase Inhibitor,[18] anti-microbial,[19] anti-parasitic,[20] anti-viral,[21] anti-cancer[22] and anti-inflammation[23] activities among many others.

The naturally occurring hybrid skeletons having quinoline and oxygen based heterocyclic motifs have attracted prodigious attention from chemists and pharmacologists working in the field of natural products owing to their simple structures and noteworthy bioactivities. Some of such hybrid molecules obtained from microorganisms and flowering plants are shown in Figure 2 and found to possess several bioactivities. Graveoline, a quinoline based hybrid alkaloid extracted from *Vepris punctate* was found to demonstrate significant herbicidal activity and cytotoxicity against A2780 cell lines.[24] Also, 2-(3,4-

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Ultrasound assisted a one pot multicomponent and greener synthesis of 1,2,3-triazole incorporated aurone hybrids: Cathepsin B inhibition, anti-cancer activity against AGS cell line, and *in-silico* docking evaluation

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ABSTRACT

Cathepsin B represents a group of lysosomal-encapsulated cellular cysteine proteases, whose upregulation is the critical risk factor for cancer progression and in the regulation of degenerative processes like apoptosis. Therefore, cysteine cathepsins are used as effective biomarkers for cancers and other neurodegenerative disorders and have become specific targets in drug designing. To diversify the pharmacological potential of aurones, a total of eighteen novel 1,2,3-triazole decorated aurone hybrids were synthesized in very good yields, utilizing click chemistry and an ultrasound-assisted one-pot, multicomponent and greener protocol, straight from hydroxy-substituted aurones. These hybrids have been evaluated as useful cathepsin B inhibitors and further explored their *in-vitro* study over AGS cell line using MTT assay. The *in-vitro* cathepsin B inhibitory potential of the synthesized hybrids revealed that the hybrid **3p** possesses a very significant inhibition (% inhibition = 85.02) at the concentration of 10^{-6} M compared to the standard aspirin (% inhibition = 48.21 at 10^{-7} M) and curcumin (% inhibition = 57.72 at 10^{-7} M), which further supported by the *in-silico* studies. In addition to this, the cytotoxic assay of the hybrids showed that the hybrids **3d** (IC_{50} = 24 μM), **3i** ($IC_{50} \approx$ 24 μM), and **3m** (IC_{50} = 26 μM) exhibit comparable anti-tumor activity against AGS cell line than the standard, oxaliplatin (IC_{50} = 29 μM). The results suggested that the reported novel aurone-1,2,3-triazole hybrids are a promising candidate for the development of new cathepsin B inhibitors as well as anti-cancer leads.

1. Introduction

Cancer is a group of appealing diseases which generally arise due to the transformation of healthy cells into tumor cells. This transformation generally occurs due to altered cellular repair mechanism controlled by genetic factors in response to exposure towards certain carcinogens (biological, chemical, or physical). Inspite of significant developments in methods of cancer diagnosis and treatment (Radiotherapy/Chemotherapy/Surgery etc.) in last few years, cancer is still a leading cause of death worldwide. The major hurdles in cancer treatment include detection in later stages, resistance towards various drugs used in chemotherapy, and ability to differentiate between normal and cancerous cells. The researchers across the world are continuously working for the design and development of newer cytotoxic agents with magnified efficacy, minimal toxicity and for effective cancer treatment by following diverse approaches. One of these approaches involve designing of therapeutic molecules which target various enzymes like cysteine proteases and their receptors thereby suppressing their activity [1,2]. These proteases are known to play significant role in the progression of various oncogenic processes [3], and various other tissue degenerative diseases [4,5], like, rheumatoid arthritis, osteoarthritis, inflammation [6], Alzheimer's [7], multiple sclerosis, and pancreatitis [8], etc. in humans. The inhibition of cathepsin proteases is further necessitated for restricting their role in development of both intrinsic and acquired resistance towards chemotherapy and radiation therapy, used in cancer treatment [9]. Cathepsin B is one such ubiquitously expressed cysteine protease whose over-expression is correlated with metastatic and invasive proliferation of cancer [10,11]. Recent data have shown that the progression of some

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Novel 1,2,3-triazole-aurone hybrids as cathepsin B inhibitors: One-pot synthesis, anti-proliferative, and drug modeling studies

Bhavna Saroha [a], Gourav Kumar [a], Suresh Kumar [a,*], Meena Kumari [b], Manishita Rani [a], Neera Raghav [a], Pranab Kumar Sahoo [c], Sushmita Ghosh [c], Sutapa Mahata [c], Vilas D. Nasare [c]

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ABSTRACT

In the present study, we have designed a series of novel 1,2,3-triazole-aurone hybrids, which were synthesized by a one-pot click reaction between a terminal alkyne and an *in-situ* generated azide, and evaluated as potential cathepsin B inhibitors. The structures of the synthesized compounds were confirmed by various spectroscopic techniques (^{1}H & ^{13}C NMR and HRMS data). The *in-vitro* cathepsin B inhibitory study of the synthesized compounds showed that the hybrids named **3o**, **3p**, and **3r** are the excellent inhibitors with percentage inhibition of 83.05–87.16% at the concentration of 10^{-5} M, in comparison to standards, Aspirin (48.21% at 10^{-7} M), and Curcumin (52.27% at 10^{-7} M). The docking study was also in support of the *in-vitro* assay. Furthermore, the anti-proliferative impact of these synthesized compounds was also evaluated against the gastric adenocarcinoma cell line (AGS cell line). The *in-vitro* MTT assay suggested that out of all the synthesized hybrids, compounds **3a** with an IC_{50} value of 16 μM and **3b** with an IC_{50} value of 11 μM possessed maximum cytotoxic activity against the AGS cell line in comparison to the reference, Oxaliplatin (IC_{50} = 29 μM).

1. Introduction

Cathepsin B is a ubiquitously expressed mammalian lysosomal peptidase that possesses both carboxypeptidase and endopeptidase activities. The carboxypeptidase activities of the enzyme play diverse roles in various physiological processes like protein processing, wound healing and apoptosis [1], etc. In contrast, the endopeptidase activities like degradation of the extracellular matrix are extremely up-regulated in several pathological conditions like cancer [2,3], inflammation [4], parasitic infection, and neurodegeneration [5,6], etc. The altered trafficking of cathepsin B cause increased proteolytic activity, which promotes the invasion and metastasis of tumor cells, thereby leading to malignant progression and poor patient prognosis.

Thus, to avoid the extreme up-regulation of these cathepsin B enzyme molecules, their activity is regulated at every level, starting from their biosynthesis via compartmentalization into lysosomes, controlled activation of their pro-enzyme forms, and by their endogenous protein inhibitors like cystatins [7]. In addition to these endogenous regulators, various exogenous protein inhibitors of cathepsin B have been designed either by extraction from natural sources or by synthetic preparatory methods. The analysis and interpretation of x-ray crystal structures of cathepsin B complex with its inhibitors provide further insights into designing various new small molecular weight cathepsin B inhibitors. Our research group is also working actively in the field of medicinal chemistry to design and develop novel heterocyclics as inhibitors of cathepsin B for the treatment of several diseases, like neural disorders, cell proliferation, and various others.

In this process, we have achieved a lead in developing some novel aurone derivatives as potent anti-cancer [8] and cathepsin B inhibitors [9]. Aurones (benzofuranones) are privileged structures in medicinal chemistry depicting a wide range of biological activities [10–13], like anti-cancer [14,15], anti-alzheimer [16,17], anti-inflammatory [18], and various other activities. The pharmacological profile of these aurones can further be tuned by making various other structural modifications [19, 20]. Besides aurones; several other heterocyclic skeletons depicting cathepsin B inhibition and significant anti-cancer activity have been developed, including triazoles [21], chalcones [22], and flavones [23] (Fig. 1) by various research groups. Based on our previous results, we aimed to develop the hybrid compounds of aurones with other biologically active heterocyclic skeletons as novel therapeutic molecules with

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Review

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Future Medicinal Chemistry

Polyglycerol-based hydrogels and nanogels: from synthesis to applications

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Hydrogels and nanogels have emerged as promising materials for biomedical applications owing to their large surface area and tunable mechanical and chemical properties. Their large surface area is well suited for bioconjugation, whilst the interior porous network can be utilized for the transport of valuable biomolecules. The use of biocompatible hydrophilic building blocks/linkers for the preparation of hydrogels and nanogels not only avoids undesired side effects within the biological system, but also retains high water content, thereby creating an environment which is very similar to extracellular matrix. Their tunable multivalency and hydrophilicity and excellent biocompatibility, together with ease of functionalization, makes polyglycerol macromonomers well suited for synthesizing cross-linked networks that can be used as extracellular matrix mimics. Here we provide an overview of the synthesis of polyglycerol-based hydrogels and nanogels for various biomedical applications.

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Hydrogels are 3D cross-linked networks capable of retaining a large amount of water. Due to the possibility to tune their biocompatibility, molecular flexibility, stiffness and binding affinity for biomolecules by various strategies, they have been widely explored as mimics of extracellular matrix. Such matrix is a heterogeneous structure unique to each tissue that contains the physical, biochemical and biomechanical components needed for cell proliferation and communication. The development of extracellular matrices with the desired properties is one of the most important steps in tissue engineering and has been benefited largely from advances in the design of different classes of cross-linked hydrogels [1]. Besides tissue engineering, hydrogels have made a significant contribution in the fields of drug delivery, pathogen inhibition, biomolecule immobilization and the production of hygiene products, wound dressings and contact lenses [2]. The conjugation of suitable ligands on the surface of cross-linked networks further facilitates the delivery of encapsulated guests to the target site as well as improves their affinity to bind with specific pathogens.

The current field of hydrogel research commenced with the preparation of a polyhydroxyethylmethacrylate (pHEMA) hydrogel by Wichterle and Lim in 1960, when these materials were utilized for contact lens applications [3]. The first nanogel was prepared three decades later by self-aggregation of cholesterol-bearing polysaccharides in water that resulted in physically cross-linked nanosized structures [4]. Nanogels are fabricated using various methodologies, such as inverse miniemulsion, inverse nanoprecipitation and microfluidics, and with various cross-linking species. They have received significant attention in recent years owing to their nanosized features and easily tailored chemical and physical properties and have been used as space-filling agents, delivery vehicles for bioactive molecules [5–8], biosensors [9–12], bioimaging [13–16] and antifouling agents [17,18], and also as tissue engineering elements [19–22].

Several excellent review articles have been published concerning hydrogel and nanogel design [23–26], but here we will focus on polyglycerol (PG)-based systems, which have been extensively explored in the past decade.

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Enzymatic synthesis of glycerol, azido-glycerol and azido-triglycerol based amphiphilic copolymers and their relevance as nanocarriers: A review

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ABSTRACT

Amphiphilic polymeric nanocarriers have attained immense attention for transporting drugs and other bioactive species to the living systems owing to their high loading capacity and efficient internalization. To avoid the side-effects of undesired interactions within the biological system, the use of biocompatible building blocks is most crucial in preparing polymeric amphiphiles. The excellent biocompatibility and multivalency of both glycerol and triglycerol make them suitable monomers to construct macromolecular skeletons. Besides these, easy availability and remarkable aqueous solubility further enlarge their use in synthetic chemistry and give ample possibilities for creating fascinating entities for practical applications. The conversion of glycerol into azido-glycerol and azido-triglycerol further helped in differential functionalization of their polymers with various hydrophobic and hydrophilic groups in different ratios thereby assisting in tuning the amphiphilicity of resulting functionalized polymers. Herein, we review the enzymatic synthesis of glycerol, azido-glycerol and azido-triglycerol based amphiphilic polymeric architectures as nanocarriers for various bio-active species. Enzymatically synthesized linear copolymers synthesized by selective esterification of primary hydroxyl groups of glycerol and its derivatives with suitable diacids/diesters are explored in this review.

1. Introduction

Current advances in the field of drug delivery have revealed the substantial importance of amphiphilic polymeric architectures derived from bio-based monomers as proficient nanocarriers for the transport of bioactive molecules to the target site within the biological system [1–6]. To confront the challenges faced by most of the drugs which include low water solubility, high drug doses and a short lifetime in the bloodstream [7–11], researchers across the world have focused to improve the pharmacokinetics of the drugs by developing amphiphilic polymeric nanocarriers produced from biocompatible starting materials. Among the huge list of various starting monomeric building blocks, glycerol, possessing excellent biocompatibility, is highly successful in catching the eye of researchers [12–15]. Since glycerol is obtained as a by-product in huge amounts (~10% w/w) from bio-diesel productions, it is easily available at a very low cost across the world [16]. It is also

Abbreviations: ATRP, Atom transfer radical polymerization; CAC, Critical aggregation concentration; CAL B, *Candida antarctica* lipase B; CLSM, Confocal laser scanning microscopy; CMC, Critical micelle concentration; CNT, Carbon nanotube; CuAAC, Copper-catalyzed azide-alkyne cycloaddition; DAPI, 4′,6-Diamidino-2-Phenylindole; DBTO, Dibutyltin oxide; DCC, N,N'-Dicyclohexylcarbodimide; DIPEA, N,N-Diisopropylethylamine; DLS, Dynamic light scattering; DMF, Dimethylformamide; FACS, Fluorescence-assisted cell sorting; FDA, Food and drug administration; FTIR, Fourier transform infrared; G1, First generation; GPC, Gel permeable chromatography; GRAS, Generally recognized as safe; hPG, hyperbranched polyglycerol; MALDI-TOF, Matrix-assisted laser desorption/ionization-Time of flight; MTX, Methotrexate; N435, Novozym 435; NMR, Nuclear magnetic resonance; PBI, Perylene bisimide; PBS, Phosphate buffer saline; PEG, Polyethylene glycol; PDI, polydispersity index; PG, Polyglycerol; SWCNT, Single-walled carbon nanotube; TEM, Transmission electron microscopy; THF, Tetrahydrofuran; 2-MeTHF, 2-Methyltetrahydrofuran.

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Review

A decennary update on diverse heterocycles and their intermediates as privileged scaffolds for cathepsin B inhibition

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ABSTRACT

The identification of x-ray crystal structure of cathepsin B (CTSB) in the early 90's enabled researchers to embark on a journey to understand and demystify its multiple catalytic mechanisms (endopeptidase/carboxypeptidase/peptidyl-dipeptidase) in diverse physiological processes and their switching into one another under different conditions. The engagement of CTSB in different pathological conditions due to its over-expression further highlighted the enhanced research interest around the domain. The occurrence of over-expressed CTSB in various diseases like Alzheimer's, cancer, arthritis, cardiovascular, *etc.*, and the use of CTSB inhibitors for the treatment of these diseases have established its involvement in different pathological conditions. Such an understanding tempted researchers to design, synthesize, and screen diverse classes of compounds against CTSB. This in turn, helped in understanding their interactions with the active sites of the enzyme. Heterocyclic compounds comprise a very rich and broad class of medicinally important compounds that also hold great potential for CTSB inhibition. This review covers the CTSB inhibition potential of various natural and synthetic heterocyclic scaffolds. Researchers working in the fields of molecular modeling, drug design and development, and enzyme inhibitors can benefit significantly from this review.

1. Introduction

The continuous emergence of newer insights with the ongoing research in the realm of medicinal chemistry facilitates a better understanding of different physiological processes in biological systems, their regulatory pathways, and the association of their malfunctioning with various diseases. The regulation of these physiological processes is done either through enzymes/hormones/receptors, or some other biological molecules. These molecules play a vital role in the proper functioning of the biological system; however, malfunctioning of some of these regulatory biological molecules is also linked with various diseases. Cathepsin B is one such lysosomal encapsulated cysteine protease enzyme [1–3], which is ubiquitously expressed and involved in several physiological processes [4–7], such as protein degradation and processing, maintaining intracellular homeostatic metabolic activity, tissue remodeling, inflammatory responses against antigens, apoptosis *etc.* The activity of cathepsin B is controlled by various endogenous inhibitors (Stefins and Cystatins) under normal physiological conditions. The loss of balance between cathepsin B and its inhibitors is marked by the over-expression and unusual localization (cytoplasm/ membrane/

Abbreviations: 1L-1β, cytokine interleukin-1β; Aβ, β-amyloid; A549, lung cancercell line; ADME/Tox, Absorption, Distribution, Metabolism, Excretion and Toxicity; APP, Alzheimer's amyloid precursor protein; BANA, N-α-Benzoyl-D, L-arginine-β-naphthylamide hydrochloride; E64d, Aloxistatin (cysteine protease inhibitor); ERG/EWG, Electron releasing groups/Electron withdrawing groups; GI_{50}, concentration causing 50 % cell growth inhibition; HEPG2, liver cancer cell line; HSC-4, human tongue squamous carcinomacell line; IC_{50}, Half-maximal inhibitory concentration; k777, *N*-[(2*S*)-1-[[(*E*,3*S*)-1-(benzenesulfonyl)-5-phenylpent-1-en-3-yl]amino]-1-oxo-3-phenylpropan-2-yl]-4-methylpiperazine-1-carboxamide; K_i, inhibition constant; MCF7, breast cancer cell line; MDA-MB-435, metastatic human breast cancer; MTT, (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium; NLRP3, NLR Family Pyrin Domain Containing 3; p62, ubiquitin-binding protein (also known as SQSTM1) involved in autophagy; Ri, Relative inhibition; RA, Residual activity; SRB, Sulforhodamine B; SK-LU-1, lung adenocarcinoma cell line; CaSki, HeLa, cervical cancer cell line; DU-145, PC3, prostate cancercell line.

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