

RECENT DEVELOPMENTS IN SCIENTIFIC RESEARCH II

EDITED BY

Prof. Dr. Ayşegül GÜMÜŞ

Prof. Dr. Selçuk GÜMÜŞ



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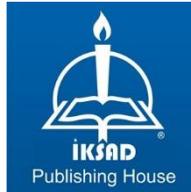
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PREFACE

There has been a significant development in science for a century or more, which has been quite accelerated for the past twenty-three years. The idea behind the present book lays on presenting a part of the ongoing studies in Faculty of Science and Engineering, Architecture and Design Faculty of Bartın University. This book is a compilation of five chapters relating to chemistry, biochemistry and physical chemistry. In the first chapter of this book, synthesis and theoretical applications on chemosensors obtained by condensation of quinoline carboxaldehyde and aminoanthracene has been reported, in the second chapter, sulfonamide inhibitors have been discussed as potential treatment for acute myeloid leukemia, in the third chapter, a wide information has been revealed in the area of biophotovoltaics, in the fourth chapter, research results from bioactivity of N-substituted cyclic derivatives of thiourea and phenylthiourea has been presented, in the fifth chapter, TADF properties of pyrazine based OLEDs are examined. In the last chapter, nanocomposite and nanohybrid gel polymer electrolytes for safe and high performing lithium metal batteries have been discussed deeply. The efforts of our extreme contributors of this book are highly commendable. We would especially like to express our gratitude to the İKSAD Publishing family, scientific committee, authors and readers who contributed to the preparation, layout and printing of the book.

The editors and authors dedicated this book to the 100th Anniversary of Republic of Türkiye.

Prof.Dr. Ayşegül GÜMÜŞ

Prof.Dr. Selçuk GÜMÜŞ

CHAPTER 1

QUINOLINE-ANTHRACENE CONJUGATES: SYNTHESIS AND INVESTIGATION OF ELECTRONIC AND SENSING PROPERTIES

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INTRODUCTION

Heterocyclic compounds play a crucial role in various aspects of chemistry, biology, medicine, and industry (Welch et al. 2010.; Fryatt et al. 2004; Michael, 2008). Design and synthesis of simple heterocyclic molecules for the detection of metal ions is very important since this method of detection has several advantages over other methods such as simplicity, high sensitivity, high efficiency, selectivity, low cost, remarkable selectivity, easy handling and real time monitoring capability (Lee et al., 2016; Ghorai et al., 2016; Kose e. al., 2015).

Among the organic molecules, Schiff bases have attracted a lot of attention with their characteristic features like ease of preparation, structural diversity, variable coordination ability, biological activity, thermal stability and they have applications in many different fields. In the last decade, many studies have been carried out on the design, synthesis and various applications of new Schiff base complexes. Bi-, tri-, tetradentate Schiff bases containing O and N atoms are of interest due to their ability to form various transition metal complexes and their biomedical activities. Schiff bases have promising optical response towards metal ions due to their unique photophysical and chemical properties. High chelating ability, the ease of synthesis and relatively high yield are the advantages of Schiff base compounds (Kim et al., 2013). The probe's photophysical properties will change when it binds a metal ion, which can be observed optically. Photoinduced electron/energy transfer (PET), charge transfer (LMCT and MLCT), intramolecular charge transfer (ICT), excimer or exciple formation, and excited-state intra-/intermolecular proton transfer (ESPT) are just a few of the underlying mechanisms of these changes (Wu et al., 2011; Valeur et al., 2000).

The design and synthesis of sensors that selectively detect metal ions have a very important place in biological and environmental processes. Although there are many commercially available metal sensors, chemists are still designing simpler, easily synthesized sensors with higher sensitivity, selectivity and reliability to meet the need.

Fluorescent metal sensors are widely used in biological and environmental research because of its significant advantages, such as its generally non-destructive nature, high efficiency, high sensitivity, and capability of real-time monitoring. Ionophore and fluorophore are the two main components of fluorescent probes intended for sensing. While the former unit chelates with metal ions, the latter fluorophore unit transforms diagnostic occurrences into analytical signals. Due to their excellent photoluminescence properties and chemical stability, pyrene and anthracene derivatives were widely used in the development of fluorescence (FL) sensors. These derivatives were demonstrated to be excellent fluorescents. Lee et al. (2014) reported an anthracene-based receptor **1**, which displays highly selective and sensitive fluorescence “off–on” sensing to Zn^{2+} (Figure 1).

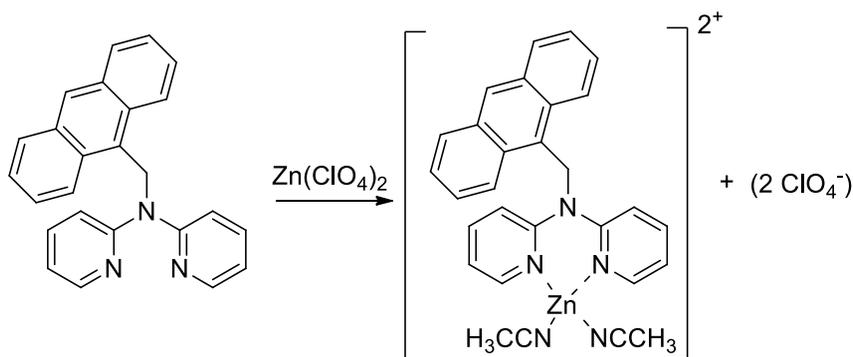


Figure 1. Anthracene-based Zn^{2+} sensor

Shellaiah et al. (2016) reported the synthesis of novel anthracene and pyrene-based Schiff bases and investigated their sensing abilities. Pyrene-based derivative was employed as fluorescence turn-on sensors towards Cu^{2+} and anthracene-based derivative was utilized as Fe^{3+} sensor (Figure 2).

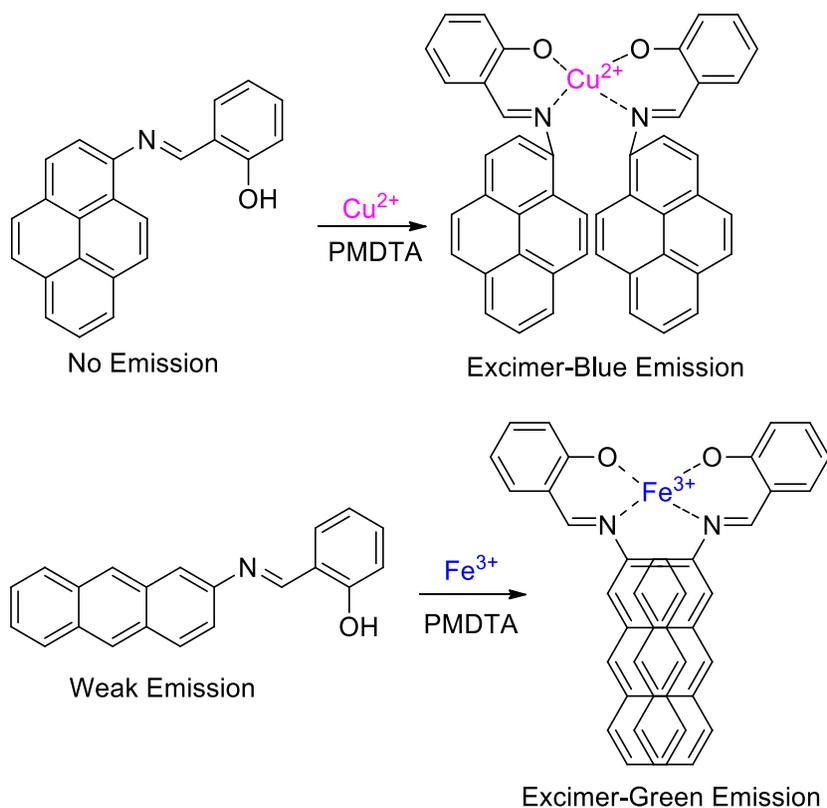


Figure 2. Anthracene and pyrene-based sensors

Quinoline is one of the most important N-based heterocycles that attracts the attention of researchers with its wide applications in medicinal, bioorganic, and industrial chemistry as well as in the field of synthetic organic chemistry (Matada et al., 2021). Their derivatives have been found to possess various biological activities like anti-malarial, anti-bacterial, anti-fungal, anti-asthmatic, antihypertensive, anti-inflammatory, and antiplatelet activity. Quinoline-based derivatives have indeed gained significant attention in recent literature, particularly in the field of fluorescence sensing. This is primarily attributed to their unique spectroscopic properties and the large-conjugated molecular structure of the quinoline unit (Gao et al., 2013; Weng et al., 2009; Meng et al., 2012). Quinoline and its derivatives often exhibit strong fluorescence, making them suitable candidates for

fluorescence-based applications. Their emission properties can be tuned by modifying the chemical structure, allowing for the design of sensors with specific emission wavelengths.

The 8-hydroxyquinoline (8-HQ) unit is also widely used in many different fields, including supramolecular chemistry, material and medicinal chemistry. Its derivatives are employed as light-emitting diodes (OLED), dye-sensitized solar cells (DSSC), and metal chelators (Rohini et al., 2020). A Schiff base was synthesized from a pyrene and 8-hydroxyquinoline for selective determination of Fe^{3+} ions in aqueous medium (Figure 3) (Mukherjee and Talukder, 2016). The receptor exhibits a "turn-on" response towards Fe^{3+} over other metal ions.

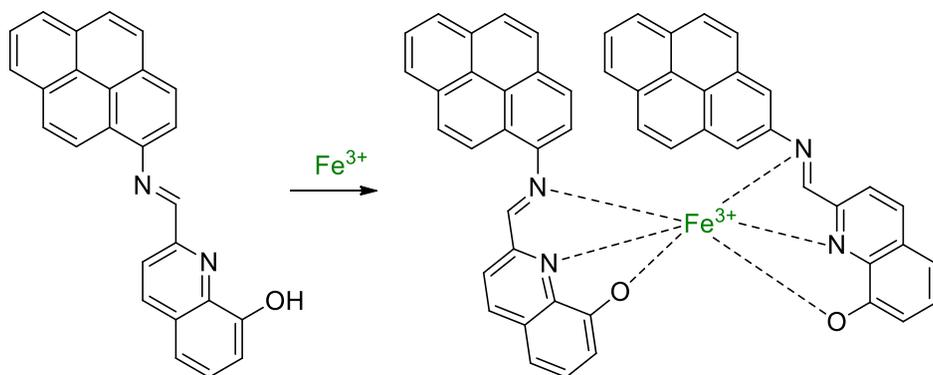


Figure 3. Quinoline-based turn-on luminescent chemosensor

Some 8-O-substituted 8-HQ ethers are very useful molecules for creating 'turn-off' fluorescence sensors for desired metals. For example, Vaswani and Keranen synthesized a simple 8-HQ derivative that detects the Hg^{+2} ion in water with high sensitivity and selectivity (Vaswani and Keranen, 2009)(Figure 4).

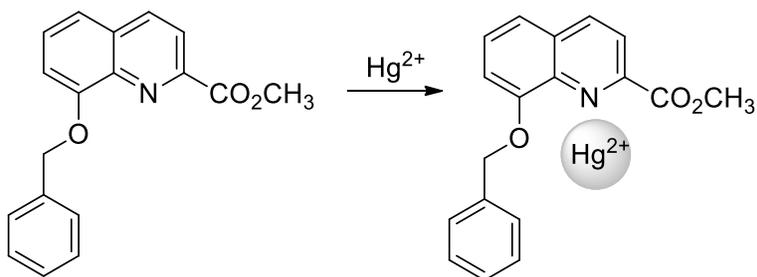


Figure 4. 'Turn-off' fluorescent Hg sensor

Herein, we aimed to synthesize anthracene-quinoline Schiff base derivatives, investigate their metal sensing properties and get some data on their electronic properties (Figure 5). In this study, fluorescence chemosensors were designed based on the ionophore-bridge-fluorophore approach. The anthracene unit was chosen as the fluorophore in the structure of the designed chemosensors. Receptoric quinoline groups that will interact with the metal ion are included in the structure with an imine bridge. The imine unit, which is located as the linker in the designed chemosensor system was chosen due to its thermal stability and high coordination properties.

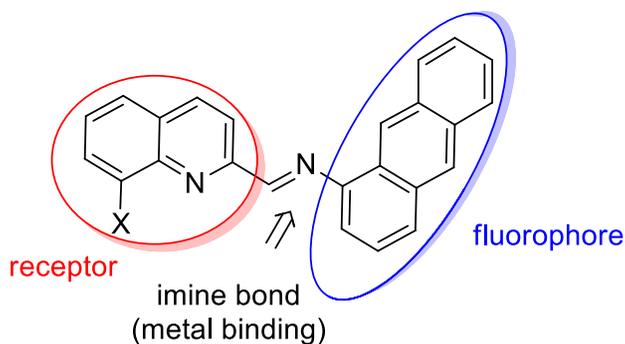
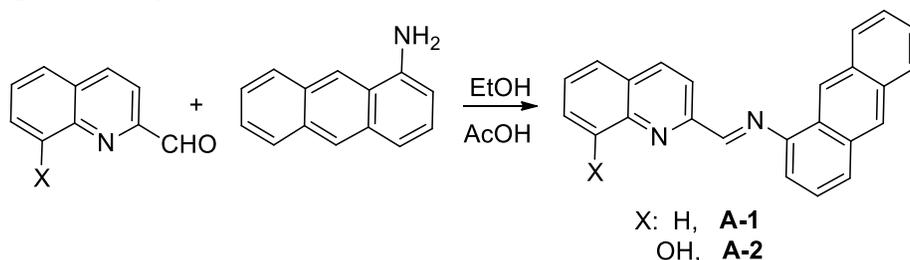


Figure 5. Anthracene-quinoline Schiff base

1. RESULTS AND DISCUSSION

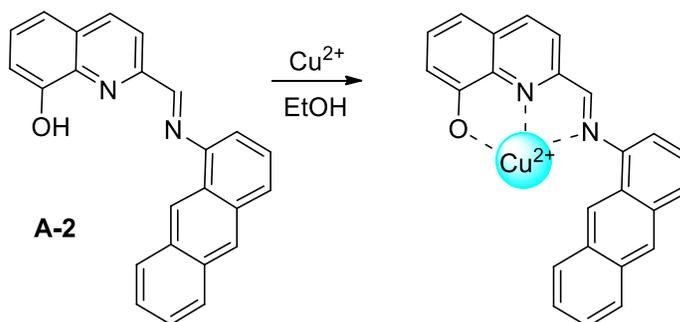
The chemosensors **A-1** and **A-2** have been synthesized in high yield by Schiff base condensation of quinoline carboxaldehyde and aminoanthracene in 1:1 M ratios in anhydrous ethanol under reflux

condition for 5 h (Scheme 1) and characterized by ^1H and ^{13}C NMR spectrometry.



Scheme 1. Synthesis of target Schiff bases

Metal sensing abilities of synthesized Schiff bases were investigated by reacting them with acetates of Cu, Co and Ni metals in ethanol by refluxing condition. Only **A-2** ligand was coordinated Cu ion and isolated as brown solid. **A-1** ligand did not make complexation with any metal ion. This can be explained by the presence of extra binding site, OH in **A-2** compound.



Scheme 1. Complex formation of Schiff base **A-2**

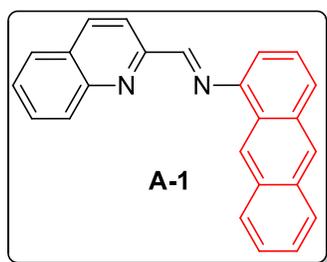
In addition to synthesizing the target compounds experimentally, we have also conducted theoretical calculations on Schiff bases and their complexes. Density Functional Theory has been used to compute some structural and electronic properties of the compounds at the B3LYP/6-31G(d,p) level of theory.

2. EXPERIMENTAL

2.1. General Schiff-Base Synthesis Procedure

Aldehyde (1 mmol) and amine (1 mmol) were dissolved in 20 mL of ethanol. The reaction mixture was stirred at room temperature by adding 2-3 drops of acetic acid. The resulting solids were filtered and purified.

(E)-*N*-(quinolin-2-ylmethylene)anthracen-1-amine, **A-1**.



Yellow solid. mp:122-124 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 8.98 (s, 2H), 8.65 (d, $J=8.5$ Hz, 1H), 8.46 (s, 1H), 8.36 (d, $J=8.6$ Hz, 1H), 8.22 (d, $J=8.5$ Hz, 1H), 8.09-8.07 (m, 1H), 8.05-8.02 (m, 1H), 7.96-7.92 (m, 2H), 7.82-7.78 (m, 1H), 7.67-7.62 (m, 1H), 7.52-7.47 (m, 3H), 7.19 (dd, $J=0.7$ ve 7.0 Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): δ 160.9, 154.9, 148.4, 147.9, 136.8, 132.1, 132.0, 131.7, 130.0, 129.8, 129.0, 128.7, 128.4, 128.0, 127.8, 127.8, 127.7, 127.2, 126.1, 125.7, 125.4, 122.8, 119.0, 111.6 (Figure 6).

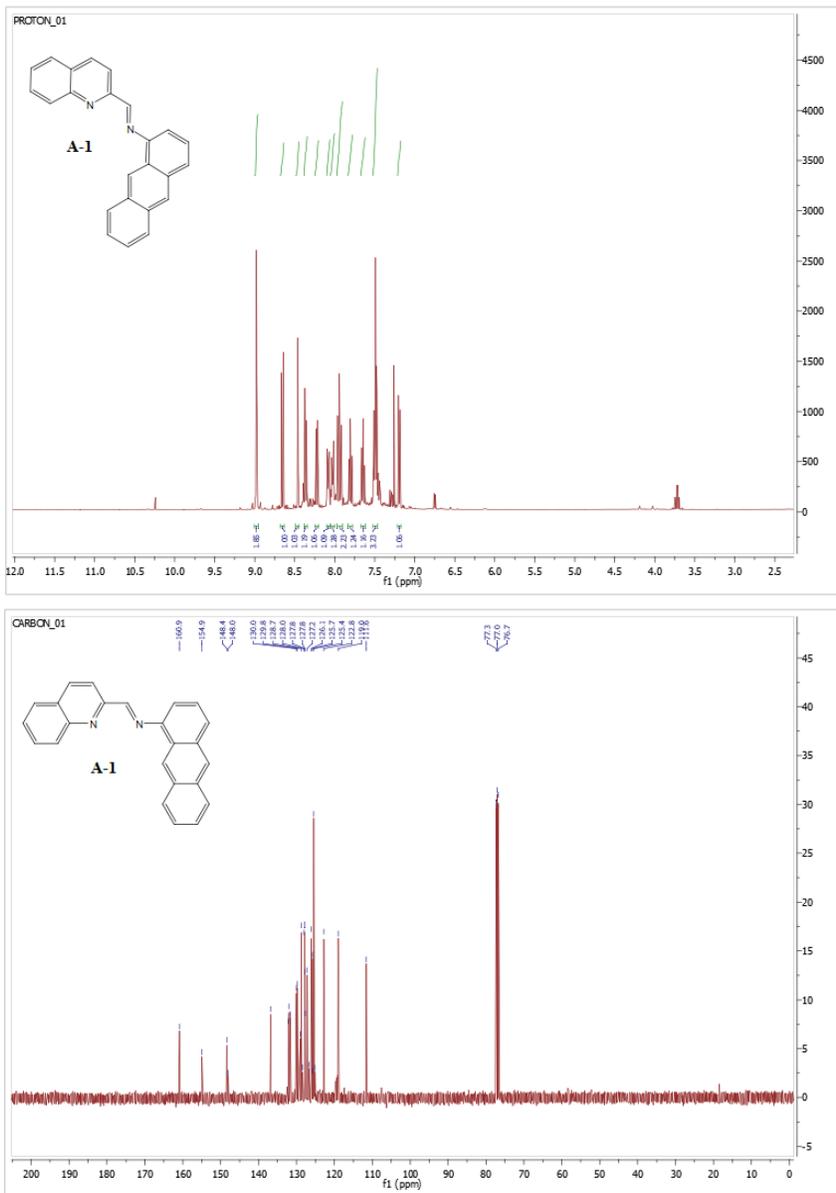
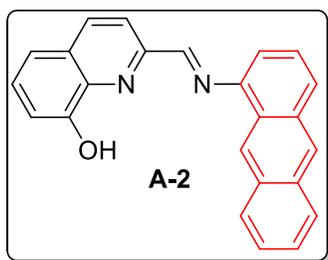


Figure 6. ^1H and ^{13}C NMR spectra of compound **A-1**.

(E)-2-((anthracen-1-ylimino)methyl)quinolin-8-ol, **A-2**.



The data are given in our previous study (Gümüş et al. 2018)

Apart from the synthesis of compounds in target, some computational calculations have also been performed on compounds **A-1** and **A-2**. Very important structural and electronic properties have been obtained via computations after application of Density Functional Theory at B3LYP/6-31G(d,p) level of theory. Gaussian 16 package program has been used through the computations (Frisch et al. 2016). Three-dimensional geometries of the compounds have shown that each of the two structures possesses a valuable central cavity where complexation with metal cations may take place (Figure 7).

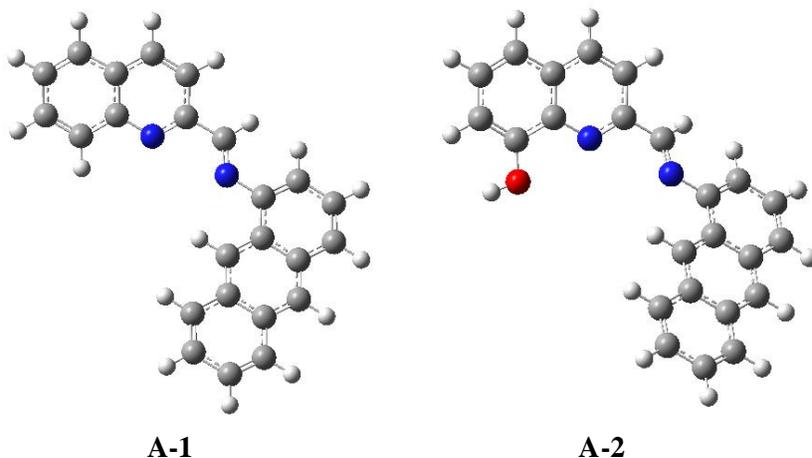


Figure 7. Three dimensional geometries of compounds **A-1** and **A-2** obtained from computational calculations in the gaseous phase.

As can be seen from the structures in Figure 7, **A-2** has greater potential to coordinate to a metal cation since it contains an –OH group which attracts electron deficiencies via its lone pairs. The metal complex formation capacity of **A-2** is expected to be enhanced by the existence of the aforementioned electron rich group.

Electron localization throughout a compound can be nicely represented by careful consideration of the molecular electrostatic potential map. Especially for a complex structure it is valuable tool to represent the positions where electrons are located more or less. Electron distribution throughout the structure is strongly effected by the presence of the electronegative atoms or strongly electron withdrawing or donating groups. It is useful to know the positions in a molecule for nucleophilic attack or electrophilic interactions. In the present case, electron rich positions are points for better cation chelation.

3D-electrostatic potential maps of **A-1**, **A-2** and their Mg and Cu complexes (**A-1_Mg**, **A-1_Cu**, **A-2_Mg** and **A-2_Cu**) are given in Figure 8. The schemes show clearly that electron distribution pattern of the main compounds has been changed drastically upon coordination with Mg^{2+} and Cu^{2+} . The cations possess +2 charge before coordination meaning an electron deficiency. This positive charge on the cation has been distributed through structure upon electron donation from the nitrogen lone pairs in the case of **A-1** and nitrogen and oxygen lone pairs in the case of **A-2**. In the parent structures there are red, yellow and green colored regions indicating nonuniform electronic structure, however, a more uniform electron distribution has been obtained after metal cation chelation process. When Mg and Cu metals are compared, Mg cations could not coordinate well because we can not observe total decrease of the +2 charge. This situation is indicated by a blue sign on the cation.

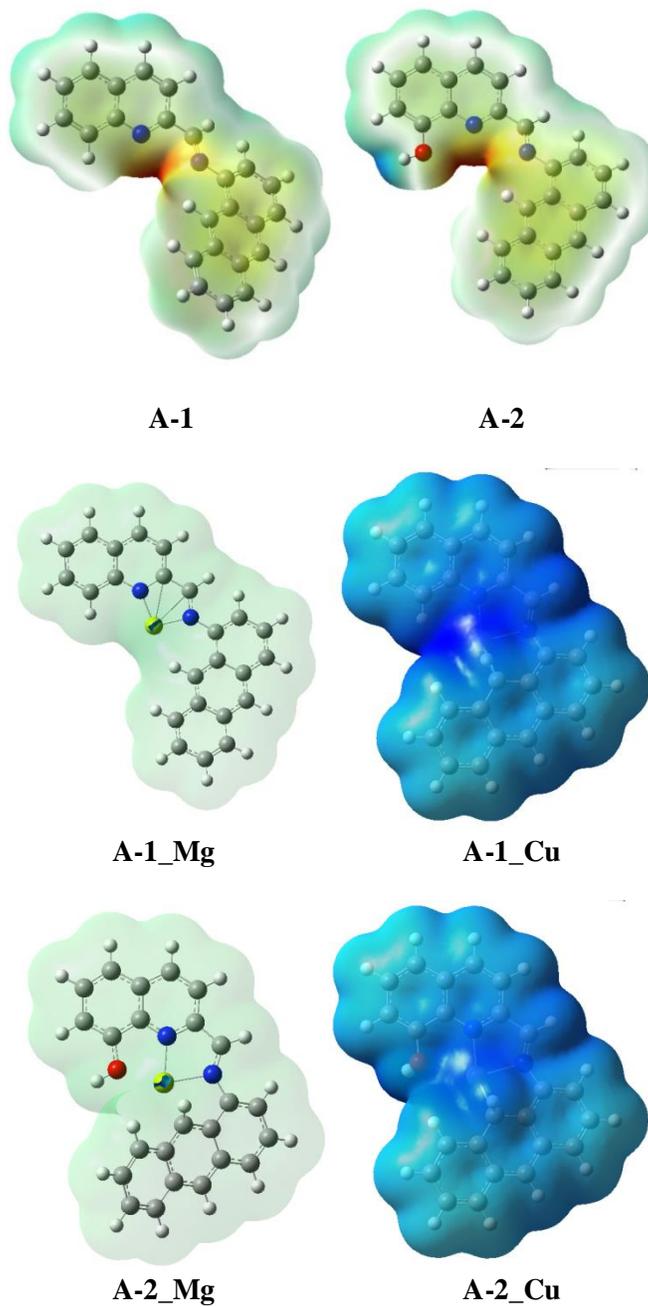


Figure 8. Molecular electrostatic potential maps of the structures under consideration.

Their HOMO and LUMO orbitals are a significant factor influencing the structural and electrical properties of the structures. While LUMO is predominantly generated quinoline part together with the metal, as is expected known that LUMO represents the electron deficient sites in a structure, HOMO is found on the anthracene portions of the parent molecule, respectively. Another crucial factor in determining whether a material is an insulator, conductor, or semiconductor is the energy difference between HOMO and LUMO. Our parent structure exhibits semi-conductor properties with a HOMO-LUMO energy gap (ΔE) of around 3.0 eV, whereas the complex can be classified as an conductor or at worst a semi-conductor with ΔE of 0.80 eV.

HOMO and LUMO distribution is also important for compounds since LUMO represents the electron acceptor moiety whereas HOMO mostly located on the electron rich part. This general situation has also been observed in the present case as well, because anthracene contributes to HOMO of the systems. Metal cations are electron deficient thus, they are mainly expected to form the LUMO of the structures.

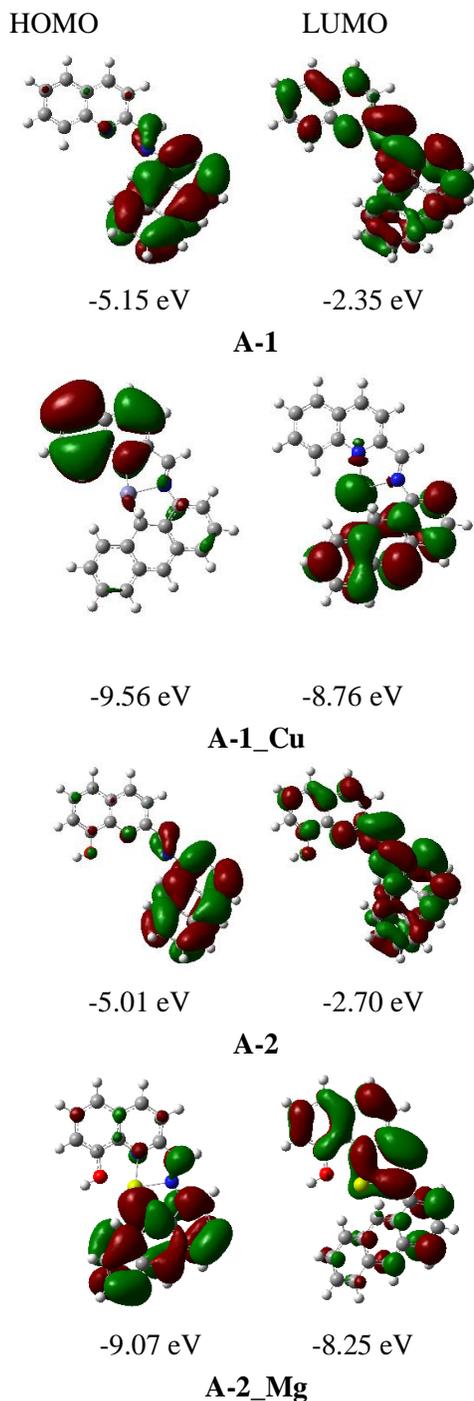
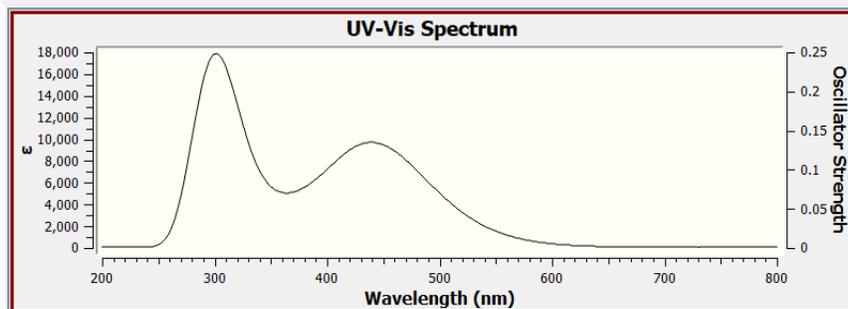
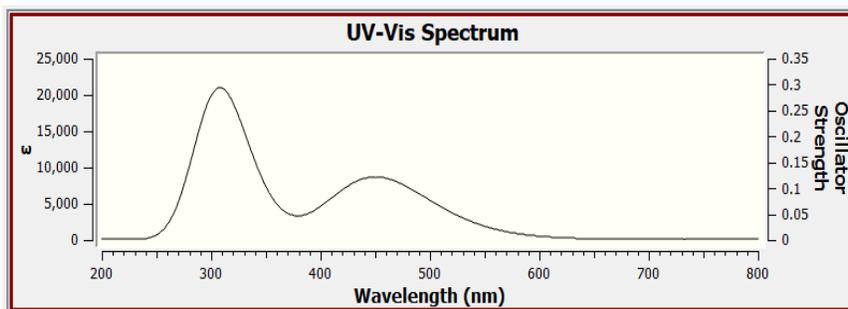


Figure 9. HOMO and LUMO orbital schemes

As a result of metal coordination, the electronic properties of the structure change enormously. One way of observing this change and proving the coordination is to calculate the absorption spectra by applying the Time-Dependent Density Functional Theory (TDDFT-Time Dependent Density Functional Theory). TDDFT application was performed with B3LYP/6-311G(d,p) calculation method. 20 excitation levels were taken into account to obtain UV-VIS spectra. The absorption spectrum of the **8** structure has one sharp band at 230 nm (Figure 8). In addition, two weak bands were calculated at 320 nm and 370 nm. When the structure **8** is coordinated with Zn^{2+} , a very broad band replace the two broad bands in the absorption spectrum of the molecule. Moreover, the sharpest band has disappeared. In addition, a red shift is observed in the bands. The redshift in the pass bands may be due to the decrease in the HOMO-LUMO energy gap due to the conductivity of the metal to the structure.

A-1



A-2

Figure 8. UV-VIS spectra for A-1 and A-2.

3. CONCLUSION

In conclusion, fluorescent Schiff bases by condensation of quinoline and anthracene derivatives in good yields. Aminoanthracene was reacted with quinoline carboxaldehyde in ethanol and transformed to Schiff bases by imine bond. Schiff base-metal complex A2-Cu was synthesized by using metal acetate salts.

The target compounds and their complexes with Mg^{2+} and Cu^{2+} were the subject of structural and electronic data collection using theoretical calculations at the B3LYP/6-31G(d,p) level of theory. Since the molecule's charge distribution has completely changed as a result of its interaction with the metal cation, the molecular electrostatic potential maps have demonstrated well complexation. To achieve a more uniform charge distribution, some electronegative atoms' negative charge growth was forced towards the cation. Through complex development, the atoms' and groups' contributions to border molecular orbitals have also changed. The LUMO of the final complex structure mainly forms on a metal atom. Lastly, using the same technique, the absorption spectra for **A-1** and **A-2** were calculated. The absorption bands of the two structures do not differ much from each other due to their very similar structure.

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CHAPTER 2

BIOPHOTOVOLTAICS: THEIR TECHNOLOGY AND APPLICATIONS

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INTRODUCTION

i. The significance of green energy

Throughout human history, the global population's continuous growth has paralleled an increasing demand for energy. From ancient times to the present day, the necessity for energy has been a constant. While the natural environment provides a means to meet this energy demand, countries, until recent times, predominantly satisfied their energy needs through the utilization of fossil fuels. The turning point came during the oil crisis of the 1970s, a period when the world faced the realization that finite resources, such as oil, could be depleted through extensive consumption. This realization prompted a significant shift towards seeking energy solutions from renewable sources-energy derived from naturally replenished resources (Sekar & Ramasamy, 2015).

Shifting towards green energy, sourced from renewable outlets with minimal carbon footprint, emerges as a hopeful solution for future generations, diminishing reliance on fossil fuels like coal, oil, and natural gas. The burning of these fossil fuels emits detrimental substances into the air, amplifying worldwide environmental challenges such as global warming and climate change. The increasing global population intensifies the demand for energy, highlighting the urgency of transitioning to renewable sources. Renewable energy has not only become a crucial aspect of environmental sustainability but has also evolved into a competitive tool for nations to assert technological dominance without resorting to traditional conflicts. As traditional energy sources face gradual depletion, the significance of renewable energy continues to grow. The lower carbon emissions associated with renewable sources contribute to a healthier environment, further emphasizing the importance of green energy technology (Kruse et al., 2005). Additionally, the decreasing costs of eco-friendly technologies contrast with the rising expense of fossil fuels, prompting increased investment and focus on innovative green technologies over the past three decades (Rodrigo et al., 2007). Sustainable sources encompassing the world's renewable energy solutions include wind energy, solar

energy, geothermal energy, hydraulic/hydroelectric energy, hydrogen energy biomass energy (including biofuel energy), tidal energy, and wave energy (Lewis & Nocera, 2006). These sources, rooted in the environment, provide a perpetual and sustainable energy solution. In essence, renewable energy harnesses natural processes, generating energy at a pace that surpasses the rate of depletion of resources used. While the initial installation costs of green energy technologies may be high, the long-term investment value is well-established, necessitating the commitment of investors to drive further advancements. The geographical context plays a pivotal role in maximizing the benefits of renewable energy. Photovoltaic technologies, particularly solar power, outshine other green energy types such as wind and hydropower due to their lower maintenance requirements and the absence of noisy turbines (Faaij, 2006). In the Renewables 2017 Global Status Report shows that despite geographical disadvantages, European countries, as highlighted, have successfully acquired a significant portion of their energy from renewable sources (*RENEWABLES 2017 GLOBAL STATUS REPORT*, n.d.). Solar energy, generated through the transformation of solar rays into heat and electricity using solar panels, emerges as the most widely utilized natural energy source. Its attractiveness lies in its environmental friendliness, global accessibility, and immense potential. Solar power, available to every sunlight-receiving country, holds substantial allure, with the sunlight hitting the Earth in an hour equaling the world's annual energy consumption. Solar power comes in two primary types: photovoltaic and thermal. Photovoltaic technologies convert solar radiation into electrical power using semiconductor cells, constituting a system based on obtaining direct electricity from sunlight (Cevik et al., 2019). Solar thermal technology, on the other hand, finds usage in heating buildings, water, and cooking food by harnessing the sun's heat and providing natural lighting. In conclusion, the narrative underscores the transformative potential of green energy, particularly solar power, as a friendly of environmentally and sustainable solution to meet the world's escalating energy needs. The collective effort towards investing in and advancing renewable technologies is essential for a more sustainable and resilient future.

The field of photovoltaics, a prominent subject in this century, has undergone continuous development, achieving higher efficiencies over time. The journey began with Alexandre-Edmond Becquerel's discovery of the photovoltaic effect in an electrolytic cell in 1839. This effect, observed in solids, was later replicated in the late 19th century. A significant milestone occurred in 1954 at Bell Laboratories, where the first photovoltaic cell utilizing a crystalline silicon semiconductor was developed, albeit with a modest efficiency of 4%. Despite theoretical calculations suggesting efficiencies of up to 40%, practical implementations have yet to reach such high productivity values. The challenge lies in the complexity of factors influencing energy efficiency, making it a multifaceted consideration in the development of photovoltaic technologies [8]. The ongoing pursuit of higher efficiencies in photovoltaics reflects the dedication to optimizing this sustainable energy source for widespread use and integration into the global energy landscape (Green, 2006; Sekar & Ramasamy, 2015).

Both solar cells and plants are capable of harnessing energy from sunlight, albeit employing distinct methods. Photovoltaic solar cells, for example, harness sunlight and transform it into electrical energy using the photovoltaic effect (Green, 2006). In the contrary, plants use sunlight to harvest energy and convert it into chemical energy through the process of photosynthesis. While their approaches differ, both solar cells and plants essentially achieve the same outcome – the conversion of solar energy to usable forms, electricity, and chemical energy, respectively (Yongjin et al., 2009). A notable advancement in solar cell technology is the utilization of Photoelectrochemical cells (PECs). These cells operate similarly to the electrolysis of water, producing electrical energy or hydrogen. Another innovative technology, Biological Photovoltaic Cells (BPC) (McCormick et al., 2011), combine solar power with the life cycle of living organisms to convert solar energy into electrical energy. BPC shares similarities with microbial fuel cells, employing photosynthetic microorganisms that utilize light for the water photolysis and contribute electrons to the system. Often referred to as bio-solar panels or photo-microbial fuel

cells, these systems leverage sunlight to hydrolyze water, making the only electron donor in the end system water itself, distinguishing them from microbial fuel cells, where the electron donor is typically organic matter. In the realm of Biological Photovoltaics (BPV)(McCormick et al., 2011), photosynthetic microorganisms exhibit the ability to self-sustain. Their cultivation is cost-effective, and the metabolites stored in their cells enable power production even in environments lacking direct sunlight, presenting BPV as a more advantageous option compared to conventional photovoltaic cells. This innovative approach holds promise for sustainable energy solutions, merging biological processes with solar technology for enhanced efficiency and environmental compatibility(Sawa et al., 2017; Zhang et al., 2011).

Environmentally friendly applications take precedence over modern industrialized technology, and nanotechnology emerges as a crucial asset in mitigating environmental pollution. Nanoscience finds applications in both current and prospective work scenarios, showcasing its significance. In the realm of nuclear technology, nanomaterials have proven effective in the creation of high-temperature components, contributing to advancements in safety and performance (Shah et al., 2015). Additionally, the synthesis of high-temperature superconductivity cables using nanomaterials at the nanoscale further exemplifies the versatility of nanotechnology in nuclear applications . Nanomaterials play a pivotal role in smart energy consumption and storage, facilitating the advancement of technologies promoting energy efficiency such as LED lighting, sensors, batteries, microbatteries, and supercapacitors (Petrinin, 2015; Sher et al., 2013). This integration enhances the efficiency and storage capacity of energy systems, aligning with sustainable and smart energy consumption practices. Water technology benefits significantly from nanotechnology, with nanomaterial dyes utilized to prevent marine corrosion and aging(Cevik et al., 2019). These advancements underscore the potential of nanotechnology in promoting sustainable water management practices. Research endeavors in fossil fuel technology focus on the application of nanomaterials for CO₂ capture, oil recovery assistance

through nanoparticles, and the synthesis of nanosize catalysts (Sher et al., 2013). These efforts represent critical strides toward addressing environmental challenges associated with fossil fuel usage. In solar energy applications, nanomaterials contribute to the design of thin films and the tailoring of electronic structures, enhancing the efficacy and efficiency of solar energy systems (Liu et al., 2010). This intersection of nanotechnology and solar energy underscores their collaborative potential for sustainable energy solutions. In summary, the multifaceted applications of nanotechnology across various sectors highlight its pivotal role in advancing environmentally friendly technologies. The integration of nanomaterials not only tackles existing environmental concerns but also propels technological innovations toward a more sustainable and ecologically conscious future.

ii. Thylakoid Membrane

Chloroplasts, similar to mitochondria, play a vital role in metabolic energy production and originated through endosymbiosis. Distinguished by their larger and more intricate structure compared to mitochondria, chloroplasts serve a crucial function beyond ATP production—they are primarily responsible for the photosynthetic conversion of CO₂ into carbohydrates. The pivotal physiological process executed by pigmented chlorophyll encompasses the absorption of sunlight, subsequently transforming it into energy storage molecules, namely ATP and NADPH. This intricate mechanism is facilitated by the liberation of oxygen during the cleavage of water molecules. Consequent to this light-dependent phase, the stored ATP and NADPH are harnessed in the biosynthesis of organic compounds utilizing carbon dioxide. Notably, within the structural framework of chloroplasts, characterized by the outer and inner envelope membranes, a third internal membranous structure manifests itself as the thylakoid membrane. The thylakoid structures, encapsulated by thylakoid membranes, are the sites where light-dependent reactions occur in photosynthesis. Within the chloroplast, thylakoid membranes are organized into discrete discs called granum, or singularly grana, interconnected by an intergranular structure. Thylakoid membranes

play a pivotal role in orchestrating the light-dependent reactions within chloroplasts and cyanobacteria. These membranes encompass a complex milieu consisting of stroma, thylakoid lumen, proteins associated with Photosystem I (PSI) and Photosystem II (PSII), as well as the ATP synthase enzyme. Within chloroplasts, an array of light-absorbing pigments and electron transport proteins are intricately embedded in the thylakoid membrane. The absorption of light energy by pigments initiates a sequence of events where electrons, liberated during the process of water oxidation, traverse through a sequence of molecular entities, including PSI, plastoquinone (PQ), the cytochrome *b₆f* complex, plastocyanin (PC), and PSII, ultimately reaching ferredoxin (Fdx). Subsequently, the reduced Fdx serves a crucial role by either reducing thioredoxins (Trx) through ferredoxin:thioredoxin reductase (FTR) or NADP through ferredoxin:NADP reductase (FNR). Moreover, protons released into the thylakoid lumen during water oxidation and by plastoquinone are utilized in the synthesis of ATP (Meyer et al., 2009). This intricate interplay of molecular components within the thylakoid membrane underscores its significance in driving the essential processes of light reactions in photosynthetic organisms. This intricate process underscores the sophisticated molecular machinery within chloroplasts, essential for the fundamental energy transformations supporting plant life.

Thylakoid membranes, sourced from plant cells, demonstrate prolonged viability following isolation, offering an extended timeframe for their utilization compared to alternative isolation methods for obtaining thylakoids. These thylakoids have found application in bio-solar energy conversion. In efforts to enhance performance relative to other systems, nanomaterials derived from nanowires (Ryu et al., 2018), carbon nanotubes (Calkins et al., 2013; Sekar et al., 2014), and graphene (Büyükharmar, 2020; N. Yang et al., 2012) have been integrated into isolated thylakoids.

iii. Photosynthesis

It would be accurate to assert that plants exhibit a remarkable level of intelligence, potentially surpassing humans, as they harbor an incredibly intelligent energy source within their structures. In the realm of renewable energy, emphasis has been placed on energy efficiency, with plants standing out as exemplars. Over the course of billions of years, plants have adeptly harnessed solar power through photosynthesis, demonstrating an unparalleled efficiency in energy utilization. Photosynthesis, a pivotal process, involves plants converting sunlight energy, carbon dioxide, and water into essential molecules required for their growth. The life cycles of phototrophic bacteria, plants, cyanobacteria, and algae contribute directly or indirectly to human life growth and living standards, influencing both bodily health and energy requirements. Notably, a substantial portion of nutrient needs for various living organisms is met through the contributions of plants. Furthermore, the photosynthetic processes of phototrophic bacteria, plants, cyanobacteria, and algae serve as the foundation for energy storage in the form of essential end products like coal, petroleum, and natural gas. This stored energy, resulting from millions of years of photosynthesis, plays a critical role in sustaining life and meeting diverse energy demands (Armaroli & Balzani, 2007).

Green phototrophic bacteria, plants, cyanobacteria, and algae employ solar energy to synthesize organic materials by assimilating chlorophyll from their leaves, carbon dioxide (CO₂) from the air, and water from their foliage. Photosynthesis relies on the utilization of energy from photons in the visible spectrum. Pigments, such as chlorophylls, xanthophylls, and carotenoids, serve as light-absorbing substances, with each pigment absorbing specific wavelengths and reflecting unabsorbed light. Within chloroplasts, these pigments selectively transmit or reflect green light while absorbing blue and red light, leveraging the absorbed light rays for photosynthesis. The characteristic green color of chlorophyll arises from its reflective properties toward green light ("Frontmatter," 2002). Photosystems PSI (P700) and PSII (P680) play integral roles in the photosynthetic

process, featuring intricate pigments. Photons from the sun reach PSII, initiating the stimulation of electrons in chlorophyll A molecules, leading to an elevation in their energy levels. As these electrons traverse between molecules, their energy diminishes slightly. Concurrently, H⁺ is transported into the thylakoid cavity through the electron transport systems. The electron stimulation persists as PSII transitions to PSI, contributing to an accumulation of H⁺ ions. This concentration disparity fuels ATP production, functioning analogously to a mechanical machine. Throughout these events, water undergoes oxidation, supplying electrons to the system to replace those utilized. The by-products of light stage reactions—ATP and NADP—sequester these electrons. This intricate interplay of molecules and light reactions underscores the remarkable complexity of the photosynthetic machinery (Caffarri et al., 2014).

Utilizing solar energy, plants engage in the absorption of carbon dioxide and water, releasing oxygen as a byproduct. A notable aspect of this process is its complete absence of environmentally harmful residues, rendering it a wholly renewable activity. In the pursuit of harnessing solar energy with utmost efficiency, cleanliness, and cost-effectiveness, scientists have delved into the realm of artificial or bioengineering photosynthesis (J. H. Kim et al., 2014). This inquiry, originally posed a century ago by G. Ciamician (Ciamician, 1912), seeks to emulate the photosynthetic mechanisms of plants. A particularly compelling avenue within this research involves the concept of solar-induced water splitting, wherein water is cleaved into oxygen and hydrogen using solar energy (Walter et al., 2010). This application holds considerable promise, as it aligns with the quest for hydrogen production as a future fuel for combustion. The research landscape has thus focused significantly on the realm of photocatalytic water splitting, underscoring its importance in advancing this technology. In order to elucidate these discussions, it is imperative to establish clear definitions for both artificial photosynthesis and natural photosynthesis (Cevik et al., 2018; Rosenbaum et al., 2010).

Natural photosynthesis embodies a solar-to-chemical energy conversion mechanism characterized by a sequence of photo-induced electron transfer reactions. This intricate process involves the participation of light-harvesting complexes, protein-metal clusters, and diverse redox biocatalysts. Within this intricate framework, a myriad of complex molecules engage in the absorption of energy through light interactions, ultimately leading to the oxidation of water. The natural photosynthetic process unfolds through two discernible stages: light reactions and the Calvin cycle. Light reactions transpire within the grana, a constituent of the chloroplast. During this phase, water undergoes photolysis, resulting in the release of oxygen, generation of ATP, and formation of NADPH. Subsequently, the Calvin cycle takes place in the stroma, involving the conversion of carbon dioxide into sugars. This process relies on ATP for energy and utilizes NADPH as a source of reducing power. The orchestrated interplay of these processes underscores the sophisticated nature of natural photosynthesis as a pivotal mechanism for harnessing solar energy and synthesizing complex organic molecules.

Both reactions are contingent on sunlight, with light reactions transpiring when the sun is shining. Interestingly, even the dark cycle reactions rely on the occurrence of light cycle reactions, happening consecutively. It's noteworthy that only sunlight photons are not utilized in dark cycle reactions. Within the realm of artificial photosynthesis, the process undergoes a deliberate reengineering wherein photosensitizers, electron mediators, electron donors, and redox enzymes are strategically employed to facilitate solar-driven redox reactions (J. H. Kim et al., 2014).

Artificial photosynthesis, mirroring the processes of photosynthesizing organisms, replicates the principles of natural photosynthesis. In this artificial counterpart, a molecular device or photovoltaic system takes the place of the natural photosynthetic reaction occurring in leaves, leading to distinct end products. The commonality resides in the successive stages that encompass the capture of sunlight, followed by the storage of energy within the

chemical bonds of a solar fuel. In both natural and artificial photosynthesis, hydrogen serves as the end product. Notably, in artificial photosynthesis, hydrogen can be stored and utilized in fuel cells, representing a futuristic green technology as an alternative to conventional gasoline consumption. Alternatively, the generated hydrogen can be chemically linked to CO₂, facilitating the synthesis of hydrocarbons, and enabling the formation of higher molecular weight hydrocarbons (Soni et al., 2016). The reconstruction entails the optimization of photosensitizers, electron mediators, electron donors, and redox enzymes to enable solar-driven synthesis of chemicals (J. H. Kim et al., 2014).

Artificial photosynthesis holds diverse applications, including solar fuels, photoelectrochemistry encompassing processes like photoelectrochemical H₂ and O₂ evolution, and photoelectrocatalytic CO₂ reduction, as well as pollutant degradation. Furthermore, it finds application in fuel cells and biohydrogen production from sunlight, contributing to the green energy field (Tachibana et al., 2012; Wang et al., 2015; J. Yang et al., 2013). In this context, scientists are actively working towards optimizing the reconstruction of photosensitizers, electron mediators, electron donors, and acceptors within photosynthetic reaction centers, along with redox enzymes for the solar synthesis of chemicals (He et al., 2009; Nishio et al., 2010; Yildiz et al., 2017). Efficient and directed electron transfer between each component of the artificial photosynthetic system is a critical consideration for these applications. Artificial systems incorporate chromophores that absorb visible light, analogous to chlorophyll in natural systems. The challenge lies in achieving effective electron transfer during transport and efficiently funneling energy from chromophores to central sites to discrete charges in the system. Replicating natural photosynthesis is a complex task, and the commonly used manganese catalyst in man-made setups faces challenges due to its instability. Catalyst degradation and additional reactions can impede the functionality of the system (Hasan et al., 2014).

Nanotechnology serves as a nature-inspired approach for artificial photosynthesis, aiming to produce clean and sustainable fuel. In this context, eco-friendly nanoparticles were developed by introducing zinc sulfide onto the indium-based quantum dots surface. Moreover, researchers successfully synthesized novel nanoparticles closely resembling artificial photosynthesis by capturing carbon on a larger scale. Another noteworthy development involved the creation of a hybrid system, integrating semiconducting nanowires with bacteria to emulate natural photosynthesis (D. Kim et al., 2014; Lineberry et al., 2023).

iv. Cyanobacteria and algae based bio-photovoltaic fuel cells

Photovoltaics of biological represent a technology harnessing photosynthetic organisms to derive energy from light. Devices within this category, recognized as microbial fuel cells, bioelectrochemical fuel cells, or photo-bioelectrochemical fuel cells, are contemporary forms of energy conversion technology. In photovoltaic systems incorporating biological organisms, electrons are liberated through the photolysis of water into hydrogen and oxygen, subsequently transferred to the anode. A complementary reaction on the cathode surface modifies the potential equilibrium of the reaction chamber, inducing a potential difference that initiates the flow of electrons (Bombelli et al., 2011). The orchestrated movement of electrons from the anode to the cathode culminates in the generation of electrical energy, subsequently harnessed by an external circuit.

In biological photovoltaic fuel cells, akin to conventional fuel cells, reactions occur within the anodic and cathodic semicells. Oxygenic photosynthetic biomaterials, specifically algae and cyanobacteria, play a pivotal role in the anodic half-cell reactions. Harnessing light energy, these organisms engage in the oxidation of water, generating electron fractions. Subsequently, the liberated electrons exit the cell and participate in the reduction of the anode (Cevik et al., 2018; Hasan et al., 2014).

The reaction of cathodic, characterized by a higher potential than the anode, governs the direction of electron flow. In this process, oxygen undergoes reduction to form water at the cathode surface. Employing electron carriers and catalytic materials for reaction acceleration can enhance the overall efficiency in the system. The regeneration of water establishes a closed loop within the reaction chamber, ensuring a continuous flow of electrons. Consequently, this configuration yields a photobioelectrochemical fuel cell, where the sole energy source is light for generating the photocurrent (Bombelli et al., 2011).

Utilizing complete organisms in biological photovoltaic energy conversion systems is a prevalent and enduring approach. Algae and cyanobacteria are the predominant organisms employed in bio-photovoltaic systems. While the cell membranes introduce electron flow resistance towards the anode, leading to reduced efficiency, the incorporation of photosystem proteins in their natural milieu allows for the operation of cells under diverse conditions, ensuring prolonged usage.

- Algae-based biological photovoltaic systems

Green algae, taxonomically and dimensionally distinct from plants, constitute a diverse assemblage of photosynthetic organisms. Their differentiation from photosynthetic bacteria is discernible through distinctive biochemical characteristics. Algae, categorized into six primary groups, encompassing Rhodophyta (red algae), Chlorophyta (green algae), Chrysophyta (golden-yellow algae, diatoms), Dinoflagellata (dinoflagellates), Phaeophyta (brown algae), and Euglenophyta, assume a pivotal ecological role across various habitats. Serving as primary producers in food chains, they contribute significantly to oxygen production, an indispensable element for the metabolic processes of heterotrophic organisms.

In the development of bio-photovoltaic devices utilizing algae, green algae species are commonly employed as photosynthetic microorganisms. Photosynthesis takes place within the chloroplast, a

subcellular organelle structure in algae. Efficient electrochemical linkage of these structures to the electrode during photosynthesis under the light is crucial for generating photocurrent. Achieving maximum efficiency necessitates rapid electron transfer. To expedite electron transfer and optimize efficiency, bio-photovoltaic devices incorporate soluble nanomaterials, composite structures, and conductive polymers as mediators.

In bio-photovoltaic systems reliant on light-dependent processes and employing algae, the generation of photocurrent is initiated by the light-induced separation of water, distinct from the biological oxidation of organic compounds. Light-triggered water oxidation leads to the liberation of protons, electrons, and oxygen, with electrons transiently stored as NADPH. Subsequently, NADPH serves as a reducing agent in the conversion of CO₂. This intricate sequence, spanning from water oxidation to NADPH generation, is orchestrated by Photosystem II (PSII) and Photosystem I (PSI) — two membrane proteins integral to the chains of photosynthetic electron transfer. These proteins are strategically located within the thylakoid membrane. PSII functions as the exclusive enzyme complex catalyzing light-induced water degradation, resulting in the release of protons into the thylakoid lumen. Electrons liberated during this process are conveyed to the diffusible membrane-bound mediator, plastoquinone (PQ), which transports electrons to the cytochrome b6F complex. Proton transfer from the cytoplasm to the thylakoid lumen persists concomitantly with the formation of PQ and plastohydroquinone. Soluble mediators in the thylakoid membrane, such as plastocyanin (PC) or cytochrome c6, facilitate electron transfer between the cytochrome b6F complex and PSI. The subsequent light-induced degradation transpires in PSI, where electrons are generated by ferredoxin and ferredoxin-NADP-reductase, subsequently reduced to NADPH. The catalysis of ATP formation, involving adenosine diphosphate (ADP) and phosphate, is orchestrated by the ATP synthase enzyme, mediating communication between the cytoplasm and the thylakoid lumen (Hasan et al., 2015).

Bio-photovoltaic systems utilizing algae are designed to generate photocurrent through the aforementioned light-dependent energy conversion process. Two distinct electron transfer mechanisms have been identified:

(a) Direct Electron Transfer (DET): Involves the direct transfer of electrons from the reaction center (PSI and PSII) to the electrode without the involvement of any mediator.

(b) Mediated Electron Transfer: Encompasses the transfer of electrons through the reaction center, facilitated by a mediator/carrier, towards the electrode.

Employing a mediator in electron transfer establishes an electron transfer pathway that connects the algae to the electrode. This facilitates faster electron transfer, enabling the attainment of higher photocurrent. Mediators, such as lipid-soluble polymers, soluble ionic molecules (hexacyanoferrate and quinones), and nanomaterials, are utilized in bio-photovoltaic fuel cells.

In academic literature, it is noted that combining various chemical and nanotechnological materials in bio-photovoltaic fuel cell production results in high yields of photocurrent.

Hasan et al. (Hasan et al., 2015) conducted an investigation involving Direct Electron Transfer (DET) and mediated electron transfer mechanisms utilizing *Paulschulzia pseudovolvox* (algae) in a bio-photovoltaic fuel cell. To establish an effective linkage between algae and the electrode, the researchers employed osmium polymer derivatives as lipid-soluble mediators. The study delved into the influence of soluble mediators, specifically hexacyanoferrate $[\text{Fe}(\text{CN})_6]^{3-/4-}$ (FCN) and p-benzoquinone (PBQ), on the photocurrent density. The objective was to assess their impact on the electrical connection between algae and the electrode. The experimental setup involving a graphite electrode and algae demonstrated successful formation of the electrode structure. DET was achieved by illuminating light, revealing the capacity of electrons to traverse both the cytoplasmic and extracellular membranes to reach the electrode. The

lipid-soluble osmium polymer, with its ability to pass through the extracellular membrane, facilitated a more efficient electron wiring to the electrode. Notably, the quinone mediator exhibited the highest photoactivity. This is attributed to its compact structure, enabling it to permeate the cytoplasmic membrane and establish a connection between the reaction centers (Photosystem II and Photosystem I) and the anode. The interaction with transmembrane proteins facilitated enhanced electricity production in the bio-photovoltaic fuel cell.

Nanomaterials serve as mediator-like structures in light-dependent systems based on photosynthetic microorganisms. Carbon nanotubes, graphene, as well as gold and platinum nanoparticles, are preferred due to their high biocompatibility and excellent electron transport properties. Commonly used anode materials in bio-photovoltaic fuel cells include Indium Tin Oxide (ITO) coated glass and poly(ethylene terephthalate) (PET), chosen for their high light transmittance, low internal resistivity, and stable structure. Fong-Lee and colleagues devised a specialized anode platform for a bio-photovoltaic fuel cell by incorporating graphene onto the ITO surface (Ng et al., 2014). The photosynthetic oxygenic material *Chlorella* sp. was introduced into the fuel cell to create a biofilm on the anode surface. Nanomaterials have been observed to enhance electron transfer, particularly in measurements based on the DET method under cyclic light on-off conditions. This observation suggests that nanoscale structures can establish close interactions with algae, making intimate contact with the extracellular membrane. Additionally, the design of the electrode and fuel cell plays a crucial role in increasing photocurrent density in bio-photovoltaic devices. The anode design, a critical step in water separation, and the cathodic design, where water is regenerated, must be carefully considered. Controlling the flow of electrons and protons within the cell, addressing issues such as other reactive species and electron recombination in the environment, is vital. Failure to manage these parameters may lead to reduced electron and proton transfer, consequently diminishing the photocurrent output of the fuel cell.

In bio-photovoltaic fuel cells, water is reduced on the anode surface to release oxygen and hydrogen, which are then recombined on the cathode surface, forming a closed loop. Two distinct designs for the cathode in bio-photovoltaic fuel cells are utilized. In the literature has got two bio-photovoltaic fuel cells developed by McCormick et al. (McCormick et al., 2011). In this study a closed-cell type where oxygen and hydrogen are separated from water on the anode side, and the isolated oxygen and hydrogen are transformed back into water on the cathode surface. Also, it has an air cathode in contact with air in cell. The key distinction in this cell type lies in the use of oxygen from the air while water is formed on the cathode side. A biofilm is developed on the ITO anode surface using *Chlorella vulgaris* and *Dunaliella tertiolecta* from the green algae species. Controlled conditions during biofilm formation facilitate a closer interaction between the anode and algae, resulting in higher photocurrents in bio-photovoltaic fuel cells. McCormick et al. conducted biofilm formation under controlled conditions for 30 days, during which they performed photocurrent measurements (McCormick et al., 2011).

Bio-photovoltaic fuel cells represent promising alternatives in renewable energy conversion systems, and ongoing research in this field signals continuous advancements. The developmental trajectory toward commercial and everyday applications is underway, suggesting that it may evolve into a prospective energy generation system in the near future.

- Cyanobacteria-based biological photovoltaic systems

The impressive diversity in cyanobacteria morphology is characterized by distinct variations, showcasing differences not only in single-cell or filamentous forms but also among different species. Cyanobacteria possess smaller cell sizes compared to algae, and their intracellular membrane structures are simpler than those of eukaryotic algae. In cyanobacteria, photosynthetic respiration unfolds within the chlorophyll pigments located in the cytoplasm. Concurrently, respiratory electron transport, NADPH generation, and ATP formation transpire within the thylakoid membrane, where chlorophyll pigments

are also present. Unlike higher plants, cyanobacteria house both photosynthetic and respiratory systems within the thylakoid membranes in the cytoplasm. Consequently, the surplus electrons generated during photosynthesis can easily interact with the cytoplasm, potentially leading to oxidative stress. Moreover, cyanobacteria employ specialized mechanisms to safeguard against photodamage caused by high light, enabling their survival in diverse ecological conditions (Cevik et al., 2018; Hasan et al., 2014, 2015; McCormick et al., 2011; Nishio et al., 2010; Yehezkeli et al., 2012).

Due to these distinctive characteristics, cyanobacteria serve as valuable photosynthetic biomaterials in bio-photovoltaic fuel cells. Additionally, their utilization in such systems eliminates the need for intricate isolation processes, providing a practical and versatile means of generating electricity from a new generation solar energy.

- Electron transport mechanism in cyanobacteria

Photosynthesis serves as the mechanism employed by plants and bacteria to convert light energy into chemical energy. The pivotal step involves the sunlight-induced splitting of water into oxygen and hydrogen during photosynthesis. In cyanobacteria, this process takes place within two complex membrane proteins known as PSI and PSII, or reaction centers, located in the thylakoid membrane within the cytoplasm. When photons from a light source reach the PSII reaction center (P680 protein complex), they are absorbed and elevate electrons to higher energy levels. These high-energy electrons are captured by electron acceptors (Qa and Qb) in the PQ complexes, then transferred to the cytochrome b₆f complex, and further conveyed to the PSI complex. The P700 reaction center, absorbing another photon, generates higher energy level electrons, which are transported by electron acceptors phylloquinone and ferredoxin to reduce NADP⁺ to NADPH, leading to ATP formation (Wey et al., 2019; Yehezkeli et al., 2013).

In the study conducted by Cevik and colleagues, ferrocene-cored poly(amidoamine) (PAMAM) dendrimers, denoted as FcPAMAM,

were utilized as soluble mediators, exhibiting a notable enhancement in photocurrent density within cyanobacteria. The investigation focused on elucidating the potential electron flow through the reaction center facilitated by FcPAMAM dendrimers. Additionally, hexacyanoferrate and p-benzoquinone (PBQ) were employed as alternative electron carriers in the same experimental context. In accordance with the initial hypothesis, the highest achieved photocurrent density was consistently observed in systems mediated by hexacyanoferrate and PBQ.

The electron transfer from cyanobacterial cell membranes to the electrode mediated by soluble mediators can be elucidated through three potential pathways:

(a) Direct Electron Transfer (DET): The commencement of electron transfer transpires at Photosystem II (PSII), progressing sequentially to Photosystem I (PSI) and culminating in the generation of NADPH. Water-soluble mediators, namely FcPAMAM, p-benzoquinone (PBQ), and hexacyanoferrate (FCN), exhibit the capacity to engage in molecular interactions with the respiratory system, capturing freely diffused electrons. The redox-active sites of these soluble mediators play a pivotal role in facilitating electron transfer from the photosynthetic reaction center to the electrode, as outlined in the relevant literature (Çevik et al., 2018).

(b) Electron Transfer from PSII Complex to the Electrode: Another plausible electron transfer pathway, involves PSII-PQ-cytb6f-(Mediator)-electrode, respectively. Soluble mediators can diffuse (depending on their sizes) and establish close interactions with complexes and the quinone pool, given that quinone complexes diffuse in the stroma and lumen (Haehnel, 1977).

(c) Potential Oxidation-Reduction Mechanism: The electron transfer process occurs during the formation of NADPH through the action of ferredoxin (FAD) from the cytb6F complex. Soluble mediators like ferricyanide ($[\text{Fe}(\text{CN})_6]^{3-}$) can be reduced by passing through the pores in the outer membrane, then react with these charged

molecules through the transmembrane proteins located in the cytoplasmic membrane (Çevik et al., 2018).

Cyanobacteria stand out as a preferred choice among photosynthetic organisms for harnessing sunlight in bio-photovoltaic fuel cells, owing to their exceptional productivity, suitability for direct electricity generation, and facile adaptation to diverse environmental conditions.

Several bio-photovoltaic fuel cell investigations employing cyanobacteria, including *Synechocystis* sp. PCC 6803 (Bombelli et al., 2011), *Shewanella oneidensis* (Gorby et al., 2006), *Leptolyngbia* sp. (Hasan et al., 2015), *Microcystis aeruginosa* (Bolch & Blackburn, 1996), and *Synechococcus* sp. PCC 7942 (Torimura et al., 2001), are documented in the literature. These studies predominantly employ redox mediators to facilitate the transfer of extracellular electrons to the electrode. Various mediators, such as hexacyanoferrate (FCN) and PBQ along with their derivatives, have been explored in bio-photovoltaic fuel cell research to enhance electron transfer efficiency (Hasan et al., 2014).

Light-induced bio-photovoltaic fuel cell assessments can be conducted through various cell configurations, such as the measurement of photocurrent density using a widely employed potentiostat device. In this arrangement, cyanobacteria are affixed to the electrode surface through physical adsorption and secured with a semipermeable dialysis membrane, which also serves as the anode in the system.

A standard 3-electrode measurement setup is employed in the reaction cell, comprising an Ag/AgCl reference electrode and a platinum plate counter electrode. To drive the photosynthetic water decomposition, a fiber optic light source is introduced into the system. On the anode surface, water undergoes reduction to produce oxygen and hydrogen, while the platinum electrode, functioning as the cathode, catalyzes the recycling of hydrogen and oxygen in the medium back

into water. The potentiostat is utilized to measure the electron flow resulting from the variance in the two reaction potentials.

To enhance the photocurrent density, diverse configurations of bio-photovoltaic fuel cells can be devised, and the photocurrent density is quantified employing a multimeter and fuel cell design as crafted by Fong-Lee et al. (Ng et al., 2014).

The induction of photosynthetic biomaterial onto the ITO, serving as the anode, facilitated biofilm formation, and photocurrent measurements were acquired using the DET method. Bio-photovoltaic fuel cells exhibit the capability to be interconnected in a serial arrangement, akin to battery systems, enabling the combination of multiple fuel cells to achieve elevated current densities. Fong-Lee and colleagues systematically evaluated the performance of bio-photovoltaic fuel cells fabricated and connected in series and parallel, reporting favorable outcomes (Ng et al., 2014).

The design of fuel cells at a reduced scale allows for high current density measurements on the same platform. However, in such systems, a structured environment must be established to maintain constant values of a nutrient medium within a fluid system, promoting the prolonged viability of photosynthetic organisms and the production of robust biofilms. While continuous fluid systems are optimal for achieving superior results, the integration of bioreactors introduces additional challenges platform comprising small-scale bio-photovoltaic systems devised by Lee and Choi (Lee & Choi, 2014). A continuous flow environment is facilitated by the microfluidic channels interconnecting the fuel cells in series. This setup enables the continuous monitoring of environmental conditions and growth parameters for cyanobacteria.

In the composite fuel cell constructed through the air cathode method, carbon served as the anode material. Subsequent to the formation of a biofilm on the carbon surface, measurements were conducted using the DET method.

In cyanobacteria-based bio-photovoltaic fuel cells, both lipid-soluble polymers and chemical soluble ionics are utilized, similar to algae-based systems. The presence of electron respiratory membranes in the cytoplasm makes cyanobacteria more amenable to electrochemical mediator binding than algae. Lipid-soluble polymers establish interactions with the extracellular membrane, anchoring cyanobacteria to the electrolyte. Given the smaller size of ionic hexacyanoferrate and quinone structures, they can effectively reach the reaction center proteins. Consequently, the anode in the bio-photovoltaic cell facilitates a higher electron transfer rate, resulting in an elevated photocurrent density. In a noteworthy study, Hasan et al. achieved mediated electron transfer using an osmium-derivative polymer in a bio-photovoltaic fuel cell featuring *Leptolyngbia* sp. The polymer and cyanobacteria were immobilized onto the graphite electrode through the physical adsorption method, and light energy was efficiently converted into electrical energy using a fiber optic light source.

The body of research on energy conversion systems involving cyanobacteria and algae, specifically bio-photovoltaic fuel cells, is expanding steadily. Ongoing investigations aim to achieve enhanced photocurrent density and sustainable systems. In conjunction with innovative cell and electrode designs, efforts are directed toward mitigating factors that impede efficient electron transfer. During photosynthesis, the splitting of water generates reactive organic species (ROS) in addition to oxygen and hydrogen, especially in conditions of high light intensity and prolonged exposure. This heightened ROS release induces cellular stress and diminishes photosynthetic activity (Sharma et al., 2012).

- Eliminating ROS from reaction centers

Throughout the photosynthesis process initiated by light, the concentration of Reactive Oxygen Species (ROS) within the membrane environment experiences an elevation. ROS includes singlet oxygen (O_2), superoxide (O_2^-), hydroxyl radicals (OH^\cdot), and hydrogen peroxides (H_2O_2) resulting from the breakdown of water molecules by

PSII (Sharma et al., 2012). The presence of ROS adversely affects the reaction center environment and proteins, leading to the destruction or inhibition of the electron transfer mechanism's efficiency and functionality. Hydroxyl and singlet oxygen radicals, known for their high reactivity, induce the oxidation of lipid layers. Although superoxide and hydrogen peroxide are less harmful in comparison, they can still penetrate the membrane, causing significant damage to cells and disrupting the respiratory electron transfer chain (Mubarakshina et al., 2006). Enzymes like Superoxide Dismutase (SoD) and Catalase (Cat) play a crucial role in neutralizing superoxide radicals and hydrogen peroxide, converting them into O_2 and H_2O , thereby shielding cells from radical attacks (Matsumoto et al., 1991). In studies conducted by Cevik et al. and Hasan et al. (Hasan et al., 2014), SoD and Cat were employed to enhance the photocurrent density from photosynthetic microorganisms by safeguarding against ROS. The findings indicated a substantial increase in photocurrent density—65% and 30%, respectively—compared to the control after the addition of SoD and Cat (Hasan et al., 2014).

The augmentation in photocurrent density is attributable to the reaction facilitated by Superoxide Dismutase (SoD) and Catalase (Cat), which contribute to the destruction or conversion of Reactive Oxygen Species (ROS) into a harmless form. Moreover, the enhanced photosynthetic stability achieved through the use of SoD and Cat surpasses that of the control electrode, elucidating the enzymatic breakdown of ROS. However, it's important to note that the relatively short lifespan of enzymes (Hsu et al., 1986) might have limited their efficacy in safeguarding algae and cyanobacteria cells from ROS during prolonged measurements.

v. Future Perspective

Environmentally friendly applications hold greater significance than contemporary industrialized technologies. In this context, nanotechnology-based Bio-Photovoltaic (BPV) systems emerge as a boon for mitigating environmental pollution. Nanotechnology is primarily harnessed to enhance the efficiency of current systems and

position them as potential devices for future applications. An exemplary instance involves the fusion of superconductive nanomaterials with BPV systems, paving the way for a novel and promising area of research. Furthermore, in the realm of intelligent energy generation and storage, the utilization of batteries, micro-batteries, and supercapacitors represents additional domains where BPVs will find application. Anticipated future studies on super-bio-capacitors suggest that BPV systems could be employed more efficiently. Additionally, tailored BPV systems designed for LED lighting and battery charging are poised to emerge as imminent applications.

CONCLUSION

This chapter underscores the significance of nanotechnology in Bio-Photovoltaics (BPVs), solar energy conversion systems that generate electricity through photosynthesis reactions occurring in the thylakoid membrane. Researchers have extensively explored the process of harvesting energy from BPVs to develop highly efficient systems. Numerous reports have been published on BPVs, focusing on both direct and indirect electricity generation utilizing soluble conductive mediators, demonstrating successful results in converting sunlight into electricity. However, there remains room for improving efficiency. The integration of nanomaterials with BPVs has exhibited remarkable enhancements in power output. Nanotechnological advancements in BPV systems initially focused on creating functional surfaces to better incorporate biological components into electrodes. The increased efficiency of anode and cathode electrodes in applications, owing to a large surface area-to-volume ratio, represents another key improvement. The application of nanomaterials such as carbon nanotubes and graphene has been studied extensively in both small and large-scale BPV applications, emphasizing the significance and utilization of green energy production. The well-known electron transport mechanism in cyanobacteria and algae has been leveraged to transform newly designed systems into photovoltaic devices through nanomaterial incorporation, demonstrating improved energy conversion

rates in BPV systems. The ongoing studies suggest that nanotechnology will further enhance energy exchange rates, paving the way for industrial applications.

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CHAPTER 3

BIOACTIVITY OF N-SUBSTITUTED CYCLIC DERIVATIVES OF THIOUREA AND PHENYLTHIOUREA: FROM SIMPLICITY TO COMPLEXITY

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INTRODUCTION

Multicomponent reactions (Zhu&Bienayme, 2005; Domling, 2005) are usually considered as a process where three or four reagents are combined in one phase. They are synchronous reactions and create obstacles to accurately determine the intermediates which are intermediate phase. The organic substances obtained through these reactions are very difficult and multi – stage to synthesize by other methods. The most interesting point is that the compounds obtained by this method are polar molecules and bioactive substances. They are widely used in the synthesis of heterocyclic compounds that comprise the major constituents of medicines (Kappe, 2000; Armstrong et al., 1996). Fine organic synthesis, as well as these reactions of great importance in medical chemistry ensure the direct intramolecular interaction of complex molecules (Weber, 2002; Domling, 2006). According to comparative studies conducted, as the combination of three components is sufficiently profitable in terms of creating new products at one phase, such type of reactions is considered to be the most useful one among multi component reactions (Tietze & Rackelmann, 2004; Ugi et al., 2003).

The first reaction of three components at a single phase, as it is known, was conducted by Italian chemist Petro Biccinelli and included into the world literature under the name “Biccinelli condensation”. This chemical reaction reflects the synthesis of 3,4-dihydropyrimidine-2(1H)-ones based on urea, ethyl acetoacetate and benzaldehyde (Biginelli, 1893). Although the Biccinelli reaction approach for the synthesis of dihydropyrimidine 2(1H)-ones varies, these methods are nevertheless applicable in the case of specifically substituted aromatic and aliphatic aldehydes despite certain challenges including low efficiency and a lengthy reaction time. Nevertheless, despite these challenges and the fact that 125 years have passed since the single-phase three-component condensation method was first applied, interest in this field of study has not decreased on the contrary, it has grown, and the aforementioned area has expanded significantly with the use of all three components. All things considered, there are a lot of patents

and scholarly articles about "Bicinelli condensation" that have been published recently. In this review article presented, the scientific and practical results of research conducted in this area for near 5-10 years are preferred.

Enzymes are biological catalysts that accelerate chemical reactions in living organisms and provide a 100% product yield without allowing any byproducts to form. Most of these biological catalysts have a protein structure and are not affected by the chemical reaction that occurs (Tokalı et al., 2023; Bayrak et al., 2023). In other words, there is no change in the structure of the enzymes as a result of the reaction. In addition, enzymes are macromolecules synthesized by living cells. Enzymes, which also have regulatory properties, play a role in the occurrence of reactions by exhibiting maximum activity under optimal conditions. Enzyme catalysis is far superior to chemical catalysis. Except for catalytic RNA molecules (Ribozymes), which have a catalytic function but are not in protein structure, all enzymes are substances in protein structure. They constitute the largest and most specialized group of proteins. Since enzymes with a protein structure are encoded by DNA, all events in cells are regulated and controlled at the DNA level. Enzymes work specifically and have three important aspects in terms of catalysis; They are specific, chemoselective and extremely fast. Biochemical reactions occur at low energy and body temperature (Alagöz et al., 2023; Basri et al., 2023). In these aspects, enzymes differ from other catalysts. The substances on which enzymes act are called "substrates". One of the most important areas of research on enzymes is the inhibition properties of enzymes. The region that allows the formation of the enzyme-substrate complex includes only a certain region of the enzyme. Because enzymes are large, whereas substrates are small molecules. In this case, a region on the enzyme is needed where the substrate is bound and finally converted into the product, and this region is called the "active site". At least one amino acid plays a specific role in the active site. Substances that affect the formation of the enzyme-substrate complex and reduce enzyme activity

are called "Enzyme Inhibitors", and this phenomenon is called "Enzyme Inhibition"(Tokalı et al., 2023).

Enzymes that catalyze the entry of a water molecule into esters to form acids and alcohols are esterases, which belong to the hydrolases class. The biological functions, substrate and protein structures of esterases vary. Esterases can be divided into four main groups according to the type of reaction they catalyze: Acetyl esterases: This group of esterases are generally effective on aliphatic substrates. Ex. Acetic acid. Aryl esterases: The esterases in this group are inhibited by inhibitors bearing sulfhydryl groups and are effective on aromatic substrates (Tokalı et al., 2023; Celik et al., 2023). Carboxyl esterases: They are inhibited by organophosphors (OPs) and are effective on longer chain aliphatic groups than acetic acid. Ex. Butanoic acid. Cholinesterases: Organic phosphorus compounds irreversibly suppress cholinesterase. The findings reflect the accumulation of acetylcholine in nerve endings. In addition to aliphatic esters, they also choose choline esters as substrates. Acetylcholine is a neurotransmitter substance, which is the acetyl ester of choline, secreted from the synapses of autonomic ganglia and the ends of nerve fibers lining the skeletal muscle (Tuzun et al., 2023). Acetylcholinesterase (AChE; EC 3.1.1.7) is a nonspecific enzyme that hydrolyzes acetylcholine, which has a lipotropic effect and is found free or combined with phospholipids in tissues. Acetylcholine is an ester of great biological importance, which not only carries nerve impulses from the nerve endings to the organ it affects, or from the nerve ending to a second nerve cell, but also enables the generation of bioelectrical current along nerve and muscle fibers. Acetylcholinesterase (AChE) inactivates acetylcholine in the synaptic cleft. In other words, acetylcholinesterase cleans up the mess by breaking down the chemicals accumulated in front of the nerve ending and removing them from there. Thus, no possible disruption in nerve conduction occurs (Behcet et al., 2023). Cholinesterases have been defined as enzymes that hydrolyze choline esters. As a result of research carried out at different substrate concentrations, it was determined that there are two types of

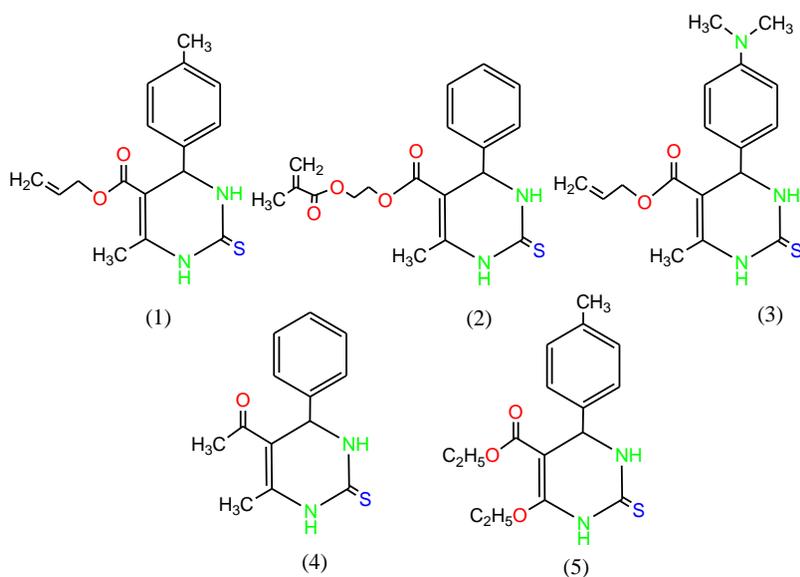
cholinesterase enzymes with kinetically different properties. The first of these is true (Acetylcholinesterase) cholinesterase, which exhibits high activity at low substrate concentrations but is inhibited at high substrate concentrations and is localized in human erythrocytes. The second enzyme is Pseudocholinesterase (Butyrylcholinesterase), whose activity increases as the substrate concentration increases and is localized in human serum. As a result of subsequent studies, it was determined that real cholinesterase in erythrocytes hydrolyzes only choline esters, while pseudocholinesterase in serum also hydrolyzes ester molecules that are not in the choline structure. As a result, cholinesterases take control of the cholinergic system by destroying acetylcholine, a neurotransmitter, by releasing it from cholinergic synapses. Butyrylcholinesterase hydrolyzes both butyrylcholine and acetylcholine, but hydrolyzes butyrylcholine more rapidly. The pH range in which cholinesterases show the best activity is the physiological pH range (Yalazan et al., 2023; Gumus et al., 2023).

Carbonic anhydrase (CA; Carbonate hydrolyase, EC 4.2.1.1) is a metalloenzyme that contains metal ions and reversibly catalyzes the hydration of CO_2 and dehydration of HCO_3^- . Carbonic anhydrase was first purified from bovine erythrocytes. CA enzyme was found first in vertebrates and mammals, and later in higher plants, algae and some bacteria. In humans, CA is present in tissues such as the stomach, intestinal tract, nervous system, reproductive system, lungs, kidneys, skin and eyes. In the 1940s, Keilin and Martin reported that sulfonamides inhibited carbonic anhydrase (Huseynova et al., 2022). Despite this, the isolation studies of carbonic anhydrase yielded results after four years. This enzyme is one of the most active enzymes found in nature and is found not only in mammals but also in other animals and plants. In humans, it is found in tissues such as brain, lung, stomach, pancreas, liver, kidneys, muscle tissue and especially red blood cells. It is one of the most important buffer systems in the human body. CA is a very important enzyme that not only enables the CO_2 formed during respiration to be dissolved in water, transported and eliminated from the body, but also plays a role in many physiological

events such as acid-base balance, ion exchange and regulation of the cardiovascular system (Guzel et al.,2022; Aggul et al., 2022).

1. N-alkyl(aril)tetrahidropirimidinthiones

Based on these models, a variety of biologically significant reactions are studied. The most crucial components in the targeted production of pharmaceuticals with physiological effects are thioureas. Organic substances containing a sulfur atom are known as thioureas. Among all the classes of organic compounds, none is as versatile and has as many uses as thioureas. Thiourea, in fact, has a remarkable impact on practically all areas of chemistry (Shakeel& Altaf,2016; Schroeder, 1955). They are very important from a commercial, industrial, and scientific standpoint. Commercial applications for thioureas include textiles, elastomers, polymers, dyes, and photographic film (Mertschenk et al.,2000; Schreiner, 2003). Thioureas are employed as intermediates in several organic synthetic processes and have important applications in organic synthesis (Alcolea et al.,2016). The biological activity of thioureas, which makes them useful in both industry and medicine, is another noteworthy characteristic. Thioureas are therefore employed in agriculture as a herbicide (Shuxian& Yangang, 2003), as a booster against the growth of hazardous fungi (Wu et al.,2012), as a booster against insects (Tunaz& Uygun, 2004), and as a booster for plant germination and root development (Yaova et al.,1997; Shuxian& Yangang, 2003). Infections (D’Cruz& Uckun, 1999), antivirals, antioxidants (Venkatesh& Pandeya, 2009), antidepressants, antiallergatives (Hargrave et al.,1983), antibacterials, anti-inflammatory (Sondhi et al., 2000), antiepileptic (Love et al.,1972), and anti-cancer are among the medical conditions for which thioureas are utilized (Maddani &Prabhu, 2010). N-alkyl(aril)tetrahidropirimidinthiones (1-5), which are cyclic thiocarbamides derivatives, were synthesized from thiourea, β -diketones and substituted benzaldehydes (Scheme 1).



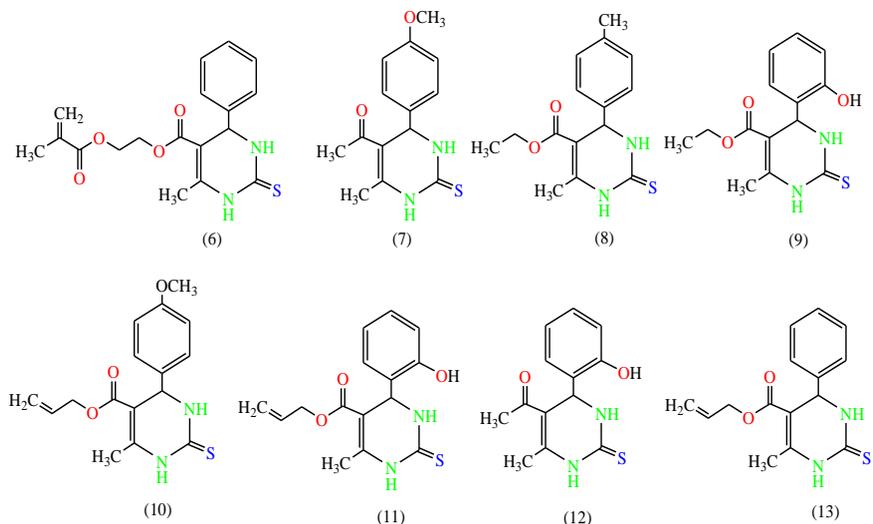
Scheme 1. N-alkyl(aryl)tetrahydropyrimidinethiones

These compounds take on a tautomeric form that includes the thiol functionality, which is known to interact with metal ions from the active sites of metalloenzymes, including the carbonic anhydrases (CAs, EC 4.2.1.1) and other enzymes. This superfamily of widely distributed enzymes is responsible for catalyzing the reversible hydration of carbon dioxide to bicarbonate and protons (H^+), an important metabolic activity. The cytosolic human isoforms I and II (hCA I and II) were evaluated for inhibition by the recently synthesized N-alkyl(aryl)tetrahydropyrimidine thiones. The newly synthesized thiones successfully blocked both isoforms. For hCA I and hCA II, respectively, the range of K_i values was 218.5 ± 23.9 – 261.0 ± 41.5 pM and 181.8 ± 41.9 – 273.6 ± 41.4 pM. The field of non-sulphonamide CA inhibitors may benefit from the intriguing insights this understudied class of compounds may provide (Sujayev et al., 2016).

2. 4,5-disubstituted-2-thioxo-1,2,3,4-tetrahydropyrimidines

Synthesis of 4,5-disubstituted-2-thioxo-1,2,3,4-tetrahydropyrimidines (6–13) was carried out using β -diketones,

thiourea, and aromatic aldehydes, including benzaldehyde, p-anisaldehyde, o-tolualdehyde, and salicylaldehyde (Scheme 2).



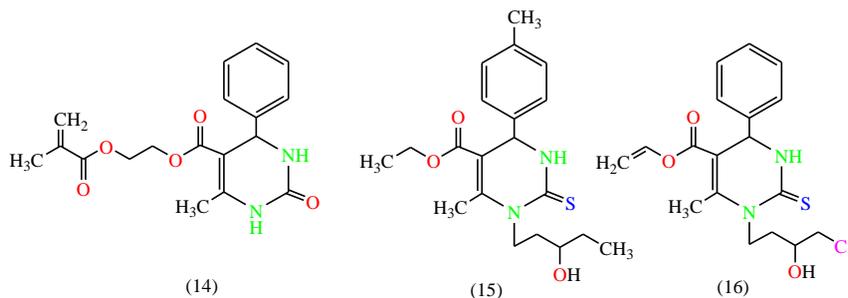
Scheme 2. 4,5-disubstituted-2-thioxo-1,2,3,4-tetrahydropyrimidines

The current study's cyclic thioureas (6–13) showed potent inhibitory patterns against the hCA isoforms, AChE, and BChE enzymes. Furthermore, these substances showed potent antioxidant properties in various bioassays. These substances were shown to be potential inhibitors of the enzymes AChE and BChE as well as CA isoenzymes. All heterocyclic thioureas (6–13) in this investigation showed nanomolar K_i values; these substances have the ability to selectively inhibit cytosolic CA I and II isoenzymes as well as AChE and BChE enzymes. They can also be applied as novel antioxidants in the pharmaceutical business, among other fields (Garibov et al., 2016).

3. Some tetrahydropyrimidine-5-carboxylates

The required cyclic urea was produced via the reaction of substituted benzaldehyde with methylene active substances, such as 2-(methacryloyloxy) ethyl acetoacetate and urea, in the presence of TFAA (14). We have offered the transformation of the acquired compounds at the following stage. Thus, allyl 1-(3-chloro-2-

hydroxypropyl)-4-metil-6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate was produced by the reaction of epichlorohydrin (15). In parallel, ethyl 1-(2-hydroxybutyl)-4-methyl-6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate was synthesized by the reaction of 1,2-epoxobutane (16) (Scheme 3).

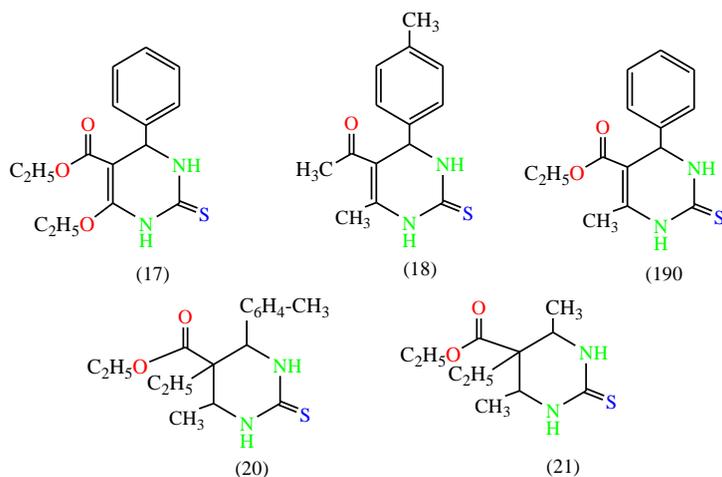


Scheme 3. Some tetrahydropyrimidine-5-carboxylates

The present study's novel tetrahydropyrimidine-5-carboxylates (XIV–XVI) showed potent inhibitory patterns against the hCA isoforms, AChE, and BChE enzymes. These substances also showed promising metal chelating abilities. It was possible to identify the probable CA isoenzymes and AChE and BChE enzyme inhibitors in novel tetrahydropyrimidine-5-carboxylates (XIV–XVI). All of the novel tetrahydropyrimidine-5-carboxylates found in this work have K_i values at the nanomolar level, and these compounds had the ability to selectively inhibit the cytosolic CA isoenzymes as well as the enzymes AChE and BChE. In related applications, they can also be employed as metal chelators (Sujayev et al.,2016).

4. Tetra(hexa)hydropyrimidinethione-carboxylates

An effective technique for producing tetra(hexa)hydropyrimidinethione-carboxylates (17–21) in the presence of trifluoroacetic acid (TFAA) is based on the three-component condensation of thiourea with its various aldehydes and β -diketones (Scheme 4).

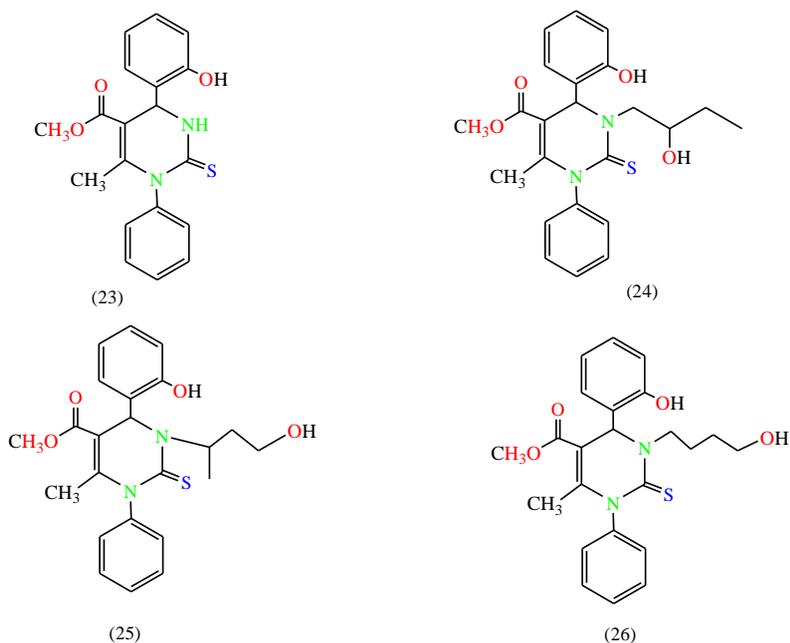


Scheme 4. Tetra(hexamethyl)hydropyrimidinethione-carboxylates

The novel cyclic thioureas (17–21) employed in this investigation were found to be efficient inhibitors of cholinesterase enzymes (AChE and BChE) as well as hCA isoforms (hCA I and II). All new cyclic thioureas (1–5) were found to have nanomolar K_i values in this study, and these compounds have the ability to selectively inhibit the cytosolic CA isoenzymes as well as the AChE and BChE enzymes. However, these compounds exhibited efficient metal-chelating capabilities and can be applied as metal chelators in associated fields (Farzaliyev et al., 2017).

5. N-substituted derivatives of phenylthiourea

An effective method has been developed for the synthesis of 1-(4-(2-hydroxyphenyl)-6-methyl-1-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone (22) in the presence of trifluoroacetic acid, based on the three-component condensation of phenylthiourea with its salicylaldehyde and methyl-3-oxobutanoate (Scheme 5).

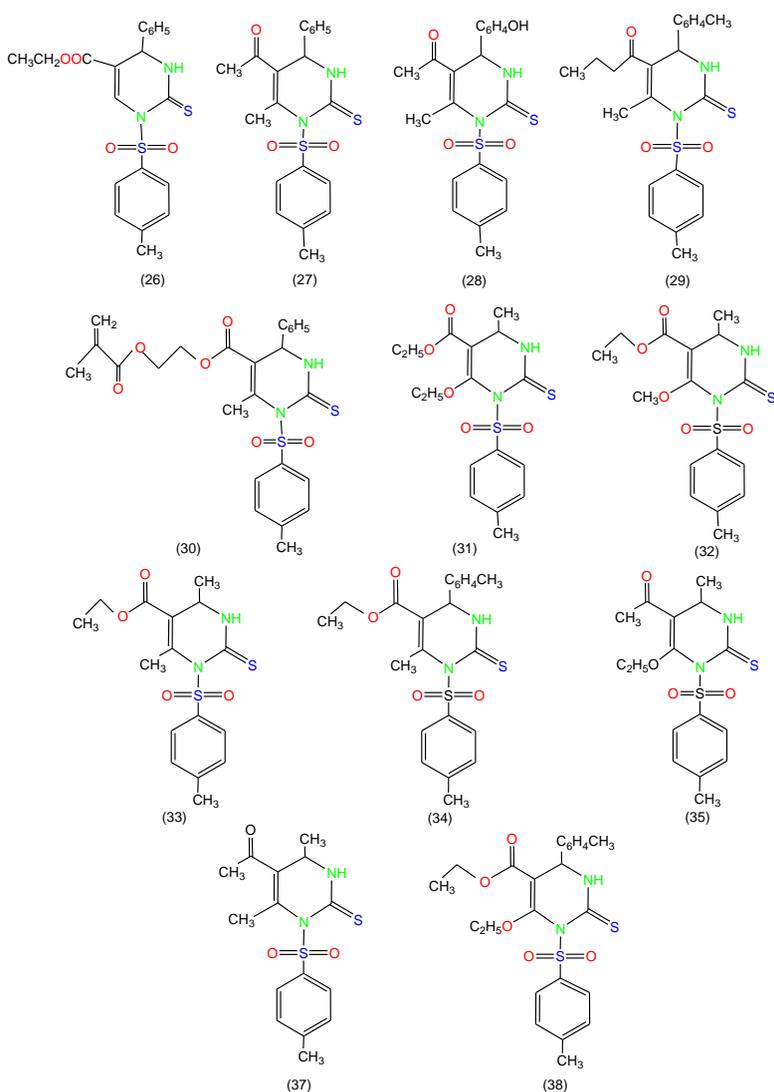


Scheme 5. N-substituted derivatives of phenylthiourea

All of the novel N-substituted tetrahydropyrimidines based on phenylthiourea (23–25) had their nanomolar level of K_i values determined in this study. These derivatives can selectively inhibit α -glycosidase, AChE, and both cytosolic CA enzymes and isoenzymes. As a result, these compounds have potential uses in the pharmaceutical sector as new inhibitors. As previously mentioned, new N-substituted tetrahydropyrimidines derived from phenylthiourea (23-25) may be a promising therapeutic option for the management of a number of illnesses, including epilepsy, glaucoma, neurological disorders, gastric and duodenal ulcers, and mountain sickness. Additionally, as CAIs for osteoporosis, α -GLYIs for diabetes, and AChEIs for the treatment of AD and PD (Gariboy&Gojaeva, 2012).

6. Hetarylsulfonamide derivatives of thiourea

Hetarylsulfonamide derivatives of thiourea (26-37) were synthesized from different tetrahydropyrimidinethiones and aryl sulfonyl chloride (Scheme 6).



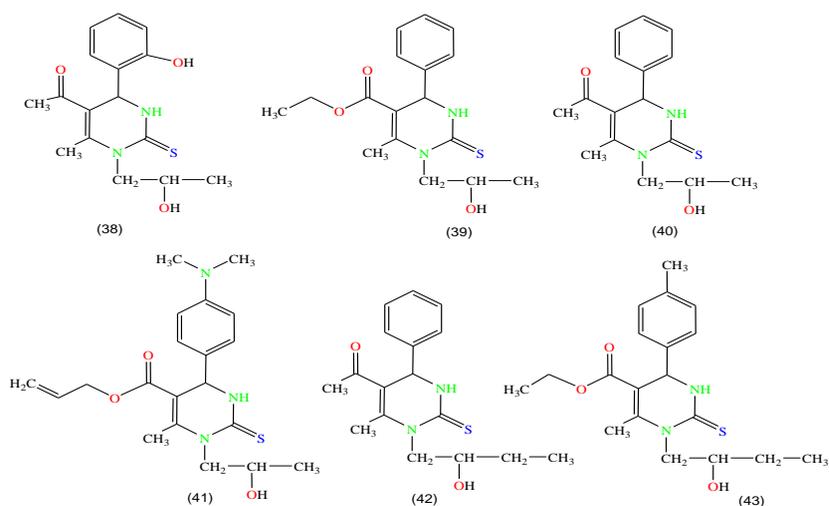
Scheme 6. Hetarylsulfonamide derivatives of thiourea

These compounds were examined for their ability to chelate metals and to identify the time interval during which inhibition of carbonic anhydrase (CA) isozymes I and II (hCA I and II), butyrylcholinesterase (BChE), and acetylcholinesterase (AChE) occurred between two physiologically relevant compounds. High levels of AChE were found in red blood cells and the brain. In this study, we concentrate on novel hetaryl sulfonamides (26-37) that demonstrated potent inhibitory profiles against hCA isoforms as well as BChE and

AChE enzymes. Since this common sulfonamide inhibitor has anticonvulsant qualities, we also defined the AZA data. Furthermore, the compounds' IC₅₀ values were examined; compound 8 proved to be the most effective inhibitor of hCA II. The AChE and BuChE enzymes both hydrolyze ACh and show that AChE levels are preserved in AD patients. The main pharmacological target in this study for controlling AD symptoms has been the AChEIs. Additionally, the amino acid sequences of human AChE and BuChE are comparable by 65%. Additionally, these substances demonstrated efficient metal chelating action when ferrozine and Fe²⁺ ions were present (Sujayev et al., 2018).

7. Conversion productions of tetrahydropyrimidine thiones with epoxides

Although the chemical conversion of epoxides with different organic compounds has been widely studied, their reactions with cyclic thioureas – pyrimidine thiones have not been investigated so far. Pyrimidine-containing compounds for each species physiologically active substances that Taking into account the fact that the compounds containing pyrimidine are every type of physiological active substances, certain scientific and practical investigations were conducted on these compounds which cannot be found in world literature data and need detail research, the impact of functional groups in their composition was studied and dependence among the composition, structure and functional properties of new substance was determined. Thus, nucleophilic substitution reactions of 1,2-epoxypropane and 1,2-epoxybutane pyrimidinethiones were conducted and new compounds were obtained (38-43) (Sujayev, 2016). The general reaction scheme is as follows:



Scheme 7. Conversion productions of tetrahydropyrimidine thiones with epoxides

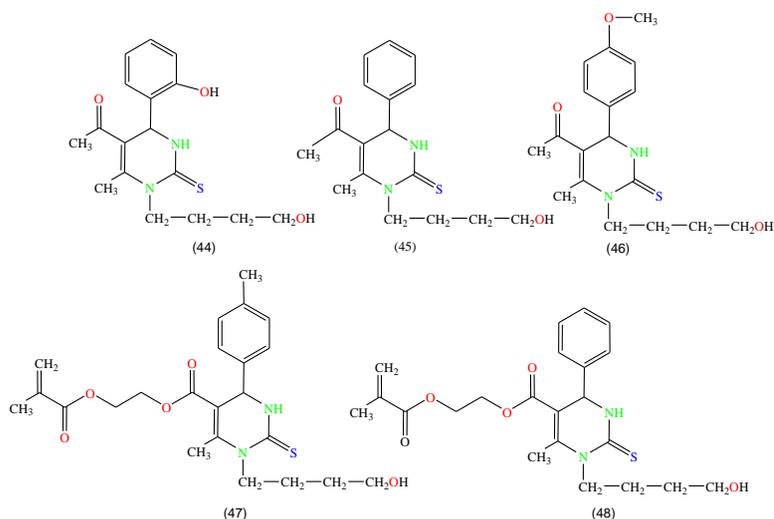
It has been noted that the nucleophilic substitution and elimination reactions are more common in organic synthesis. In this study, it is assumed that the reactions refer to nucleophilic substitution reactions. In the nucleophilic substitution reactions, loaded and unloaded particles may act in several different combinations as reagents. In the synthesis conducted, such a solvent was chosen that the nucleophilic reagents could be completely solved for the reaction to occur rapidly. In some reactions, the solvent used caused certain difficulties in the elimination of the resulting product from the reaction environment unless the original substances are well mixed together. In this nucleophilic conversion reaction, the substitution occurs in the position N1, but not N2. As in the position N2, the nitrogen atom is surrounded by phenyl radicals and thione (C=S) fragment, which creates spatial difficulty and the length of communication is shortened. Therefore, the nucleophilic reagent cannot enter there in practice. However, as the length of communication N-H is greater in the position N1, the substitution occurs in the same position.

Drugs that block AChE have recently become available for the treatment of AD, myasthenia gravis, and other illnesses. The new pyrimidine-thiones (38–43) that were employed in this study

demonstrated effective documented inhibition profiles against the AChE enzyme as well as the hCA isoforms. All of the novel pyrimidine-thiones (38–43) had their nanomolar level of K_i values evaluated in this investigation, and these compounds have the ability to selectively inhibit AChE and other cytosolic CA isoenzyme enzymes. These substances can therefore be applied as innovative inhibitors in the pharmaceutical sector, among other fields. As previously mentioned, new pyrimidine-thiones (38–43) represent promising candidates as medications for the treatment of several conditions, including osteoporosis, neurological disorders, glaucoma, epilepsy, gastric and duodenal ulcers, mountain sickness, and AD and PD as AChEIs (Farzaliyev et al., 2017).

8. N-Substituted derivatives of thiourea with 4-Chlorine-Butanol-1

The reaction of tetrahydropyrimidine thiones synthesized by known method with 4-chlorine-butanol-1 as nucleophilic reagent was conducted. The process was performed in 1:1:1 mol ratio of the initial substances in acetylacetone and ethyl alcohol environment. The triethylamine was taken as a catalyst and the compounds (44-48) were synthesized with an output of 65-70% as a result of the reaction (Scheme 8).



Scheme 8. N-Substituted derivatives of thiourea with 4-chlorine-butanol-1

The reaction occurs at the expense of the active hydrogen atom in the NH group. The activity of the hydrogen atom of this group is related to the electrone-acceptor properties of the carbonyl group in the pyrimidine ring and the radical in the fourth position (Taslimi et al., 2018).

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CHAPTER 4

SULFONAMIDE INHIBITORS AS POTENTIAL TREATMENTS OPTIONS FOR ACUTE MYELOID LEUKEMIA

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INTRODUCTION

The request for a new chemotherapeutic anticancer remains marvelous in the field of medicinal chemistry. The recording of sulfonamide compounds as anticancer and antibacterial in the early 30s was the starting of the most fascinating era of chemotherapeutic factors. Since the preface of prontosil over 90 years ago, sulfa drug molecules have been extensively utilized to therapy a broad spectrum of cancer or microbial diseases (Akıncıoğlu et al., 2014; Gokcen et al., 2016). Hence, due to the rapid emergence of sulfonamide resistor organism cells and the extension of more potent drugs have limited their clinical utility. Indeed, the sulfonamide family is recorded as a pharmacophore factor that is present in plenty of biologically active compounds, particularly in anticancer or antimicrobial factors (Gokcen et al., 2016). Multiple sulfonamide derivatives have broad biological activities such as anticancer, antifungal, antiglaucoma, anti-obesity, antidiuretic, antibacterial, antiepileptic and anti-inflammatory factors (Gul et al., 2016; Bilginer et al., 2020). However, one of their biological functions is carbonic anhydrase isoenzyme inhibitors (CAIs), which linked to anti-glaucoma agents, diuretics, and antiepileptics, in the management of duodenal ulcers, gastric, osteoporosis, and mountain sickness, neurological disorders, and idiopathic intracranial hypertension (Boztas et al., 2015; Yigit et al., 2018). Also, it is well known that some sulfonamide derivatives had antiacetylcholinesterase and antibutyrylcholinesterase activities (Taslimi et al., 2017; Yamali et al., 2020) with low cytotoxicity towards oral squamous cancer cell carcinoma cell lines (Ozmen Ozgün et al., 2019) and antioxidant abilities (Taslimi et al., 2017). Antioxidants are active compounds that inhibit lipid peroxidation and production of free radical species (Gulcin, 2006; Gulcin, 2009), thereby leading to chain reactions that may damage the cells of organisms (Gulcin, 2010; Gulcin, 2020). It was reported that they have acts as effective lactoperoxidase (Koksal et al., 2017), α -glycosidase (Lolak et al., 2020) and glutathione S-transferase (Taslimi et al., 2020) inhibitors linked to some global diseases. Sulfonamide derivatives represent a significant group of

medicinally key compounds and are known to having extensive varieties of biochemical activities that contain antibacterial drugs, saluretics, CAIs, antithyroid factors, anticancer drugs (Bayrak et al., 2019; Boztas et al., 2019). Sulfonamides remain the most extensively utilized anticancer or antibacterial factors in the world because of their low toxicity, low cost, and wonderful activity against popular bacterial diseases. Also, the anticancer and antimalarial activity of diverse benzenesulfonamides is also recorded (Boztas et al., 2019). A potent inhibitor of Pfmrk, a cyclin-dependent protein kinase (CDK) from *P. falciparum*, is isoquinoline sulfonamide. Indeed, sulfonamides are the basis for diverse drug classes, considered as sulfa drugs (Daryadel et al., 2018). Sulfonamide derivatives include sulfonamide scaffold (SO_2NH_2) in its chemical structure (Figure 1). These molecules have gained much attention due to their several biochemical processes in pharmaceutic and agricultural regions. The key sulfonamides of the type RSO_2NH_2 (where R may be an aromatic, heterocyclic, and aliphatic moiety) constitute a considerable group of drugs, comprising several kinds of pharmacological agents possessing anti-CA, diuretic, antibacterial, antiviral, protease inhibitory, cyclooxygenase 2 (COX2) inhibitory, and among others. These molecules are also utilized in the therapy of meningitis, conjunctivitis, streptococcal pharyngitis, trachoma, malaria, bacillary dysentery, toxoplasmosis, and nocardiasis (Erdemir et al., 2018; Genc Bilgili et al., 2019).

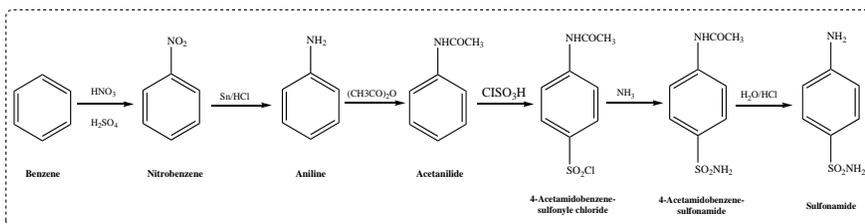


Figure 1. General synthesis route of simple sulfonamide as scaffold of sulfonamide derivatives

AML is a disease as genetically heterogeneous in plenty of molecular alterations and recurrent genetic are predictive of an answer

to therapy. Most patients were recently treated with traditional therapy, and the only medication used in clinical practice was all-trans retinoic acid (atRA), which is effective in treating a subset of AML patients whose retinoic acid (RA) receptor rearrangements are detected (Wang et al.,2017; Tallman et al., 2019). Clinical trials failed to demonstrate the therapeutic efficacy of atRA, despite the fact that it enhanced blast cell separation and was initially noted to have important anti-leukemic potential in AML lacking Retinoic acid receptor alpha (RARA) rearrangements. Indeed, AML is a root cell-driven disease that recently addressed the effect of atRA on leukemic cells and recorded that it varied extensively depending on the identification of the relative driver lesions. Pending the search for new drugs against AML, diverse drug aims have emerged (Patel et al.,2012; Papaemmanuil et al., 2016). Between the successful are the progressive multifocal leukoencephalopathy (PML)-RARA fusion protein for acute promyelocytic leukemia, all-trans retinoic acid has become the control treatment and the Fms-like tyrosine kinase-3 (FLT3), with various drugs aimed at the active mutant. Indeed, one class of proteins recorded as potential AML drug aims are the Moloney murine leukemia virus (PIM) and Moloney murine leukemia virus-1 (PIM1) kinases. PIM1 kinase enzyme plays a key role in diverse oncogenic pathways such as cell survival and cell cycle progression and is also radial in hematopoiesis (Marcucci et al.,2014; Marcucci et al.,2011). Hence, PIM1 enzyme is considered in multiple cancers, containing leukemias. For instance, the AML process involves an increased level of the enzyme lysine-specific demethylase 1 (LSD1), especially in poor-differentiated AML that has chromosomal translocation. To overcome the separation blockage in AML, a combination of LSD1 inhibitors and all-trans retinoic acid has been administered. (Li et al., 2013). As a result, targeting the LSD1 enzyme is becoming essential for treating AML. The majority of the sulfonamide class is used in drug development, and several of the planar amides have a tetrahedron-shaped three-dimensional structure (Groschel et al., 2013). In this chapter, we examined the effects of a few sulfonamide derivatives on AML therapy candidates, including tyrosine kinase (TK), FLT3,

histone deacetylase, LSD1, sphingosine kinase, MCL1, and CA isoenzymes.

1. FLT3 inhibitors and acute myeloid leukemia in recent decade

AML is frequently associated with mutated genes that encode the kind III receptor tyrosine kinase FLT3. Five immunoglobulin-like extracellular domains and transmembrane domains make up FLT3's significant structural components. Hematopoietic cell differentiation, proliferation, lymphocytes, and apoptosis are all significantly influenced by the FLT3 enzyme. Mutations in FLT3 typically result in aberrant activation; autophosphorylation triggers downstream signaling pathways when ligands are not bound by lymphocytes, causing aberrant proliferation of hematopoietic cells and a variety of hematological malignancies, including AML (Pratz et al., 2010; Piloto et al., 2007). The FLT3 enzyme has two main types of mutations: internal tandem duplication (ITD) mutations in the juxtamembrane domain and point mutations in the activation ring of the TK domain. When compared to other forms of AML, the FLT3-ITD mutation is linked to poor anticipation. According to certain studies, aberrant FLT3 enzyme activation is linked to one-third of AML patients (Sato et al., 2011; Weisberg et al., 2012). Furthermore, a variety of anti-AML inhibitors, such as the first-generation FLT3 inhibitors Sunitinib, Dovitinib, Sorafenib, and Lestaurtinib, have entered the market. Only a small percentage of AML patients will experience a decrease in peripheral blood and bone marrow blasts when using TK inhibitors of the FLT3 enzyme as AML monotherapy, and these effects are typically temporary (Zhou et al., 2009).

1.1. Sulfonamide derivatives and FLT3 inhibitors

The Flt3 enzyme was found to be an oncogenic kinase involved in multiple leukemias in one study. It is most commonly connected to AML. Promising outcomes have been observed when FLT3 inhibitors disrupt AML. Novel sulfonamide-based FLT3 inhibitors were

synthesized by using the crystal structures of two inhibitors complexed within FLT3, namely F6M and quizartinib (Larrosa-Garcia & Baer, 2017). Remarkably, the compounds exhibited micromolar level activity against the related oncogenic kinase VEGFR2 in addition to low anti-FLT3 activity. Using sulfonamide groups as preferred scaffolds, new Flt3 inhibitors with micromolar potencies were synthesized with success. Percentage inhibition of these compounds was in the range 0-60 μM levels (Abutayeh et al., 2019) (Figure 2).

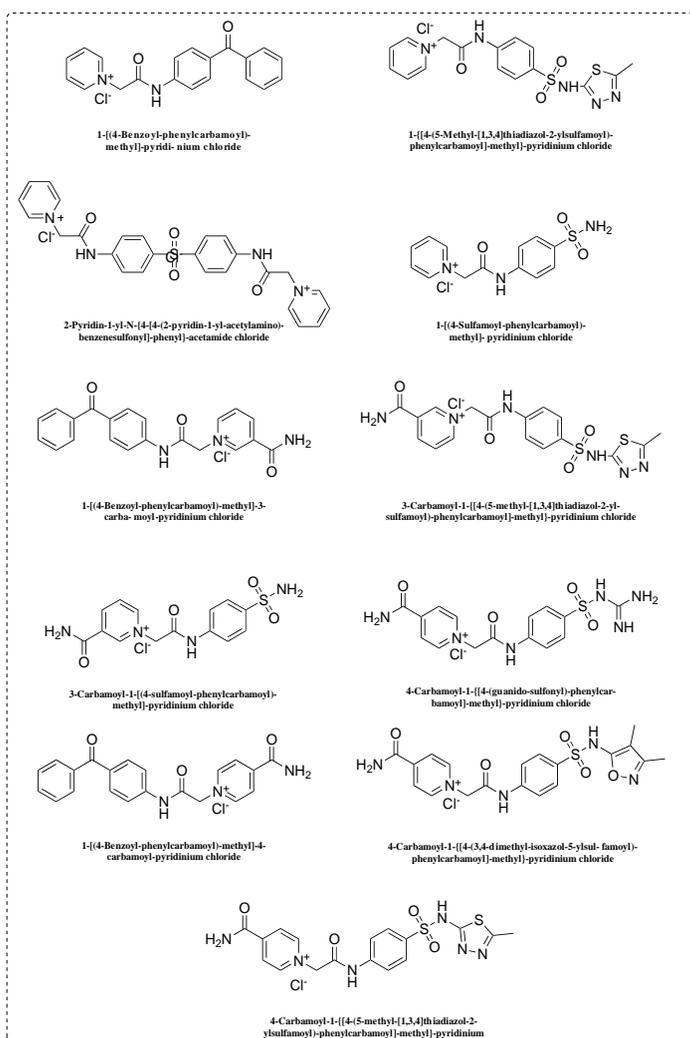


Figure 2. Some pyridinium acetamide derivatives including fusion with pyridine, nicotinamide and isonicotinamide

In other research, FLT3 inhibitors appear to provide a promising treatment option for AML based on clinical assessments and preliminary clinical trial data. Furthermore, due to the inability of direct FLT3 inhibitors to completely inhibit FLT3, early clinical results were only moderately successful (Stirewalt& Radich et al., 2003). As FLT3 inhibitors, they have created a novel class of molecules derived from 3-phenyl-1H-5-pyrazolylamine that show strong FLT3 inhibition and good selectivity toward a number of receptor TKs. Two classes of FLT3 inhibitors were identified based on structure-activity relationships, and some potent compounds from these two series showed potency similar to FLT3 inhibitors sorafenib and ABT-869 in terms of FLT3-ITD inhibition and wt-FLT3 enzyme inhibition on cell growth (MV4; 11 cells and MOLM-13). Furthermore, the chosen compound demonstrated the ability to eradicate cancers in mouse xenograft models made of MOLM-13 and MV4;11 cells. Many factors have been developed to directly inhibit the activity of both wild type and mutated FLT3 enzymes. ABT-869, sunitinib, lestaurtinib, and sorafenib are just a few of the factors that have been investigated as potential agents for treating AML. These factors have been brought to light recently due to the occurrence and poor forecast associated with FLT3 and the resistant nature of this disease associated with the mutant forms (Li, 2004).

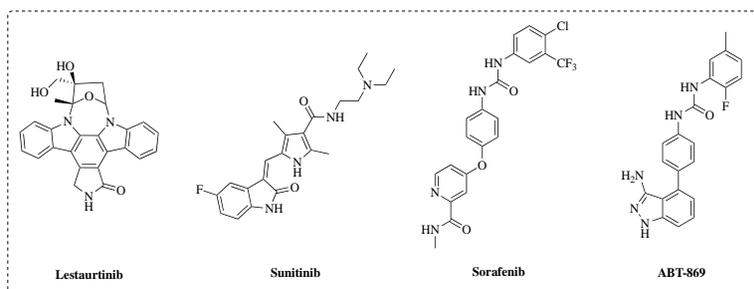


Figure 3. Some putative FLT3 enzyme inhibitors

1.2. FLT3 tyrosine kinase inhibitors in acute myeloid leukemia: clinical implications and limitations

One of the most prevalent gene mutations in AML is internal replication of the FLT3 gene, which is linked to a poor prognosis. While intensive chemotherapy has a high recovery rate, more patients eventually experience relapses. FLT3 mutations have become a desirable target for a particular molecular therapeutic approach during the last ten years. Although treating FLT3 mutant AML by targeting its tyrosine kinase receptors has produced encouraging results, the majority of patients experience inconsistent and insufficient responses (Kayser & Levis et al., 2014). Compared to FLT3, newer and more targeted compounds appear to have more power and variety. Induction of resistance-induced induction has become a clinical issue during tyrosine kinase inhibitor treatment. Thus, the current focus of clinical research is on optimizing targeted therapies and possible treatment options to overcome resistance. This chapter covers the use of TKI as a therapeutic strategy, its limitations, mechanisms of TKI resistance, and potential new approaches to enhance FLT3 inhibitor therapy in the treatment of FLT3 mutant AML (Levis et al., 2004).

1.3. FLT3 Inhibitors in Acute Myeloid Leukemia: Current Status and Future Directions

Most patients with acute AML express the tyrosine kinase 3 (FLT3) receptor, which is involved in controlling the survival, proliferation, and differentiation of hematopoietic stem cells and precursors. AML patients frequently have FLT3 mutations that result in constructive signaling, such as point mutations in the tyrosine kinase domain in 5% of cases and explosive internal amplification (ITD) in the joutamembrane domain in 25% of patients. Following chemotherapy and transplantation, AML patients with FLT3-ITD have a high recurrence rate, a brief recurrence rate, and an overall survival rate (Larrosa-Garcia & Baer, 2017). In order to improve clinical outcomes for patients with AML with FLT3 mutation, a number of FLT3 signaling inhibitors have been discovered and tested in clinical trials both alone and in conjunction with chemotherapy. Although clinical responses to inhibitory monotherapy are often incomplete and fleeting, resistance quickly grows. Numerous combination treatments have been suggested to boost FLT3 inhibitor efficacy and either prevent or cause resistance. Studies are being conducted on compounds containing

downstream kinase inhibitors, phosphatase activators, proteasome inhibitors, epigenetic therapies, and other signal-modifying medications. The translation and clinical research status of FLT3 inhibitors in AML and novel hybrid approaches is compiled in this chapter (Ravandi et al., 2013).

2. Histone deacetylase inhibitors and acute myeloid leukemia

In clinical therapy, resistance to chemotherapy, despite continued treatment, is often seen after the initial response. The MDR1 promoter can be induced using anticancer drugs, environmental stress, and epigenetic mechanisms such as DNA dimethylation. Histone diestylase inhibitors (HDACi) such as trichostatin A or valproate induce apoptosis or stop growth or restore the suppressed myeloid differentiation in AML (Christian & Ghadiri, 2009). Several HDACi have been introduced in the treatment of leukemia. They were used alone or in combination with DNA or all-trans retinoic acid methylation agents. These studies have shown clinical improvements. HDACi can be synergized with some DNA-binding drugs in experimental models (Ozmen Ozgün et al., 2019). Therefore, combination therapy is considered in clinical trials. HDACis are well-known anti-cancer drugs that have shown encouraging outcomes in clinical studies. On the other hand, little is understood mechanically about their decision to eliminate cancerous cells while leaving healthy cells unaltered. HDACis has been identified as a specific inhibitor of Down syndrome-associated myeloid leukemia outbreaks (DS-AMKL) by genome-based chemical genomics. An analysis of HDACis's anti-leukemic activity showed that important autophagy proteins like ATG7 are transcriptionally active. As a result, autophagy is suppressed, a lysosomal degradation process that can shield cells from unneeded organelles and proteins (Suzuki et al., 1999).

2.1. Sulfonamide derivatives and histone deacetylase inhibitors

Histone diastylase (HDAC) inhibition is becoming a new treatment option for cancer in humans. New hydroxamate anilides of the hydroxamate sulfonamide that can inhibit human HDAC enzymes and cause an overgrowth of histone cells in human cancer cells have been designed and synthesized. These substances do not exist in normal cells, but they specifically inhibit proliferation and cause cell cycle disruptions in a variety of human cancer cells (Lavoie et al., 2001).

Sulfonamide anilides have a reversible growth-inhibiting effect on human cancer cells *in vitro* that is dependent on histone acetylation induction. Human colon tumors implanted in naked mice can grow tumors much slower when treated with sulfonyl chloride (SO_2Cl_2) in toluene containing L-proline benzyl ester hydrochloride. When used together, the two do not exhibit appreciable toxicity, in contrast to MS-275, another anilide-based HDAC inhibitor that lowers red and white blood counts as well as spleen weight in mice (Oh et al., 2007). Currently, there is interest in using HDAC inhibitors as anticancer agents, according to another study. Histone diacylases play a crucial role in both rebuilding the chromatin structure and controlling the transcriptional activity of genes. It has been reported that a variety of synthetic and small molecule HDAC inhibitors, including scriptriptide, oxamate flatin, suberoylanilide hydroxamic acid (SAHA), and MS-275, can suppress cell proliferation and differentiate multiple cell lines. This work examines the development of two new families of powerful HDAC inhibitors, hydroxamic acid sulfonamides and anilides, as well as direct-chain derivatives like TSA, that have recently been made in our labs (Berrediem et al., 2004). Certain compounds have the ability to cause over-acetylation of histones in human cancer cells and inhibit recombinant human HDAC recombinant enzymes purified by IC_{50} in the nanomolar to micromolar range. In a different investigation, a range of hydroxamic acids, sulfonamides, and anilides were produced and investigated as HDAC inhibitors that could cause human cancer cells to overly acetylate their histones. Reversing HDAC activity offers a fresh method for regulating the cell cycle. A panel of human tumors and normal cell lines was used to screen potential candidates. They cause apoptosis, stop the cell cycle, and selectively inhibit proliferation in human cancer cells, but not in normal cells. There is a description of the connections between the activity structure, antiproliferative activity, and *in vivo* effect (Bouchain et al., 2003). Inhibition of the HDAC enzyme surfaced as a novel cancer treatment strategy in another study. A series of novel derivatives of sulfonamides were prepared and tested for their capacity to inhibit human HDAC. Strong enzyme-inhibiting compounds were identified by their antiproliferative effects in cell culture and low nanomolar IC_{50} values against enzymes derived from HeLa cell extracts. The essential requirements of the activity are identified by a general summary of the structure-activity relationships in this collection. These include the direction of the sulfonamide bond and the replacement patterns on the central phenyl ring. The distance of

alkyl between the aromatic head group and the sulfonamide function also affects the inhibitory activity of HDAC (Finn et al., 2005).

3. LSD1 inhibitors and acute myeloid leukemia

A marker of malignancy in the blood, abnormal epigenetic modification is linked to the onset of leukemia. Multiple enzymes simultaneously play a role in the highly dynamic process of epigenetic regulation, making it a possible target for therapy. Lysine, methylase 1 (LSD1, also called KDM1A), is a nuclear homologous amino oxidase that targets lysine 4 histone H3, lysine mono and dimethyl 4 histone H3, and lysine 9 histone H3. It is an epigenetic modification enzyme. As a coenzyme, flavin adenine dinucleotide (FAD) was employed by Puts (H3K4me1 / 2, H3K9me1 / 2) (Metzger & Wissmann, 2005). Evidence indicates that acute myeloid leukemia (AML), particularly AML with chromosomal translocation, frequently has elevated LSD1 and poor differentiation. To break the differentiation barrier in AML, a combination of all-trans retinoic acid (ATRA) and LSD1 inhibitors has been used. As a result, LSD1 is becoming the main target for AML treatment (Sheng et al., 2018).

3.1. Sulfonamide derivatives and LSD1 inhibitors

Lysine-specific methylase 1 (LSD1) has been found to be an appealing therapeutic target in a number of cancers. It regulates the methylation of lysine in residues K4 and K9 in histone H3. This work involved the synthesis of a number of novel benzohydrazides (E)-N-(2,3-dihydro-1H-inden-1-ylidene) and their biological assessment for possible LSD1 inhibitory activity. With IC₅₀ values of 1.4 μM, 4-(2-aminocyclopropyl)-N-phenylbenzenesulfonamide demonstrated the highest inhibitory activity of LSD1. Certain antiproliferative properties of this compound have been demonstrated against cancer cell lines that overexpress LSD1. These findings imply that these ideal compounds could be effective LSD1 inhibitors against cancer, a possibility that merits more research (Liang et al., 2020). In another study, acute myeloid leukemia (AML) patients frequently had elevated levels of Lysine-specific methylase 1 (LSD1), which frequently resulted in tumorigenesis. A large number of LSD1 inhibitors based on transylpromine (TCP) scaffolds have advanced to clinical trials in recent years. The amino site of cyclopropane motifs was altered in the majority of TCP derivatives. Here, they modify various sulfonamide

groups in order to perform a systematic study of the structure-activity relationships after first adding a sulfonamide group to the TCP benzene rings of series one compounds. TCP's ability to target LSD1 was greatly enhanced by the addition of sulfonamides. Furthermore, they discovered that their ability to inhibit the proliferation of AML cells was markedly enhanced by Boc-linked LSD1 inhibitors, also referred to as b-series compounds (Cusan et al., 2018).

4. MCL1 inhibitors and acute myeloid leukemia

One of the gene regions that is frequently amplified in human cancers is MCL1, and patient resistance to cytotoxic drugs and recurrence are frequently linked to its expression. Numerous tumor types, including multiple myeloma (MM), acute myeloid leukemia (AML), chronic myeloid leukemia, acute B cell lymphoblastic leukemia, hepatocellular carcinoma, and certain small cell lung cancers, have been identified as MCL1 dependent. Furthermore, MCL1 targets and enhances both acquired and innate resistance to a variety of cytotoxic agents (Tanaka et al., 2013). Treatments include the selective inhibitor of B-cell lymphoma 2 (BCL2) of venetoclax MCL1, a protein belonging to the BCL2 family that prevents the induction of apoptosis in many cancers, thereby promoting cell survival. Increased MCL1 expression highlights the potential of MCL1 inhibitors as anticancer medications by inducing tumorigenesis and resistance to anticancer therapies (Petros et al., 2014).

4.1. Sulfonamide derivatives and Mcl-1 inhibitors

A member of the BCL2 protein family, which controls programmed cell death, is myeloid cell leukemia (MCL1). One of the main genetic abnormalities in human cancer is MCL1 amplification, whose overexpression prevents apoptosis from occurring and serves as a resistance mechanism to many chemotherapy drugs. MCL1 mainly mediates its effects by interacting with proapoptotic proteins that contain BH3, which use four hydrophobic pockets in their binding groove to achieve a high affinity for the target. Here, they go over how structure-based design and component-based approaches were used to find MCL1 inhibitors. These novel inhibitors typically select 500 times more B-cell lymphoma-extra large (Bcl-xL) and bind nanomolar amounts to MCL1. When wrapped in MCL1, the X-ray structures of MCL1 lead inhibitors offer comprehensive details on how these tiny

molecules bind to the target and are frequently utilized to direct compound optimization (Follows et al., 2019). According to a different study, MCL1 is an anti-apoptotic protein expressed in a number of human solid tumors as well as blood cancers. Treatment for MCL1-mediated resistance that works well is small molecule inhibition of MCL1. As a result, the pharmaceutical industry has conducted a great deal of research on it. Biaryl sulfonamide is blown from a plate through the top, revealing a new class of small inhibitors called MCL1. The interaction between protein and MCL1/Bid protein can be disrupted in vitro through pharmaceutical chemistry with the aid of SBDD compounds (Belmar& Fesik, 2015).

5. Sphingosine kinase 1 and acute myeloid leukemia

Through its role as a ligand for a family of five G proteins, the active lipid sphingosine 1-phosphate (S1P), which is produced by sphingosine kinase 1 (SPHK1), enhances several key biological features of cancer, including cell survival and proliferation. High expression of SPHK1 in solid tumors has been linked in numerous studies to poor prognosis, chemical resistance, and faster disease progression (Van Brocklyn et al., 2005). In fact, tumor progression in mouse models of different types of solid human cancers has been effectively stopped by targeting SPHK1 with small molecule inhibitors or by genetic ablation. Numerous recent investigations have proposed the involvement of SPHK1 in leukemia. For instance, suppression of SPHK1 has been demonstrated to cause reduced growth of subcutaneous U937 AML subcellular cell lines in mice, direct induction of cell death in HL-60 AML cells, and susceptibility of leukemia cells to chemotherapy; however, the mechanism of action and efficacy in primary AML have not been investigated. The function and targeting of SPHK1 in primary cells, including stem cells and constituents, from AML patients was studied [Sobue et al.,2008]. They discovered that both isolated CD34+/CD38-/CD123+ leukemic stem and progenitor cells (LSPCs) and early AML outbreaks are susceptible to SPHK1 inhibition in vitro and in mice bitten orthotopically. In human AML cells, inhibition of SPHK1 results in MCL1 degradation and caspase-dependent cell death. In AML xenografts from orthopedic patients, SPHK1 inhibitors lessen the burden of leukemia and increase survival time (Ricci et al., 2009).

5.1. Sulfonamide derivatives and Sphingosine kinase 1 inhibitors

Among the extensively researched pharmacological targets for cancer and inflammatory disorders is sphingosine kinase 1 (SPHK1). In cancer treatment, the recently identified SPHK1 small inhibitors are advised. The selection and potency of first-generation inhibitors, however, present significant difficulties. A collection of small molecules containing urea, sulfonylurea, sulfonamide, and sulfonyl tertiary groups have been created and synthesized in an effort to find potent SPHK1 inhibitors (Roy et al., 2020). Fluorescence binding and isothermal titration calorimetry were used to determine the binding affinity of these inhibitors. Then, it was observed that there was excellent sub-micromolar binding to SPHK1 and significant inhibition of SPHK1 activity with excellent IC₅₀ values. According to molecular binding studies, these compounds form a sizable number of hydrogen bonds and van-walt interactions and fit neatly into the SPHK1 sphingosine-binding pocket. As strong and selective inhibitors of SPHK1, a variety of small molecules with distinct scaffolds, such as diarylsulfonyltriurea, benzothiazole-based sulfonylurea and sulfonamide, anthracene-based urea, and diaryl-substituted thiazole-based sulfonamide, may be employed, provided that necessary in vivo validation is completed (Lynch et al., 2016) (Figure 4).

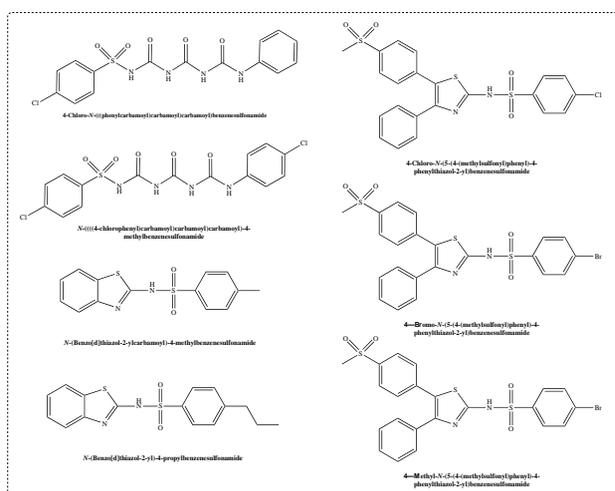


Figure 4. Some potent and selective inhibitors of SPHK1

6. DNA methyltransferase inhibitors and acute myeloid leukemia

DNA methyltransferases (DNMTs) are potential epigenetic targets for the treatment of acute myeloid leukemia (AML). They carry out the epigenetic modification of DNA methylation. The US Food and Drug Administration has approved the use of two DNMT inhibitors, azacitidine and decitabine, to treat high-risk myelodysplastic syndromes. This is supported by the availability of the first clinical data in AML (Stresmann&Lyko, 2008). The treatment of AML has benefited most from epigenetic therapy advancements. The number of DNMT inhibitors is increasing at the moment. At various stages of leukemia, such as prior to chemotherapy, as maintenance therapy, before allogeneic stem cell transplantation (SCT), or following a recurrence after SCT, these factors may be prescribed (Yoo et al., 2012).

6.1. Sulfonamide derivatives and DNA methyltransferase inhibitors

The development of novel epi drugs for the treatment of cancer and other diseases is attracting the attention of human DNMT inhibitors. Molecular pools expose light to clarify the mechanism of action of compounds that are reportedly inhibited by DNMT and to further interpret the structure-activity relationship. A logic based on the unique sulfonamide compound SW155246 activity structure—which was recently identified as a human DNMT1 inhibitor with high-efficiency screening—was presented in this instance (Medina-Franco et al., 2014) (Figure 5).

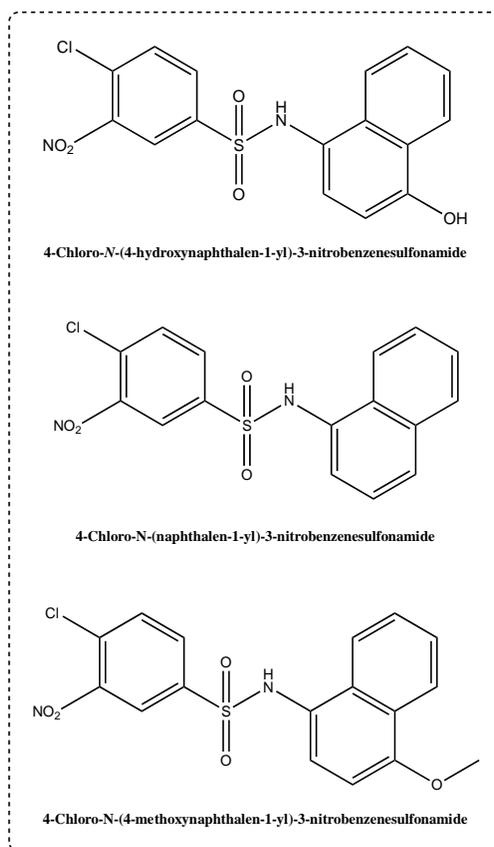


Figure 5. Some distinct sulfonamides that reported as a human DNMT1 inhibitors

7. Carbonic anhydrase I, II, III and acute myeloid leukemia

Cancer is one of the leading causes of death, a global health problem. Antibodies made against the bodies own antigens are detected in the serum of people with cancer. In recent years, CA I, and CA II antibody antibodies have been shown in some autoimmune diseases and carcinomas, but the underlying mechanisms of this immune response have not yet been elucidated (Huseynova et al., 2019). The aim of this study was to evaluate CA I, and CA II antibodies in patients with acute myeloid leukemia (AML) and to provide a new perspective on the basics of autoimmunity. New information about CA III involvement in several cancers has rekindled interest in developing new enzyme inhibitors. CA III has recently been suggested to be associated

with acute myeloid leukemia and the progression of liver carcinoma (Okten et al.,2019).

7.1. Sulfonamide derivatives and Carbonic anhydrase I, II, III inhibitors

Sulfonamide derivatives had strong inhibition effects on CA isoenzymes. Also, CA IV has been shown to be effective as inhibitors of tumor cell growth in vitro with GI_{50} (molarite inhibiting the production of 50% tumor cell growth inhibitor), typically in the range of 0.1 to 30 μ M against multiple leukemias, cell lung Not small cancer cell lines, ovary, melanoma, colon, CNS, kidney, prostate and breast (Oztaskin et al., 2017). In another study, new sulfonamides as CA inhibitors were prepared by reacting aromatic sulfonamides or cyclic heterocycles containing amino, imino or hydrazino with N,N-diakylthiocarbamates in the presence of oxidizing agents. This method produces N,N-dialkylthiocarbamylsulfenamido-sulfonamides that are strong inhibitors of human CA I and CA II as well as bovine CA IV (bCA IV) (Taslimi&Gulcin, 2018). The inhibition constants for the most active compounds range from 8–10 to 9–10 M (for isozymes II and IV). Three variations of this novel class of CA inhibitors were also investigated for their ability to inhibit the growth of tumor cells in vitro. Strong growth inhibition against multiple cancers, including non-small cell lung, ovarian, melanoma, colon, CNS, kidney, prostate, and breast cancer cells, was demonstrated by these sulfonamides (Gulcin et al.,2020; Gulcin&Taslimi, 2018).

8. Conclusions

Many structurally based studies on drug design and discovery have led to a thorough understanding of the parameters controlling tight binding and selectivity for a number of different enzymes. Successful stories include phenols, carboxylic acids, polyamines, borols, diols, boronic acids, coumarins, and sulfonamides. An anticancer sulfonamide is currently undergoing Phase I clinical trials as a result of these discoveries. There aren't any comprehensive crystallographic data

available for many inhibitor groups. Extensive structural analysis of every class of enzymes could propel the field forward and have therapeutic implications for AML.

9. Future prospects

All these data show that the primary sulfonamides constitute an important class of compounds that give rise to highly valuable drugs and drug candidates for plenty of situations, like AML, glaucoma, cancer, dandruff, inflammation, just to mention the most investigated ones.

10. Expert opinion

Sulfonamides have been used recently in AML and as an anticancer agent. According to all of these data, primary sulfonamides are an important class of compounds that lead to highly valuable drugs and drug candidates for many different conditions, including dandruff, cancer, inflammation, glaucoma, AML, and inflammation, to name just a few of the most researched ones. Many clinically used medications, such as diuretics (chlorthalidone, indapamide, thiazides, and furosemide), CA inhibitors (acetazolamide, dorzolamide, brinzolamide, dichlorphenamide), antiepileptics (zonisamide), the antipsychotic sulpiride, or COX2 inhibitors (celecoxib and valdecoxib) contain the primary sulfonamide. In addition, new medications like pazopanib and apricoxib were introduced that included this class. The primary class of sulfonamides that have been thoroughly studied recently includes pazopanib, a multi-targeted receptor tyrosine kinase inhibitor of other enzymes, COX2 inhibitors, and CAIs. Acute lymphoblastic leukemia cells, also known as AML cells, are the starting point of acute leukemia, a blood cancer that progresses quickly. Rapid clonal accumulation of lymphoid or immature myeloid clusters brought on by the accumulation of multiple carcinogenic mutations with multistage cytopenia is the cause of acute leukemias. Leukemia's most common cause of death is AML, whereas childhood cancer's most common type is ALL. Even with intensive chemotherapy and hematopoietic stem cell

transplantation, the 5 year overall survival for AML is less than 50% in young patients, less than 10% in patients over 65, and less than 80% for ALL in young patients and in patients over 65 years is less than 20%.

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Declaration of interest

The authors declare that they have no financial relationships or affiliations with any organization or entity that could have a financial conflict or financial interest in the topics or materials covered in the manuscript. This covers grants or pending or received patents, expert testimony, honoraria, employment, stock ownership or options, and royalties.

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CHAPTER 5

TADF PROPERTIES OF A PYRAZINE BASED OLEDs

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INTRODUCTION

The share of lighting systems in world electricity consumption is approximately 19% size. Lighting technology is one of the fastest advancing technologies in the world and Scientists have been studying electricity consumption from lighting for many years. It focuses on the design of devices that can minimize Nowadays, commercialized and same with approximately 95% less energy than the classical bulbs invented by Edison Light Emitting Diodes (LED) bulbs, which can emit bright light, have become very popular in recent years. It is used in this way. In addition, it can be produced on thinner, lighter and more flexible surfaces. OLED type display and illumination technology R&D process is ongoing and both aesthetic and It is a technology that can provide great ease of use.

The availability of various organic materials, the properties of these materials It can be adjusted by chemical means, it is much simpler and cheaper than inorganic materials. The fact that it can be processed by different methods has made LED gain great importance. Bernanose and colleagues in 1953 and Pope and colleagues in 1963 for the first organic after manufacturing electroluminescent cells, using light-emitting polymers They started to design light emitting diodes (OLED).

A luminous body emits light, a physical quantity that when it strikes the eye stimulates nerves to give the feeling of sight. The electromagnetic spectrum as a whole is only partially visible to human sight. Despite having highly developed skills to see light, humans can only see a very small portion of the electromagnetic spectrum, which ranges from the deepest violet (400 nm) to the deepest red (750 nm). Light's hue varies depending on its frequency and wavelength. A minimum excitation energy between 1.8 and 3.1 eV is necessary for the emission of wavelengths that correspond to the visible area (Kalyani et al. 2017).

Incandescence and luminescence are two conceivable natural phenomena that might produce light in practical situations. When a

substance is heated to a high enough temperature, it begins to glow. Incandescence is the process of light being released from heat energy. Incandescent light is produced when heated atoms or molecules release some of their thermal vibrations as electromagnetic radiation. The sun produces this kind of light the most frequently. By means of incandescence, the sun provides practically all of the heat, light, and other energy types required for life on our planet. On the other hand, luminescence is a technique of emitting light without producing heat. It is a cool emission induced by the migration of electrons within a substance from more energy states to less energetic states. Photon absorption, chemical or biological interactions, the activity of subatomic particles, radiation, or stress on a crystal can all contribute to this. The luminescent substance itself, not the incident radiation, determines the wavelength of light that is emitted (Fourassier, 1984; Mc Keever, 1985).

In 1852, it was experimentally proven that some compounds exhibit fluorescence, which is the ability to instantly emit light in a spectral region different from the incident light (for example, yellow light) after absorbing light from a restricted spectrum range, such as blue light. As a result, fluorescence is the ability of some atoms and molecules to absorb light at a specific wavelength and then emit light of a larger wavelength after a short period of time. This short period of time is referred to as the fluorescence lifespan (Sparks et al., 2014). After being excited by ultraviolet or visible light, excited electrons release the extra energy as photons, returning to the ground state (singlet state), where the excitation energy is released as fluorescence. The system's multiplicity is maintained during these changes. On the other hand, delayed luminescence, which involves forbidden energy state transitions, is known as phosphorescence (Kalyani et al. 2017). As a single-singlet transition is considerably more likely to occur than a triplet-singlet transition, phosphorescence occurs over a longer period of time (Schlyer et al. 1994). Figure 1 displays a condensed Jablonski diagram that demonstrates fluorescence and phosphorescence. The intersystem crossing (ISC) procedure will be successful when (S1-T1)

is lower than 0.6 eV for all types of ligands, according to Reinhoudt's empirical criterion (deSa et al. 2000).

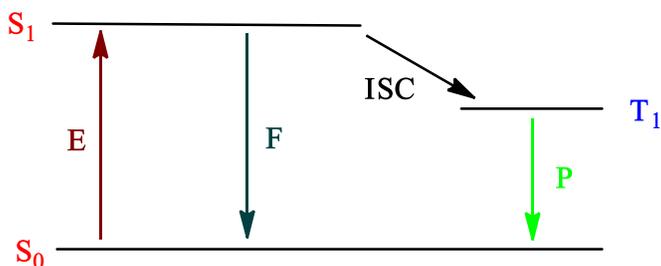


Figure 1. Simplified diagram showing fluorescence and phosphorescence. (**E**, **F** and **P** stand for Excitation, Fluorescence and Phosphorescence, respectively)

LEDs have been around for close to 50 years, but up until a decade ago, they were only applied to electrical equipment as indicator lamps. Due to its great efficiency, high reliability, durable design, and lack of poisonous metals, LED technology took off after its first development. A wider range of applications, including lighting, traffic lighting, indicators, electronic billboards, car headlights, flashlights, searchlights, cameras, store signs, destination signs on vehicles, general illumination, visual display, decorative purposes, etc., have been made possible by the search for brighter LEDs. The newest uses for LEDs that perform better and better make use of organic materials.

The acronym OLED stands for Organic Light Emitting Diode. OLED is an unconventional light source that has the potential to displace traditional lighting sources. It is a display device that sandwiched carbon-based films between two charged electrodes, a metallic cathode and a clear anode, which was often made of glass (Binggeli, 2012). The organic films are made up of an emissive layer, an electron-transport layer, a hole-injection layer, and a hole-transport layer (Tsai et al., 2014). These organic arrays use less energy and

provide brighter light (Liu et al., 2014; Zhang et al. 2002; Xiaoxiao et al. 2014).

Eastman Kodak developed OLED technology in the early 1980s. It is starting to replace LCD technology in portable devices like PDAs and mobile phones because it is more powerful, lighter, faster, brighter, and thinner than LCDs, uses less power, offers higher contrast, and is less expensive to produce (Patel and Prajapati, 2014).

When an electric field is applied to an OLED, electrons move through the lowest unoccupied molecular orbital (LUMO), while holes move through the highest occupied molecular orbital (HOMO) and combine with the emitter molecules to form triplet or singlet excitons. The injected positive and negative charges recombine in the emissive layer of the OLED cell when voltage is applied, producing electro luminescent light. OLED displays are emissive devices, as opposed to LCDs, which modulate transmitted or reflected light instead of emitting light (Kalyani et al. 2017).

In this work, we have constructed a series of pyrazine based (2-((3,6-dimethylpyrazin-2-yl)methylene)malononitrile) (Figure 2) compounds and investigated the structural and electronic properties theoretically at the level of Density Functional Theory. These D-A type compounds may be potential candidates for organic solar cell applications or organic light emitting diodes or fluorescent organic materials.

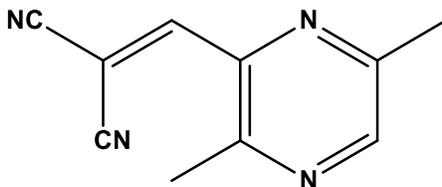


Figure 2. Structure of the parent compound (2-((3,6-dimethylpyrazin-2-yl)methylene)malononitrile)

2. METHOD OF CALCULATION

All compounds' three-dimensional ground state (S_0) geometries were optimized using DFT (Kohn and Sham, 2015) in combination with the Gaussian 16W (Frisch et al., 2016) package software and the hybrid functionals B3LYP and CAM-B3LYP. B3LYP is made up of the nonlocal correlation functional of Lee, Yang, and Parr (LYP) (Lee et al., 1988) and Becke's three parameter exchange functional (B3) (Becke, 1988). The parameters of the functions are fitted empirically while being constrained to the uniform electron gas (Zhao and Truhlar, 2006; Zhao and Truhlar, 2006; Zhao and Truhlar, 2008; Karton et al., 2008). The suite significantly improves one of the greatest shortcomings in DFT approaches by responding very well to dispersion forces.

Vibrational evaluations for each molecule were performed using the same basis set as the associated geometry optimizations. No compound's frequency study produced any imaginary frequencies, proving that each molecule's structure corresponds to at least a local minimum on the potential energy surface. The 3N-6 vibrational degrees of freedom underwent the typical mode analysis, where N is the number of atoms in the molecule.

To determine the compounds' minimal energy geometries, the low-lying triplet (T) and singlet excited states (S) were relaxed. By utilizing TD-DFT with a variety of hybrid functionals and basis sets, the vertical excitation energies and oscillator strengths for the lowest triplet and singlet transitions at the optimum ground state equilibrium geometries were discovered (Casida et al., 1998). The electronic absorption spectra, including maximum absorption wavelengths, oscillator strengths, and major configuration assignment by employing TD-DFT, were obtained using optimized ground state structures. Despite a few outliers, evidence from the literature indicates that the analysis of the excitation energies with PBE0, wB97XD, and CAM-B3LYP functionals predicts the best agreement with the experimental data (Yanez et al., 2017). Therefore, for TD-DFT computations B3LYP/6-31G(d,p), B3LYP/6-311+G(d,p), B3LYP/cc-PVTZ and

CAM-B3LYP/6-311+G(d,p) methods have been applied and the results have been compared.

3. RESULTS AND DISCUSSION

People have been pushed to look for new concepts and uses due to the desire for large-scale power generation that is economically feasible and based on ecologically friendly materials with endless availability and variety. Compared to their inorganic equivalents like Si, organic semiconductor materials are less expensive. Organic photovoltaics have the potential to produce solar cells with extraordinarily high optical absorption coefficients, allowing for the fabrication of thin, flexible devices.

The radiative exciton fraction for fluorescent molecules is commonly estimated to be 0.25 (Baldo et al., 1999; Segal et al., 2003). But the addition of phosphorescent emitters could raise this value all the way to 1 (Baldo et al., 1998; Wilson et al., 2001; Sun et al., 1999). However, it is highly likely that the cost of producing an OLED device would rise due to the requirement for rare metals like iridium or platinum, which enable effective spin-orbit coupling (Adachi et al., 2001; OBrien et al., 1999; Baldo et al., 1999). OLEDs using fluorescent and phosphorescent emitters have a classical limit of external quantum efficiency of 5% and 20%, respectively. Recently, a potential idea to increase device efficiency above these limits has been the conversion of non-radiative triplets to radiative singlets (Meerholz and Müller, 2001).

A lot of attention has been paid to TADF emitters recently, and numerous new compounds with this behavior have been created (Endo et al., 2009; Endo et al., 2011; Endo et al., 2011; Czerwieńiec and Yersin, 2011; Leidl et al., 2013). It is feasible to reduce the energy gap EST between the lowest excited singlet (S1) and triplet (T1) state by spatially separating the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). Reverse intersystem crossing (RISC), a thermally induced mechanism, effectively converts triplet excitons to singlet excitons as a result, according to Boltzmann statistics. This technique is frequently referred to as singlet harvesting

since the emission results from the degradation of the S1 state (Endo et al., 2011). Thus, by raising the radiative exciton percentage, it is possible to boost the fluorescence efficiency of OLEDs. As a result, it has been claimed that OLEDs have external quantum efficiency metrics that are considerably over the classical limit and are comparable to systems that use phosphorescent emitters (Leitl et al., 2013).

The electron-electron repulsion between the electron orbitals in the triplet state is therefore minimized by a small EST value, which denotes a tiny overlap integral between the wave functions of a luminous molecule's ground and excited states (Endo et al., 2009). In this context, the molecule's ground state corresponds to the HOMO level, and its excited state corresponds to the LUMO level. Localizing the electron densities of the HOMO and LUMO states on the donor and acceptor moieties, respectively, is an effective method to reduce the overlap between the wave functions (Endo et al., 2011). This effect is also enhanced by additional steric separation that is created by adding a spiro junction or bulky substituents between the acceptor and donor units (Endo et al., 2011).

With all these information from the literature in hand, we have designed a series of Donor-Acceptor (D-A) type pyrazine based (2-((3,6-dimethylpyrazin-2-yl)methylene)malononitrile) derivatives in order to suggest potential TADF emitters (Figure 2). The parent compound (2-((3,6-dimethylpyrazin-2-yl)methylene)malononitrile) was synthesized from benzil (Khodae et al., 2012) and used as a precursor to obtain novel pyrazinoporphyrazines. The importance of dicyanopyrazine derivatives has been mentioned mainly in the chemical industry, food, agricultural and medicinal chemistry (Lee et al., 2005). In this work, the pyrazine has been connected with two cyano groups attached to a double bond (**A**) was the acceptor, benzene (**1**), anthracene (**2**), pyrene (**3**), triphenylamine (**4**), Pyrido[2,1,6-de]quinolizine (**5**) (Figure 3).

The idea of the present study emerged from the extensive spectroscopic investigations of the parent pyrazine compound performed in the literature (Khodae et al., 2012; Nishida et al., 2004;

Ivanov et al., 2006). Containig a well acceptor moiety in its structure, combination of **1** with donor units may produce potential TADF compounds.

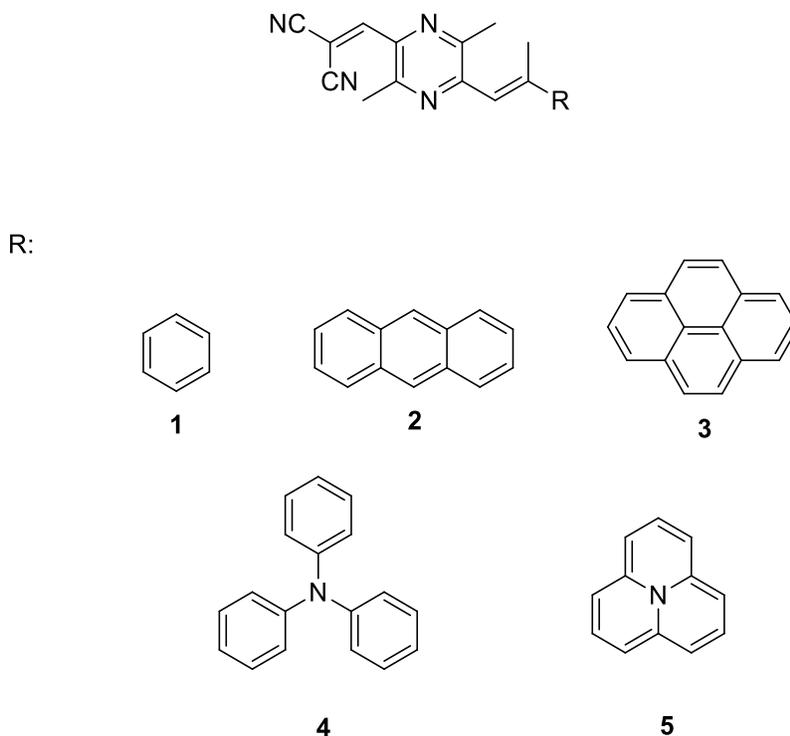


Figure 3. Structures of potential TADF compounds

3.1. Semiconductor Properties

The conjugation of π -electrons serves as the foundation for the electrical structure of all organic semiconductors. Single and double carbon-carbon bonds alternate in a conjugated organic system. Single bonds are referred to as σ -bonds and are connected to localized electrons, whereas double bonds are made up of two σ -bonds. Due to the mutual overlap of pi orbitals along the conjugation path, which results in the

wave functions delocalizing over the conjugated skeleton, the π -electrons are mobile and can move between carbon atoms. Lowest Unoccupied Molecular Orbital (LUMO) refers to the empty π^* -bands, and Highest Occupied Molecular Orbital (HOMO) refers to the occupied π -bands. Semiconductor materials have band gaps (E) that range from 0.5 to 4 eV (Atkins et al., 2006).

Frontier molecular orbital energies of the compounds were computed at the level of B3LYP/6-311+G(d,p) and the results are given in Table 1. All computed band gap (ΔE) values have been found to be below 4 eV. As expected, the combination of donor units with acceptors is expected to reduce the inter-frontier molecular orbital energy gap of a compound due to extension of the conjugation path. The parent compound (**A**) had a band gap of 3.90 eV which was ennarrowed by the attachment of donor units. Therefore all the compounds carry the potential of usage as semiconducting materials. The narrowest band gaps among all have been obtained for compound **5**.

Table 1. Results of computations (All data are in eV)

Compound	DFT			TD-DFT (ΔE_{ST})			
	B3LYP/6-311+(d,p) HOMO	LUMO	ΔE	B3LYP 6-311+(d,p)	B3LYP 6-311+(d,p)	cc-pvtz 6-311+(d,p)	CAM- B3LYP 6-311+(d,p)
A	-6.90	-3.00	3.90	0.44	0.22	0.21	0.50
1	-6.25	-2.96	4.20	0.42	0.47	0.48	0.44
2	-5.49	-3.16	2.30	0.24	0.12	0.11	0.27
3	-5.54	-2.94	2.60	0.36	0.11	0.09	0.25
4	-5.39	-2.84	2.40	0.12	0.09	0.10	0.06
5	-4.44	-2.64	1.80	0.07	0.08	0.07	0.09

Figure 4-5 shows the compounds' geometry-optimized structures and 3D-frontier molecular orbital energy schemes. The HOMO and LUMO schemes provide details on the reactivity of the

compounds. While LUMO demonstrates the Lewis acidity of the comparable solution, HOMO offers basicity. Therefore, research into frontier molecular orbitals is crucial. Since these schemes influence the reactivity centers, it is equally crucial to understand which atoms contribute to these orbitals. It is essential for the compounds to have distinct HOMO and LUMO to provide low exchange energy in order for them to be suitable candidates for TADF. This goal can be successfully accomplished through steric hindrance, which causes twisting between donor and acceptor units. (Nakagawa et al., 2012; Mehes et al., 2012; Nasu et al. 2013). In D-A structures, the HOMOs are mostly found on the donor moieties (Figures 4-5), whereas the LUMOs are found over the acceptor core and are made up of pyrazine and strongly electron-withdrawing cyano units. Because of the significant dihedral angles (about 25–90°) between the donor units and the phenanthrene pyrazine core, which contains cyano, there is a distinct spatial separation of the HOMO and LUMO. On the donor and acceptor sections of the system, respectively, the HOMO and LUMO orbitals are clearly dispersed.

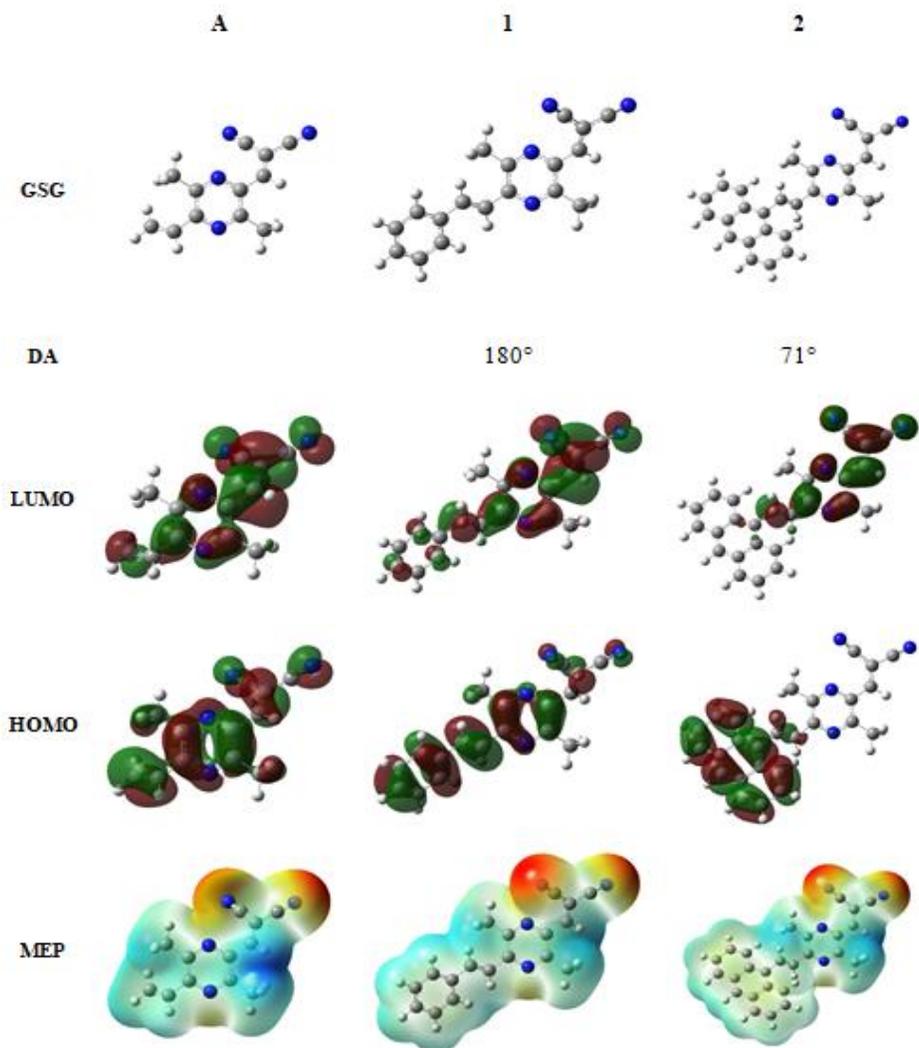


Figure 4. Ground State Geometry (GSG), Dihedral Angle (DA), HOMO, LUMO and MEP of A, 1 and 3.

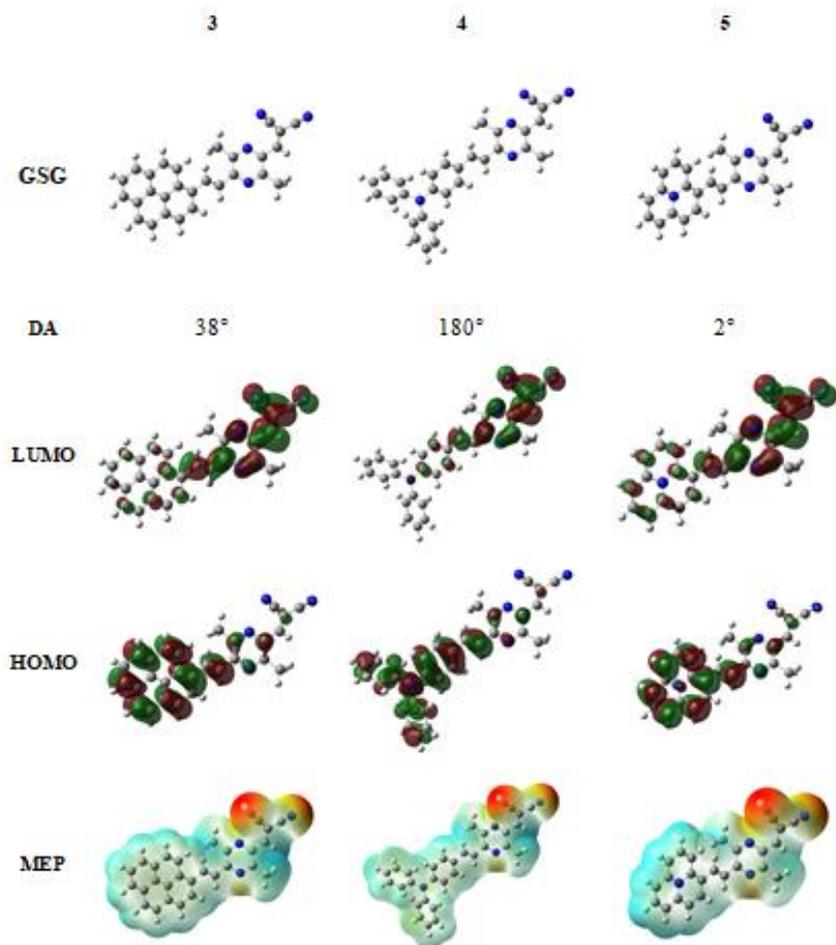


Figure 5. Ground State Geometry (GSG), Dihedral Angle (DA), HOMO, LUMO and MEP of 3-5.

The stiff planar pyrazine molecule (A) has a core ring that is fully conjugated, two enes on either side, and cyano groups. As a result, HOMO and LUMO are dispersed throughout the structure. Two methyl groups have been added to successfully separate the frontier molecular orbitals by obstructing the substituents' (R) free rotation (Figure 4). Figures 4 and 5 show the structures of 1–5 that have been geometrically optimized. Except for compound 1, where they were unable to be suitably separated due to excessive conjugation, the tilted structures from planarity with dihedrals depicted in the images produced nicely separated HOMO and LUMO. HOMO and LUMO energy levels have changed enough for the compounds upon altering the substituent, to possess better semiconducting ability.

Recently, the literature has looked at the possible OLED applications of oligomeric thiophene systems (Sengoku et al., 2012)]. Therefore, by switching the substituent with hing conjugation systems, we sought to separate HOMO-LUMO distribution along with potential lowering of the interfrontier molecular orbital energy gap due to extension of the conjugation. HOMO and LUMO could be distinguished, despite the fact that geometry optimized structures did not produce even more slanted structures. On the other hand, the introduction of the expanded system resulted in a narrowing of the HOMO-LUMO energy gap because of an increase in HOMO energy. (Figures 4 and 5).

The literature has extensively examined anthracene (Aydemir et al., 2016), pyrene (Shan et al., 2017), triphenylamine (Wang et al., 2015), carbazole (Çiçek et al., 2018), pheoxazine (Li et al., 2017), and acridine (Seo et al., 2016) based OLED and TADF systems. As a result, combining the current 2-((3,6-dimethylpyrazin-2-yl)methylene)malononitrile with each of the aforementioned compounds may result in molecules that could be used as OLED and TADF candidates. Figures 4 and 5 show the geometry-optimized structures and frontier orbitals of compounds 1–5. Compounds 2 and 3's donor-acceptor dihedral angles of 71° for anthracene and 38° for pyrene show promise for achieving excellent separation of the HOMO-

LUMO distribution across the system. Compounds 2-5 produce good semiconductor materials that may be used in OLED devices since all of the HOMOs are situated on the donor portion and all of the LUMOs are positioned on the acceptor part.

3.2. TADF Properties

Getting a narrow energy gap (E_{ST}) between the S_1 and T_1 states is one of the key design factors for TADF molecules. Only when a molecule's lowest-energy transition has a low singlet-triplet exchange energy does it meet this condition (Turro, 1991). Intramolecular donor-acceptor (D-A)-type molecules, like the one in this instance, are the main focus of current trends in research into novel TADF emitters (Li et al., 2014). To create full-color TADF molecules with their HOMO and LUMO localized on various constituents, suitable donor-acceptor units must be carefully chosen. Time-Dependent Density Functional Theory (TD-DFT) computations were done at the B3LYP/6-31G(d,p), B3LYP/6-311+G(d,p), B3LYP/cc-PVTZ, and CAM-B3LYP/6-311+G(d,p) levels to learn more about the geometric and electrical structures of **1-5**. For compounds **1** through **5**, Table 1 lists the HOMO and LUMO energies as well as the energy difference between singlet- and triplet-excited states.

Narrower E_{ST} values are the result of the border molecular orbitals' distinct separation. With CAM-B3LYP/6-311+G(d,p) level, ΔE_{ST} data for **A** itself was calculated to be 0.50 eV. The ΔE_{ST} values for **1**, **2**, and **3** were a little lower than the parent values but still need improvement. Compounds **1** through **5** have all been identified as the top possibilities for TADF emitters since ΔE_{ST} values below 0.50 are thought to be productive for TADF potential. Compounds **4** and **5** have been calculated to have even degenerate T_1 and S_1 levels, a totally twisted geometry, and a very highly separated HOMO-LUMO distribution. They can therefore be regarded as the most viable choices for TADF emitter. Thus, for practically all of the compounds, but especially for **4** and **5**, the ΔE_{ST} values anticipated by the TD-DFT calculations are modest enough to allow for thermal repopulation of the S_1 state via T_1 - S_1 reverse intersystem crossing (RISC). Since they have

the best separated HOMO and LUMO schemes and the narrowest S_1 - T_1 energy differential of all, **5**, may have the maximum potential as TADF emitters. The HOMO-LUMO transition, which relates to an intramolecular charge transfer (ICT) with low exchange energy, can explain all computed lowest-energy excited states.

The anthracene derivative (**2**) has a distinct HOMO-LUMO distribution and a 71° dihedral angle; it is estimated to have an ΔE_{ST} of 0.27 eV, which is fairly low to be a contender. The dihedral angle of the pyrene substituted system (**3**) is 38° , and its ΔE_{ST} was determined to be 0.25 eV. The parent structure's triphenyl amine and pyrido[2,1,6-de]quinolizine substituted derivatives had the narrowest ΔE_{ST} data, indicating the most qualified candidates.

4. CONCLUSIONS

Nonlinear optical phenomena form the basis of many components of optical sensing, optical communications systems, and materials research. Nonlinear optics allows us to change the color of a light beam to change its shape in space and time, and to create the shortest events ever made by humans. Recall that, in normal linear optics, a light wave acts on a molecule, which vibrates and then emits its own light wave that interferes with the original light wave. Pyrazine based organic systems are quite important due to their ability to act as medicinal use, chemosensors, optical material and many others. Therefore, investigation of compounds having potential to act as a nonlinear optic materials has gained very fast interest of the scientific community recently. In this article pyrazine based potential NLO molecules (**1-5**) have been computationally considered for lightening of its electronic and structural properties. Ususally, NLO materials can also show OLED activity, thus, the present structures have also been subjected to theoretical analysis in order find their semiconducting abilities. Moreover, thermally activated delayed fluorescence activity has been computed to investigate how much these newly designed compounds carry the potential to increase the quantum yield of excitation followed by emission, namely fluorescence.

Mostly preferred donors have been paired with a well-known acceptor, 2-((3,6-dimethylpyrazin-2-yl)methylene)malononitrile, to create prospective TADF emitters. Their structural and electrical characteristics were calculated by applying density functional theory at various theoretical levels. Due to their well-separated HOMO-LUMO orbitals and ΔE_{ST} data, the proposed compounds **4** and **5** were chosen as the best candidates for TADF emitters. On the other hand, because each has an interfrontier molecular orbital energy gap that is less than 4.0 eV, they can all be employed as semiconductors.

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CHAPTER 6

NANOCOMPOSITE AND NANOHYBRID GEL POLYMER ELECTROLYTES FOR SAFE AND HIGH PERFORMING LITHIUM METAL BATTERIES

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1. INTRODUCTION

Lithium-ion batteries (LIBs) have gained widespread popularity in the fields of portable electronics, electric vehicles, and grid storage due to their remarkable characteristics. These include their exceptional energy density, power density, and extended cycle life. The high energy density of LIBs allows them to store a significant amount of energy in a compact size, making them ideal for portable electronic devices. Additionally, their high power density enables them to deliver a substantial amount of power quickly, which is crucial for applications such as electric vehicles. Moreover, LIBs exhibit a long cycle life, meaning they can undergo numerous charge and discharge cycles without significant degradation in performance. This longevity makes them reliable and cost-effective for grid storage systems. Overall, the exceptional features of LIBs have propelled their extensive use in various industries, revolutionizing the way we power our devices and vehicles. The discovery of intercalation electrodes by Whittingham in the 1970s laid the foundation for LIB development. In the subsequent decades, Goodenough and his colleagues played a pivotal role by developing crucial cathode materials such as layered, spinel, and polyanion. Additionally, Yoshino's pioneering work involved the creation of the first safe LIB prototype, which employed LiCoO_2 as the positive electrode and carbon/graphite as the negative electrode. Since then, remarkable advancements have been achieved in increasing energy density, power density, cycle life, cost-effectiveness, and safety of lithium-ion batteries (Liu, 2021).

Sony was the first company to commercialize Yoshino's LIB prototype in 1991 (Yoshio,2009) and according to the Grandview Market Analysis Report (2022), the global lithium-ion battery market was valued at USD 54.4 billion in 2023. Moreover, there are projections indicating a compound annual growth rate (CAGR) of 20.3% from 2024 through 2030.

Considering the pressing reality of the worldwide climate crisis and the diminishing reserves of fossil fuels, the United States and

European Union have devised strategic technology roadmaps to encourage the widespread utilization of electric vehicles (EVs) and gradually phase out conventional fossil fuel vehicles by 2030 and 2050, respectively. This shift towards electric-powered transportation also underscores the imperative requirement for advanced battery technologies that surpass the existing lithium-ion technology (300 Wh/kg) based on intercalation chemistry (Choi, 2016).

One of the main components that will allow for a low-carbon civilization is battery technology. because they efficiently store electricity produced by renewable energy sources and serve as a power supply for electric vehicles, both of which contribute to the reduction of greenhouse gas emissions. Batteries are anticipated to serve as key facilitators, expediting the transition towards sustainable and intelligent mobility. By offering clean, affordable, and secure energy solutions, they have the potential to mobilize the industry towards embracing a cleaner and circular economy (to achieve all significant components of the UN Sustainable Development Goals). If it is possible to achieve all four objectives simultaneously, namely making them more affordable, safe, ultra-high performing, and sustainable, it would be a significant advancement. Put differently, batteries are an essential technological tool in the fight against carbon dioxide emissions from the energy, transportation, and industrial sectors. But in order to meet our sustainability targets, batteries will need to operate at a level well above what they can do now. Ultra-high performance encompasses exceptional longevity and dependability, enhanced safety and environmental sustainability, and energy and power performance that approaches theoretical boundaries. Additionally, for these battery technologies to be commercially viable, they must be scalable in order to allow for large-scale production at a reasonable cost. (Battery 2030+ Roadmap, 2023).

LIBs, or lithium-ion batteries, consist of two electrodes: the cathode, which is the positive electrode, and the anode, which is the negative electrode. These electrodes are separated by a porous separator material. (Armand, 2008). The electrolyte is very important for the

cycle life of the battery and it is made up of a lithium salt, such as lithium hexafluorophosphate (LiPF_6), lithium perchlorate (LiClO_4), lithium triflate (LiCF_3SO_3), lithium perbromate (LiBrO_4) and lithium bis(trifluoromethanesulfonyl)imide (LiTFSI), dissolved in an appropriate organic solvent (for example, a mixture of ethylene carbonate (EC) and dimethyl carbonate (DMC)). The cathode and anode active materials are coated onto aluminum and copper foil current collectors, respectively. The electrolyte plays a crucial role in enabling the movement of ions between the anode and cathode, thereby maintaining a balanced charge. Additionally, it enables the extraction of electrical energy through the external circuit. On the other hand, the separator serves the purpose of preventing any short circuits between the two electrodes, while it still allows the transfer of lithium ions. Discharging process involves the movement of lithium ions as they migrate from the anode and intercalate into the gaps present between the layers of cathode crystals. This phenomenon is scientifically termed as intercalation. On the other hand, during the charging process, the lithium ions relocate from the cathode, which is situated on the positive side of the battery, and insert themselves into the anode (Ghiji, 2020).

Electrochemical behavior of lithium-ion batteries are heavily dependent on the electrolyte. This is primarily because of the interfacial reactions that take place between the electrodes and the electrolyte. Electrolyte must be compatible with both the positive and negative electrodes, current collectors and separator. An ideal electrolyte should also not undergo any chemical and electrochemical reactions as it comes into contact with electrode surfaces that have strong oxidation/reduction properties. This situation is only achieved by the deposition of a solid electrolyte interface (SEI) on the surface of anode (kinetic protection). Formation of the protective SEI layer depends on the characteristics of the additives, impurities, solvents and dissolved substances present in the electrolyte. Solutes must have high solubility in the solvent and stability over a wide temperature range. Other factors affecting electrolyte selection are cost, safety, health and environmental compatibility (Xing, 2022).

Depending on the composition of the electrolyte solution, in the initial charge carbonate-based electrolytes are reduced against Li/Li^+ at the negative electrode (i.e. graphite electrode) between the voltages from 1.5 to 0.7 V. Therefore, the electrode-electrolyte interface film (SEI) forms on the anode as an electronically insulating but permeable layer to lithium ions. SEI film, as a passivation layer on the anode, is a critical structure for high current efficiency and battery voltage, cycle life and safety. Carbonates such as Li_2CO_3 and ROCO_2Li are indispensable components of the SEI layer due to their acceptable Li^+ conductivity (Wang, 2018).

The rising popularity of electric vehicles and portable/wearable devices has created a growing need for lithium-ion batteries (LIBs) that are both extremely safe and affordable, while also providing high energy density for lasting longer on a single charge. Unfortunately, even conventional LIBs consisting of a graphite anode and lithium cobalt oxide (LiCoO_2) cathode, have an average theoretical energy density of only 387 Wh/kg (Cohn, 2017). Specific capacity of a battery is greatly influenced by the cathode and anode materials. In the context of anode materials, scientists have been diligently searching for alternatives to the conventional carbon-based anodes in order to enhance the specific capacity. A notable avenue of exploration involves the substitution of lithium metal for traditional carbon-based anodes. This substitution is expected to result in a higher specific capacity, and thus, researchers are actively investigating its feasibility (Qi, 2021). Because it can provide the highest possible capacity of $3860 \text{ mAh}\cdot\text{g}^{-1}$, lithium metal as an anode material has drawn tremendous research attention of researchers worldwide (Hatzell, 2020). However, lithium is a highly reactive metal that grows dendrites during the cycling of lithium-metal batteries (LMBs) and this may trigger thermal runaway behaviour which is more serious for LMBs. Therefore, it is crucial to acknowledge that the thermal stability and mechanical strength of electrolytes play a vital role in ensuring the safety of LMBs operating under long-term and extreme conditions. Consequently, the pursuit of safe electrolyte technologies to enhance the safety of LMBs has

become an area of utmost importance and is considered critically significant in research (Yan, 2014).

Currently, commercial LIBs face certain constraints due to their liquid organic electrolytes. These limitations include flammability, thermal instability, and the tendency of organic solvents to volatilize strongly. Consequently, there is a high risk of fire and explosion in situations of overcharge and short circuit. However, the implementation of all solid-state electrolytes offers notable benefits such as a higher shear modulus, flexibility, and non-inflammability. These advantages have the potential to greatly enhance the safety and energy density of LIBs, making them the most efficient energy storage technology for future generation of emerging energy storage systems (Ji, 2023). However, the successful commercialization of all-solid-state batteries remains a significant obstacle due to several unresolved issues. These include the electrochemical instability caused by high voltage levels exceeding 4.5 V (vs. Li/Li⁺), the incompatibility between lithium metal interfaces, and the inadequate ionic conductivity. Overcoming these challenges is crucial for the realization of viable all-solid-state batteries in the future. (Chai, 2016).

Substitution of organic liquid electrolytes by all solid-state electrolytes is a fundamental approach to tackle safety issues, particularly in the context of lithium metal batteries (LMBs). The investigation into solid-state electrolytes, which are composed of polymers, ceramics, or their combinations, has recently progressed towards viable real-world implementations. (Kalhoff, 2015). Certain inorganic electrolytes have been found to exhibit ionic conductivity that is comparable to, or even surpasses, that of commercially available liquid electrolytes. Nevertheless, solid-state batteries (SSBs) incorporating these inorganic electrolytes often exhibit suboptimal performance due to inadequate interfacial contact between the electrolyte and electrode (Wang, 2020). Therefore, broad applications of solid electrolytes are still in its infancy due to their limited performance compared to liquid electrolytes (Ren, 2021). The realm of solid electrolyte technologies has witnessed a significant focus on

polymer electrolytes (PEs). This can be attributed to their remarkable ability to maintain a consistent volume throughout the charge and discharge cycle, thereby ensuring stability. Additionally, PEs offer a high level of safety, making them an appealing choice. Furthermore, their ease of manufacturing further enhances their appeal (Gao,2021). Polymer electrolytes find extensive application across a wide range of sectors, encompassing consumer electronics, electric vehicles, and energy storage systems. Moreover, their utilization extends to medical and military domains, where the paramount considerations of safety and dependability hold utmost significance (Chattopadhyay,2023). Utilization of polymer electrolytes holds promise in preventing severe challenges, such as leakage of the electrolyte, flammability, and lithium dendrite formation, thereby bolstering the thermal and electrochemical stabilities of LMBs (Castillo, 2021).

Solid polymer electrolytes (SPEs), which are made up of a lithium salt dispersed in the solid polymer matrix, have better mechanical strength along with chemical, electrochemical, and thermal stability than that of conventional liquid electrolytes. Combination of SPEs and lithium metal anode is attractive for high batteries having long service life but their ionic conductivity at ambient temperature and large electrolyte/electrode interfacial resistance are main drawbacks for their commercial applications (Lee, 2023). Gel polymer electrolytes (GPEs) was introduced to overcome the weaknesses of SPEs by absorbing liquid electrolyte into polymer matrix. As a compromise, gel polymer electrolytes (GPE), which consist of a liquid organic electrolyte containing a polymer matrix and lithium salt, have advantages of both liquid and solid-state electrolytes (Hu,2020). GPEs present distinct advantages over solid electrolytes when it comes to enhancing the connection with electrodes (Li, 2023). Considerable advancements have been achieved in the enhancement of GPEs, resulting in their extensive utilization across diverse battery systems. Similar to liquid electrolytes, GPEs can provide high ionic conductivity, while they have superior electrochemical stability with

functional additives, flexible processability, and no leakage (Cui,2017). Within a GPE structure, polymer chains intertwine to create a polymer network characterized by interlinked pores. These pores play a crucial role in enhancing the efficient uptake of the liquid organic electrolyte and facilitating Li^+ mobility . The liquid component plays an important role in enhancing ionic conductivity and interfacial stability, while the polymer matrix provides relatively higher mechanical strength and sufficient shape flexibility. The presence of the liquid component is crucial for improving both ionic conductivity and interfacial stability, whereas the polymer matrix is responsible for imparting greater mechanical strength and shape flexibility. At this stage, GPEs are the most promising electrolytes that can be easily adapted to existing battery technologies. Effective trapping of the liquid component within the polymer matrix can eliminate the leakage problem and enables the use of GPEs in LMBs. Moreover, the remarkable flexibility and elasticity of polymer structures enable them to withstand the adverse effects of electrode volume changes and dendrite puncture-induced short circuits in traditional separators. As a result, the development and production of advanced GPEs are considered a logical approach to achieving both safety and longevity in LMBs (Ren, 2021).

In this review article, state-of-the art polymer electrolytes are discussed with special emphasis of safety issues with conventional liquid electrolytes, gel polymer electrolytes, in situ polymerization method, nanocomposite (NCGPEs) and nanohybrid polymer electrolytes (NHGPEs).

2. SAFETY ISSUES WITH LIQUID ORGANIC ELECTROLYTES

Determination of an appropriate electrolyte is crucial for maintaining high performing and safe LIB, as the electrolyte serves as a critical interfacial component responsible for ion transport and interfacial stability towards the electrodes. Electrolytes utilized in LIBs must fulfill a range of requirements. High boiling point, low vapor pressure and melting point are essential characteristics that allow for a broad range of operating temperatures. Additionally, favorable

transport properties that facilitate the rapid movement of lithium ions between the anode and cathode, as well as chemical and electrochemical stability to preserve the integrity of the electrolyte during the charge-discharge process, are vital. Other important properties include high ionic conductivity to achieve high power by facilitating the movement of lithium-ion cations, the ability to form solvates with salts at low temperatures (particularly for low-temperature cells), and the formation of an SEI film to prevent side reactions between anode and electrolyte. The deterioration of the aluminum material, which functions as the current collector, is also a significant aspect to consider. To avoid corrosive pitting of the collector, it is imperative for the electrolyte to passivate the electrolyte-aluminum interface (Pigłowska, 2021).

The conventional liquid organic electrolytes consist of carbonate solvents, such as ethylene carbonate (EC), diethyl carbonate (DEC), ethyl methyl carbonate (EMC), dimethyl carbonate (DMC), and propylene carbonate (PC). It is important to note that these solvents are flammable and have the potential to cause a catastrophic failure if subjected to excessive heat, internal short circuits, or battery penetration (Zhou, 2021). Cyclic carbonates, primarily PC and EC, exhibit a significantly high dielectric constant. This characteristic increases solubility of lithium salts that possess high viscosity, owing to the strong intermolecular interactions. However, high dielectric constant also hampers the movement of ions. On the other hand, linear carbonates demonstrate lower viscosity due to their linear structure, which increases degree of freedom of solvent molecules (as shown in Table 1). The electrolyte viscosity can be effectively reduced and electrolyte conductivity can be enhanced through incorporating linear carbonates, such as EMC, DMC and DEC. To optimize cell capacity and cycling performance, a combination of linear and cyclic carbonates is frequently used, such as the EC/DMC mixture in a 1:1 weight ratio or EC/EMC in a 3:7 ratio by volume. This mixture positively impacts the cell capacity. Nevertheless, lower viscosity of this mixture is linked to a lower flash point, which raises safety concerns (Pigłowska, 2021).

Regrettably, these linear carbonates possess a significant level of volatility and flammability, exhibiting flash points (FPs) within the range of room temperature (approximately 16 to 33°C). When combined with an oxidant and a source of ignition, they have the potential to initiate fires and explosions. To address the fire risk associated with the electrolyte, one approach is to employ non-flammable solvents or incorporate flame-retardant additives into the electrolyte composition (Hess, 2015). Examples of flame-retarding solvents used in the electrolyte include trimethyl phosphate (TMP), triethyl phosphate (TEP), tributyl phosphate (TBP), and triphenyl phosphate (TPP). Among the various options, TMP is especially appealing because can dissolve lithium salts at high concentrations, besides it has high dielectric constant, low viscosity and wide liquid temperature window (- 46 to 197°C). Nevertheless, stability of TMP is compromised in the presence of lithium metal, leading to its decomposition at a potential of 1.2 V versus the Li/Li⁺ reference electrode. Moreover, utilization of TMP does not provide a fundamental solution to the dendrite problem as it is unable to form a stable SEI on the surface of lithium metal (Zhou, 2021).

Stability of lithium metal anode is heavily dependent on SEI. However, SEI layer undergoes continuous reforming and consumes electrolyte during cycling. Consequently, Li metal anodes (LMAs) experience significant capacity loss, with Coulombic efficiencies above 95% (Sayavong, 2023). The rational design of a stable SEI has been hindered by the inability to control its structure and stability. In order to improve battery performance of LMBs having liquid electrolyte, Gao et al. designed an SEI by using a reactive polymer composite (RPC) having inorganic nanoparticle and two dimensional (2D) nanomaterial that effectively mitigates electrolyte consumption during SEI formation and maintenance. They coated RPC as the three dimensional host on the lithium metal anode to stabilize SEI layer. The SEI layer in this RPC stabilized lithium metal electrode comprised lithium fluoride nanoparticles, and graphene oxide sheets, a polymeric lithium salt. Notably, this structure displays distinct characteristics compared to the

SEI derived from organic electrolyte and demonstrates exceptional passivation properties, uniformity, and mechanical durability. By utilizing the polymer-inorganic SEI, they achieved efficient lithium deposition, high capacity and and stable cycling of 4 V Li|NMC532 cells. This study revealed that polymer/inorganic composition of the SEI layer with 3D RPC host structure outstandingly stabilized and effectively suppressed electrolyte decomposition. As a result, Li metal batteries can undergo stable cycling even with limited electrolyte, marking a significant advancement in reducing electrolyte consumption. Additionally, this technique was proficiently broadened to devise stable SEI films for sodium and zinc anodes (Gao, 2019). Even though, stabilization of SEI by using this 3 D host of RPC having nanoparticles and nanomaterials is a progress for reducing organic electrolyte loss in LMBs and so obtaining stable discharge profile for 200 cycles, this design is still not sufficient for practical applications of LMBs. In addition, the utilization of ionic liquids (IL) in GPEs holds great promise due to their exceptional electrochemical properties, which set them apart from organic solvents. In contrast to the safety hazards posed by organic solvents, IL offer a safer alternative for various applications (Garaga, 2023).

Table 1: A compilation of carbonate solvents along with their enhanced attributes in comparison to traditional solvent constituents, wherein “+”/“-” denotes a favorable/disfavorable impact on the electrochemical system, while “0” indicates no apparent effects (Pigloska,2021).

Solvent	EC	PC	EMC	DEC	DMC
Melting point	+	-	-	-	0
Boiling point	+	+	-	-	-
Viscosity	+	+	-	-	-
Dielectric constant	+	+	-	-	-
Construction to SEI	+	-	-	-	-
Flash point	+	+	-	-	-
Safety	+	0	-	-	-
Anodic stability	+	+	0	0	0

3. GEL POLYMER ELECTROLYTES

Composition of GPEs allows for their classification into three distinct categories. These categories are comprised of GPEs with plasticizers, GPEs with inorganic fillers, and GPEs that contain both plasticizer and inorganic filler. The presence of lithium salt is essential in the electrolyte as it facilitates the movement of ions within the polymer framework. Additionally, the polymer itself provides the required mechanical strength to accommodate the electrolyte. The utilization of inorganic fillers in GPEs can be traced back to the early 1980s when researchers aimed to increase mechanical stability of the polymer matrix (Huy, 2021). To enhance properties of polymer matrices and achieve high performance in LIBs, blending, copolymerization, and crosslinking techniques are commonly employed. Within GPEs, the liquid electrolyte is securely held by the polymer through physical and chemical cross-linking, resulting in improved stability and functionality (Kim,2010).

Polymer matrices commonly employed in GPEs encompass polyethylene oxide (PEO) (Xue,2015), poly (vinylidene fluoride) (PVDF) (Balakrishnan, 2023), poly(methyl methacrylate) (PMMA) (Hosseinioun, 2019) and polyacrylonitrile (PAN) (Liu, 2016). GPEs can be fabricated by encapsulating liquid electrolytes within various polymer hosts. In this scenario, salt solutions are confined within the polymeric framework, facilitating the process of ionic conduction, while the host polymer imparts mechanical stability. The characteristics and structure of the GPE are contingent upon the specific type and quantity of salt and solvent incorporated within polymer matrix (Tafur, 2014). Preparation of GPEs involves primarily two different techniques, which are determined by inherent characteristics of preparation process. One approach utilizes a porous polymer matrix that enables uptake of the liquid electrolyte by swelling. This objective can be accomplished through two methods: selectively extracting a solvent from a polymer solution or directly creating fibrous structures with inherent porosity within the polymer matrix. Solution casting and phase inversion are the two widely studied processes under this

technique. In solution casting process, a polymer, such as PEO and PVDF-HFP or blend of these two is dissolved the liquid electrolyte containing lithium salt and organic solvents. The polymer concentration is usually in the range of 5-20% by weight of the GPE (Song,1999). Since high cycle life cannot be achieved in lithium polymer batteries obtained with this technique, they have not been preferred in recent years. In the second method, polymer membrane with a microporous and channeled morphology is prepared by different methods (mostly by phase inversion approach). This membrane replaces the separator so there is no need to use additional separator. Then, by soaking the polymer membrane in organic electrolyte, which usually contains 1-1.2 M lithium salt (LiPF_6 , LiTFSI , etc.), the membrane becomes electrochemically active and so the gel polymer electrolyte is obtained (Liu,2016). When compared to polymer membrane obtained by solution casting, GPE membrane by phase inversion method, which has interconnected and open micropores, has a much higher surface area compared to the conventional organic electrolyte/separator system, thus increasing ion storage and Li^+ mobility (high t_{Li^+}) (Pu,2006). Although the Li^+ transference number of PVDF-HFP based GPEs is higher than other polymer matrix materials, the ionic conductivities of GPEs are lower than liquid organic electrolytes. When this approach is used, the performance of lithium-ion polymer batteries can be increased by adding ionic liquids (ILs) or nano-sized materials or both into the GPE system. In a 2023 study, blend ethyl-methyl imidazolium bis(trifluoromethanesulfonyl)imide (EMIMTFSI) and PVDF-HFP was combined with 3% Al_2O_3 nanofibers (by weight of GPE), characterized by diameters of 2–6 nm and lengths of 200 - 400 nm. This formulation yielded about 200% increase in the ionic conductivity of GPE (Garaga, 2023).

To summarize, GPEs can be synthesized by means of phase inversion, solution casting and in situ polymerization methods. These techniques have been acknowledged for their energy efficiency, cost-effectiveness, and environmentally friendly attributes when compared to alternative approaches for GPE preparation (Kim, 2019). The

application of suitable nanoparticles and nanomaterials in GPEs has recently emerged as a highly promising strategy. This advancement is focused on improving mechanical strength of the membrane, enhancing ionic conductivity, and facilitating efficient transfer of Li^+ ions. Ultimately, it leads to superior performance of GPEs in LIBs (Long,2016).

3.1. Anion receptors and single ion conducting gel polymer electrolytes

SPEs that consist of a polymer matrix and lithium salt are commonly referred to as bi-ionic conductors. In these conductors, the cations form bonds with the polar groups of the polymer electrolyte, leading to a faster movement of anions. As a result, anions contribute more to the overall ionic conductivity compared to cations. However, the migration of anions towards the anode can lead to a significant concentration polarization, which in turn causes a notable decrease in conductivity and an increase in cell impedance over time. The property known as t_{Li^+} plays a crucial role in determining whether the conductivity is solely attributed to lithium ions. Typically, lithium ion transport occurs not only with free lithium ions but also with ions of varying sizes that are combined within the system (Jo, 2002). To reduce polarization, two approaches are implemented to limit the movement of anions. The initial approach is to bond anions to the polymer's main chain (backbone), which is a prevalent method for obtaining single ion-conducting polymers. The second approach involves incorporating an anion receptor that exhibits a preference for interacting with anions. The recognition and binding of these receptors to anions are facilitated through hydrogen bond interactions, covalent binding of the anion, or Lewis acid-base interactions. Recently, utilization of boron-based anion receptors as electrolyte additives in lithium-ion batteries and metal-air batteries has gained momentum due to the growing interest in their potential. These receptors, commonly used in biosensors, are being studied for developing high capacity batteries that can operate efficiently at elevated voltages. Boron-based anion receptors have the potential to serve as electrolyte additives in carbonated electrolyte

solutions. This potential benefit resides in their capacity to enhance cycling efficiency of lithium-ion, lithium metal and lithium air batteries, while also enhancing the transfer of lithium ions and the conductivity of ions. Furthermore, these anion receptors have been found to have a crucial role in stabilizing SEI layer on the surface of anode (Reddy, 2014). However, presence of insoluble inorganic salts, including LiF, Li₂O₂, and Li₂CO₃, within the SEI layer poses challenges in terms of electron and lithium ion transportation. Consequently, this leads to an increase in impedance and a decline in capacity. To overcome these obstacles, anion receptors within the SEI layer exhibit a specific binding attraction force, which facilitates the dissolution of anions such as F⁻, OH⁻, and O²⁻. This dissolution process enables the removal of these anions from the SEI layer, thereby mitigating the impedance increase and capacity loss (Choi, 2013).

Several studies have demonstrated that boron anion receptors, including tris(pentafluorophenyl)borane (TPFPB), have a positive impact on the formation and thermal stability of the solid electrolyte interphase (SEI) on the graphite anode. This effect is particularly observed during the initial galvanostatic cycling of lithium-ion batteries that utilize a carbonaceous meso-carbon microbead (MCMB) anode. The presence of boron anion receptors enhances the SEI formation and improves its resistance to thermal degradation, thereby contributing to the overall performance and longevity of the battery system (Sun, 2003). The research conducted by Amine et al. demonstrated that the incorporation of TFPB additive at concentrations lower than 3% in LiPF₆-based liquid organic electrolytes has a significant impact on the performance of NMC cathode/graphite anode batteries. Specifically, this additive enables the battery to charge and discharge at high power levels. This improvement can be attributed to the role of TFPB in breaking down the accumulated LiF within the SEI layer, acting as an anion receptor. Consequently, the impedance decreases, resulting in enhanced lithium ion conductivity (Qin, 2010).

The incorporation of boron anion receptors as additives to the polymer electrolyte has yielded promising results. As a result, recent

research efforts have been focused on the development of single-ion-conducting polymer electrolytes. This involves the covalent immobilization of anionic groups on the polymer backbone, which selectively allows the mobility of Li^+ cations throughout the polymer matrix. Compared to binary ionic conductors, these ion-selective polymers offer several advantages in battery operation, such as minimizing cell polarization and dendrite growth. These findings underscore the potential of utilizing these polymer electrolytes to enhance the efficiency and performance of batteries (Gao, 2021). Wang et al. successfully synthesized polymeric lithium tartaric acid borate (PLTB) with boron incorporated into the main polymer chain. This synthesis was accomplished in a single step. The researchers then proceeded to create a microporous membrane by combining PVDF-HFP and PLTB, which was subsequently gelled with PC. Despite achieving a high t_{Li^+} above 0.90, the resulting ionic conductivity at 20°C was below 0.15 mS/cm . In subsequent experiments, the team tripled the ionic conductivity and obtained a t_{Li^+} value above 0.90 by gelling the polymer membrane with a conventional liquid electrolyte. However, the achieved ionic conductivity was still insufficient for the efficient operation of this technology at high charge-discharge rates or low temperatures, such as those required for electric vehicles (Wang, 2013).

In a 2023 study by Wang *et. al*, the successful synthesis of a novel GPE membrane, known as polyethyleneimine (PEI)/PVDF-HFP cross-linked membrane and electrolyte (PPCM GPE), has been reported. The presence of PEI molecular chains, which contain amine groups, played a significant role in the formation of this membrane. These amine groups acted as abundant anion receptors and effectively immobilized the anions present in the electrolytes. The unique cross-linked structure of PPCM, combined with the utilization of its amine groups, resulted in a high t_{Li^+} value of 0.70. By incorporating PPCM GPE into the assembled cells, the battery performance was significantly improved due to the enhanced ionic conductivity and Li^+ transference number. This highlights the potential practical application of

Li/PPCM/LFP full cells in the field of LMBs. To further enhance the safety and rate capabilities of LMBs, a feasible approach involves the development of porous polymer membranes that possess a gradient distribution of pores and are rich in anion receptors (Wang, 2023).

3.2. *In situ* polymerized gel polymer electrolytes

The conventional manufacturing methods for polymer electrolytes are commonly known as *ex situ* processes. In these processes, the polymer electrolytes are prepared as separate films and then assembled into the battery. However, this approach often leads to inadequate physical contact between the *ex situ* polymer electrolytes and the electrodes due to the presence of voids within the electrodes. As a result, the polymer electrolyte films prepared in this manner are unable to fully penetrate the porous cathodes in *ex situ* processes, resulting in a significant decrease in the utilization of active materials and achievable energy density. To address this issue and enhance the interfacial contact between the electrolytes and electrodes, an alternative method called *in situ* polymerization of polymer electrolytes has been proposed. This approach involves the polymerization of electrolytes directly within the battery. *In situ* polymerization has emerged as a highly promising technique for reducing interfacial resistance and improving interfacial compatibility, thereby enabling the production of commercial lithium-based batteries. In comparison to *ex situ* processes, the *in situ* polymerization process is compatible with the production of existing liquid-based batteries. This eliminates the need for additional preparation of electrolyte films or the evaporation of solvents. This compatibility further emphasizes the potential of *in situ* polymerization as a viable manufacturing method for various types of batteries (Xiao,2023). Moreover, in addition to the advantages stated earlier, it has the ability to enhance the overall design of bare cells. This is achieved by injecting the precursor material before the polymerization process, enabling the desired shapes to solidify and improving the form factor. The enhancement of mechanical performance without the need to increase the thickness of the glassy polymer electrolyte (GPE) can be achieved through the utilization of *in*

situ polymerization in conjunction with the cross-linked network design flexibility (Shim,2017). Additionally, it is a method that is scalable, easy to produce, and fast (Ren,2021).

In the *in situ* polymerization, a lithium-ion cell is fabricated by assembling the liquid precursor solution consisting of lithium salt, organic solvent composition, monomer(s), reaction initiator and electrolyte additives with an anode, separator and cathode. The resulting battery is then heated at 60-80 °C or exposed to UV light, and gelation occurs through *in situ* polymerization within the battery. This technique is called *in situ* polymerization. The obtained GPEs by this method has a higher viscosity than liquid electrolyte and consists of homogeneously dispersed lithium solution within a cross-linked based polymer network (e.g. poly-acrylate, polyamide, etc.) and thus the *insitu* formation of GPE results in the development of a superior electrode/electrolyte interface. This interface exhibits enhanced receptivity towards Li⁺ ion migration, thereby promoting homogeneous Li⁺ dispersion and preventing the formation of Li dendrites in the LMBs (Chen,2021). This method allows rapid preparation of GPE films in the battery and improvement of their electrochemical compatibility. Chemical cross-linking results in an irreversible gel. Therefore, chemically cross-linked GPEs have superior thermal and dimensional stability at high temperatures compared to physically cross-linked GPEs. The structure and properties of polymer chains are significantly influenced by monomers. In the synthesis of chemically cross-linked GPEs, acrylate cross-linkers are commonly used due to their fast cross-linking reaction (Choi,2009).

Preparation of GPEs by thermal *in situ* method in batteries is based on free radical polymerization and cross-linking (Park,2023). For this purpose, free radical initiator, liquid electrolyte, vinyl monomers (acrylate, methacrylate, acrylonitrile, carbonate derivatives, etc.) and multifunctional cross-linkers (trimethylolpropane triacrylate (DTPA), poly(ethylene glycol) diacrylate (PEGDA), ethoxylated trimethylolpropane triacrylate (ETPTA), etc.) are commonly used (Chae,2023). Acrylate-based polymers are known to provide high ionic

conductivity and reduce the interface resistance between the electrode and the gel polymer electrolyte. Moreover, their stability against electrochemical oxidation has made them promising polymer matrices for electrolytes with high electrochemical stability, especially in high energy density lithium battery cells. For example, polyethylcyanoacrylate (PECA), which has strong coordinating and high electrochemical stability due to the nitrile groups in its structure, is one of the promising matrices for polymer electrolytes. Cui *et al.* synthesized PECA-based GPE thanks to a rapid and reproducible *in situ* polymerization strategy. They obtained PECA-based GPE with high efficiency by anionic polymerization of ethylcyanoacrylate (ECA) with 4 M LiClO₄ solution prepared in EC/DMC solvent mixture with volumetric ratio 1:1. Resulting GPE had the ionic conductivity of 2.7 mS cm⁻¹ at room temperature and it was electrochemically stable up to 4.8 V. In addition, LiFePO₄/PECA-GPE/Li and LiNi_{1.5}Mn_{0.5}O₄/PECA-GPE/Li batteries produced with this electrolyte had a stable charge/discharge profile as well as high C-rate and battery cycle performances. By this study, high electrochemical stability was achieved thanks to the nitrile functional groups of the polymer. In addition, the interaction of nitrile and ester functional groups with Li⁺ ions contributed to the increase in the solubility of the lithium salt and efficient charge transfer (Cui,2017).

Liu *et al.* polymerized PEGDA in organic liquid electrolyte by *in situ* thermal polymerization, where PEGDA polymer was the polymer matrix, while cellulose acetate (CA) which has a large number of polar groups was used as an additive. High ionic conductivity (8.81 mS.cm⁻¹ at 30°C) and high lithium transference number (0.79) were obtained in GPE and the electrochemical stability window was measured as 4.56 V. Addition of CA increased the ion-dipole interaction, which facilitated the transport of Li⁺ ions. With the structural analysis of the GPE, it was observed that as an additive CA improved the electrode/electrolyte interface by reducing the viscosity in the polymerization of PEGDA (Liu,2020).

In another recent study, published in the journal *Nature* in 2022, which draws attention to the importance of using poly(ethyleneglycol) diacrylate (PEGDA) polymer as a polymer matrix, it was reported that by in situ polymerization of PEGDA and butyl acrylate (BA) in the presence of succinonitrile and LiTFSI, elastomeric solid polymer electrolyte having superior mechanical properties was obtained. Operating at room temperature with a voltage of 4.5 V, the LMB, incorporating a $\text{LiNi}_{0.83}\text{Mn}_{0.06}\text{Co}_{0.11}\text{O}_2$ cathode, achieved an energy density surpassing 410 Wh/kg. This exceptional performance was attributed to the presence of an in situ formed elastomer, which facilitated the development of a 3D interconnected crystalline phase consisting of ion conductive plastic crystals. Furthermore, the solid-state PEGDA-co-BA electrolyte employed in this system exhibited a remarkable Coulombic efficiency of 100%, ensuring efficient charge and discharge processes. Additionally, this electrolyte demonstrated excellent adaptability to volume changes, enabling the LMB to endure long-term lithium plating and stripping cycles (Lee, 2022).

In GPEs, the solvent is encapsulated within the GPE. When phase inversion method is used along with electrochemical activation of the membrane with the liquid electrolyte, electrolyte uptake is an important parameter because high electrolyte uptake of the polymer matrix results in high conductivity. The high electrolyte uptake is closely related to the porosity of the polymer membrane (Zhang, 2014). The polymer electrolytes, which are composed of PVdF/PAN, PVdF-co-HFP/PAN, PEO/PMMA, PEO/Polyurethanes, and P(VdF-co-HFP)/PVAc blends, have been thoroughly examined as the primary material for the polymer electrolyte matrix. In a recent novel study, the miscibility of the PVdF/PMMA blend polymer electrolyte is improved through a unique approach. This involves the in-situ polymerization of methyl methacrylate monomers within the PVdF matrix. The phase inversion membrane composed of PVdF/PMMA blend displayed a uniform microporous structure that boosts a high level of porosity. This unique structure allows for exceptional electrolyte uptake, with an impressive increase of above 400%. Moreover, the membrane exhibits

excellent retention capabilities and a reduced contact angle, further enhancing its overall efficiency. The application of the in-situ blend electrolyte proves to be highly advantageous in rechargeable lithium-ion batteries, even under extreme temperature conditions. Its superior performance can be attributed to its unique composition and optimized properties ($5.2 \text{ mS}\cdot\text{cm}^{-1}$ ionic conductivity, electrochemical stability up to 4.8 V vs. Li), enabling enhanced battery performance and stability (Balakrishnan, 2023). The enhanced characteristics of the GPE ensures the benefit of utilizing the in-situ polymerization technique to improve the electrochemical capabilities of the GPE.

3.3. Nanocomposite Gel Polymer Electrolytes

Studies have continuously been done on composite polymer electrolytes (CPEs) to overcome the shortcomings of both the low ionic conductivity of SPEs and the low mechanical strength of GPEs. Although the ionic conductivities of GPEs can reach $10^{-3} \text{ S}\cdot\text{cm}^{-1}$, their low mechanical strength and poor interfacial properties are obstacles to their practical applications (Long,2016). Thermal, mechanical and electrochemical properties of CPEs depend on the properties of the filler, such as particle size, porosity, concentration, surface area, and interaction between polymer chains and the filler (Kim,2014).

The mechanical strength of polymer electrolytes, especially GPEs, is mainly determined by the polymer matrix. As a result of the combination of the polymer-salt system with the solvent, which is a plasticizer, the solvent reduces the crystalline phase of the polymer matrix. This promotes segmental movement of the polymer matrix and positively affects the ionic conductivity of GPE, while reducing the mechanical strength of the polymer matrix (Hassoun,2015). In this case, dendritic Li can easily pierce GPEs and cause a short circuit between the cathode and anode (An,2022). In order to overcome the shortcomings of both the low ionic conductivity of solid-state polymer electrolytes and the low mechanical strength of GPEs and to improve their ion transport properties, studies on composite polymer electrolytes (CPEs) have been focused on in recent years The addition of inorganic fillers to the polymer/salt system has proven to be a highly effective

approach in enhancing the electrochemical performance of gel-state polymer electrolytes (GPEs). This strategy has demonstrated promising results by improving the electrolytic conductance, as well as enhancing the mechanical and thermal stability of the GPEs. The incorporation of these inorganic fillers has shown great potential in advancing the overall performance of GPEs (Huy, 2021).

Lithium-ion transference number (t_{Li^+}), which constitutes the share of lithium ion in the total current carried in the electrolyte, is another critical parameter in achieving good cycling performance in lithium-ion batteries. Although, ideally the t_{Li^+} value is desired to be close to 1, most electrolytes having high conductivities may have a t_{Li^+} value less than 0.5 due to the concentration polarization of ions that occurs during repeated charge/discharge cycles. This causes long cycle performance to deteriorate. The t_{Li^+} value of lithium-ion batteries can be increased by adding single-ion conductors and Lewis acids, such as ceramic fillers (SiO_2 , Al_2O_3 and TiO_2) and boron-based anion receptors to the electrolyte. When boron anion receptors are used, this improvement is due to the ability to effectively trap anions of lithium salts, thanks to the Lewis acid-base interaction between the empty p orbital of boron and the basic anion of the lithium salt. By improving the electrochemical properties of the electrolyte, the performance and cycle life of the battery increases (Reddy, 2014). The addition of fillers can interfere with the arrangement of polymer chains, reducing the crystallinity of the polymer matrix and thus increasing the amorphous region for better Li^+ migration. Additionally, thermal stability, mechanical durability and electrochemical stability can be improved because all of these three properties are closely dependent on the structure of the polymer electrolyte (Boaretto, 2020). For example, Cho *et al.* synthesized GPE from PAN-PEGDA, $LiPF_6/LiCF_3SO_3$ salt mixture and nano-structured inorganic filler materials (e.g., TiO_2 , Al_2O_3 , $CaCO_3$, $CaTiO_3$, $BaTiO_3$) and improved the discharge capacity and cycle life of the LMB (Huy, 2021). Higher ionic conductivity and lower interface resistance between Li metal and GPE were obtained in all three polymer nanocomposite GPEs having added nanostructured

inorganic fillers, compared to GPEs without added nanostructured inorganic fillers. The reason behind this better Li^+ transport is the fact that the high surface area of nanoparticles improves chemical stability by affecting cross-linking in the polymer electrolyte (Cho, 2007). Boron compounds, which are used as Lewis acids especially in lithium ion batteries, improve the electrochemical properties of the electrolyte by acting as anion receptors. This improvement is due to boron's ability to effectively retain anions of lithium salts, thanks to the Lewis acid-base interaction between the empty p orbital and the basic anion of the lithium salt. By improving the electrochemical properties of the electrolyte, the performance and cycle life of the battery increases (Reddy,2014).

Wang *et al.* prepared a polymer nanocomposite membrane consisting of poly(acrylonitrile-co-vinylacetate), PMMA and TiO_2 nanoparticles by blending and gelled it with 1 M LiPF_6 electrolyte solution to obtain GPE-PAVM: TiO_2 . The ionic conductivity of this electrolyte was found to be approximately 10 times that of the liquid electrolyte prepared with a commercial separator. In addition, thanks to the interaction with TiO_2 , the t_{Li^+} value of GPE-PAVM: TiO_2 was 0.7 by fixing PF_6^- ions and the suppression of PF_6^- degradation enabled high electrochemical stability up to 6.5 V (vs. Li/Li^+). The immobilization of PF_6^- ions also resulted in the formation of a stable solid electrolyte interface and 71% capacity retention of the $\text{LiPO}_4/\text{GPE-PAVM}:\text{TiO}_2/\text{graphite}$ battery after 1000 charge/discharge cycles at 20°C (Wang,2016).

Liu *et al.* conducted a study in which they synthesized a cross-linked GPE through thermal *in situ* polymerization. Synthesized GPE was composed of cellulose acetate (CA) as the matrix, cross-linker PEGDA, and layered hexagonal boron nitride (BN). The polymerization process occurred in a single step at a temperature of 70°C . When CA and BN were combined using the azobisisobutyronitrile (AIBN) polymer initiator, the presence of polar groups in CA and the Lewis acid properties of BN contributed to an increase in the ionic conductivity of the gel polymer electrolyte. The

interaction between the Lewis acid-base properties of GPE and BN resulted in a reduction of ion pairing, thereby enabling the efficient transportation of Li^+ ions. The incorporation of 1% BN into the GPE demonstrated a synergistic effect with the CA matrix, leading to a GPE with remarkable properties. This included a high ionic conductivity of $8.9 \text{ mS}\cdot\text{cm}^{-1}$ at 30°C , electrochemical stability up to 5.5 V, and excellent thermal stability. results of this study emphasize the considerable potential of boron nitride as a valuable additive in improving the efficiency of GPEs (Liu,2021).

3.4. Nanohybrid Gel Polymer Electrolytes

In order to successfully commercialize LMBs, it is crucial to optimize not only the high ionic conductivity values achieved in GPEs but also their t_{Li^+} values and mechanical properties. While GPEs may exhibit favorable ionic conductivity, it is imperative to concurrently enhance the t_{Li^+} values and mechanical properties to ensure their viability in the market. In light of recent advancements in research, the integration of nanoparticles or nanomaterials with chemical bonding into a polymer matrix through in situ polymerization has proven to be a successful approach in improving the mechanical and electrochemical properties of GPEs. By this method, uniform dispersion nanomaterial in polymer matrix is ensured. Based on scientific research findings, thermal *in-situ* polymerization of surface-functionalized nanomaterials and crosslinking monomers is a promising method because nanohybrid GPEs (NHGPEs) having high mechanical strength, ionic conductivity and t_{Li^+} can be synthesized for high-performance and safe LMBs (Shin,2016). Numerous studies have provided evidence that inorganic materials have the potential to enhance both mechanical strength and electrochemical stability. However, the inherent characteristics of inorganic nanoparticles, such as high surface energy and low zeta potential, often result in particle agglomeration and inadequate contact between fillers and polymers. This, in turn, compromises the conduction of Li^+ ions. To address the challenges faced by LMBs, it is imperative to explore methods that can enhance the affinity of fillers for the polymer matrix and establish a uniform pathway for Li^+

transport. This can be achieved by developing composite polymer electrolytes (CPEs) with high ionic conductivity. Recent research has shown that surface modification of inorganic particles has yielded significant advancements in improving both ionic conductivity and interface contact in CPEs. By functionalizing the particles with organic groups, the surface energy difference between fillers and the polymer matrix can be minimized, leading to improved interfacial adhesive strength. This chemical bonding enhances the compatibility between organic and inorganic materials, facilitating the homogenization of lithium-ion flow. Moreover, grafting functional groups onto particle surfaces can introduce new properties to nanoparticles. The performance of CPEs is greatly influenced by the properties of the filler, including particle size, porosity, concentration, surface area, and the interaction between polymer chains and inorganic fillers. Despite the performance enhancement achieved through the addition of inorganic fillers, effectively dispersing these materials within the polymer electrolyte matrix remains a challenge that requires further investigation. Particularly, the homogeneous dispersion of nano-sized inorganic filler materials with high surface area in the polymer matrix is difficult to achieve, often resulting in agglomeration and the formation of crystal structures (phase separation) in CPEs (Wu, 2023).

During the production of nanocomposites, one of the ways to improve the interaction between the polymer and the synthesized nanoparticles (NPs) is to make chemical crosslinking through in-situ polymerization by using polymerizable active nanoparticles and nanomaterials (Zhai,2017). When fillers are physically blended with polymers without any covalent bonding, agglomeration of fillers and poor polymer-ceramic interaction are inevitable and the ionic conductivity of the electrolyte is restricted, thus shortening battery life (Wu,2023). In situ polymerization can effectively solve the problems of inadequate interface between electrode and electrolyte, which is the main reason behind the poor cycling performance due to high interfacial resistance. For this purpose, polymerizable functional groups are used as cross-linkers and nanohybrid composite polymer

electrolytes with a polymeric network with high shear modulus and conductivity can be obtained as a result of in-situ polymerization with surface-functionalized nano-fillers (Chae,2023). As a proof-of-concept example of the fact that chemical bonding increases the interface compatibility between inorganic and organic materials and facilitates the homogenization of lithium-ion flow, Shin et al. effectively synthesized stringy PAN membranes through the integration of mesoporous SiO₂ nanoparticles that were modified with methacrylate groups (MA-SiO₂). Subsequently, a nanocomposite GPE, which was cross-linked in-situ, was fabricated by utilizing a composite membrane, mesoporous MA-SiO₂ nanoparticles, and electrolyte solution containing a limited amount of tri(ethylene glycol) diacrylate (TEGDA). By effectively encapsulating the electrolyte solution, this cross-linked nanocomposite GPE ensured the absence of solvent leakage and exhibited desirable interfacial properties. Utilization of mesoporous SiO₂ nanoparticles in the in-situ chemical cross-linking process proved to be more effective than non-porous SiO₂ nanoparticles in achieving superior battery performance including discharge capacity, rate capability, capacity retention, and stability during cycling tests at high temperature (Shin,2016).

In another study using PEGDA crosslinker, Zhan et al. developed a partially cross-linked PEO-based composite solid electrolyte (p-V-SiO₂/PEO CPE) containing silica NPs functionalized with porous vinyl group (p-V-SiO₂) as inorganic filler and PEGDA as cross-linker. The electrochemical performance of p-V-SiO₂/PEO CPE containing p-V-SiO₂ cross-linked to PEGDA is much higher than that of p-SiO₂/PEO CPE containing only inactive porous SiO₂ NPs (p-SiO₂) added as filler. While ionic conductivity quadrupled, thermal stability and mechanical strength were also higher. In addition, while only below 10% capacity loss was observed after 300 cycles at 60°C and 0.5C cycle rate, the capacity decay was lost at a much faster rate in p-SiO₂/PEO CPE without polymer cross-linking and complete capacity loss was observed before the 200th cycle (Zhan,2021).

4. CONCLUSIONS

In conclusion, the limited energy density and high cost of lithium-ion batteries are the primary reasons why they have not yet become prevalent in electric vehicles and grid-scale energy storage systems. Overcoming the two challenges is of utmost significance for widespread adoption of lithium-ion batteries in these applications. These are battery safety and energy density per unit mass and volume. The safety problem that manifests itself with explosions and fires in the battery is caused by the formation of lithium dendrite that occurs with the use of existing liquid electrolyte. The problem of dendrite formation can be comprehensively eliminated with solid-state electrolytes, but in the current situation, the ionic conductivity of solid-state electrolytes is very low at room temperature. On the other hand, by using GPE technology, in which liquid electrolyte is trapped inside polymer matrix, it is possible to prevent lithium dendrite formation without compromising ionic conductivity. With GPEs, the electrochemical stability of the electrolyte can be improved, and so it is possible to make electrolytes currently suitable for 4 V systems operable at 5 V levels. Thus, the energy density in the battery can be increased. If these developments are achieved, it will be possible to produce batteries with energy density beyond 500 Wh/kg.

Main goal of this review was to gather recent literature on gel polymer electrolytes, with a particular focus on the in situ polymerization technique and the utilization of anion receptor groups within the polymer structure, inorganic fillers, nanofillers, and nanomaterials. The research findings suggest that the thermal in situ polymerization of acrylate monomers, in conjunction with surface-functionalized nano-fillers and nanomaterials, offers a considerable potential for the production of GPEs. These electrolytes possess desirable attributes including enhanced ionic conductivity, selective lithium ion mobility (high t_{Li^+}), extensive electrochemical stability, and superior mechanical properties. By this method, versatile nanostructured nanocomposite and nanohybrid gel polymer electrolytes can be developed for safe and high-performing LMBs. For this reason,

further research efforts focusing on use of surface functionalized nanomaterials chemically cross-linked to the polymer matrix for safe and affordable LMBs is necessary. This will not only boost manufacturing of robust lithium-metal batteries but also have impact on the implementation of non-lithium-metal based battery technologies by employing similar nanostructured polymer electrolytes.

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