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Research Article

Recent updates on the synthesis and clinical evaluation of Styryl Benzene Imidazole used in Pharmaceutical Preparations

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Abstract

Styryl benzene imidazole is synthesized directly in a single reaction step by condensation of cinnamaldehyde with o-phenylenediamine using a catalyst such as boric acid in the water solvent, that successfully forming a molecule of "styryl-benzimidazole" in which the styryl group is directly attached to the benzimidazole ring. The molecule of "styryl benzene imidazole" consists of a benzene ring directly connected to an imidazole ring (forming a benzimidazole unit), with a styryl group (a vinyl group with a phenyl ring attached) extending from one of the carbon atoms of the imidazole ring. The drug treats conditions such as hyperplasia of smooth muscle cells, which are generally caused by revascularization surgery and organ transplantation. Styryl benzimidazole can reversibly change color upon exposure to light due to isomerization between the cis and trans forms.

INTRODUCTION

Benzimidazole is an important heterocyclic aromatic dicyclic compound containing a benzene ring adjacent to an imidazole ring and it is also a constituent of vitamin B_{12}. It was discovered by Hoebrecker that has attracted considerable attention from researchers in the recent years. Benzimidazoles exhibit metal coordination ability; therefore, they can effectively reduce the corrosion of metals and alloys. Benzimidazoles are also very important intermediates inorganic reactions and their derivatives serve as corrosion inhibitors for many corrosive solutions. Styryl benzene imidazole is a compound containing a styryl benzene moiety and an imidazole ring [1]. It is a versatile compound with applications in pharmaceuticals, materials science, and agriculture. To synthesize a styryl benzene imidazole, a common approach has been used as condensation reaction between a suitable benzaldehyde derivative (containing a "styryl" group) and an o-phenylenediamine, thus essentially creating a benzimidazole ring with a styryl group attached at the 2-position. This is usually achieved by a one-pot reaction with a suitable catalyst (boric acid) or under acidic conditions depending on the specific synthetic method. This reaction usually gives the desired product by a nucleophilic addition and cyclization mechanism [2].

CHEMICAL STRUCTURE

The molecule "styryl benzene imidazole" consists of a benzene ring attached directly to an imidazole ring (forming a benzimidazole unit), with a styryl group (a vinyl group with a phenyl ring attached) extending from one of the carbon atoms of the imidazole ring; essentially, this is a benzimidazole with a styrene substituent on one of its nitrogen atoms.

- **Benzimidazole ring:** A fused ring system with a 6-membered benzene ring and a 5-membered imidazole ring sharing two carbon atoms.
  - **Styryl group:** A vinyl group (-CH=CH-) with a phenyl ring attached to one end of basic group of compounds.
- **Chemical formula:** $C_{16}H_{12}N_2$ (assuming the styryl group is attached to the 2-position of the benzimidazole).
- **Structure:** A benzene ring fused to an imidazole ring, with a vinyl group extending from the 2-position of the imidazole ring and a phenyl ring attached to the other end of the vinyl group[3].

Figure 1(E)-2-styryl-1H-benzo[d]imidazole

The exact location of the styryl group on the benzimidazole ring can vary depending on the particular molecule. Due to the presence of aromatic rings and double bonds in the styryl group, the molecule is considered planar and can exhibit interesting electronic properties. It shows properties such as strong UV-Vis absorption, photochromic potential, high thermal stability, and the ability to be easily modified with various substitutions to fine-tune. Its properties are very useful for applications in areas such as materials science, dye chemistry, and drug development; depending on the particular structure, it can also exhibit interesting fluorescent behavior and the potential to selectively bind to certain molecules due to its donor-acceptor properties[4].

ANALYTICAL PROPERTIES

• **Optical isomerism:** The styryl benzene group of styryl benzene imidazole can undergo isomerization from the trans form to the cis form upon exposure to UV light. This results in changes in the absorption and luminescence spectra of the compound.

- **Deprotonation:** Deprotonation of the NH_3 proton of the imidazole in imidazole styryl benzene can increase the rate constant and quantum yield of the photoisomerization.

• **Stability:** Benzimidazole, a part of styryl benzene imidazole, is stable and has improved bioavailability[5].

OPTICAL PROPERTIES

- **Strong UV-Vis absorption:** The extended conjugated system of the styryl group attached to the benzimidazole ring produces strong absorption in the UV-Vis spectrum, making it a potential candidate for dyes and optical materials.
- **Optical pigments:** Depending on the substitution, styryl benzimidazole can undergo reversible color changes upon exposure to light due to isomerization between the cis and trans forms[6].

CHEMICAL PROPERTIES

- **Synthetic versatility:** The structure can be easily modified by introducing different substitutions to the benzimidazole ring or the styryl group, allowing fine-tuning of its properties.
- **Donor-acceptor properties:** The electron-rich benzimidazole ring acts as a donor while the styryl group can act as an acceptor, allowing for potential interactions with other molecules.

POTENTIAL APPLICATIONS

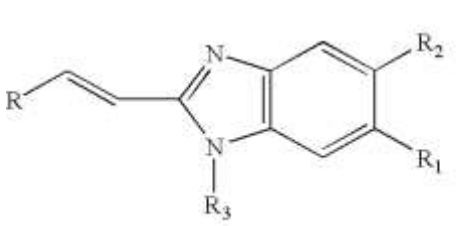
- **Organic dyes:** Due to its strong absorption properties, styryl benzimidazole can be used as a dye for a variety of applications such as solar cells, optical sensors, and fluorescent imaging.
- **Photosensitizers:** The photochromic properties can be used in applications such as switches, smart windows, and optical data storage.
- **Chemical sensors:** With appropriate chemical functionality, styryl benzimidazole can be designed to selectively bind to specific molecules, allowing for the development of chemical sensors.
- **Drug discovery:** Several styryl benzimidazole derivatives have shown potential biological activity, opening up possibilities for drug development. [7,8].

SYNTHESIS OF STYRYL BENZIMIDAZOLE

A series of novel styryl imidazole derivatives were designed and synthesized using nano-SiO_2 as an efficient catalyst. The synthesized compounds were characterized by single-handed ^{13}C NMR spectroscopic study. The important features of this nano catalyst are high product yield, short reaction time and wide substrate utilization range. The proton and ^{13}C chemical shifts of the synthesized compounds were calculated. Single crystal XRD analysis was performed to confirm the structure of MDPI (1-(3-methoxyphenyl)-4,5-dimethyl-2-phenyl-1H-imidazole) and showed that the imidazole ring is essentially a planar and triclinic crystal [9].

The optimization of MDPI compound was performed by DFT at B3LYP/6-31G(d,p) using Gaussian-03. The imidazole derivatives have been used to fabricate highly sensitive fluorescent chemical sensors for the detection of metal ions. The steps involved in the synthesis of styryl benzene Imidazole start with materials such as benzaldehyde derivatives containing styryl groups (e.g., cinnamaldehyde) and o-phenylenediamine heated in a suitable solvent with a potential catalyst (boric acid) in aqueous solvent [10]

The condensation reaction starts after mixing the benzaldehyde derivative with o- phenylenediamine in a suitable solvent (e.g., ethanol, acetic acid). Optionally, a catalyst (e.g., a metal salt such as zinc chloride) can be added to facilitate the reaction. The mixture is heated to promote condensation and ring formation, forming styryl benzimidazole. The product obtained after the reaction is (E)-2-styryl-1H-benzo[d]imidazole. The present invention relates to a styryl benzimidazole group of formula I and a styryl benzimidazoldione of formula II.



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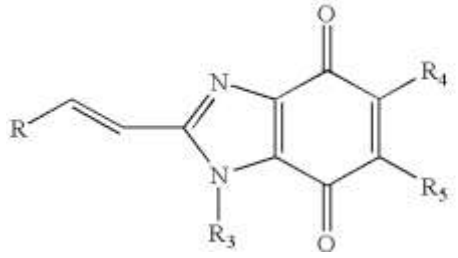
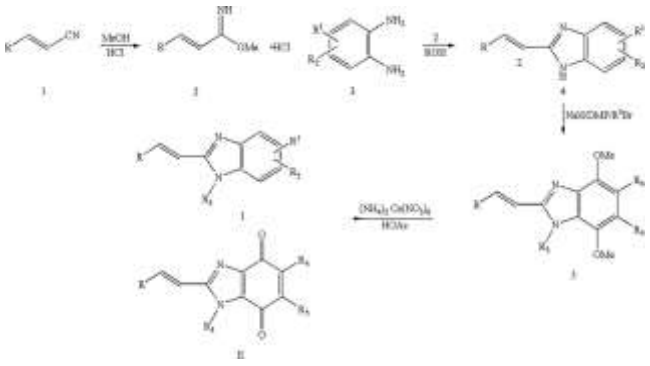


II

wherein R is a phenyl or phenyl substituted by a halogen, hydroxyl, alkoxy having 1 to 6 carbon atoms, alkyl having 1 to 6 carbon atoms, trifluoromethyl or R is a furyl, pyridyl or quinolinyl; R1 and R2 are hydrogen, halogen, alkyl having 1 to 6 carbon atoms, alkoxy having 1 to 6 carbon atoms, nitro, carboxyl, alkoxycarbonyl having 2 to 7 carbon atoms or aryloxycarbonyl having 7 carbon atoms with 12 carbon atoms; R3 is hydrogen, alkyl having 1 to 6 carbon atoms, aryl having 6 to 12 carbon atoms or arylalkyl having 7 to 12 carbon atoms; R4 and R5 are hydrogen or alkyl having 1 to 6 carbon atoms; or pharmaceutically acceptable salts. The compounds were prepared according to the general reaction sequence described in the scheme below [11,12].



mino-ether hydrochloride (2) is prepared by reacting a suitable nitrile with alcohol and excess hydrogen chloride at 0°C. Reaction of (2) and a suitable 1,2-diaminobenzene in refluxing ethanol gives the corresponding 2-styryl benzimidazole (4). Alkylation of (4) with alkyl, aryl or arylalkyl halides in dimethyl-formamide using sodium hydride as base gives the compound of formula I. The compound of formula II is obtained by oxidation of 1,4-dimethoxy derivatives of formula I with ammonium and cesium nitrate. Two equivalents of ammonium and cesium nitrate are dissolved in a 1:4 water/acetonitrile mixture and added drop wise to a solution of 1,4-dimethoxy styryl benzimidazole and suitable acetic acid. Heat the mixture at 40°C for 1 hour to obtain the compound of formula II [13].

Pharmaceutically acceptable acid salts are those derived from organic and inorganic acids such as: acetic, lactic, citric, fumaric, tartaric, succinic, maleic, malonic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methane sulfonic, methylbenzene sulfonic and other acids known to be similar. For compounds with acid substituents such as carboxylic acids, pharmaceutically acceptable salts include alkali metal salts (sodium or potassium), alkaline earth metal salts (calcium or magnesium) and ammonium salts [14].

ESSENTIAL CONSIDERATIONS

- **Composition ratios:** Generally, equivalent molar amounts of cinnamaldehyde and o-phenylenediamine are used.

• **Isomerism:** Depending on the synthesis conditions, you may need to consider the possibility of forming different geometrical isomers (E or Z) of the styryl group.

- **Substitutions:** The synthesis can be modified to incorporate different substitutions on the benzene ring of the styryl and o-phenylenediamine groups, allowing for the generation of a variety of derivatives.
- **Nucleophilic attack:** The amino group of the o-phenylenediamine attacks the electrophilic carbon of the aldehyde group in cinnamaldehyde, forming an imine intermediate.
- **Cyclization:** The second amino group of the o-phenylenediamine then attacks the adjacent carbon, resulting in the formation of a benzimidazole ring with a styryl group attached.

- **Reaction conditions:** The reaction usually proceeds at moderate temperatures with stirring, and the product can be precipitated and purified by recrystallization.

• **Corrosion inhibitor:** Due to its structure, styrylbenzene imidazole has been investigated as a potential corrosion inhibitor for metals such as carbon steel [15,16]. derivatives of this compound to different substitution possibilities that could be biologically

DRUG ADMINISTRATION

The drug may be administered systemically by intravenous injection, typically at a dose of 0.1 to 10 mg/kg/hour for 5 to 30 days, or subcutaneously at lower doses, or orally at higher doses than intravenous injection. Local delivery of the compounds of the present invention may also be achieved via transdermal, or other local routes using suitable sustained-release devices such as carrier matrices, as appropriate [18].

PHARMACEUTICAL FORMULATIONS

The compounds may be administered in pure form or with a solid or liquid pharmaceutical carrier to the patient requiring treatment. The ingredients may be formulated using common excipients, such as bulking agents, disintegrants, binders, lubricants, flavoring agents, etc. The solid carrier used may include one or more substances that can also function as a bulking agent, bulking agent, lubricant, solubilizer, suspending agent, bulking agent, sliding agent, compression aid, binder, tablet disintegrant, or encapsulating material [19].

- In powder form, the carrier is a finely divided solid and mixed with the finely divided active ingredient.
- In tablets, the active ingredient is mixed with a carrier having the required compressive properties in appropriate proportions and compressed into the desired shape and size.
- Powders and tablets should preferably contain up to 99% active ingredient.

Examples: Calcium phosphate, magnesium stearate, talc, sugar, lactose, dextrin, starch, gelatin, cellulose, methylcellulose, sodium carboxylmethylcellulose, polyvinylpyrrolidine, low melting point wax, and ion exchange resins [20].

The liquid excipient may be used to prepare solutions, suspensions, emulsions, syrups, and elixirs. The active ingredient of the present invention may be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both, or a pharmaceutically acceptable oil or grease. The liquid excipient may contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickeners, colorants, viscosity modifiers, stabilizers, or osmotic modifiers [21].

Examples: Liquid carriers for oral and parenteral use include water (cellulose derivatives, preferably sodium carboxylmethylcellulose solution), alcohols (monohydric and polyhydric alcohols, glycols) and their derivatives, as well as oils (fractionated coconut oil and peanut oil).For parenteral use, carriers may also be petroleum esters such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid preparations for injection. Liquid pharmaceutical ingredients are sterile solutions or suspensions that can be administered, for example, by intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously [22].

PHARMACOLOGICAL PROPERTIES

- **Antibacterial:** It can block the microtubules of bacteria, fungi, and helminths
- **Antiviral:** Benzimidazole derivatives have been used to treat viral infections
- **Anticancer:** Styryl Benzimidazole can inhibit the growth of cancer cells
- **Anti-inflammatory:** Benzimidazole derivatives can help reduce inflammation
- **Analgesic:** Styryl Benzimidazole derivatives can help relieve pain
- **Antispasmodic:** It can help reduce spasms and

abdominal discomfort

- **Antianxiety:** Some benzimidazole derivatives have shown antianxiety activity
- **Anticonvulsant:** Styryl benzimidazole have shown anticonvulsant activity
- **Antihypertensives:** Styryl Benzimidazole may help control high blood pressure [23,24]
- **Antidiabetics:** It may treat diabetes by affecting glucose metabolism and insulin secretion.

OTHER APPLICATIONS

Pharmaceuticals: It has a wide range of pharmacological applications, including antiviral, antifungal, antioxidant, and anticancer properties.

- **Materials science:** Styryl Benzimidazoles are used in materials science.
- **Agriculture:** Styryl Benzimidazoles are used in agriculture.

derivatives of this compound to different

- **Corrosion inhibition:** (E)-2-styryl-1H-benzo[d]imidazole can be used as a green corrosion inhibitor [25].

CONCLUSION

This review article focuses on the synthesis and characterization of styryl benzene imidazole used as several pharmaceutical preparations. The styryl benzene imidazole structure has been synthesized due to it is different substitution possibilities that may be several biologically active potentials. It was reported that the styryl benzimidazoles are mainly effective in revascularization surgery and organ transplantation, such as coronary angioplasty, vascular bypass grafting, coronary artery bypass grafting, and heart transplantation. Other conditions associated with unwanted vascular proliferation include hypertension, asthma, and congestive heart failure. This molecule was possessing very impressing activity but some time researcher promising new
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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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