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Review

Imidazopyridines as a source of biological activity and their pharmacological potentials—Infrared and Raman spectroscopic evidence of their content in pharmaceuticals and plant materials

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ABSTRACT

Derivatives of imidazopyridine are used in medicinal chemistry due to their biological and pharmaceutical properties. This review article presents imidazopyridine pharmacological activity as antiinflammatory, anticancer, antiviral, antiosteoporotic, antiparasitic, and antihypertensive agents by studying its various synthesized derivatives. Some of compounds with imidazopyridine skeleton are used in psychiatry and autoimmune disorders. The presented data suggest that IR and Raman spectra measurements are a good methods for identification and characterization of the compounds containing imidazopyridine core. Two stretching vibrations: $\nu_{as}(\Phi)$ and $\nu_{s}(\Phi)$ are of a diagnostic importance. The appearance of these bands in the IR and Raman spectra of some plants, tissues and pharmaceuticals confirms the presence of imidazopyridine skeleton in these substances.

Contents

1. Introduction

Imidazopyridine skeleton is an important part of various biologically active compounds in plants, pharmaceuticals and human enzymes. It forms the class of compounds, similar to purine and benzimidazole. Being organic heterocyclic compounds they are used for syntheses of different chemical–biological tools and therapeutic agents. In the present article their anticancer, antiviral, antiparasitic, antiosteorporotic, and anti-inflammatory properties have been presented.

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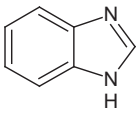
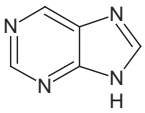


Scheme 1. Benzimidazole (**1**).



Scheme 2. Purine (**2**).

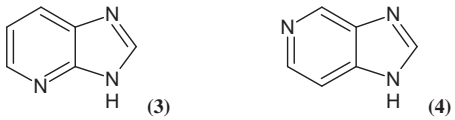
Benzimidazole (**1**) contains the fusion of benzene and imidazole. Its molecular formula is $C_7H_6N_2$, molecular weight—118.13594, melting point—170–172 °C. Polycyclic compounds are worth studying for numerous reasons. Plenty of them are biologically active molecules. Some complexes of transition metal salts with benzimidazole derivatives have been extensively studied as models of some biological substances.[1] Benzimidazole and its derivatives are known to play crucial roles in the structure and function of a lot of biologically important compounds, generally by virtue of their coordination to metal ions. It occurs in nature as a part of vitamin B12. The therapeutic properties of drugs containing benzoimidazole encouraged medicinal chemists to synthesize a large number of novel chemotherapeutics.[2] Their pharmaceutical properties include antiviral[3] and antitumoral;[4] antifungal and antimycotic;[5] antihistaminic and antiallergic;[6] antimicrobial,[7] antidiabetic,[8] and anthelmintic[9] activities. Benzimidazole and a series of substituted benzimidazole analogs are fundamental compounds of polymers[10–13] and corrosion inhibitors (Scheme 1).[11–16]

Purines (**2**) are aza analogs of benzimidazole. Their biological and pharmaceutical properties are used in medicinal chemistry.[17] Purine is the core of the drugs such as clofarabine, nelarabine and forodesine. Their promising activity in patients with relapsed and refractory acute lymphoblastic leukemia was experimentary confirmed.[18] The purine nucleoside analogs constitute a group of cytotoxic agents with activity in low-grade lymphoid malignancies.[19] Allopurinol is another purine analog of the xanthine oxidase inhibitor that decreases uric acid production. Purine bases and other antioxidant compounds of this type play important protective roles in atherogenesis (Scheme 2).[20]

2. Pharmacological activities of imidazopyridines

Imidazopyridine (deazapurine **3**, **4**) has been recognized as a crucial compound from pharmacological point of view. It is structurally related to the intracellular modulator adenosine, and so they have been shown to possess biological activity as adenosine receptor ligands,[21] antiviral and antitumor agents,[22–25] and enzyme inhibitors (Scheme 3).[26–29]

Deazapurines constitute a fragment of compounds that belong to a large group of nucleoside antibiotics. They exhibit a wide variety of antiviral, antibacterial, antitumor, and cancerostatic properties due to their similarity to pyrimidine and purine nucleosides. The nucleoside antibiotics and their parent nucleosides have very similar conformational preferences. As a result, these antibiotics easily get incorporated in growing chains of RNA and DNA by mimicking their parent nucleosides and then bring about the inhibition of protein, RNA, or DNA syntheses. The experimental observations corroborate these deductions, and thus a correlation has been obtained between the conformation and the biological activity of



Scheme 3. 1-Deazapurine (**3**) (imidazo[4,5-*b*]pyridine) and 3-deazapurine (**4**) (imidazo[4,5-*c*]pyridine).

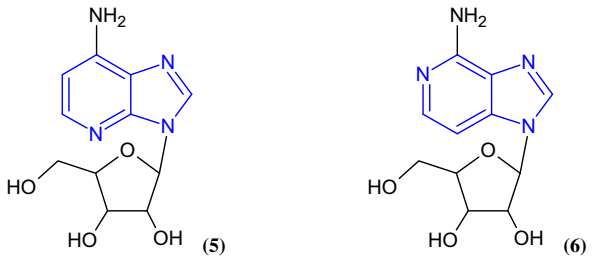
nucleoside antibiotics. It follows from conformational similarity between the nucleoside antibiotics and their parent nucleosides which gives rise to their biological activity. A few of these antibiotics have been tested on animals and humans as potential drugs against cancer and viral diseases.

2.1. Imidazopyridines as antiinflammatory agents

Searching of new and effective drugs in antiinflammatory therapy is still important direction of the studies. Though imidazopyridine derivatives are associated with a broad spectrum of pharmacological activities they also have anti-inflammatory activity, various 1-deazapurine nucleosides have been found to be active. 1-Deazapurine nucleoside, for example 1-deazaadenosine (**5**) is an inhibitor of adenosine deaminase (ADA).[24,26] ADA is an enzyme of the purine metabolism which catalyzes the irreversible deamination of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively.[26] This enzyme has been found in microorganisms, plants, invertebrates, and in all mammalian cells. In mammalian cells ADA plays a role in the differentiation and maturation of the lymphoid system. Deazapurines as adenosine receptor agonists were studied on models of rat and human receptor subtypes.[21]

3-Deazaadenosine (DZA, **6**) compound has been recognized as a potential inflammatory inhibitor. This structural analog of adenosine with imidazo[4,5-*c*]pyridine fragment was studied as an anti-inflammatory and anti-proliferative drug, on plaque progression and vasa vasorum neovascularization in mice.[30] Smaller lesion volume in animals treated with 3-deazaadenosine was closely associated with a reduced vasa vasorum neovascularization, suggesting a direct relationship between lesion growth and vasa vasorum development. 3-Deazaadenosine prevents atherosclerotic lesion formation by its antiinflammatory properties (Scheme 4).

Another imidazopyridine analog, ageladine A (**7**) has shown anti-inflammatory activity. This compound has been isolated in small amounts from the marine sponge *Agelas nakamurai*.[31] It has been described as ageladine A which inhibits various subtypes of matrix metalloproteinases (MMPs). Ageladine A showed MMP-12 inhibitory activity with a half maximal inhibitory concentration (IC_{50}) = 3.66 μM. IC_{50} for its analog is 0.86 μM.[32] It has been considered to be associated with inflammatory diseases caused by macrophages infiltration such as skin diseases,[33,34] atherosclerosis,[35] aneurysms[36] and cancers (Scheme 5).[37–39]



Scheme 4. 1-Deazaadenosine (**5**) and 3-deazaadenosine (**6**).