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Invited review

Aziridine alkaloids as potential therapeutic agents

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ABSTRACT

The present review describes research on natural aziridine alkaloids isolated from both terrestrial and marine species, as well as their lipophilic semi-synthetic, and/or synthetic analogs. Over 130 biologically active aziridine-containing compounds demonstrate confirmed pharmacological activity including antitumor, antimicrobial, antibacterial effects. The structures, origin, and biological activities of aziridine alkaloids are reviewed. Consequently this review emphasizes the role of aziridine alkaloids as an important source of drug prototypes and leads for drug discovery.

1. Introduction

Three-membered heterocycles are highly reactive molecules, in part due to ring strain. As a consequence of their high reactivity, these small heterocycles play an important role in organic chemistry and as intermediates in synthesis of both organic [1] pharmaceutical [2] and natural product intermediates. Among three-membered heterocycles, aziridines constitute a particularly versatile class of molecule, and as discussed in recent book [3], both physical properties and chemical reactions of aziridines have been the subject of numerous theoretical and experimental investigations which have proved invaluable in understanding the mechanism of drug action of pharmaceuticals containing azriridine warheads for instance, the antitumor drug FR900482 [4].

Aziridines, the nitrogenous analogs of epoxides, are a group of natural and/or synthetic organic compounds sharing the aziridine functional group which is a three-membered heterocycle with one amine group and two methylene groups. Aziridine (ethylene imine, ethylenimine, azacyclo-propane, aziran, binary ethyleneimine, dimethylenimine, or ethyleneimine) has molecular structure $HN{=}C_2H_4$. The aziridine possesses bond angles of 59.7° which compared with cyclopropane and oxirane molecules, are considerably smaller than that found in hydrocarbons (109.47°) [5]. Bonding within this type of compound can be explained by invoking a banana bond model (see Fig. 1). Bond angle changes about a central atom can profoundly modulate the electronic properties of a molecule [6,7]. In cyclic amines (1-azacycloalkanes), two bond hybrids which participate in the C–N bonds must increase their p character upon decrease of the C–N–C angle about the amine nitrogen atom. As a consequence, increased s character is seen in the hybrid involved in the N–H bond and the nitrogen lone pair [8–10]. This hybridization effect of the nitrogen atom induces a decrease of pyramidalization of the N-substituent resulting in a continuous increase of the basic strength upon ring expansion from three- to six-membered cyclic amines. This structural relationship is a manifestation of the Thorpe–Ingold effect [11], i.e., the smaller the C–N–C angle (α), the larger the pyramidalization angle (β) (Fig. 1).

The proton affinities, as well as the solution basicities (pK_{BH^+}), of aziridine derivatives are much smaller than those of the corresponding pyrrolidines and piperidines, though the basic strength of

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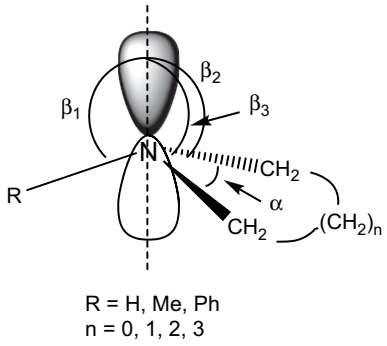

Fig. 1. The view of the C–N–C bond angles in the cyclic amines.

azetidines is close to those of pyrrolidines and piperidines. Aziridine is less basic than acyclic aliphatic amines with a pK_a of 7.98 for the conjugate acid due to increased character of the nitrogen free electron pair [12].

The theoretical difference electron density contours in the three-membered ring planes of aziridine (NCC), cyclopropane (CCC) and oxirane (OCC) molecules were calculated by the CNDO/2 MO method, and showed essentially the same bonding electron distributions as the corresponding contours in the more complex molecules mentioned above [13].

The effect of N-methylation on the resonance positions decreases with ring size. N-alkylaziridines display β and γ effects analogous to acyclic amines; the β effect decreases with branching at the α-carbon. Ring alkyl groups also induce typical β and γ shifts, and the effect of γ substitution depends on the degree of β-C branching. The influence of ring Me groups on aziridine shifts is additive except for *cis*-2,3- and 1,2-dimethylaziridine in which steric interactions and distortions of molecular geometry probably play a role [14].

While the aziridine group is known as a useful reaction intermediate [1,15], it is also an interesting structural fragment in bioactive compounds. The aziridine's proton accepting properties, its rigidity and its potential reactivity can all contribute to specific molecular interactions with proteins, and indeed several important natural products such as mitomycin C [16], porfiromycin [17], and carzinophilin A [18] contain the aziridine functionality. A number of saccharide derivatives containing the aziridine group have been made, mostly as intermediates [19], but also as glycosidase inhibitors [20].

The toxicity of aziridine derivatives will depend on its own structure and activity whilst sharing the general characteristics of the aziridine group. As powerful alkylating agents, aziridines have an inherent *in vivo* potency, often based primarily on toxicity rather than specific activity. As an electrophile, substituted aziridines are subject to attack and ring-opening by endogenous nucleophiles such as nitrogenous bases in DNA base pairs, resulting in potential mutagenicity [1,21].

Several groups of rare natural alkaloidal metabolites incorporating the cyclobutane [22], peroxy [23,24], and azetidine moieties [25], and/or their synthetic counterparts possess a broad spectrum of biological activities.

Aziridine alkaloids also belong to a rare and somewhat neglected group of natural products which are known to play a seminal role in the secondary metabolism of some micro-organisms, plants and various marine organisms [26]. The aziridine-containing compounds have been of interest as both immuno-modulatory and anticancer agents since the late 1950s [27]. Aziridines are inherently strained making them attractive for study in terms of reactivity and pharmacodynamic action. Ethylenimine (or aziridine, **1**) and some of its simple derivatives, are commercial products in different fields of applied chemistry [28]. Observations of the toxic action of aziridines have prompted extensive investigations involving their synthesis and pharmacological activity, allowing selection and advancement of suitable substances as putative cancer chemotherapeutic agents. Notably a few are enjoying regular clinical use [29]. Bayer strain encourages ring-opening reactions of aziridines in the presence of nucleophiles, imparting useful alkylating properties, despite their powerful mutagenic and toxic activities [30].

Aziridines are highly valuable heterocyclic compounds and are widely used during the synthesis of numerous drugs and biologically active natural products (and their derivatives) [31–36]. Many aziridine alkaloids have anticancer, antibacterial, and/or antimicrobial activity against selected cancer cell lines, pathogenic bacteria, and/or micro-organisms strongly indicating that the presence of the aziridine ring in natural as well as synthetic compounds is essential for such activities [37–40].

This article reviews natural aziridine alkaloids, with high antitumor, antimicrobial and antibacterial activities and also highlights those semi-synthetic derivatives and analogs which possess therapeutic promise.

2. Natural aziridine alkaloids

The simple alkaloid, ethylenimine (aziridine, azacyclo-propane, or aziran, **1**) was detected in various foodstuffs including bakers' yeast (*Saccharomyces cerevisiae*) autolyzate [41], in the volatile flavoring constituents of cooked chicken, beef and pork [42] and beef flavor [43]. Two metabolites (**1**) and aziridine-2-carboxylic acid (**2**) were isolated from mushrooms *Agaricus silvaticus* (class Basidiomycetes), both of which have been synthesized [44]. Aziridine-2-carboxylic acid (**2**) as well as aziridine-containing peptides are vital intermediates in the synthesis of various amino acid and peptide derivatives [45]. Furthermore, **2** and related compounds represent interesting substrates for clarifying enzyme mechansims, but also as the warhead of novel irreversible proteases inhibitors with a number of potential therapeutic applications [46,47].

More complex aziridines are found in various plant sources. For instance, 1-methyl-aziridine (**3**) was detected using GC–MS within onion bulbs (*Allium cepa*, class Liliopsida, order Asparagales, family Alliaceae) [48]. Flue-cured tobacco (*Nicotiana tabacum*, family Solanaceae) contains 4-(1-aziridinyl)-3-buten-2-one (**4**) [49]. Natural aziridine alkaloids (**2**, **5**–**11**) were detected and isolated from distillate and residue in extractions of dried matter of *Petasites japonicus* (family Asteraceae, Japanese name Fuki) [50] is also known as bog rhubarb or giant butterbur. It is native to Japan, where the spring growth is relished as a vegetable. Consequently its pharmacological properties are of considerable importance.