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Review Article

Biological Overview on Azrines

Mohammad Asif

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Corresponding Author:

Mohammad Asif*

Department of Pharmacy, GRD (P.G) IMT, Dehradun, 248009, India

*Email Id- aasif321@gmail.com

ABSTRACT

The azrines moiety is an important and showed some important biological activities. Recently, much attention has been focused on azrines derivatives for their scarcity of their pharmacological activities. Various substituted azrines derivatives were also reported to show antibacterial and cytotoxic properties. The combination of two or more heterocyclic and non-heterocyclic systems enhances or other substitution affect their biological profile than parent nuclei. We considered some compounds bearing azrines in their molecular framework.

Key-words: Azrines; antibacterial; cytotoxic.

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INTRODUCTION:

Azrines derivatives have been reported to possess variety of activities against microbial organisms. Azrines derivatives also showed other anticipated biological activities. Azrines also used in synthesis of various intermediates compounds for industrial purposes. These compounds have different functionalities in their structures. Azrines are widely used as antibacterial and cytotoxic. Some azrines azrines compounds have various functional groups.[1-13]

Azirine compounds and their biological activities:

Azirines are three membered heterocyclic unsaturated compounds containing a nitrogen atom and related to the saturated analogue aziridine. They are highly reactive yet have reported in a few natural products such as Dysidazirine. There are two isomers of azirine: 1*H*-azirines with a carbon-carbon double bond are not stable and rearrange to the tautomeric 2*H*-azirine, a compound with a carbon-nitrogen double bond. 2*H*-Azirines can be considered strained imines and are isolable. 2*H*-Azirines are most often obtained by the thermolysis of vinyl azides[14,15]. The *2H*-azirine is a photoproduct.[16-18] The two segments of the peptaibol antibiotic antiamoebin I, nonapeptide Ac-Phe-Aib-Aib-Aib-D,L-Iva-Gly-Leu-Aib-Aib-OH and heptapeptide Z-Hyp-Gln-D,L-Iva-Hyp-Aib-Pro-Pheol, have been prepared as mixtures of the epimers containing D,L-Iva. All α,α-disubstituted α-amino acids were introduced by the 'azirine/oxazolone method', in which amino or peptide acids are coupled with the corresponding 2H-azirin-3-amines.[19] The heterocyclic marine product, acremolin, from a 1H-azirine to a substituted N^2,3-ethenoguanine (5-methyl-7-isopropyl-4,5-dihydro imidazo[2,1-b]purine).[20] A 3,4,4'-trihydroxanthene-fused pyrrole was synthesized by the reaction of 2,3,4,4a-tetrahydro-1H-xanthen-1-one with 3-phenyl-2H-azirine in the presence of LDA. The non-cytotoxic, and suited to labeling living cells for imaging assay.[21] The structural characterization of copper (II) and palladium (II) complexes with aziridine ligands as 2-dimethylaziridine $HNCH_2CMe_2$ (a), the bidentate N-(2-aminoethyl) aziridines $C_2H_4NC_2H_4NH_2$ (b) or $CH_2CMe_2NCH_2CMe_2NH_2$ (c) as well as the unsaturated azirine NCH_2CPh (d), Cleavage of the cyclometallated Pd(II) dimer $[\mu\text{-}Cl(C_6H_4CHMeNMe_2\text{-}C,N)Pd]_2$ with ligand a yielded compound $[Cl(NHCH_2CMe_2)\ (C_6H_4CHMe_2NMe_2\text{-}C,N)Pd]$ (1a). The reaction of the aziridine complex trans-$[Cl_2Pd(HNC_2H_4)_2]$ with an excess of aziridine in the presence of AgOTf gave the ionic chelate complex trans-$[(C_2H_4NC_2H_4NH_2\text{-}N,N')_2Pd](OTf)_2$ (2b) which contains the new ligand b formed by an unexpected insertion and ring opening reaction of two aziridines (aziridine dimerization). $CuCl_2$ reacted in pure HNC_2H_4 or $HNCH_2CMe_2$ (b) again by "dimerization" to give the tris-chelated ionic complex $[Cu(C_2H_4NC_2H_4NH_2\text{-}N,N')_3]Cl_2$ (3b) or the bis-chelated complex $[CuCl(C_2H_2Me_2NC_2H_2Me_2NH_2\text{-}N,N')_2]Cl$

(4c). By addition of 2H-3-phenylazirine (d) to $PdCl_2$, trans-[$Cl_2Pd(NCH_2CPh)_2$] (5d) was formed. Cytotoxic effects of these complexes were examined on HL-60 and NALM-6 human leukemia cells and melanoma WM-115 cells. The antimicrobial activity was also determined. The growth of Gram-positive bacterial strains (*S. aureus, S. epidermidis, E. faecalis*) was inhibited by almost all tested complexes at the concentrations of 37.5-300.0 μg mL(-1). However, MIC values of complexes obtained for Gram-negative *E. coli* and *P. aeruginosa*, as well as for *C. albicans* yeast, mostly exceeded 300 μg mL(-1). The highest antibacterial activity was achieved by complexes 1a and 2b. Complex 2b also inhibited the growth of Gram-negative bacteria.[22] Bioorthogonal ligation reaction between p-nitrodiphenylazirine and dimethyl fumarate, photoinduced azirine-alkene cycloaddition provides a rapid and highly selective route to protein conjugation at neutral pH and room temperature in biological medium.[23] Analogues of the antifungal marine natural product (E)-dysidazirine were evaluated against fungal pathogens. A simple SAR was developed which provides insight into the mechanism of action of long-chain 2H-azirine carboxylates.[24] The 2-azetidinones and 2H-azirines show antibacterial and cytotoxic activities, the biological properties of molecules containing both 2H-azirine and 2-azetidinone functions in the same structure, 2H-azirine-2-azetidinones and 2H-azirines were synthesized from 2-formyl-3-phenyl-2H-azirine-N-arylimines with diphenylketene. None of them showed antibacterial activity on the tested strains, but both 2H-azirine-2-azetidinones showed cytotoxicity against four tumor cell lines (HL-60, leukemia; HCT-8, colon cancer; MDA-MB-435, melanoma; and SF-295, CNS). The IC_{50} values of ranged from 1.1 to 10.5 μM and from 3.8 to 26.6 μM for 2. The mechanism of cell growth inhibition of towards HL-60 cell line was also investigated. Membrane damage, cell viability, DNA synthesis inhibition and morphological changes were evaluated. The preliminary findings suggested that compounds induce apoptosis.[25]. Some antibacterials, (4E)-(R)-antazirine have been isolated from the marine sponge Siliquariaspongia sp. Motualevic acid F is the first long-chain 2H-azirine 2-carboxylic acid to be found in nature. Carboxylic acid-containing compounds inhibit the growth of *Staphylococcus aureus* and methicillin-resistant *S. aureus* at 1.2-10.9 μg/mL.[26] Three new omega-halogenated long-chain 2H-azirines were isolated from the sponge *Dysidea fragilis*. Their structures showed heterogeneity in the composition of the terminal 1,1-dihalo-vinyl group and enantiomeric ratios at C2 of the azirine-2-carboxylate ester terminus. Azirine-2-carboxylate esters were shown to racemize spontaneously. The biosynthesis of the azirine carboxylate family of natural products that involves enzyme-catalyzed free radical halogenation followed by elimination of hydrohalic acid.[27] The 3-iodo-2,4,5,6-tetrafluorophenyl azide and 3,5-diiodo-2,4,6-trifluoro phenyl azide form the corresponding nitrenes as primary photoproducts in photostationary equilibria with their azirine and ketenimine isomers.[28] The photochemical behavior of

the azirine, methyl 2-chloro-3-methyl-2H-azirine-2-carboxylate (MCMAC) was investigated in low-temperature matrixes.[29] A simple and efficient stereoselective synthesis of aziridine-2-phosphonate, and -phosphine oxide by diastereoselective addition of Grignard reagents to 2H-azirine phosphonate and -phosphine oxide is reported. Similarly, the addition of heterocyclic amines and benzenethiol to aziridines and yield functionalized aziridines. These aziridines are used as intermediates for the regioselective synthesis of beta-aminophosphine oxides 6 and beta-aminophosphonates, as well as alpha-aminophosphonates. Phenylsulfenyl-substituted alpha-aminophosphorus derivatives are obtained directly from benzenethiol and 2H-azirine phosphonates and -phosphine oxides.[30] The photochemistry of 3-methyl-2-(1-naphthyl)-2H-azirine was investigated. The photolysis of the azirine with the short-wavelength light (>300 nm) caused the C-C bond cleavage of the 2H-azirine ring to produce the nitrile ylide.[31] The C,C-dicyanoketenimines were generated by flash vacuum thermolysis of ketene N,S-acetals or by thermal or photochemical decomposition of alpha-azido-beta-cyanocinnamonitrile. In the latter reaction, 3,3-dicyano-2-phenyl-1-azirine 12 is also formed. Nucleophilic substitution reactions of 2-halo-2H-azirines with potassium phthalimide and aniline allowed the preparation of substituted 2H-azirines. The reactions of 2-bromo-2H-azirine with methylamine led to the synthesis of alpha-diimines. 2-Halo-2H-azirines were also established as building blocks for the synthesis of a range of heterocyclic compounds, namely, quinoxalines 10a-10d, 3-oxazoline, and 2H-[1,4]oxazines.[32] Chemical reactions are described for the formation of aziridine-2-one and di-azirine-3-one derivatives as potential precursors for the original synthesis of amino-acids, proteins, pyrimidines, purines, nicotinamide and flavin.[33] The 2H-Azirine 2-carboxylate esters, the smallest unsaturated nitrogen heterocycle, are readily prepared in enantiomerically pure form via the base-induced elimination of sulfenic acid (RSOH) from nonracemic N-sulfinylaziridine 2-carboxylate esters. Optimum yields were obtained when the aziridine was treated with TMSCl at -95 degrees C followed by LDA, which was attributed to the improved leaving group ability of an silicon-oxonium species. By using this new methodology the first asymmetric syntheses of the marine cytotoxic antibiotics (R)-(-)- and (S)-(+)-dysidazirine were accomplished.[34] Laser flash photolysis of 2-fluoro, 4-fluoro, 3,5-difluoro, 2,6-difluoro, and 2,3,4,5,6-pentafluorophenyl azides produces the corresponding singlet nitrenes. The influence of two ortho-fluorine substituents on the cyclization is pronounced. In the case of the singlet 2-fluorophenylnitrene system, evidence is presented that the benzazirine is an intermediate and that the corresponding singlet nitrene and benzazirine interconvert. Ab initio calculations at different levels of theory on a series of benzazirines, their isomeric ketenimines, and the transition states converting the benzazirines to ketenimines were performed.[35] The contribution of the extent of nitrogen protonation on the in vivo binding of methamphetamine in the brain, the

enantiomers of [N-methyl-11C]β,β-difluoro amphetamine were prepared for use in positron emission tomography (PET) studies. Thus, the enantiomers of β,β-difluoroamphetamine were prepared from trans-β-methylstyrene, via bromination, conversion into the azirine, fluorination and resolution as the tartrate salts.[36] A series of bis[(carbamoyloxy) methyl] pyrrolines were synthesized from an aziridine, or a 2H-azirine in a sequence involving 1,3-dipolar cycloaddition reactions. The antineoplastic activities of the pyrrolines were compared to the corresponding pyrroles.[37] (Anderson and Milowsky. 1986).

Conclusions: The azirine derivatives possessed mainly antimicrobial and cytotoxic activities. Though some of the compounds possess only modest biological activity, we hope to find a potent simple structural agent which can mimic the activity of the complex azirine through structural modifications of compounds. The literature reveals that azirine has biological potential, and the easy synthetic routes for synthesis have taken attention of the chemists, pharmacologists and researchers. The new class of substituted azirine has shown biological activities. The biological profile of these new generations of azirines presents much progress with regards to the old compounds. By the present scenario it can be concluded that azirine have potential which remain to be disclosed till date. Therefore, the synthesis of new compounds has become an important goal for researchers in recent years. For this purpose, various compounds incorporating a azirine ring have been synthesized and biological activities have been reported. Recently, it has been reported that a considerable number of azirine derivatives bear different biological activities. Among these compounds, azirine derivatives show various biological activities.

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