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Extended Abstract

Design and Evaluation of New Phosphorus Substituted Aziridines as Antiproliferative Agents †

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Covalent bond formation has become a safe and effective strategy applied not only by nature but also by the pharmaceutical industry to improve disease pharmacology. In the history of modern medicine, covalent drugs have been broadly used in many therapies for a wide range of human diseases [1]. Many modern drugs hold electrophilic moieties acting as "warheads" that capture the active sites by reacting with endogenous nucleophilic functionalities (e.g., thiols and amines).

In the domain of natural products and related compounds, the aziridine moiety is an illustrative class of warhead, which may react with nucleophilic partners of target enzymes and share a similar reaction mechanism to allow the formation of covalent bonds. Aziridines are also important synthetic targets themselves, since they appear in naturally occurring compounds with applications in medicinal chemistry [2]. Aziridines, as powerful alkylating agents, may act as covalent drugs, having an intrinsic *in vivo* potency by means of their capability to act as DNA cross-linking agents via nucleophilic ring opening of the three-membered heterocyclic compounds [3].

This work describes an efficient diastereoselective synthetic methodology for the preparation of phosphorus substituted cyanoaziridines though the nucleophilic addition of TMSCN, as a cyanide source, to the C–N double bond of 2*H*-azirine derivatives. The aziridine ring, in these new cyanoaziridines, can be activated by simple *N*-acylation or *N*-tosylation. In addition, the cytotoxic effect on cell lines derived from human lung adenocarcinoma (A549) and human embryonic kidney (HEK293) was screened. *N*–H and *N*-Substituted cyanoaziridines showed excellent activity against the A549 cell line in vitro. Moreover, selectivity towards cancer cell (A549) over (HEK293) and nonmalignant cells (MCR-5) has been observed.

References

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