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JSM Chemistry

Editorial

Heterocyclic substituted 9-Anilinoacridines as Topoisomerase II Inhibitors

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Submitted: 07 July 2018

Accepted: 07 July 2018

Published: 09 July 2018

ISSN: 2333-6633

EDITORIAL

9-anilinoacridines play an important role in the field of antitumor DNA-intercalating agents [1], due to their antiproliferative properties. Several anticancer agents with 9-anilinoacridines such as amascrine, and nitracrine have been developed. These agents are able to crosslink cellular DNA and thereby interfere with the DNA replication by inhibiting DNA topoisomerase II (topoII). Generally, topo II inhibitors are showing significant anticancer activity. Their strong activity was due to the ability of acridine nucleus to intercalate into DNA base pair, stabilizing the DNA-topoII cleavable complex 'ternary complex' which involves DNA, intercalated compound and topo II [2].

However, because of their high reactivity, they are biologically unstable because both Amsacrine (m-AMSA) and CI-921 possess a methane sulfonyl and a methoxy function at C-1' and C-3' of the 9-anilino ring and readily undergo reversible oxidation either chemically or microsomally giving the quinonediimine and more than 50%of the dose is excreted as the glutathione conjugate. The half-life of m-AMSA in the presence of fresh mouse blood at 37°C is 30 min. To improve the drawbacks of 9-anilinoacridines, one effective strategy is to design and synthesize to overcome the above problems. Many research papers are reported about the topoisomerase inhibition activity of 9-anilinoacridines [3-9].

As a part of our ongoing research on searching new potent antitumor agents as topoisomerase II inhibitors, we have developed 9-anilinoacridine analogues bearing various heterocyclic residues like isoxazole, pyrazole, thiazine and oxazine on 9-anilinoacridine rings against topoisomerase II [10-12]. The docking studies of the designed molecules against topo II (pdb id: 1ZXM) revealed that all the heterocyclic substituted 9-anilinoacridines have significant binding affinity towards topo II when compared to the standard drugs like ledacrine. The high binding affinities of the molecules are mainly due to their high lipophilic profile and formation of hydrogen bonding with receptor.

The compounds which have more Glide score when compared with standard were synthesized and characterized by physical and spectral data's. Then they are evaluated for anti tumour activity by short term in vitro method. There is a good correlation between the Glide score and in vitro anti tumour activity. The compounds with good Glide scores produce significant anti tumour activity.

ACKNOWLEDGEMENTS

The authour thank our Vice Chancellor Dr.B.Suresh, JSS University, Mysuru, our principal Dr.S.P.Dhanabal, Department of Pharmaceutical analysis, Department of Pharmaceutical Biotechnology, Department of Pharmacology, JSS College of pharmacy, Ooty for the technical support.

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Cite this article

Cave DD, Ilisso CP, Mosca L, Pagano M, Martino E, et al. (2017) The Anticancer Effects of S-Adenosylmethionine on Breast Cancer Cells. JSM Chem 5(3): 1049.