ANTIOXIDANT ACTIVITY OF NOVEL 4-OXO-AZETIDINE DERIVATIVES SYNTHESIZED FROM SCHIFF BASES

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ABSTRACT

The synthesized 4-Oxo-Azetidines which are established by spectral and analytical data are evaluated for their antioxidant activity. The activity of all compounds is identified by using nitric oxide and superoxide radical scavenging methods against Alkaline Dimethyl Sulphoxide (DMSO). The derivatives with chlorine substituent either at ortho or para on phenyl ring exhibited maximum activity in both methods. Least activity is shown by the compound having ortho nitro group on benzene ring.

Keywords: 4-Oxo-Azetidine, Schiff base, Antioxidant activity.

INTRODUCTION

4-oxo-Azetidines are 4-membered cyclic amides derived from Schiff bases which contain β-lactam unit as an essential structural feature of its molecule1. Monocyclic Azetidinones are usually referred to as Azetidin-2-ones or 2-oxo azetidine, based on the nomenclature of parent heterocycle, Azetidine. The utility of 4-oxo-Azetidines as synths for various biologically active compounds, as well as their recognition as cholesterol absorption inhibitors and enzyme inhibitors has given in various studies2,3. Free radicals are types of Reactive Oxygen Species (ROS), which include all highly reactive oxygen containing molecules4,5. They are capable of attacking the healthy cells of the body, causing them to lose their structure and function. Cell damage caused by the free radicals appears to be a major contribution to aging and degenerative disease of aging such as cancer, cardiovascular diseases, cataract, immune system decline, liver disease, diabetes mellitus, inflammation, renal failure and brain dysfunction6,7.

EXPERIMENTAL WORK:

A new series of 4-Oxo-Azetidine derivatives (4i-4o) from Schiff bases are synthesized8,9. The Schiff base derivatives on treatment with dioxane and triethylamine afforded targeted compounds (4i-4o). The structure of all synthesized compounds has been established on the basis of their spectral (IR, H&13C NMR and Mass) and analytical data. The purity of the compounds was confirmed by TLC. All the synthesized compounds were evaluated for their antioxidant activity.

SCHEME

The list of synthesized compounds (4i–4o).

4i) N- (3-chloro - 2(4'-chloro phenyl) -4-oxo-azetidine-1-yl) nicotinamide.
Where R = p-chloro (4i), m-bromo(4j),o-chloro (4k),o-methoxy(4l),o,p-dimethoxy(4m),3',4',5' trimethoxy (4n), o-nitro (4o).

4j) N-(3-chloro -2 (3'-bromo phenyl) -4-oxo-azetidine-1-yl) nicotinamide
4k) N-(3-chloro -2 (2'-chloro phenyl) -4-oxo-azetidine-1-yl) nicotinamide
4l) N-(3-chloro -2 (2'-methoxy phenyl) -4-oxo-azetidine-1-yl) nicotinamide
4m) N-(3-chloro -2 (2', 4'- dimethoxy phenyl) -4-oxo-azetidine-1-yl) nicotinamide
4n) N-(3-chloro -2 (3', 4', 5' - trimethoxy phenyl) -4-oxo-azetidine-1-yl) nicotinamide
4o) N-(3-chloro -2 (2'-nitro phenyl) -4-oxo-azetidine-1-yl) nicotinamide

Control was prepared without compound but with an equivalent amount of buffer. Then 0.5ml of the incubation mixture was mixed with 0.5 ml of Griess reagent (Sulphanilamide 1%, o-phosphoric acid 2% and naphthyl ethylene diamine dihydro chloride 0.1%) and the absorbance was measured at 546 nm against blank (DMSO). The experiments were performed in triplicate. From the absorbance the percent of scavenging activity was calculated as follows and the results were shown in Table 1.

\[
\text{Scavenging activity (\%) = } \frac{[A_{546}(\text{control}) - A_{546}(\text{sample})]}{A_{546}(\text{control})} \times 100
\]

Assay of Superoxide Radical Scavenging Activity\[15\]:
Superoxide radical scavenging activity was assayed by nitro blue tetrazolium system. The reaction mixture containing 0.1ml of nitro blue tetrazolium (1mg/ml in DMSO) and 0.3ml of synthesized compounds (4i-4o) or standard in DMSO was added (1ml of DMSO containing sodium hydroxide 5mM in 0.1 ml of water) to give a final volume of 1.4ml and the absorbance was measured at 560nm against blank (DMSO). The percentage scavenging of superoxide radical was calculated by using above formula. The results were shown in Table 2.

RESULTS AND DISCUSSION:
The nitric oxide assay has been widely used to evaluate the free radical scavenging effectivness of various antioxidant substances.
Table 1: Nitric oxide Radical Scavenging activity for 4-oxo-Azetidine derivatives (4i-4o)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Conc. (µg/ml)</th>
<th>STD.</th>
<th>CTRL</th>
<th>4i</th>
<th>4j</th>
<th>4k</th>
<th>4l</th>
<th>4m</th>
<th>4n</th>
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Table 2: Superoxide Radical Scavenging activity for 4-oxo-Azetidine derivatives (4i-4o)

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Nitric oxide generated as a result of decomposition of sodium nitroprusside in aqueous medium interacts with oxygen at physiological pH to produce nitrite ions, which are measured by using Griess reagent. The nitrite ions were subjected to diazotization followed by azo coupling reaction to yield an azo dye, measured by an absorption band at 546 nm. The scavenging ability of the synthesized compounds was compared with ascorbic acid as a standard. Compounds 4k & 4m produced better scavenging ability (Table 1). Compounds 4i, 4j, 4l and 4m showed moderate radical scavenging activity and 4o compound showed least activity when compared to standard.

Even though superoxide radical is a weak oxidant, it gives rise to the generation of powerful and dangerous hydroxyl radical along with single oxygen, both of them lead to rise to the generation of powerful and dangerous hydroxyl radical when compared to standard.

The experimental results suggest that 4k showed better scavenging activity whereas 4i, 4j & 4m exhibited moderate activity. Least activity is identified for the compounds 4i, 4m & 4o.

CONCLUSIONS

4-Oxo-Azetidines exhibited significant moderate activity when compared with standard ascorbic acid. Strong antioxidant activity was observed for N-(3-chloro-2-(2-chloro phenyl)-4-oxo-azetidine-1-yl) nicotinamide (4k) in both methods. The antioxidant capacity of the compounds were found to be 8.02 to 90.12 for different concentrations (25-200 µg/ml).

REFERENCES


