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SYNTHESIS AND ANTIMITOTIC ACTIVITY OF CHLORO SUBSTITUTED CYANOACETYL HYDRAZONE DERIVATIVES

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ABSTRACT: The aim of this study were to synthesize and antimitotic activity of the cyanoacetyl hydrazones derivatives. The synthesized compounds were subjected to antimitotic studies by alliumcepa root meristamatic cells. The mitotic activity was observed in various concentrations of cyanoacetyl hydrazones. Antimitotic – activity of the synthesized compounds were observed in higher concentrations. Antimitotic activity of cyanoacetyl hydrazones were dose dependent. Increase in the concentrations is directly proportional to the activity.

KEYWORDS: cyanoacetyl hydrazones, meristamatic cells, MI (mitotic index), antimitotic activity, allium cepa.

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1. INTRODUCTION

Heterocycles form by far the largest of the classical divisions of organic chemistry. Moreover, they are of immense importance not only both biologically and industrially but also to the functionating of any developed human society as well. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles. Synthetic heterocyclic compounds can and do participate in chemical reactions in the human body. Moreover, all biological processes are expressed through chemical reaction. Such fundamental manifestation of life as the provision of energy, transmission of nerve impulses, sight, metabolisms and transfer of genetic information are all based on chemical interactions involving participation of many heterocyclic compounds such as vitamins, enzymes. The present study was designed to examine the effect of chloro substituted cyanoacetyl hydrazones on cell divisions in the root meristems of allium cepa to reveal the cytotoxic

effect induced by the compounds.

2. MATERIALS AND METHODS

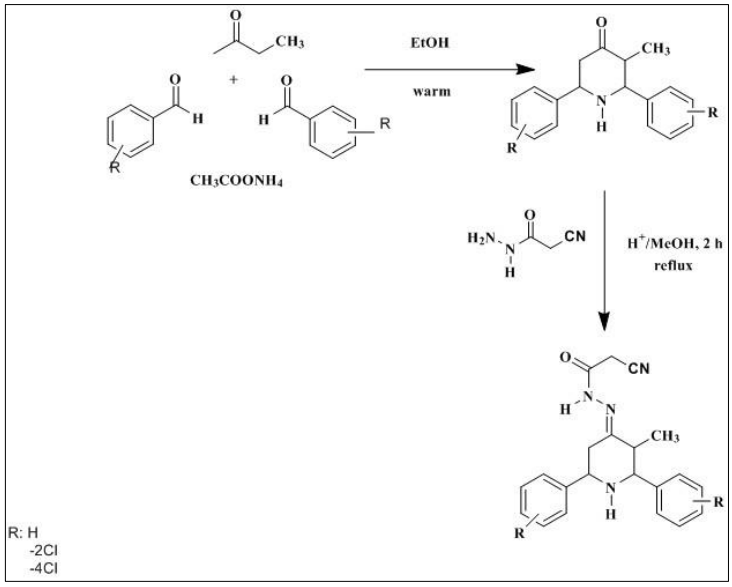
Chemicals were from E. Merck (India). IR (KBr) spectra were recorded on a Perkin-Elmer 157 infrared spectrometer (ν in cm–1) and NMR spectra were recorded on a Bruker spectrometer DPX-300MHz (Bruker, Germany) by using $CDCl_3$ as solvent with TMS as an internal standard.

Preparation of S1, S2 and S3

3-methyl-2,6-diphenylpiperidin-4-one was prepared by adopting the literature method [1-6].

Preparation of 3-methyl-2,6-diphenylpiperidin-4-one cyanoacetyl hydrazone

A mixture of 3-methyl-2,6-diphenylpiperidin-4-one (0.1 mol), cyanoacetic hydrazide (0.1 mol) in the presence of few drops of concentrated acetic acid in methanol was refluxed for 2 hours. After the completion of reaction, the reaction mixture was cooled to room temperature. The solid washed with warm water and recrystallized by methanol to afford 3-methyl-2,6-diphenylpiperidin-4-one cyanoacetyl hydrazone.



Scheme 1

Determination of antimitotic activity

Evaluation of antimitotic activity using *Allium cepa* roots

Antimitotic activity study was carried out by lit method [7-9].

Exposure to text samples

Various concentrations of S1, S2 and S3 were prepared i.e; 10 µg/mL, 20 µg/mL, 30 µg/mL. The onions were divided into four groups. The first group assigned as control (tap water). Second group is allium cepa roots were dipped in S1. Third group is allium cepa roots were dipped in S2. Fourth group is allium cepa roots were dipped in S3. Fifth group is allium cepa roots were dipped in the methotrexate (0.10 mg/mL) was used as a standard control. All the groups were kept at 25°C for 96 h in direct sunlight. The root length, root number and the mitotic index were recorded after 96 h.

$$\% \text{ of root growth inhibition} = \frac{\text{Control} - \text{Test}}{\text{Control}} \times 100$$

Determination of MI:

Mitotic index was calculated by

$$MI = \frac{\text{Number of dividing cells}}{\text{Total number of cells}} \times 100$$

3. RESULTS AND DISCUSSION

S1- 3-methyl-2,6-diphenylpiperidin-4-one cyanoacetylhydrazone

S2- 3-methyl-2,6 di(bis-*o*-chloro phenyl) piperidin-4-one cyanoacetyl hydrazone

S3- 3-methyl-2,6 di(bis-*p*-chloro phenyl) piperidin-4-one cyanoacetyl hydrazone

Antimitotic activity of compounds (S1, S2 and S3) using Allium cepa root meristamatic cells

The inhibitory effect of (S1,S2 and S3) were compared with standard anticancer drug methotrexate. Increase in average mean root length (8.10mm), average mean root numbers (7) and mitotic index (87.50%) observed in control group after 96 hrs of experimental period.The average mean root length at 10, 20,and 30µg/mL of compound (S1) was 6.70mm, 3.80mm and 2.20mm at 96 hr respectively while standard shows 2.60mm. The average mean root numbers at 10, 20 and 30µg/mL of compound (S1) was 5,4 and 3 at 96 hr respectively while standard shows 3 numbers. The mitotic index at 10, 20, and 30 µg/mL of compound (S1) was 81.55, 66.66 and 35.89% at 96 hr respectively while standard shows 36.76%.The average mean root length at 10, 20 and 30µg/mL of compound (S2) was 5.70mm, 3.70mm and 2.90mm at 96 hr respectively while standard shows 2.60mm. The average mean root numbers at 10, 20, and 30µg/mL of compound (S2) was 6, 5 and 3 at 96 hr respectively while standard shows 3 numbers. The mitotic index at 10, 20, and 30 µg/mL of compound (S2) was 75.51 , 64.62 and 40.53% at 96 hr respectively while standard shows 36.76%. The average mean root length at 10, 20and 30µg/mL of compound (**S3**) was 6.10mm, 4.90mm and 3.40mm at 96 hr respectively while standard shows 2.60mm. The average mean root numbers at 10, 20,and 30µg/mL of compound (S**3**) was 6,4 and 4 at 96 hr respectively while standard shows 3 numbers. The mitotic index at 10, 20, and 30 µg/mL of compound (S**3**) was 75.82, 66.70 and 49.72% at 96 hr respectively while standard shows 36.76%.The water control shows normal growth with greater root length and numbers. Treatment with different concentrations (10,20, and 30 µg/mL) of compounds (S1,S2 and S3) show decreased the growth gradually in dose dependent manner. The highest dose as 30µg/mL of compound (S1) has significant activity in root length, number and mitotic index and near to the standard. In the present study mitotic index of different concentrations of extract clearly indicates the efficiency in theinhibition of growth of cancer cells either by affecting

microtubules or encouraging microtubule formation, and thus stopping the microtubules from being broken down. This makes the cells become so clogged with microtubules that they cannot continue to grow and divide [10-20]. This research has proceeded to determine the antimitotic effect of the S1, and S2 and S3. The antimitotic activity in the following order: S1> S2> S3.

Table: 1 Effect Of Compounds (S1, S2 and S3) on MI Of *Allium cepa* roots

Group	S1			S2			S3		
	Avg Root Growth (mm)	Avg Root Numbers	Mitotic Index (%)	Avg Root Growth (mm)	Avg Root Numbers	Mitotic Index (%)	Avg Root Growth (mm)	Avg Root Numbers	Mitotic Index (%)
Water (Control)	8.10	7	87.5	8.10	7	87.5	8.10	7	87.5
10 µg/ml	6.70	5	81.53	5.70	6	75.51	6.10	6	75.82
20 µg/ml	3.80	4	66.66	3.70	5	64.62	4.90	4	66.70
30 µg/ml	2.20	3	35.89	2.90	3	40.53	3.40	4	49.72
Std Methotrexate (0.1mg/ml	2.60	3	36.76	2.60	3	36.76	2.60	3	36.76

Fig 1: Control(Water) Std (Methotrexate) (0.1mg/ml)

Fig 2: 30µg/ml of compounds S1, S2, S3

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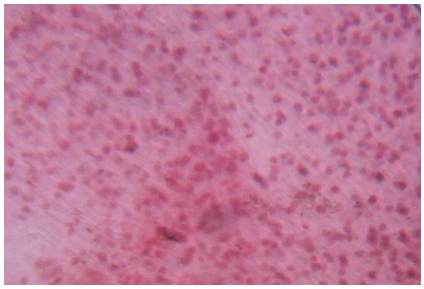
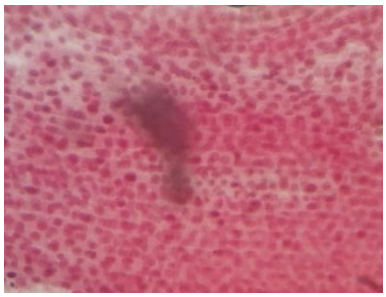
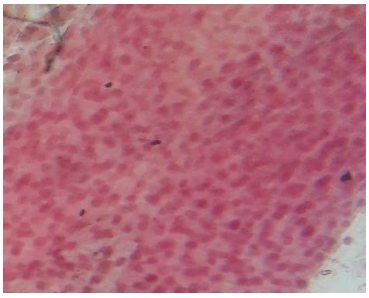


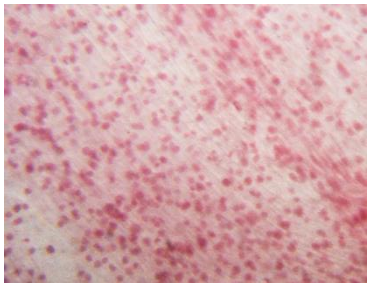
Water(Control)



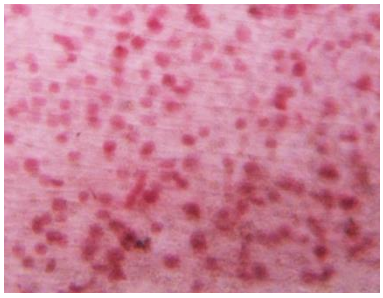
Std (Methotrexate) (0.1mg/ml



30µg/ml (S1)



30µg/ml (S2)



30µg/ml (S3)

Fig. 3: Photomicrograph of Compounds (S1, S2, S3) on mitotic Index of *Allium cepa*

4. CONCLUSION

Synthesized a series of new chloro substituted cyanoacetyl hydrazone derivatives obtained with good yield. Among the three compounds, S1 has greated activity than S2 and S3. The antimitotic activity in the following order: S1> S2> S3. As a result of this cells arrest in mitosis and eventually die by apoptosis. Our findings support the reported therapeutic use of this compound as a antimitotic or anticancer agent in the Indian system of medicine.

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CONFLICT OF INTEREST

None Declared

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