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SYNTHESIS, CHARACTERIZATION, *INVITRO* ANTIDIABETIC ACTIVITY AND ANTIMITOTIC ACTIVITY OF SOME ALKYL/HALO SUBSTITUTED CYANOACETYL HYDRAZONE DERIVATIVES

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Abstract

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. The present study describes about the synthesis and characterization and biological studies of novel alkyl/halo substituted cyanoacetyl hydrazone derivatives. The synthesized compounds characterized by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectral studies. The synthesized compounds subjected to antimitotic, invitro anti diabetic activities.

This in vitro study explores the antidiabetic properties of synthesized compounds and it can be considered as a potential for the management of type-II diabetes mellitus. The synthesized compound subjected to preliminary antimitotic studies by Allium cepa root MERISTAMATIC CELLS.

***Keywords**: cyanoacetyl hydrazone, antidiabetic activity, acorbose, antimitotic activity, meristamatic,*

1. Introduction

Heterocyclic systems having piperidine are found to possess better biological activity. They aroused great interest in the past and recent years due to their wide variety of biological properties and their presence in biologically active pharmaceutical ingredients. The emphasis on the synthesis of the above said heterocycles can be recognized owing to their presence in the molecular structure of numerous alkaloids and drugs.

Hydrazones and their derivatives constitute an important class of compounds that has found wide utility in organic synthesis. The chemistry of carbon-nitrogen double bond of hydrazone is becoming the backbone of condensation reaction in benzo-fused N-heterocycles, also it constitutes an important class of compounds for new drug development. Many reports are available on the conformation of various substituted 2,6-diarylpiperidin-4-ones, have elaborately discussed the conformation of 2,6-diarylpiperidin-4-ones with or without alkyl substituent at C-3 and C-3/C-5 positions[1-3]. Certain small molecules act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally potent molecules. Recently, cyanoacetyl hydrazones have attracted great attention due to their diverse biological and pharmacological properties.

Diabetes mellitus results from the defects in the insulin secretion and action, this may be characterized by chronic hyperglycemia, which is connected with the carbohydrates, protein and lipid metabolism. Globally mortality rate 9% is recorded due to the diabetes. Diabetes mellitus a well-known endocrine disorder and it is most common in India now a day. The reason may be life style and genetic factors. The treatment of diabetes need to spent vast amount of resources including medicines, diets,

physical training and along with serious complications often resulting in high death rate. Therefore there is a need for searching of a new class of compounds to overcome diabetic problems [4-6]. Thus taken above into considerations synthesized compounds were screened for their in-vitro antidiabetic activity and to find out the comparative potential of the compounds. In the present study is to screen for *in vitro* inhibition of alpha-amylase enzyme activity of synthesized compounds and compared with standard as Acarbose.

The general principles of the mechanisms of mitosis are best and most easily studied in the actively growing regions of plants such as a shoot or root apex. In *Allium cepa L.* root tip model root system of plant cells is commonly used as a test for investigating environmental pollution factors, toxicity of chemical compounds and evaluating potential anticancer properties. It has been used since 1938. It is very comfortable as it is easy to make preparations of onion roots. They contain rather homogenous meristematic cells, having only 16 chromosomes, which are very long, well visible and get stained easily. The test is a fast and inexpensive method, allowing the investigation of universal mechanisms for meristamatic plant cells and extrapolation on animal cells. The aim of this work will be investigated the antimitotic activity of synthesized compounds.

3. Materials and Methods

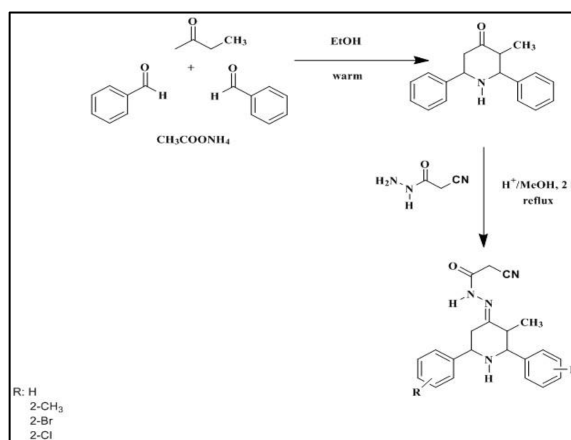
Chemicals were procured from E. Merck (India), S. D. Fine Chemicals (India) and reagent/solvents were used without distillation procedure. Melting points were taken in open capillary tubes and are uncorrected. IR (KBr) spectra were recorded on a Perkin-Elmer 157 infrared spectrometer (ν in cm–1) and NMR spectra were recorded on a Bruker spectrometer DPX-300MHz (Bruker, Germany) by using $CDCl_3$ as solvent with TMS as an internal standard. All the spectral data are consistent with the assigned structures of the desired product and the progress of the reactions was monitored on silica gel G plates using iodine vapour as visualizing agent.

Preparation of S1, S2 and S3

3-methyl-2,6-diphenylpiperidin-4-one was prepared by adopting the literature method. Condensation of 2-butanone, substituted aldehydes and ammonium acetate in warm ethanol in the ratio of 1:2:1 respectively afforded the formation of 3-methyl-2,6-diphenylpiperidin-4-ones.

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 product was separated by filtration and washed with warm water and recrystallized by methanol to afford 3-methyl-2,6-diphenylpiperidin-4-one cyanoacetyl hydrazone.



Scheme1

In vitro antidiabetic activity

In vitro α-amylase inhibition study

In vitro α-amylase inhibition assay was carried out by the method of Apostolidis (2007) [7-9]

Reagents

- 20mm Phosphate buffer (pH 6.9).
- α-amylase (0.5mg/ml)
- 0.5% starch
- 96 % 3,5-dinitrosalicylic acid (DNS)

Procedure

Various concentrations of the synthesized compounds were prepared i.e; 100 µg/ml, 200 µg/ml, 300 µg/ml, 400µg/ml & 500 µg/ml using phosphate buffer (pH 6.9). 500 µl of synthesized compounds to separate test tube and 500 µl of 20 % phosphate buffer pH 6.9, containing α-amylase at a concentration of 0.5 mg/ml were incubated at 25°C for 10 min. After pre incubation, 1000µl of 0.5% starch solution in 20 % phosphate buffer, pH 6.9 was added. The reaction mixtures were then incubated at 25°C for 10 min. The reaction was stopped with 500µl of 96 % 3, 5-dinitrosalicylic acid (DNS) color reagent. The test tubes were then incubated in a boiling water bath for 5 min and cooled to room temp. Absorbance (A) was measured at 540 nm. Acarbose was used as positive control and the

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inhibitory activity of α- amylase and percent of inhibition was calculated as follows:

$$\% \text{ of inhibition} = \frac{(\text{Control O.D.} - \text{Test O.D.})}{\text{Control O.D.})} \times 100$$

Control incubations represent 100% enzyme activity and were conducted in a similar way by replacing sample. For blank incubation (to allow for absorbance produced by the extract), enzyme solution was replaced by buffer solution and absorbance recorded. Separate incubation carried out for reaction t = 0 was performed by adding samples to DNS solution immediately after addition of the enzyme. The experiment was done in triplicate. IC_{50} value was calculated by using regression analysis.

Determination of antimitotic activity

Evaluation of antimitotic activity using Allium cepa roots

Antimitotic activity study was conducted as per the methods reported by previous workers with modifications (Grant, 1982; Fiskesjo, 1988;Shweta*et al*. 2014) [11-12].

Allium cepa bulbs:

Approximately equal size bulbs (40±10 g) of the onions (*Allium cepa* L.) were obtained from the local vegetable market at Thanjavur, Tamil Nadu, India. Any onions that were dry, moldy or have started shooting green leaves were discarded.

Growing Allium cepa meristems:

The outer scales were removed from the healthy onion bulbs leaving the root primordia intact. These bulbs were grown in dark for 48 h over 100 ml of tap water at ambient temperature until the roots have grown to approximately 3 cm. The water was changed daily during this period. The viable bulbs were then selected and used for subsequent studies.

Exposure to text samples

The bulbs with root tips grown up to 2-3 cm were removed from the water and placed on a layer of tissue paper to remove excess of water. Various concentrations of the S1,S2 and S3 were prepared i.e; 10 µg/mL, 20 µg/mL, 30 µg/mL. The bulbs were divided into four groups. The first group served as control (tap water). Second group is Allium cepa roots were dipped in the compound *S1*. Third group is Allium cepa roots were dipped in the compound *S2*. Fourth group is Allium cepa roots were dipped in the compound *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 incubated at 25±2°C for 96 h away from direct sunlight. The test samples were changed daily with fresh ones. The length of roots grown during incubation (newly appearing roots not included), root number and the mitotic index were recorded after 96 h. The % of root growth inhibition was calculated by

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

The effective concentration for 50% root length inhibition (EC_{50} value) was determined by plotting the treatment concentrations against mean root lengths as percentage of water control group.

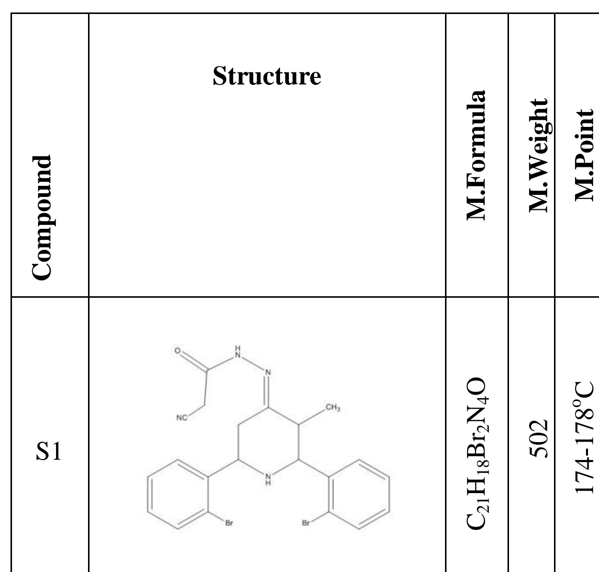
Microscopic studies and determination of mitotic index:

After 96 h, the root tips were fixed with fixing solution of acetic acid and alcohol (1:3). Squash preparations were made by staining the treated roots with acetocarmine stain (Badria et al., 2001)[13]. For each root tip, the numbers of mitotic cells and total meristematic cells were counted manually in 5-8 fields of view using high resolution (100x) bright field light microscope. The mitotic index was calculated by

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

4. Results and Discussion

Table 1. The physical data of synthesized Cyanoacetyl hydrazone derivatives



Compound	Structure	M.Formula	M.Weight	M.Point
S1		$C_{21}H_{18}Br_2N_4O$	502	174-178°C

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S2		$C_{21}H_{18}Cl_2N_4O$	412	180-182°C
S3		$C_{23}H_{26}N_4O$	374	141-144 °C

3-methyl-2,6 di(bis-*o*-bromo phenyl) piperidin-4-one cyanoacetyl hydrazone (S1): Yield. 79.65%. mp. 174-178 °C. **FT-IR(KBr) ν_{max} (cm^{-1}):** 3099-2931 (C-H Aliphatic &Aromatic stretching), 1681 (C=O), 1567 (C=N), 2265 (C≡N), 3308-3179 (N-H). **^{13}C NMR(300 MHz, $CDCl_3$) δ ppm:** 130.10 (C-2 ipso carbon), 130.62 (C-6 ipso carbon), 128.59-129.54 (Aromatic carbons), 166.34 (C=O), 159.54 (C=N), 125.18 (C≡N), 25.11 (CH_2 carbon of cyanoacetohydrazone moiety), 65.86 (C-2), 59.64 (C-6), 39.14 (C-3), 25.23 (C-5), 12.19 (3-CH_3). **^{1}H NMR(300 MHz, $CDCl_3$), δ ppm:** 7.53- 7.31 (m,8H Aromatic protons) 10.79 (b s, 1H, N-H, Hydrazone Moiety), 2.50 (b s, 1H, N-H Piperidin moiety), 3.35 (q, 2H, CH_2 –Protons in hydrazone moiety), 0.91((d, J = 6.6Hz, 3H, 3-CH_3), 3.88 (dd, $J^3_{a,e}$ = 3Hz, $J^3_{a,a}$ = 10.2Hz, 1H, H-6a), 3.35(d, $J^3_{a,a}$ = 10.2Hz, 1H, H-2a), 2.50 (dd, $J^3_{a,e}$ = 11.4Hz, $J^3_{a,a}$ = 11.7 Hz, 1H, H-5a), 3.35 (dd, $J^3_{a,e}$ = 2.1 Hz, $J^2_{a,e}$ = 12Hz, 1H, H-5e), 2.51(m, 1H, H-3a Proton).

3-methyl-2,6 di(bis-*o*-chloro phenyl) piperidin-4-one cyanoacetyl hydrazone (S3) : Yield. 80.69% . mp. 180-182°C. **FT-IR(KBr) ν_{max} (cm^{-1}):** 3099-2933 ((C-H Aliphatic &Aromatic stretching), 1681 (C=O), 1570 (C=N), 2266 (C≡N), 3311-3183 (N-H). **^{13}C NMR(300 MHz, $CDCl_3$) δ ppm:**132.27 (C-2 ipso carbon), 133.68 (C-6 ipso carbon), 127.51-129.27 (Aromatic carbons) 165.09 (C=O), 154.98 (C=N), 115.08 (C≡N), 24.17 (CH_2 carbon of cyanoacetohydrazone moiety), 63.31 (C-2), 56.55 (C-6), 34.00 (C-3), 28.21 (C-5), 11.14 (3-CH_3). **^{1}H NMR(300 MHz, $CDCl_3$), δ ppm:** 7.42-7.32(m, 8H, Aromatic Protons), 10.09 (b s, 1H, N-H, Hydrazone Moiety), 2.24 (b s, 1H, N-H Piperidin moiety), 3.42 (q, 2H, CH_2 –Protons in hydrazone moiety), 0.971 (d, J = 6Hz, 3H, 3-CH_3) 3.73(dd, $J^3_{a,e}$ = 3Hz, $J^3_{a,a}$ = 10.2Hz, 1H, H-6a), 3.3(d, $J^3_{a,a}$ = 10.2Hz, 1H, H-2a), 2.98 (dd, $J^3_{a,e}$ = 11.4Hz, $J^3_{a,a}$ = 12 Hz, 1H, H-5a), 3.4(dd, $J^3_{a,e}$ = 2.1 Hz, $J^2_{a,e}$ = 12Hz, 1H, H-5e), 2.67(m, 1H, H-3a Proton).

3-methyl-2,6 di(bis-*o*-methyl phenyl) piperidin-4-one cyanoacetyl hydrazone (S3) : Yield. 82.6%. mp. 141-144 °C. **FT-IR(KBr) ν_{max} (cm^{-1}):** 3025-2852 (C-H Aliphatic & Aromatic stretching), 1674 (C=O), 1568 (C=N), 2267 (C≡N), 3440-3184 (N-H). **^{13}C NMR(300 MHz, $CDCl_3$) δ ppm:**139.98 (C-2 ipso carbon), 140.49(C-6 ipso carbon), 126.49-129.77 (Aromatic carbons), 164.48 (C=O), 158.05 (C=N), 114.35 (C≡N), 24.16 (CH_2 carbon of cyanoacetohydrazone moiety), 76.57 (C-2), 56.12 (C-6), 44.89 (C-3), 34.56 (C-5), 11.15 (3-CH_3) 19.20 (*o*-CH_3). **^{1}H NMR(300 MHz, $CDCl_3$), δ ppm :** 7.32-7.13 (m, 8H, Aromatic Protons), 10.09 (b s, 1H, N-H, Hydrazone Moiety), 2.09 (b s, 1H, N-H Piperidin moiety), 3.50 (q, 2H, CH_2 –Protons in hydrazone moiety), 0.92 (d, J = 6Hz, 3H, 3-CH_3), 3.89 (dd, $J^3_{a,e}$ = 3Hz, $J^3_{a,a}$ = 10.2Hz, 1H, H-6a), 3.11 (d, $J^3_{a,a}$ = 10.2Hz, 1H, H-2a), 2.39 (dd, $J^3_{a,e}$ = 11.4Hz, $J^3_{a,a}$ = 11.7 Hz, 1H, H-5a), 3.07(dd, $J^3_{a,e}$ = 2.1 Hz, $J^2_{a,e}$ = 12Hz, 1H, H-5e), 2.57 (m, 1H, H-3a Proton), 2.33 (s, 3H, *o*-CH_3 protons).

Antidiabetic activity of compounds S1, S2 and S3

α-Amylase inhibitory activity

The *in vitro* antidiabetic activity of the synthesized compounds were investigated through α-Amylase inhibitory activity. The inhibitory activities of compounds reported in Table 2. The compounds were comparable with standard antidiabetic drug viz. Acarbose. The compounds showed inhibitory effect on α-Amylase with varying degrees of inhibition. The maximum inhibition was seen with the standard drug Acarbose. Among the various doses (100 µg/ml, 200 µg/ml, 300 µg/ml, 400µg/ml & 500 µg/ml) of compounds.

The mean inhibition activity of compound S1 was 39.36±0.28% for 100 µg/ml, 49.20±0.34% for 200 µg/ml, 62.36±0.47% for 300 µg/ml, 73.39±0.52% for 400 µg/ml and 84.30±0.58% for 500µg/ml for α-Amylase.

The mean inhibition activity of compound S2 was 38.85±0.26% for 100 µg/ml, 46.52±0.31% for 200 µg/ml, 69.03±0.43% for 300 µg/ml, 88.31±0.54% for 400 µg/ml and 92.28±0.65 % for 500µg/ml for α-Amylase.

The mean inhibition activity of compound S3 was 46.19±0.50% for 100 µg/ml, 47.25±0.40% for 200 µg/ml, 49.20±0.71% for 300 µg/ml, 50.61±0.09% for 400 µg/ml and 61.06±0.58% for 500µg/ml for α-Amylase.

The mean inhibition zone for standard is 19.63±0.57% for 100 µg/ml, 35.61±0.68% for 200 µg/ml, 56.84±0.68% for 300 µg/ml, 73.28±0.16% for

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400 and 86.75±1.02% for 500 µg/ml for α-Amylase.

Table 2. In *vitro* α-amylase inhibition (S1, S2 and S3)

Concentration	S1	S2	S3	Standard Acarbose
	% of inhibition			
100µg/ml	39.36± 0.28	38.85± 0.26	46.19± 0.50	19.63± 0.57
200µg/ml	49.20± 0.34	46.52± 0.31	47.25± 0.40	35.61± 0.68
300µg/ml	62.36± 0.47	69.03± 0.43	49.20± 0.71	56.84± 0.68
400µg/ml	73.39± 0.52	88.31± 0.54	50.61± 0.09	73.28± 0.16
500 µg/ml	84.30± 0.58	92.28± 0.65	61.06± 0.95	86.75± 1.02

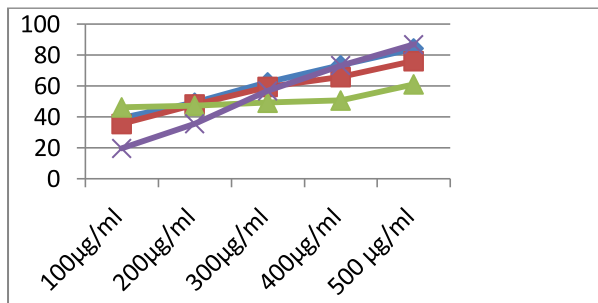

Fig 1: Effect of S1, S2 and S3 on inhibition of α Amylase activity

α-Amylase is one of the main enzymes in human body that is responsible for the breakdown of starch to more simple sugars. α-Amylases hydrolyze complex polysaccharides to produce oligosaccharides and disaccharides which are then hydrolyzed by α -glycosidase to monosaccharide which are absorbed through the small intestines into the hepatic portal vein and increase postprandial glucose levels[8]. The present findings exhibited a concentration dependent inhibition of α-amylase activity by the S1, S2 and S3. The lowest inhibition of α-amylase activity of S1, S2, S3 and Acarbose were 39.36±0.28, 38.85±0.26, 46.19±0.50 and 19.63±0.57 in the concentration of 100µg/ml respectively while the highest inhibition of α-amylase activity of S1, S2, S3 and Acarbose were 84.30±0.58, 92.28±0.65, 61.06±0.95and 86.75±1.02 % in the concentration of 500µg/ml respectively. The greatest effect of S1 (500 µg/ml) was found to be near to standard Acarbose. From the present study it can be concluded that S3 showed marked *in vitro* antidiabetic effect against the α-amylase activity (Table 2 and Figure 1). Present finding is in agreement with Gupta [9] study.

Amylase inhibitors are also known as starch blockers because they prevent dietary starch from being absorbed by the body and thereby lower postprandial glucose levels. Slowing the digestion and breakdown of starch may have beneficial effects on insulin resistance and glycemic index control in people with diabetes. In our investigation we found that compounds moderately inhibited α-amylase.

From the result it was observed that, compound S1 shows good anti diabetic activity than S2, and S3 due to the presence of electron with drawing group [10].

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

The antimitotic activity was screened using Allium cepa root meristamatic cells which have been used extensively in screening of drugs with antimitotic activity. The inhibitory effect of compounds(S1,S2 and S3) were evaluated on the growth and mitotic activity of Allium cepa root meristems and the effect was compared with standard anticancer drug methotrexate. A progressive 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 compound (S1) and methotrexate produced root decay and decreased the root length and root number significantly at 96 h as compared to control. The average mean root length at 10, 20,and 30µg/mL of compound (S1) was 6.20mm, 5.00mm, 3.4mm at 96 hr respectively while standard shows 2.60mm. The average mean root numbers at 10, 20, and 30µg/mL of compound (S1) 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 (S1) was 74.62, 60.64 and 49.62 at 96 hr respectively while standard shows 36.76%.

The compound (S2) and methotrexate produced root decay and decreased the root length and root number significantly at 96 h as compared to control. 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 compound (S3) and methotrexate produced root decay and decreased the root length

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and root number significantly at 96 h as compared to control. The average mean root length at 10, 20,and 30µg/mL of compound (S3) was 6.20mm, 4.00mm and 2.40mm at 96 hr respectively while standard shows 2.60mm. The average mean root numbers at 10, 20, and 30µg/mL of compound (S3) was 6, 5 and 4 at 96 hr respectively while standard shows 3 numbers. The mitotic index at 10, 20, and 30 µg/mL of compound (S3) was 76.92 , 67.70 and 51.72% 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.

The roots of all plants have distinguished regions, one of them being the region of cell division that lies beyond the root cap and extends a few mm after that. Cell of this region undergo repeated divisions. The fate of cell division is higher in this region compare to that of the other tissues. This region is called the meristamatic region. This division is similar to the above mentioned cancer division in humans. Hence, these meristamatic cells can be used for preliminary screening of drugs with anticancer activity[14-17].

Cytotoxicity at all concentrations test extract were evidenced by evaluating macroscopic parameters, i.e., reduction in root number and root length both of which were indicative of root growth inhibition. In the present study mitotic index of different concentrations of extract clearly indicates the efficiency in the inhibition 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. The rate of tumor growth is dependent upon a balance between the rates of proliferation and apoptosis.

Table: 3 Effect of Compounds (S1,S2 and S3) on Root length, Root number and Mitotic Index of Allium cepa roots

Group	S1			S2			S3		
	Root Growth	Root Numbers	MI(%)	Root Growth	Root Numbers	MI (%)	Root Growth (mm)	Root Numbers	MI (%)
Water (Conl)	8.1	7	87.5	8.1	7	87.5	8.1	7	87.5
10 µg/ml	6.2	6	74.62	5.7	6	75.51	6.2	6	76.92
20 µg/ml	5.0	5	60.64	3.7	5	64.62	4.0	5	67.70
30 µg/ml	3.4	3	49.62	2.9	3	40.53	2.4	4	51.72
Std Methotrexat (0.1mg/ml	2.6	3	36.76	2.6	3	36.76	2.6	3	36.76

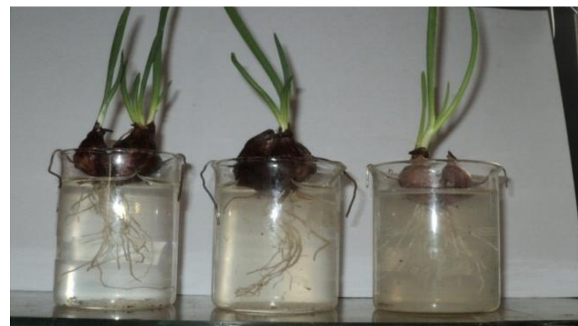

Fig.2 Various Concentrations of Compound 10µg/ml, 20µg/ml, 30µg/ml

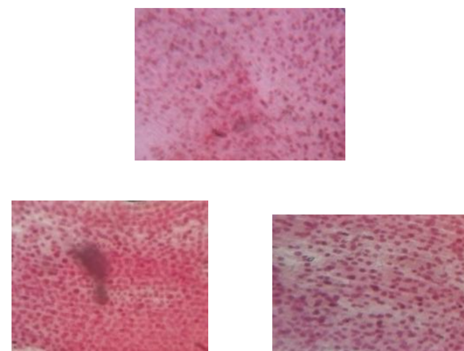

Fig.3 Photomicrograph of Compounds (S1,S2,S3) on mitotic Index of Allium cepa.

6. Conclusions

Synthesized a series of new Cyanoacetyl hydrazone derivatives obtained with good yield. All the compounds were characterized by using IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. The synthesized compounds possess potential antidiabetic activity compared to commercial drug Acarbose and hence clearly proved their pharmaceutical and medicinal importance of synthesized compounds. Among the three compounds, S1 has greated activity than S2 and S3. The antimitotic activity, among the three compounds, S2 has greated activity than S1 and S3. Maximum numbers of non dividing cells were observed. As a result of this cells arrest in mitosis and eventually die by apoptosis. Our findings support the reported therapeutic use of these compounds as antidiabetic agent and anticancer (antimitotic) agent in the Indian system of medicine.

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