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SYNTHESIS, CHARACTERIZATION AND ANTI-OBESITY ACTIVITY OF N-ACETYLCYANOACETYL HYDRAZONE DERIVATIVE

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ABSTRACT

Pancreatic lipase or triglycerol acylhydrolase, the major lipolytic enzyme synthesized and secreted by the pancreas, plays an important role in the efficient digestion of triglycerides.

Pancreatic lipase is responsible for the hydrolysis of 50-70% of the total dieatary fats. It removes fatty acids from the α –apdsitions of dietary triglycerides, yielding β-monoglycerides and long chain saturated and poly unsaturated fatty acids as the lipolytic products. The bioactive heterocyclic compounds present an exciting opportunity. Inhibition of digestive enzymes is one of the most widely studied mechanisms used to determine the potential efficacy of anti-obesity agents. The majority of pharmacetutical products that mimic heterocyclic compounds can and do participate in chemical reactions in the humanbody. The present study describes about the synthesis and the present study describes about the synthesis and characterization and biological studies of novel alkyl/halo substituted cyanoacetyl hydrazone derivatives. The synthesized compounds were characterized by FT-IR, 1H-NMR and 13C-NMR spectral studies. From this study it is obvious that the compounds inhibit the activity of pancreatic lipase, which indicates its protective role in treating obesity. The present study also confirmed that the ease of nucleophilic substitution depends on nucleophilicity. All these observations gave impetus to start a research program for the synthesis of new hydroazone derivatives containing the heterocyclic fraction.

Keywords: cyanoacetyl hydrazone, pancreaticlipase, anti-obesity

INTRODUCTION

Organic chemistry and medicinal chemistry are becoming very important chemicals. The primary objective of an organic chemist is to work towards the isolation, characterization and synthesis of new compounds that are suitable for use as drugs. Pharmaceutical chemistry is a discipline on the incorporation of chemistry and pharmacology, the chemistry, incorporation and development of pharmaceuticals shaped. However their derivatives with N–C linkages have been used in the fields of medicinal and pharmaceutical chemistry and have been reported to exhibit a variety of biological activities **[1]**.

Medicinal chemistry always leads to drug discovery and development. The introduction of synthetic substances as drugs began in the late nineteenth and early twentieth century's. Initially this development focused on isolated natural products from plant and animal sources but as knowledge increased, a wide range of synthetic compounds such as drugs developed. The original pharmacologically active compound from which these synthetic analogs are developed is known as the lead compound **[2]**.

The work of a medicinal chemist is focused on the discovery of lead compounds with specific medicinal properties. This includes the development of more effective and safer analogues of these existing and new lead compounds. Molecular manipulation of a promising lead is a major approach for the discovery of a new drug. This involves attempts to remove, replace, or replace individual groups with similar activity in a compound, or add a new fraction to the original lead compound. This could potentially result in enhancing activity, warding off unwanted side effects, and preventing the development of resistance, particularly by infectious micro-organisms **[3]**.

Hydrazones and their derivatives form an important class of compounds that have found widespread utility in organic synthesis. The chemistry of the carbon–nitrogen double bond of hydrazones is becoming the backbone of the condensation reaction in benzo – fused N-heterocyclics, also forming an important class of compounds for new drug development. Studies in heterocyclic compounds are two particular sources of interest Subject. First these are their steady streams of discovery of new heterocyclic compounds playing

important roles in the metabolism of all living cells and secondly the increasing availability of suitable intermediates for large-scale production of heterocyclic compounds. Many important compounds contain heterocyclic rings, for example most vitamins B-complex, alkaloids, antibiotics chlorophyll, hemin, plant pigments, amino acids, drugs, enzymes, DNA, RNA etc. A lot of research has been done to synthesize New heterocycles with therapeutic value and industrial applications **[4-9]**.

Obesity is defined as excessive fat accumulation of impair health. Body mass index (BMI) is a crude population measure of obesity commonly used to classify overweight and obesity in adults; Classified as the weight of a person, which is worse than the square of the height in meters (kg/m2). A person with a BMI of 30 or greater is generally considered obese, while a person with a BMI equal to or greater than 25 is considered overweight **[10]**.

The prevalence of obesity varies from country to country and depends on a number of factors, including gender, age, educational achievement, annual household income, employment status, and social class **[11-12]**. Obesity is regarded as an extremely costly health problem, with the direct medical costs of being overweight and obesity accounting for approximately 5.0% to 10% of United States health care spending **[13]**.

Obesity is a common disorder usually caused by the interaction of genetic, nutritional and environmental factors **[14]**. It has now become one of the most important health issues of modern society around the world. It is often associated with other diseases such as arteriosclerosis, high blood pressure, cancer, diabetes and osteoarthritis **[15, 16]**. The incidence of obesity is increasing rapidly, and it is revealed that around 500 million adults worldwide are obese **[17]**.

Pancreatic lipase (PL) is an enzyme, which is secreted from the pancreas and plays an excellent role in the absorption of triglyceride in the small intestine. Dietary fat is made up of about 95% triacylglycerol (TG). Pancreatic lipase hydrolyzes water-insoluble triacylglycerol in the intestinal lumen and is thus used for dietary fat absorption. Pancreatic lipase inhibitors considered a valuable therapeutic agent for the treatment of diet-induced obesity **[18]**.

One of the screening strategies used in anti-obesity drug discovery is to search for potent lipase inhibitors from natural products. Medicines that come from natural sources are safer and more efficient, even if they are toxic, but less harmful than pure

synthetic ones. Attention is being paid to the discovery of novel natural bioactive compounds as the foundation of new drug discovery as previously reliable standard drugs become less effective against emerging new strains of many drug-resistant strains **[19]**.

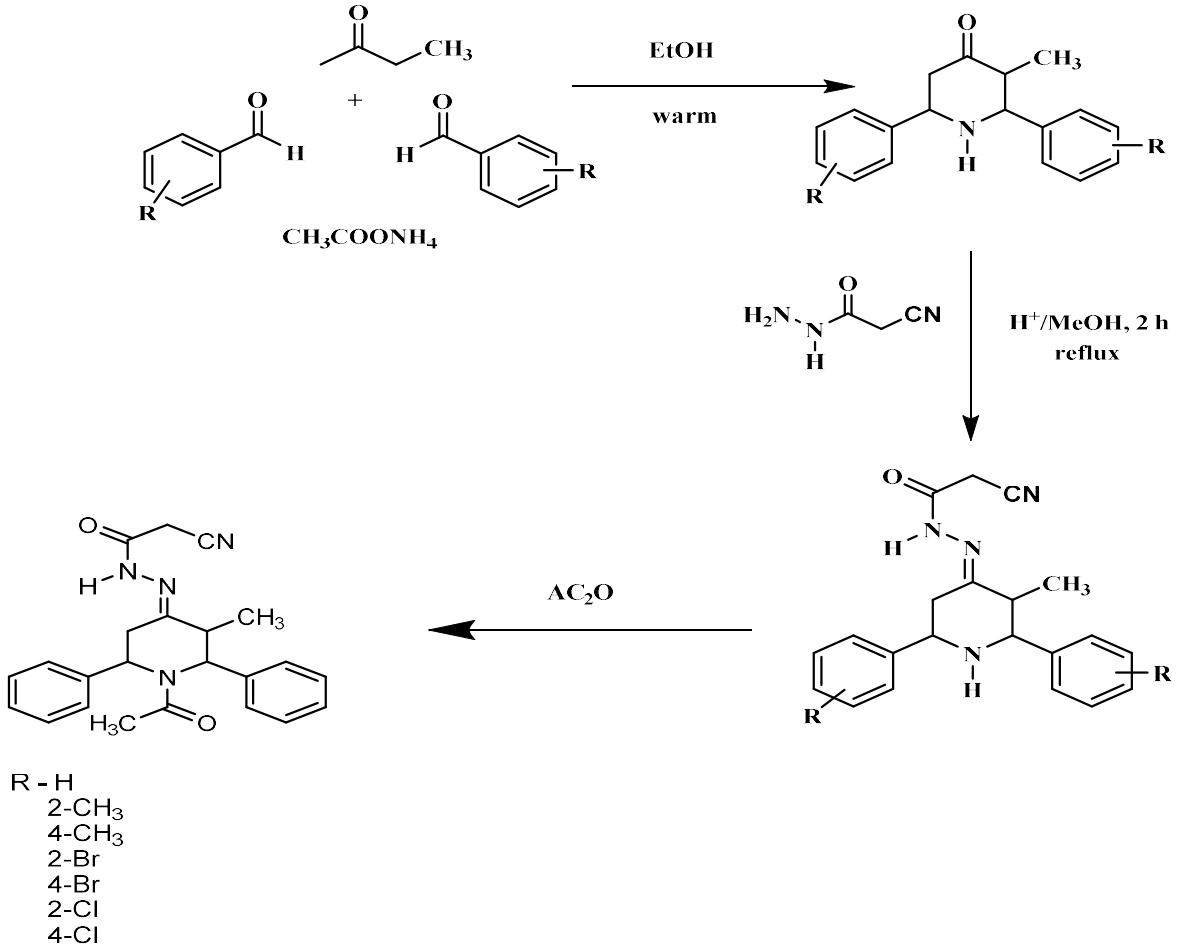
MATERIALS AND METHODS

All chemicals (solvents and reagents) were obtained from AR grade Sigma/Aldrich and Merck. was purchased from foreign companies (Hi-Media and Sigma/Aldrich) and was not used with further purification and distillation. Local chemicals have not been used in the research work. The purity of these chemicals was 98–99.9%. Other reagents used were ammonium acetate and cyanoacetic hydrazide (Merck). Analytical grade solvents such as ethanol, methanol, ethyl acetate, chloroform (CHCl3) and n-hexane were used without further distillation. The synthesized compounds were increased to yield and purified by recrystallization with the appropriate solvent system.

IR spectra were recorded in an AVATAR-330 FT-IR spectrophotometer (Thermo Nicolet) and only notable absorption levels (mutual centimeter) are listed. 1H NMR spectra were recorded on a BRUKER AMX 300 MHz and 300 MHz NMR was performed on a BRUKER AMX 300 MHz NMR spectrometer operating at 100 MHz. For recording ^{1}H NMR spectrum of compound solution were prepared by dissolving about 10mg of the compound in 0.5 ml of $CDCl_3$ was used as solvent while for ^{13}C NMR spectra, about 50 mg of the compound was dissolved in the same volume of the respective solvents. TMS (Tetra methyl silane) was used as a internal standard.

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

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. Then cyclized by 0.1 mol of acetic anhydride.



In vitro Anti-obesity activity

Anti-obesity activity determined by the method of

Pancreatic lipase inhibitory (Anti-obesity) activity of compounds

Pancreatic lipase activity was modified from that previously described by Kim *et al*. (2010) and Anil Kumar *et al* (2011) method.

Reagents

1. Olive oil
2. Phosphate Buffer (pH 6)
3. Porcine pancreatic lipase (1 mg/ml; 0.1 mm potassium phosphate buffer (pH 6.0)
4. Acetone
5. Ethanol
6. Sodium hydroxide (0.02M)
7. Oxalic acid ((0.01M)
8. Standard: Orlistat

Procedure

Different concentrations (100, 200, 300, 400 and 500µg/ml) of sample were taken and each concentration of the sample (100µl) was mixed with 8 ml of olive oil,

0.4 ml phosphate buffer and 1 ml of Porcine pancreatic lipase and it were incubated for 60 min. The reaction was stopped by the addition of 1.5 ml of a mixture containing acetone and 95 % ethanol (1:1). The appearance of pink colour from yellow colour shows the liberated fatty acids, which was determined by titrating the solution against 0.02 M sodium hydroxide (standardized by 0.01 M oxalic acid) using phenolphthalein as an indicator. Similar concentrations of positive control as Orlistat (Standard) are used. The Lipase activity of the control was checked without inhibitor (sample). Percentage inhibition of lipase activity was calculated using the formula:

Lipase inhibition = A −B/A × 100

Where A is lipase activity, B is activity of lipase when incubated with the sample.

Orlistat was used with the same concentrations as a positive control. The data were expressed as percentage inhibition, which was calculated using the formula,

Lipase Inhibition =A -B/A × 100 where, *A* is the lipase activity B is activity of lipase when incubated with the sample.

The concentration of the synthesized compounds which inhibits 50% of enzyme activity is termed as the IC50. orlistat were used as controls. A standard dose response curve was plotted at all the different concentrations. From the plotted curves, the IC50 value for each of the synthesized compounds was calculated. The data were combined and identified as mean ± standard deviation (SD).

RESULT AND DISCUSSION

N-acetyl 3-methyl-2,6-diphenylpiperidin-4-one cyanoacetylhydrazone (S1): Yield. 79.65%.

Mp. 160-163^{o}C. FT-IR (KBr) νmax (cm-1): 3062-2935(C-H Aliphatic & Aromatic stretching), 1720(C=O), 1495 (C=O piperidin moiety), 1647(C=N), 2261 (C≡N), 3424-3269(N-H).

13C NMR(300 MHz, CDCl3) δ ppm :141.48(C-2 ipso carbon), 141.17 (C-6 ipsocarbon), 127.59-128.72(Aromatic carbons), 209.53(C=O Piperidin moiety), 23.13 (CH3 carbon of Piperidin moiety),173.10(C=N), 126.82(C≡N), 43.07(CH2 carbon of cyanoacetohydrazone moiety) , 76.65(C-2), 77.50(C-6), 46.23(C-3),23.46(C-5), 13.63(3-CH3).1H NMR(300 MHz, CDCl3),

δ ppm: 7.25-7.10 (Aromatic Protons), 6.17 (N-H HydrazoneMoiety), 3.59 (CH3 – Protons in Piperidin moiety), 3.28 (CH2 – Protons in hydrazone moiety), 0.86 (3-CH3), 3.90 (H-6a), 3.53

(H-2a), 2.23 (H-5a), 2.90 (H-5e), 2.58 (H-3a Proton).

N-acetyl 3-methyl-2, 6 (bis-*o*-bromo phenyl) piperidin-4-one cyanoacetyl hydrazone (S2): Yield. 79.65%. Mp.179-181^{o}C. FT-IR (KBr) νmax (cm-1): 3099-2931 (C-H Aliphatic &Aromatic stretching), 1681 (C=O), 1567 (C=N), 2265 (C≡N), 3308-3179 (N-H).

13C NMR(300 MHz, CDCl3) 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 (CH2 carbon of cyanoacetohydrazone moiety),65.86 (C-2), 59.64 (C-6), 39.14 (C-3), 25.23 (C-5), 12.19 (3-CH3). 1H NMR (300 MHz, CDCl3), δ ppm: 7.53- 7.31 (Aromatic protons) 10.79 (N-H, Hydrazone Moiety), 2.50 (N-H Piperidin moiety), 3.35 (CH2 –Protons in hydrazonemoiety), 0.91((3-CH3), 3.88 (H-6a), 3.35(H-2a), 2.50 (H-5a), 3.35 (H-5e), 2.51(H-3a Proton).

N-acetyl 3-methyl-2, 6 (bis-*o*-chloro phenyl) piperidin-4-one cyanoacetyl hydrazone (S3) : Yield. 80.69%. Mp.142-145^{o}C. FT-IR(KBr) νmax (cm-1): 3070-2939((C-H Aliphatic &Aromatic stretching), 1633 (C=O),1470 (C=O piperidinmoiety) 1416(C=N), 2262 (C≡N), 3419-3259 (N-H). 13C NMR(300 MHz, CDCl3) δ ppm: 139.58 (C-2 ipso carbon),133.81(C-6 ipso carbon), 128.17-132.84 (Aromatic carbons), 172.49(C=O Piperidin moiety), 21.55(CH3 carbon of Piperidin moiety), 139.79(C=N), 128.17(C≡N), 22.97(CH2 carbon of cyanoacetohydrazone moiety) , 48.05(C-2), 58.59(C-6), 39.15(C-3), 39.43(C-5), 13.52(3-CH3). 1H NMR(300 MHz, CDCl3), δ ppm: 7.237.48(Aromatic Protons), 7.50 (N-H Hydrazone Moiety), 3.17 (CH3 –Protons in Piperidin moiety), 3.20 (CH2 –Protons in hydrazone moiety), 1.17 (3-CH3)3.73(H-6a), 3.3(H-2a), 2.98 (H-5a), 3.4(H-5e), 2.67(H-3a Proton).

N-acetyl 3-methyl-2,6 (bis-*o*-methyl phenyl) piperidin-4-one cyanacetyl hydrazone (S4): Yield. 82.6%. Mp. 179-181^{o}C.FT-IR(KBr) νmax (cm-1): 3024-2977((C-H Aliphatic &Aromatic stretching), 1716 (C=O),1490 (C=O piperidin moiety)1650(C=N), 2337 (C≡N), 3428-3066 (N-H). 13C NMR(300 MHz, CDCl3) δ ppm: 137.42 (C-2 ipso carbon), 136.89(C-6 ipsocarbon), 126.75-131.45(Aromatic carbons), 172.49(C=O Piperidin moiety), 22.62(CH3 carbon of Piperidin moiety),140.90(C=N), 126.22(C≡N), 24.28(CH2 carbon of cyanoacetohydrazone moiety) , 52.14(C-2), 57.53(C-6), 39.14(C-3),22.78(C-5), 18.94(3-CH3). 1H NMR(300 MHz, CDCl3), δ ppm: 6.88-7.31(Aromatic Protons), 7.42 (N-H Hydrazone Moiety),

2.32(CH3 –Protons in Piperidin moiety), 3.21 (CH2 –Protons in hydrazone moiety), 1.106 (3-CH3) 3.73(H-6a),3.3(H-2a), 2.98 (H-5a), 3.4(H-5e), 2.67(H-3a Proton).(3-CH3), 3.89 (H-6a), 3.11 (H-2a), 2.39 (H-5a), 3.07(H-5e), 2.57(H-3a Proton), 2.33 (*o*-CH3 protons).

N-acetyl 3-methyl-2,6 (bis-p-bromo phenyl) piperidin-4-one cyanoacetyl hydrazone (S5): Yield. 79.65%. Mp. 186-189^{o}C.IR (cm-1): 3025-2852 (C-H Aliphatic & Aromatic stretching), 1674 (C=O), 1568 (C=N), 2267 (C≡N), 3440-3184 (N-H).13C NMR (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 (CH2 carbon of cyanoacetohydrazone moiety), 76.57 (C-2), 56.12 (C-6), 44.89 (C-3), 34.56 (C-5), 11.15 (3-CH3) 19.20 (*o*-CH3). 1H NMR (δ ppm) : 7.32-7.13 (Aromatic Protons), 10.09 (Hydrazone Moiety),2.09 (N-H Piperidin moiety), 3.50 (CH2 –Protons in hydrazone moiety), 0.92 (3-CH3), 3.89 (H-6a), 3.11 (H-2a), 2.39(H-5a), 3.07(H-5e), 2.57 (H-3a Proton), 2.33 (*o*-CH3 protons).

3-methyl-2,6 (bis-p-chloro phenyl) piperidin-4-one cyanoacetyl hydrazone (S6) : Yield. 80.69% . Mp.118-120^{o}C. IR **(cm^{-1}):** 3100-2875(C-H Aliphatic & Aromatic stretching), 1687 (C=O), 1592 (C=N), 2261 (C≡N), 3295-3198 (N-H). **^{13}C NMR (δ ppm):** 140.78 (C-2 ipso carbon), 141.63(C-6 ipso carbon), 130.55-130.75 (Aromatic carbons), 164.36 (C=O), 155.48 (C=N), 114.18 (C≡N), 23.96 (CH_2 carbon of cyanoacetohydrazone moiety), 67.56 (C-2), 58.98 (C-6), 44.27 (C-3), 35.72 (C-5), 11.31 (3-CH_3). **^{1}H NMR (δ ppm) :**7.26-7.51(Aromatic Protons), 9.83 (N-H Hydrazone Moiety), 2.09 (N-H Piperidin moiety), 3.77 (CH_2 –Protons in hydrazone moiety), 0.89 (3-CH_3), 3.90 (H-6a), 3.51 (H-2a), 2.18 (H-5a), 2.97 (H-5e), 2.55 (H-3a Proton).

3-methyl-2,6 (bis-*p*-methyl phenyl) piperidin-4-one cyanoacetyl hydrazone (S7) :Yield. 78.69%. Mp. 120-122 ^{o}C. **FT-IR(KBr) ν_{max} (cm^{-1})**: 3026-2963(C-H Aliphatic & Aromatic stretching), 1701 (C=O), 1638 (C=N), 2266 (C≡N), 3195-3097(N-H). **^{13}C NMR(300 MHz, $CDCl_3$) δ ppm**: 139.33 (C-2 ipso carbon), 139.83 (C-6 ipso carbon), 126.42-129.38 (Aromatic carbons), 164.87 (C=O), 158.07 (C=N), 114.13 (C≡N), 24.56 (CH_2 carbon of cyanoacetohydrazone moiety), 68.92 (C-2), 60.46 (C-6), 45.34 (C-5), 36.16 (C-3), 12.10 (3-CH_3), 21.13(*p*-CH_3) . **^{1}H NMR(300 MHz, $CDCl_3$), δ ppm :** 7.14-7.36 (Aromatic Protons), 9.01(N-H, Hydrazone Moiety), 2.06 (N-H Piperidin moiety), 3.73 (CH_2 –

Protons in hydrazone moiety), 0.89 (3-CH_3), 3.87 (H-6a), 3.49 (H-2a), 2.24 (H-5a), 2.83 (H-5e), 2.57 (H-3a Proton), 2.06 (p-CH_3 protons).

Anti obesity activity

In the current scenario, obesity is a major public health problem with approximately 1.9 billion adults (aged 18 years and older) worldwide and approximately 600 million of them are clinically obese. The disease is characterized by an increase in the size of the adipocytes, which leads to an increase in the amount of fat in the disease of adipota. Microbes such as germline are cured in order to increase the adipocytes. Thus, inhibition of digestion and absorption of dietary fat is a first key to treating obesity. This inhibition involve lipase enzyme, the principle lipolytic enzyme synthezied and secreted by the pancreas. There is an increase in the amount of damage to the testes. The substrates for the lipase enzyme are long-chain triacylglycerols, which are separated from the surface phase by the aqueous medium. Thus, the lipase enzyme must be adsorbed on the substrate lipid surface and the nature of the substrate surface has an important role for lipase activity.

Inhibition of pancreatic lipase is an attractive targeted approach for the discovery of potent anti-obesity agents for the treatment of obesity. One of the screening strategies used in anti-obesity drug discovery is to search for potent lipase inhibitors from synthesized compounds. In this study, we screened synthesized compounds as potential anti-obesity agents by monitoring their anti-lipase activity. Concentration – dependently on the *in vitro* assay.

The activity of the compounds was determined by comparison with the anti-obesity of Pancreatic lipase. The test compound was measured for the decrease in clot weight at different concentrations. The different concentrations compared about or list at as standard drug **[20-22]**.

Pancreatic lipase inhibitory activity of synthesized compound is given in **Figure 1**.

In the present study, anti-obesity activity analysis of compounds (low concentration

(100 **µg/ml**) to higher concentration (500 **µg/ml**). Synthesized compound$BCAHACO_2$ (S1) significantly inhibited lipase with low concentration was 14.25% while the higher concentration was 76.45%.Anti-obesity activity analysis of compounds (low concentration (100 **µg/ml**) to higher concentration(500 **µg/ml**). Synthesized compound 2-$BrCAHACO_2$(S2)

significantly inhibited lipase with low concentration was 17.46% while the higher concentration was 83.47%.

anti-obesity activity analysis of compounds (low concentration (100 **µg/ml**) to higher concentration (500 **µg/ml**). Synthesized compound 2- $ClCAHACO_2$(S3) significantly inhibited lipase with low concentration was 18.07% while the higher concentration was 85.93%.anti-obesity activity analysis of compounds (low concentration(100 **µg/ml**) to higher concentration(500 **µg/ml**). Synthesized compound 2-$MeCAHACO_2$ (S4) significantly inhibited lipase with low concentration was 19.54% while the higher concentration was 87.45%.

anti-obesity activity analysis of compounds (low concentration (100 **µg/ml**) to higher concentration (500 **µg/ml**). Synthesized compound 4-$BrCAHACO_2$(S5) significantly inhibited lipase with low concentration was 14.39% while the higher concentration was 78.05%.

Anti-obesity activity analysis of compounds (low concentration (100 **µg/ml**) to higher concentration (500 **µg/ml**). Synthesized compound4-$ClCAHACO_2$(S6) significantly inhibited lipase with low concentration was 16.94% while the higher concentration was 81.26%.

anti-obesity activity analysis of compounds (low concentration(100 **µg/ml**) to higher concentration(500 **µg/ml**). Synthesized compound 4-$MeCAHACO_2$(S7) significantly inhibited lipase with low concentration was 15.79% while the higher concentration was 80.45%.

Table 1: Anti-obesityactivity (Pancreatic lipase inhibitory activity) of Synthesized compound

Samples	Concentrations (µg/ml)					IC_{50} value (µg/ml)
	100	200	300	400	500	
S1	**14.25±0.99**	**23.56±1.64**	**39.69±2.77**	**60.81±4.25**	**76.45±5.35**	**343.49**
S2	**17.46±1.22**	**30.21±2.11**	**47.63±3.33**	**68.95±4.82**	**83.47±5.84**	**302.59**
S3	**18.07±1.26**	**30.62±2.14**	**49.81±3.48**	**71.68±5.01**	**85.93±6.01**	**293.05**
S4	**19.54±1.36**	**33.29±2.33**	**51.65±3.61**	**72.43±5.07**	**87.45±6.12**	**283.52**
S5	**14.39±1.01**	**24.65±1.72**	**40.98±2.86**	**61.04±4.27**	**78.05±5.46**	**337.75**
S6	**16.94±1.18**	**29.46±2.06**	**45.98±3.21**	**66.49±4.65**	**81.26±5.68**	**311.85**
S7	**15.79±1.10**	**27.43±1.92**	**43.54±3.04**	**65.91±4.61**	**80.45±5.63**	**320.11**
Std. (Orlistat)	**21.61±1.51**	**37.48±2.62**	**56.93±3.98**	**78.52±5.49**	**92.46±6.47**	**259.56**

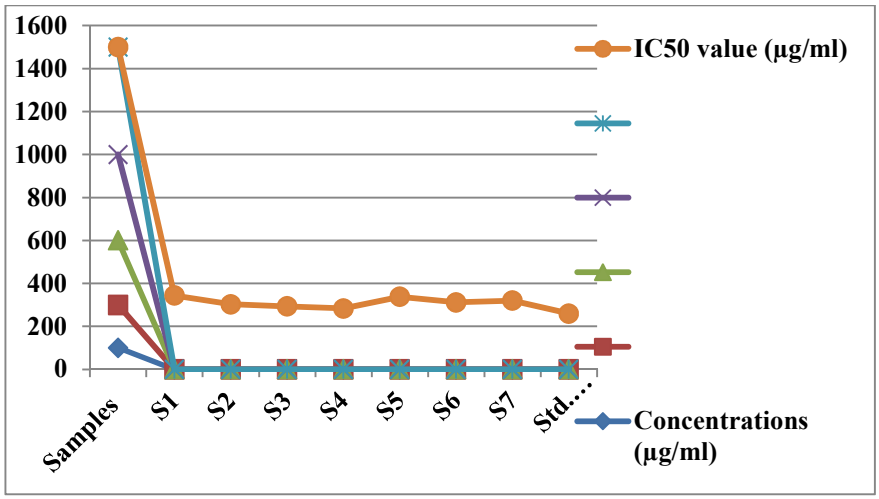


Figure 1: Anti-Obesity activity Graph

CONCLUSION

The structure of the synthesized compound is established on the basis of their analytical and spectral data (IR, ^{1}H NMR, ^{13}C NMR).The synthesized compound was subjected to preliminary anti-obesity by pancreatic lipase inhibitory activity. The result from the study showed that the N-acetyl -3-methyl cyano acetyl hydrazone derivatives had excellent anti-obesity activity that was comparable to the activity of Orlistat. The study revealed that few of the synthesized such as N- acetyl -3-methyl cyano acetyl hydrazone derivatives exhibited high total potent pancreatic lipase inhibitory effects. Strong positive correlation between synthesized bioactives and that of the anti - lipase activity was observed. It can be concluded from the present study that N-acetyl -3-methyl cyano acetyl hydrazone derivatives provide convencing anti-obesity. This research may provide a basic for in vivo study and strong foundation for future development of synthesized compounds with great applications in prevention and treatment of obesity.

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