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# SYNTHESIS AND EVALUATION OF XANTHINE-BASED COMPOUNDS AS ANTI-OBESITY AGENTS

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**ABSTRACT**

The work was carried out with an object to synthesize xanthine products and assess the anti-obesity action of the synthesized compounds. The conjugates were yellow to brown in color and obtained in 68-71 % yields and were slightly soluble in water, insoluble in methanol and DMSO while they were soluble in chloroform. The confirmation of the structures of the compounds was done by $^1$H-NMR, mass, and IR spectral study. SAO1-5 were found to be hypophagic and restrict the intake of food by the mice and the hyperphagic effect of (±) - 8- OH-DPAT was antagonized by SAO.

**Keywords:** Xanthine, Hypophagic, 5-Hydroxytryptamine, Obesity, Food Intake.

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## INTRODUCTION

Obesity is a medical condition characterized by an excessive accumulation of body weight, disproportionately high levels of adipose tissue. From a thermodynamic perspective, obesity arises from a disparity between energy intake and energy expenditure, posing a significant health risk and resulting in a diminished life expectancy.1 Obesity heightens the probability of developing a range of diseases and ailments that are associated with higher death rates. The aforementioned conditions encompass Type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), metabolic syndrome (MetS), chronic kidney disease (CKD), hyperlipidemia, hypertension, nonalcoholic fatty liver disease (NAFLD), specific types of malignancies, obstructive sleep apnea, osteoarthritis, and depression.[2] Synthetic medication represents a viable therapeutic approach for the management of obesity. Despite the significant significance of managing obesity, the availability of anti-obesity drugs remains constrained. During the last thirty years, only a limited number of medications for treating obesity, such as orlistat, lorcaserin, topiramate, bupropion, setmelanotide, and liraglutide, have been created or authorized by the US Food and Drug Administration (FDA). Xanthine, also known as 3,7-dihydropurine-2,6-dione, is a purine base comprised of a pyrimidine ring fused with an imidazole ring. It contains nitrogen as its core atom. The presence of structural fragments in a wide range of natural and synthetic medicinally active substances renders it a fundamental and indispensable component of numerous natural goods.[8] Heterocyclic compounds bearing xanthine[9], thiazolidinedione[10], alkoxyaurone[11] and morpholine[12] have been investigated widely for antiobesity action. Considering the widespread use of xanthine-based products like caffeine in weight management, in the present work we have attempted to synthesize few xanthine-based compounds and assess their anti-obesity action.

## EXPERIMENTAL

The synthesized compounds underwent characterization to determine their melting point, solubility, yield, and structural elucidation. The elucidation of the structure was conducted using spectroscopic research, including NMR, Mass, and IR techniques. The melting points were calculated using the open capillary method and were not adjusted using an electrically heated testing device. Thin layer chromatography was employed to assess the purity and homogeneity of the compounds, with silica gel G serving as the stationary phase on glass plates. The spots were visualized using a TLC cabinet equipped with both long and short UV light. The compounds were subjected to a solvent system consisting of chloroform and methanol in a ratio of 9:1. The qualitative determination of the solubility of all the produced compounds was conducted


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in various solvents.[13] The sample was agitated in 1 mL of solvent in a test tube and visually examined to ensure the absence of solid particles. The steps involved in the synthesis of xanthine derivatives has been presented in the Fig.-1 below.

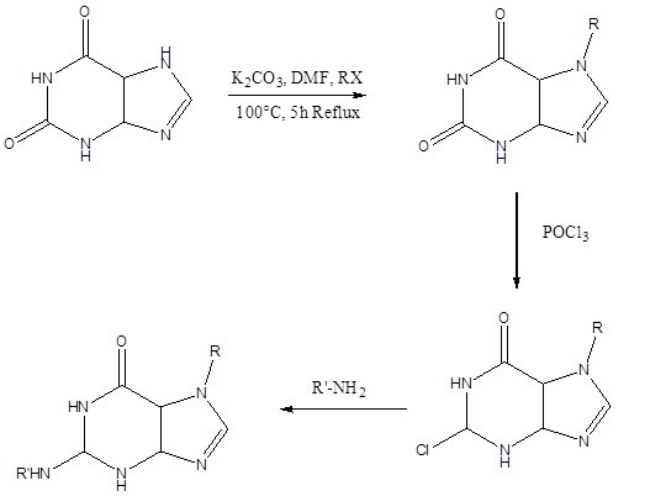



Fig.-1: Scheme for Synthesis of Xanthine Derivatives

**Synthesis of 7-substituted-3,4,5,7-tetrahydro-1H-purine-2,6-dione**

Benzylchloride was added at room temperature to a mixture consisting of xanthine (3.8 mmol), 0.55 g (4 mmol) anhydrous K2CO3, and DMF (20 mL, 4 mmol). Following the completion of the reaction, which lasted for a duration of 4 hours, the mixture underwent concentration. Subsequently, 20 mL of water was introduced to the residue, followed by extraction using ethyl acetate (15 mL ± 3). The organic phases were then combined and subjected to sequential washes with 1 mol/L HCl, saturated NaHCO3 solution, and brine. Finally, the mixture was dried using anhydrous Na2SO4. The removal of the solvent resulted in the recrystallization of the residue from ethanol/water, yielding the title chemical.[14]

**Synthesis of 2-chloro-7-substituted-1,2,3,4,5,7-hexahydropurin-6-one**

The reaction involved the reflux of a solution containing 7-substituted-3,4,5,7-tetrahydro-1H-purine-2,6-dione (3.7 mmol) and POCl3 (20 ml) for a duration of 5 hours. The reaction mixture underwent in vacuum concentration, and the resulting residue was divided between a solution of CHCl3 and a saturated NaHCO3 solution. The organic layer was then washed with brine, dried, and concentrated. The raw substance was separated on a silica gel using a mixture of CHCl3 and MeOH at a ratio of 20:1 as an eluent. This resulted in the formation of 2-chloro-7-substituted-1,2,3,4,5,7-hexahydropurin-6-one, which was then subjected to recrystallization using MeOH.[15]

**General Procedure for the Synthesis of 2-amino-7-substituted-1,2,3,4,5,7-hexahydropurin-6-one Derivatives**

Overnight, a solution was prepared by reusing a mixture of 2-chloro-7-substituted-1,2,3,4,5,7-hexahydropurin-6-one (0.003mol), a suitable amine (2 ml), and acetonitrile (40 ml). The reaction mixture was concentrated under vacuum conditions, and the remaining substance was purified through recrystallization using ethylacetate–Methanol. This process resulted in the formation of derivatives of 2-amino-7-substituted-1,2,3,4,5,7-hexahydropurin-6-one.[15]

**General Method for Synthesis of 7-benzyl-2-(phenylamino)-1,2,3,4,5,7-hexahydropurin-6-one (SAO)**

A mixture of 2-chloro-7-substituted-1,2,3,4,5,7-hexahydropurin-6-one (0.003 mol), substituted aniline (2 ml) and acetonitrile (40 ml) were refluxed overnight. In order to obtain 7-benzyl-2-(phenylamino)-1,2,3,4,5,7-hexahydropurin-6-one, the reaction mixture was concentrated in vacuo and the resulting residue was purified through recrystallization using ethylacetate-methanol.

**7-benzyl-2-(phenylamino)-1,2,3,4,5,7-hexahydropurin-6-one, SAO1**
Color – yellow; $^1$HNMR ($CDCl_3$, δ ppm) – 8.08, 6.82, 5.31, 4.40 (C-H, xanthine), 6.65 to 7.33 (C-H, aromatic), 4.11 (N-H, aniline), 1.44 (N-H, xanthine); FT-IR ($cm^{-1}$) – 3619 $cm^{-1}$ (amine), 1770 $cm^{-1}$ (carbonyl), 1464 $cm^{-1}$ (imine), 1172 $cm^{-1}$ (C-N) and bending vibrations at around 815 $cm^{-1}$ (C-N) and 749 $cm^{-1}$ (C-N-C); m/e – 340.1 ($M^+$+2).

**7-benzyl-2-(3-chlorophenylamino)-1,2,3,4,5,7-hexahydropurin-6-one, SAO2**
Color – orange; $^1$HNMR ($CDCl_3$, δ ppm) – 8.08, 6.83, 5.34, 4.43 (C-H, xanthine), 6.60 to 7.32 (C-H, aromatic), 4.37 (N-H, aniline), 1.42 (N-H, xanthine); FT-IR ($cm^{-1}$) – 3565 $cm^{-1}$ (amine), 1740 $cm^{-1}$ (Carbonyl), 1464 $cm^{-1}$ (Imine), 1171 $cm^{-1}$ (C-N) and bending vibrations at around 844 $cm^{-1}$ (C-N), 754 $cm^{-1}$ (C-N-C) and 671 (C-Cl); m/e – 353.2 ($M^+$+1).

**7-benzyl-2-(3-bromophenylamino)-1,2,3,4,5,7-hexahydropurin-6-one, SAO3**
Color – yellow; $^1$HNMR ($CDCl_3$, δ ppm) – 8.08, 5.36, 4.42 (C-H, xanthine), 6.98 to 7.32 (C-H, aromatic), 4.37 (N-H, aniline), 1.41 (N-H, xanthine); FT-IR ($cm^{-1}$) – 3524 $cm^{-1}$ (amine), 1740 $cm^{-1}$ (Carbonyl), 1464 $cm^{-1}$ (Imine), and bending vibrations at around 749 $cm^{-1}$ (C-N) and 666 $cm^{-1}$ (C-N-C); m/e – 366.2 ($M^+$).

**7-benzyl-2-(3-nitrophenylamino)-1,2,3,4,5,7-hexahydropurin-6-one, SAO4**
Color – light brown; $^1$HNMR ($CDCl_3$, δ ppm) – 8.22, 6.82, 5.31, 4.40 (C-H, xanthine), 7.11 to 8.20 (C-H, aromatic), 4.37 (N-H, aniline), 1.43 (N-H, xanthine); FT-IR ($cm^{-1}$) – 3619 $cm^{-1}$ (amine), 1770 $cm^{-1}$ (Carbonyl), 1463 $cm^{-1}$ (imine), 1171 $cm^{-1}$ (C-N) and bending vibrations at around 812 $cm^{-1}$ (C-N) and 747 $cm^{-1}$ (C-N-C); m/e – 415.1 ($M^+$+1).

**7-benzyl-2-(3-fluorophenylamino)-1,2,3,4,5,7-hexahydropurin-6-one, SAO5**
Color – light brown; $^1$HNMR ($CDCl_3$, δ ppm) – 8.08, 6.61, 5.34, 4.43 (C-H, xanthine), 6.83 to 7.32 (C-H, aromatic), 4.37 (N-H, aniline), 1.43 (N-H, xanthine); FT-IR ($cm^{-1}$) – 3648 $cm^{-1}$ (amine), 1740 $cm^{-1}$ (C=O), 1464 $cm^{-1}$ (C=N), and bending vibrations at around 749 $cm^{-1}$ (C-N); m/e – 430.1 ($M^+$+2).\

**Antiobesity Study**
Six female Swiss albino mice, weighing between 20 and 25 grams, were accommodated in cages in laboratory settings, where they were provided with unrestricted access to food and water. The animals were utilized subsequent to a minimum of two days of acclimation to the laboratory environment.

**Drugs Used and Grouping of Animals**
The synthesized compounds were dispersed in deionized water and given orally at a dosage of 0.5 g/kg. Deionized water was used to dissolve Fluoxetine HCl and (±)-8-Hydroxy-2-(dipropylamino)tetralinhydrobromide (± 8-OH-DPAT). Both medicines were intraperitoneally delivered at a constant volume of 1 ml/100 g body weight. Group-1 (Vehicle control): Allowed normal diet; Group-2 to 6 (Test treatment): Mice administered with 0.5g/kg, p.o test suspension; Group -7 (Fluoxetine treatment): This group served as standard and administered with fluoxetine solution (10 mg/kg, intraperitoneally); Group -8 (± 8-OH-DPAT pretreatment): Mice administered with ± 8-OH-DPAT (0.1 mg/kg, intraperitoneally); Group -9 (pretreated with ± 8-OH-DPAT): Mice treated with ± 8-OH-DPAT half hour preceding to administration of test compounds; Group -10 (± 8-OH-DPAT pretreatment): Mice treated with ± 8-OH-DPAT half hour preceding to administration of fluoxetine.

**Study of Effect of Test Compounds on Food Intake[16]**
The mice were housed in test cages, with each group consisting of six mice. The control group received a vehicle treatment, while the other groups received different medication treatments. Prior to the experiment, the provision of food and water was withheld for a duration of 1 hour. Oral administration of test compounds was conducted, followed by the presentation of preweighed sweetened chow (5 g) to the several groups of mice in petri dishes within the test cages after a duration of 15 minutes. The quantity of food that remained was measured at intervals of 0.5, 1, 2, 3, and 4 hours, and the total food intake per mouse (g/20 g body weight) was computed.

**Study of Effect of Fluoxetine on Food Intake**

Similar to the test substances, mice were housed in groups of six in test cages, which consisted of a control group treated with a vehicle and different groups receiving different pharmacological treatments. Prior to the experiment, the provision of food and water was withheld for a duration of 1 hour. Intraperitoneal administration of fluoxetine hydrochloride was conducted, followed by the presentation of preweighed sweetened chow (5 g) to the several groups of mice in petri dishes within the test cages after a duration of 15 minutes. The quantity of food that remained was measured at intervals of 0.5, 1, 2, 3, and 4 hours, and the total food intake per mouse (g/20 g body weight) was computed.

**Study of Effect of ± 8-OH-DPAT Pretreatment Food Intake Ability**

Prior to the experiment, the provision of food and water was withheld for a duration of 1 hour. The animals were intraperitoneally delivered 8-OH-DPAT at a dosage of 0.1 mg/kg, intraperitoneally. Following a 15-minute period, preweighed sweetened chow (5 g) was presented to the several groups of mice in petri dishes within the test cages. The quantity of food that remained was measured at intervals of 0.5, 1, 2, 3, and 4 hours, and the total food intake per mouse (g/20 g body weight) was computed.

**Study of Effect of ± 8-OH-DPAT Pretreatment Food Intake Ability by Test Compounds**

Prior to the experiment, the provision of food and water was withheld for a duration of 1 hour. The rats were intraperitoneally injected 8-OH-DPAT at a dosage of 0.1 mg/kg. Following a 30-minute interval, the animals were subjected to the administration of test chemicals. Subsequently, after a 15-minute period, preweighed sweetened chow (5 g) was provided to the various groups of mice in petri dishes within the test cages. The quantity of food that remained was measured at intervals of 0.5, 1, 2, 3, and 4 hours, and the total food intake per mouse (g/20 g body weight) was computed.

**Study of Effect of ± 8-OH-DPAT Pretreatment Food Intake Ability by Fluoxetine**

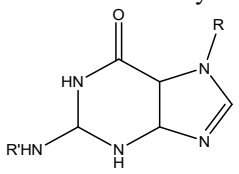
Prior to the experiment, the provision of food and water was withheld for a duration of 1 hour. The rats were intraperitoneally injected 8-OH-DPAT at a dosage of 0.1 mg/kg. Following a 30-minute interval, the animals were subjected to the administration of fluoxetine. Subsequently, after a 15-minute period, preweighed sweetened chow (5 g) was provided to the several groups of mice in petri dishes within the test cages. The quantity of food that remained was measured at intervals of 0.5, 1, 2, 3, and 4 hours, and the total food intake per mouse (g/20 g body weight) was computed.

## RESULTS AND DISCUSSION

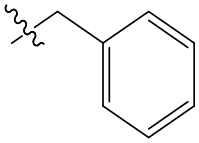
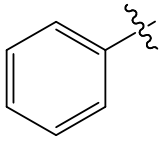
The xanthine derivatives (**SAO1-5**) were synthesized in three steps commencing with reaction of benzyl chloride with xanthine in presence of potassium carbonate to yield the 7-benzyl compound. The 2-keto group of this compound was reacted with Phosphorous oxychloride to obtain a 2-chloro derivatives. The 2-chloro derivative was subjected to a nucleophilic substitution with various anilines to yield the desired compounds SAO1 to SAO5.

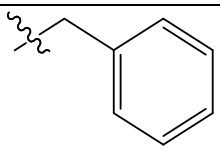
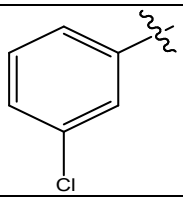
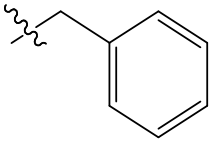
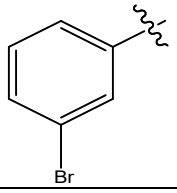
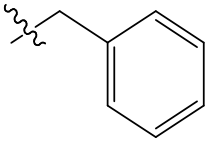
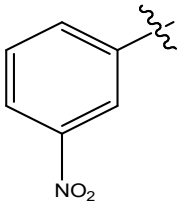
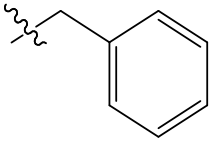
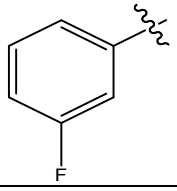
The synthesized conjugates were characterized by determining the practical yield, melting point, solubility and spectral studies. The physicochemical properties are shown in Table-1.

Table-1: Physical Characteristics of Synthesized Compounds




**SAO1-5**

| Compound code | R | R’ | Yield (%) | $R_f$ Value | Melting point (°C) |
|---|---|---|---|---|---|
| SAO1 |  |  | 71 | 0.44 | 304-307 |

| | | | | | |
|---|---|---|---|---|---|
| SAO2 |  |  | 72 | 0.56 | 310-311 |
| SAO3 |  |  | 71 | 0.54 | 301-303 |
| SAO4 |  |  | 68 | 0.63 | 302-305 |
| SAO5 |  |  | 71 | 0.61 | 310-313 |

All the compounds were soluble in chloroform and slightly soluble in water.

The confirmation of the structures of the compounds was done by $^{1}$H-NMR, mass and IR spectral study. The stretching vibrations at around 3400 $cm^{-1}$ (N-H), 1740 $cm^{-1}$ (C=O), 1464 $cm^{-1}$ (C=N), 1171 $cm^{-1}$ (C-N-C) and bending vibrations at around 875 $cm^{-1}$ (C-N) and 759 $cm^{-1}$ (C-N-C) ring deformation were present in the FT-IR spectra of the compounds. In the $^{1}$HNMR spectra the peaks at chemical shift value of 8.08, 6.82, 5.59 and 4.40 corresponding to the proton of xanthine ring (C-H), 4.11 corresponding to the proton of xanthine nitrogen (N-H), 1.44 corresponding to the proton of xanthine ring (N-H) and 6.9 to 7.3 corresponding to the protons of the aromatic rings were present in all the compounds. The fragment peaks of molecular ion or isotope were found in the mass spectra of the compounds.

**Anti-Obesity Action**

The ability of rodents to consume sweetened chow or a high-fat diet is a highly effective model for study of the anti-obesity action of drugs. A standard chow died provides 12.98% fat energy, 58.62% carbohydrates and 28.40% proteins, contributing to total of 1243.6 kcal/100g. On the contrary, a high fat diet (sweetened chow) usually contains 50.52% fat, 31.50% carbohydrates, and 17.98% proteins, contributing to 1765.8 kcal/100g.

The anti-obesity effect of the synthesized molecules was assessed by observing the effect of the molecule on the food intake habit of experimental mice. The amount of food remained unconsumed post 4 hours of treatment in each group was weighed and the food intake in grams was calculated per 20 g body weight (Table-2 and 3).

Table-2: Weight of Food Unconsumed by Mice

| | | Weight of HFD remaining (g) | | | | |
|---|---|---|---|---|---|---|
| | Treatment | 0.5 h | 1h | 2h | 3h | 4h |
| Group I | Vehicle | 4.52 | 4.21 | 3.97 | 3.71 | 3.54 |
| Group II | SAO1 | 4.56 | 4.35 | 4.12 | 3.91 | 3.79 |
| Group III | SAO2 | 4.57 | 4.34 | 4.11 | 3.94 | 3.75 |
| Group IV | SAO3 | 4.55 | 4.35 | 4.11 | 3.87 | 3.78 |
| Group V | SAO4 | 4.56 | 4.32 | 4.07 | 3.89 | 3.76 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Group VI | SAO5 | 4.61 | 4.38 | 4.15 | 3.96 | 3.84 |
| Group VII | Fluoxetine | 4.77 | 4.67 | 4.41 | 4.18 | 3.85 |
| Group VIII | 8-OH-DPAT | 4.17 | 3.58 | 3.44 | 3.19 | 3.03 |
| Group IX | 8-OH-DPAT + SAO1 | 4.69 | 4.48 | 4.31 | 4.19 | 3.95 |
| Group X | 8-OH-DPAT + Fluoxetine | 4.65 | 4.58 | 4.44 | 4.24 | 4.03 |

Table-3: Weight of Food Consumed by Mice

| | | Cumulative Food intake/mouse (g/20g body weight) | | | | |
|---|---|---|---|---|---|---|
| | Treatment | 0.5 h | 1h | 2h | 3h | 4h |
| Group I | Vehicle | 0.48 | 0.79 | 1.03 | 1.29 | 1.46 |
| Group II | SAO1 | 0.44 | 0.65 | 0.88 | 1.09 | 1.21 |
| Group III | SAO2 | 0.43 | 0.66 | 0.89 | 1.06 | 1.25 |
| Group IV | SAO3 | 0.45 | 0.65 | 0.89 | 1.13 | 1.22 |
| Group V | SAO4 | 0.44 | 0.68 | 0.93 | 1.11 | 1.24 |
| Group VI | SAO5 | 0.39 | 0.62 | 0.85 | 1.04 | 1.16 |
| Group VII | Fluoxetine | 0.23 | 0.33 | 0.59 | 0.82 | 1.15 |
| Group VIII | 8-OH-DPAT | 0.83 | 1.42 | 1.56 | 1.81 | 1.97 |
| Group IX | 8-OH-DPAT + SAO1 | 0.31 | 0.52 | 0.69 | 0.81 | 1.05 |
| Group X | 8-OH-DPAT + Fluoxetine | 0.35 | 0.42 | 0.56 | 0.76 | 0.97 |

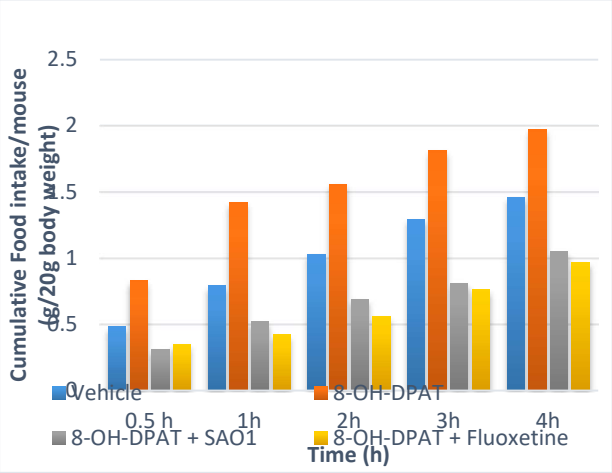



Fig.-2: Effect of Co-administration of (±) - 8- OH-DPAT + SAO1 and (±) - 8- OH-DPAT + Fluoxetine on Food Intake in Mice

As clearly visible from the Fig.-2, fluoxetine and SAO1-5 are hypophagic and restrict the intake of food by the mice. On the other hand (±) - 8- OH-DPAT is a known agonist of 5-hydroxytryptamine and exhibits hyperphagic action (Fig.-2). On co-administration of (±) - 8- OH-DPAT with either SAO1 or fluoxetine, it was found that the hyperphagic effect of (±) - 8- OH-DPAT was antagonized by both SAO1 and fluoxetine. The reduction in food intake was calculated with reference to the food intake exhibited by hyperphagic animals (Table-4).

Table-4: Percent Reduction in Food Intake by Treated Animals

| | Percent reduction in food intake as compared to 8-OH-DPAT | | | | |
|---|---|---|---|---|---|
| Treatment | 0.5 h | 1h | 2h | 3h | 4h |
| 8-OH-DPAT + SAO1 | 62.65 | 63.38 | 55.76 | 55.24 | 46.70 |
| 8-OH-DPAT + Fluoxetine | 57.83 | 70.42 | 64.10 | 58.01 | 50.76 |

The reduction in food intake was converted to percentage reduction and the plot of reduction with time was obtained. It is visible from the plot that SAO was immediate in exhibiting anorexic effect while its anorexic potential started to lower by the 4$^{th}$ hour. Both SAO and fluoxetine were effective in reducing the food

intake by about 50% by the 4th hour. The result of the study showed that 8-OH-DPAT, a 5-HT1A agonist, causes inhibition of the endogenous satiety system and increases food intake at low doses. Moreover, previous research has provided evidence indicating that the hyperphagic properties of 8-OH-DPAT can be attributed to the diminished production and release of 5-HT resulting from the drug's agonistic activity on somatodendritic 5-HT1A autoreceptors located in the raphe nuclei.[17] The observed suppression of hyperphagia produced by 8-OH-DPAT by fluoxetine aligns with previous research findings. Therefore, it is probable that SAO1-5 may similarly exert its influence on food consumption via 5-HT1A receptors, as it effectively counteracted hyperphagia generated by 8-OH-DPAT.

## CONCLUSION

The aim of this investigation has been to create xanthine-based molecules and evaluate their anti-obesity action by assessing the outcome on food consumption by mice. The synthesis was accomplished in three steps starting with xanthine. The compounds are expected to act by exerting their effect on food intake through 5-HT1A receptors.

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## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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