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SYNTHESIS OF NOVEL XANTHINE DERIVATIVES AND EVALUATION OF THEIR HYPOPHAGIC EFFECT

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ABSTRACT

The objective of this work was to synthesize xanthine derivatives and evaluate the anti-obesity action. The compounds 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. Compounds 4a-e 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 them.

Keywords: Xanthine, obesity, hyperlipidemia, food intake, cardiovascular

INTRODUCTION

Obesity is a term applied to excess body weight with an abnormally high proportion of body fat. Thermodynamically speaking, it's an imbalance between energy intake and energy expenditure leads to obesity that presents a risk to health, leading to reduced life expectancy **[1]**. Obesity increases the likelihood of various diseases and conditions which are linked to increased mortality. These include Type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), metabolic syndrome (MetS), chronic kidney disease (CKD), hyperlipidemia, hypertension, nonalcoholic fatty liver disease (NAFLD) and certain types of cancers, obstructive sleep apnea, osteoarthritis, and depression

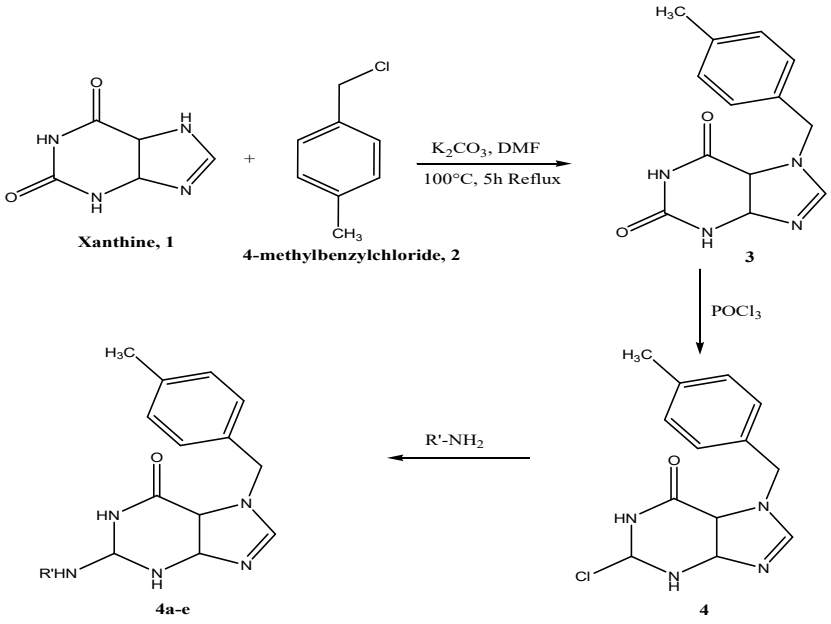
[2]. Synthetic medication is one of therapeutic options to treat obesity. In spite of the importance of controlling obesity, available anti-obesity medications are limited. Over the past three decades, only few obesity-treatment drugs like orlistat, lorcaserin, topiramate, bupropion, setmelanotide and liraglutide have been developed or approved by the US Food and Drug Administration (FDA) **[3-7]**.

Xanthine or 3,7-dihydropurine-2,6-dione is a purine base containing nitrogen as a central atom and composed of a pyrimidine ring fused with an imidazole ring. It is an essential core element of diverse natural products because their structural fragments are found in various natural and synthetic medicinally active compounds **[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.

MATERIAL AND METHODS

All the synthesized compounds were characterized for melting point, solubility, yield and elucidation of the structure. The melting points were determined by open capillary method and are uncorrected. The steps involved in the synthesis of xanthine derivatives has been presented in the **Scheme 1** below **(Figure 1)**.



R'NH- 4-methylaniline, chloroaniline, bromoaniline, nitroaniline, fluroaniline

Figure 1: Scheme for synthesis of xanthine derivatives

Synthesis of 7-(4-methylbenzyl)-3,4,5,7-tetrahydro-1H-purine-2,6-dione, 2

To a mixture of xanthine (3.8 mmol), 0.55 g (4 mmol) anhydrous K_2CO_3 and DMF (20 mL, 4 mmol) was added 4-methylbenzylchloride at room temperature. After the reaction was completed (4 hours) the mixture was concentrated, water (20 mL) was added to the residue and extracted with ethyl acetate (15 mL × 3), the organic phases were combined and washed with 1 mol/L HCl, saturated $NaHCO_3$ solution, and brine successively, dried with anhydrous Na_2SO_4. The solvent was removed and the residue was recrystallized form ethanol/water to afford title compound **[13]**.

Synthesis of 2-chloro-7-(4-methylbenzyl)-3,4,5,7-tetrahydro-1H-purine-6-one, 3

A mixture of 7-(4-methylbenzyl)-3,4,5,7-tetrahydro-1H-purine-2,6-dione (3.7 mmol) and $POCl_3$ (20 ml) was refluxed for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between chloroform and saturated sodium bicarbonate solution and the organic layer was washed with brine, dried and concentrated. The crude product was chromatographed on silica gel using $CHCl_3$–MeOH (20 : 1) as an eluent to give 2-chloro-7-(4-methylbenzyl)-3,4,5,7-tetrahydro-1H-purine-6-one, which was recrystallized from MeOH **[14]**.

General procedure for 2-amino-7-(4-methylbenzyl)-3,4,5,7-tetrahydro-1H-purine-6-one derivatives

A mixture of 2-chloro-7-(4-methylbenzyl)-3,4,5,7-tetrahydro-1H-purine-6-one (1.5 mmol), appropriate amine (1 ml) and acetonitrile (20 ml) were refluxed overnight. The reaction mixture was concentrated *in vacuo* and the residue was purified by recrystallization from AcOEt–MeOH to give 2-amino-7-(4-methylbenzyl)-3,4,5,7-tetrahydro-1H-purine-6-one **[14]**.

Antiobesity study

Female Swiss albino mice weighing 20–25 g, were housed six per cage with free access to food and water at laboratory conditions. The animals were used following at least a 2-day period of adaptation to the laboratory conditions.

Drugs Used and Grouping of Animals

The synthesized compounds were suspended in distilled water and administered at a dose of 0.5 g/kg, p. o. Fluoxetine HCl and (±)-8-Hydroxy-2-(dipropylamino)tetralin hydrobromide (± 8-OH-DPAT) were dissolved in distilled water. Both these drugs were administered intraperitoneally at constant volume of 1 ml/100 g body weight.

Group-1 (Vehicle control): Normal mice which developed in normal condition and give 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 (± 8-OH-DPAT pretreatment): Mice treated with ± 8-OH-DPAT 30 minutes prior to administration of test compounds; Group -10 (± 8-OH-DPAT pretreatment): Mice treated with ± 8-OH-DPAT 30 minutes prior to administration of fluoxetine

Study of effect of test compounds on food intake [15]

Mice were kept in groups of six in test cages and included a vehicle-treated control group and the various drug treatment groups. The food and water were withheld 1 h before the experimentation. Test compounds were administered orally and after 15 min preweighed sweetened chow (5 g) was presented to the different groups of mice in petri dishes in the test cages. The amount remaining was weighed after 0.5, 1, 2, 3 and 4 h intervals and the cumulated food intake/mouse (g/20 g body weight) was calculated. Fluoxetine hydrochloride was administered as the standard drug intraperitoneally.

Study of effect of ± 8-OH-DPAT pretreatment food intake ability

The food and water were withheld 1 h before the experimentation. 8-OH-DPAT (0.1 mg/kg, i. p.) was administered intraperitoneally to the animals and after 15 min preweighed sweetened chow (5 g) was presented to the different groups of mice in petri dishes in the test cages. The amount remaining was weighed after 0.5, 1, 2, 3 and 4 h intervals and the cumulated food intake/mouse (g/20 g body weight) was calculated.

Study of effect of ± 8-OH-DPAT pretreatment food intake ability

The food and water were withheld 1 h before the experimentation. 8-OH-DPAT (0.1 mg/kg, i. p.) e was administered intraperitoneally to the animals. After 30 min, test compounds were administered to these animals and after 15 min preweighed sweetened chow (5 g) was presented to the different groups of mice in petri dishes in the test cages. The amount remaining was weighed after 0.5, 1, 2, 3 and 4 h intervals and the cumulated food intake/mouse (g/20 g body weight) was calculated. Fluoxetine was administered as the standard drug.

Results and Discussion

The xanthine derivatives (**4a-e**) were synthesized in three steps commencing with

reaction of 4-methyl 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 4a to 4e.

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

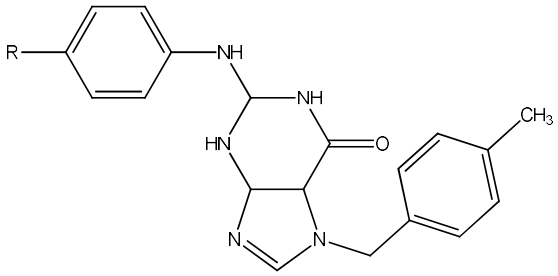


Table 1: Physical characteristics of synthesized compounds

Compound code	R	Yield (%)	R_f Value	Melting point (°C)
4a	CH_3	69	0.51	197-199
4b	Cl	70	0.63	165-167
4c	Br	68	0.57	200-203
4d	NO_2	69	0.61	180-184
4e	F	65	0.68	222-224

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

7-(4-methylbenzyl)-2-(p-tolylamino)-3,4,5,7-tetrahydro-1H-purin-6(2H)-one, 4a

Color – Brown; ^{1}HNMR ($CDCl_3$, δ ppm) – 8.08, 6.82, 5.31, 4.40, 6.65 to 7.33, 4.11, 1.44; FT-IR (cm^{-1}) – 3619 cm^{-1}, 1770 cm^{-1}, 1464 cm^{-1}, 1172 cm^{-1} and bending vibrations at around 815 cm^{-1} and 749 cm^{-1}; m/e – 350.3 (M^++2)

2-((4-chlorophenyl)amino)-7-(4-methylbenzyl)-3,4,5,7-tetrahydro-1H-purin-6(2H)-one, *4b*

Color – Yellow; ^{1}HNMR ($CDCl_3$, δ ppm) – 8.08, 6.83, 5.34, 4.43, 6.60 to 7.32, 4.37, 1.42; FT-IR (cm^{-1}) – 3565 cm^{-1}, 1740 cm^{-1}, 1464 cm^{-1}, 1171 cm^{-1} and bending vibrations at around 844 cm^{-1}, 754 cm^{-1} and 671; m/e – 369.2 (M^++1)

2-((4-bromophenyl)amino)-7-(4-methylbenzyl)-3,4,5,7-tetrahydro-1H-purin-6(2H)-one, 4c

Color – Orange; ^{1}HNMR ($CDCl_3$, δ ppm) – 8.08, 5.36, 4.42, 6.98 to 7.32, 4.37, 1.41; FT-IR (cm^{-1}) – 3524 cm^{-1}, 1740 cm^{-1}, 1464 cm^{-1}, and bending vibrations at around 749 cm^{-1} and 666 cm^{-1}; m/e – 413.2 (M^+)

7-(4-methylbenzyl)-2-((4-nitrophenyl)amino)-3,4,5,7-tetrahydro-1H-purin-6(2H)-one, 4d

Color – Brown; ^{1}HNMR ($CDCl_3$, δ ppm) – 8.22, 6.82, 5.31, 4.40, 7.11 to 8.20, 4.37, 1.43; FT-IR (cm^{-1}) – 3619 cm^{-1}, 1770 cm^{-1}, 1463 cm^{-1}, 1171 cm^{-1} and bending vibrations at around 812 cm^{-1} and 747 cm^{-1}; m/e – 380.5 (M^++1)

2-((4-fluorophenyl)amino)-7-(4-methylbenzyl)-3,4,5,7-tetrahydro-1H-purin-6(2H)-one, 4e

Color – Brown; ^{1}HNMR ($CDCl_3$, δ ppm) – 8.08, 6.61, 5.34, 4.43, 6.83 to 7.32, 4.37, 1.43; FT-IR (cm^{-1}) – 3648 cm^{-1}, 1740 cm^{-1}, 1464 cm^{-1}, and bending vibrations at 749 cm^{-1}; m/e – 355.1 (M^++2)

The stretching vibrations of N-H, C=O, C=N, C-N-C and bending vibrations due to C-N and C-N-C ring deformation were present in the FT-IR spectra of the compounds.

In the ^{1}HNMR spectra the peaks at chemical shifts corresponding to the proton of xanthine ring (C-H), xanthine nitrogen (N-H), protons of the aromatic rings were present in all the compounds. In all the compounds peaks at chemical shift of methyl group (CH_3) was also present. The fragment peaks of molecular ion or isotope were found in the mass spectra of the compounds.

Anti-obesity action

The ability of rodent to consume sweetened chow or high fat diet is a highly effective model for study of anti-obesity action of drugs.

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.

As clearly visible from the **Figure 2**, fluoxetine and 4a-4e 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 **(Figure 3)**. On co-administration of (±) - 8- OH-DPAT with either 4a or fluoxetine, it was found that the hyperphagic effect of (±) - 8- OH-DPAT was antagonized by both 4a-4e and fluoxetine.

The reduction in food intake was calculated with reference to the food intake exhibited by hyperphagic animals **(Figure 4)**.

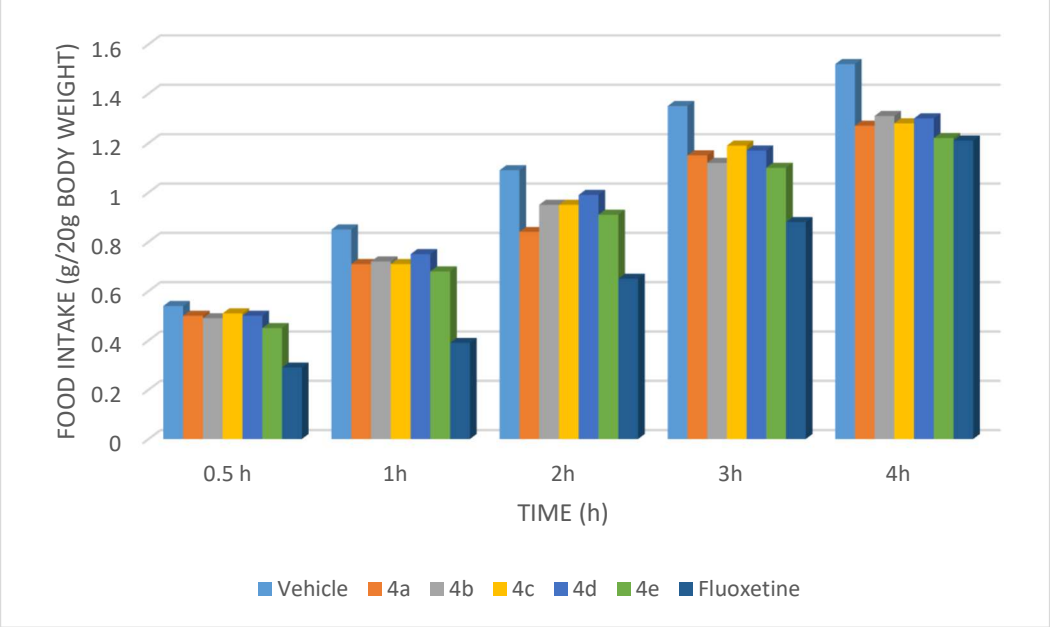


Figure 2: Effect of 4a-e and fluoxetine on food intake in mice

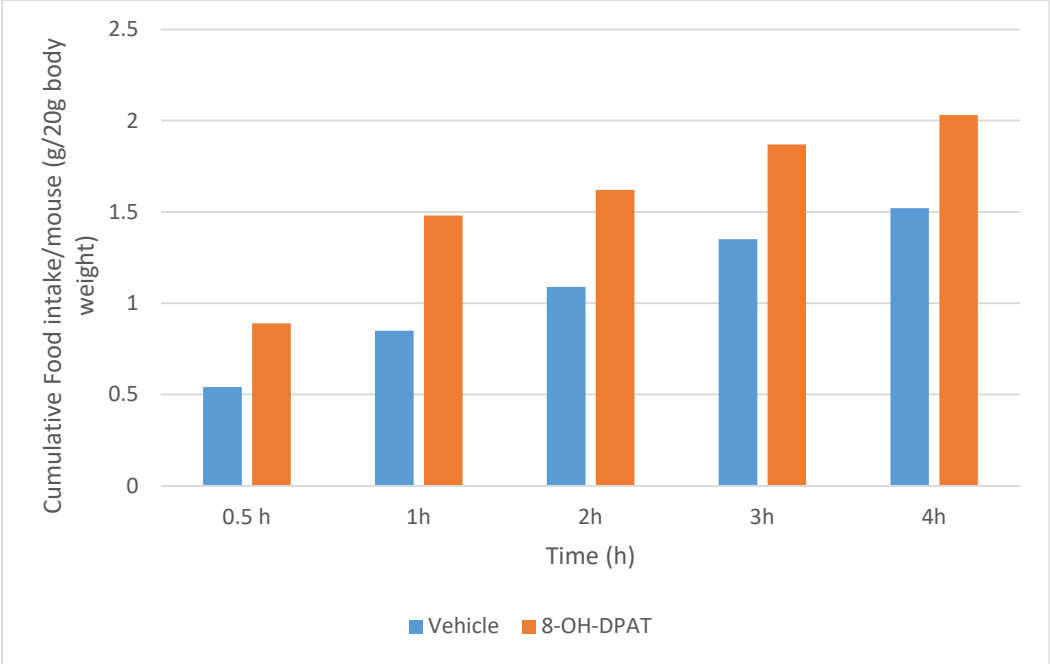


Figure 3: Effect of (±) - 8- OH-DPAT on food intake in mice

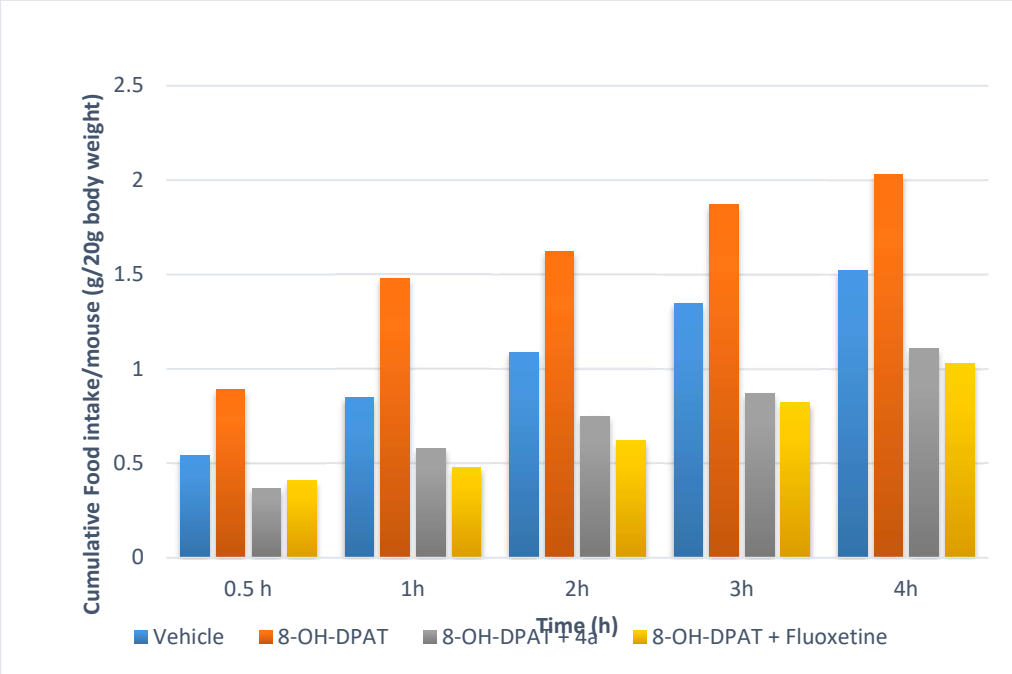


Figure 4: Effect of co-administration of (±) - 8- OH-DPAT + 4a and (±) - 8- OH-DPAT + fluoxetine on food intake in mice

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 4th 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. The antagonism of 8-OH-DPAT-induced hyperphagia by fluoxetine is also consistent with the earlier findings **[16]**. Thus, it is likely that 4a-4e may also mediate its effect on food intake through 5- HT1A receptors as well since it significantly antagonized 8-OH-DPAT-induced hyperphagia.

CONCLUSION

The objective of the present investigation was to develop xanthine based molecules and evaluate their anti-obesity action by studying the effect on food intake by mice. The synthesis was accomplished in three steps starting from xanthine. The compounds are expected to act by exerting their effect on food intake through 5- HT1A receptors.

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