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SYNTHESIS OF SOME NOVEL 1,3,6-TRISUBSTITUTED-1*H*-THIAZOLO[3,2-*f*]PURINE-2,4-DIONES AND XANTHINE SCHIFF BASES AS POTENIAL ANTI-ASTHMATIC AND ANTI-INFLAMMATORY AGENTS

Alaa M. Hayallah[1,4*], Reham Abu Shmeis[2] and Ahmad A. Talhouni[3]

[1]*Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Assiut University, Assiut, Egypt*
[2]*Department of Basic Pharmaceutical Sciences (Analytical Chemistry), Faculty of Pharmacy, Israa University, Amman, Jordan*
[3]*Department of Applied Pharmaceutical Sciences (Pharmacology), Faculty of Pharmacy, Israa University, Amman, Jordan*
[4]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Deraya University, El-Minia, Egypt*

*In this study, the design, synthesis and preliminary pharmacological investigation of novel 1,3-diethyl-8-disubstituted xantines **12-18**, 1,3,6-trisubstituted-1H-thiazolo[3,2-f]purine-2,4-diones **19-25** and xanthine Schiff bases **28-33** was described. 1,3-Diethyl-8-substituted xantines **12-18** were prepared by the reaction of 1,3-diethyl-8-thioxo-3,7,8,9-tetrahydropurine-2,6-dione **4** with the appropriate phenacyl bromides **5-11**. Compound **4** was in turn prepared by the reaction of 5,6-diamino-1,3-diethyluracil **3** with carbon disulfide. The derivatives **19-25** were obtained by cyclodehydration of compounds **12-18** in polyphosphoric acid (PPA). Schiff bases **28-33** were synthesized by the reaction of acetohydrazide **27** with appropriate aldehyde in refluxed ethanol. The effect of the new derivatives as potential anti-asthmatic was evaluated using acetycholine induced brocnhospasm in Guinea pigs, most of tested compounds showed significant anti-bronchoconstriction activity in comparison with aminophylline as a standard drug. Anti-inflammatory activity of the target compounds was investigated using indomethacin as a reference drug and some compounds exhibited potent anti-inflammatory activity.*

INTRODUCTION

Allergic asthma, a chronic airway disease which involves bronchial epithelium, mucus-secreting glands, lung parenchyma, and infiltrating inflammatory leukocytes, has the characteristics of lung inflammation, airway hyper-responsiveness and mucus over-production[1]. It is now widely accepted that chronic airway inflammation plays a key role in asthma[2]. This fundamental feature has been included in the most recent definitions of the disease: hence, the Global Strategy for Asthma Management and Prevention reports “asthma is a chronic inflammatory disease of the airways in which many cell types play a role, in particular mast cells, eosinophils and T-lymphocytes. In susceptible individuals, the inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and cough, particularly at night and/or early morning. Based on this consensus, all treatment guidelines focus on the importance of anti-inflammatory drugs (mainly inhaled corticosteroids) to control the disease process[3]. Thus, searching for new bronchodilators with anti-inflammatory effect remains an important and a challenging target. Several purine derivatives and condensed purines have been claimed to posess a multitude of pronounced

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*Corresponding author: Alaa M. Hayallah, E-mail: alaa_hayalah@yahoo.com

biological activities. The class of fused purines are considered attractive targets since its fundamental skeleton is analogous to naturally occurring purine alkaloids. They played an important role in cancer chemotherapy[4&5] and act as antimicrobial agents[6&7]. In addition, some purine derivatives such as theophylline and enprofylline are reported to play an important role in the treatment of asthma[8&9]. In addition, caffeine has intrinsic antinociceptive properties and is used as an adjuvant analgesic drug[10&11]. Furthermore, some 1,8-disubstituted purine-2,6-diones (PSB-53 **I**, PSB-1115 **II** and 8-substituted xanthines **III**, chart 1) were reported as potent analgesic and anti-inflammatory agents through adenosine receptor antagonism[12-14]. Moreover, thiazole and fused thiazoloheterocyclic derivatives such as thiazolo[3,2-*b*]triazoles, thiazolo[4,5-*d*] pyrimidines, Pyrido[2,3-d]pyrimidinediones and imidazo[3,4-*c*]thiazoles showed anti-noicecptive and anti-inflammatory action[15-20]. These facts motivated our interest in the present investigation towards the design and synthesis of new xanthine derivatives and 1,3,6-trisubstituted thiazolo[3,2-*f*]purine-2,4-dione, in which a third ring (thiazole) was added to the purine skeleton as shown in schemes 1-2. These derivatives were rationalized and synthesized as potential anti-asthmatic and anti-inflammatory agents.

EXPERIMENTAL

Chemical synthesis

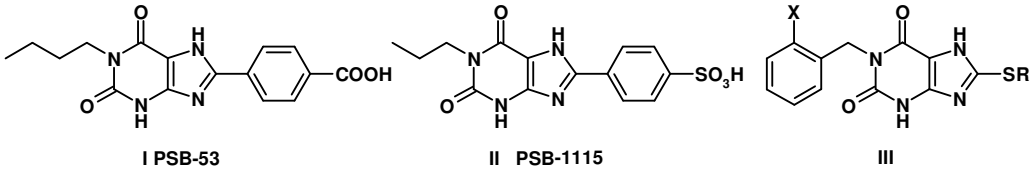
The reagents used for synthesis were purchased from Sigma-Aldrich (Gillingham – Dorset, UK) and MERCK (Schuchardt, Germany). All solvents were obtained from commercial suppliers and used without further purification. Melting points (mp) were determined on an electrothermal Stuart Scientific SMP1 (UK) melting point apparatus and were uncorrected. A thin-layer chromatography (TLC, R_f values) was carried out using TLC aluminium sheets kieselgel 60 F_{254} (MERCK) and dichloromethane/methanol (9.5:0.5) or (9:1) as a mobile phase and visualization was effected with ultraviolet lamp Spectroline ENF-240C/F (USA) at short wavelength (λ= 254 nm). All chemical yields are unoptimized and generally represent the result of a single experiment. NMR spectra were recorded on Bruker DPX 300 MHz spectrometer at Jordan University, Amman, Jordan and on a Varian EM-360 60 MHz spectrometer at Faculty of Pharmacy, Assiut University, Egypt. DMSO-d_6 was used as a solvent, unless otherwise specified, and the chemical shifts are given in δ (ppm) and the coupling constants (*J*) are in Hertz (Hz). Chemical shifts are expressed either relative to tetramethylsilane (TMS) as an internal standard or to the chemical shifts of the remaining protons of DMSO-d_6: ^{1}H: δ 2.49 ppm. Protons of NH, and OH groups were confirmed by D_2O. The MS were determined using JOEL JMS600 mass spectrometer at the Unit of Microanalysis, Assiut University, Egypt. The microanalyses for C, H, N were performed on Perkin-Elmer 240 elemental analyzer at the Micro analytical center, Faculty of Science, Cairo University, and some of them performed on a Perkin-Elmer 240 elemental analyzer at Jordan University, Jordanion, Amman, Jordan.

5,6-Diamino-1,3-diethyluracil (**3**) was prepared from N,N´-diethylurea and cyanoacetic acid followed by nitrosation and reduction as described[21&22]. Phenacyl bromides (**6-10**) were prepared from *p*-(un)substituted acetophenone derivatives by bromination in ether-dioxan in the presence of aluminum chloride as catalyst[23-25].

1,3-Diethyl-8-thioxo-3,7,8,9-tetrahydro-purine-2,6-dione (4)

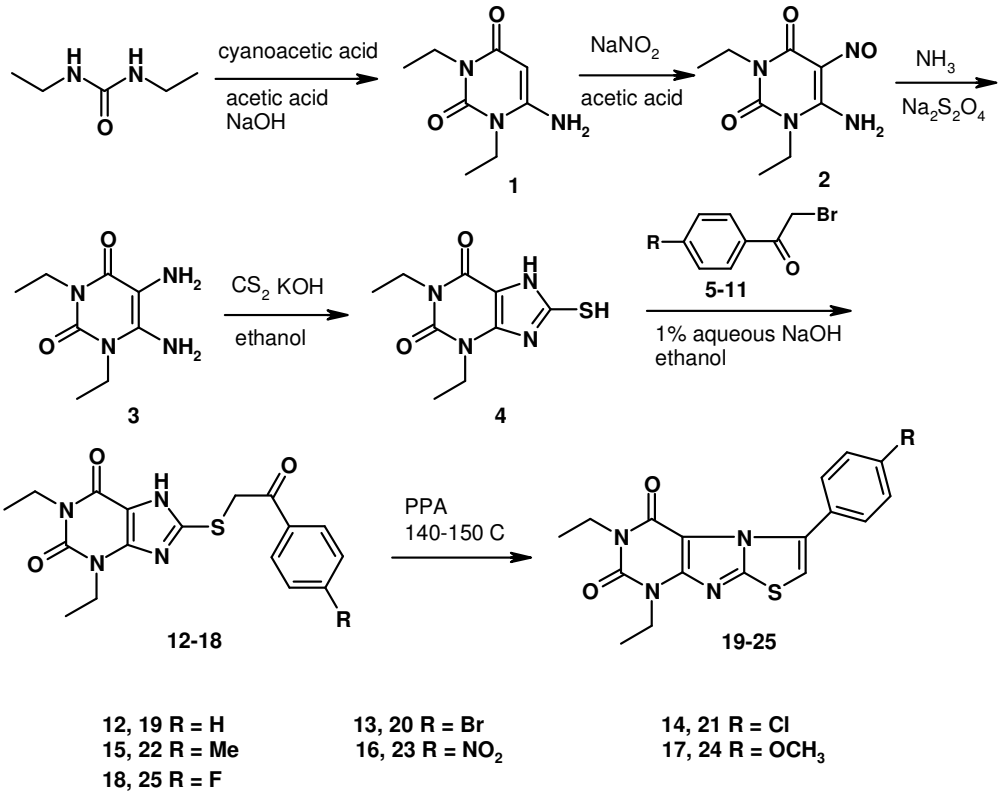
Potassium hydroxide (0.63 g, 11.26 mmol) was dissolved in 25 mL ethanol then carbon disulfide (1.4 g, 27 mmol) was added followed by the addition of 5,6-diamino-1,3-diethyluracil (2.23 g, 11.26 mmol) **3**. The reaction mixture was refluxed for 7 hrs, diluted with warm water (20 mL) and stirred well, and then acetic acid (3 mL) in water (10 mL) was added portionwise. The reaction mixture was allowed to cool in the refrigerator for 3 hrs, the product was collected by filtration and was crystallized from ethanol.

IR (KBr) ύ (cm^{-1}) 3450 (NH), 2855 (C-H aliphatic), 1712, 1633 (C=O); ^{1}H-NMR (60 MHz, DMSO-d_6): δ 13.10 (s, 1H, N7-H), 11.40 (s, 1H, N9H), 4.05-3.90 (m, 4H, $\underline{CH_2}$-CH_3), 1.10-0.90 (m, 6H, CH_2-$\underline{CH_3}$). Yield 90%, m.p. >330°C.



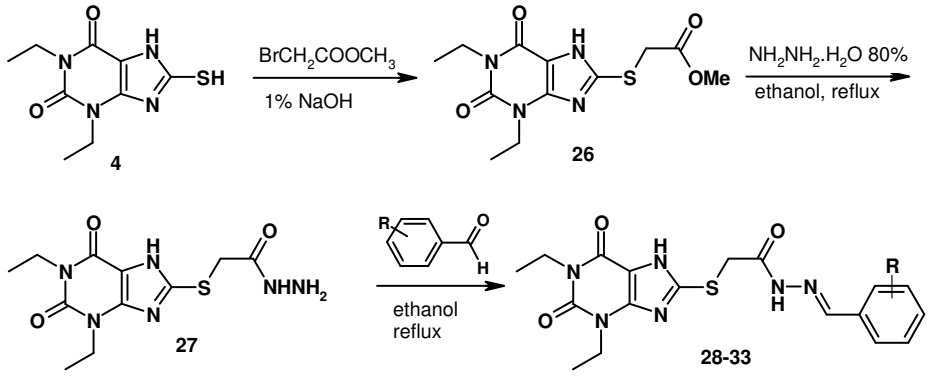
I PSB-53 II PSB-1115 III

Chart 1: Structure of PSB-53, PSB-1115 and compound **III**.



12, 19 R = H **13, 20 R = Br** **14, 21 R = Cl**
15, 22 R = Me **16, 23 R = NO_2** **17, 24 R = OCH_3**
18, 25 R = F

Scheme 1: Synthetic route of target compounds **12-25**.



28 R = H **29 R = 4-Br** **30 R = 4-COOH**
31 R = 4-Cl **32 R = 4-$N(CH_3)_2$** **33 R = 2-NO_2**

Scheme 2: Synthetic route of target compounds **28-33**.

1,3-Diethyl-8-(2-oxo-2-(un)substituted-phenyl-ethylsulfanyl-3,7,8,9-tetrahydro-purine-2,6-diones (12-18)

General procedure. A solution of **4** (0.82 g, 2.89 mmol), dissolved in aqueous sodium hydroxide (1%, 20 mL) was added in portion wise manner with stirring to a solution of the appropriately p(un)substituted phenacyl bromide (2.89 mmol) **5-11** in ethanol (5 mL). The reaction mixture was stirred at an ambient temperature for 4-5 hrs. The reaction mixture was kept at room temperature overnight and the product was collected by filtration, washed with water and crystallized from aqueous ethanol to afford compounds **12-18**.

1,3-Diethyl-8-(2-oxo-2-phenylethylsulfanyl)-3,7,8,9-tetrahydropurine-2,6-dione (12)

IR (KBr) ύ (cm^{-1}) 3435 (N-H), 3075 (Ar-H), 2900 (C-H aliphatic), 1707, 1661, 1616 (C=O), 1542 (N-H), 700, 690 (Ar-H); ^{1}H-NMR (60 MHz, DMSO-d_6): δ 13.10 (s, 1H, N7-H), 8.30-8.10 (m, 3H, ArH), 7.90-7.70 (m, 2H, ArH), 5.00 (s, 2H, CH_2), 4.20-3.80 (m, 4H, $\underline{CH_2}$-CH_3), 1.30-0.90 (m, 6H, CH_2-$\underline{CH_3}$). Yield 80%, m.p. 268-269°C. Anal. Calcd for $C_{17}H_{18}N_4O_3S$: C, 56.97; H, 5.06; N, 15.63. Found: C, 57.01; H, 4.88; N, 15.95.

8-[2-(4-Bromophenyl)-2-oxo-ethylsulfanyl]-1,3-diethyl-3,7,8,9-tetrahydropurine-2,6-dione (13)

IR (KBr) ύ (cm^{-1}) 3445 (N-H), 3075 (Ar-H), 2895 (C-H aliphatic), 1708, 1663, 1616 (C=O), 1581 (N-H), 806 (Ar-H); ^{1}H-NMR (60 MHz, DMSO-d_6): δ 13.20 (s, 1H, N7-H), 8.10 (d, 2H, J= 8.6 Hz, ArH), 7.90 (d, 2H, J= 8.6 Hz, ArH), 5.10 (s, 2H, CH_2), 4.20-3.80 (m, 4H, $\underline{CH_2}$-CH_3), 1.30-0.90 (m, 6H, CH_2-$\underline{CH_3}$). Yield 83%, m.p. 273-274°C. Anal. Calcd for $C_{17}H_{17}BrN_4O_3S$: C, 46.69; H, 3.92; N, 12.81. Found: C, 46.82; H, 3.73; N, 12.52. EI MS (*m/z*): 437.2 (M^+, 9%), 439.10 (M^++2, 8%), 183.10 (100%).

8-[2-(4-Chlorophenyl)-2-oxo-ethylsulfanyl]-1,3-diethyl-3,7,8,9-tetrahydropurine-2,6-dione (14)

IR (KBr) ύ (cm^{-1}) 3415 (N-H), 3060 (Ar-H), 2875 (C-H aliphatic), 1708, 1663, 1616 (C=O); 1546 (N-H), 1088 (C-Cl), 809 (Ar-H); ^{1}H-NMR (60 MHz, DMSO-d_6): δ 13.30 (s, 1H, N7-H), 8.20 (d, 2H, J= 8.5 Hz, ArH), 7.80 (d, 2H, J= 8.5 Hz, ArH), 5.20 (s, 2H, CH_2), 4.20-3.85 (m, 4H, $\underline{CH_2}$-CH_3), 1.30-1.00 (m, 6H, CH_2-$\underline{CH_3}$). Yield 79%, m.p. 263-264°C. Anal. Calcd for $C_{17}H_{17}ClN_4O_3S$: C, 51.97; H, 4.36; N, 14.26. Found: C, 51.91; H, 4.60; N, 14.48.

1,3-Diethyl-8-(2-oxo-2-*p*-tolylethylsulfanyl)-3,7,8,9-tetrahydropurine-2,6-dione (15)

IR (KBr) ύ (cm^{-1}) 3420 (N-H), 3100 (Ar-H), 2905 (C-H aliphatic), 1708, 1657, 1616 (C=O), 1546 (N-H), 801 (Ar-H); ^{1}H-NMR (60 MHz, DMSO-d_6): δ 13.60 (s, 1H, N7-H), 8.00 (d, 2H, J= 8.6 Hz, ArH), 7.90 (d, 2H, J= 8.6 Hz, ArH), 4.90 (s, 2H, CH_2), 4.20-3.80 (m, 4H, $\underline{CH_2}$-CH_3), 3.30 (s, 3H, CH_3), 1.40-1.00 (m, 6H, CH_2-$\underline{CH_3}$). Yield 88%, m.p. 249-250°C. Anal. Calcd for $C_{18}H_{20}N_4O_3S$: C, 58.05; H, 5.41; N, 15.04. Found: C, 57.71; H, 5.47; N, 15.20. EI MS (*m/z*): 372.34 (M^+, 3%), 349.70 (14%), 240.10 (100%).

1,3,-Diethyl-8-[2-(4-nitrophenyl)-2-oxo-ethylsulfanyl]-l-3,7,8,9-tetrahydropurine-2,6-dione (16)

IR (KBr) ύ (cm^{-1}) 3450 (N-H), 3025 (Ar-H), 2865 (C-H aliphatic),1705, 1634, 1616 (C=O), 1556 (N-H), 1512, 1333 (NO_2), 845 (Ar-H); ^{1}H-NMR (60 MHz, DMSO-d_6): δ 13.50 (s, 1H, N7-H), 8.30 (d, 2H, J= 8.6 Hz, ArH), 7.70 (d, 2H, J= 8.6 Hz, ArH), 4.95 (s, 2H, CH_2), 4.10-3.80 (m, 4H, $\underline{CH_2}$-CH_3), 1.40-1.00 (m, 6H, CH_2-$\underline{CH_3}$). Yield 79%, m.p. 270-271°C. Anal. Calcd for $C_{17}H_{17}N_5O_5S$: C, 50.61; H, 4.25; N, 17.36. Found: C, 50.60; H, 4.52; N, 17.11.

1,3,-Diethyl-8-[2-(4-methoxyphenyl)-2-oxo-ethylsulfanyl]-l-3,7,8,9-tetrahydro-purine-2,6-dione (17)

IR (KBr) ύ (cm^{-1}) 3495 (N-H), 3060 (Ar-H), 2875 (C-H aliphatic), 1707, 1641, 1620 (C=O), 1596 (N-H), 1265, 1067 (C-O), 791 (Ar-H); ^{1}H-NMR (60 MHz, DMSO-d_6): δ 13.40 (s, 1H, N7-H), 8.10 (d, 2H, J= 8.5 Hz, ArH), 7.10 (d, 2H, J= 8.5 Hz, ArH), 5.15 (s, 2H, CH_2), 4.10-3.70 (m, 7H, $\underline{CH_2}$-CH_3 and OCH_3), 1.30-0.95 (m, 6H, CH_2-$\underline{CH_3}$). Yield 83%, m.p. 260-261°C. Anal. Calcd for $C_{18}H_{20}N_4O_4S$: C, 55.66; H, 5.19; N, 14.42. Found: C, 55.43; H, 4.99; N, 14.40.

1,3,-Diethyl-8-[2-(4-fluorohenyl)-2-oxo-ethylsulfanyl]-l-3,7,8,9-tetrahydropurine-2,6-dione (18)

IR (KBr) ύ (cm^{-1}) 3400 (N-H), 3060 (Ar-H), 2875 (C-H aliphatic), 1707, 1664, 1616 (C=O), 1541 (N-H), 1230 (C-F); ^{1}H-NMR (60 MHz, DMSO d_6): δ 13.70 (s, 1H, N7-H), 8.20-7.90 (m, 2H, ArH), 7.40-7.10 (m, 2H, ArH), 5.30 (s, 2H, CH_2), 4.00-3.60 (m, 4H, $\underline{CH_2}$-CH_3), 1.20-0.90 (m, 6H, CH_2-$\underline{CH_3}$). Yield 84%, m.p. 262-263°C. Anal. Calcd for $C_{17}H_{17}FN_4O_3S$: C, 54.25; H, 4.55; N, 14.88. Found: C, 53.99; H, 4.80; N, 14.60. EI MS (*m/z*): 375.78 (M^+, 6%), 253.34 (14%), 123.05 (100%).

General procedure for preparation of compounds 19-25. To a stirred freshly prepared polyphosphoric acid from phosphorus pentaoxide (8 g) and phosphoric acid (6 mL) was added the appropriate 1,3-diethyl-8-(2-oxo-2-(un)substitutedphenyl-ethylsulfanyl-3,7,8,9-tetrahydropurine-2,6-dione; compounds **12-18** (5.3 mmol) and the reaction mixture was heated at 140-150 °C for 5-6 hrs. The reaction mixture was cooled, poured into ice-water and neutralized with sodium carbonate solution. The precipitated solid was filtered off, washed with water and crystallized from DMF/water to afford target compounds **19-25**.

1,3-Diethyl-6-phenylthiazolo[3,2-*f*]purine-2,4(1*H*,3*H*)-dione (19)

^{1}H-NMR (60 MHz, DMSO-d_6)**:** δ 7.60 (br s, 5H, ArH), 7.35 (s, 1H, C7-H), 4.20 (q, J= 7.1 Hz, 2H, $\underline{CH_2}$-CH_3), 3.8 (q, J= 7.1 Hz, 2H, $\underline{CH_2}$-CH_3), 1.40-0.90 (m, 6H, CH_2-$\underline{CH_3}$). Yield 84%, m.p. >300°C. Anal. Calcd for $C_{17}H_{16}N_4O_2S$: C, 59.98; H, 4.74; N, 16.46. Found: C, 59.93; H, 4.56; N, 16.16.

6-(4-Bromophenyl)-1,3-diethylthiazolo[3,2-*f*]purine-2,4(1*H*,3*H*)-dione (20)

^{1}H-NMR (60 MHz, DMSO-d_6): δ 7.70-7.40 (m, 4H, ArH), 7.30 (s, 1H, C7-H), 4.20-3.5 (m, 4H, $\underline{CH_2}$-CH_3), 1.60-1.00 (m, 6H, CH_2-$\underline{CH_3}$). Yield 84%, m.p. >330°C. Anal. Calcd for $C_{17}H_{15}BrN_4O_2S$: C, 48.70; H, 3.61; N, 13.36. Found: C, 48.21; H, 3.61; N, 13.85.

6-(4-Chlorophenyl)-1,3-diethylthiazolo[3,2-*f*]purine-2,4(1*H*,3*H*)-dione (21)

^{1}H-NMR (60 MHz, DMSO-d_6): δ 7.70 (m, 4H, ArH), 7.30 (s, 1H, C7-H), 4.35-3.80 (m, 4H, $\underline{CH_2}$-CH_3), 1.50-0.90 (m, 6H, CH_2-$\underline{CH_3}$). Yield 84%, m.p. 252-253°C. Anal. Calcd for $C_{17}H_{15}ClN_4O_2S$: C, 54.47; H, 4.03; N, 14.95. Found: C, 54.50; H, 4.29; N, 15.15. EI MS (*m/z*): 374.29 (M^+, 34%), 276.69 (100%), 136.09 (76%).

1,3-Diethyl-6-*p*-tolylthiazolo[3,2-*f*]purine-2,4(1*H*,3*H*)-dione (22)

^{1}H-NMR (60 MHz, DMSO-d_6): δ 7.60 (d, 2H, J= 8.5 Hz, ArH), 7.30 (d, 2H, J= 8.5 Hz, ArH), 7.20 (s, 1H, C7-H), 4.30-3.70 (m, 4H, $\underline{CH_2}$-CH_3), 3.05 (s, 3H, CH_3), 1.40-0.90 (m, 6H, CH_2-$\underline{CH_3}$). Yield 84%, m.p. 270-271°C. Anal. Calcd for $C_{18}H_{18}N_4O_2S$: C, 61.00; H, 5.12; N, 15.81. Found: C, 60.73; H, 5.12; N, 16.11.

1,3-Diethyl-6-(4-nitrophenyl)thiazolo[3,2-*f*]purine-2,4(1*H*,3*H*)-dione (23)

^{1}H-NMR (60 MHz, DMSO-d_6): δ 7.90 (d, 2H, J= 8.6 Hz, ArH), 7.40 (d, 2H, J= 8.6 Hz, ArH), 7.30 (s, 1H, C7-H), 4.40-3.90 (m, 4H, $\underline{CH_2}$-CH_3), 1.40-0.90 (m, 6H, CH_2-$\underline{CH_3}$). Yield 80%, m.p. >300°C. Anal. Calcd for $C_{17}H_{15}N_5O_4S$: C, 52.98; H, 3.92; N, 18.17. Found: C, 52.88; H, 4.15; N, 18.05. EI MS (*m/z*): 385.20 (M^+, 12%), 354.12 (64%), 120.12 (100%).

1,3-Diethyl-6-(4-methoxyphenyl)thiazolo-[3,2-*f*]purine-2,4(1*H*,3*H*)-dione (24)

^{1}H-NMR (60 MHz, DMSO-d_6)**:** δ 7.80 (d, 2H, J= 8.6 Hz, ArH), 7.40 (d, 2H, J= 8.6 Hz, ArH), 7.35 (s, 1H, C7-H), 4.40-3.90 (m, 7H, $\underline{CH_2}$-CH_3 and OCH_3), 1.40-0.90 (m, 6H, CH_2-$\underline{CH_3}$). Yield 84%, m.p. 294-295°C. Anal. Calcd for $C_{18}H_{18}N_4O_3S$: C, 58.36; H, 4.90; N, 15.12. Found: C, 58.10; H, 4.69; N, 15.15.

1,3-Diethyl-6-(4-fluorophenyl)thiazolo[3,2-*f*]purine-2,4(1*H*,3*H*)-dione (25)

^{1}H-NMR (60 MHz, DMSO-d_6): δ 7.90-7.70 (m, 2H, ArH), 7.40-7.30 (m, 2H, ArH), 7.30 (s, 1H, C7-H), 4.30-3.90 (m, 4H, $\underline{CH_2}$-CH_3), 1.40-1.00 (m, 6H, CH_2-$\underline{CH_3}$). Yield 83%, m.p. 293-294°C. Anal. Calcd for $C_{17}H_{15}FN_4O_2S$: C, 56.97; H, 4.22; N, 15.63. Found: C, 56.60; H, 4.40; N, 15.20.

Methyl [(1,3-diethyl-2,6-dioxo-2,3,6,7 tetrahydro-*1H*-purin-8-yl)thio]acetate (26)

To a stirred solution of **4** (0.8 g, 2.56 mmol) in aqueous sodium hydroxide 1% w/v (10 mL), a solution of methyl bromoacetate (0.45 g, 3.33 mmol) dissolved in ethanol (5 mL) was added in a portion wise manner. The reaction mixture was stirred at the ambient temperature for 8 hrs. The reaction mixture was cooled in a refrigerator for 3 hrs. The product was filtered, washed with water, diethyl ether & dried.

^{1}H-NMR (300 MHz, DMSO-d_6): δ 13.00 (s, 1H, N7-H), 4.40 (s, 2H, SCH_2), 4.10 (q, 2H, J= 7.0 Hz, CH_2-CH_3), 3.90 (q, 2H, J= 7.0 Hz, CH_2-CH_3), 3.55 (s, 3H, OCH_3), 1.10 (t, 3H, J= 7.0 Hz, CH_2-CH_3), 0.90 (t, 3H, J= 7.0 Hz, CH_2-CH_3). Yield 86.1%, m.p. 222-224°C.

1,3-Diethyl-2,6-dioxo-2,3,6,7-tetrahydro-*1H*-purine-8-yl thioacetohydrazide (27)

To a stirred solution of methyl [(1,3-diethyl-2,6- dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl)thio]acetate **26** (0.5 g, 1.6 mmol) in absolute ethanol (6.5 mL), hydrazine hydrate 80% (0.2 mL) were added. The reaction mixture was refluxed for 2 hrs, and then cooled. The formed precipitate was filtered, washed with diethyl ether, and dried to afford the hydrazide derivative **27**.

^{1}H-NMR (300 MHz, DMSO d6): δ 7.6 (br s, 3H, $NHNH_2$), 4.40 (q, J= 7.0 Hz, 2H, CH_2-CH_3), 3.93-3.86 (m, 4H, CH_2-CH_3 & SCH_2), 1.11-1.07 (m, 6H, CH_2-CH_3). Yield 96.8%, m.p. 295-297°C.

General procedure for synthesis of Schiff's bases (28-33)

To a stirred solution of 1,3-Diethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purine-8-yl thioacetohydrazide **27** (1.18 mmol) in ethanol (15 mL), an equimolar amount of the appropriate aldehyde (1.18 mmol) was added. Few drops of glacial acetic acid were added and the solution was refluxed for 8-10 hrs. The reaction mixture was cooled to the ambient temperature and the formed precipitate was filtered, washed with ethanol and dried. The products were recrystallized from ethanol to yield the target compounds **28-33**.

***N*-(Benzylidene)-2-(1,3-diethyl-2,3,6,7-tetrahydro-2,6-dioxo-*1H*-purine-8-ylthio) acetohydrazide (28)**

^{1}H-NMR (300 MHz, DMSO-d_6): δ 13.60 (s, 1H, N7-H), 11.60 (s, 1H, CONH), 7.90 (s, 1H, N=CH), 7.90-7.70 (m, 2H, Ar-H), 7.60-7.40 (m, 3H, Ar-H), 4.45 (s, 2H, SCH_2), 4.00 (q, 2H, J= 7.0 Hz, CH_2-CH_3), 3.85 (q, 2H, J= 7.0 Hz, CH_2-CH_3), 1.00 (t, 3H, J= 7.0 Hz, CH_2-CH_3), 0.90 (t, 3H, J= 7.0 Hz, CH_2-CH_3). Yield 80%, m.p. 280-281°C. Anal. Calcd for $C_{18}H_{20}N_6O_3S$: C, 53.99; H, 5.03; N, 20.99. Found: C, 54.20; H, 5.39; N, 20.74.

***N*-(4-Bromobenzylidene)-2-(1,3-diethyl-2,3,6,7-tetrahydro-2,6-dioxo-*1H*-purine-8-ylthio)acetohydrazide (29)**

^{1}H-NMR (300 MHz, DMSO-d_6): δ 13.70 (s, 1H, N7-H), 11.70 (s, 1H, CONH), 7.90 (s, 1H, N=CH), 7.70 (d, 2H, J= 8.60 Hz, Ar-H), 7.60 (d, 2H, J= 8.60 Hz, Ar-H), 4.4 (s, 2H, SCH_2), 3.95 (q, 2H, J= 7.0 Hz, CH_2-CH_3), 3.85 (q, 2H, J= 7.0 Hz, CH_2-CH_3), 1.06 (t, 3H, J= 7.0 Hz, CH_2-CH_3), 0.90 (t, 3H, J= 7.0 Hz, CH_2-CH_3). Yield: 85.2%, m.p. 267-268°C Anal. Calcd for $C_{18}H_{19}BrN_6O_3S$: C, 45.10; H, 4.00; N, 17.53. Found: C, 45.04; H, 4.25; N, 17.15.

***N*-(4-Carboxybenzylidene)-2-(1,3-diethyl-2,3,6,7-tetrahydro-2,6-dioxo-*1H*-purine-8-ylthio)acetohydrazide (30)**

^{1}H-NMR (300 MHz, DMSO-d_6): δ 13.60 (s, 1H, N7-H), 12.40 (s, 1H, COOH), 11.10 (s, 1H, CONH), 7.85 (s, 1H, N=CH), 7.90 (d, 2H, J= 8.60 Hz, Ar-H), 7.70 (d, 2H, J= 8.60 Hz, Ar-H), 4.65 (s, 2H, SCH_2), 4.00 (q, 2H, J= 7.0 Hz, CH_2-CH_3), 3.90 (q, 2H, J= 7.0 Hz, CH_2-CH_3), 1.10 (t, 3H, J= 7.0 Hz, CH_2-CH_3), 0.90 (t, 3H, J= 7.0 Hz, CH_2-CH_3). Yield: 81%, m.p. 277-278°C. Anal. Calcd for $C_{19}H_{20}N_6O_5S$: C, 51.34; H, 4.54; N, 18.91. Found: C, 51.60; H, 4.25; N, 19.00.

***N*-(4-Chlorobenzylidene)-2-(1,3-diethyl-2,3,6,7-tetrahydro-2,6-dioxo-*1H*-purine-8-ylthio)acetohydrazide (31)**

^{1}H-NMR (300 MHz, DMSO-d_6): δ 13.50 (s, 1H, N7-H), 11.30 (s, 1H, CONH), 7.60 (s, 1H, N=CH), 7.70 (d, 2H, J= 8.60 Hz, Ar-H), 7.60 (d, 2H, J= 8.60 Hz, Ar-H), 4.45 (s, 2H, SCH_2), 3.95 (q, 2H, J= 7.0 Hz, CH_2-CH_3), 3.80 (q, 2H, J= 7.0 Hz, CH_2-CH_3), 1.10 (t, 3H, J= 7.0 Hz, CH_2-CH_3), 0.90 (t, 3H, J= 7.0 Hz, CH_2-CH_3). Yield: 83%, m.p. 270-271°C Anal. Calcd for $C_{18}H_{19}ClN_6O_3S$: C, 49.71; H, 4.40; N, 19.32. Found: C, 49.55; H, 4.55; N, 19.10.

2-(1,3-Diethyl-2,3,6,7-tetrahydro-2,6-dioxo-*1H*-purine-8-ylthio)-*N*-(4-dimethyl-aminobenzylidene)acetohydrazide (32)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 13.70 (s, 1H, N7-H), 11.20 (s, 1H, CONH), 7.70 (s, 1H, N=CH), 7.40 (d, 2H, J= 8.50 Hz, Ar-H), 6.70 (d, 2H, J= 8.50 Hz, Ar-H), 4.40 (s, 2H, SCH_2), 3.90 (q, 2H, J= 7.0 Hz, CH_2-CH_3), 3.80 (q, 2H, J= 7.0 Hz, CH_2-CH_3), 2.90 (s, 6H, $N(CH_3)$), 1.10 (t, 3H, J= 7.0 Hz, CH_2-CH_3), 0.90 (t, 3H, J= 7.0 Hz, CH_2-CH_3). Yield: 79%, m.p. 258-259°C Anal. Calcd for $C_{20}H_{25}N_7O_3S$: C, 54.16; H, 5.68; N, 22.11. Found: C, 54.40; H, 5.90; N, 21.90.

2-(1,3-Diethyl-2,3,6,7-tetrahydro-2,6-dioxo-*1H*-purine-8-ylthio)-*N*-(2-nitobenzyl-idene)acetohydrazide (33)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 13.60 (s, 1H, N7-H), 11.90 (s, 1H, CONH), 7.80 (s, 1H, N=CH), 7.50-8.10 (m, 4H, ArH), 4.50 (s, 2H, SCH_2), 4.05 (q, 2H, J= 7.00 Hz, CH_2-CH_3), 0.90 (q, 2H, J= 7.00 Hz, CH_2-CH_3), 1.08 (t, 3H, J= 7.0 Hz, CH_2-CH_3), 0.90 (t, 3H, J= 7.0 Hz, CH_2-CH_3), Yield: 77%, m.p. 259-263°C. Anal. Calcd for $C_{18}H_{19}N_7O_5S$: C, 48.53; H, 4.30; N, 22.01. Found: C, 48.20; H, 4.55; N, 22.20.

Pharmacology

Bronchodilator activity

The bronchodilator activity was carried out using Kesler and Canning's method[26] with minor modifications[27]. Male Hartley Guinea pigs, 300-400 g were anesthetized with urethane (1 g/kg *i.p.*) and positioned ventral side up on a wooden pad. The trachea was connected to a pump for artificial respiration, stainless steel hooks were passed between two cartilage rings on either side of the trachea, one hook was sutured to a fixed bar, and the other hook was sutured to an isometric force transducer (Universal oscillograph). When the animals were stabilized, a bronchospasm was stimulated with acetylcholine (0.2 mg/kg *i.p.*). After two similar responses to spasm inducing injections, target compounds (dissolved in distilled water with a minimal amount of 1 N NaOH)[28] or aminophylline as a reference standard were administered (2.5-10 mg/kg *i.p.*), and acetylcholine was administered again three to five minutes later. The effects of the test compounds were expressed as a means of percentage inhibition of five experiments ± S.E.M. of the induced bronchospasm for three doses (2.5, 5, and 10 mg/kg body weight). The ID_{50} value in each case (Table 1) was calculated by linear regression[29]. At the end of each experiment, animals were killed by cervical dislocation.

Anti-inflammatory activity

The anti-inflammatory activity of all newly synthesized compounds was determined according to paw induced edema method[30] in comparison to indomethacin as a reference drug. The test is based on the pedal inflammation in rat paws induced by sub plantar injection of carrageenan suspension (0.2 mL of 1% solution in normal saline) in the right hind paw of the rats.

Male albino rats 120-150 g were divided into groups (5/ group). The thickness of rat paw was measured by Varnier Caliper (SMIEC, China) before and after 1 hr of carrageenan injection to determine the induced inflammation. The tested compounds of a dose (75 mg/kg) were injected i.p. to the animals. The control group received a vehicle (1% NaCMC) while the reference group received indomethacin (10 mg /kg).

Results of anti-inflammatory activity of the tested compounds and the reference drug were listed in (Table 2 and Figs. 1-3).

The percentage of edema and percentage of edema inhibition were calculated[30] where:

$$\%\ \text{Variation (edema)} = \frac{(V_R - V_L)}{V_R} \times 100$$

$$\%\ \text{Edema inhibition} = \frac{(V_R - V_L)_{control} - (V_R - V_L)_{treated}}{(V_R - V_L)_{control}} \times 100$$

V_R: Average right paw thickness, V_L: Average left paw thickness.

Gastric ulceration

Male albino rats were divided into groups (6/ group), the rats were fasted for 24 hrs[31]. The tested compounds **14, 15, 21-23**, **30**, and indomethacin were administered orally as a suspension in 1% NaCMC. After 6 hrs, the rats were killed, the stomach were removed for macroscopic and microscopic investigation. "Ulcer" was defined as at least one lesion that was 0.5 mm or more in length[31]. All lesions of more than 0.1 mm in length were summed to obtain ulcer index. The results are illustrated in table 3.

Table 1: Inhibitory effects of the test compounds **12-25** and **28-33** on acetylcholine induced bronchospasm in anaesthetized Guinea-pigs.

Compound	Dose mg/kg *ip*	% Decrease of acetylcholine induced bronchospasm in guinea pigs	ID_{50} mg/kg *ip*
Aminophylline	2.5	22.6 ± 1.3	5.8
	5	48.4 ± 1.3	
	10	78.5 ± 1.2	
12	2.5	20.6 ± 1.26	7.7
	5	38.4 ± 1.39	
	10	60.9 ± 1.61	
13	2.5	13.3 ± 1.4	10.8
	5	34.8 ± 1.2	
	10	44.6 ± 1.7	
14	2.5	11.2 ± 1.3	11.9
	5	31.5 ± 1.5	
	10	41.2 ± 1.9	
15	2.5	22.1 ± 1.1	6
	5	47.3 ± 1.5	
	10	76.2 ± 1.8	
16	2.5	---	>20
	5	8.1 ± 0.55	
	10	11.7 ± 0.90	
17	2.5	21.8 ± 1.2	6.2
	5	46.5 ± 1.4	
	10	75.4 ± 1.7	
18	2.5	---	>20
	5	9.2 ± 0.55	
	10	11.9 ± 0.90	
19	2.5	10.8 ± 1.1	12
	5	23.5 ± 0.90	
	10	42.3 ± 1.8	
20	2.5	---	>20
	5	7.0 ± 0.68	
	10	11.5 ± 0.95	
21	2.5	19.8 ± 1.3	8.8
	5	33.5 ± 1.5	
	10	55.5 ± 1.2	
22	2.5	16.7 ± 1.7	8.5
	5	36.2 ± 1.1	
	10	58.7 ± 0.90	
23	2.5	---	>20
	5	7.2 ± 0.78	
	10	11.1 ± 0.75	
24	2.5	16.3 ± 1.3	7.7
	5	35.7 ± 1.2	
	10	62.5 ± 1.4	
25	2.5	2.9 ± 0.4	>20
	5	9.8 ± 1.5	
	10	17.8 ± 1.3	

Table 1: Continued.

Compound	Dose mg/kg *ip*	% Decrease of acetylcholine induced bronchospasm in guinea pigs	ID_{50} mg/kg *ip*
28	2.5	13.5 ± 1.0	11.8
	5	30.0 ± 1.5	
	10	40.3 ± 1.8	
29	2.5	27.3 ± 2.2	7.6
	5	37.6 ± 2.7	
	10	63.1 ± 1.8	
30	2.5	20.5 ± 1.4	6.4
	5	42.8 ± 1.6	
	10	68.3 ± 1.7	
31	2.5	19.5 ± 1.3	7.3
	5	40.8 ± 1.6	
	10	62.9 ± 1.9	
32	2.5	21.2 ± 1.9	7.5
	5	40.1 ± 1.3	
	10	63.4 ± 1.2	
33	2.5	16.7 ± 1.8	8.6
	5	36.2 ± 1.1	
	10	56.7 ± 0.90	

Table 2: Edema inhibition effect of compounds **12-25** and **28-33** compared to indomethacin on carrageenan induced paw edema in rats.

Compd. No.	Percentage of paw edema inhibition					
	0.5 hr	1 hr	2 hrs	3 hrs	4 hrs	5 hrs
12	11.13 ± 1.20	18.78 ± 1.40	33.98 ± 0.60	42.11 ± 0.90	57.02 ± 1.22	57.38 ± 1.14
13	08.99 ± 1.60	17.93 ± 1.10	29.65 ± 1.30	42.74 ± 1.20	50.73 ± 0.60	55.30 ± 0.70
14	20.30 ± 1.65	39.66 ± 1.36	50.70 ± 1.44	60.66 ± 0.65	70.34 ± 1.64	77.43 ± 1.12
15	22.13 ± 1.32	40.99 ± 0.76	58.20 ± 0.80	62.80 ± 1.82	70.33 ± 1.76	74.22 ± 1.14
16	12.63 ± 1.08	20.68 ± 1.11	34.85 ± 1.13	44.42 ± 1.14	44.65 ± 1.41	61.74 ± 1.36
17	09.30 ± 1.57	29.20 ± 2.12	30.35 ± 1.41	48.90 ± 1.10	49.90 ± 1.55	71.30 ± 0.92
18	16.30 ± 1.31	39.20 ± 1.00	51.44 ± 0.67	60.40 ± 2.05	66.70 ± 1.27	70.40 ± 0.60
19	12.33 ± 0.77	20.11 ± 0.65	34.15 ± 0.96	44.30 ± 1.11	58.11 ± 1.19	60.23 ± 1.11
20	10.42 ± 0.43	19.10 ± 0.90	30.12 ± 1.31	45.20 ± 1.54	51.66 ± 0.93	58.43 ± 1.52
21	23.15 ± 1.28	53.15 ± 1.23	58.13 ± 1.20	64.10 ± 0.98	79.90 ± 0.94	80.76 ± 1.32
22	24.32 ± 1.82	56.30 ± 1.11	62.10 ± 0.68	66.34 ± 0.88	80.90 ± 0.58	81.77 ± 1.21
23	14.10 ± 1.21	25.15 ± 0.67	37.45 ± 0.96	45.20 ± 0.67	51.77 ± 2.08	64.55 ± 0.83
24	18.20 ± 0.90	33.10 ± 0.86	38.15 ± 2.10	53.88 ± 1.22	64.88 ± 0.73	73.08 ± 0.72
25	20.11 ± 1.17	42.12 ± 1.23	57.70 ± 2.22	64.80 ± 2.11	74.55 ± 1.21	79.80 ± 0.54
28	11.13 ± 0.62	18.78 ± 1.55	33.98 ± 0.89	42.11 ± 1.08	57.02 ± 1.35	55.38 ± 2.04
29	08.99 ± 1.22	17.93 ± 2.01	29.65 ± 0.78	42.74 ± 1.10	50.73 ± 1.29	57.30 ± 1.17
30	22.70 ± 1.35	51.90 ± 2.33	57.58 ± 0.83	64.42 ± 1.33	82.39 ± 0.92	81.20 ± 1.49
31	23.34 ± 1.60	55.27 ± 1.42	61.47 ± 1.24	65.68 ± 1.11	82.60 ± 1.19	80.95 ± 1.37
32	12.63 ± 1.46	20.68 ± 1.10	34.85 ± 1.12	44.42 ± 2.10	44.65 ± 0.43	61.74 ± 0.87
33	08.35 ± 1.37	31.22 ± 1.23	32.68 ± 0.84	50.32 ± 1.32	50.52 ± 1.22	72.14 ± 0.82
Control	----	----	----	----	----	----
INM	19.37 ± 1.82	41.15 ± 0.88	55.74 ± 1.14	65.75 ± 0.86	76.70 ± 1.46	80.98 ± 0.56

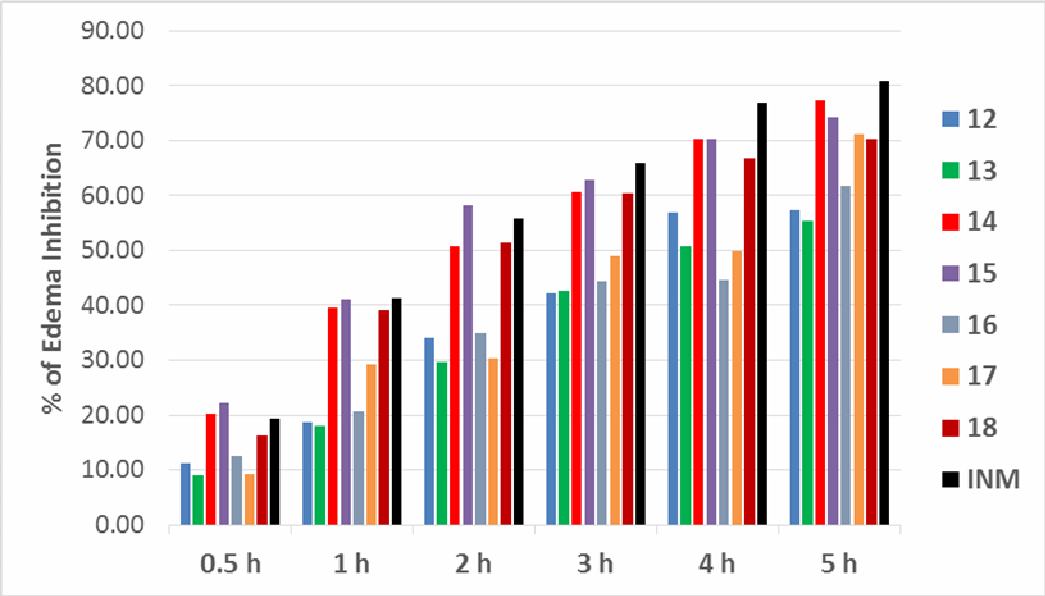


Fig. 1: Anti-inflammatory activity of compounds **12-18** and indomethacin.

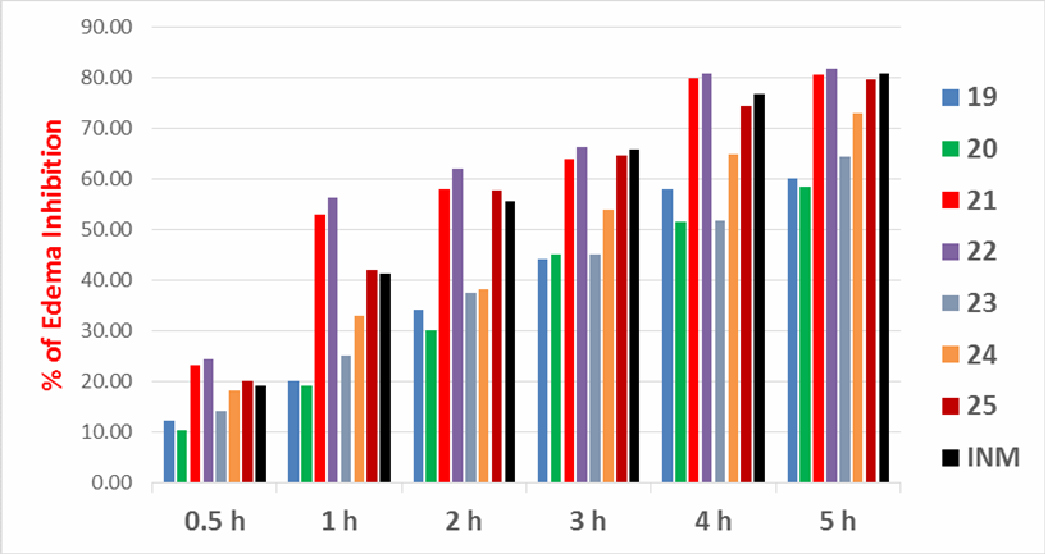


Fig. 2: Anti-inflammatory activity of compounds **19-25** and indomethacin.

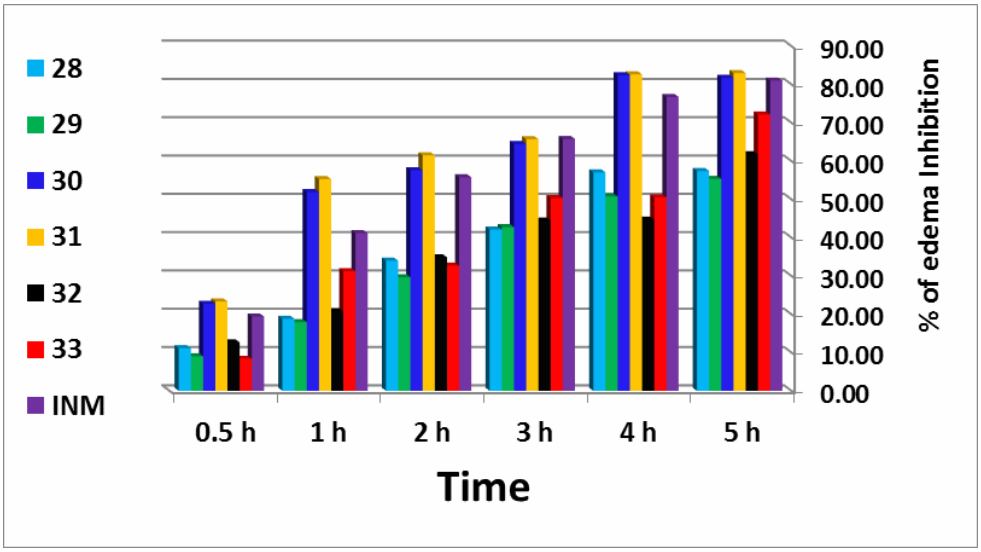


Fig. 3: Anti-inflammatory activity of compounds **28-33** and indomethacin.

Table 3: Ulcerogenic effects of compounds **14, 15, 23-25, 30** and indomethacin in rats.

Compd. No.	Dose mg /kg	Ulcer score*	Ulcer Index ± SEM
14	30	1/6	1.17 ± 0.38
	50	1/6	1.33 ± 0.14
	75	4/6	2.80 ± 0.45
15	30	0/6	0.00
	50	1/6	2.20 ± 0.40
	75	3/6	2.40 ± 0.35
23	30	1/6	0.90
	50	2/6	1.70 ± 0.12
	75	2/6	2.19 ± 0.19
24	30	0/6	0.00
	50	1/6	1.10 ± 0.32
	75	1/6	1.70 ± 0.35
25	30	0/6	0.00
	50	0/6	0.00
	75	2/6	2.15 ± 0.28
30	30	0/6	0.00
	50	0/6	0.00
	75	2/6	1.80 ± 0.36
INM	10	3/6	1.90 ± 0.37
	30	5/6	4.00 ± 0.54
	50	Not tessted	

*Number of rats with lesions that were more than 0.5 mm in length per total numbers.

RESULTS AND DISCUSSION

Chemistry

The general synthetic route to obtain the designed 1,3-diethyl-8-disubstituted purine2,6-diones **12-18**, 1,3-diethyl-6-disubstituted thiazolo[2,3-f]purine-2,4-diones **19-25** and the intermediates used in their preparations is presented in scheme 1. 1,3-diethyl-8-thioxo-3,7,8,9-tetrahydropurine-2,6-dione **4** was synthesized by reaction of 5,6-diamino-1,3-diethyl-1*H*-pyrimidine-2,4-dione **3** with carbon disulfide in the presence of potassium hydroxide[32]. Their structures were verified by ^{1}H-NMR. Compound **4** was subjected to the interaction with the prepared phenacyl bromides **5-11**[23-25] in the presence of potassium hydroxide to give the required 1,3,8-trisubstituted purine-2,6-diones **12-18**. The structure elucidation of these newly synthesized derivatives was confirmed by elemental and spectral data (see exp. Part).

The ^{1}H-NMR spectra of compounds **12-18** are characterized by the appearance of the methylene protons of S-CH_2-CO at δ 4.90 to 5.30 ppm and also the introduced aromatic moiety, in addition to the presence of N7-H signal is a strong support for an S-alkylation reaction rather than an N-alkylation. It is well known that mercaptopurines undergo S-alkylation at a lowered temperature while at an elevated one N7-H is also attacked[33]. The use of glacial acetic acid or ethanolic solution of hydrochloric acid in cyclodehydration of compounds **12-18** to obtain the required 3,6-disubstituted thiazolo[3,2-*f*]purine-2,4-diones **19-25** did not succeed, after 2 days reflux of compound **12** and **13**, the ^{1}H-NMR indicated the opened derivative not the cyclized one. The new 3,6-disubstituted thiazolo[2,3-f]purine-2,4-diones **19-25** were synthesized by cyclodehydration of compounds **12-18** using polyphosphoric acid (PPA). In the ^{1}H-NMR data of compounds **19-25**, both methylene protons of S-CH_2-CO and N7-H proton disappeared, in addition to the appearance of C7-H as downfield proton (7.20-7.35 ppm) which was a strong evidence for ring cyclization. The structures of the new prepared compounds were verified based on spectroscopic data and further confirmed by elemental analyses and mass spectrometry.

The reaction of thione derivative **4** (scheme2) with bromomethylacetate afforded the ester derivative **26** which was consequently reacted with hydrazine hydrate in refluxed ethanol to produce 1,3-diethyl-2,6-dioxo-2,3,6,7-tetrahydro-*1H*-purine-8-yl thioacet-hydrazide **27**.

Schiff bases of **28-33** were prepared by the reaction of 1,3-diethyl-2,6-dioxo-2,3,6,7-tetrahydro-*1H*-purine-8-yl thioacetohydrazide **27** with equimolar amounts of the appropriate (un)substituted benzaldehydes in ethanol in the presence of few drops of glacial acetic acid (Scheme 2).

Comparative study of the ^{1}H-NMR of hydrazide derivative **27** with its Schiff bases **28-33** easily revealed the disappearance of the NH2 group signal and the appearance of N=CH signals at 7.40-7.90 ppm in addition to protons of the introduced aromatic moiety. As these findings were observed in the ^{1}H-NMR spectra of Schiff bases, it can safely conclude the formation of compounds **28-33** on the expense of the NH2 group. The structures of formed Schiff bases were also further confirmed by elemental analyses (see exp. part).

Pharmacology

Bronchodilator activity

The newly synthesized compounds (**12-25** and **28-33**) were investigated for *in vivo* bronchodilator activity by acetylcholine induced bronchospasm in anaesthetized Guinea pigs using aminophylline as a reference standard. The bronchodilator effect was expressed as a means of percentage inhibition of five experiments ± S.E.M. of the induced bronchospasm for three doses (2.5, 5, and 10 mg/kg body weight), ID_{50} value in each case was calculated by linear regression. Results are shown in table 1. Three compounds (**15**, **17** and **30**) exhibited a bronchodilator activity nearly similar to that of aminophylline (ID_{50} 5.8 mg/kg). The rest of the compounds showed good to moderate to good activity in comparison with aminophylline. Some of these derivatives showed weak activity such as compounds **16, 19, 20, 23** and **25**

Regarding the biological results of 1,3-Diethyl-8-(2-oxo-2-(un)substitutedphenyl-ethylsulfanyl-3,7,8,9-tetrahydro-purine-2,6-diones **12-18**, most of them showed good to excellent activity (ID_{50} values: 6.0-11.9 mg/kg).

In this series, the introduction of *p*-methyl (compound **15**) or *p*-methoxy group (compound **17**) presents the most active compounds (ID_{50} values: 6 mg/kg**,** and 6.2 mg/kg respectively), while presence of the strong electron withdrawing groups (compounds **16** and **18**) highly decreased the bronchodilator activity (ID_{50} values: >20 mg/kg).

Cyclodehydration of derivatives **12-18** to produce the rigid thizaolopurine-dione derivatives **19-25** resulted in most cases a marked decrease in bronchodilator activity (**12** vs **19**, **13** vs **20** and **15** vs **22** and **17** vs **24**) except compound **21** which has *p*-Cl phenyl group showed slightly enhanced activity **(14** vs **21)**.

Schiff's base compounds **28-33** showed moderate to very good activity (ID_{50} values: 6.4-11.8 mg/kg). One of them, compound **30** exhibited an antibronchoconstrictive activity nearly similar to that of aminophylline (ID_{50} values: 6.4). The introduction of substituents on Schiff's bases phenyl moiety enhanced the activity of all derivatives (Table 1). The best one was the 4-carboxy derivatives **30**, exhibited remarkable activity.

Anti-inflammatory activity

All newly synthesized compounds **12-25** and **28-33** were tested *in vivo* for their anti-inflammatory effect using carragennan induced paw edema in rats using indomethacin (10 mg/kg) as a reference drug[30]. The results of the tested compounds and indomethacin were presented as the time course dependent size of edema and percentage of edema inhibition at a dose (40 mg/kg) and time intervals 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 hrs (Table 2 and Figs. 1-3).

All of the tested compounds showed moderate to potent anti-inflammatory effect. The derivatives 1,3-diethyl-8-substituted xanyhines **12-18** showed significant activity in comparison to that of indomethacin, they exhibited inhibition of induced edema ranged from 55-77%, table 2 and figure 1. The derivatives **14, 15, 17** and **18** were the most potent in this series (Fig. 1). The results revealed that the substituted phenyl derivatives are better than unsubstituted one. The interesting thing that the activity of the tested compounds increased after cyclization (after the addition of the thiazole ring to the purinedione skeleton) **19-25**. The derivatives **21, 22** and **25** showed equipotent activity to that of indomethacin (Fig. 2).

Schiff's base compounds **28-33** displayed moderate to potent anti-inflammatory activities. Compounds **30** and **31** showed potent activities when compared to that of indomethacin. While the anti-inflammatory activities of the rest compounds were moderate to very good and revealed edema inhibition ranged from 55-81% as illustrated in (Table 2 and Fig. 3). Compound **30** which exhibited very good anti-asthmatic activity also showed here potent anti-inflammatory activity.

Gastric ulceration

The test was carried out in rats according to a reported method[31], Compounds **14, 15, 23-25,** and **30** were selected for this test. Compounds **15**, **24**, **25** and **30** showed no ulcerogenic effect at dose 30 mg/kg. Furthermore, compounds **25** and **30** exhibited no ulcerogenic effect at dose 50 mg/kg. All tested compounds showed less gastric ulceration than indomethacin at higher doses (25-75 mg/kg). The results are shown in table 3.

Conclusion

The design, synthesis and preliminary pharmacological investigation of novel 1,3-diethyl-8-disubstituted xantines **12-18**, 1,3,6-trisubstituted-1*H*-thiazolo[3,2-*f*]purine-2,4-diones **19-25** and xanthine Schiff bases **28-33** was described. The structures of the newly synthesized compounds were verified using IR, ^{1}H-NMR, mass spectrometery as well as elemental anaylses. The effect of the new derivatives as potential anti-asthmatic was evaluated using acetycholine induced brocnhospasm in guinea pigs, most of tested compounds showed significant anti-bronchoconstriction activity in comparison with aminophylline as a standard drug. Furthermore, anti-inflammatory activity of the target compounds was investigated using indomethacin as a reference drug and some compounds exhibited potent anti-inflammatory activity.

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نشرة العلوم الصيدلية
جامعة أسيوط

تخليق بعض مشتقات ٦،٣،١-ثلاثي مستبدلات الثيازولو [3,2-*f*]البيورين-٢،٤-داي أون وقواعد شيف لمشتقات الزانثين الجديدة كموسعات للشعب الهوائية وكمضادات للالتهابات

علاء عرفات حيالله[١،٤] – ريهام ابو شميس[٢] – أحمد التلهونى[٣]

[١]قسم الكيمياء العضوية الصيدلية ، كلية الصيدلة ، جامعة أسيوط ، أسيوط ، مصر

[٢]قسم العلوم الصيدلية الأساسية (تحليلية) ، كلية الصيدلة ، جامعة الاسراء ، عمان ، الأردن

[٣]قسم العلوم الصيدلية التطبيقية (فارماكولوجى) ، كلية الصيدلة ، جامعة الاسراء ، عمان ، الأردن

[٤]قسم الكيمياء الصيدلية ، كلية الصيدلة ، جامعة دراية ، المنيا ، مصر

لقد تم في هذه الدراسة تصميم وتخليق والتحقق الدوائي الأولي لبعض مشتقات ٣،١-ثنائي ايثيل-٨-مستبدل الزانثين و ٦،٣،١-ثلاثي مستبدلات الثيازولو [3,2-*f*]البيورين-٢،٤-داي أون وقواعد شيف لمشتقات الزانثين.

تم تحضير المركبات ١٢-١٨ من خلال تفاعل المركب ٤ مع مشتقات بروميدات الفناسيل المناسبة ٥-١١. وتم تحضير المركب ٤ بدوره عن طريق تفاعل ٣،١-ثنائي ايثيل-٦،١-ثنائي أمينواليوراسيل مع ثنائي كبريتيد الكربون. لقد تم الحصول على المشتقات ١٩-٢٥ عن طريق حلقنة المركبات ١٢-١٨ في حمض متعدد الفوسفوريك. تم تخليق قواعد شيف ٢٨-٣٣ من خلال تفاعل المركب ٢٧ مع الألدهيد المناسب في الإيثانول.

تم اختبار تأثير المركبات الجديدة كموسعات للشعب الهوائية باستخدام الخنازير الغينية والتى تم حقنها بالاستيل كولين الذى يسبب تشنجات بالقصبة الهوائية. وكشفت النتائج البيولوجية أن معظم المركبات أظهرت نتائج جيدة جدا بالمقارنة لعقار الأمينوفيلين كمعيار والذي استخدم كعقار مرجعى.

وتم أيضاً إختبار نشاط المركبات المستهدفة كمضات للالتهابات ومعظمهم أظهر نشاطاً بيولوجياً جيد إلى ممتاز كمضادات للالتهابات مقارنة مع عقار الإندوميثاسين كعقار مرجعى.