Research Article

Synthesis and Biological Activity of Xanthene Derivatives as Antiasthamatic Agents

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ABSTRACT

Plan: To develop some 1,3-dimethyl-7-[2-(piperazin-1-yl)acetyl]-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione derivatives for their antiasthamatic activity. **Objective:** Xanthene derivatives are known for their vasodilatory activity. Development of Phosphodiesterase 3 inhibitors is current area of interest for development of anti-asthmatic agents. Many compounds containing xanthene nucleus are also found to possess a number of pharmacological activities. Thus a new series of 1,3-dimethyl-7-(2-(piperazin-1-yl)acetyl)-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione has been synthesized, characterized and screened for the vasodilator activity. **Methodology:** In our present study the intermediate 27-(chloroacetyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione [A] was prepared via reaction of theophylline and chloroacetyl chloride. This compound was treated with Piperazine in presence of methanol followed by hydrazine hydrate to yield the key intermediate 1,3-dimethyl-7-(2-(piperazin-1-yl)acetyl)-2,3,6,7-tetrahydro-1H-purine-2,6-dione (B). This compound was treated with various substituted aromatic amines to get the title compounds [1-12]. The title compounds were characterized by MP, TLC, IR, UV, and NMR & Mass spectrum. The compounds were screened for pulmonary vasodilator activity. **Outcome:** All compounds showed significant activity compared to standard Cilostazol. 7-(2-{4-[1-(3,4-di-chlorophenyl) ethyl]piperazin-1-yl}acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (8) was most active derivative from the series. 7-(2-{4-[(2,4-di-nitrophenyl)methyl]piperazin-1-yl}acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione (6) and 7-(2-{4-[1-(4-hydroxyphenyl)ethyl]piperazin-1-yl}acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione (4) showed moderate to mild activity. **Conclusion:** Activity of the derivatives with di-chloro substitution indicated that the compounds with electron withdrawing groups are showing significant activity than other compounds which indicated mechanistic details of all the compounds in near future would lead to potent anti-asthmatic compounds.

Key words: Xanthene, Phosphodiesterase, Bioactivity, Smooth muscle relaxants.

INTRODUCTION

Asthma is a chronic inflammatory condition in which there is reversible blockage of airflow and airway hyper-responsiveness whose cause is not completely understood.[1] Hyper-responsiveness is due to the wide range of stimulus like irritant chemicals, pollen grains, stimulant drugs, pollutants, cold air etc. As per WHO about 100 to 150 million people suffer from asthma world-wide and this number is increasing. It is not just health problem of developed countries but in developing countries also, occurrence of asthma is increasing. In India around 15-20 million patients are asthmatic. It can't be

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cured completely, but only controlled by proper treatment.[2] In asthma due to inflammation and hyper-sensitivity the airway passage easily becomes narrow.[3-4] Due to hyper-sensitivity coughing, chest tightness, wheezing, and breathlessness these symptoms are frequently worse in night. Usually narrowing of the airway passage is reversible, but in patients having chronic asthma, sometimes irreversible airflow obstruction occurs which leads to asthmatic attack and finally death. Therefore, there is need of rational drug design as an anti-asthmatic drug. Due to emerging trends in drug design various targets are also identified for anti-asthmatic class of drugs. Now a days research is mainly focused on the Phosphodiesterase (PDE) system because it plays an important role in smooth muscle relaxation.[5] PDE3 and PDE4 are considered as potential targets for intervention in asthma therapy.[6] PDE3 inhibitors have subsequently been shown to relax vascular and airway smooth muscle, inhibit platelet aggregation and induce lipolysis, suggesting involvements of PDE3 in the regulation of this physiological and pathophysiological processes.[7-9] The xanthene nucleus is important component of various anticancer, antimicrobial, antitussive agents. Here we report development of 12 novel xanthene derivatives as potential antiasthamatic agents.

MATERIALS AND METHODS

Synthesis of 7-(chloroacetyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (A)

In 250 ml round bottom flask (RBF) 1 mol theophylline and 2 mol chloroacetyl chloride were taken and stirred vigorously to get a uniform mixture. The mixture was stirred with heating until the temperature of mixture was raised to 100°. 125 ml of 1.6 N NaOH was added uniformly over a period of 5-8 hrs. The temperature of mixture was maintained at 100°. After completion of reaction, it was filtered to remove precipitated NaCl, and reaction mixture was further concentrated to get compound A.

Synthesis of 1,3-dimethyl-7-[2-(piperazin-1-yl) acetyl]-2,3,6,7-tetrahydro-1H-purine-2,6-dione (B)

1 mol of compound A was taken in RBF. To this 1 mol of piperazine was added and reaction mixture was refluxed for 30 min on water bath. The reaction mixture was then concentrated to get fine crystals of compound B.

Synthesis of 1,3-dimethyl-7-[2-(piperazin-1-yl) acetyl]-2,3,6,7-tetrahydro-1H-purine-2,6-dione derivatives (1-12)

In 250 ml round bottom flask (RBF) 5 ml tetrahydrofuran (THF), 1 mol of compound B and 1 mol of corresponding amine was taken. To this, 1mol sodium borohydride $NaBH_4$ and 0.5 g silica chloride were added and reaction mixture was stirred at room temperature. After completion of the reaction, the mixture was filtered and the residue was washed with CH_2Cl_2 to get the different derivatives as shown in Table 1. The scheme of synthesis is presented in Figure 1.

BIOLOGICAL ACTIVITY

Isolated adult goat tracheal tissue was obtained from slaughter house. Trachea was cut into individual rings 2-3 cm long and 1cm wide tracheal muscle was washed in a bath containing standard Krebs-Henseleit solution (Concentration in gm/L; KCl-0.35; $CaCl_2$-0.3; $MgSO_4$- 0.16; $NaHCO_3$-32.0; KH_2PO_4-0.164; NaCl-6.9; Glucose-2.0) maintained at 37 ± 0.5°, a stream of oxygen was bubbled through the oxygen tube in organ bath. One end was tied to aerator tube and other thread to force transducer through sigmoid lever to detector of Biopac- M.P. 35 with forced transducer. Tissue was equilibrate in physiological Krebs-Henseleit solution prepared freshly for 45 min in organ bath. During which, the bathing solution was changed at every 15 min. The results were calculated as a concentration of test compounds required for the maximum relaxation using Cilostazol standard.

RESULTS

In the first step of synthetic protocol reaction between theophylline and chloracetyl chloride leads to formation of aromatic/heterocyclic xanthine derivative. This reaction is Schotten Baumann reaction which was carried out in presence of sodium hydroxide for 5-8 hrs at 100° and stirred until a precipitate was formed. In the second step we synthesized Piperazine derivative of xanthine. In the last step there was formation of polyfunctional xanthine derivatives which involved reductive amination of various aldehydes or ketones yielding substituent's on the piperazine nitrogen. Synthesis of all final compounds was confirmed from the results of chemical, physicochemical, chromatographic and spectral analysis. The biological activity of synthesized compounds was evaluated on goat trachea which showed that compound (8) 7-(2-{4-[1-(3,4-dichlorophenyl)ethyl]piperazin-1-yl} acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione was the most active derivative from the series of synthesized compounds. Compounds like 6, 1, 4, and 7 showed moderate to mild activity compared with Cilostazol as standard.

1. 1,3-dimethyl-7-(2-{4-[(3-nitrophenyl)methyl] piperazin-1-yl}acetyl)-2,3,6,7-tetrahydro-1H-purine-2,6-dione

   M. P.: 190-192°

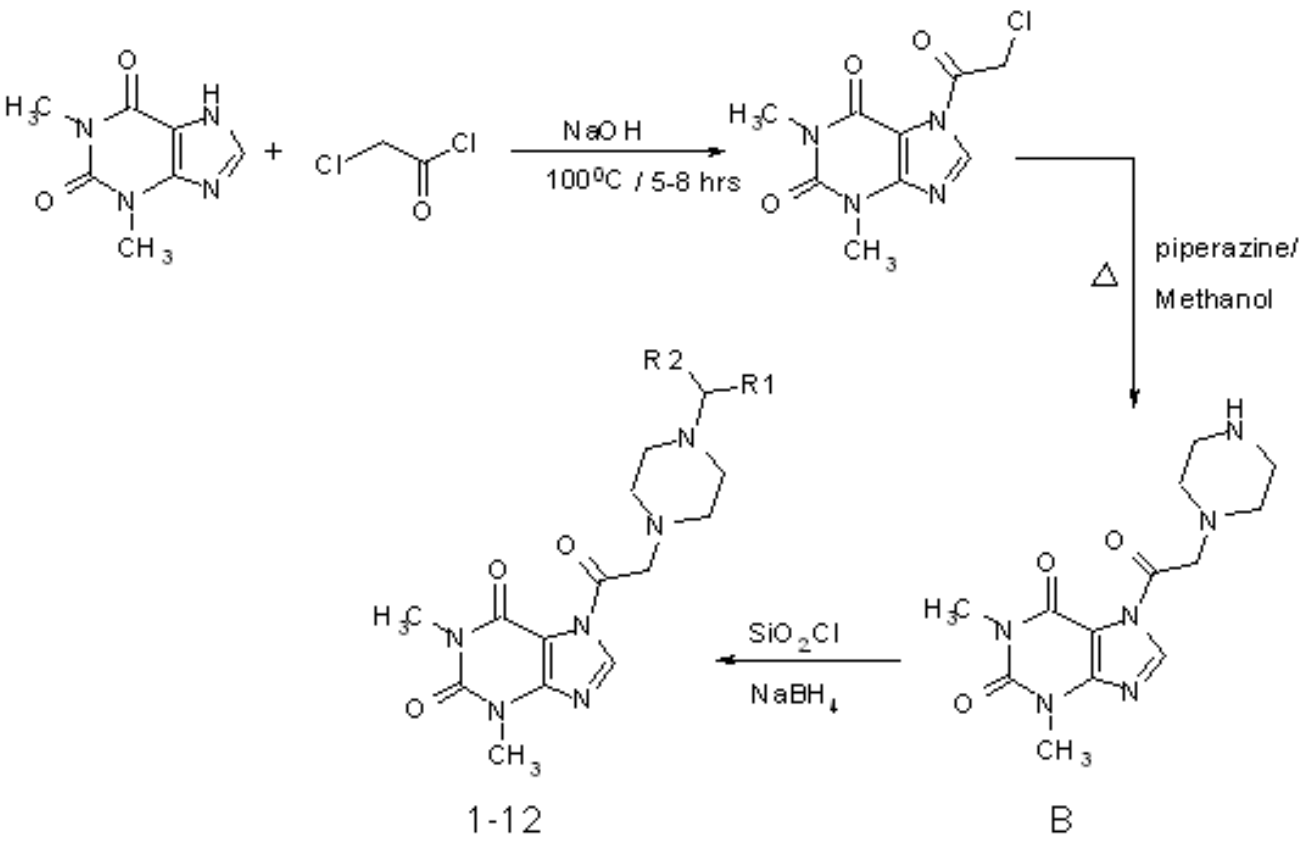

Figure 1: Scheme of Synthesis

Table 1: Various Derivatives Synthesized

R1	R2
H	3-NO_2-C_6H_5
CH_3	CH_3
H	4-F-C_6H_5
CH_3	4-OH-C_6H_5
CH_3	4-NH_2-C_6H_5
H	2,4-NO_2-C_6H_5
CH_3	2,4-Cl-C_6H_5
CH_3	3,4-Cl-C_6H_5
CH_3	3-NO_2-C_6H_5
CH_3	4-Br-C_6H_5
CH_3	2,5-OCH_3-C_6H_5
H	4-Br-C_6H_5

Table 2: Biological Activity of synthesized derivatives

Sample code	ED_{80} (M)	Sample code	ED_{80} (M)
1	3×10^{-4}	7	3×10^{-4}
2	4×10^{-4}	8	1×10^{-4}
3	7×10^{-4}	9	4×10^{-4}
4	3×10^{-4}	10	4×10^{-4}
5	4×10^{-4}	11	5×10^{-4}
6	2×10^{-4}	12	5×10^{-4}
		Cilostazol	1×10^{-4}

Rf: 0.62 [n-Hexane: ethyl acetate (8.5:1.5)]

UV- 276 nm

IR- (KBr) 1720 cm^{-1} (C-N Str), 1677 cm^{-1} (C=O Str), 1566 cm^{-1} (Ar-NO2), 1440 cm^{-1} (C-H def), 1107 cm^{-1} (C-H def), 950 cm-1 and 885 cm^{-1} (Ar-C=C def)

1H NMR- ($CDCl_3$, 500 MHz), 3.40 (6H, H_3C-N at 1 and 3, s), 7.90 (1H, CH s), 3.47 (2H, CH_2 at 2', s), 2.35 (4H, 2' and 6' CH_2 Piperazine, t), 2.48 (4H, 3' and 5' CH_2 Piperazine, t), 3.66 (2H, CH_2 at 4' Piperazine, s), 7.8-8.3 (4H, 4H Aromatic 4' Piperazine, m).

MASS- 440.35 (M+1)

2. 1,3-dimethyl-7-{2-[4-(propan-2-yl)piperazin-1-yl] acetyl}-2,3,6,7-tetrahydro-1H-purine-2,6-dione

M. P.: 188-190°

Rf: 0.56 [n-Hexane: ethyl acetate (8.5:1.5)]

UV- 273 nm

IR- (KBr) 3026 cm^{-1} (Ar-CH Str), 2819 cm^{-1} (C-H Str), 1703 cm^{-1} (C=O Ketone), 1654 cm^{-1} (sec. NH), 1560 cm^{-1} (Ar-C=C), 1442 and 1319 cm^{-1} (N-H def).

1H NMR- ($CDCl_3$, 500 MHz,): 3.30 (6H, H_3C-N at 1 and 3, s), 7.85 (1H, CH s), 3.34 (2H, CH_2 at 2', s),

2.25 (4H, 2' and 6' CH_2 Piperazine, t), 2.28 (4H, 3' and 5' CH_2 Piperazine, t), 3.36 (1H, CH at 4' Piperazine, q), 1.7 (6H, CH_3 at 5", d).

MASS- 349 (M+1)

3. 7-(2-{4-[(4-fluorophenyl)methyl]piperazin-1-yl} acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione

M. P.: 210-212°

Rf: 0.71 [n-Hexane: ethyl acetate (8.5:1.5)]

UV- 265 nm

IR- (KBr) 3087 cm^{-1} (Ar-CH Str), 2789 cm^{-1} (C-H Str), 1701 cm^{-1} (C=O Ketone), 1656 cm^{-1} (sec. NH), 1580 cm^{-1} (Ar-C=C), 1485 and 1379 cm^{-1} (N-H def).

1H NMR- ($CDCl_3$, 500 MHz,): 3.51 (6H, H_3C-N at 1 and 3, s), 7.84 (1H, CH s), 3.49 (2H, CH_2 at 2', s), 2.75 (4H, 2' and 6' CH_2 Piperazine, t), 2.81 (4H, 3' and 5' CH_2 Piperazine, t), 3.56 (2H, CH_2 at 4' Piperazine, s), 7.1-8.2 (4H, Aromatic 4' Piperazine, m).

MASS- 413 (M+1)

4. 7-(2-{4-[1-(4-hydroxyphenyl)ethyl]piperazin-1-yl} acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione

M. P.: 216-218°

Rf: 0.63 [n-Hexane: ethyl acetate (8.5:1.5)]

UV- 275 nm

IR- (KBr) 3562 cm-1 (Ar-OH), 3245 cm^{-1} (Ar-NH), 3006 cm^{-1} (Ar-CH Str), 1677 cm^{-1} (C=O Str.),1635 cm^{-1} (C=C str), 1566 cm^{-1} (Ar-C=C), 1461 cm^{-1} (CH def), 1440 and 1317 cm^{-1} (N-H def).

1H NMR- ($CDCl_3$, 500 MHz,): 3.21 (6H, H_3C-N at 1 and 3, s), 7.90 (1H, CH s), 3.19 (2H, CH_2 at 2', s), 2.65 (4H, 2' and 6' CH_2 Piperazine, t), 2.69 (4H, 3' and 5' CH_2 Piperazine, t), 2.37 (1H, CH at 4' Piperazine, q), 5.25 (1H OH at 7' Phenyl, s), 1.5 (3H, CH_3 at 7', d), 7-8.1 (4H, Aromatic at 7', m).

MASS- 425 (M+1)

5. 7-(2-{4-[1-(4-aminophenyl)ethyl]piperazin-1-yl} acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione

M. P.: 180-182°

Rf: 0.59 [n-Hexane: ethyl acetate (8.5:1.5)]

UV- 279 nm

IR- (KBr) 3289 cm^{-1} (Ar-NH), 3746 cm^{-1} (Ar-CH Str), 2822 cm^{-1} (C-H Str), 1603 cm^{-1} (C=O Ketone), 1600 cm^{-1} (sec. NH), 1560 cm^{-1} (Ar-C=C), 1441 and 1356 cm-1 (N-H def).

1H NMR- (CDCl3, 500 MHz,): 3.11 (6H, H_3C-N at 1 and 3, s), 7.92 (1H, CH s), 3.00 (2H, CH_2 at 2', s), 2.55 (4H, 2' and 6' CH_2 Piperazine, t), 2.59 (4H, 3' and 5' CH_2 Piperazine, t), 2.17 (1H, CH at 4' Piperazine, q), 6.25 (2H NH 7' Phenyl, s), 1.4 (3H, CH_3 at 7',d),7-8.0 (4H, Aromatic at 7', m).

MASS- 426 (M+1)

6. 7-(2-{4-[(2,4-dinitrophenyl)methyl]piperazin-1-yl} acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione

M. P.: 232-234°

Rf: 0.64 [n-Hexane: ethyl acetate (8.5:1.5)]

UV- 281 nm

IR- (KBr) 3134 cm^{-1} (Ar-NH), 3006 cm^{-1} (Ar-CH Str), 2839 cm^{-1} (C-H Str), 1796 cm^{-1} (C=O Ketone), 1645 cm^{-1} (sec. NH), 1560 cm^{-1} (Ar-C=C), 1478 and 1335 cm^{-1} (N-H def).

1H NMR- ($CDCl_3$, 500 MHz,): 3.51 (6H, H_3C-N at 1 and 3, s), 7.96 (1H, CH s), 3.49 (2H, CH_2 at 2', s), 2.45 (4H, 2' and 6' CH_2 Piperazine, t), 2.47 (4H, 3' and 5' CH_2 Piperazine, t), 3.79 (2H, CH_2 at 7', s), 7.9-8.5 (3H, Aromatic at 7', m).

MASS- 485 (M+1)

7. 7-(2-{4-[1-(2,4-dichlorophenyl)ethyl]piperazin-1-yl} acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione

M. P.: 210-212°

Rf: 0.58 [n-Hexane: ethyl acetate (8.5:1.5)]

UV- 263 nm

IR- (KBr) 3147 cm^{-1} (Ar-NH), 3082 cm^{-1} (Ar-CH Str), 2863 cm^{-1} (C-H Str), 1722 cm^{-1} (C=O Ketone), 1654 cm^{-1} (sec. NH), 1541 cm^{-1} (Ar-C=C), 1489 and 1332cm-1 (N-H def).

1H NMR- ($CDCl_3$, 500 MHz,): 3.51 (6H, H_3C-N at 1 and 3, s), 7.91 (1H, CH s), 3.40 (2H, CH_2 at 2', s), 2.41 (4H, 2' and 6' CH_2 Piperazine, t), 2.44 (4H, 3' and 5' CH_2 Piperazine, t), 3.6 (1H, CH at 4' Piperazine, q), 1.6 (3H, CH_3 at 7', d), 7.8-8.2 (3H, Aromatic at 7', m).

MASS- 477 (M+1)

8. 7-(2-{4-[1-(3,4-dichlorophenyl)ethyl]piperazin-1-yl} acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione

M. P.: 202-204°

Rf: 0.74 [n-Hexane: ethyl acetate (8.5:1.5)]

UV- 262 nm

IR- (KBr) 3247.90 cm^{-1} (Ar-NH), 1677.90 cm^{-1} (C=O str), 1633.99 cm^{-1} (C=C str), 1440.29 cm^{-1} (C-H def),1188.07 cm^{-1} (C-N str), 1170.07 cm^{-1} (Ar C-H), 950.60 cm^{-1} (C=C def), 742.58 cm^{-1} (Ar-Cl).

1H NMR- ($CDCl_3$, 500 MHz,): 3.54 (6H, H_3C-N at 1 and 3, s), 7.94 (1H, CH s), 3.49 (2H, CH_2 at 2', s), 2.40 (4H, 2' and 6' CH_2 Piperazine, t), 2.43 (4H, 3' and 5' CH_2 Piperazine, t), 3.76 (1H, CH at 4' Piperazine, q), 1.8 (3H, CH_3 at 7', d), 7.9-8.5 (3H, Aromatic at 7', m).

MASS- 479 (M+1)

9. 1,3-dimethyl-7-(2-{4-[1-(3-nitrophenyl)ethyl] piperazin-1-yl}acetyl)-2,3,6,7-tetrahydro-1H-purine-2,6-dione

M. P.: 196-198°

Rf: 0.59 [n-Hexane: ethyl acetate (8.5:1.5)]

UV- 278 nm

IR- (KBr) 3142 cm^{-1} (Ar-NH), 3012 cm^{-1} (Ar-CH Str), 2820 cm^{-1} (C-H Str), 1736 cm^{-1} (C=O Ketone), 1658 cm^{-1} (sec. NH), 1570 cm^{-1} (Ar-C=C), 1445 and 1322 cm^{-1} (N-H def).

1H NMR- ($CDCl_3$, 500 MHz,): 3.62 (6H, S, H_3C-N at 1 and 3, s), 7.89 (1H, CH s), 3.52 (2H, CH_2 at 2', s), 2.47 (4H, 2' and 6' CH_2 Piperazine, t), 2.48 (4H, 3' and 5' CH_2 Piperazine, t), 3.80 (1H, CH at 4' Piperazine, q), 1.9 (3H, CH_3 at 7', d), 8.0-8.8 (4H, Aromatic at 7', m).

MASS- 455 (M+1)

10. 7-(2-{4-[1-(4-bromophenyl)ethyl]piperazin-1-yl} acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione

M. P.: 182-184°

Rf: 0.75 [n-Hexane: ethyl acetate (8.5:1.5)]

UV- 266 nm

IR- (KBr) 3185 cm^{-1} (Ar-NH), 3053 cm^{-1} (Ar-CH Str), 2882 cm^{-1} (C-H Str), 1710 cm^{-1} (C=O Ketone), 1632 cm^{-1} (sec. NH), 1575 cm^{-1} (Ar-C=C), 1445 and 1300 cm^{-1} (N-H def).

1H NMR- (CDCl3, 500 MHz,): 3.4 (6H, S, H_3C-N at 1 and 3, s), 7.96 (1H, CH s), 3.4 (2H, CH_2 at 2', s), 2.3 (4H, 2' and 6' CH_2 Piperazine, t), 2.38 (4H, 3' and 5' CH_2 Piperazine, t), 3.70 (1H, CH at 4' Piperazine, q), 1.91 (3H, CH_3 at 7', d), 7.8-8.1 (4H, Aromatic at 7', m)

MASS- 488 (M+1)

11. 7-(2-{4-[1-(2,5-dimethoxyphenyl)ethyl]piperazin-1-yl}acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione

M. P.: 190-192°

Rf: 0.65 [n-Hexane: ethyl acetate (8.5:1.5)]

UV- 261 nm

IR- (KBr) 3200 cm^{-1} (Ar-NH), 3082 cm^{-1} (Ar-CH Str), 2820 cm^{-1} (C-H Str), 1701 cm^{-1} (C=O Ketone), 1651 cm^{-1} (sec. NH), 1575 cm^{-1} (Ar-C=C), 1445 and 1309 cm^{-1} (N-H def).

1H NMR- ($CDCl_3$, 500 MHz,): 3.6 (6H, S, H_3C-N at 1 and 3, s), 7.91 (1H, CH s), 3.1 (2H, CH_2, s), 2.28 (4H, 2' and 6' CH_2 Piperazine, t), 2.31 (4H, 3' and 5' CH_2 Piperazine, t), 3.64 (1H, CH at 4' Piperazine, q), 3.83 (6H-OCH_3 at 2" and 5" phenyl, s), 1.81 (3H, CH_3 at 7', d)7.6-8.1 (3H, Aromatic at 7', m).

MASS- 471 (M+1)

12. 7-(2-{4-[(4-bromophenyl)methyl]piperazin-1-yl} acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione

M. P.: 216-218°

Rf: 0.52 [n-Hexane: ethyl acetate (8.5:1.5)]

UV- 265 nm

IR- 3274 cm^{-1} (Ar-NH), 3001 cm^{-1} (Ar-CH Str), 2809 cm^{-1} (C-H Str), 1693 cm^{-1} (C=O Ketone), 1624 cm^{-1} (sec. NH), 1500 cm^{-1} (Ar-C=C), 1441 and 1309 cm^{-1} (N-H def).

1H NMR- ($CDCl_3$, 500 MHz,): 3.4 (6H, S, H_3C-N at 1 and 3,s), 7.88 (1H, CH s), 3.2 (2H, CH_2, s), 2.30 (4H, 2' and 6' CH_2 Piperazine, t), 2.34 (4H, 3' and 5' CH_2 Piperazine, t), 3.70 (2H, CH_2 at 4' Piperazine, s), 7.7-8.5 (4H, Aromatic, m).

MASS- 474 (M+1)

Biological activity

Results were calculated as ED_{80} which is the molar dose required producing 80% of the relaxation produced by standard Cilostazol. The tested compounds produced tracheal smooth muscle relaxant activity ranging from 1 x 10^{-4} M to 7 x 10^{-4} M and standard drug Cilostazol produced 1 x 10^{-4} M activity. Compound 8 showed very good activity as compared to the other compounds. Compounds 6, 1, 4 and 7 also had comparable activity, all these compounds have activity that is close and comparable to that produced by the standard drug, Cilostazol as shown in Table 2.

CONCLUSION

Synthesized xanthene derivatives showed profound biological activity which proves therapeutic efficiency of the xanthene nucleus for development of potent anti-asthmatic agents.

Activity of Compound (8) 7-(2-{4-[1-(3,4-dichlorophenyl) ethyl]piperazin-1-yl}acetyl)-1,3-dimethyl-2,3,6,7-tetrahydro-1*H*-purine-2,6-dione with di-chloro substitution indicating the compounds with electron withdrawing groups showing significant activity than other compounds which indicates mechanistic details of all the synthesized compounds in near future would lead to potent anti-asthmatic compounds. Thus there is need to study these compounds at the molecular level by using different

enzymatic assays to develop potent anti-asthmatic drug like candidate. These studies can confirm identification of novel lead compounds for further investigation which may produce therapeutic agents for treatment of various respiratory disorders like pulmonary hypertension, asthma etc.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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