EXPERIMENTAL WORK

Melting points of the synthesized compound were observed on melting point apparatus (Veego). Fourier Transform Infrared (FT-IR) or Attenuated total reflectance spectra were recorded on Agilent Technology carx 600 series FT-IR spectrophotometer by using pellets of potassium bromide ($\nu_{\text{max}}$ in cm$^{-1}$) and Alpha-T IR resolution software (Bruker). Nuclear magnetic resonance (NMR) spectroscopy was done by using Bruker Advance-II 400 MHz spectrometer by dissolving in CDCl$_3$ and DMSO-d$_6$ (ppm). Elemental analysis was carried out on Perkin Elmer series II-2400 analyzer. The results were observed within the limits. TLC was performed on pre-coated plates with silica gel G. The chromatographic spots were seen in the iodine or UV-chamber. All reagents used were of analytical grade. Solvents were dried by standard methods if necessary.

6-AMINO-1,3-DIMETHYL-5-NITROSORACIL (128)

A mixture of $N,N'$-dimethylurea (1.0 g, 11.36 mmol), cyanoacetic acid (1.0 g, 11.76 mmol) and acetic anhydride (2 ml) were refluxed at 70-80 °C for 3 h excluding moisture. The excess anhydride and acetic acid formed during the reaction were separated under vacuum. The oily residue so obtained was cooled (0-5 °C) and a solution of 5 % sodium hydroxide (20 ml) was added slowly with stirring resulting in precipitation of 6-amino-1, 3-dimethyluracil (3). Sodium nitrite solution (1.0 g, 14.49 mmol in 8 ml of water) was then added to cool, stirred mixture and acidified by the drop wise slow addition of acetic acid (2 ml) over a period of one hour resulting in red-violet precipitates. The mixture was further kept on stirring overnight at room temperature. The resultant mixture was further cooled, filtered off, washing was done with water, ethanol and finally dried with diethyl ether to obtain 128 (1.8 g, 84.7 %), mp 235-240 °C.
5, 6-DIAMINO-1,3-DIMETHYLURACIL (129)

The compound 128 (1.0 g, 5.43 mmol) was allowed to dissolve in concentrated ammonium hydroxide (8 ml) with slight warming. The sodium dithionite (2.74 g, 15.73 mmol) was then added slowly with stirring and warming. The salt dissolved and underwent a series of color changes. The solution was further kept on stirring at room temperature for almost two hours, followed by cooling. The precipitate so obtained was filtered off, washing was done with few drops of cool water and dried to obtain 129 (0.76 g, 82.16 %), mp 208-211°C.

8-[4-(METHYL-2-PHENOXYACETATE)]-1,3-DIMETHYLXANTHINE (134)

Methylchloroacetate (2 ml) was poured in refluxing suspension of 4-hydroxybenzaldehyde (1 g, 8.20 mmol) in ethyl methyl ketone (20 ml) at 70-80 °C. Dried potassium carbonate (3.0 g) was added to maintain the anhydrous conditions. After completion, suspension was filtered, reduced to obtain oily residue of methyl-2-(4-formylphenoxy) acetate (132) which was used as such for next reaction.

To the stirred solution of 5,6-diamino-1,3-dimethyluracil (1 g, 5.88 mmol; 129) in methanol-acetic acid (8:2, 10 ml), added slowly the compound 132 in the reaction mixture. The mixture was kept on stirring at room temperature overnight for completion. Precipitated product was filtered-off, washed and dried to afford compound 133 (0.79 g, mp 238-246 °C), which was used as such for further reaction.

The Schiff base 133 (1 g, 2.88 mmol) was refluxed in thionyl chloride (15 ml) at 70-80 °C for one hour. The excess acid was distilled off and the residue was neutralized with ammonium hydroxide. The precipitate so obtained was cooled, filtered-off, and washed with ice-cold water. The product was dried to obtain the cyclized ester 134 (0.70 g, 70.42 %), mp > 280 °C.

Spectral and elemental analysis:

FT-IR ν<sub>max</sub> (KBr) cm<sup>-1</sup>: 3167 (-N-H), 3033 (-CH), 2954 (Ali-CH), 1747 (carbonyl), 1689 (C=O), 1648 (C=N).
Generalized method for the synthesis of 8-[4-(2-oxoethoxysulphonamide)-phenyl]-1,3-dimethyl-xanthine derivatives (141-146)

The cyclized ester 134 (1 g, 2.90 mmol) was suspended in DMF (10 ml) while stirring and refluxed to obtain a clear solution. Various sulphonamides [sulphanilamide (2 g, 11.62 mmol), sulphapyridine (1.50 g, 6.00 mmol), sulphathiazole (1.5 g, 3.92 mmol), sulfanilic acid (1.5 g, 8.66 mmol), sulfadiazine (1.48 g, 6.00 mmol) and sulfamethizole (1.50 g, 5.50 mmol)] were then added to the reaction mixture, refluxed and progress of reaction was checked by TLC. After completion, solvent was removed using rotary evaporator. The residue left was washed with solvent (diethyl ether) to remove excess amines. The precipitates were filtered-off, washed and dried to obtain the desired derivatives (141-146).

8-[4-(2-OXOSULPHANILAMIDETHOXY)-PHENYL]-1,3-DIMETHYLXANTHINE (RY-060, 141)

Yield: 2.26 g, 75.83 %, mp 172-174 °C (decomp.).

Spectral and elemental analysis:

FT-IR ν_{max} (KBr) cm⁻¹: 3477 (-NH asym.), 3383 (-NH sym.), 3318 (-NH), 3242 (Ar-CH), 1688 (C=O-NH), 1648 (C=O), 1626 (C=N), 1150 (-SO₂⁻).

¹H-NMR (400 MHz, DMSO-d₆): δ 7.99 (d, 2H, -NH, J_{ortho}= 8.52Hz), 7.34(d, 2H, Ar-H, J_{ortho}= 8.56Hz), 6.81 (s, 4H, Ar-H), 6.52(d, 2H, Ar-H, J_{ortho}= 8.50Hz), 5.71 (s, 2H, -NH₂ ), 4.80 (s, 2H, -OCH₂), 2.80 (s, 3H, -NCH₃) and 2.64 ppm (s, 3H, -NCH₃).

¹³C-NMR (100 MHz, DMSO-d₆): δ 27.65-29.75 (N-CH₃), 64.53 (O-CH₂), 112.44-162.36 (Ar-C) and 166.87 ppm (C=O).

Cal. for C₂₁H₂₀N₆O₆S: C,52.06%, H,4.16%, N,17.35%, Found: C,51.16%, H, 4.75%, N, 16.83%.
8-[4-(2-OXOSULPYRIDINETHOXY)-PHENYL]-1,3-DIMETHYLXANTHINE (RY-061, 142)

Yield: 2.13 g, 91 %, mp 230-234 °C (decomp.).

Spectral and elemental analysis:

FT-IR $\nu_{\text{max}}$ (KBr) cm$^{-1}$: 3416 (-NH), 3363 (-NH), 3313 (-NH), 3242 (Ar-CH-stretch), 1748 (C=O-NH), 1687 (C=N), 1648 (C=O), 1368 (-SO$_2$-), 1263 (C-O), 1185 (C-N).

$^1$HNMR (400MHz, DMSO-d$_6$): $\delta$ 13.71 (s, 1H, -NH), 9.93 (s, 1H, -NH), 8.10 (d, 2H, Ar-H, $J_{\text{ortho}}$= 8.48Hz), 7.95 (s, 1H, Ar-H), 7.65 (t, 1H, Ar-H, $J_{\text{meta}}$= 1.76Hz, $J_{\text{ortho}}$= 6.88Hz), 7.58 (d, 2H, Ar-H, $J_{\text{ortho}}$= 8.8Hz), 7.08 (d, 2H, Ar-H, $J_{\text{ortho}}$= 8.64Hz), 6.90 (t, 1H, Ar-H, $J_{\text{meta}}$= 1.0 Hz, $J_{\text{ortho}}$= 5.6Hz), 6.71 (s, 1H, Ar-H), 6.57 (d, 2H, Ar-H, $J_{\text{ortho}}$= 8.68Hz), 5.94 (s, 2H, -OCH$_2$), 4.90 (s, 1H, -NH), 2.73 (s, 3H, -NCH$_3$), 2.51 (s, 3H, -NCH$_3$).

$^{13}$CNMR (100MHz, DMSO-d$_6$): $\delta$ 27.75 (N-CH$_3$), 29.73 (N-CH$_3$), 64.54 (O-CH$_2$), 112.11 -152.70 (Ar-CH), 154.10 (C=O), 159.09 (C=O) and 168.95 ppm (C=O).

Cal. for C$_{26}$H$_{23}$N$_7$O$_6$S: C, 55.61%, H, 4.13%, N, 17.46%, Found: C, 54.74%, H, 4.61%, N, 16.8%.

8-[4-(2-OXOSULPHATHIAZOLETHOXY)-PHENYL]-1,3-DIMETHYLXANTHINE (RY-062, 143)

Yield: 2.30 g, 99 %, mp 193-196 °C (decomp.).

Spectral and elemental analysis:

FT-IR $\nu_{\text{max}}$ (KBr) cm$^{-1}$: 3467 (-NH), 3363 (-NH), 3141 (Ar-CH-stretch), 1746 (C=O-NH), 1688 (C=N), 1648 (C=O), 1239 (C-O), 1142 (-SO$_2$-).

$^1$HNMR (400MHz, DMSO-d$_6$): $\delta$ 12.70 (s, 1H, -N-H), 12.46 (s, 1H, -NH), 8.09 (s, 2H, Ar-H), 7.45 (s, 1H, Ar-H), 7.18 (s, 1H, Ar-H), 7.09 (s, 1H, Ar-H), 6.94 (s, 1H, Ar-H), 6.74 (s, 1H, Ar-H), 6.57 (s, 1H, Ar-H), 6.25 (s, 1H, Ar-H), 6.15 (s, 1H, Ar-H), 5.84 (s, 2H, -OCH$_2$), 4.89 (s, 1H, -NH), 2.73 (s, 3H, -NCH$_3$) and 2.51 ppm (s, 3H, -NCH$_3$).
Experimental work

13C-NMR (100 MHz, DMSO-d6): δ 29.01 (N-CH₃), 31.73 (N-CH₃), 65.54 (O-CH₂), 109.11 (Ar-CH), 112.39 (Ar-C), 114.93 (2 Ar-CH), 122.05 (2 Ar-CH), 124.89 (Ar-C), 125.65 (2 Ar-CH), 128.02 (2 Ar-CH), 135.85 (Ar-C), 138.70 (Ar-CH), 142.27 (Ar-C), 151.18 (Ar-C), 153.27 (Ar-C), 158.70 (2 Ar-C), 151.10 (C=O), 154.09 (C=O) and 168.95 ppm (C=O).

Cal. for C₂₄H₂₁N₇O₆S₂: C, 51.79%; H, 4.73%; N, 18.27%; Found: C, 52.74%, H, 5.74%, N, 16.67%.

8-[4-[(CARBOXYAMINO)BENZENESULFONIC ACID]-ETHOXY]-PHENYL]-1,3-DIMETHYL XANTHINE (RY-063, 144)

Yield: 0.62 g, 26.72%, mp >270 °C.

Spectral and elemental analysis:

FT-IR νmax (KBr) cm⁻¹: 3522 (-NH), 3169 (Ar-CH), 1742 (C=O-NH), 1701 (C=N), 1656 (C=O), 1243 (C-O), 1187 (-SO₃H).

1H-NMR (400 MHz, DMSO-d6): δ 13.61 (s, 1H, -OH), 8.12 (d, 2H, Ar-H, Jortho= 8.96Hz), 8.09 (s, 1H, Ar-H), 7.14 (d, 2H, Ar-H, Jortho= 8.8Hz), 7.07 (d, 2H, Ar-H, Jortho= 8.52Hz), 4.95 (s, 2H, -OCH₂), 3.74 (s, 2H, -NH), 2.95 (s, 3H, -NCH₃) and 2.79 ppm (s, 3H, -NCH₃).

13C-NMR (100 MHz, DMSO-d6): δ 27.74 (N-CH₃), 29.72 (N-CH₃), 64.55 (O-CH₂), 114.92 (3 Ar-CH), 121.91 (2 Ar-CH), 125.21 (Ar-C), 126.42 (Ar-C), 127.90 (Ar-C), 128.01 (2 Ar-CH), 147.23 (Ar-C), 148.51 (Ar-C), 149.70 (Ar-C), 151.17 (2 Ar-C), 154.10 (C=O), 159.09 (C=O) and 168.94 ppm (C=O).

Cal. for C₂₁H₁₉N₅O₇S: C 51.95%, H 3.94%, N 14.43%, Found: C 52.02%, H 4.15%, N 13.96%.

8-[4-{(2-OXOSULPHADIAZINETHOXY)-PHENYL]-1,3-DIMETHYLXANTHINE (RY-064, 145)

Yield: 0.68 g, 72.03%, mp 245-248 °C (decomp.).

Spectral and elemental analysis:
FT-IR ν\text{max} (KBr) cm\textsuperscript{-1}: 3434 (-NH), 1653 (C=O), 1596 (C=N), 1577 (C=C), 1475 (NH), 1319 (-SO\textsubscript{2}-), 1185 (C-N), 1092 (C-O).

\textsuperscript{1}HNMR (400MHz, DMSO-d\textsubscript{6}): δ 13.64 (s, 1H, -NH), 11.29 (s, 1H, -NH), 8.46 (d, 2H, Ar-H, \textit{J}\textsubscript{ortho}= 4.28Hz), 8.10 (d, 1H, Ar-H, \textit{J}\textsubscript{ortho}= 8.24Hz), 7.69 (d,2H, Ar-H, \textit{J}\textsubscript{ortho}= 8.2Hz), 7.05 (d, 1H, Ar-H, \textit{J}\textsubscript{ortho}= 8.2Hz), 6.97 (s, 2H, Ar-H), 6.70 (s, 1H, Ar-H), 6.58 (d,2H, Ar-H, \textit{J}\textsubscript{ortho}=8.2Hz), 5.92 (s, 2H, -OCH\textsubscript{2}), 4.86 (s, 1H, -NH), 2.91 (s,3H, -NCH\textsubscript{3}) and 2.76 ppm (s,3H, -NCH\textsubscript{3}).

\textsuperscript{13}C-NMR (100 MHz, DMSO-d\textsubscript{6}): δ 27.69 (N-C\textsubscript{H}3), 29.75 (N-C\textsubscript{H}3), 64.62 (O-C\textsubscript{H}2), 112.02-157.21 (Ar-C), 158.98 (C=O) and 168.78 ppm (C=O).

Cal. for C\textsubscript{25}H\textsubscript{22}N\textsubscript{8}O\textsubscript{6}S: C,53.38%, H,3.94%, N,19.92%, Found: C,52.28%, H,4.18%, N,19.18%.

8-[4-(2-OXOSULPHAMETHIZOLETHOXY)-PHENYL]-1,3-DIMETHYL-XANTHINE (RY-065, 146)

Yield: 1.90 g, 82.25 %, mp 172-174 °C (decomp.).

Spectral and elemental analysis:

FT-IR ν\text{max} (KBr)cm\textsuperscript{-1}: 3463 (-NH), 3216 (C-H), 2923 (CH), 1671 (C=O), 1597 (C=N), 1297 (-SO\textsubscript{2}-), 1142 (C-S), 1086 (C-O).

\textsuperscript{1}HNMR (400MHz, DMSO-d\textsubscript{6}): δ 12.99 (s, 1H, -NH), 8.24 (d, 2H, Ar-H, \textit{J}\textsubscript{ortho}= 5.64 Hz), 7.42 (s, 3H, Ar-H), 7.22 (s, 1H, Ar-H), 6.80 (s, 2H, Ar-H), 6.00 (s, 2H, -OCH\textsubscript{2}), 5.38 (s, 1H, -NH), 4.85 (s, 1H, -NH), 2.83 (s, 3H, -NCH\textsubscript{3}), 2.45 (s, 3H, -NCH\textsubscript{3}) and 1.25 ppm (s, 3H, -CH\textsubscript{3}).

\textsuperscript{13}C-NMR (100 MHz, DMSO-d\textsubscript{6}): δ 16.02 (CH\textsubscript{3}), 27.72 (N-CH\textsubscript{3}), 29.53 (N-CH\textsubscript{3}), 64.50 (O-CH\textsubscript{2}), 112.51 (4 Ar-CH), 114.54 (2 Ar-C), 127.47 (4 Ar-CH), 127.98 (3 Ar-C), 152.19 (2 Ar-C, C=O), 158.94 (Ar-C, C=O) and 168.61 ppm (C=O).

Cal. for C\textsubscript{23}H\textsubscript{20}N\textsubscript{8}O\textsubscript{6}S\textsubscript{2}: C 48.58%, H 3.55%, N 19.71%, Found: C 47.23%, H 3.33%, N 18.70%.
6-AMINO-1,3-DIPROPYL-5-NITROUSOURACIL (147)

A mixture of $N, N'$-dipropylurea (1.0 g, 6.94 mmol), cyanoacetic acid (1.5 g, 17.64 mmol) and acetic anhydride (2.5 ml) was refluxed at 70-80 °C (3 h) excluding moisture. The excess anhydride and acetic acid formed during the reaction were removed under vacuum. The residue was then cooled (0-5°C) and a solution of 5% sodium hydroxide (40 ml) was added with stirring resulting in precipitation of 6-amino-1, 3-dipropyluracil. A sodium nitrite solution (1.0 g, 14.49 mmol in 8 ml of water) was added to cool, stirred mixture and acidified with acetic acid dropwise (2 ml) over a period of one hour resulting in red-violet precipitates. The mixture was then kept on stirring at room temperature for a period of overnight. The mixture so obtained was then cooled, filtered off, washing was done with water and diethyl ether followed by drying to get 6-amino-1, 3-dipropyl-5-nitrosouracil 147 (1.33 g, 63.63 %), mp 215-220 °C.

5, 6-DIAMINO-1,3-DIPROPYLURACIL (148)

The 6-amino-1,3-dipropyl-5-nitrosouracil (1g, 4.16 mmol) was dissolved in ammonium hydroxide concentrated (8 ml). The sodium dithionite (2.74 g, 15.73 mmol) was then added slowly with stirring. The salt dissolved and underwent a series of color changes. The solution was kept on stirring for further two hours at room temperature followed by cooling in an ice bath. The precipitates so obtained were filtered off, washing was done with few drops of cool water followed by drying to get 5, 6-diamino-1, 3-dipropyluracil (148, 0.76 g, 80.85 %), mp 128-132 °C.

General procedure for the synthesis of various 8-[4-(2-aminoethoxy]-3-methoxyphenyl)-1,3-dipropylxanthine derivatives (170-175)

Various amines such as 4-(2-chloroethyl)-amino hydrochlorides (1 g), [4-(2-chloroethyl)-morpholine hydrochloride (152, 5.36 mmol), 4-(2-chloroethyl)-piperidine hydrochloride (153, 5.42 mmol), 2-chloro-$N,N'$-dimethyl ethanamine (154, 6.93 mmol), 1-(2-chloroethyl)-pyrrolidine (155, 5.88 mmol), 2-chloro-$N,N'$-diethyl ethanamine (156, 5.82 mmol) and 1-(2-chloroethyl)-phthalimide (157, 4.77 mmol)] were added to the refluxing suspension of 3-methoxy-4-hydroxy-
Experimental work

Benzaldehyde (149, 1 g, 6.56 mmol) in ethyl methyl ketone (20 ml). Dried potassium carbonate (3.0 g) was added to avoid incorporation of any moisture. After completion, suspension was filtered and reduced on rotary evaporator to afford the targeted compounds 158-163.

To the stirred solution of 158-163 in ethanol (5 ml), added 5, 6-diamino-1,3-dipropyluracil (148, 1 g, 4.42 mmol) with ethanol and acetic acid (8:2, 10 ml) and refluxed. After completion, excess amount of solvent was recovered using rotary evaporator. Added ice cold water in to the reaction mixture, filtered-off and washed to afford 164-169.

The Schiff bases 164-169 (1 g) were refluxed in thionyl chloride (15 ml) for 1 h at 70-80 °C. Excess solvent was reduced under vacuum and residue so obtained was neutralized to result in precipitation. The reaction mixture cooled, filtered off and washed with cold water to obtain various 8-(4-(2-aminoethoxy)-3-methoxyphenyl)-1, 3-dipropylxanthine derivatives (170-175).

8-[4-(2-MORPHOLINOETHOXY]-3-METHOXYPHENYL]-1,3-DIPROPYL XANTHINE (RY-067, 170)

Yield: 1.46 g, 69.56 %, mp 234-238 °C.

Spectral and elemental analysis:

FT-IR \( \nu_{\text{max}} \) (KBr)cm\(^{-1}\): 3410 (NH), 3202 (CH), 2959 (CH), 1691 (C=O), 1647 (C=N), 1556 (NH-bend), 1478 (H-C=C-H), 1271 (CN), 1168 (CO).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) 11.06 (s, 1H, -NH), 7.75 (s, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 6.96 (s, 1H, Ar-H), 4.31 (s, 3H, -OCH\(_3\)), 3.95 (s, 4H, 2 x -OCH\(_2\)), 3.75 (s, 2H, -OCH\(_2\)), 2.89 (s, 4H, 2 x -NCH\(_2\)), 2.63 (s, 6H, 3 x -NCH\(_2\)), 1.47 (s, 4H, 2 x -CH\(_2\)) and 0.99 ppm (s, 6H, 2 x -CH\(_3\)).

\(^13\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta \) 10.08-11.10 (2 CH\(_3\)), 20.01 (2 CH\(_2\)), 44.72 (2 N-CH\(_2\)), 53.37-54.01 (3 N-CH\(_2\)), 56.20-62.01 (3 O-CH\(_2\)), 65.57 (O-CH\(_3\)), 112.51 (Ar-CH), 114.41-115.56 (2 Ar-C), 119.54 (2 Ar-CH), 123.47 (Ar-C), 146.98-151.08 (3 Ar-C), 149.94 (C=O) and 152.61 ppm (C=O).
Cal. for C_{24}H_{33}N_{5}O_{5}: C, 61.13%; H, 7.06%; N, 14.85% Found: C, 63.15%; H, 6.37%; N, 16.38%.

8-[4-(2-PIPERIDINOETHOXY)-3-METHOXYPHENYL]-1,3-DIPROPYL-XANTHINE (RY-069, 171)

Yield: 0.97 g, 99 %, mp 137-141 °C.

Spectral and elemental analysis:

FT-IR ν_{max} (KBr) cm^{-1}: 3565 (NH), 2920 (Ali-CH), 1698 (C=O), 1650 (C≡N), 1516 (NH-bend), 1460 (Ar-C≡C), 1258 (C-N), 1209 (C-O).

¹H-NMR (400 MHz, CDCl₃): δ 7.66 (s, 1H, Ar-H), 7.22 (s, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 4.07 (s, 1H, -NH), 3.90 (s, 4H, 2 x -NCH₂), 3.73 (s, 6H, 3 x -NCH₂), 3.01 (s, 2H, -OCH₂), 2.75 (s, 3H, -OCH₃), 1.68 (s, 10H, 5 x -CH₂) and 1.18 ppm (s, 6H, 2 x -CH₃).

¹³C-NMR (100MHz, CDCl₃): δ 10.08-11.10 (2 CH₃), 20.01 (2 CH₂), 24.73 (3 CH₂), 43.72 (2 N-CH₂), 54.01 (3 N-CH₂), 56.07 (O-CH₂), 67.57 (O-CH₃), 112.51 (Ar-CH), 115.41 (Ar-C), 119.54-120.02 (2 Ar-CH), 123.47 (Ar-C), 146.98 (Ar-C), 150.08 (Ar-C), 151.08 (Ar-C), 151.94 (C≡O), 153.61 (C≡O) and 154.08 ppm (Ar-C).

Cal. for C_{25}H_{35}N_{5}O_{4}: C, 63.94%; H, 7.51%; N, 14.91%, Found: C, 64.18%; H, 6.28%; N, 15.34%.

8-[4-{2-(DIMETHYLAMINO)-ETHOXY}-3-METHOXYPHENYL]-1,3-DIPROPYL-XANTHINE (RY-071) (172)

Yield: 0.71 g, 71.42 %, mp 169-171 °C.

Spectral and elemental analysis:

FT-IR ν_{max} (KBr) cm⁻¹: 3565 (NH), 2920 (Ali-CH), 1699 (C=O), 1650 (C≡N), 1517 (NH-bend), 1460 (H-C≡C-H), 1259 (cyano), 1179 (CO).

¹H-NMR (400MHz, CDCl₃): δ 7.69 (s, 1H, -NH), 6.94 (s, 3H, Ar-H), 3.91 (s, 6H, -3 x -NCH₂), 3.00 (s, 6H, 2 x -NCH₂), 2.49 (s, 3H, -OCH₃), 2.46 (s, 2H, -OCH₂), 1.62 (s, 4H, 2 x -CH₂) and 0.85 ppm (s, 6H, 2 x -CH₃).
\textbf{Experimental work}

\textbf{\textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}):} \(\delta\) 10.08 (CH\textsubscript{3}), 11.10 (CH\textsubscript{3}), 21.07(CH\textsubscript{2}), 23.01 (CH\textsubscript{2}), 43.72 (N-CH\textsubscript{2}), 45.05 (N-CH\textsubscript{2}), 47.09 (2 N-CH\textsubscript{3}), 54.01 (N-CH\textsubscript{2}), 56.07 (O-CH\textsubscript{2}), 66.57 (O-CH\textsubscript{3}), 107.51-153.85 (Ar-C), 154.94 (C=O) and 157.61 ppm (C=O).

\textbf{Cal. for C\textsubscript{22}H\textsubscript{31}N\textsubscript{5}O\textsubscript{4}:} C 61.52\%, H 7.27\%, N 16.31\%, O 14.90\%, \textbf{Found:} C 61.54\%, H 6.75\%, N 16.65\%.

\textbf{8-[4-\{2-(PYRROLIDIN-1-YL)-ETHOXY\}-3-METHOXYPHENYL]-1,3-DIPROPYLXANTHINE (RY-073) (173)}

\textbf{Yield:} 0.95 g, 99 \%, mp 139-141 °C (decomp.).

\textbf{Spectral and elemental analysis:}

\textbf{FT-IR} \(\nu_{\text{max}}\) (KBr) cm\textsuperscript{-1}: 3565 (NH), 2918 (Ali-CH), 1698 (C=O), 1649 (C=N), 1516 (NH-bend), 1460 (Ar-C=C), 1259 (C-N), 1038 (C-O).

\textbf{\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}):} \(\delta\) 7.70 (s, 1H, Ar-H), 6.94 (s, 2H, Ar-H), 4.13 (s, 1H, -NH), 3.70 (s, 10H, 5 \times NCH\textsubscript{2}), 3.38 (s, 2H, -OCH\textsubscript{2}), 3.14 (s, 3H, -OCH\textsubscript{3}), 1.67 (s, 8H, 4 \times CH\textsubscript{2}) and 0.96 ppm (s, 6H, 2x-CH\textsubscript{3}).

\textbf{\textsuperscript{13}C-NMR (100MHz, CDCl\textsubscript{3}):} \(\delta\) 11.01-12.08 (2 CH\textsubscript{3}), 21.06 (2 CH\textsubscript{2}), 23.97 (2 CH\textsubscript{2}), 44.78-55.67 (5 N-CH\textsubscript{2}), 56.62 (O-CH\textsubscript{3}), 62.06 (O-CH\textsubscript{2}), 107.86-154.45 (Ar-C) and 157.98 ppm (C=O).

\textbf{Cal. for C\textsubscript{24}H\textsubscript{33}N\textsubscript{5}O\textsubscript{4}:} C,63.29\%, H,7.31\%, N,15.38\%, O,14.05\%, \textbf{Found:} C 64.16\%, H 7.50\%, N 14.32\%.

\textbf{8-[4-\{2-(DIETHYLAMINO)-ETHOXY\}-3-METHOXYPHENYL]-1,3-DIPROPYLXANTHINE (RY-075, 174)}

\textbf{Yield:} 0.90 g, 90.45 \%, mp 117-120 °C (decomp.).

\textbf{Spectral and elemental analysis:}

\textbf{FTIR} \(\nu_{\text{max}}\) (KBr) cm\textsuperscript{-1}: 3565 (-NH), 2920 (Ali-CH), 1698 (carbonyl), 1649 (CN), 1516 (NH-bend), 1460 (Ar-C=C), 1259 (C-N), 1021 (C-O).
Experimental work

$^1$H-NMR (400 MHz, CDCl$_3$): δ 8.04 (s, 1H, -NH), 7.31 (s, 3H, Ar-H), 4.34 (s, 4H, -NCH$_2$), 4.06 (t, 2H, -NCH$_2$), 3.92 (t, 2H, -OCH$_2$), 3.88 (s, 3H, -OCH$_3$), 3.47 (s, 2H, -CH$_2$), 1.82-1.77 (q, 2H, -NCH$_2$), 1.67-1.61 (q, 2H, -NCH$_2$) and 0.97-0.91 ppm (q, 10H, 2 x -CH$_2$, 2 x -CH$_3$).

$^{13}$C-NMR (100 MHz, CDCl$_3$): δ 10.91 (CH$_3$), 11.04 (CH$_3$), 14.04 (2 CH$_3$), 20.80 (CH$_2$), 20.85 (CH$_2$), 42.13 (2 N-CH$_2$), 44.41-54.08 (3 N-CH$_2$), 47.40 (O-CH$_2$), 55.80 (O-CH$_3$), 113.81-151.74 (C=O) and 154.22 ppm (C=O).

Cal. for C$_{24}$H$_{35}$N$_5$O$_4$: C 63.00%, H 7.71%, N 15.31%, O 13.99%, Found: C 64.52%, H 6.67%, N 13.32%.

8-[4-{2-(PHTHALIMIDO)-ETHOXY}-3-METHOXYPHENYL]-1,3-DIPROPYL-XANTHINE (RY-077, 175)

Yield: 0.60 g, 60.24 %, mp 86-90 °C.

Spectral and elemental analysis:

FT-IR $\nu_{\text{max}}$ (KBr) cm$^{-1}$: 3028 (NH), 2961 (Ali-CH), 1768 (C=O), 1704 (C=O), 1648 (C=N), 1542 (NH-bend), 1462 (Ar-C=C), 1260 (C=N), 1088 (CO).

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.79 (s, 4H, Ar-H), 7.67 (s, 3H, Ar-H), 7.67 (s, 1H, -NH), 3.97 (s, 6H, 3 x -NCH$_2$), 3.70 (s, 5H, -OCH$_2$), 1.62 (s, 4H, 2 x -CH$_2$) and 0.92 ppm (s, 6H, 2x-CH$_3$).

$^{13}$C-NMR (100MHz, CDCl$_3$): δ 10.08 (CH$_3$), 11.01 (CH$_3$), 42.21 (CH$_2$), 39.45 (N-CH$_2$), 40.85 (N-CH$_2$), 56.62 (O-CH$_3$), 66.45 (O-CH$_2$), 107.07-156.62 (Ar-C), 158.04 (C=O) and 167.99 ppm (C=O).

Cal. for C$_{28}$H$_{29}$N$_5$O$_6$: C 63.28%, H 5.51%, N 13.19%, O 18.06%, Found: C 64.46%, H 6.03%, N 14.51%.

General procedure for the synthesis of 8-[3-(2-aminoethoxy)-4-methoxyphenyl]-1,3-dipropyl-xanthine derivatives (188-193)

Various amines such as 4-(2-chloroethyl)-amino hydrochlorides (1 g), [4-(2-chloroethyl)-morpholine hydrochloride (152, 5.36 mmol), 4-(2-chloroethyl)-piperidine hydrochloride (153, 5.42 mmol), 2-chloro-N,N-dimethyl ethanamine
Experimental work

(154, 6.93 mmol), 1-(2-chloroethyl)-pyrrolidine (155, 5.88 mmol), 2-chloro-\(N,N\)-diethyl ethanamine (156, 5.82 mmol) and 1-(2-chloroethyl)-phthalimide (157, 4.77 mmol) were added to the refluxing suspension of 3-methoxy-4-hydroxybenzaldehyde (150, 1 g, 6.58 mmol) in ethyl methyl ketone (20 ml). Dried potassium carbonate (3.0 g) was added to avoid incorporation of any moisture. After completion, suspension was filtered and reduced on rotary evaporator to afford targeted compounds 176-181.

To the stirred solution of 176-181 in ethanol (5 ml), added 5, 6-diamino-1,3-dipropyluracil (148, 1 g, 4.42 mmol) with ethanol and acetic acid (8:2, 10 ml) and refluxed for 12 h. After completion, excess amount of the solvent was reduced. Added ice cold water to the residue and filtered to afford 182-187.

The Schiff bases 182-187 (1 g) were refluxed in thionyl chloride (15 ml) for 1 h at 70-80°C. Excess solvent was reduced at rotary evaporator and residue so obtained was neutralized, to result in precipitation. The reaction mixture cooled, filtered off and washed with cold water to obtain the targeted compounds 188-193.

8-[3-(2-MORPHOLINOETHOXY)-4-METHOXYPHENYL]-1,3-DIPROPYL-XANTHINE (RY-079, 188)

Yield: 0.99 g, 99 %, mp 192-195 °C (decomp.).

Spectral and elemental analysis:

FT-IR \(\nu_{\text{max}}\) (KBr) cm\(^{-1}\): 3564 (NH), 3179 (CH), 2961 (CH), 1699 (C=O), 1654 (C=N), 1543 (NH), 1488 (Ar-C=C), 1262 (C-N), 1210 (C-O).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 11.43 (s, 1H, -NH), 7.59 (s, 1H, Ar-H), 6.84 (s, 2H, Ar-H), 4.28 (s, 3H, -OCH\(_3\)), 4.04 (s, 6H, 3 x -OCH\(_2\)-), 3.81 (s, 4H, 2 x -NCH\(_2\)-), 3.03 (m, 6H, 3 x -NCH\(_2\)-), 1.76 (s, 2H, -CH\(_2\)-), 1.60 (s, 2H, -CH\(_2\)-) and 0.89 ppm (s, 6H, 2 x CH\(_3\)).

\(^13\)C-NMR (100MHz, CDCl\(_3\)): \(\delta\) 10.08-11.10 (2 CH\(_3\)), 20.01 (2 CH\(_2\)), 44.72 (2 N-CH\(_2\)), 53.37-54.01 (3 N-CH\(_2\)), 56.20-62.01 (3 O-CH\(_2\)), 65.57 (O-CH\(_3\)), 112.51 (Ar-
Experimental work

(CH), 114.41-115.56 (2 Ar-C), 119.54 (2 Ar-CH), 123.47 (Ar-C), 146.98-151.08 (3 Ar-C), 149.94 (C=O) and 152.61 ppm (C=O).

Cal. for C_{24}H_{33}N_{5}O_{5}: C 61.13%, H 7.05%, N 14.85%, O 16.96%, Found: C 32.95%, H 4.58%, N 7.66%.

8-[3-(2-PIPERIDINOETHOXY)-4-METHOXYPHENYL]-1,3-DIPROPYL XANTHINE (RY-081; 189)

Yield: 0.99 g, 99.2 %, mp 199-202 °C (decomp).

Spectral and elemental analysis:

FT-IR_{\text{max}} (KBr)cm^{-1}: 3447 (NH), 3123 (CH), 2959 (CH), 1697 (C=O), 1652 (C=N), 1541 (NH), 1486 (Ar-C=C), 1260 (C-N), 1210 (CO).

^{1}H-NMR (400 MHz, CDCl_{3}): \delta 7.64 (s, 1H, Ar-H), 7.19 (s, 1H, Ar-H), 6.83 (s, 1H, Ar-H), 4.20 (s, 1H, -NH), 4.07 (s, 4H, 2x-NCH_{2}^{-}), 3.83 (s, 6H, 3x-NCH_{2}^{-}), 2.83 (s, 2H, -OCH_{2}^{-}), 2.54 (s, 3H, -OCH_{3}), 1.58 (s, 10H, 5x-CH_{3}) and 0.88 ppm (s, 6H, 2x-CH_{3}).

^{13}C-NMR (100 MHz, CDCl_{3}): \delta 11.25 (2 CH_{3}), 21.30 (2 CH_{2}), 23.97 (3 CH_{2}), 43.16 (2 N-CH_{2}), 45.20-55.03 (3 N-CH_{2}), 56.31 (O-CH_{3}), 66.80 (O-CH_{2}), 107.86 - 149.99 (Ar-C), 150.90 (C=O), and 157.98 ppm (C=O).

Cal. for C_{25}H_{35}N_{5}O_{4}: C 63.95%, H, 7.52%, N 14.81%, O 13.63% Found: C 64.42%, H 8.11%, N 13.76%.

8-[3-(2-(DIMETHYLAMINO)ETHOXY)-4-METHOXYPHENYL]-1,3-DIPROPYL XANTHINE (RY-083; 190)

Yield: 0.40 g, 40.81 %, mp 205-208 °C (decomp.).

Spectral and elemental analysis:

FT-IR_{\text{max}} (KBr)cm^{-1}: 3421 (NH), 3199 (CH), 2964 (CH), 1663 (C=O), 1650 (C=N), 1542 (NH), 1462 (Ar-C=C), 1259 (C-N), 1179 (C-O).
**Experimental work**

¹H-NMR (400 MHz, CDCl₃): δ 6.94 (s, 3H, Ar-H), 3.98 (m, 13H, -NH, 3 x -NCH₂⁻, 2 x -NCH₃), 1.81 (m, 3H, -OCH₃), 1.67 (m, 2H, -OCH₂⁻) and 0.96 ppm (m, 10H, 2 x -CH₂, 2x-CH₃).

¹³C-NMR (100MHz, CDCl₃): δ 10.08 (CH₃), 11.10 (CH₃), 21.07(CH₂), 23.01 (CH₂), 43.72 (N-CH₂), 45.05 (N-CH₂), 47.09 (2 N-CH₃), 54.01 (N-CH₂), 56.07 (O-CH₂), 66.57 (O-CH₃), 107.51-153.85 (Ar-C), 154.94 (C=O) and 157.61 ppm (C=O).

Cal. for C₂₂H₃₁N₅O₄: C 61.52%, H 7.27%, N 16.31%, O 14.90%.

Found: C 61.54%, H 6.75%, N 16.65%.

8-(3-[2-(PYRROLIDIN-1-YL)-ETHOXY]-4-METHOXYPHENYL]-1,3-DIPROPYL XANTHINE (RY-085; 191)

**Yield:** 0.84 g, 84.03 %, mp 145-148 °C (decomp.).

**Spectral and elemental analysis:**

FT-IR νmax (KBr) cm⁻¹: 3744 (NH), 2961 (Ali-CH), 1698 (C=O), 1655 (C=N), 1552 (NH-bend), 1519 (Ar-C=C), 1258 (C-N), 1181 (C-O).

¹H-NMR (400MHz, CDCl₃): δ 7.62 (s, 1H, Ar-H), 6.84 (s, 2H, Ar-H), 4.36 (s, 1H, -NH), 3.88 (s, 4H, 2 x -NCH₂⁻), 3.82 (s, 6H, 3 x -NCH₂⁻), 3.32 (s, 2H, -OCH₂⁻), 3.17 (s, 3H, -OCH₃), 1.76 (s, 4H, 2 x -CH₂⁻), 1.60 (s, 4H, 2 x -CH₂⁻) and 0.88 ppm (s, 6H, 2xCH₃).

¹³C-NMR (100MHz, CDCl₃): δ 11.01-12.08 (CH₃), 21.06 (CH₂), 23.97 (CH₂), 44.78-55.67 (N-CH₂), 56.62 (O-CH₃), 62.06 (O-CH₂), 107.86 -154.45 (Ar-C) and 157.98 ppm (C=O).

Cal. for C₂₄H₃₃N₅O₄: C 63.29%, H 7.31%, N 15.38%, O 14.05%.

Found: C 64.02%, H 6.15%, N 14.67%.

8-(3-[2-(DIETHYLAMINO)-ETHOXY]-4-METHOXYPHENYL)-1,3-DIPROPYL XANTHINE (RY-087, 192)

**Yield:** 0.99 g, 99 %, mp 185-188 °C (decomp.).

**Spectral and elemental analysis:**
FT-IR ν\(_{\text{max}}\) (KBr) cm\(^{-1}\): 3615 (NH), 2959 (All-CH), 1699 (C=O), 1651 (C=N), 1547 (NH), 1463 (Ar-C=C), 1257 (C-N), 1175 (C-O).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 11.26 (s, 1H, -N\(_2\)H), 6.87 (s, 3H, Ar-\(H\)), 3.87 (m, 10H, 5 x -NCH\(_2\)-), 1.70 (s, 2H, -OCH\(_3\)-), 1.48 (s, 3H, -OCH\(_3\)), 1.09 (s, 4H, 2 x -CH\(_2\)-) and 0.88 ppm (s, 12H, 4x-CH\(_3\)).

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 10.91 (CH\(_3\)), 11.04 (CH\(_3\)), 14.04 (CH\(_3\)), 20.80 (CH\(_2\)), 20.85 (CH\(_2\)), 42.13 (N-CH\(_2\)), 44.41-54.08 (3 N-CH\(_2\)), 47.40 (O-CH\(_2\)), 55.80 (O-CH\(_3\)), 113.81-151.55 (Ar-C), 151.74 (C=O) and 154.22 ppm (C=O).

Cal. for C\(_{24}\)H\(_{35}\)N\(_5\)O\(_4\): C 63.00%, H 7.71%, N 15.31%, O 13.99% Found: C 64.13%, H 7.20%, N 16.93%.

8-[3-{2-(PHthalimido)-ethoxy}-4-methoxyphenyl]-1, 3-dipropyl xanthine (RY-089; 193)

Yield: 0.80 g, 80.54 %, mp 266-270 °C (decomp.).

Spectral and elemental analysis:

FT-IR ν\(_{\text{max}}\) (KBr) cm\(^{-1}\): 3186 (NH), 2960 (CH), 1742 (carbonyl), 1694 (carbonyl), 1651 (C=N), 1525 (NH), 1490 (Ar-C=C), 1264 (C-N), 1145 (C-O).

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 13.25 (s, 1H, -N\(_2\)H), 8.99 (s, 1H, Ar-\(H\)), 7.92 (s, 1H, Ar-\(H\)), 7.55 (d, 2H, Ar-\(H\), \(J_{\text{orto}}\)= 7.48 Hz), 6.88 (d, 2H, Ar-\(H\), \(J_{\text{orto}}\)= 8.32 Hz), 4.01 (t, 2H, -NCH\(_2\)-, \(J_1\)=7.00, \(J_2\)=6.92), 3.87 (s, 2H, -NCH\(_2\)-), 3.85 (s, 2H, -NCH\(_2\)-), 3.82 (s, 3H, -OCH\(_3\)), 1.74 (m, 2H, -OCH\(_3\)-), 1.58 (m, 2H, -CH\(_2\)-) and 0.88 ppm (m, 8H, -CH\(_2\)-, 2 x -CH\(_3\)).

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 10.92 (CH\(_3\)), 11.03 (CH\(_3\)), 42.98 (2 CH\(_2\)), 39.45 (N-CH\(_2\)), 44.33 (2 N-CH\(_2\)), 55.45 (O-CH\(_3\)), 64.37 (O-CH\(_2\)), 107.07-119.91 (3 Ar-CH), 114.41 (Ar-C), 123.55 (Ar-C), 127.27 (2 Ar-CH), 132.33 (2 ArCH, 2 ArC), 146.63 (Ar-C), 149.98 (2 Ar-C), 151.02 (C=O), 156.62 (Ar-C), 158.04 (C=O) and 167.99 ppm (2 C=O).

Cal. for C\(_{28}\)H\(_{29}\)N\(_5\)O\(_6\): C 63.27%, H 5.50%, N 13.18%, O 18.06% Found: C 62.88%, H 5.33%, N 14.63%.
General procedure for the synthesis of 8-[4-(2-aminoethoxy)-phenyl]-1,3-dipropylxanthine derivatives (206-211)

Various amines such as 4-(2-chloroethyl)-amino hydrochlorides (1 g), [4-(2-chloroethyl)-morpholine hydrochloride (152, 5.36 mmol), 4-(2-chloroethyl)-piperidine hydrochloride (153, 5.42 mmol), 2-chloro-N,N'-dimethyl ethanamine (154, 6.93 mmol), 1-(2-chloroethyl)-pyrrolidine (155, 5.88 mmol), 2-chloro-N,N'-diethyl ethanamine (156, 5.82 mmol) and 1-(2-chloroethyl)-phthalimide (157, 4.77 mmol)] were added to the refluxing suspension of 3-methoxy-4-hydroxy-benzaldehyde (130, 0.83 g, 6.81 mmol) in ethyl methyl ketone (20 ml). Dried potassium carbonate (3.0 g) was added to avoid incorporation of any moisture. After completion, suspension was filtered and reduced on rotary evaporator to afford the targeted compounds 194-199.

To the stirred solution of 194-199 in ethanol (5 ml), added 5, 6-diamino-1,3-dipropyluracil (148, 1 g, 4.42 mmol) with ethanol and acetic acid (8:2, 10 ml) and refluxed. After completion, excess amount of the solvent was evaporated at rotary evaporator. Added ice cold water to the residue and filtered to afford 200-205.

The Schiff bases 200-205 (1 g) were refluxed in thionyl chloride (15 ml) for 1 h at 70-80°C. Excess solvent was reduced at rotary evaporator and residue so obtained was neutralized to result in precipitation. The reaction mixture was cooled, filtered off and washed with cold water to obtain desired derivatives 206-211.

8-[4-(2-MORPHOLINOETHOXY)-PHENYL]-1,3-DIPROPYLXANTHINE (RY-091, 206)

Yield: 0.90 g, 90.54 %, mp 140-145 °C (decomp.).

Spectral and elemental analysis:

FT-IR $\nu_{\text{max}}$(KBr) cm$^{-1}$: 3179 (NH), 2962 (Ali-CH), 1696 (C=O), 1646 (C=N), 1558 (NH), 1469 (Ar-C=C), 1247 (C-N), 1178 (C-O).
Experimental work

\[^1\]H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 12.75 (s, 1H, -NH), 8.35 (d, 1H, Ar-H, \(J_{\text{ortho}}=8.6\)), 8.21 (m, 1H, Ar-H), 7.48 (d, 1H, Ar-H, \(J_{\text{ortho}}=8.8\)), 7.00 (m, 1H, Ar-H), 4.10 (m, 10H, 5\(\times\) NCH\(_2\)), 3.70 (s, 6H, 3\(\times\) OCH\(_2\)), 1.83 (m, 4H, 2\(\times\) CH\(_2\)) and 1.03-0.89 ppm (m, 6H, 2\(\times\) CH\(_3\)).

\[^{13}\]C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 11.23 (CH\(_3\)), 11.45 (CH\(_3\)), 20.01 (CH\(_2\)), 21.35 (CH\(_2\)), 44.39 (2 N-CH\(_2\)), 54.02 (3 N-CH\(_2\)), 65.64 (2 O-CH\(_2\)), 66.08 (O-CH\(_2\)), 111.10 -156.41 (2 ArC) and 162.75 (C=O) and 168.05 ppm (C=O).

Cal. for C\(_{23}\)H\(_{31}\)N\(_5\)O\(_4\): C 62.57%, H 7.08%, N 15.86%, O 14.49%, Found: C 60.57%, H 6.18%, N 14.16%.

8-[4-(2-PIPERIDINOETHOXY)-PHENYL]-1,3-DIPROPYLXANTHINE (RY-093, 207)

Yield: 0.99 g, 99 %, mp 165-170 °C (decomp.).

Spectral and elemental analysis:

FT-IR\(v_{\text{max}}\) (KBr) cm\(^{-1}\): 3168 (NH), 2960 (Ali-CH), 1696 (carbonyl), 1648 (C=N), 1526 (NH-bend), 1468 (Ar-C=C), 1250 (C-O), 1180 (C-N).

\[^1\]H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.15 (d,2H, Ar-H, \(J_{\text{ortho}}=7.76\)Hz), 6.92 (d, 2H, Ar-H, \(J_{\text{ortho}}=7.24\)Hz), 4.37 (s, 1H, -NH-), 4.16-4.01 (m, 2H, -OCH\(_2\)-), 3.15-2.77 (m,10H, -5 \(\times\) NCH\(_2\)-), 1.85-1.55 (m, 10H, 5 \(\times\) CH\(_2\)), 1.01-0.89 (m, 6H, 2xCH\(_3\)).

\[^{13}\]C NMR (100MHz, CDCl\(_3\)): \(\delta\) 10.20-10.38 (CH\(_3\)), 20.30 (CH\(_2\)), 25.52 (CH\(_2\)), 44.56 (N-CH\(_2\)), 53.75 (N-CH\(_2\)), 65.64 (O-CH\(_2\)), 108.23-151.41 (Ar-C), 155.75 (C=O) and 159.05 ppm (C=O).

Cal. for C\(_{24}\)H\(_{33}\)N\(_5\)O\(_3\): C 65.58%, H 7.57%, N 15.93%, O 10.92%, Found: C 64.98%, H 7.01%, N 14.97%.

8-[4-{2-(DIMETHYLAMINO)-ETHOXY}-PHENYL]-1,3-DIPROPYLXANTHINE (RY-095; 208)

Yield: 0.99 g, 99 %, mp 160-162 °C (decomp.).

Spectral and elemental analysis:
FT-IRv_{max} (KBr) cm^{-1}: 3564 (NH), 3110 (Ar-CH), 2961 (Ali-CH), 1696 (C=O), 1645 (C=N), 1540 (NH), 1459 (H-C=C-H), 1255 (C-N), 1176 (C-O)

¹H-NMR (400 MHz, CDCl₃): δ 13.01 (s, 1H, -NH), 8.20 (s, 2H, Ar-H), 7.45 (s, 1H, Ar-H), 6.98 (s, 1H, Ar-H), 4.06 (s, 6H, 2 x -NCH₃), 3.14 (m, 2H, -OC₂H₅), 1.77 (s, 6H, 3 x -NCH₂-) and 0.92-0.60 ppm (s, 10H, 2 x CH₃, 2xCH₃)

¹³C-NMR (100MHz, CDCl₃): δ 10.37 (C₃H₃), 11.53 (CH₃), 21.24 (2 CH₂), 43.66 (2 N-CH₂), 45.80 (2 N-CH₃), 57.70 (N-CH₂), 65.64 (O-CH₂), 115.23 (Ar-C), 121.67 (Ar-C), 150.89 (Ar-C), 152.41 (2 Ar-C), 119.10 (2 Ar-CH), 132.90 (2 Ar-CH), 151.75 (C=O) and 156.05 ppm (C=O).

Cal. for C₂₁H₂₉N₅O₃: C 63.14%, H 7.32%, N 17.53%, O 12.01%, Found: C 60.14%, H 6.82%, N 16.83%.

8-[4-(2-PYRROLIDINOETHOXY)-PHENYL]-1,3-DIPROPYLXANTHINE (RY-097, 209)

Yield: 0.99 g, 99 %, mp 170-176 °C (decomp.).

Spectral and elemental analysis:

FT-IR v_{max} (KBr) cm^{-1}: 3564 (NH), 3175 (CH), 2960 (CH), 1696 (C=O), 1645 (C=N), 1540 (NH), 1459 (H-C=C-H), 1255 (C-N), 1176 (C-O).

¹H-NMR (400MHz, CDCl₃): δ 8.19 (s, 2H, Ar-H), 6.98 (s, 2H, Ar-H), 4.31 (s, 1H, -N H), 4.15-4.05 (m, 10H, 5 x -NCH₂), 3.20-2.98 (m, 2H, -OCH₂), 1.96 (s, 4H, 2 x -CH₂), 1.84 (m, 2H, -CH₂), 1.71 (m, 2H, -CH₂) and 1.01-0.94 ppm (m,6H, 2xCH₃).

¹³C-NMR (100MHz, CDCl₃): δ 11.25 (CH₃), 11.49 (CH₃), 20.08 (CH₂), 21.36 (CH₂), 25.56 (2 CH₂), 44.05 (2 N-CH₂), 54.08-56.67 (3 N-CH₂), 66.07 (O-CH₂), 108.31 (Ar-C), 114.67 (2 Ar-CH), 128.89 (2 Ar-CH), 121.45 (Ar-C), 149.96 (Ar-C), 152.87 (C=O), 156.08 (2 Ar-C) and 156.78 ppm (C=O).

Cal. for C₂₃H₃₁N₅O₃: C, 64.93%, H 7.35%, N 16.47%, O 11.29%, Found: C 65.34%, H 8.31%, N 15.12%.
8-[4-{2-(DIETHYLAMINO)-ETHOXY}-PHENYL]-1,3-DIPROPYLXANTHINE (RY-099, 210)

Yield: 0.99 g, 99 %, mp 160-162 °C (decomp.).

Spectral and elemental analysis:

FT-IR $\nu_{\text{max}}$(KBr) cm$^{-1}$: 3647 (NH), 3174 (Ar-CH), 2961 (Ali-CH), 1695 (C=O), 1648 (C=N), 1554 (NH), 1468 (Ar-C=C), 1249 (C-O), 1178 (C-N)

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 12.75 (s, 1H, -NH), 8.16 (m, 2H, Ar-H), 6.95 (m, 2H, Ar-H), 4.48 (s, 2H, OCH$_2$), 4.30-3.86 (m, 4H, 2 x -NCH$_2$), 3.45-3.23 (s, 2H, -NC$_2$H$_5$), 1.84-1.69 (m, 4H, 2 x -NCH$_2$), 1.39-1.25 (s, 4H, 2 x -CH$_2$) and 0.99 ppm (m, 12H, 4xCH$_3$).

$^{13}$C-NMR (100MHz, CDCl$_3$): $\delta$ 10.08-11.24 (2 CH$_3$), 13.08 (2 CH$_3$), 20.08 (CH$_2$), 21.34 (CH$_2$), 44.03-53.78 (5 N-CH$_2$), 66.07 (O-CH$_2$), 107.89 (Ar-C), 114.67 (2 Ar-CH), 121.45 (Ar-C), 128.89 (2 Ar-CH), 150.04 (Ar-C), 152.87 (C=O), 156.08 (2 Ar-C) and 156.78 ppm (C=O).

Cal. for C$_{23}$H$_{33}$N$_5$O$_3$: C 64.61%, H 7.78%, N 16.38%, O 11.23%, Found: C 62.61%, H 8.08%, N 16.38%.

8-[4-{2-(PHTHALIMIDO)-ETHOXY}-PHENYL]-1,3-DIPROPYLXANTHINE (RY-101, 211)

Yield: 0.99 g, 99 %, mp > 280 °C.

Spectral and elemental analysis:

FT-IR $\nu_{\text{max}}$(KBr) cm$^{-1}$: 3316 (NH), 3192 (CH), 2963 (CH), 1693 (carbonyl), 1644 (C=N), 1560 (NH), 1476 (H-C=C-H), 1271 (C-O), 1178 (C-N).

$^1$H-NMR (400 MHz, DMSO-$_d_6$): $\delta$ 13.28 (s, 1H, -NH), 7.98 (s, 4H, Ar-H), 6.84 (s, 4H, Ar-H), 4.05 (s, 2H, -OCH$_2$), 3.91 (s, 6H, 3 x -NCH$_2$), 1.79-1.63 (m, 4H, -2CH$_2$), 0.94 (t, 6H, 2 x -CH$_3$), $J_1$=6.16, $J_2$=6.12).

$^{13}$C-NMR (100 MHz, DMSO-$_d_6$): $\delta$ 10.8-11.01 (2 CH$_3$), 20.02 (2 CH$_2$), 39.04-44.89 (3 N-CH$_2$), 66.04 (O-CH$_2$), 114.32 (2 Ar-CH, Ar-C), 123.76 (Ar-C), 128.05
Experimental work

(4 Ar-CH), 131.44 (2 Ar-CH), 132.24 (2 Ar-C), 150.78 (Ar-C), 152.04 (C=O), 156.04 (2 Ar-C), 156.87 (C=O) and 167.09 ppm (2 C=O).

**Cal. for C\textsubscript{27}H\textsubscript{27}N\textsubscript{5}O\textsubscript{5}:** C 64.66%, H 5.43%, N 13.96%, O 15.95%, **Found:** C 66.59%, H 5.76%, N 14.72%.

**General procedure for the synthesis of various 8-[3-(2-amino ethoxy)-phenyl]-1,3-dipropylxanthine derivatives (224-229)**

Various amines such as 4-(2-chloroethyl)-amino hydrochlorides (1 g), [4-(2-chloroethyl)-morpholine hydrochloride (152, 5.36 mmol), 4-(2-chloroethyl)-piperidine hydrochloride (153, 5.42 mmol), 2-chloro-N,N'-dimethyl ethanamine (154, 6.93 mmol), 1-(2-chloroethyl)-pyrrolidine (155, 5.88 mmol), 2-chloro-N,N'-diethyl ethanamine (156, 5.82 mmol) and 1-(2-chloroethyl)-phthalimide (157, 4.77 mmol)] were added to the refluxing suspension of 3-methoxy-4-hydroxy-benzaldehyde (151, 1 g, 8.20 mmol) in ethyl methyl ketone (20 ml). Dried potassium carbonate (3.0 g) was added to avoid incorporation of any moisture. After completion, suspension was filtered and reduced on rotary evaporator to afford the targeted compounds 212-217.

To the stirred solution of 194-199 in ethanol (5 ml), added 5, 6-diamino-1,3-dipropyluracil (148, 1 g, 4.42 mmol) with ethanol and acetic acid (8:2, 10 ml) and refluxed. After completion, excess amount of the solvent was evaporated at rotary evaporator. Added ice cold water to the residue and filtered to afford 218-223.

The Schiff bases 218-223 (1 g) were refluxed in thionyl chloride (15 ml) at 70-80 °C for 1 h. Excess solvent was reduced under vacuum and residue so obtained was neutralized to result in precipitation. The reaction mixture was cooled, filtered and washed with cold water to obtain desired derivatives 224-229.

**8-[3-(2-MORPHOLINOETHOXY)-PHENYL]-1,3-DIPROPYLXANTHINE (RY-103, 224)**

**Yield:** 0.50 g, 50.42 %, mp 150-155 °C (decomp.).
Spectral and elemental analysis:

FT-IR $\nu_{\text{max}}$ (KBr) cm$^{-1}$: 2962 (Ar-CH), 1701 (carbonyl), 1655 (CN), 1548 (Ar-C=C), 1258 (CO).

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.45 (s, 2H, Ar-H), 7.03 (m, 2H, Ar-H), 4.06 (m, 4H, -2OCH$_2$-), 2.09 (m, 1H, NH), 1.76 (m, 2H, -OCH$_2$-), 1.69 (m, 4H, 2 x -NCH$_2$-), 1.41 (m, 2H, -NH$_2$), 1.25 (m, 2H, -CH$_2$-), 0.95 (m, 6H, 3 x -CH$_2$), 0.07 (m, 6H, -2 x -CH$_3$).

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 10.08-11.01 (2 CH$_3$), 20.01 (2 CH$_2$), 44.39 (2 N-CH$_2$), 54.02 (3 N-CH$_2$), 65.64 (2 O-CH$_2$), 66.08 (O-CH$_2$), 111.10 -156.41 (ArC) and 162.75 (C=O) and 168.05 ppm (C=O).

Cal. for C$_{23}$H$_{31}$N$_5$O$_4$: C 62.57%, H 7.08%, N 15.86%, O 14.49%, Found: C 60.57%, H 6.18%, N 14.16%.

8-[3-(2-PIPERIDINOETHOXY)-PHENYL]-1,3-DIPROPYLXANTHINE (RY-105, 225)

Yield: 0.40 g, 40.27 %, mp 180-185 °C (decomp.).

Spectral and elemental analysis:

FT-IR $\nu_{\text{max}}$ (KBr) cm$^{-1}$: 3196 (-NH), 2933 (Ar-CH), 2787 (Ali-CH), 1698 (carbonyl), 1655 (CN), 1553 (H-C=C-H), 1259 (CO), 1186 (C-N).

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.83 (d, 2H, Ar-H), 7.37 (s, 1H, Ar-H), 7.00 (s, 1H, Ar-H), 4.17 (m, 6H, 3 x -NCH$_2$-), 2.92 (s, 2H, -OCH$_2$-), 2.65 (s, 4H, 2 x -NCH$_2$-), 1.86 (s, 2H, -CH$_2$), 1.68 (s, 6H, 3 x -CH$_2$), 1.49 (s, 2H, -CH$_2$), 1.01 (m, 6H, 2xCH$_3$).

$^{13}$C-NMR (100MHz, CDCl$_3$): $\delta$ 11.37-11.53 (2 CH$_3$), 21.24-25.56 (5 CH$_2$), 47.28-57.70 (5 N-CH$_2$), 65.64 (O-CH$_2$), 108.23-151.41 (5 Ar-C), 119.10 (2 Ar-CH), 129.90 (2 Ar-CH), 155.75 (C=O) and 159.05 ppm (C=O).

Cal. for C$_{24}$H$_{33}$N$_5$O$_3$: C 65.58%, H 7.57%, N 15.93%, O 10.92%, Found: C 64.98%, H 7.01%, N 14.97%.
8-[3-{2-(DIMETHYLAMINO)-ETHOXY}-PHENYL]-1,3-DIPROPYLXANTHINE (RY-107, 226)

Yield: 0.86 g, 86.33 %, mp >280 °C (decomp.).

Spectral and elemental analysis:

FT-IR ν\text{max.} (KBr) cm\(^{-1}\): 3177 (-NH), 2960 (Ar-CH), 1695 (C=O), 1653 (C=N), 1550 (Ar-C=C), 1256 (C-O), 1175 (C-N).

\(^1\)H-NMR (400 MHz, DMSO-\text{d}_6): δ 7.30-6.91 (m, 4H, Ar-H), 4.01-3.83 (m, 4H, -OCH\(_2\), -NCH\(_2\)), 1.93-1.55 (m, 4H, 2 x -NCH\(_2\)), 1.80 (s, 4H, 2 x -CH\(_2\)), 0.85 (s, 12H, 2 x -NCH\(_3\), 2 x -CH\(_3\)).

\(^{13}\)C-NMR (400 MHz, DMSO-\text{d}_6): δ 10.37-11.53 (2 CH\(_3\)), 21.24 (2 CH\(_2\)), 43.66 (2 N-CH\(_2\)), 45.80 (2 N-CH\(_3\)), 57.70 (N-CH\(_2\)), 65.64 (O-CH\(_2\)), 115.23-152.41 (5 Ar-C), 119.10-132.90 (4 Ar-CH) and 151.75-156.05 ppm (2 C=O).

Cal. for C\(_{21}\)H\(_{29}\)N\(_5\)O\(_3\): C 63.14%, H 7.32%, N 17.53%, O 12.01%, Found: C 60.14%, H 6.82%, N 16.83%.

8-[3-(2-PYRROLIDINOETHOXY)-PHENYL]-1,3-DIPROPYLXANTHINE (RY-109, 227)

Yield: 0.99 g, 99 %, mp 230-235 °C (decomp.).

Spectral and elemental analysis:

FTIR ν\text{max.} (KBr) cm\(^{-1}\): 3223 (-NH), 2962 (Ar-CH), 1694 (C=O), 1648 (C=N), 1451 (Ar-C=C), 1254 (C-N).

\(^1\)H-NMR (400MHz, DMSO-\text{d}_6): δ 13.76 (s, 1H, -NH), 7.31 (m, 4H, Ar-H), 4.42 (s, 2H, -OCH\(_2\)), 3.96 (s, 6H, 3 x -NCH\(_2\)), 3.89 (s, 4H, 2 x NCH\(_2\)), 2.08 (d, 4H, 2 x -CH\(_2\)), 1.77 (d, 4H, 2 x -CH\(_2\)) and 0.91 ppm (s, 6H, 2 x -CH\(_3\)).

\(^{13}\)C-NMR (100 MHz, DMSO-\text{d}_6): δ 10.08-11.01 (2 CH\(_3\)), 20.08-25.56 (4 CH\(_2\)), 44.05 (2 N-CH\(_2\)), 54.08-56.67 (3 N-CH\(_2\)), 66.07 (O-CH\(_2\)), 114.67-128.89 (4 Ar-CH, Ar-C), 121.45 (Ar-C), 150.04 (Ar-C), 152.87 (C=O), 156.08 (2 Ar-C) and 156.78 ppm (C=O).
Cal. for C\textsubscript{23}H\textsubscript{33}N\textsubscript{5}O\textsubscript{3}: C 64.93\%, H 7.35\%, N 16.47\%, O 11.28\%, Found: C 65.34\%, H 8.31\%, N 15.12\%.

8-[3-{2-(DIETHYLAMINO)-ETHOXY}-PHENYL]-1,3-DIPROPYLXANTHINE (RY-111, 228)

Yield: 0.76 g, 76.92 \% mp 100-105 °C (decomp.).

Spectral and elemental analysis:

FTIR $\nu_{\text{max}}$ (KBr) cm$^{-1}$: 3181 (NH), 2961 (CH), 1743 (carbonyl), 1696 (C=O), 1651 (cyano), 1549 (H-C=C-H), 1257 (C-N).

$^1$HNMR (400 MHz, DMSO-d$_6$): δ 13.72 (s, 1H, -NH), 7.8 (m, 1H, Ar-H), 7.40 (m, 2H, Ar-H), 7.05 (m, 1H, Ar-H), 4.40 (m, 2H, -OCH\textsubscript{2}-), 4.07 (t, 2H, 2 x -NCH\textsubscript{2}-), 3.92 (m, 4H, 2 x -NCH\textsubscript{2}-), 1.79 (q, 4H, 2 x -NCH\textsubscript{2}-), 1.30 (m, 6H, 2 x -CH\textsubscript{3}) and 0.93 ppm (m, 8H, 2 x -CH\textsubscript{3}).

$^{13}$CNMR (100 MHz, DMSO-d$_6$): δ 10.08-11.01 (2 CH\textsubscript{3}), 13.08 (2 CH\textsubscript{3}), 20.08 (2 CH\textsubscript{2}), 44.03-53.78 (5 N-CH\textsubscript{2}), 66.07 (O-CH\textsubscript{2}), 114.67-150.04 (Ar-C), and 156.78 ppm (C=O).

Cal. for C\textsubscript{23}H\textsubscript{33}N\textsubscript{5}O\textsubscript{3}: C 64.61\%, H 7.78\%, N 16.38\%, O 11.23\%, Found: C 62.61\%, H 8.08\%, N 16.38\%.

8-[3-{2-(PTHALIMIDO)-ETHOXY}-PHENYL]-1,3-DIPROPYLXANTHINE (RY-113, 229)

Yield: 0.80 g, 80.69 \%, mp 274-280 °C (decomp.).

Spectral and elemental analysis:

FT-IR $\nu_{\text{max}}$ (KBr) cm$^{-1}$: 3192 (-NH-), 2963 (Ar-CH-), 2876 (Ali-CH-), 1695 (C=O), 1644 (C=N), 1464 (Ar-C=C), 1262 (C-N), 1186 (C-O).

$^1$H-NMR (400 MHz, CDCl$_3$): δ 13.66 (s, 1H, -NH), 7.56 (m, 2H, Ar-H), 7.25 (t, 3H, Ar-H, $J_{\text{ortho}}=7.88$Hz, $J_{\text{ortho}}=7.84$Hz), 6.87 (d, 2H, Ar-H, $J_{\text{para}}=1.96$Hz), 6.85 (d, 1H, Ar-H, $J_{\text{para}}=1.59$Hz), 4.05 (t, 2H, -OCH\textsubscript{2}-, $J_1=7.00$, $J_2=7.48$), 3.90 (t, 2H, -NCH\textsubscript{2}-, $J_1=7.32$, $J_2=7.52$), 1.77 (m, 4H, 2 x NH\textsubscript{2}-), 1.61 (m, 4H, 2 x -CH\textsubscript{2}-) and 0.93 ppm (m, 6H, 2x-CH\textsubscript{3}).
$^{13}$CNMR (100MHz, CDCl$_3$): δ 10.8-11.01 (2 CH$_3$), 20.02 (2 CH$_2$), 39.04-44.89 (3 N-CH$_2$), 66.04 (O-CH$_2$), 114.32 (2 Ar-CH, Ar-C), 123.76 (Ar-C), 128.05 (4 Ar-CH), 132.44 (2 Ar-CH, 2 Ar-C), 150.78 (Ar-C), 152.04 (C=O), 156.04 (2 Ar-C), 156.87 (C=O) and 167.09 ppm (2 C=O).

Cal. for C$_{27}$H$_{27}$N$_5$O$_5$: C 64.66%, H 5.43%, N 13.96%, O 15.95%, Found: C 62.15%, H 6.13%, N 14.16%.

BIOLOGICAL ACTIVITY

Bronchospasmolytic activity (in vivo)

Experimental animals

Guinea-pigs (Male; Dunkin Hartley) of 220-280 g, were obtained from LLRUAS, Hisar after the approval of IAEC, Banasthali University (BV/IAEC/2016/I dated 08.10.2016, Ref. No. BV/3421/16-17). The experimental animals so procured were kept in standard conditions as prescribed with proper food and water. They were monitored for 12 h day and night cycle for experimentation.

Drugs used

Histamine hydrochloride (bronchospasm agent), theophylline (standard drug), carboxymethyl cellulose (suspending agents) and test compounds (synthesized compound).

Experimental protocol

Guinea pigs (n =5) were designated as I for control animals (fed with carboxymethyl cellulose and water); II for positive animals (carboxymethyl cellulose, theophylline and water) and III for test animals (carboxymethyl cellulose, test drug and water). The assigned animal groups were allowed for fasting before treatment. The experimental animals were exposed in histamine chamber with histamine aerosol for 5 min after dosing of 1 h. Prior to exposure; animals received test drug (50 mg/kg), theophylline (50 mg/kg) and carboxymethyl cellulose orally, respectively. Different in vivo pharmacological behaviors of each animal was observed such as bronchospasm, jerks, death or survival. The animals were allowed to remain in the chamber for 15 min, if survived, animals were removed from the chamber and placed in fresh atmosphere with proper diet.