Synthesis of 3-benzylxanthine and lumazine analogues

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Several xanthines (**7–13**) are prepared by the cyclisation of 1-benzyl-5,6-diaminouracil with single-carbon inserting agents such as aromatic aldehydes, formamides, acetic anhydride, carbon disulfide, and nitrous acid. Treatment of 6-amino-1-benzyl-5-nitrosouracil with anilinobenzylidene derivatives (**14–18**) affords 7-hydroxyxanthines (**19–23**). Cyclisation of the diaminouracil **3** with glyoxal, benzil, and diethyl oxalate leads to lumazines (**25–28**).

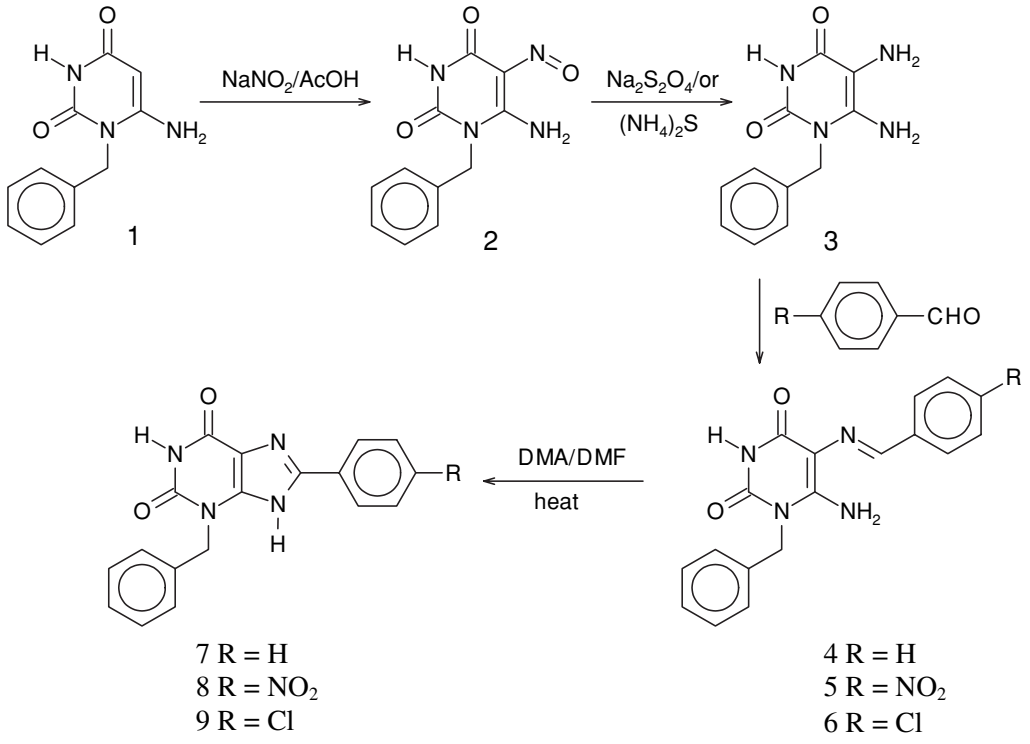
Keywords: uracils; xanthines, lumazines, fused 1,2,3-triazoles, fused pyrimidines

Various biological activities have been reported for xanthine and lumazine derivatives.[1-5] Many of the potential anti-HIV drugs for the acquired immunodeficiency syndrome are of the nucleoside types. The partially substituted heterocyclic compounds are important as bases for the nucleoside synthesis.[6] Hence, some 3-benzylxanthine and lumazine analogues are expected to exhibit biological activities and serve as precursors for the nucleosides. The 6-amino-5-nitrosouracils[7-14] and 5,6-diaminouracils[13, 15, 16] derivatives are the most important and useful key intermediates for the synthesis of fused pyrimidines. Further, the 5-benzylideneaminouracil derivatives are cyclised easily to xanthines using mild oxidising agents such as iodine[17] and sodium periodate.[18]

Results and discussion

We report a convenient sequence starting with 6-amino-1-benzyluracil[19, 20] (**1**) by reaction with sodium nitrite in acetic acid to afford the 5-nitroso analogue **2**,[13] which upon reduction afforded 1-benzyl-5,6-diaminouracil[13] (**3**). Condensation of various aldehydes with compound **3** in ethanol at room temperature gave the corresponding Schiff bases **4–6** in good yield, which upon refluxing with DMF in presence of dimethylamine (DMA) afforded 3-benzylxanthines **7–9** (Scheme 1). The suggested structures of the compounds were supported by their ^{1}H NMR spectra. Compound **7** showed a singlet at δ 5.18 due to the benzyl methylene group and two signals at 10.94 and 13.70 ppm for NH(1) and NH(9), respectively, in addition to the multiplet for the aromatic protons centred at δ 7.23. The disappearance of the benzylidene CH proton, which appeared in its precursor **4** at δ 9.70, confirmed the successful cyclisation. The ^{13}C NMR spectra showed 14 signals, in agreement with the suggested structure.

3-Benzylxanthine (**10**) has been prepared by treatment of diaminouracil **3** with triethyl orthoformate[13] and by the oxidation of 3-benzyl-2-methylthiopurin-6-one by hydrogen peroxide in acetic acid, followed by hydrolysis.[8] 3-Benzyl-8-azaxanthines and 8-thioxanthines have been prepared by



Scheme 1

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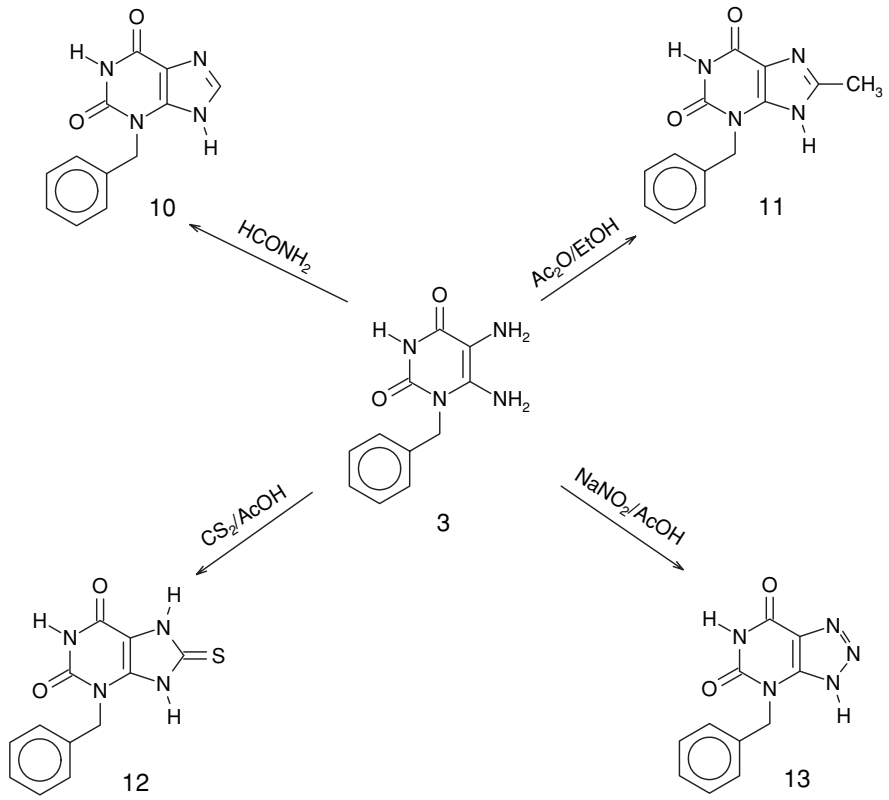


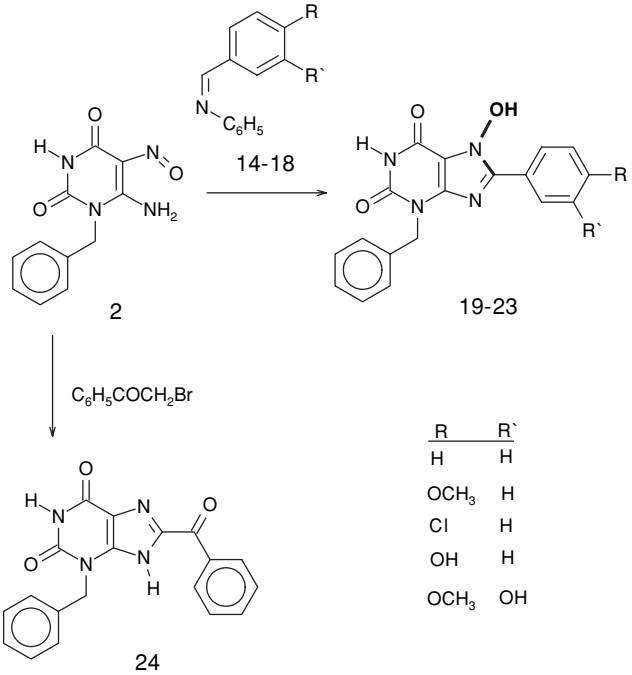
Scheme 2

the alkylation of 8-azaxanthines[9] and the displacement of 8-bromoxanthine by NaSH,[11] respectively. In this work, one-carbon insertion into the diaminouracil **3** has been achieved using formamide, or acetic anhydride in ethanol, whereby the cyclisation in **3** gave the imidazolopyrimidine **10** and its 8-methyl analogue **11,** respectively. Reaction of **3** with carbon disulfide in acetic acid gave 3-benzyl-8-thioxanthine (**12**), and 3-benzyl-8-azaxanthine (**13**) was prepared by the addition of nitrous acid to compound **3** (Scheme 2). The structures of the compounds were based on their spectral analysis. All the spectra show a multiplet centred at 7.23 corresponding to the aromatic protons. The ^{1}H NMR spectrum of **10** showed a singlet at δ 8.0 due to CH-8, and the two NH-1 and NH-9 protons appeared at δ 11.18 and 14.29 ppm, respectively. Compound **11** showed a singlet at δ 2.35 for methyl-8, and two singlets for NH-1, NH-9 protons at δ 11.06 and 13.15 respectively. Compound **12** showed three singlets for NH-1, NH-7 and NH-9 protons at δ 11.93, 13.02, and 13.48, respectively. Compound **13** showed the two singlets for NH-1, NH-9 protons at δ 11.58 and 15.88, respectively.

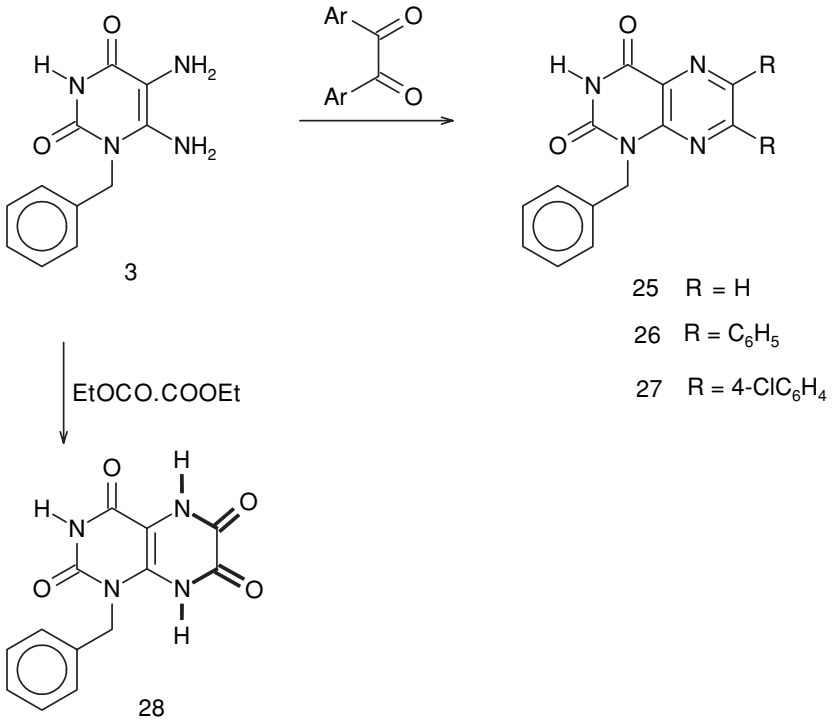
The oxidation of guanine by peroxy acids produced purine-*N*-oxide[21, 22] and then 7-hydroxyxanthine.[23] The 7-hydroxyxanthine and its 8-alkyl- or 8-aryl derivatives were prepared from 6-amino-5-nitrosouracils by the reaction with aliphatic or aromatic aldehydes.[7,24-27] Due to the various biological activities[21] exhibited by these compounds, we present herein a versatile synthetic procedure for 8-aryl-3-benzyl-7-hydroxyxanthines (**19–23**) via a transamination process using aldehyde-anils **14–18**. Thus, reaction of **14–18** with 6-amino-1-benzyl-5-nitrosouracil (**2**) took place by the elimination of aniline to give **19–23** (Scheme 3). The ^{1}H NMR spectra of compounds **19–23** showed a characteristic singlet for N-OH-7 at δ 13.52–13.86, NH-1 at δ 11.13–11.22 and NCH_2-3 protons at δ 5.15–5.19.

The reaction of compound **2** with phenacyl bromide in the presence of $ZnCl_2$ led to the formation of 8-benzoyl-3-benzylxanthine **24**. The ^{1}H NMR spectrum indicated the presence of signals at δ 12.73 characteristic of NH-9 of the imidazole ring and δ 11.93 for the NH-1 of the pyrimidine ring. The benzyl methylene group appeared at 5.39 ppm. There was no signal attributable to the CH_2 of a phenacyl group, indicating that the cyclisation had taken place.

Various methods for the synthesis of 6-substituted pteridines have been reported by the condensation of 5, 6-diaminopyrimidines with two-carbon sources,[11,28] or by the



Scheme 3



Scheme 4

treatment of pyrazine derivatives with ethyl chloroformate.[29] The route which involves an intramolecular cycloaddition of 2,5-diazahexatriene is remarkable for its potential selectivity and simplicity, and is applicable to various aryl groups. Reaction of 5-arylideneamino-6-amino-1,3-dimethyluracils with an excess of triethyl orthoformate in DMF gave 6-aryl-1,3-dimethyllumazines.[30-32] In this work, the condensation of 1-benzyl-5,6-diaminouracil (**3**) with dicarbonyl compounds such as glyoxal, benzil and 4,4'-dichlorobenzil in ethanol in the presence of triethylamine (TEA) led to lumazines **25–27** (Scheme 4). The ^{1}H NMR spectrum of compound **25**[11] was in agreement with the suggested structure showing a singlet at δ 10.54 for NH-3 and two singlets for methine CH-6 and 7 protons at δ 8.86 and 8.56, respectively. The aromatic protons showed a multiplet centred at δ 7.28 ppm and methylene protons of the benzyl at δ 5.34. On the other hand, the reaction of compound **3** with diethyl oxalate led to the formation of lumazine-6,7-dione **28**. The ^{1}H NMR spectrum of **28** showed a broad signal at δ 11.73 for 2 NH-5, 8, a singlet at δ 11.51 for NH-3 of the pyrimidine ring, aromatic protons at δ 7.31, and a singlet at δ 5.23 for the benzyl methylene group.

Experimental

Melting points were determined using an Electrothermal Mel-Temp II apparatus. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer in DMSO-d_6 and TMS as an internal standard (chemical shifts in δ, ppm). Elemental analyses were obtained at the Microanalytical Centre, Cairo University, Giza, Egypt.

6-Amino-1-benzyluracil (**1**): This compound was prepared according to a reported method.[19,20]

6-Amino-1-benzyl-5-nitrosouracil (**2**):[13] A mixture of acetic acid (3.0 ml) and sodium nitrite (3.0 g, 4.60 mmol) in water (2.0 ml) were added dropwise to 6-amino-1-benzyluracil (**1**) (1.0 g, 4.60 mmol) suspended in water (20 ml) with stirring at room temperature. The violet crystals were separated by filtration and dried in vacuum to give 0.88g (78%), m.p. 215–217 °C (dec.). ^{1}H NMR (DMSO-d_6): δ 13.46 (s, 1H, =NH), 11.76 (s, 1H, NH), 9.21 (s, 1H, N–O–H), 7.30 (m, 5H, aromatic), 5.17 (s, 2H, CH_2).

1-Benzyl-5,6-diaminouracil (**3**): *Method A*:[13] A solution of $Na_2S_2O_4$ (6.5 g, 37.3 mmol) in 15 ml of H_2O was added slowly to compound **2** (1.9 g, 7.7 mmol) in NaOH (40 ml, 2N) with stirring for 15 minutes at room temperature. The reaction mixture was neutralised using acetic acid (8.0 ml). The formed precipitate was collected by filtration, washed by ether, and dried in a vacuum desiccator to give 1.7 g (95%), m.p. 250–252 °C.

Method B: Compound **2** (2.0 g, 8.12 mmol) was added over 15 minutes to $(NH_4)_2S$ solution (14.0 ml) at 70–80 °C with stirring. The formed precipitate was collected by filtration, washed with ether and dried in a vacuum desiccator to give 1.7 g (90%).

6-Amino-1-benzyl-5-(arylmethyleneamino)uracils (**4–6**): *General method:* 1-Benzyl-5,6-diaminouracil (**3**) (0.4 g, 1.7 mmol) was dissolved in absolute ethanol (15 ml) and the aromatic aldehydes (1.7 mmol) benzaldehyde, 4-nitrobenzaldehyde, or 4-chlorobenzaldehyde were added with stirring at room temperature for 30 min. The product was collected by filtration, washed with methanol and recrystallised from a mixture of methanol/DMF (2:1)

6-Amino-1-benzyl-5-benzylidenaminouracil (**4**): M.p. 310–312 °C; yield 0.46 g (84%). ^{1}H NMR: δ 10.89 (s, 1 H, NH), 9.70 (s, 1 H, HC=), 7.88 (d, 2 H, NH_2), 7.81 (m, 10 H, 2 Ph), 5.21 (s, 2 H, CH_2). ^{13}C NMR: δ 44.9 (CH_2), 98.9, 124.1, 126.2, 127.1, 128.3, 128.4, 136.1, 138.4, 144.0, 146.9, 149.3, 154.0, 157.9. Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.48. Found: C, 67.39; H, 4.97; N, 17.15 %.

6-Amino-1-benzyl-5-(4-nitrobenzylidenamino)uracil (**5**): M.p. 293–295 °C; yield 0.43 g (79%). ^{1}H NMR: δ 11.00 (s, 1H, NH), 9.79 (s, 1 H, HC=), 8.19 (d, 2 H, 2 aromatic-H), 8.15 (d, 2 H, 2 aromatic-H), 7.59 (s, 2 H, NH_2), 7.34 (m, 5 H, Ph), 5.25 (s, 2 H, CH_2). ^{13}C NMR: δ 44.6 (CH_2), 99.6, 123.6, 126.3, 127.2, 127.8, 128.5, 136.0, 144.8, 146.3, 146.9, 149.2, 154.8, 157.9. Calcd. for $C_{18}H_{15}N_5O_4$: C, 59.17; H, 4.13; N, 19.16. Found: C, 59.04; H, 4.11; N, 18.97 %.

6-Amino-1-benzyl-5-(4-chlorobenzylidenamino)uracil (**6**): M.p. 327–329 °C; yield 0.35 g (63%). ^{1}H NMR: δ 10.90 (s,1 H, NH), 9.68 (s, 1 H, HC=), 7.92 (d, 2 H, *J*=8.2, 2 aromatic-H), 7.43–7.41 (d, 2 H, 2 aromatic-H), 7.31 (m, 7 H, NH_2, Ph), 5.21 (s, 2 H, CH_2). ^{13}C NMR: δ 45.0 (CH_2), 108.2, 127.0, 127.4, 127.5, 127.9, 128.3, 128.9, 134.7, 137.0, 148.5, 149.6, 150.7, 154.4. Calcd. for $C_{18}H_{15}ClN_4O_2$: C, 60.93; H, 4.26; N, 15.79. Found: C, 60.79; H, 4.21; N, 15.63 %.

8-Aryl-3-benzylxanthines (**7–9**): *General method:* Compounds **4–6** (0.4 g, 1.2 mmol) were dissolved in DMF (5.0 ml) and then dimethylamine (DMA) (0.5 ml) was added. The mixture was refluxed overnight and the product was filtered, washed with ethanol and recrystallised from acetic acid.

3-Benzyl-8-phenylxanthine (**7**): M.p. >350 °C; yield 0.4 g (64%). ^{1}H NMR: δ 13.85 (s, 1H, NH), 11.20 (s, 1H, NH), 8.12 (d, 2H, 2 aromatic-H), 7.33 (m, 8H,8 aromatic-H), 5.20 (s, 2 H, CH_2). ^{13}C NMR: δ 45.2 (CH_2), 108.5, 126.4, 127.2, 127.7, 128.3, 128.8, 129.0,

130.0, 137.2, 149.9, 150.0, 150.9, 154.5. Calcd. for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 67.83; H, 4.41; N, 17.73 %.

3-Benzyl-8-(4-nitrophenyl)xanthine (**8**): M.p. >350 °C; yield 0.31 g (78%). ^{1}H NMR: δ 13.70 (s, 1H, NH(9)), 10.94 (s,1H, NH(3)), 8.10 (d, 2H, *J*=8.3, 2 aromatic-H), 7.54 (d, 2H, *J*=8.3, 2 aromatic-H), 7.31 (m, 5H, Ph), 5.18 (s, 2H, CH_2). ^{13}C NMR: δ 45.2 (CH_2), 108.6, 127.2, 127.7, 127.7, 128.1, 128.9, 129.00, 134.9, 137.2, 148.8, 149.8, 150.9, 154.4. Calcd. for $C_{18}H_{13}N_5O_4$: C, 59.50; H, 3.60; N, 19.27. Found: C, 59.62; H, 3.49; N, 19.01 %.

3-Benzyl-8-(4-chlorophenyl)xanthine (**9**): M.p. >350 °C; yield 0.28 g (70%). ^{1}H NMR: δ 13.95 (s, 1 H, NH(9)), 11.24 (s, 1 H, NH(3)), 8.11 (d, 2H, 2 aromatic-H), 7.58 (d, 2H, 2 aromatic-H), 7.32 (m, 5 H, Ph), 5.18 (s, 2 H, CH_2). ^{13}C NMR: δ 45.0 (CH_2), 108.4, 127.2, 127.5, 127.5, 128.0, 128.3, 129.0, 134.8, 137.0, 148.6, 149.7, 150.8, 154.4. Calcd. for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; N, 15.88. Found: C, 61.07; H, 3.65; N, 15.63 %.

3-Benzylxanthine (**10**):[8, 13] Formamide (0.8 g, 1.77 mmol) was added to a solution of compound **3** (0.4 g, 1.7 mmol) in absolute ethanol (15 ml). The reaction mixture was heated under reflux for 6 hrs. The precipitate was collected by filtration, washed with ethanol and recrystallised from a mixture of DMF/EtOH to give colourless crystals, m.p. 312–314 °C (lit.[8, 13] >250 °C). Yield: 0.18 g (45%). ^{1}H NMR: δ 14.29 (s, 1H, NH), 11.18 (s, 1H, NH), 8.26 (s, 1H, CH(8)), 7.43 (m, 5H, Ph), 5.13 (s, 2H, CH_2). ^{13}C NMR: δ 45.00 (CH_2), 107.1, 127.2, 127.5, 128.3, 137.1, 140.6, 140.7, 149.2, 150.9, 154.7. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.46; H, 4.09; N, 22.98 %.

3-Benzyl-8-methylxanthine (**11**): Compound **3** (0.4 g, 1.7 mmol) was dissolved in absolute ethanol (15 ml) and acetic anhydride (0.17 g) was then added. The mixture was heated under reflux for 6 hrs. The precipitate was filtered, washed with ethanol and recrystallised from acetic acid into colourless crystals, m.p. 344–346 °C, yield 0.27 g (69%). ^{1}H NMR: δ 13.15 (s, 1H, NH), 11.06 (s, 1H, NH), 7.30 (m, 5H, Ph), 5.09 (s, 2H, CH_2), 2.35 (s, 3H, CH_3). ^{13}C NMR: δ 14.2 (CH_3), 45.0 (CH_2), 106.7, 127.1, 127.4, 128.3, 137.2, 149.6, 150.4, 150.9, 154.1. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.92; H, 4.72; N, 21.86. Found: C, 60.97; H, 4.75; N, 21.95 %.

3-Benzylxanthine-8-thione (**12**): Carbon disulfide (0.40 g, 5.2 mmol) was added to a solution of compound **3** (0.4 g, 1.7 mmol) in glacial acetic acid (10 ml). The mixture was refluxed for 6 h. After cooling, the precipitate was filtered and recrystallised from acetic acid giving pale yellow crystals, m.p. 257–259 °C Yield 0.21 g (46%). ^{1}H NMR: δ 13.48 (s, 1H, NH), 13.02 (s, 1H, NH), 11.93 (s, 1H, NH), 7.29 (m, 5H, Ph), 5.06 (s, 2H, CH_2). ^{13}C NMR: δ 45.7 (CH_2), 97.8 (C5), 126.6, 127.3, 128.4, 128.5, 135.8, 149.7, 152.6, 171.9. Calcd. for $C_{12}H_{10}N_4O_2S$: C, 52.55; H, 3.67; N, 20.43. Found: C, 52.23; H, 3.62; N, 20.37 %.

3-Benzyl-8-azaxanthine (**13**): A cooled solution of sodium nitrite (0.12 g, 1.7 mmol) in water (2.0 ml) was added dropwise to compound **3** (0.4 g, 1.7 mmol) in conc HCl (5.0 ml) with stirring for 1 h. The precipitate was filtered and recrystallised from methanol. m.p. >320 °C, yield 0.21 g (52%). ^{1}H NMR: δ 15.88 (s, 1H, NH), 11.58 (s, 1H, NH), 7.36 (m, 5H, Ph), 5.09 (s, 2H, CH_2). ^{13}C NMR: δ 46.2 (CH_2), 108.1, 127.4, 127.4, 128.3, 128.4, 136.1, 150.7, 154.2. Calcd. for $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.79. Found: C, 54.28; H, 3.68; N, 28.54 %.

Benzylideneaniline derivatives (**14–18**): These compounds were prepared according to the reported procedure.[32] An equimolar mixture of aniline (0.5 mmol) and aromatic aldehyde (0.5 mmol) in absolute ethanol (5 ml) was stirred under reflux for 10 minutes. After cooling, the formed precipitate was filtered, washed with ether and recrystallised from ethanol to give the desired imine.

8-Aryl-3-benzyl-7-hydroxyxanthines (**19–23**): *General method*: Imines **14–18** (2.0 mmol) were added to a solution of compound **2** (2.0 mmol) in glacial acetic acid (10 ml) with stirring. The reaction mixture was heated under reflux, whereupon the colour started to fade and heating was continued for 6 hrs. After cooling, the formed precipitate was filtered and washed with ethanol.

3-Benzyl-7-hydroxy-8-phenylxanthine (**19**): M.p. >330 °C; yield 0.4 g (64%). ^{1}H NMR: δ 13.75 (s, 1H, OH), 11.07 (s, 1H, NH), 7.68 (m, 10H, 2 Ph), 5.18 (s, 2H, CH_2). Calcd. for $C_{18}H_{14}N_4O_3$: C, 64.66; H, 4.22; N, 16.75. Found: C, 64.39; H, 4.03; N, 16.56 %.

3-Benzyl-7-hydroxy-8-(4-methoxyphenyl)xanthine (**20**): M.p. 347–349 °C, yield 0.35 g (53%). ^{1}H NMR: δ 13.63 (s, 1 H, OH), 11.15 (s, 1 H, NH), 8.06 (d, 2 H, 2 aromatic-H), 7.19 (m, 5 H, 6 aromatic-H), 7.06 (d, 2 H, 2 aromatic-H), 5.17 (s, 2 H, CH_2), 3.82 (s, 3 H, OCH_3). ^{13}C NMR: δ 45.0 (CH_2), 55.3 (OCH_3), 107.6, 114.3, 121.1, 127.2, 127.6, 127.97, 128.3, 137.1, 149.8, 150.0, 150.8, 154.3, 160.8. Calcd. for $C_{19}H_{16}N_4O_4$: C, 62.63; H, 4.42; N, 15.37. Found: C, 62.79; H, 4.53; N, 15.42 %.

3-Benzyl-8-(4-chlorophenyl)-7-hydroxyxanthine (**21**): M.p. >350 °C, yield 0.29 g (43%). ^{1}H NMR: δ 13.86 (s, 1 H, OH), 11.22 (s, 1 H, NH), 8.12 (d, 2 H, 2 aromatic-H), 7.38 (m, 5 H, ph), 7.26 (d, 2 H, 2 aromatic-H), 5.19 (s, 2 H, CH_2). ^{13}C NMR: δ 45.0 (CH_2), 108.1, 126.3, 127.2, 127.6, 128.3, 128.6, 128.9, 130.1, 137.1, 149.7, 150.8, 154.4. Calcd. for $C_{18}H_{13}ClN_4O_3$: C, 58.62; H, 3.55; N, 15.19. Found: C, 58.41; H, 3.53; N, 15.04 %.

3-Benzyl-7-hydroxy-8-(4-hydroxyphenyl)xanthine (**22**): M.p. 348–350 °C, yield 0.32 g (45%). ^{1}H NMR: δ 13.61 (s, 1H, OH), 11.10 (s, 1H, NH), 10.02 (s, 1H, OH), 7.96 (d, 2H, 2 aromatic-H), 7.33 (m, 5H, Ph), 6.87(d, 2H, 2 aromatic-H), 5.17 (s, 2H, CH_2). ^{13}C NMR: δ 45.0 (CH_2), 107.6, 115.6, 119.7, 127.2, 127.5, 128.1, 128.3, 137.2, 149.9, 150.8, 154.3, 159.4. Calcd. for $C_{18}H_{14}N_4O_4$: C, 61.71; H, 4.02; N, 15.99. Found: C, 61.65; H, 3.87; N, 15.83 %.

3-Benzyl-7-hydroxy-8-(3-hydroxy-4-methoxyphenyl) xanthine (**23**): M.p. 327–329 °C, yield 0.39 g (61%). ^{1}H NMR: δ 13.52 (s, 1H, OH), 11.13 (s, 1H, NH), 9.58 (s, 1H, OH), 7.71 (d, 1H, *J*=1.9, 1 aromatic-H), 7.62 (d, 1H, 1 aromatic-H), 7.31 (m, 5H, Ph), 6.88 (d, 1H, *J*=2.1, 1 aromatic-H), 5.17 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3). ^{13}C NMR: δ 45.0 (CH_2), 55.6 (OCH_3), 107.4, 110.0, 115.7, 119.8, 120.1, 127.2, 127.5, 128.3, 137.2, 147.7, 148.7, 149.9, 150.5, 150.8, 154.2. Calcd. for $C_{19}H_{16}N_4O_5$: C, 59.99; H, 4.24; N, 14.72. Found: C, 59.87; H, 4.19; N, 14.52 %.

6-Benzoyl-3-benzylxanthine (**24**): A mixture of compound **2** (0.5 g, 2.0 mmol), phenacyl bromide (0.4 g, 2.0 mmol) and $ZnCl_2$ (1.3 g) was heated in an oil bath for 1 h. The mixture was cooled, washed with water and recrystallised from DMF to give colourless crystals. m.p. >320 °C, yield 0.3 g (42%). ^{1}H NMR: δ 12.73 (s, 1H, NH(9), 11.93 (s, 1H, NH(3)), 8.19 (t, 2H, 2 aromatic-H), 7.25 (m, 8H, 8 aromatic-H), 5.39 (s, 2H, NCH_2). Calcd. for $C_{19}H_{14}N_4O_3$: C, 65.88; H, 4.07; N, 16.17. Found: C, 65.74; H, 3.98; N, 16.11 %.

1-Benzyllumazine (**25**):[11] Compound **3** (0.4 g, 1.7 mmol) was dissolved in absolute ethanol (15 ml) and then glyoxal (0.1 g, 1.7 mmol) was added. The mixture was heated under reflux for 5 h. The formed precipitate was collected by filtration and washed with ethanol and recrystallised from DMF to give colourless crystals, m.p. 242–244 °C (lit.[11] 235–237 °C), yield 0.17 g (40%) ^{1}H NMR: δ 10.54 (s, 1H, NH), 8.68 (d, 1H, 1 aromatic-H), 8.56 (s, 1H, 1 aromatic-H), 7.27 (m, 5H, Ph), 5.34 (s, 2H, CH_2). ^{13}C NMR: δ 44.0 (CH_2), 127.0, 127.1, 128.2, 129.1, 136.8, 139.7, 147.2, 149.0, 150.0, 159.8. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.03. Found: C, 61.32; H, 3.77; N, 21.83 %.

1-Benzyl-6,7-diaryllumazines: Benzil or 4,4'-dichlorobenzil (1.7 mmol) was added to a solution of compound **3** (1.7 mmol) and triethylamine (TEA) (3 drops) in absolute ethanol (15 ml). The mixture was heated under reflux for 6 h. The formed precipitate was filtered, washed with ethanol and recrystallised from acetic acid as yellow crystals.

1-Benzyl-6,7-diphenyllumazine (**26**): M.p. 201–203 °C (lit.[11, 29] 197–200 °C), yield 47%. ^{1}H NMR: δ 11.89 (s, 1H, NH), 7.25 (m, 15H, 3 Ph), 5.28 (s, 2H, CH_2). Calcd. for $C_{25}H_{18}N_4O_2$: C, 73.87; H, 4.46; N, 13.78. Found: C, 73.64; H, 4.43; N, 13.61 %.

1-Benzyl-6,7-bis-(4-chlorophenyl)lumazine (**27**): M.p. 235–237 °C, yield 56%. ^{1}H NMR: δ 12.1 (s, 1H, NH), 7.97 (d, 4H, 4 aromatic-H), 7.71 (d, 4H, 4 aromatic-H), 7.44 (m, 5H, Ph), 5.39 (s, 2H, CH_2). Calcd. for $C_{25}H_{16}Cl_2N_4O_2$: C, 63.17; H, 3.39; N, 11.78. Found: C, 63.08; H, 3.31; N, 11.56 %.

1-Benzyllumazine-6,7-dione (**28**): Diethyl oxalate (0.25 g, 1.7 mmol) was added to a solution of compound **3** (0.4 g, 1.7 mmol) in glacial acetic acid (10 ml). The mixture was heated under reflux for 6 h. The precipitate was filtered, washed with ethanol and recrystallised from DMF to pale yellow crystals, m.p. 341–343 °C, yield 0.19 g (39%). ^{1}H NMR: δ 11.73 (s, 1H, NH), 11.51 (s, 2H, 2 NH-5,8), 7.30 (m, 5H, Ph), 5.23 (s, 2H, CH_2). ^{13}C NMR: δ 44.0 (CH_2), 126.6, 127.1, 128.3, 135.1, 136.5, 149.0, 151.6, 156.1, 156.7, 156.8. Calcd. for $C_{13}H_{10}N_4O_4$: C, 54.54; H, 3.52; N, 19.57. Found: C, 54.47; H, 3.50; N, 19.32 %.

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