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Photochemistry synthesis. Part 1: Syntheses of xanthine derivatives by photolysis of 1-(5′-oxohexyl)-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (pentoxifylline): an ambident chromophore

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Abstract

We investigated the use of photochemistry to make novel derivatives of pentoxifylline. Under conditions that favour singlet excited states, we obtained 1-allyl-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione, (*R**,*R**)-(±)-1-{[2-hydroxy-2-methylcyclobutyl]methyl}-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione and 1-(5-hydroxyhexyl)-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione. Naphthalene or molecular oxygen increases the yields and triplet sensitisers (acetophenone, benzophenone and acetone) decrease the yields. Efficient intramolecular triplet energy transfer from the carbonyl to the xanthine moiety allows the carbonyl moiety to react from a singlet excited state only. In solvents with an α-hydroxyalkyl hydrogen under conditions that favour triplet excited states, we obtained 8-substituted pentoxifylline derivatives: 8-(1-hydroxy-1-methylethyl)-3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1*H*-purine-2,6-dione in isopropanol, 8-(1-hydroxymethyl)-3,7-dimethyl-1-(5-oxo-hexyl)-3,7-dihydro-1*H*-purine-2,6-dione in methanol and 8-(1-hydroxyethyl)-3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1*H*-purine-2,6-dione in ethanol. The xanthine moiety reacts from a triplet state via a radical mechanism and yields are considerably improved by the addition of catalytic amounts of di-*tert*-butyl peroxide.

Keywords: Photochemistry; Pentoxifylline; Xanthines; Ambident chromophore

1. Introduction

Xanthine derivatives are considered privileged structures[1] with a higher-than-average probability of demonstrating bioactivity. Pentoxifylline [1-(5′-oxohexyl)-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione] **1** is a 1-(5′-oxohexyl)xanthine derivative. It is sold under the trade name Trental® and is used to treat peripheral and cerebrovascular diseases and poor regional microcirculation (intermittent claudication). Pentoxifylline acts by increasing erythrocyte deformability,[2] inhibiting platelet aggregation,[3] reducing blood viscosity[4] and diminishing fibrinogen concentration.[5] It also improves tumour perfusion, influences cytokine-mediated inflammation[6] and has been investigated as an antitumour agent.[7]

The key reaction in the patented synthesis of pentoxifylline is the coupling of 1-halohexan-5-one with an alkali metal salt of theobromine **2** at N-1.[8] Apart from this patent we could not find any references to the synthesis of pentoxifylline or its derivatives. Efforts to prepare 1-allyl-3,7-dimethylxanthine via the reaction of theobromine **2** at N-1 with allyl bromide failed. We believe the low reactivity to be due to electronic factors, since amides are known to be difficult to deprotonate and alkylate due to electron withdrawal by the adjacent carbonyl group.[9] The N-1 functionality of theobromine is a diamide and is thus even less reactive.[10] Since the two sp^2 carbonyl carbons adjacent to N-1 are planar and unlikely to interfere sterically with approaching electrophiles, low reactivity of the N-1 moiety due to steric hindrance, as previously reported,[11] should be minimal.

Our efforts to synthesise derivatives of pentoxifylline for pharmaceutical screening were hampered by the scarcity of

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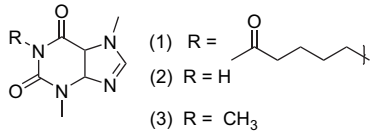
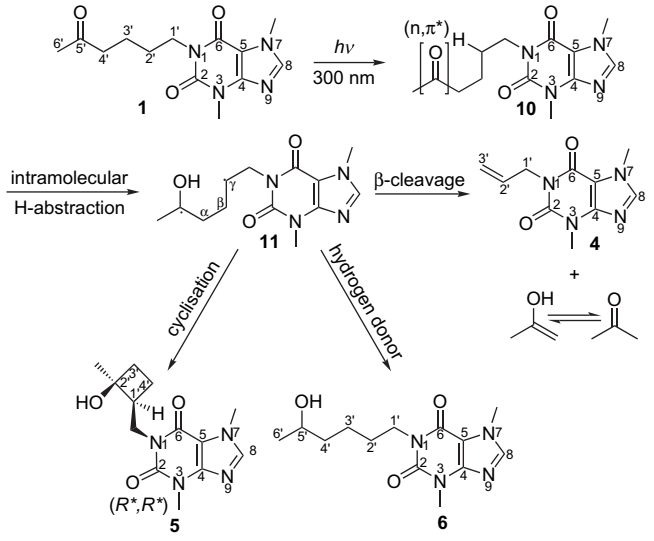


synthetic methods to increase the scope of derivatives for testing, and by the low reactivity of N-1 of theobromine towards alkylation with electrophiles. We now report a series of photochemical reactions relevant to the syntheses of novel pentoxifylline analogues.

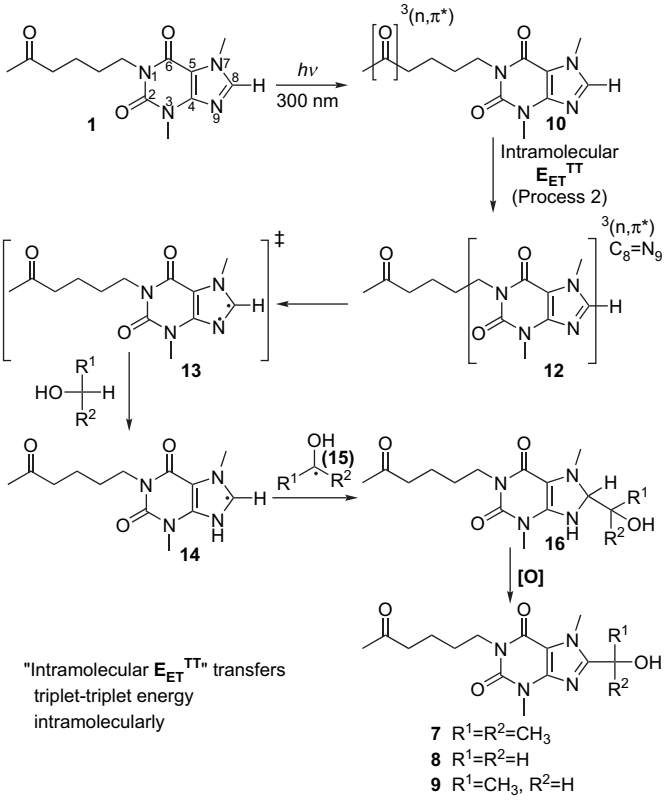
2. Results

Photolysis of pentoxifylline **1** in nonpolar solvents (toluene or benzene) and certain polar solvents (water, ethanol, methanol and ethanol/water or methanol/water; 50:50, respectively) at 300 nm with oxygen gave three products (Scheme 1): 1-allyl-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **4**, (*R**,*R**)-(±)-1-{[2-hydroxy-2-methyl-cyclobutyl]-methyl}-3,7-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione **5** and 1-(5-hydroxyhexyl)-3,7-di-methyl-3,7-dihydro-1*H*-purine-2,6-dione **6**. Photolysis of pentoxifylline in alcoholic solvents with at least one hydrogen on the oxygen-bearing carbon yielded the following 8-substituted pentoxifylline derivatives: 8-(1-hydroxy-1-methylethyl)-3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1*H*-purine-2,6-dione **7** in 2-propanol, 8-(1-hydroxymethyl)-3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1*H*-purine-2,6-dione **8** in methanol and 8-(1-hydroxyethyl)-3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1*H*-purine-2,6-dione **9** in ethanol (Scheme 2).



Scheme 1.

Pentoxifylline is an ambident chromophore with an aliphatic carbonyl chromophore and a xanthine chromophore (two carbonyls and an imine group embedded in the aromatic system), separated by a linear, saturated butane moiety. We thus sought conditions that would selectively facilitate reactions at either the carbonyl or xanthine moieties, respectively. Conditions and associated yields are collated in Table 1.



Scheme 2.

The yield of the reduction product **6** did not increase with addition of the hydrogen donor TBTH as confirmed by HPLC (Table 2).

3. Discussion

3.1. Reaction mechanism

The formation of products **4** and **5** can be explained by photochemical generation of an n,π*-excited aliphatic carbonyl group **10** that collapses to a 1,4-diradical intermediate **11** via intramolecular hydrogen abstraction from the γ-carbon (Scheme 1). Subsequent Norrish type II fission or β-cleavage, and Yang cyclisation then affords **4** and **5**, respectively. The reduction product (lisophylline) **6** results from intermolecular hydrogen abstraction by the n,π*-excited aliphatic carbonyl group **10**. Maximum yields were obtained in toluene with naphthalene as singlet sensitiser and in ethanol with oxygen as singlet sensitiser.

In the case of products **7**, **8** and **9**, we postulate that the imine excited state **12** collapses to a diradical **13** that abstracts a hydrogen radical from the alcohol (C—H-bond fission), similar to hydrogen abstraction by an $^3(n,\pi^*)$ carbonyl group [Scheme 2]. The two resulting radicals **14** and **15** then combine, probably in a solvent cage, to produce the unstable 8-substituted intermediate **16**. Re-establishment of aromaticity follows to yield the 8-substituted **7**, **8** or **9**. It is unclear whether di-*tert*-butyl peroxide is involved in this oxidation step.

Table 1
Yields (%) of products from the photolysis of pentoxifylline in different solvents and with different additives

	Solvent	Additive	% Yield					
			4	**5**	**6**	**7**	**8**	**9**
1	Toluene	None	32	8	7	—	—	—
2	Toluene	Naphthalene[a]	48	12	9	—	—	—
3	Toluene	Benzophenone[a]	8	2	1	—	—	—
4	Toluene	Acetophenone[a]	10	2	2	—	—	—
5	Toluene	TBTH[b]	28	7	6	—	—	—
6	Toluene	Oxygen[d]	40	9	7	—	—	—
7	2-Propanol	None	8	2	2	22	—	—
8	2-Propanol	Oxygen[d]	30	8	7	—	—	—
9	2-Propanol	Acetone (50%)	17	5	4	55	—	—
10	2-Propanol	DTBP[c]	8	2	—	36	—	—
11	2-Propanol	Water (50%)	12	3	3	20	—	—
12	Methanol	None	10	3	2	19	10	—
13	Methanol	Oxygen[d]	46	11	9	—	—	—
14	Methanol	Acetone (50%)	8	2	2	28	6	—
15	Methanol	DTBP[c]	7	2	1	—	48	—
16	Methanol	Water (50%)	11	3	3	—	—	—
17	Ethanol	None	10	3	2	22	—	9
18	Ethanol	Oxygen[d]	50	13	10	—	—	—
19	Ethanol	Acetone (50%)	8	2	2	30	—	7
20	Ethanol	DTBP[c]	—	—	—	—	—	66
21	Ethanol	Water (50%)	12	3	3	—	—	—
22	Acetone	None	10	3	—	7	—	—
23	Water	None	16	4	2	—	—	—
24	Benzene	None	40	10	—	—	—	—

[a] Naphthalene, acetophenone and benzophenone were used at a concentration of 0.05 mmol/L.
[b] Two equivalents was added (600 μL/50 mL).
[c] Di-*tert*-butyl peroxide (DTBP) was used in a catalytic amount (2 mL/50 mL).
[d] Atmospheric air was bubbled through the reaction mixture to provide oxygen.

Table 2
HPLC results from the crude reaction mixtures obtained after the radiation in toluene of (i) pure pentoxifylline and (ii) pentoxifylline with tributyltin hydride

(i) Compound	Retention time (min)	% Area	(ii) Compound	Retention time (min)	% Area
4	8.871	32	**4**	8.928	31
5	9.777	8	**5**	9.816	8
6	8.266	2	**6**	8.303	2
1	9.499	53	**1**	9.551	54

3.2. Sensitisation and quenching studies

Our investigation into experimental conditions that optimise product yields supports a hypothesis that the carbonyl moiety of pentoxifylline reacts from a singlet excited state and the xanthine moiety from a triplet excited state.

In agreement with Wagner's report[12] that polar solvents appreciably enhance the quantum efficiency of type II photoeliminations from triplet aliphatic carbonyls and Yang's[13] report that there is no polar solvent effect on singlet-state carbonyl quantum yields, we observed no increase in yields of products **4**, **5** and **6** in polar solvents (water, methanol, ethanol or acetone).

The observation that the ratio between the two diradical-derived products **4** and **5** remained about 4:1 under various reaction conditions correlates with reports that singlet excited biradicals mainly cleave in preference to cyclisation.[13]

The presence of naphthalene or oxygen, both triplet quenchers and singlet sensitisers, increases the yield of the carbonyl-derived products **4** and **5** significantly and the yield of xanthine derived products **7**, **8** and **9** is drastically reduced with oxygen (Table 1). Although singlet–singlet energy transfer is less common than triplet–triplet energy transfer, it is not unusual. Naphthalene is a well-known triplet quencher but it also absorbs light very efficiently at about 320 nm to sensitise the formation of singlet ketones.[14] Because of the big energy difference between S_1 and T_1 in naphthalene (90 vs 61 kcal/mol, respectively),[15] the rate of intersystem crossing to triplet naphthalene is low and the singlet excited state predominates. This increased the lifetime of singlet excited naphthalene and allows singlet sensitisation of the carbonyl moiety (ca. 85 kcal/mol)[16] of pentoxifylline.

The presence of triplet sensitisers (acetophenone, benzophenone and acetone) decreases the yield of carbonyl-derived products significantly [from 32 to 8% and from 8 to 2% for **4** and **5**, respectively] and increases the yield of xanthine-derived products. This supports the hypothesis that triplet excitation does not play a role in the photochemistry of the carbonyl-derived products of pentoxifylline and plays a big role in the photochemistry of the xanthine moiety. The singlet energy state of conjugated aromatic carbonyl groups (76 kcal/mol for benzophenone)[16] is lower than those of unconjugated aliphatic ketones (about 85 kcal/mol)[16] rendering singlet intermolecular quenching of the carbonyl moiety energetically possible.

Owing to the close intramolecular proximity of the carbonyl and xanthine chromophore in pentoxifylline, a nearest neighbour collision is not required for triplet energy transfer from the carbonyl to the xanthine moiety (process 2 in Scheme 2) and the process should be extremely efficient. The T_1 values for the carbonyl and xanthine moieties of pentoxifylline should resemble those of acetone (78 kcal/mol)[16] and caffeine **3** (61 kcal/mol),[17] respectively, and make triplet energy transfer energetically favourable. Many examples of intramolecular triplet–triplet energy transfers have been reported.[18] This efficient transfer will limit the lifetime and concentration of the carbonyl triplet state and the carbonyl group will only be able to react from the singlet excited state, explaining our observations. The S_1 energy of caffeine is much higher than that of acetone (104[17] and 85[16] kcal/mol, respectively) implying that intramolecular singlet energy transfer from the carbonyl to the xanthine chromophore will be impossible.

The carbon–hydrogen bond on the oxygen-bearing carbon of aliphatic alcohols is weaker to homolysis than the adjacent oxygen–hydrogen bond. Hydrogen radical abstraction from isopropanol by the excited triplet xanthine moiety thus yields an α-hydroxyalkyl radical **15**. This radical attacks the 8-position (Scheme 2) to yield the 8-substituted product **7**. The triplet nature of this reaction is indicated by the increase in yield from 22 to 55% by addition of 50% acetone to isopropanol. The yield in pure acetone is low (7%). The addition of acetone did not have the same beneficial effect in the case of ethanol and methanol, probably indicating less stable radical intermediates and stronger C–H bonds. By using catalytic amounts of di-*tert*-butyl peroxide as photo-initiator, we increased the yields of the methanol and ethanol derived products **8** and **9** from 10 to 48%, and 9 to 66%, respectively. Photolysis of di-*tert*-butyl peroxide at 254 nm gives *tert*-butoxy radicals that abstract the α-hydrogen of alcohols[19] and amines.[20]

Reaction at the 8-position of pentoxifylline is in agreement with the work of Salomon and Elad[19,20] who produced C-8 substituted derivatives of caffeine **3** (α-hydroxyalkyl,[19] α-aminoalkyl[20] or α-alkoxyalkyl[21]), photochemically from alcohols, amines, ethers and cyclic ethers. The free radical nature of this C-8 alkylation reaction was demonstrated by the increased yield from about 20 to 65% after addition of di-*tert*-butyl peroxide. These reactions were considered important in the investigation of the mechanism of radical damage to DNA. In the presence of photochemically produced singlet oxygen, C-8 of caffeine was oxidised to yield uric acid derivatives.[22]

Turro[23] demonstrated that Norrish type I α-cleavage of carbonyl chromophores takes place predominantly from the triplet excited state in a process that is more than two orders of magnitude faster than from the singlet excited state. Absence of α-cleavage products under our reaction conditions may, however, simply be due to the fact that α-cleavage generally requires the α-carbon to be tertiary substituted or attached to a strong radical stabilising group.[24]

β-Cleavage of the carbonyl moiety in pentoxifylline to form **4** yields acetone as a side product (Scheme 1). This may explain the isolation of small quantities of the 8-(1-hydroxy-1-methylethyl)xanthine derivative **7** in methanol and ethanol as solvents (Scheme 2). Interestingly **7** is not formed in toluene or benzene by the same mechanism, as was confirmed with HPLC.

The absence of lisophylline **6** in photolysis experiments, where toluene is replaced with benzene, suggests that benzylic hydrogens may act as a hydrogen source. Efforts to increase the yield of lisophylline **6** with tributyltin hydride failed, probably because tributyltin hydride reduces triplet- but not singlet excited carbonyl groups.[25] The intramolecular nature of the competing Norrish type II fission and Yang cyclisation reactions probably contributes to the poor yields of products arising from intermolecular photoreduction.

3.3. Relative configuration of (R,R*)-(±)-1-{[2-hydroxy-2-methylcyclobutyl]-methyl}-3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione (**2**)*

The relative 1,2-cis-configuration of the cyclobutane ring was confirmed by the NOE associations indicated in Figure 1. The cis-isomer is defined as the isomer where the 2′-OH substituent and the xanthine moiety are suprafacial on the cyclobutane ring (*R**,*R**-isomer).

Yang cyclisations generally occur with a high degree of stereoselectivity.[26] The relative configuration of the *cisoid* conformation in the biradical transition state [**11**, Scheme 1] is controlled by steric interactions as bonding between the two ends (C-1 and C-4) of the biradical commences. Moorthy and Mal[27] pointed out that the solvation of the hydroxy group increases its steric bulk and changes the major product from trans in nonpolar solvents such as benzene to cis in a polar solvent such as acetonitrile or methanol. The absence of the trans-product in our reaction in nonpolar solvents indicates that hydrogen bonding between the hydroxy group (2′-OH) and the N-1 and carbonyl groups of the xanthine moiety overrules steric factors in the transition state.

4. Conclusion

We synthesised five new derivatives of pentoxifylline photochemically. We demonstrated that 8-substitution on the xanthine chromophore takes place from a triplet state via a radical mechanism. The aliphatic carbonyl chromophore reacts from a singlet state due to rapid intramolecular triplet energy loss to the xanthine moiety. We optimised conditions that selectively facilitate reactions from the carbonyl or xanthine moieties, respectively.

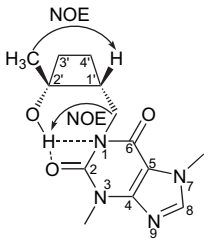


Figure 1.

5. Experimental

5.1. General

5.1.1. Photochemical reactions

Photochemical reactions were performed with a RAYONET PHOTOCHEMICAL REACTOR manufactured by SOUTHERN NEW ENGLAND ULTRAVIOLET COMPANY. Middletown, Connecticut, USA, equipped with 16 CAT. NO. RPR-3000 Å lamps.

5.1.2. NMR spectra

NMR experiments were carried out on a Bruker spectrometer (600 MHz).

5.1.3. Mass spectra

High-resolution mass spectra were recorded at 70 eV on a VG 70 SEQ mass spectrometer with a MASPEC II data system.

5.1.4. IR spectra

IR spectra were recorded on a Bruker Tensor 27 FT-IR single beam instrument. The standard sample cell used was a Pike Miracle single-bounce attenuated total reflectance (ATR) cell equipped with a ZnSe single crystal. Measurements were taken over a range of 400–4000 cm^{-1}, no carrier was used and a background run was performed in each case.

5.2. Syntheses

5.2.1. Extraction of pentoxifylline from commercially available tablets

Pentoxifylline was extracted from Trental® tablets with toluene and crystallised from chloroform as white needles, mp: 104–106 °C. Found M^+ 278.13825, $C_{13}H_{18}N_4O_3$ requires M^+ 278.13789, M^+ 278 (100), *m/e* 235 (16.5), 221 (100), 207 (21.2), 193 (75.7), 180 (88.5), 137 (13.2), 109 (29.1), 82 (9.1), 67 (18.3), 55 (11.1). IR: ν_{max} 2916, 2848, 1700, 1657, 1432, 761, 752 cm^{-1}. ^1H: δ ($CDCl_3$) 1.64–1.67 (m, 4H, 2′-H and 3′-H), 2.14 (s, 3H, 6′-H), 2.50 (t, J=7.5 Hz, 2H, 4′-H), 3.57 (s, 3H, N_3–CH_3), 3.98 (s, 3H, N_7–CH_3), 4.02 (t, J=12 Hz, 2H, 1′-H), 7.51 (s, 1H, 8-H). ^{13}C: δ ($CDCl_3$) 20.9 (C-3′), 27.4 (C-2′), 29.7 (N_3–C), 29.9 (C-6′), 33.6 (N_7–C), 40.8 (C-1′), 43.2 (C-4′), 107.6 (C-5), 141.4 (C-8), 148.8 (C-4), 151.5 (C-2), 155.3 (C-6), 208.7 (C-5′).

5.3. Photochemical transformations

5.3.1. 1-Allyl-3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione **4**, (R*,R*)-(±)-1-{[2-hydroxy-2-methylcyclo-butyl]-methyl}-3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione **5** and 1-(5-hydroxyhexyl)-3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione **6**

Pentoxifylline (278 mg, 1 mmol) and naphthalene (320 mg, 2.5 mmol) were dissolved in toluene (50 ml). The solution was flushed with nitrogen and irradiated for 24 h at 300 nm under nitrogen. The solvent was removed under vacuum. TLC (hexane/ethylacetate/acetone/methanol; 2:7:0.5:0.5) yielded the following compounds.

(a) Compound **4**, R_f 0.32 (62 mg, 48%), as *white needles* from methanol, mp: 142–143 °C. Found M^+ 220.09563, $C_{10}H_{12}N_4O_2$ requires M^+ 220.09603, M^+ 220 (100), *m/e* 205 (61.9), 193 (4.5), 180 (5.6), 165 (9.3), 109 (29), 82 (12), 67 (21.4), 55 (14). IR: ν_{max} 3121, 2953, 1704, 1650, 1542, 765, 744 cm^{-1}. ^1H: δ ($CDCl_3$) 3.59 (s, 3H, N_3–CH_3), 4.00 (s, 3H, N_7–CH_3), 4.64 (d, J=5.8 Hz, 2H, 1′-H), 5.19 (dd, J=10.3, 1.3 Hz, 1H, 3′-H_A), 5.26 (dd, J=17.2, 1.3 Hz, 1H, 3′-H_B), 5.93 (ddd, J=17.2, 10.3, 5.8 Hz, 1H, 2′-H), 7.52 (s, 1H, 8-H). ^{13}C: δ ($CDCl_3$) 29.5 (N_3–*C*), 33.4 (N_7–*C*), 43.1 (C-1′), 107.4 (C-5), 117.3 (C-3′), 132.1 (C-2′), 141.3 (C-8), 148.7 (C-4), 151.1 (C-2), 154.8 (C-6).

(b) Compound **5**, R_f 0.26 (15 mg, 12%), as *white needles* from methanol, mp: 148–149 °C. Found M^+ 278.13789, $C_{13}H_{18}O_3N_4$ requires M^+ 278.13669, M^+ 278 (15.8), *m/e* 250 (12), 221 (100), 205 (18.3), 193 (11.5), 180 (94.3), 137 (10.5), 109 (26.2), 83 (11.4), 69 (19.2), 55 (24.9). IR: ν_{max} 3277, 1698, 1645, 1433, 1233, 763, 746 cm^{-1}. ^1H: δ ($CDCl_3$) 1.14 (s, 3H, C-2′–CH_3), 1.79–1.82 (m, 2H, 4′-H), 1.90–1.95 (m, 3H, 3′-H), 2.40–2.45 (m, 1H, 1′-H), 3.61 (s, 3H, N_3–CH_3), 4.00 (s, 3H, N_7–CH_3), 4.17 (dd, J=14, 11 Hz, 2H, N_1–CH_2), 7.53 (s, 1H, 8-H). ^{13}C: δ ($CDCl_3$) 29.0 (C-2′–C), 29.4 (N_3–C), 29.8 (C-3′–C), 32.7 (C-4′–C), 33.6 (N_7–C), 40.8 (C-1′), 44.6 (N_1–C), 74.6 (C-2′), 107.6 (C-5), 141.4 (C-8), 148.7 (C-4), 151.5 (C-2), 155.3 (C-6).

(c) Compound **6**, R_f 0.14 (14 mg, 11%), as *white needles* from chloroform, mp: 169–170 °C. Found M^+ 280.15261, $C_{13}H_{20}N_4O_3$ requires M^+ 280.15354, M^+ 280 (22.4), *m/e* 265 (6.7), 236 (10.5), 221 (22.5), 193 (29.2), 180 (100), 137 (8.3), 109 (17.6), 82 (5.1), 67 (9.8). IR: ν_{max} 2960, 2921, 2851, 1696, 1652, 1460, 761, 751 cm^{-1}. ^1H: δ ($CDCl_3$) 1.20 (d, J=6.3 Hz, 3H, 6′-H), 1.52 (m, 4H, 2′-H and 3′-H), 1.70 (m, 2H, 4′-H), 3.58 (s, 3H, N_3–CH_3), 3.78 (m, 1H, 5′-H), 3.99 (s, 3H, N_7–CH_3), 4.03 (t, J=7.5, 7.3 Hz, 2H, 1′-H), 7.50 (s, 1H, 8-H). ^{13}C: δ ($CDCl_3$) 22.9 (C-3′), 23.5 (C-6′), 27.9 (C-2′), 29.7 (N_3–C), 33.6 (N_7–C), 38.8 (C-4′), 41.1 (C-1′), 67.9 (C-5′), 107.7 (C-5), 141.4 (C-8), 148.8 (C-4), 151.5 (C-2), 155.4 (C-6).

5.3.2. 8-(1-Hydroxy-1-methylethyl)-3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione **7**

Pentoxifylline (278 mg, 1 mmol) was dissolved in isopropanol (50 mL). The solution was flushed with nitrogen and irradiated for 24 h at 300 nm under nitrogen. The solvent was removed under vacuum. TLC (hexane/ethylacetate/acetone/methanol; 2:7:0.5:0.5) yielded compound **7**, R_f 0.53 (29 mg, 22%), as *white needles* from acetone, mp: 191–192 °C. Found M^+ 336.18119, $C_{16}H_{24}N_4O_4$ requires M^+ 336.17976, M^+ 336 (100), *m/e* 318 (82), 275 (19.6), 261 (56), 247 (12), 233 (39), 220 (64), 206 (16), 193 (9.2), 180 (71), 165 (11.2), 109 (35.1), 82 (9.9), 67 (14.2), 55 (20.3). IR: ν_{max} 2363, 2340, 1701, 1640, 1656, 1429, 760, 750 cm^{-1}. ^1H: δ ($CDCl_3$) 1.59–1.65 (m, 4H, 2′-H and 3′-H), 1.68 (s, 6H, 2″-H and 3″-H), 2.12 (s, 3H, 6′-H), 2.48 (t, J=6.9 Hz, 2H, 4′-H), 3.49, (s, 3H, N_3–CH_3),

3.95 (t, J=6.9 Hz, 2H, 1′-H), 4.15 (s, 3H, N_7–CH_3). ^{13}C: δ ($CDCl_3$) 20.9 (C-2′), 27.4 (C-3′), 29.4 and 29.6 (C-2″ and C-3″), 29.9 (C-6′), 31.4 (N_3–C), 34.0 (N_7–C), 40.7 (C-1′), 43.2 (C-4′), 70.8 (C-1″), 108.5 (C-5), 146.7 (C-8), 151.4 (C-4), 155.3 (C-2), 157.0 (C-6), 208.9 (C-5′). The fractions with R_f 0.32, 0.26 and 0.14 correspond to products **4**, **5** and **6**.

*5.3.3. 8-(1-Hydroxymethyl)-3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione **8***

Pentoxifylline (278 mg, 1 mmol) was dissolved in methanol (100 mL). The solution was flushed with nitrogen and irradiated for 24 h at 300 nm under nitrogen. The solvent was removed under vacuum. TLC (hexane/ethylacetate/acetone/methanol; 2:7:0.5:0.5) yielded compound **8**, R_f 0.18 (62 mg, 48%), as *white needles* from chloroform, mp: 177–178 °C. Found M^+ 308.14830, $C_{15}H_{22}N_4O_4$ requires M^+ 308.14846, M^+ 308 (27), *m/e* 290 (18), 247 (13), 233 (100), 219 (18), 206 (8.7), 193 (27.2), 180 (67.5), 137 (7.5), 109 (26.4), 82 (14.7), 67 (11.1). IR: ν_{max} 3245, 1703, 1655, 1442, 1033, 761, 752 cm^{-1}. ^{1}H: δ ($CDCl_3$) 1.62–1.68 (m, 4H, 2′-H and 3′-H), 2.14 (s, 3H, 6′-H), 2.50 (t, J=7.1 Hz, 2H, 4′-H), 3.54 (s, 3H, N_3–CH_3), 4.01 (t, J=7.0 Hz, 2H, 1′-H), 4.00 (s, N_7–CH_3), 4.76 (s, 2H, 1″-H). ^{13}C: δ ($CDCl_3$) 20.9 (C-2′), 27.4 (C-3′), 29.6 (C-6′), 29.9 (N_3–C), 32.0 (N_7–C), 40.8 (C-1′), 43.2 (C-4′), 56.6 (C-1″), 108.3 (C-5), 147.4 (C-8), 151.3 (C-4), 151.5 (C-2), 155.3 (C-6), 208.8 (C-5′). The fractions R_f 0.32, 0.26 and 0.14 correspond to products **4**, **5** and **6** described above.

*5.3.4. 8-(1-Hydroxyethyl)-3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione **9***

Pentoxifylline (278 mg, 1 mmol) was dissolved in ethanol (100 mL). The solution was flushed with nitrogen and irradiated for 24 h at 300 nm under nitrogen. The solvent was removed under vacuum. TLC (hexane/ethylacetate/acetone/methanol; 2:7:0.5:0.5) yielded compound **9**, R_f 0.32 (98 mg, 66%), as *white needles* from chloroform, mp: 186–187 °C. Found M^+ 322.16408, $C_{15}H_{22}N_4O_4$ requires M^+ 322.16411, M^+ 322 (89), *m/e* 322 (89), 306 (24), 265 (54), 263 (35), 237 (44), 219 (100), 208 (25), 193 (8), 180 (12), 131 (28), 100 (10), 82 (14), 69 (59), 67 (25), 42 (31). IR: ν_{max} 3414, 2925, 1700, 1638, 1454, 763, 755 cm^{-1}. ^{1}H: δ ($CDCl_3$) 1.63 (d, J=6.7 Hz, 3H, 2″-H), 1.65 (m, 4H, 2′-H and 3′-H), 2.14 (s, 3H, 6′-H), 2.50 (t, J=7.1 Hz, 2H, 4′-H), 3.52 (s, 3H, N_3–CH_3), 4.00 (t, J=7.2 Hz, 2H, 1′-H), 4.00 (s, 3H, N_7–CH_3), 4.99 (dd, J=12.6, 6.5 Hz, 2H, 1″-H). ^{13}C: δ ($CDCl_3$) 20.9 (C-2′), 22.1 (C-2″), 27.4 (C-3′), 29.6 (C-6′), 29.9 (N_3–C), 32.1 (N_7–C), 40.7 (C-1′), 43.2 (C-4′), 62.9 (C-1″), 108.5 (C-5), 146.7 (C-8), 151.4 (C-4), 155.3 (C-2), 157.0 (C-6), 208.9 (C-5′).

5.4. Sensitisation and solvent influence studies

5.4.1. Standard procedures

Pentoxifylline (278 mg, 1 mmol) was dissolved in the solvent (50 mL) as indicated in Table 1. The additive indicated in Table 1 was added (naphthalene, acetophenone and benzophenone at a concentration of 0.05 mmol/L, tributyltin hydride (600 μL/50 mL), di-*tert*-butyl peroxide (DTBP) in a catalytic amount (2 mL/50 mL) and atmospheric air was bubbled through the reaction mixture to provide oxygen). The solvent was flushed with nitrogen and irradiated under nitrogen (unless oxygen was used in which case air was bubbled through) for 24 h. The solvent was removed under reduced pressure and the product purified by TLC (hexane/ethylacetate/acetone/methanol; 2:7:0.5:0.5). Yields are noted in Table 1.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.01.007.

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