

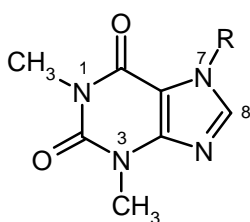
SYNTHESIS OF 8-SUBSTITUTED XANTHINE DERIVATIVES BY SUZUKI CROSS-COUPLING REACTION[‡]

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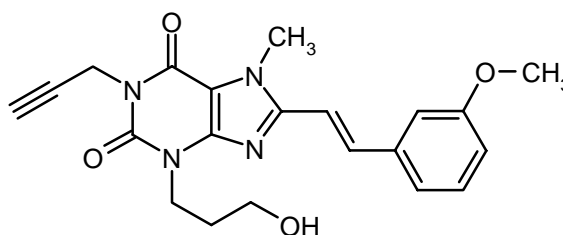
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Abstract - A Suzuki cross-coupling reaction procedure was developed to prepare 8-substituted 3,7-dihydropurine-2,6-dione (xanthine) derivatives. 8-Halogen-substituted xanthines were reacted with phenyl- and styrylboronic acids. The best results were obtained using tetrakis(triphenylphosphine)palladium(0) and tripotassium phosphate in dimethylformamide. The developed procedure allows for a convergent synthesis of pharmacologically active 8-substituted xanthine derivatives.

Xanthines, like the naturally occurring derivatives caffeine (**1**) and theophylline (**2**), are an important class of adenosine receptor (AR) antagonists.^{1,2}



1 Caffeine R = CH₃
2 Theophylline R = H



3 MSX-2

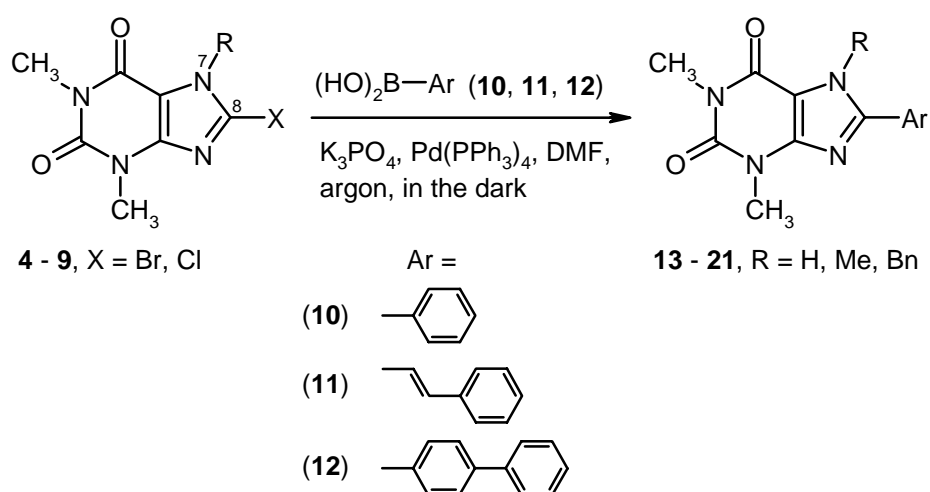
The introduction of an 8-substituent, such as a phenyl or an (*E*)-styryl residue greatly enhances affinity of xanthine derivatives for certain receptors.³ 8-Styrylxanthine derivatives, e.g. 3-(3-hydroxypropyl)-7-methyl-1-propargyl-8-[(*m*-methoxy)styryl]xanthine (MSX-2, **3**) belong to the most potent and selective A_{2A} AR antagonists.⁴ Our goal was to develop a convenient synthetic pathway for the preparation of 8-substituted 1,3-di- and 1,3,7-trisubstituted xanthines, in a 1- or 2-step procedure, as potential adenosine

[‡] Dedicated to Prof. Dr. Kurt Eger on the occasion of his 60th birthday.

receptor antagonists. The classical pathway for the preparation of 8-substituted xanthine derivatives follows the *Traube* purine synthesis.⁵ The residue, which is to become the 8-substituent, is introduced at an early stage by coupling of a suitable carboxylic acid, or an aldehyde, respectively, with a 5,6-diaminouracil derivative, followed by ring closure to the xanthine derivative. In some cases, the ring closure can be problematic due to side reactions,⁶ and the final products may be difficult to purify. Therefore, it would be desirable to introduce an 8-substituent in the last step. Substitution of xanthines in the 8-position has been performed by the *Heck* reaction of 8-bromocaffeine and 2-propene acid *tert*-butyl ester,⁷ and according to the method of *Barton* by a radical reaction of cycloalkyl radicals with 1,3-dipropylxanthine, or caffeine, respectively.⁸ However, none of the above methods has found broad application for the preparation of 8-substituted xanthine derivatives, possibly due to moderate yields. To the best of our knowledge, no Suzuki cross-coupling reaction of 8-chloro- or 8-bromoxanthines has been described to date.

In the present study we investigated whether aryl and styryl substituents could be introduced into the 8-position of xanthines by a Suzuki cross-coupling reaction with 8-halogen-substituted xanthine derivatives in the presence of a palladium catalyst. This method appeared to be attractive due to the high chemo-, regio-, and stereoselectivity and the mild reaction conditions associated with Suzuki coupling reactions.⁹ We have now successfully performed such coupling reactions with various boronic acids (see Scheme 1).

Scheme 1 (for substituents see Table 1)



Initial attempts to apply the catalyst palladium(II) acetate in the presence of tetrabutylammonium chloride and tripotassium phosphate failed.¹⁰ The best results were obtained by using anhydrous potassium phosphate in dimethylformamide with tetrakis(triphenylphosphine)palladium(0) as a catalyst. 8-Chloro- and 8-bromotheophylline derivatives with hydrogen (**4**, **7**), methyl (**5**, **8**) or benzyl (**6**, **9**), respectively, at the nitrogen atom N7 were used (see Scheme 1). 8-Chloro- and 8-bromoxanthine derivatives gave similar results with regard to yields and reaction times (see Table 1). As boronic acids

phenyl- (**10**), (*E*)-styryl-(**11**) and biphenyl-4-yl-boronic acid (**12**) were used. High yields were obtained by using N7-substituted xanthine derivatives. The products (**14**, **15**, **17**, **18**, **20**, **21**) could easily be purified by column chromatography. Even the coupling of xanthine derivatives with an unprotected heteroatom hydrogen bond (compounds (**4**) and (**7**)), could be achieved. However, in these cases the yields were lower as compared to the N7-substituted xanthines. In two experiments (**7** → **16**, and **4** → **19**) yields were below the detection limit of ¹H NMR spectroscopy and thus the products could not be isolated. In those cases appropriate protecting groups may be used at N7. Three of the synthesized products (**18**, **20**, **21**) are new xanthine derivatives which have not been previously described in the literature.

Table 1. Starting compounds, reaction times and yields of 8-substituted xanthine derivatives

starting compound	X	R	Ar	reaction time (day)	yield (%)	product
4	Br	H	phenyl	3	19	13
5	Br	Me	phenyl	6	63	14
6	Br	Bn	phenyl	5	48	15
7	Cl	H	phenyl	7	6	13
8	Cl	Me	phenyl	4	49	14
9	Cl	Bn	phenyl	5	38	15
4	Br	H	(<i>E</i>)-styryl	2	27	16
5	Br	Me	(<i>E</i>)-styryl	1	58	17
6	Br	Bn	(<i>E</i>)-styryl	1	42	18
7	Cl	H	(<i>E</i>)-styryl	2	-	16
8	Cl	Me	(<i>E</i>)-styryl	1	44	17
9	Cl	Bn	(<i>E</i>)-styryl	1	45	18
4	Br	H	biphenyl-4-yl	1	-	19
5	Br	Me	biphenyl-4-yl	1	48	20
6	Br	Bn	biphenyl-4-yl	1	54	21
7	Cl	H	biphenyl-4-yl	2	11	19
8	Cl	Me	biphenyl-4-yl	1	71	20
9	Cl	Bn	biphenyl-4-yl	1	48	21

In conclusion, we have developed a new convenient convergent synthetic access to the pharmacologically important class of 8-substituted xanthine derivatives. The new method would be suitable for

combinatorial synthesis, e.g. on solid phase by attachment of the xanthine nucleus to the polymer via the N7-position. Pharmacological evaluation of the new compounds will be described elsewhere.

EXPERIMENTAL

NMR spectra were measured on a Bruker 500 spectrometer (^1H : 500 MHz, ^{13}C : 126 MHz). The chemical shifts of the remaining protons of the deuterated solvents served as internal standard: ^1H : δ : DMSO- d_6 = 2.49, CDCl_3 = 7.24; ^{13}C : DMSO- d_6 = 39.7, CDCl_3 = 77.0. Melting points were taken on a Büchi B-535 melting point apparatus and are uncorrected. TLC was performed on silica gel-coated aluminum plates 60 F₂₅₄ (Merck). Compounds were detected by UV (254 nm). Elemental analyses were performed in the Pharmaceutical Institute (Bonn-Endenich) on a VarioEL apparatus (Elementar Analysensysteme GmbH). Mass spectra were recorded on an MS-50 (A. E. I., Manchester).

DMF was distilled under argon from P_2O_5 . THF was distilled under argon from potassium. Phenylboronic acid (**10**), 8-bromotheophylline (**4**), 4-bromobiphenyl and $\text{Pd}(\text{PPh}_3)_4$ were purchased from Fluka Chemical Co. 8-Chlorotheophylline (**7**) and *n*-butyllithium (1.6 M in hexane) were obtained from Aldrich Chemical Co. (*E*)-Styrylboronic acid (**11**) was prepared according to a literature procedure.¹¹ Biphenyl-4-ylboronic acid (**12**) was prepared following a literature procedure with a slight modification.^{12,13} *n*-Butyllithium was used instead of magnesium turnings. N7-methyl- and N7-benzyl-substituted xanthines were prepared by alkylation of 8-halogenated theophyllines as described below. $\text{B}(\text{OMe})_3$ was distilled before use and stored over molecular sieve 4 Å under argon.¹⁴

All experiments were performed in glassware which was evacuated and purged with argon three times, heated with a heat gun and cooled to rt *in vacuo*. The reactions were performed in the dark. The sequence of the addition of the reagents had no effect on the success of the reactions. After completion of the reactions, the mixtures were evaporated *in vacuo* and the residues were purified by column chromatography on silica gel (63-200 μm).

N7-Alkylated xanthine derivatives (5, 6, 8, 9)

*Typical procedure according to literature*⁷: 8-Bromotheophylline (**4**) or 8-chlorotheophylline (**7**), respectively, (1.93 mmol) was suspended in DMF (20 mL). After the addition of K_2CO_3 (533 mg, 3.86 mmol) and benzyl bromide (458 μL , 3.86 mmol) or methyl iodide (156 μL , 2.51 mmol) respectively, the mixture was stirred for 6 h at rt. Then, water (40 mL) was added and the mixture was cooled to 4 °C for 2 h. The product was collected by filtration, washed with water (10 mL), and dried in a vacuum desiccator.

8-Bromo-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (5)

Yield: 71%; mp: 206 °C (lit., mp 206 °C)¹⁵. ¹H-NMR (CDCl₃): 3.37 (s, 3H, N1-CH₃), 3.53 (s, 3H, N3-CH₃), 3.94 (s, 3H, N7-CH₃). ¹³C-NMR (methanol-*d*₄): 28.4 (N1-CH₃), 30.2 (N3-CH₃), 36.9 (N7-CH₃), 109.8 (C5), 128.6 (C8), 148.5 (C4), 151.7 (C2), 154.9 (C6).

7-Benzyl-8-bromo-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (6)

Yield: 96%; mp: 164 °C (lit., mp 164-165 °C)¹⁶. ¹H-NMR (DMSO-*d*₆): 3.21 (s, 3H, N1-CH₃), 3.39 (s, 3H, N3-CH₃), 5.51 (s, 2H, N7-CH₂), 7.23-7.36 (m, 5H, H_{arom}). ¹³C-NMR (DMSO-*d*₆): 27.8 (N1-CH₃), 29.7 (N3-CH₃), 49.5 (N7-CH₂), 108.5 (C5), 127.2 (Ar), 128.0 (Ar), 128.3 (C8), 128.9 (Ar), 135.7 (Ar), 148.0 (C4), 150.8 (C2), 153.9 (C6).

8-Chloro-1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione (8)

Yield: 79%; mp: 187 °C (lit., mp 187-188 °C)¹⁷. ¹H-NMR (CDCl₃): 3.37 (s, 3H, NCH₃), 3.51 (s, 3H, NCH₃), 3.92 (s, 3H, NCH₃). ¹³C-NMR (DMSO): 28.0 (N1-CH₃), 29.8 (N3-CH₃), 32.7 (N7-CH₃), 108.2 (C5), 138.9 (C8), 147.1 (C4), 151.3 (C2), 154.6 (C6).

7-Benzyl-8-chloro-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione (9)

Yield: 98%; mp: 152 °C (lit., mp 152 °C)¹⁸. ¹H-NMR (DMSO-*d*₆): 3.22 (s, 3H, N1-CH₃), 3.39 (s, 3H, N3-CH₃), 5.52 (s, 2H, N7-CH₂), 7.28 (m, 3H, H_{arom}), 7.35 (m, 2H, H_{arom}). ¹³C-NMR (DMSO-*d*₆): 27.8 (N1-CH₃), 29.7 (N3-CH₃), 48.6 (N7-CH₂), 107.5 (C5), 127.4 (Ar), 128.2 (Ar), 128.9 (Ar), 135.6 (Ar), 138.0 (C8), 147.0 (C4), 150.8 (C2), 154.0 (C6).

(*E*)-Styrylboronic acid (dihydroxy-(*E*)-styrylborane) (11)

Phenylacetylene (5.5 mL, 50.0 mmol) and catecholborane (50.0 mL, 50.0 mmol) were heated to 70 °C in a sealed tube under an argon atmosphere for 7 h. The solution was subsequently evaporated to dryness *in vacuo*. To the residue, water (35 mL) was added and the mixture was stirred at rt overnight. The formed precipitate was collected by filtration and washed with pentane (10 mL). The crude material was recrystallized from hot water. Yield: 5.69 g (77%); mp: 163 °C (lit., mp 163-164 °C)¹⁹. ¹H-NMR (methanol-*d*₄): 6.40 (d, *J* = 18.2 Hz, 1H, C=CH), 7.32 (d, *J* = 7.4 Hz, 1H, H_{arom}), 7.36 (d, *J* = 18.2 Hz, 1H, C=CH), 7.38 (dd, *J* = 7.4 Hz, 6.9 Hz, 2H, H_{arom}), 7.55 (d, *J* = 6.9 Hz, 2H, H_{arom}). ¹³C-NMR (methanol-*d*₄): 116.7 (Ar), 128.3 (Ar), 129.9 (Ar), 130.1 (Ar), 139.5 (Ar), 149.8 (Ar).

Biphenyl-4-yl-boronic acid [(4-biphenyl)dihydroxyborane] (12)

A solution of 4-bromobiphenyl (3.00 g, 12.9 mmol) in THF (15 mL) at -78 °C was added within 10 min to a solution of *n*-BuLi (12.9 mL, 20.6 mmol) in THF (15 mL) at -78 °C. After stirring the mixture at –

78 °C for 25 min, the obtained white suspension was added within 15 min to a cold solution (-78 °C) of B(OMe)₃ (5.0 mL, 45.0 mmol) in THF (10 mL). The reaction mixture was allowed to warm to rt overnight and was stirred for another 7 h at rt. Then the solvent was evaporated to dryness *in vacuo* and water (10 mL) was added to the oily residue. A pH value of 6-7 was obtained by the addition of 2 mol / L HCl solution. After 3 h the precipitate was collected by filtration and washed with water (10 mL). The crude material was purified by column chromatography (silica gel, 25 g, 63–200 μm), at first with CH₂Cl₂ (200 mL) and then with CH₂Cl₂ : MeOH (2.5 : 1, 80 mL) as a solvent. Yield: 1.05 g (41 %), mp: 264 °C (lit., mp 264-266 °C)¹³. ¹H-NMR (DMSO-*d*₆): 7.35 (1H, ddd, *J* = 7.25 Hz, 1.3 Hz, 1.25 Hz, H_{arom}), 7.45 (2H, dd, *J* = 7.85 Hz, 7.6 Hz, H_{arom}), 7.61 (2H, d, *J* = 8.2 Hz, H_{arom}), 7.66 (2H, ddd *J* = 7.85 Hz, 1.9 Hz, 1.6 Hz, H_{arom}), 7.86 (2H, d, *J* = 8.2 Hz, H_{arom}), 8.04 (2H, s, OH). ¹³C-NMR (DMSO-*d*₆): 125.8 (Ar), 126.9 (Ar), 127.7 (Ar), 129.1 (Ar), 134.9 (Ar), 140.3 (Ar), 141.7 (Ar). (C-B signal often not detectable in ¹³C NMR spectrum²⁰).

Suzuki coupling products (13-21)

Typical procedure: To a solution of tetrakis(triphenylphosphine)palladium(0) (50.0 mg, 43.3 μmol, 0.05 eq) in DMF (5 mL) was added 8-halogenxanthine (**4-6**) (0.866 mmol), the appropriate boronic acid (1.04 mmol) and anhydrous K₃PO₄ (404 mg, 1.91 mmol). The mixture was stirred at a temperature of 110 °C. For reaction times see Table 1. The reaction mixture was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel, about 90 g) using the appropriate eluent. For 7-unsubstituted 8-aryl xanthines, CH₂Cl₂ : MeOH (100 : 1), and for 7-substituted 8-aryl xanthines, CH₂Cl₂ : ethyl acetate (20 : 1) was used as eluent.

During the reaction of 8-bromotheophylline (**4**) to yield **16**, the formation of 4-phenylphenol (biphenyl-4-ol) as a by-product was observed and isolated in 23% yield. Reaction times and yields of the products are listed in Table 1.

1,3-Dimethyl-8-phenyl-3,7-dihydro-1*H*-purine-2,6-dione (13)

mp 389 °C (lit., mp 388-394 °C)²¹. ¹H-NMR (CDCl₃): 3.26 (s, 3H, N1-CH₃), 3.50 (s, 3H, N3-CH₃), 7.49 (m, 3H, H_{arom}), 8.12 (d, *J* = 6.6 Hz, 2H, H_{arom}), 13.81 (s, 1H).

1,3,7-Trimethyl-8-phenyl-3,7-dihydro-1*H*-purine-2,6-dione (14)

mp 178 °C (lit., mp 178 °C)⁶. ¹H-NMR (CDCl₃): 3.41 (s, 3H, N1-CH₃), 3.61 (s, 3H, N3-CH₃), 4.04 (s, 3H, N7-CH₃), 7.59 (m, 3H, H_{arom}), 7.66 (m, 2H, H_{arom}). ¹³C-NMR (CDCl₃): 28.0 (N1-CH₃), 29.8 (N3-CH₃), 33.9 (N7-C), 108.5 (C5), 128.9, 129.2, 130.4, 148.3 (C4), 151.7 (C8), 151.8, 152.1 (C2), 155.6 (C6).

7-Benzyl-1,3-dimethyl-8-phenyl-3,7-dihydro-1H-purine-2,6-dione (15)

mp 164 °C. ¹H-NMR (CDCl₃): 3.39 (s, 3H, N1-CH₃), 3.64 (s, 3H, N3-CH₃), 5.62 (s, 2H, CH₂), 7.02 (d, *J* = 6.3 Hz, 2H, H_{arom}), 7.25 (dd, *J* = 7.3 Hz, 6.3 Hz, 3H, H_{arom}), 7.45 (d, *J* = 7.3 Hz, 2H, H_{arom}), 7.48 (d, *J* = 7.3 Hz, 1H, H_{arom}), 7.56 (d, *J* = 7.0 Hz, 2H, H_{arom}). *Anal.* Calcd for C₂₀H₁₈N₄O₂: C, 69.35; H, 5.24; N, 16.17. Found: C, 69.53; H, 5.44; N, 16.39.

1,3-Dimethyl-8-(E)-styryl-3,7-dihydro-1H-purine-2,6-dione (16)

mp 357 °C (lit., mp >360 °C)²². ¹H-NMR (CDCl₃): 3.24 (s, 3H, N1-CH₃), 3.47 (s, 3H, N3-CH₃), 7.01 (d, *J* = 16.4 Hz, 1H, C=CH), 7.35 (d, *J* = 7.3 Hz, 1H, H_{arom}), 7.41 (dd, *J* = 7.9 Hz, 7.3 Hz, 2H, H_{arom}), 7.61 (d, *J* = 7.9 Hz, 2H, H_{arom}), 7.64 (d, *J* = 16.4 Hz, 1H, C=CH) (^b no N7-H signal could be detected due to rapid exchange) ¹³C-NMR (CDCl₃): 27.9 (N1-CH₃), 29.3 (N3-CH₃), 107.4 (C5), 116.0, 127.2, 129.1, 129.7, 135.1, 135.6, 148.7 (C4), 149.6 (C8), 151.3 (C2), 154.2 (C6).

1,3,7-Trimethyl-8-(E)-styryl-3,7-dihydro-1H-purine-2,6-dione (17)

mp 223 °C (lit., mp 222-223 °C)²³. ¹H-NMR (CDCl₃): 3.40 (s, 3H, N1-CH₃), 3.61 (s, 3H, N3-CH₃), 4.05 (s, 3H, N7-CH₃), 6.90 (d, *J* = 15.8 Hz, 1H, C=CH), 7.35 (d, *J* = 7.0 Hz, 1H, H_{arom}), 7.39 (dd, *J* = 7.6 Hz, 7.0 Hz, 2H, H_{arom}), 7.56 (d, *J* = 7.0 Hz, 2H, H_{arom}), 7.79 (d, *J* = 15.8 Hz, 1H, C=CH). ¹³C-NMR (CDCl₃): 27.9 (N1-CH₃), 29.8 (N3-CH₃), 31.5 (N7-CH₃), 107.8 (C5), 111.2, 127.4, 128.9, 129.5, 135.5, 138.3, 148.5 (C4), 149.9 (C8), 151.7 (C2), 155.2 (C6).

7-Benzyl-1,3-dimethyl-8-(E)-styryl-3,7-dihydro-1H-purine-2,6-dione (18)

mp 207 °C. ¹H-NMR (CDCl₃): 3.44 (s, 3H, N1-CH₃), 3.68 (s, 3H, N3-CH₃), 5.72 (s, 2H, CH₂), 6.96 (d, *J* = 15.7 Hz, 1H, C=CH), 7.37 (m, 8H, H_{arom}), 7.53 (d, *J* = 6.8 Hz, 2H, H_{arom}), 7.84 (d, *J* = 15.7 Hz, 1H, C=CH). ¹³C-NMR (CDCl₃): 28.0 (N1-CH₃), 29.8 (N3-CH₃), 47.9 (N7-CH₂), 107.4 (C5), 111.6, 126.9, 127.4, 128.2, 128.9, 129.1, 129.5, 135.4, 136.1, 138.5, 148.8 (C4), 150.0 (C8), 151.7 (C2), 155.0 (C6). *Anal.* Calcd for C₂₂H₂₀N₄O₂: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.56; H, 5.36; N, 14.96.

8-Biphenyl-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (19)

mp 333 °C (lit., mp >300 °C)²⁴. ¹H-NMR (DMSO-*d*₆): 3.27 (s, 3H, N1-CH₃), 3.51 (s, 3H, N3-CH₃), 7.40 (dd, *J* = 7.55 Hz, 7.25 Hz, 1H, H_{arom}), 7.49 (dd, *J* = 7.85 Hz, 7.6 Hz, 2H, H_{arom}), 7.74 (dd, *J* = 8.55 Hz, 1.3 Hz, 2H, H_{arom}), 7.82 (d, *J* = 8.85 Hz, 2H, H_{arom}), 8.23 (d, *J* = 8.5 Hz, 2H, H_{arom}), 13.90 (br s, 1H).

8-Biphenyl-1,3,7-trimethyl-8-(E)-styryl-3,7-dihydro-1H-purine-2,6-dione (20)

mp 230 °C. ¹H-NMR (CDCl₃): 3.43 (s, 3H, N1-CH₃), 3.63 (s, 3H, N3-CH₃), 4.09 (s, 3H, N7-CH₃), 7.39

(dd, $J = 7.35$ Hz, 7.35 Hz, 1H, H_{arom}), 7.47 (dd, $J = 7.85$ Hz, 7.35 Hz, 2H, H_{arom}), 7.62 (dd, $J = 8.4$ Hz, 1.4 Hz, 2H, H_{arom}), 7.73 (d, $J = 8.6$ Hz, 2H, H_{arom}), 7.76 (d, $J = 8.6$ Hz, 2H, H_{arom}). ^{13}C -NMR (CDCl_3): 28.0 (N1- CH_3), 29.8 (N3- CH_3), 34.0 (N7- CH_3), 108.6 (C5), 127.14, 127.15, 127.6, 128.1, 129.0, 129.6, 139.9, 143.2, 148.3 (C4), 151.7 (C8*), 151.8 (C2*), 155.6 (C6). (* no unambiguous assignment possible). MS (EI): 346.2 (M^+ , 100 %), 272.0 ($\text{M}^+ - 74.2$, 19 %), 167.1 ($\text{M}^+ - 179.1$, 26 %). HRMS: calcd MW = 346.1429, found MW = 346.1425. *Anal.* Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_2 \cdot 0.2 \text{CH}_2\text{Cl}_2$: C, 66.77; H, 5.10; N, 15.42. Found: C, 67.09; H, 5.22; N, 15.45.

7-Benzyl-8-biphenyl-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (21)

mp 228 °C. ^1H -NMR (CDCl_3): 3.40 (s, 3H, N1- CH_3), 3.66 (s, 3H, N3- CH_3), 5.68 (s, 2H, CH_2), 7.07 (d, 2H, $J = 6.9$ Hz, H_{arom}), 7.28 (m, 3H, H_{arom}), 7.37 (dd, $J = 7.25$ Hz, 7.2 Hz, 1H, H_{arom}), 7.45 (dd, $J = 7.6$ Hz, 7.55 Hz, 2H, H_{arom}), 7.60 (dd, $J = 8.5$ Hz, 1.6 Hz, 2H, H_{arom}), 7.66 (m, 4H, H_{arom}). ^{13}C -NMR (CDCl_3): 28.0 (N1- CH_3), 29.8 (N3- CH_3), 49.5 (N7- CH_2), 108.1 (C5), 126.3, 127.1, 127.3, 127.6, 127.9, 128.1, 128.9, 129.0, 129.6, 136.7, 139.8, 143.3, 148.6 (C4), 151.7 (C8), 152.4 (C2), 155.2 (C6). MS (EI): 422.2 (M^+ , 100 %), 331.2 ($\text{M}^+ - \text{C}_7\text{H}_7$, 88 %), 246.1 ($\text{M}^+ - \text{C}_3\text{H}_5\text{N}_2\text{O} - \text{C}_7\text{H}_7$, 26 %), 91.1 (C_7H_7^+ , 58 %). HRMS: calcd MW = 422.1743, found MW = 422.1742. *Anal.* Calcd for $\text{C}_{26}\text{H}_{22}\text{N}_4\text{O}_2$: C, 73.92; H, 5.25; N, 13.26. Found: C, 73.66; H, 5.28; N, 13.20.

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