Synthesis of Fused Purinoquinazolines. Three New Heterocyclic Ring Systems.

Antonio Da Settimo*, Giampaolo Primofiore, Bertacchi Maria Cristina, Federico Da Settimo, and Anna Maria Marini

Dipartimento di Scienze Farmaceutiche, Via Bonanno 6, 56126 Pisa, Italy

Received December 5, 1994

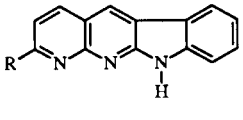
The Ullmann reaction of 8-aminotheophylline or 8-aminocaffeine with 2-chlorobenzoic acid and of 8-bromotheophylline with ethyl-2-aminobenzoate afforded derivatives of three new heterocyclic systems: purino[7,8-*a*]quinazoline-5,9,11(6*H*,8*H*,10*H*)-trione, purino[8,9-*b*]quinazoline-2,4,11(1*H*,3*H*,5*H*)-trione and purino[8,7-*b*]quinazoline-2,4,6(1*H*,3*H*,11*H*)-trione, respectively.

J. Heterocyclic Chem., **32**, 941 (1995).

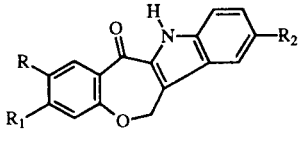
Pursuing our interest in the field of new heteropolycyclic compounds which can be related to important alkaloids containing the indole nucleus as a part of a polycyclic system, in the past we have described the synthesis of some 6*H*-indolo[2,3-*b*][1,8]naphthyridines **1** [1] and, more recently, of some 5*H*,12*H*-[1]benzoxepino[4,3-*b*]-indol-6-ones **2** [2].

In the last few years we have also reported the synthesis of molecules which contain new heterocyclic ring systems, such as a number of 5,7-dihydro-5-oxopyrido[3',2':5,6]pyrimido[1,2-*a*]benzimidazoles **3** [3] and 11-alkyl-5,11-dihydro-5-oxopyrido[2',3':4,5]pyrimido[1,2-*a*]benzimidazoles **4** [4].

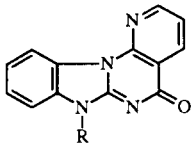
As part of our studies on new planar heteropolycyclic compounds as new potential antitumor agents, we wish now to report the synthesis of some purinoquinazoline derivatives: 8,10-dimethylpurino[7,8-*a*]quinazoline-5,9,11(6*H*,8*H*,10*H*)-triones **6**, **8** and **9**, 1,3-dimethylpurino[8,7-*b*]quinazoline-2,4,6(1*H*,3*H*,11*H*)-triones **11**, **13** and **14**, and 1,3,5-trimethylpurino[8,9-*b*]quinazoline-2,4,11(1*H*,3*H*,5*H*)-trione **17**, each one of these structures representing a new heterocyclic ring system.



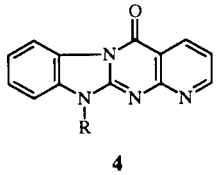
1



2



3



4

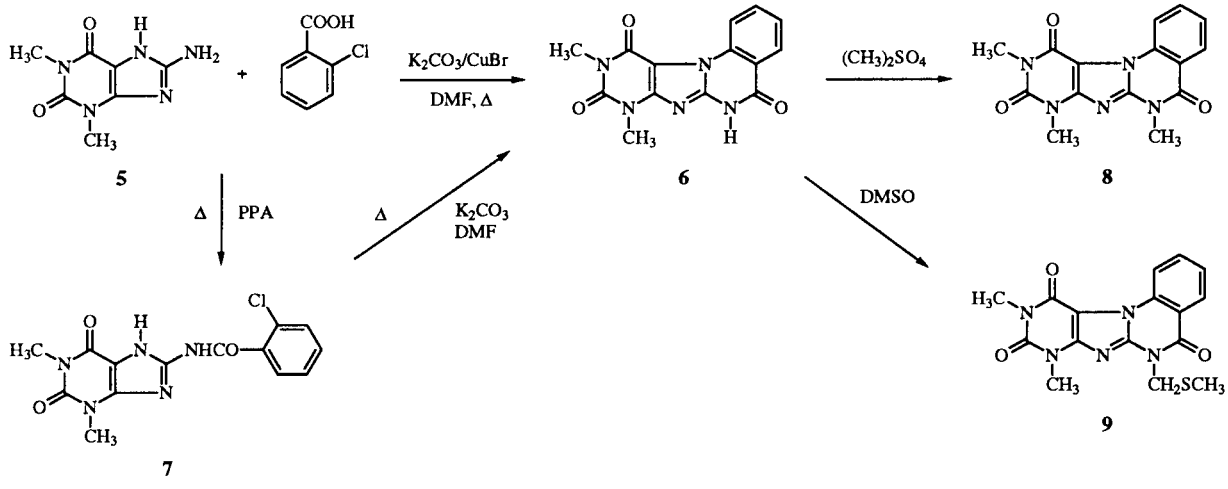
The target compound **6** was synthesized in 40% yield as shown in Scheme 1, *via* an Ullmann reaction between 2-chlorobenzoic acid and 8-aminotheophylline **5** [5,6], in the presence of anhydrous potassium carbonate and a catalytic amount of cuprous bromide. The structure of **6** was confirmed by analytical, ir, ^{1}H nmr and mass (M^+, m/z = 297) spectral data (Table 1) and chemical evidence. When 8-aminotheophylline **5** and an equimolar amount of 2-chlorobenzoic acid were heated at 120° with an excess of polyphosphoric acid (PPA), the benzamide **7** was obtained in 45% yield (Scheme 1). Its structure was confirmed by analytical, ir and ^{1}H nmr spectral data. The cyclization reaction of **7** to **6** was effected by refluxing **7** for 4 hours in DMF in the presence of anhydrous potassium carbonate [7] (Scheme 1). Crude **6** can easily be purified by sublimation and recrystallization from DMF (51% yield). The preparation of **6** from **7** confirms the structure proposed for **6**, because the cyclization of the amide **7** on the N(9) of theophylline is not possible, due to the steric hindrance of the 3-methyl group (Dreiding models) [8].

Compound **6** was methylated to **8** with dimethyl sulphate in acetonitrile solution, in the presence of potassium carbonate [9], in a satisfactory yield (68%) (Scheme 1). The structure of **8** was confirmed by analytical, ir, ^{1}H nmr and mass data (Table 1). On the other hand, methylation at the 7 position is not possible because of the steric hindrance of the 8-methyl group [8].

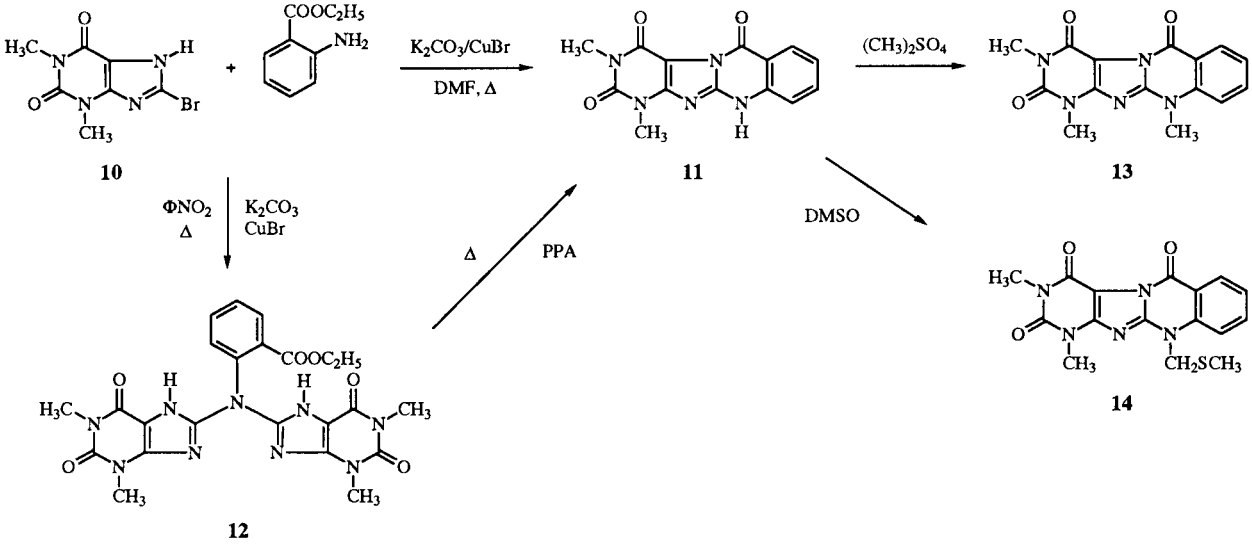
When **6** was refluxed for 10 hours in a small volume of DMSO, a mixture of **6** and of the methylthiomethyl derivative **9** was obtained (Scheme 1), which was separated by preparative tlc. A similar reaction is reported in literature for amide compounds such as isatin, phthalimide, saccharin, *etc.* [10-12]. The structure of compound **9** was mainly confirmed by elemental analysis, which revealed the presence of sulfur in the molecular formula, by the ^{1}H nmr spectrum which showed, in addition to the singlets relative to the methyl groups at the positions 8 and 10, also another CH_3 at δ = 2.35 ppm and a CH_2 at δ = 5.42 ppm, and by the mass spectrum in which the base peak at m/z = 61 was due to the CH_2SCH_3 fragment (Table 1).

The 1,3-dimethylpurino[8,7-*b*]quinazoline-2,4,6-(1*H*,3*H*,11*H*)-trione **11**, an isomer of **6**, was prepared in 45% yield *via* an Ullmann reaction between 8-bromotheophylline

Scheme 1



Scheme 2



Scheme 3

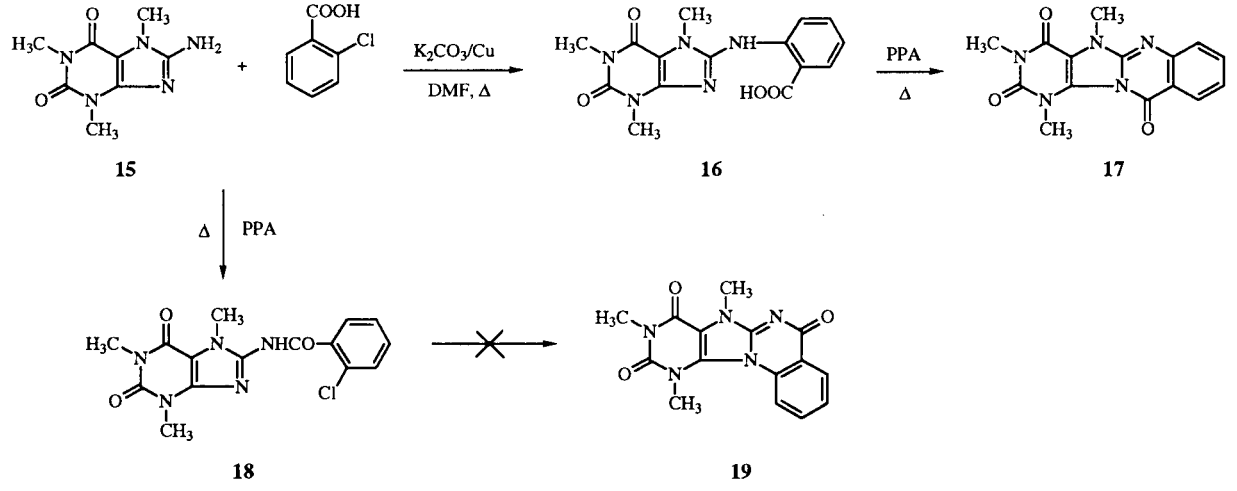
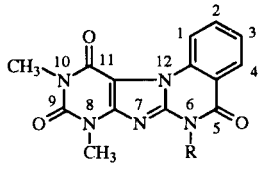


Table 1

Physical and Spectral Data of Compounds **6**, **8** and **9**



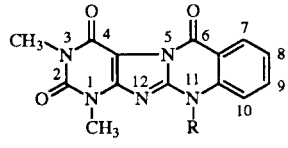
6, 8, 9

Compound No.	R	Yield (%)	Mp (°C) (recrystallization solvent)	IR (cm^{-1})	^{1}H-NMR (δ ppm) (DMSO-d_6) [a]	MS m/z (R.I. %)	Molecular Formula	Analysis(%) Calcd./Found C	H	N
6	H	40	>300 (DMF)	3150, 1680, 1640, 1600, 1510, 1220, 1130, 760.	3.32 (s, 3H, 10-CH_3), 3.47 (s, 3H, 8-CH_3), 7.45-9.65 (m, 4H, Ar-H).	M$^+$297 (100)	$C_{14}H_{11}N_5O_3$	56.57 56.48	3.73 3.81	23.56 23.65
8	CH_3	68	289-290 (DMF)	1670, 1640, 1590, 1510, 1430, 1230, 980, 760, 750.	3.34 (s, 3H, 10-CH_3), 3.52 (s, 3H, 8-CH_3), 3.67 (s, 3H, 6-CH_3), 7.50-9.65 (m, 4H, Ar-H).	M$^+$311 (100)	$C_{15}H_{13}N_5O_3$	57.88 58.00	4.21 4.25	22.50 22.38
9	CH_2SCH_3	56	278-280 (DMSO)	1690, 1640, 1600, 1580, 1540, 1500, 1220, 980, 760, 740.	2.35 (s, 3H, S-CH_3), 3.37 (s, 3H, 10-CH_3), 3.54 (s, 3H, 8-CH_3), 5.42 (s, 2H, CH_2-S), 7.55-9.75 (m, 4H, Ar-H).	M$^+$357 (7), 61 (100)	$C_{16}H_{15}N_5O_3S$	53.77 53.61	4.23 4.19	19.60 19.69

[a] Recorded on a Bruker AC-200.

Table 2

Physical and Spectral Data of Compounds **11**, **13** and **14**



11, 13, 14

Compound No.	R	Yield (%)	Mp (°C) (recrystallization solvent)	IR (cm^{-1})	^{1}H NMR (δ ppm) (DMSO-d_6) [a]	MS m/z (R.I. %)	Molecular Formula	Analysis(%) Calcd./Found C	H	N
11	H	45	>300 (DMF)	3070, 1710, 1680, 1620, 1510, 1300, 1230, 750.	3.28 (s, 3H, 3-CH_3), 3.49 (s, 3H, 1-CH_3), 7.30-8.20 (m, 4H, Ar-H).	M$^+$297 (100)	$C_{14}H_{11}N_5O_3$	56.57 56.55	3.73 3.80	23.56 23.68
13	CH_3	40	>300 (DMF)	1720, 1640, 1610, 1580, 1500, 1420, 740.	3.27 (s, 3H, 3-CH_3), 3.51 (s, 3H, 1-CH_3), 3.96 (s, 3H, 11-CH_3), 7.40-8.30 (m, 4H, Ar-H).	M$^+$311 (2), 15 (100)	$C_{15}H_{13}N_5O_3$	57.88 57.95	4.21 4.19	22.50 22.39
14	CH_2SCH_3	42	>300 (DMSO)	1720, 1680, 1650, 1600, 1500, 1220, 740.	2.25 (s, 3H, S-CH_3), 3.24 (s, 3H, 3-CH_3), 3.45 (s, 3H, 1-CH_3), 5.78 (s, 2H, CH_2-S), 7.40-8.30 (m, 4H, Ar-H).	M$^+$357 (3), 61 (100)	$C_{16}H_{15}N_5O_3S$	53.77 53.87	4.23 4.30	19.60 19.55

[a] Recorded on a Bruker AC-200.

10 and anthranilic acid ethyl ester in DMF in the presence of anhydrous potassium carbonate and a small amount of cuprous bromide (Scheme 2). The structure of **11** was confirmed by analytical, ir, ^{1}H nmr and mass data (Table 2).

When this reaction was performed with an excess of **10** in refluxing nitrobenzene, the *N*-(2-ethoxycarbonylphenyl)-di-8-theophyllinamine **12** was obtained in 41% yield (Scheme 2). Analytical data, ir and mass (M^+, m/z = 521) spectra are in agreement with the proposed structure **12**.

Compound **12** can be cyclized to **11** in 77% yield by treatment with PPA at 180° (Scheme 2).

Compound **11** was methylated to give **13** in the same conditions employed for the preparation of **8** (Scheme 2, Table 2).

Compound **14** was obtained by refluxing **11** with DMSO as described above for **9** (Scheme 2, Table 2).

When 8-aminocaffeine **15** and *o*-chlorobenzoic acid were submitted to the Ullmann reaction, only the amine **16** was isolated in 40% yield (Scheme 3). By heating compound **16** with an excess of PPA at 120°, the cyclization product **17**, an isomer of **8** and **13**, was obtained (Scheme 3).

8-Aminocaffeine **15** was synthesized from 8-aminotheophylline **5** using a method described in literature for the preparation of 7-alkyl-8-amino-1,3-dimethylxanthines [13].

When 8-aminocaffeine **15** and *o*-chlorobenzoic acid were directly heated with PPA at 120°, the amide **18** was obtained in 44% yield (Scheme 3). Numerous attempts to cyclize **18** to **19** were unsuccessful (Scheme 3), probably because the cyclization reaction at the N(9) of the xanthine nucleus was impeded by the presence of the methyl group at position 3 due to its steric hindrance, thus further confirming the structure proposed for compound **6**.

EXPERIMENTAL

Melting points were determined using a Reichert Köfler hot-stage apparatus and are uncorrected. Infrared spectra were obtained on a PYE/UNICAM mod. PU 9561 spectrophotometer in Nujol mulls. Nuclear magnetic resonance spectra were recorded on a Varian CFT-20 spectrometer, unless otherwise reported, using tetramethylsilane (TMS) as the internal standard. Mass spectra were obtained on a Hewlett-Packard 5988 A spectrometer using a direct injection probe and an electron beam energy of 70 eV. Magnesium sulfate was always used as the drying agent. Evaporations were made *in vacuo* (rotating evaporator). Analytical tlc was carried out on Merck 0.2 mm precoated silica gel aluminium sheets (60 F-254). Elemental analyses were performed by our Analytical Laboratory and agreed with theoretical values to within ± 0.4%.

8,10-Dimethylpurino[7,8-*a*]quinazoline-5,9,11(6*H*,8*H*,10*H*)-trione **6**.

A) From 8-Aminotheophylline **5**.

A suspension of 8-aminotheophylline **5** (1.95 g, 10 mmoles), 2-chlorobenzoic acid (1.56 g, 10 mmoles), anhydrous potassium carbonate (1.66 g, 12 mmoles) and 0.05 g of cuprous bromide in 5 ml of DMF was heated at 180° for 16 hours. After cooling, the reaction mixture was diluted with water and acidified with concentrated hydrochloric acid. The crude product was collected and purified by sublimation (270-300°, 0.4 mm Hg). The recrystallization solvent, yield, melting point, analytical, and spectral data are given in Table 1.

B) From 8-(2-Chlorobenzoylamino)theophylline **7**.

A suspension of **7** (0.20 g, 0.6 mmole) and anhydrous potassium carbonate (0.25 g, 1.8 mmoles) in 5 ml of DMF was refluxed for 4 hours, and then, after cooling, it was diluted with water and acidified with concentrated hydrochloric acid. The crude product was collected and purified by sublimation (0.091 g, yield 51%).

8-(2-Chlorobenzoylamino)theophylline **7**.

8-Aminotheophylline **5** (0.51 g, 2.6 mmoles) and 2-chlorobenzoic acid (0.41 g, 2.6 mmoles) were added to 6.0 g of PPA, and heated at 120° under stirring for 1 hour. The reaction mixture, after cooling, was treated with iced water. The solid obtained was collected, washed with saturated aqueous sodium hydrogen carbonate solution and with water, and then purified by recrystallization from ethanol to give 0.39 g of pure **7** (yield 45%), mp 284-286°; ir: 3170, 1680, 1640, 1500, 1320 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.27 (s, 3H, 1-CH_3), 3.43 (s, 3H, 3-CH_3), 7.67 (s, 4H, Ar-H), 12.30 (br s, 1H, 7 NH) ppm; ms: m/z (relative intensity) 333 (M^+ 7), 139 (100).

Anal. Calcd. for $C_{14}H_{12}ClN_5O_3$: C, 50.39; H, 3.62; N, 20.98. Found: C, 50.46; H, 3.57; N, 21.10.

6,8,10-Trimethylpurino[7,8-*a*]quinazoline-5,9,11(6*H*,8*H*,10*H*)-trione **8**, and 1,3,11-Trimethylpurino[8,7-*b*]quinazoline-2,4,6(1*H*,3*H*,11*H*)-trione **13**.

A solution of dimethyl sulphate (0.38 ml, 4 mmoles) in acetone (2 ml) was added dropwise, at 0°, to a suspension of anhydrous potassium carbonate (0.138 g, 1 mmole) and of **6** or **11** (0.297 g, 1 mmole) in acetonitrile (5 ml). The reaction mixture was allowed to stir at room temperature for 8 hours. The solid was collected, washed with water and purified by recrystallization. The recrystallization solvents, yields, melting points, analytical, and spectral data are given in Tables 1 and 2.

8,10-Dimethyl-6-methylthiomethylpurino[7,8-*a*]quinazoline-5,9,11(6*H*,8*H*,10*H*)-trione **9**, and 1,3-Dimethyl-11-methylthiomethylpurino[8,7-*b*]quinazoline-2,4,6(1*H*,3*H*,11*H*)-trione **14**.

A solution of **6** or **11** (0.199 g, 0.67 mmole) in DMSO (5 ml) was heated at reflux for 10 hours. After cooling, the solid collected proved to be a mixture of the starting material and of the methylthiomethyl derivative **9** or **14**, respectively. Separations of compounds **9** and **14** from the corresponding starting materials were carried out by preparative tlc on Merck 2 mm precoated silica gel glass plates (60-F 254) using chloroform:methanol = 9.5:0.5 as the eluting system. The solid recovered was purified by recrystallization (Tables 1 and 2).

1,3-Dimethylpurino[8,7-*b*]quinazoline-2,4,6(1*H*,3*H*,11*H*)-trione **11**.

A) From 8-Bromotheophylline **10**.

A suspension of 8-bromotheophylline **10** (0.78 g, 3 mmoles), ethyl 2-aminobenzoate (0.61 g, 3.7 mmoles), anhydrous potassium carbonate (0.51 g, 3.7 mmoles) and a small amount of cuprous bromide in 5 ml of DMF was heated at 180° for 70

hours. After cooling, the suspension was treated with water and acidified with concentrated hydrochloric acid. The solid was collected and purified by sublimation (270-300°, 0.4 mm Hg). The recrystallization solvent, yield, melting point, analytical, and spectral data are given in Table 2.

B) From *N*-(2-Ethoxycarbonylphenyl)-di-8-theophyllinamine **12**.

A mixture of **12** (1.5 g, 2.9 mmoles) and 15 g of PPA was heated at 180°, under stirring, for 40 minutes. The reaction mixture, after cooling, was treated with iced water and the solid formed was collected. A further amount of the product could be obtained by neutralization with concentrated ammonia of the acid mother liquor. The solids collected were combined and purified by sublimation and recrystallization from DMF obtaining 0.656 g (yield 77%) of pure **11**.

N-(2-Ethoxycarbonylphenyl)-di-8-theophyllinamine **12**.

A suspension of 8-bromotheophylline **10** (2.95 g, 10 mmoles), ethyl 2-aminobenzoate (0.5 ml, 10 mmoles), anhydrous potassium carbonate (1.49 g, 10 mmoles) and a small amount of cuprous bromide in 3 ml of nitrobenzene was heated at 220° for 15 hours. After cooling, the reaction mixture was treated with water and acidified with concentrated hydrochloric acid. The solid was collected, washed with petroleum ether 40-60° and ethanol, and purified by recrystallization from DMF to give 2.15 g (yield 41%) of pure **12**, mp >300°; ir: 1690, 1660, 1610, 1560, 1520, 1290, 1210 cm^{-1}; ms: m/z (relative intensity) 521 (M^+ 12), 29 (100).

Anal. Calcd. for $C_{23}H_{23}N_9O_6$: C, 52.97; H, 4.45; N, 24.17. Found: C, 53.03; H, 4.60; N, 24.08.

8-Aminocaffeine **15**.

Sodium hydride (0.984 g, 41 mmoles, dispersion in mineral oil) was added in small portions to a hot suspension (90°) of 7.02 g (36 mmoles) of 8-aminotheophylline **5** in 300 ml of DMF. After cooling at room temperature, iodomethane (2.25 ml, 36 mmoles) was added dropwise, and the reaction mixture was left under stirring for 16 hours. The solid obtained was collected and washed with petroleum ether 40-60° and water to give 6.48 g (yield 86%) of 8-aminocaffeine **15**, mp >300°; ir: 3370, 3300, 3200, 1670, 1620, 1520, 1210, 1020, 950 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.16 (s, 3H, 1-CH_3), 3.34 (s, 3H, 3-CH_3), 3.54 (s, 3H, 7-CH_3), 6.84 (br s, 2H, NH_2) ppm; ms: m/z (relative intensity) 209 (M^+ 74), 82 (100).

Anal. Calcd. for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 46.01; H, 5.35; N, 33.33.

N-(2-Carboxyphenyl)-8-caffeinamine **16**.

A suspension of 8-aminocaffeine **15** (0.418 g, 2 mmoles), 2-chlorobenzoic acid (0.313 g, 2 mmoles), anhydrous potassium carbonate (0.276 g, 2 mmoles) and copper powder (0.07 g) in 3 ml of DMF was refluxed for 16 hours. After cooling, the reaction mixture was treated with water and acidified with concentrated hydrochloric acid. The solid was collected, and purified by sublimation (270-300°, 0.4 mm Hg) and recrystallization from DMF to give 0.263 g (yield 40%) of pure **16**, mp >300°; ir: 1680, 1640, 1600, 1540, 1240, 1210 cm^{-1}; ^1H nmr (recorded on a Bruker AC-200) (DMSO-d_6): δ 3.24 (s, 3H, 1-CH_3), 3.47 (s, 3H, 3-CH_3), 3.81 (s, 3H, 7-CH_3), 7.10-8.60 (m, 4H, Ar-H) ppm; ms: m/z (relative intensity) 329 (M^+ 76), 15 (100).

Anal. Calcd. for $C_{15}H_{15}N_5O_4$: C, 54.71; H, 4.59; N, 21.27. Found: C, 54.63; H, 4.43; N, 21.15.

1,3,5-Trimethylpurino[8,9-*b*]quinazoline-2,4,11(1*H*,3*H*,5*H*)-trione **17**.

A mixture of compound **16** (0.33 g, 1 mmole) and 5 g of PPA was heated, under stirring, at 180° for 1 hour. After cooling, the reaction mixture was treated with iced water. The solid obtained was collected, washed with saturated aqueous sodium hydrogen carbonate solution and water, and then purified by recrystallization from DMF to give 0.20 g (yield 66%) of pure **17**, mp 292-294°; ir: 1700, 1640, 1620, 1590, 1320 cm^{-1}; ^1H nmr (recorded on a Bruker AC 200) (DMSO-d_6): δ 3.31 (s, 3H, 3-CH_3), 3.75 (s, 3H, 1-CH_3), 3.84 (s, 3H, 5-CH_3), 7.20-8.20 (m, 4H, Ar-H) ppm; ms: m/z (relative intensity) 311 (M^+ 69), 15 (100).

Anal. Calcd. for $C_{15}H_{13}N_5O_3$: C, 57.88; H, 4.21; N, 22.50. Found: C, 57.86; H, 4.26; N, 22.39.

8-(2-Chlorobenzoylamino)caffeine **18**.

A mixture of 8-aminocaffeine **15** (0.54 g, 2.6 mmoles) and 6.0 g of PPA was heated at 120°, under stirring, for 1 hour. The reaction mixture, after cooling, was treated with ice water. The solid obtained was collected, washed with saturated aqueous sodium hydrogen carbonate solution and water, and then purified by recrystallization from ethanol to give 0.40 g (yield 44%) of pure **18**, mp 228-230°; ir: 3150, 1700, 1670, 1640, 1530, 1280 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.27 (s, 3H, 1-CH_3), 3.43 (s, 3H, 3-CH_3), 3.83 (s, 3H, 7-CH_3), 7.60 (s, 4H, Ar-H), 11.40 (s, 1H, NH) ppm; ms: m/z (relative intensity) 347 (M^+ 6), 139 (100).

Anal. Calcd. for $C_{15}H_{14}ClN_5O_3$: C, 51.81; H, 4.06; N, 20.14. Found: C, 51.98; H, 4.11; N, 20.05.

Acknowledgment.

This work was supported by a grant from the Ministry of University and Scientific and Technological Research (MURST) (research fund 60%).

REFERENCES AND NOTES

[1] A. Da Settimo, G. Primofiore, V. Santerini, G. Biagi and L. D'Amico, *J. Org. Chem.*, **42**, 1725 (1977).

[2] F. Chetoni, F. Da Settimo, A. M. Marini and G. Primofiore, *J. Heterocyclic Chem.*, **30**, 1481 (1993).

[3] P. Caroti, C. Ceccotti, A. Da Settimo, F. Palla and G. Primofiore, *J. Heterocyclic Chem.*, **23**, 1833 (1986).

[4] P. Caroti, C. Ceccotti, A. Da Settimo, F. Palla and G. Primofiore, *Gazz. Chim. Ital.*, **117**, 263 (1987).

[5] B. F. Duesel, H. Berman and R. J. Schachter, *J. Am. Pharm. Assoc.*, **43**, 619 (1954).

[6] J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **82**, 3773 (1960).

[7] D. Descours and D. Festal, *Synthesis*, 1033 (1983).

[8] D. S. Bariana, *J. Med. Chem.*, **14**, 543 (1971).

[9] T. Ueda, T. Adachi, J. Sakakibara, M. Asano and J. Nakagami, *Chem. Pharm. Bull.*, **35**, 4031 (1987).

[10] O. De Lucchi, U. Miotti and G. Modena, Organic Reactions, Vol **40**, L. A. Paquette, ed, John Wiley & Sons, New York, 1991, p 157.

[11] W. Czuba, L. Kasperek, D. Prelicz, B. Borkowska, M. Bogdal, L. Krzywosinski and B. Przemyk, *Pol. J. Pharmacol. Pharm.*, **37**, 533 (1985).

[12] H. H. Otto, *Pharm. Zentralh.*, **107**, 444 (1968).

[13] T. Ueda, Y. Kawabata, N. Murakami, S. Nagai, J. Sakakibara and M. Goto, *Chem. Pharm. Bull.*, **39**, 270 (1991).