# Facile Synthesis of 3-Substituted [1,2,4]Triazino[3,4-*f*]purine-4,6,8-trione Derivatives

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A new synthetic route to build the [1,2,4]triazino[3,4-*f*]purine nucleus is described. The novel [1,2,4]-triazino[3,4-*f*]purine-4,6,8(1*H*,7*H*,9*H*)-trione derivatives were obtained by condensation of 8-hydrazinotheophylline with appropriate glyoxylic acids *via* the intermediate hydrazones.

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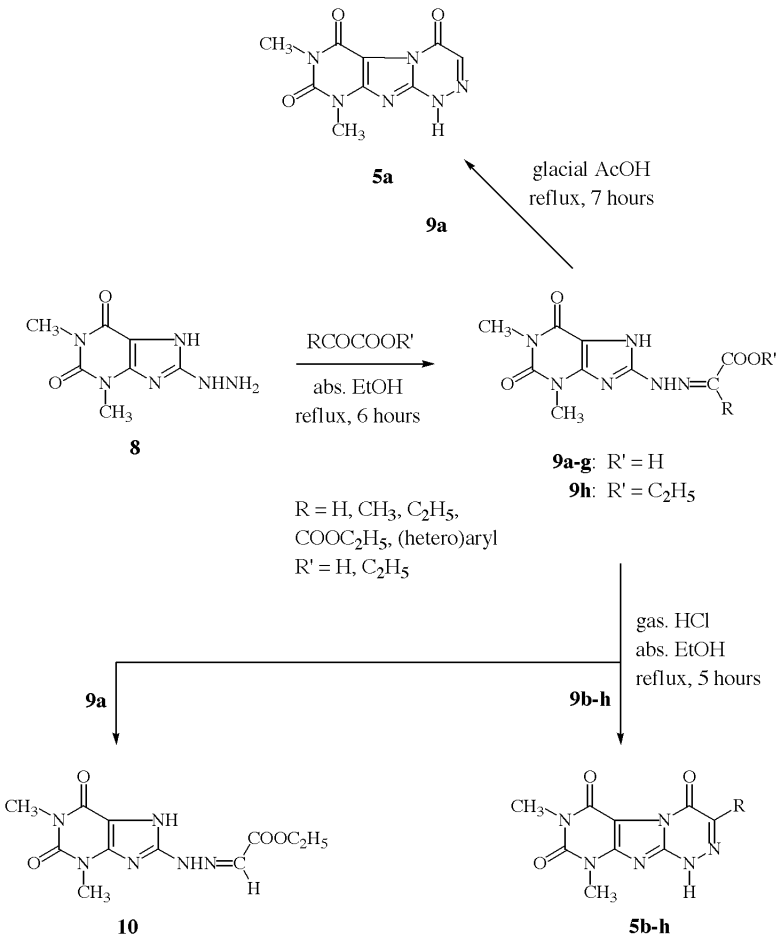
Despite great effort, until today the development of curative antitumor drugs has been only partially successful. In the ongoing search for new effective chemotherapeutic agents, a wide variety of new drugs with completely different chemical structures has been prepared and tested. These drugs can be classified into alkylating agents, nucleic acids intercalating agents, topoisomerases inhibitors, spindle poisons. DNA-binding agents demonstrated to be one of the most effective classes of anticancer drugs, whose mechanism of action involves binding either in the major or minor grooves, or intercalation between base pairs of double-stranded DNA. Generally, agents with DNA-intercalative properties are characterized by the presence of a planar chromophore, a tri- or tetracyclic ring system, to which flexible basic side chains may be bound to improve DNA binding properties [1-4].

Scheme 1



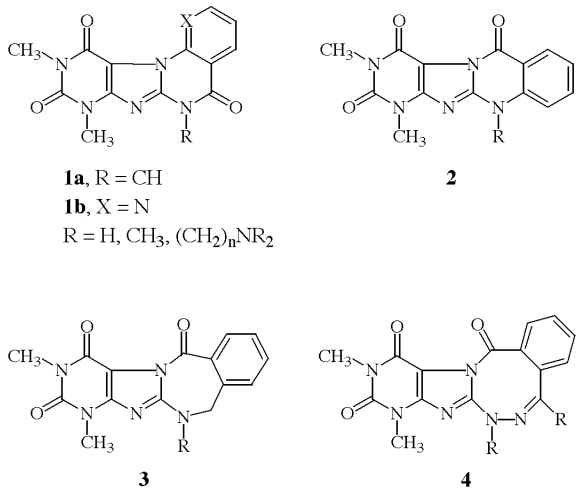



Figure 1

On the basis of these findings, in carrying out a wide program to prepare new heteropolycyclic compounds that might exhibit antiproliferative activity, in the last few years we have reported the synthesis of numerous molecules which contain the purine nucleus fused with several heterocyclic systems such as purinoquinazoline **1a**, **2** [5], purinopyridopyrimidine **1b** [6], 2,4-benzodiazepinopurine **3** and 2,3,5-triazocinopurine **4** [7] derivatives (Figure 1).

Some of these molecules, functionalized with an alkylamino-substituted side chain, showed antiproliferative activity, due to their ability to form a complex with DNA and to inhibit the topoisomerase II [6].

As a part of our research program aimed at devising new heteropolycyclic derivatives containing the purine nucleus as potential antitumor agents, we now report the synthesis of novel [1,2,4]triazino[3,4-*f*]purine-4,6,8(1*H*,7*H*,9*H*)-triones **5a-h** (Figure 2). It is worth noting that little attention has been devoted to the synthesis of the [1,2,4]-triazino[3,4-*f*]purine nucleus; only few 1,2,3,4-tetrahydro[1,2,4]triazino[3,4-*f*]purine-6,8-diones **6** [8,9] and 1,4-dihydro[1,2,4]triazino[3,4-*f*]purine-6,8-diones **7** [10-20] (Figure 2) were prepared in the literature treating opportunely 7-substituted 8-haloxanthines with the appropriate hydrazine derivative.

In the present paper we describe a new facile synthetic procedure to build this nucleus to obtain the target trione compounds **5a-h**.

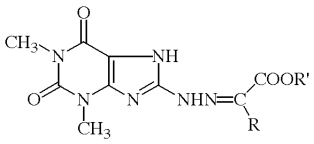
Structures of this type are interesting as they could be functionalized at position 1 with an alkylamino side chain to obtain compounds with potential antiproliferative activity [6].

The 8-hydrazinotheophylline **8**, obtained following a described procedure [21], represented the starting material for the preparation of the title compounds **5a-h**.

The reaction of **8** with the appropriate glyoxylic acid in absolute ethanol at reflux for 6 hours gave the intermediate substituted (theophyllin-8-ylhydrazono)acetic acids **9a-g**,

Table 1

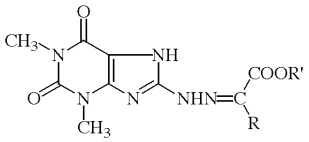
Physical Properties and Analytical Data of Theophyllin-8-ylhydrazone Derivatives **9a-h**



| Compound | R | R' | Yield(%) | Mp(°C) (recrystallization solvent) | Molecular Formula | Analysis (%) calcd/found C | H | N |
|---|---|---|---|---|---|---|---|---|
| **9a** | H | H | 74 | 245-247 | $C_9H_{10}N_6O_4$ | 40.61 | 3.79 | 31.57 |
| | | | | | | 40.51 | 3.82 | 31.61 |
| **9b** | $CH_3$ | H | 64 | 262-264(dec.) | $C_{10}H_{12}N_6O_4$ | 42.86 | 4.32 | 29.99 |
| | | | | | | 43.04 | 4.47 | 29.75 |
| **9c** | $C_2H_5$ | H | 76 | 259-260 | $C_{11}H_{14}N_6O_4$ | 44.90 | 4.79 | 28.56 |
| | | | | | | 44.90 | 4.96 | 28.52 |
| **9d** | $C_6H_5$ | H | 95 | >300 | $C_{15}H_{14}N_6O_4$ | 52.63 | 4.12 | 24.55 |
| | | | | | | 52.53 | 4.31 | 24.45 |
| **9e** | $C_6H_4$-4-$OCH_3$ | H | 68 | >300 | $C_{16}H_{16}N_6O_5$ | 51.61 | 4.33 | 22.57 |
| | | | | | | 51.90 | 4.47 | 22.87 |
| **9f** | 2-furyl | H | 74 | 230-232 | $C_{13}H_{12}N_6O_5$ | 46.99 | 3.64 | 25.29 |
| | | | | | | 46.74 | 3.76 | 25.32 |
| **9g** | 2-thienyl | H | 84 | >300 | $C_{13}H_{12}N_6O_4S$ | 44.82 | 3.47 | 24.12 |
| | | | | | | 44.94 | 3.52 | 24.25 |
| **9h** | $COOC_2H_5$ | $C_2H_5$ | 64 | 190-191 (ethanol) | $C_{14}H_{18}N_6O_6$ | 45.90 | 4.95 | 22.94 |
| | | | | | | 45.66 | 5.13 | 22.65 |

Table 2

Spectral Data of Theophyllin-8-ylhydrazone Derivatives **9a-h**



| Compound | R | R' | IR ($cm^{-1}$) | $^1$H-NMR ($\delta$ ppm) | MS m/z (%) |
|---|---|---|---|---|---|
| **9a** | H | H | 3650-2400, 1730, 1620, 1530, 1220, 1140, 1040. | 3.22 (s, 3H, 1-$CH_3$); 3.38 (s, 3H,3-$CH_3$); 7.20 (s, 1H, N=CH); 12.24-13.00 (m, 3H, exch. with deuterium oxide). | 266 (1, $M^+$); 248 (2, $M^+$-$H_2O$); 222 (18); 194 (34); 82 (100). |
| **9b** | $CH_3$ | H | 3600-2200, 1720, 1660, 1610, 1180, 1140, 1040, 960. | 2.07 (s, 3H, N=C-$CH_3$); 3.26 (s, 3H, 1-$CH_3$); 3.40 (s, 3H, 3-$CH_3$); 11.60, 11.72, 12.52 (three s, each 1H, exch.with deuterium oxide). | 262 (62, $M^+$-$H_2O$); 236 (3); 194 (20); 67 (100). |
| **9c** | $C_2H_5$ | H | 3600-2400, 1720, 1650, 1600, 1520, 1340, 1170, 1120. | 0.98 (t, 3H, $CH_2CH_3$); 2.60 (q, 2H, $CH_2CH_3$); 3.23 (s, 3H, 1-$CH_3$); 3.40 (s, 3H, 3-$CH_3$); 11.68, 11.74, 12.52 (three s, each 1H, exch. with deuterium oxide). | 294 (3, $M^+$); 276 (8, $M^+$-$H_2O$); 250 (3); 194 (28); 82 (100). |
| **9d** | $C_6H_5$ | H | 3400-2300, 1680, 1630, 1600, 1530, 1200, 1130, 970. | 3.23 (s, 3H, 1-$CH_3$); 3.39 (s, 3H, 3-$CH_3$); 7.31-7.38 (m, 3H, 3',4',5'-H); 7.79-7.91 (m, 2H, 2',6'-H); 12.04, 12.72 (two br s, each 1H, exch. with deuterium oxide). | 324 (3, $M^+$-$H_2O$); 298 (7); 194 (26); 44 (100). |
| **9e** | $C_6H_4$-4-$OCH_3$ | H | 3300-2200, 1680, 1630, 1600, 1530, 1250, 1200, 1130, 970. | 3.23 (s, 3H, 1-$CH_3$); 3.39 (s, 3H, 3-$CH_3$); 3.79 (s, 3H, $OCH_3$); 6.91 (d, 2H, 3',5'-H); 7.81 (d, 2H, 2',6'-H); 11.84, 12.64 (two br s, each 1H, exch.with deuterium oxide). | 354 (6, $M^+$-$H_2O$); 328 (13); 194 (32); 133 (97); 82 (100). |
| **9f** | 2-furyl | H | 3250-2200, 1690, 1640, 1610, 1550, 1200, 1150, 740. | 3.22 (s, 3H, 1-$CH_3$); 3.39 (s, 3H, 3-$CH_3$); 6.55 (dd, 1H, 4'-H); 6.99 (d, 1H, 3'-H); 7.71 (d, 1H, 5'-H); 12.39, 12.75 (two br s, each 1H, exch. with deuterium oxide). | 314 (1, $M^+$-$H_2O$); 288 (12); 194 (18); 44 (100). |
| **9g** | 2-thienyl | H | 3400-2200, 1720, 1680, 1650, 1600, 1570, 1530, 1260, 730, 710. | 3.22 (s, 3H, 1-$CH_3$); 3.38 (s, 3H, 3-$CH_3$); 6.98-8.05 (m, 3H, Ar-H); 12.38, 12.59 (two br s, each 1H, exch. with deuterium oxide). | 330 (4, $M^+$-$H_2O$); 304 (16); 194 (31); 82 (100). |
| **9h** | $COOC_2H_5$ | $C_2H_5$ | 1720, 1680, 1630, 1540, 1250, 1160, 1080. | 1.27 (t, 6H, $COOCH_2CH_3$); 3.22 (s, 3H, 1-$CH_3$); 3.40 (s, 3H, 3-$CH_3$); 4.31 (q, 4H, $COOCH_2CH_3$); 12.38, 13.07 (two s, each 1H, exch.with deuterium oxide). | 366 (20, $M^+$); 320 (4); 293 (18); 194 (54); 82 (100). |

which were purified by suspension in hot ethanol (Scheme 1, Tables 1 and 2). Compounds **9a-g** easily loose a molecule of water, as evidenced by the mass spectra, which show, with the exclusion of **9a,c**, only the peak relative to the molecular weight minus eighteen ($M^+$-$H_2O$).

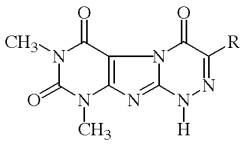
Hydrazones **9b-g** were cyclized by saturating with anhydrous hydrogen chloride in absolute ethanol at 0 °C, then refluxing the reaction mixture for 5 hours (Scheme 1). The assignment of the structure proposed for **5b-g** was supported by ir, uv, $^1$H nmr and mass spectral data (Tables 3 and 4). The cyclization on the N(9) of theophylline is not likely, due to the steric hindrance of the 3-methyl group, as reported by us for other similar cyclizations [5-7].

Surprisingly, the procedure used to cyclize the hydrazones **9b-g** was unsuccessful with the (theophyllin-8-ylhydrazono)acetic acid **9a**: in fact, the solid obtained was not the expected cyclization product **5a**, but the ethyl ester **10** (56% yield), whose structure was confirmed by analytical and spectral data. Also the extension of the reflux time from 5 to 24 hours gave the ester **10**. Compound **9a** was finally cyclized to **5a** (46% yield) by reflux in glacial acetic acid (Scheme 1, Tables 3 and 4).

From this result, it is plausible to infer that also the reaction of compounds **9b-g** proceeds *via* the corresponding esters, which, loosing ethanol intramolecularly by heating, easily cyclize to the target products **5b-g**.

Table 3

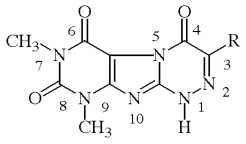
Physical Properties and Analytical Data of [1,2,4]Triazino[3,4-*f*]purine-4,6,8-trione Derivatives **5a-h**



| Compound | R | Yield (%) | Mp(°C) (recrystallization solvent) | Molecular Formula | Analysis (%) calcd/found | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **5a** | H | 46 | >300(dec.) (glacial acetic acid) | $C_9H_8N_6O_3$ | 43.55<br>43.64 | 3.25<br>3.48 | 33.86<br>33.80 |
| **5b** | $CH_3$ | 46 | >300(dec.) (dimethylformamide) | $C_{10}H_{10}N_6O_3$ | 45.80<br>45.79 | 3.84<br>3.92 | 32.05<br>32.34 |
| **5c** | $C_2H_5$ | 44 | >300(dec.) (dimethylformamide/diethyl ether) | $C_{11}H_{12}N_6O_3$ | 47.83<br>47.75 | 4.38<br>4.45 | 30.42<br>30.44 |
| **5d** | $C_6H_5$ | 58 | >300 (dimethylformamide) | $C_{15}H_{12}N_6O_3$ | 55.55<br>55.48 | 3.73<br>3.61 | 25.91<br>26.01 |
| **5e** | $C_6H_4$-4-$OCH_3$ | 70 | >300(dec.) (dimethylformamide) | $C_{16}H_{14}N_6O_4$ | 54.24<br>54.14 | 3.98<br>4.06 | 23.72<br>23.86 |
| **5f** | 2-furyl | 55 | >300 (dimethylformamide) | $C_{13}H_{10}N_6O_4$ | 49.69<br>49.60 | 3.21<br>3.44 | 26.74<br>26.67 |
| **5g** | 2-thienyl | 64 | >300 (dimethylformamide) | $C_{13}H_{10}N_6O_3S$ | 47.27<br>47.20 | 3.05<br>2.98 | 25.44<br>25.57 |
| **5h** | $COOC_2H_5$ | 50 | 280-281(dec.) (dimethylformamide) | $C_{12}H_{12}N_6O_5$ | 45.00<br>45.09 | 3.78<br>3.86 | 26.24<br>26.22 |

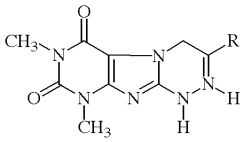
Moreover, 8-hydrazinotheophylline **8** was allowed to react with diethyl ketomalonate to afford the diethyl (theophyllin-8-ylhydrazono)malonate **9h** (Scheme 1, Tables 1 and 2); this product was easily cyclized in ethanol/hydrogen chloride to the trione **5h** bearing an ethoxycarbonyl substituent at position 3 (Scheme 1, Tables 3 and 4). Compound **5h** can be considered a potential starting material for the obtainment of amide derivatives, which can be interesting, since the antitumor activity of a series of pyrido[4,3-*b*]carbazole-1-carboxylic acid (2-dimethylaminoethyl)amides has been reported recently in the literature [22].

In conclusion, the reported synthetic procedure demonstrated to be a new versatile procedure for the facile obtainment of triazinopurinetrione derivatives, which can be useful intermediates for the preparation of potential antitumor agents.



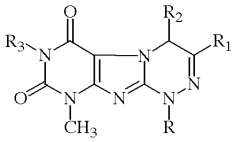
**5a-h**

R = H, $CH_3$, $C_2H_5$, $COOC_2H_5$, (hetero)aryl



**6**

R = H, $CH_2COOC_2H_5$



**7**

R = H, alkyl, acyl, (hetero)aryl
R = H, alkyl, (hetero)aryl
R = H, $CH_3$, phenyl
R = H, alkyl

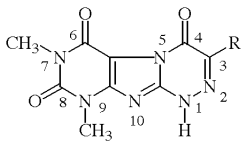
Figure 2

## 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 in dimethyl-$d_6$ sulfoxide solution with a Bruker AC 200 or a Varian Gemini 200 spectrometer using tetramethylsilane 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. Ultraviolet spectra were recorded on a PERKIN-ELMER LAMBDA 15 UV/VIS spectrophotometer in ethanol solution. Evaporations were made

Table 4

Spectral Data of [1,2,4]Triazino[3,4-*f*]purine-4,6,8-trione Derivatives **5a-h**



| Compound | R | IR ($cm^{-1}$) | $^1$H-NMR ($\delta$ ppm) | MS m/z (%) | UV $\lambda_{max}$ ($\varepsilon$) |
|---|---|---|---|---|---|
| **5a** | H | 3225, 1750, 1720, 1690, 1620, 1520. | 3.25 (s, 3H, 7-$CH_3$); 3.46 (s, 3H, 9-$CH_3$); 7.69 (s, 1H, 3-H) | 248 (77, $M^+$); 67 (100); 27 (15). | 231 (22325), 258 (10384), 291 (5959), 348 (6546). |
| **5b** | $CH_3$ | 3175, 1700, 1670, 1650, 1580, 1490, 1200, 740. | 2.29 (s, 3H, 3-$CH_3$); 3.22 (s, 3H, 7-$CH_3$); 3.43 (s, 3H, 9-$CH_3$); 13.78-15.17 (br s, 1H, 1-H, exch. with deuterium oxide). | 262 (43, $M^+$); 67 (100); 41 (11). | 209 (17307), 235 (26364), 294 (8593), 337 (7050). |
| **5c** | $C_2H_5$ | 3200, 1720, 1700, 1670, 1610,1520, 760. | 1.19 (t, 3H, $CH_2CH_3$); 2.70 (q, 2H, $CH_2CH_3$); 3.23 (s, 3H, 7-$CH_3$); 3.44 (s, 3H, 9-$CH_3$); 14.40 (s, 1H, 1-H, exch. with deuterium oxide). | 276 (100, $M^+$); 55 (24). | 209 (12131), 235 (19079), 293 (6500), 335 (5210). |
| **5d** | $C_6H_5$ | 3150, 3050, 1700, 1680, 1650, 1590, 1490, 740. | 3.24 (s, 3H, 7-$CH_3$); 3.46 (s, 3H, 9-$CH_3$); 7.39-7.47 (m, 3H, 3',4',5'-H); 7.91-8.02 (m, 2H, 2',6'-H). | 324 (27, $M^+$); 103 (42); 67 (100). | 202 (24415), 245 (29293), 354 (12488). |
| **5e** | $C_6H_4$-4-$OCH_3$ | 3150, 1700, 1660, 1590, 1500, 1480, 1240, 1160, 1020, 740. | 3.28 (s, 3H, 7-$CH_3$); 3.48 (s, 3H, 9-$CH_3$); 3.82 (s, 3H, $OCH_3$); 7.00 (d, 2H, 3',5'-H); 7.97 (d, 2H, 2',6'-H). | 354 (16, $M^+$); 133 (100). | 202 (31954), 253 (28612), 368 (15501). |
| **5f** | 2-furyl | 3150, 1710, 1640, 1580, 1490, 740. | 3.24 (s, 3H, 7-$CH_3$); 3.45 (s, 3H, 9-$CH_3$); 6.62-6.69 (m, 1H, 4'-H); 7.39 (d, 1H, 3'-H); 7.83 (d, 1H, 5'-H). | 314 (74, $M^+$); 93 (100). | 202 (17371), 258 (23216), 287 (10939), 375 (14319). |
| **5g** | 2-thienyl | 3075, 1720, 1650, 1600, 1490, 1420, 740. | 3.23 (s, 3H, 7-$CH_3$); 3.44 (s, 3H, 9-$CH_3$); 7.15 (dd, 1H, 4'-H); 7.67 (dd, 1H, 5'-H); 8.01 (dd, 1H, 3'-H). | 330 (25, $M^+$); 109 (100). | 210 (17193), 258 (18012), 381 (12719). |
| **5h** | $COOC_2H_5$ | 3125, 1730, 1690, 1640, 1580, 1480, 1270, 1130, 740. | 1.31 (t, 3H, $COOCH_2CH_3$); 3.25 (s, 3H, 7-$CH_3$); 3.47 (s, 3H, 9-$CH_3$); 4.34 (q, 2H, $COOCH_2CH_3$). | 320 (79, $M^+$); 67 (100). | 232 (28962), 267 (15566), 369 (11604). |

*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%.

4-Methoxyphenylglyoxylic acid was prepared in accordance with a reported method [23,24].

Substituted (Theophyllin-8-ylhydrazono)acetic Acids **9a-g** and Diethyl (Theophyllin-8-ylhydrazono)malonate **9h**.

General Procedure.

A suspension of 8-hydrazinotheophylline **8** (1.4 mmoles) and the appropriate glyoxylic acid or diethyl ketomalonate (1.8 mmoles) in 25 ml of absolute ethanol was refluxed for 6 hours under stirring. After cooling, the solid was collected to give the target compounds **9a-h**; **9a-g** were purified by suspension in hot ethanol and **9h** by recrystallization from ethanol (Tables 1 and 2).

3-Substituted [1,2,4]Triazino[3,4-*f*]purine-4,6,8(1*H*,7*H*,9*H*)-triones **5b-h**.

General Procedure.

An ice-cooled suspension of the hydrazones **9b-h** (1 mmole) in 9 ml of absolute ethanol was saturated, under stirring, with anhydrous hydrogen chloride, then refluxed for 5 hours. After cooling, the solid was collected and recrystallized from the appropriate solvent to give the pure title derivatives **5b-h** (Tables 3 and 4).

Ethyl (Theophyllin-8-ylhydrazono)acetate (**10**).

An ice-cooled suspension of (theophyllin-8-ylhydrazono)-acetic acid **9a** (0.133 g, 0.5 mmole) in 9 ml of absolute ethanol was saturated, under stirring, with anhydrous hydrogen chloride, then refluxed for 5 hours. After cooling, the precipitated product was collected and recrystallized from ethanol to give 0.083 g (56% yield) of pure **10**, mp 238-239 °C; ir $cm^{-1}$: ν 3150, 1680, 1630, 1600, 1520, 1130; $^1$H nmr: δ ppm 1.26 (t, 3H, $COOCH_2CH_3$), 3.21 (s, 3H, 1-$CH_3$), 3.38 (s, 3H, 3-$CH_3$), 4.21 (q, 2H, $COOCH_2CH_3$), 7.36 (s, 1H, N=CH), 12.41, 12.84 (two s, each 1H, exch. with deuterium oxide); ms: m/z (%) 294 (27, $M^+$), 248 (5), 221 (31), 194 (54), 82 (100).

*Anal*. Calcd. for $C_{11}H_{14}N_6O_4$: C, 44.90; H, 4.79; N, 28.56. Found: C, 44.96; H, 4.95; N, 28.89.

7,9-Dimethyl[1,2,4]triazino[3,4-*f*]purine-4,6,8(1*H*,7*H*,9*H*)-trione (**5a**).

A suspension of (theophyllin-8-ylhydrazono)acetic acid **9a** (0.300 g, 1.13 mmoles) in 15 ml of glacial acetic acid was refluxed for 7 hours under stirring. The solution obtained was evaporated to half volume and the precipitated solid was collected and recrystallized from glacial acetic acid to yield 0.129 g of pure derivative **5a** (Tables 3 and 4).

Acknowledgment.

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