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Il Farmaco 58 (2003) 551–556
IL FARMACO
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# Characterization and preliminary use of 1-, 2- and 3-methyl-5-phenyl-7-chloro-1,2,3-triazolo[4,5-d]pyrimidine as reaction intermediates

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Received 3 January 2003; accepted 22 April 2003

**Abstract**

This paper reports synthesis and characterization, by spectroscopic methods, of three new *N*-methyl-5-phenyl-7-chloro-1,2,3-triazolo[4,5-d]pyrimidine isomers **3a**, **3b** and **3c**. For comparison purpose the 3-benzyl-5-phenyl-7-chloro-1,2,3-triazolo[4,5-d]pyrimidine (**7**) was also prepared. Starting from the isomer mixture **3a**–**c** and the chloroderivative **7**, by nucleophilic substitution reaction with ethyl carbazate and subsequent intramolecular cyclization, the new tricyclic derivatives **5a**–**c** and **9** were prepared and tested towards the benzodiazepine and adenosine $A_1$ and $A_{2A}$ receptors.


*Keywords:* 1,2,3-Triazolo[4,5-d]pyrimidines; 1,2,3-Triazolo[4,5-e]1,2,4-triazolo; [3,4-c]Pyrimidines; Benzodiazepine receptor binding; Adenosine receptor binding

## 1. Introduction

The 7-chloro-1,2,3-triazolo[4,5-d]pyrimidines are very reactive compounds towards the nucleophilic substitution and the chlorine atom can be easily substituted with several different nucleophilic agents, to give a variety of suitable derivatives [1–6].

Moreover the 1,2,3-triazolo-pyrimidines are biologically interesting molecules [7–11] and are one of our research topics concerning the synthesis of new derivatives to evaluate their affinity towards the adenosine and benzodiazepine receptors, by binding assays [3,12–16].

On pursuing our studies, we needed to synthesize 1,2,3-triazolo[4,5-d]pyrimidine derivatives bearing a substituent with a little steric hindrance, as a methyl group, on the 1,2,3-triazole ring.

Therefore the 5-phenyl-1,6-dihydro-1,2,3-triazolo[4,5-d]pyrimidin-7-one (**1**) [17] underwent a *N*-methylation reaction with methyl iodide in methanol, in the presence of equimolar amount of sodium methoxide (Scheme 1). As expected, because the negative charge on the sodium salt of **1** can be delocalized on each one of the three nitrogen atoms of the triazole ring, a mixture of three isomers, 1-methyl- (**2a**), 2-methyl- (**2b**) and 3-methyl- (**2c**) substituted, respectively, was isolated and characterized.

Because attempts of fractionating the mixture, either by gas-chromatography or by TLC analysis failed, this mixture was directly converted to the mixture of the corresponding 7-chloroderivatives.

The chlorination reaction was carried out with thionyl chloride in chloroform/DMF, and the mixture of the three isomeric chloroderivatives **3a**, **3b** and **3c**, with well differentiated $R_f$ values at the TLC analysis (0.54, 0.46 and 0.32, respectively, ethyl acetate/petroleum ether 1:4), was fractionated by flash-chromatography through a silica-gel column.

The compounds were eluted in the following order, in the yields reported in brackets, and were characterized by analytical and spectroscopic methods: **3a** (24.5%), **3b** (38.5%) and **3c** (23.5%).

The structure attribution to the single isomers was reasonably achieved by interpretation of their $^{13}C$ NMR and UV spectra.

Our previous studies on 1,2,3-triazole derivatives [18,19] indicated that a carbon atom at the position 2

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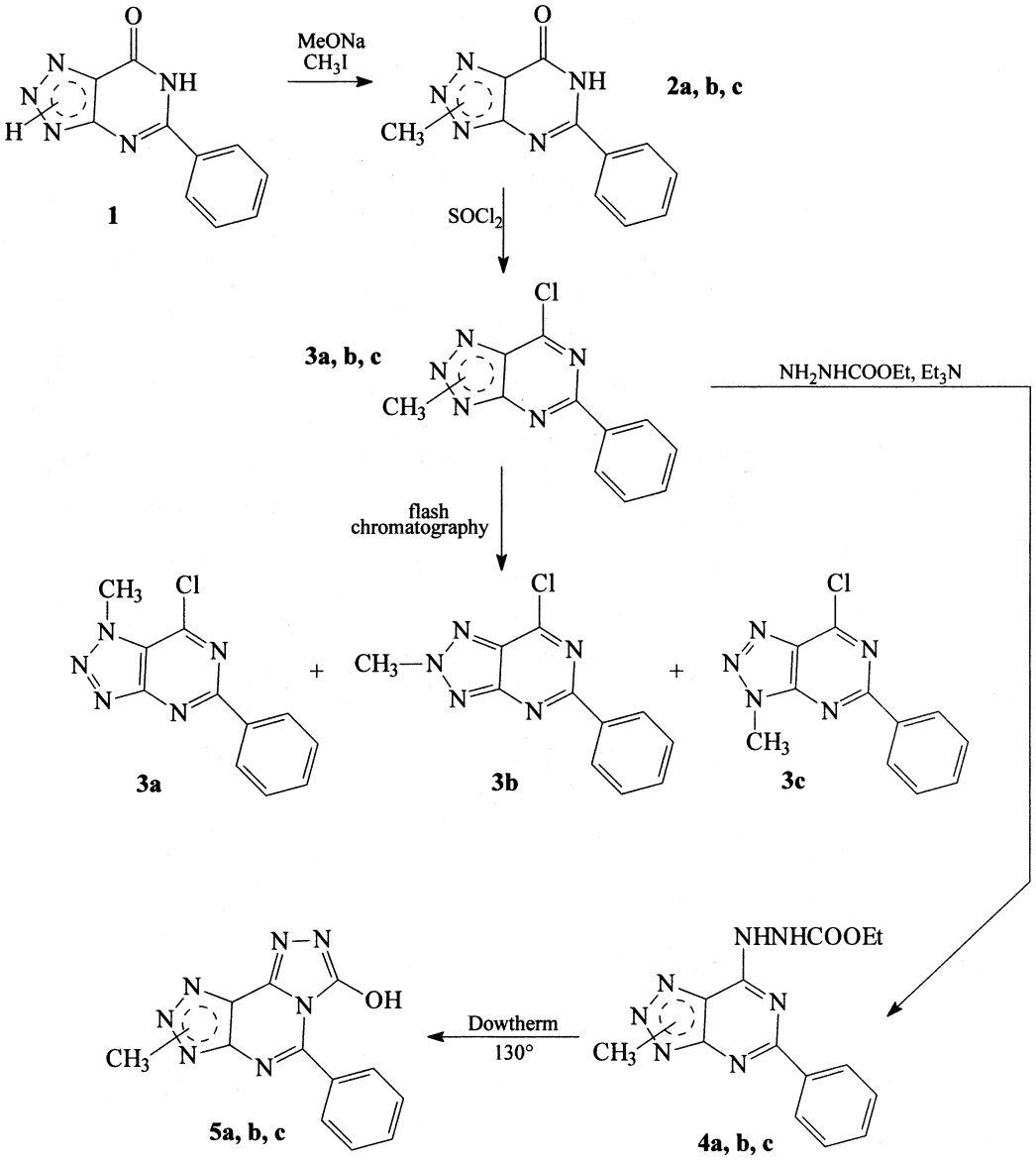
doi:10.1016/S0014-827X(03)00095-8




Scheme 1.

of a 1,2,3-triazole ring resonates at fields lower than a carbon atom bonded at the position 1 or 3, for about 5–7 ppm. The $^{13}C$ NMR spectra of the **3a**, **3b** and **3c** isomers show the following chemical shifts for the three methyl carbons: 45.0, 37.8 and 33.6 ppm, respectively. The chemical shift differences between the methyl signal which resonates at lower fields and the other two signals are 7.2 and 11.4 ppm, respectively. Thus, according to the literature, we can assign the 2-methyl substituted triazole structure, corresponding to the isomer **3b**, to the compound with the lowest methyl chemical shift (45.0 ppm). The difference between this value and the next (37.8 ppm) is 7.2 ppm and corresponds to the difference reported between a two substituted methyl and a 1 or 3 substituted methyl of 1,2,3-triazole derivatives [18,19]. The discrimination between these last two structures can be achieved by the observation that in the 1-methyl substituted compound (isomer **3a**), the methyl group is γ-gauche positioned regarding to the chlorine atom and this condition agrees with a chemical shift value remarkably shifted to higher fields. Therefore to the compound with the methyl chemical shift at 33.6 ppm, which is shifted 11.4 ppm from the 2-methyl substituted compound **3b**, we can assign the 1-methyl substituted structure, corresponding to the isomer **3a**. Finally to the compound with the methyl chemical shift at 37.8 ppm (shifted from the 2-substituted compound **3b** of 7.2 ppm) we can assign the three-substituted structure corresponding to the isomer **3c**. The γ-gauche effect is also evidenced in the $^{1}H$ NMR spectra, in fact the methyl protons of the three isomers (**3a**,**b**,**c**) resonate at 4.35, 4.62 and 4.52 ppm, respectively and really the

Table 1
Spectral data

| | | 3a | 3b | 3c | 7 |
|---|---|---|---|---|---|
| $^{13}$C NMR $\delta$ (ppm) | $\nu CH_3$ | 33.6 | 45.0 | 37.8 | |
| $^{1}$H NMR $\delta$ (ppm) | $\nu CH_3$ | 4.35 | 4.62 | 4.52 | |
| UV $\lambda_{max}$ (nm) | K band | 246.1 | 247.5 | 244.3 | 244.3 |
| | B band | 301.9 | 308.2 | 276.4 | 275.8 |

value shifted at higher fields corresponds to that of the 1-methyl substituted isomer **3a**. The important spectral values are reported in Table 1.

The UV spectra investigation led to the same conclusions, in fact, a batochromic shift of the B-benzenoid band of the two-substituted benzotriazoles with regard to those substituted in the 1 or 3 positions is described [20].

The UV spectra of the three isomers (Fig. 1) and their $\lambda_{max}$ reported in Table 1, show that compound **3b** presents a shift towards greater wavelengths (308.2 nm), which confirms the substitution in the 2 position. A further confirmation of the structure assigned to the isomers **3a** and **3c** has been obtained by the comparison of their UV spectra with the spectrum of the 3-benzylsubstituted compound **7** (Scheme 2), purposely prepared by chlorination of the corresponding 3-benzyl-5-phenyl-3,6-dihydro-1,2,3-triazolo[4,5-d]pyrimidin-7-one (**6**) [21].

The spectrum of the synthesized compound **7** is very similar to the spectrum of **3c** and different from the spectrum of **3a**, so that it confirms the 3-substituted structure assigned to the isomer **3c**. However, it is worth nothing that the B-band in consequence of the complexity of the chromophores, especially for the **3a** and **3b** spectra, appears rather flattened with a low accuracy in the determination of the $\lambda_{max}$. But it is undoubted the greater batochromic shift observed in the **3b** spectrum, also evidenced by the clear absorbance until 350 nm, whilst in the **3a** spectrum the absorbance terminates at 330 nm.

In any case, before the isomeric chloroderivatives were characterized, a **3a**,**b**,**c** mixture was employed as a model for the synthesis of new derivatives, especially tricyclic structures of our interest, to submit to binding assays and to obtain preliminary informations about their biological activity. Thus the mixture of chloroderivatives **3a**,**b**,**c** (Scheme 1) reacted with ethyl carbazate in boiling benzene, in the presence of triethylamine (TEA), to give the corresponding mixture of *N*-methyl-7-ethoxycarbonylhydrazino derivatives **4a**,**b**,**c** in 47% yield. Heating of this mixture in Dowtherm at 130 °C for 4 h, induced the intramolecular cyclization with elimination of ethanol and formation of the 1,2,4-triazole ring, to give the mixture of tricyclic *N*-methyl-substituted isomers **5a**,**b**,**c**, bearing a hydroxyl function in the 7 position.

Similarly the 3-benzyl-chloroderivative **7**, by reaction with ethyl carbazate gave the ethoxycarbonylhydrazino derivative **8** which, by heating, cyclized to the expected tricyclic derivative **9**.

## 2. Biological results

The new compounds as mixtures **4a**,**b**,**c** and **5a**,**b**,**c** together with compounds **8** and **9**, underwent binding assays either to benzodiazepine receptors or adenosine $A_1$ and $A_{2A}$ receptors.

Their ability to inhibit benzodiazepine receptor binding was measured by the concentration which was able to displace [$^3$H]-Ro 15-1788 from bovine brain membranes.

The inhibition of binding towards adenosine receptors was measured by the ability of compounds to displace [$^3$H]N$^6$-cyclohexyladenosine (CHA) from $A_1$ adenosine receptors in bovine cortical membranes and [$^3$H]-2-[*p*-(2-carboxyethyl)-phenethylamino]-5′-(*N*-ethylcarba-

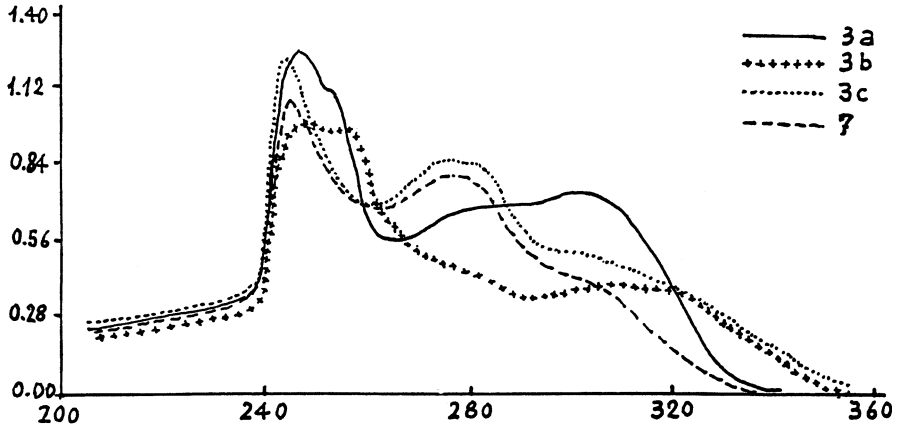
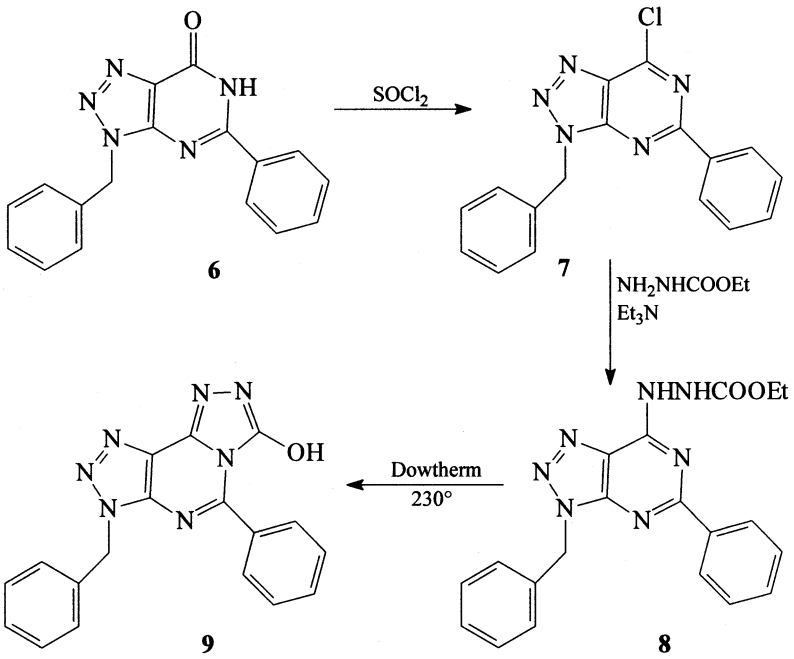



Fig. 1. UV spectra of isomer **3a**–**c** and compound **7**.




Scheme 2.

moil)-adenosine (CGS 21680) from $A_{2A}$ adenosine receptors in bovine striatal membranes.

The experimental details of the receptor binding assays are reported in a previous paper [22].

The biological evaluation towards the adenosine $A_1$ and $A_{2A}$ receptors showed the triazolo-pyrimidine isomer mixture **4a**,**b**,**c** had a moderate but interesting affinity towards the $A_1$ receptor subtype ($K_i = 137$ nM), with a high selectivity regarding to the $A_{2A}$ receptor subtype ($K_i = 5935$ nM). The corresponding benzyl-derivative **8** showed also an analogous activity with lower effectiveness ($K_i = 531$ nM) and selectivity. An almost equivalent activity was also present in the tricyclic benzylderivative **9** ($K_i = 587$ nM), whilst the mixture of the tricyclic *N*-methylated isomers **5a**,**b**,**c** showed a low $A_1$-adenosine affinity ($K_i = 1317$ nM).

The biological evaluation towards the benzodiazepine receptors showed the tricyclic isomer mixture **5a**,**b**,**c**, having H-bond donor (OH) and acceptor (N) sites, as well as derivative **9** did not inhibit the binding to these receptors, probably by the steric hindrance of the phenyl substituent in the 5 position.

Similarly the triazolo-pyrimidine isomer mixture **4a**,**b**,**c** and benzylderivative **8** are lacking of activity towards the benzodiazepine receptors.

## 3. Experimental

Melting points were determined on a Kofler hot-stage and are uncorrected. IR spectra in nujol mulls were recorded on a Mattson Genesis series FTIR spectrometer. UV spectra were obtained on a Perkin–Elmer Lambda 15 UV–Vis spectrophotometer in $CHCl_3$. $^1$H NMR and $^{13}$C NMR spectra were recorded with a Varian Gemini 200 spectrometer in DMSO-$d_6$ or $CDCl_3$ in δ units, using TMS as internal standard; in $^{13}$C NMR spectra, the signals of the triazolo-pyrimidine ring were not evidenced, probably in consequence of the quadrupolar moment of the nitrogen atoms. Mass spectra were performed with a Perkin–Elmer SCIEX mod. API III or with a Hewlett Packard MS/System 5988 A. Elemental analyses (C,H,N) were within ±0.4% of theoretical values and were performed on a Carlo Erba Elemental Analyzer Mod. 1106 apparatus. TLC data were obtained with Merck silica gel 60 $F_{254}$, aluminum sheets. Gas-chromatographic analyses were performed on a GC Erba mod. 4200 apparatus. Petroleum ether corresponds to fraction boiling at 40–60 °C.

### *3.1. Mixture of 1-methyl-5-phenyl-1,6-dihydro-, 2-methyl-5-phenyl-2,6-dihydro- and 3-methyl-5-phenyl-3,6-dihydro-1,2,3-triazolo[4,5-d]pyrimidin-7-one (**2a**,**b**,**c**)*

To a solution of sodium methoxide, obtained by reaction of 0.850 g (37.0 mmol) of sodium in 160 ml of methanol, 8.00 g (37.5 mmol) of 5-phenyl-1,6-dihydro-1,2,3-triazolo[4,5-d]pyrimidin-7-one (**1**) and 3.50 ml (56.3 mmol) of methyl iodide were added and the mixture was heated under reflux for 24 h. The solvent was evaporated in vacuo, the residue was treated with water and the insoluble material was collected by filtration. The crystallization from ethanol gave 7.47 g (yield 88%) of the title mixture; m.p. 220–260 °C; $^1$H NMR in DMSO-$d_6$: relevant signals three singlets at 4.39, 4.37 and 4.16 δ, corresponding to the *N*-methyl

groups; mass (*m*/*z*): 228 ($MH^+$). *Anal*. ($C_{11}H_9N_5O$): C, H, N.

### 3.2. 1-Methyl-5-phenyl-7-chloro-1H-1,2,3-triazolo[4,5-d]pyrimidine (**3a**), 2-methyl-5-phenyl-7-chloro-2H-1,2,3-triazolo[4,5-d]pyrimidine (**3b**) and 3-methyl-5-phenyl-7-chloro-3H-1,2,3-triazolo[4,5-d]pyrimidine (**3c**)

To a solution of 4.00 g (17.6 mmol) of **2a**,**b**,**c** isomer mixture in 80 ml of chloroform and 3 ml of DMF, 16 ml of thionyl chloride were added and the mixture was heated under reflux for 4 h. The solvent was evaporated in vacuo, the residue was treated with crushed ice and the insoluble material was collected by filtration: 3.78 g (yield 87%) of a yellow solid consisting with the mixture of the title compounds. The gas-chromatographic analysis showed, in the following order, three peaks with area 28, 40 and 29%, respectively. This solid mixture was absorbed on ≈30 g of silica gel and submitted to flash-chromatography through a silica gel column (20 × 6 cm) eluting with ethyl acetate/petroleum ether 1:4. The title compounds were separated by elution in the following order: **3a**, **3b** and **3c**; after crystallization from acetonitrile they were characterized.

**3a**: 1.010 g, yield: 23.5%; m.p. 217–220 °C; TLC: $R_f = 0.54$; GC: $t_R = 15.09$ min. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.49 (m, 2H), 7.61 (m, 3H), 4.35 (s, 3H). $^{13}$C NMR ($CDCl_3$, ppm): $\delta$ 33.6 ($CH_3$); 135.6, 132.1, 129.3, 128.9 (aromatics); 162.9, 153.7 (others). Mass (*m*/*z*): 246 ($MH^+$). UV: $\lambda_{max} = 301.9$ nm, $\log \varepsilon = 3.398$; $\lambda_{max} = 246.1$ nm, $\log \varepsilon = 3.637$. *Anal*. ($C_{11}H_8N_5Cl$): C, H, N.

**3b**: 1.658 g, yield: 38.5%; m.p. 197–200 °C; TLC: $R_f = 0.46$; GC: $t_R = 15.57$ min. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.43 (m, 2H), 7.58 (m, 3H), 4.62 (s, 3H). $^{13}$C NMR ($CDCl_3$, ppm): $\delta$ 45.0 ($CH_3$); 136.2, 131.8, 129.3, 128.9 (aromatics); 162.3, 160.2, 153.8 (others). Mass (*m*/*z*): 246 ($MH^+$). UV: $\lambda_{max} = 308.2$ nm, $\log \varepsilon = 3.205$; $\lambda_{max} = 247.0$ nm, $\log \varepsilon = 3.532$. *Anal*. ($C_{11}H_8N_5Cl$): C, H, N.

**3c**: 1.060 g, yield: 24.5%; m.p. 205–208 °C; TLC: $R_f = 0.32$; GC: $t_R = 18.11$ min. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.44 (m, 2H), 7.59 (m, 3H), 4.52 (s, 3H). $^{13}$C NMR ($CDCl_3$, ppm): $\delta$ 37.8 ($CH_3$); 135.8, 131.7, 129.1, 128.9 (aromatics); 161.4 (others). Mass (*m*/*z*): 246 ($MH^+$). UV: $\lambda_{max} = 276.4$ nm, $\log \varepsilon = 3.940$; $\lambda_{max} = 244.3$ nm, $\log \varepsilon = 4.110$. *Anal*. ($C_{11}H_8N_5Cl$): C, H, N.

### 3.3. Mixture of 1-methyl-5-phenyl-1H-, 2-methyl-5-phenyl-2H- and 3-methyl-5-phenyl-3H-7-ethoxycarbonylhydrazino-1,2,3-triazolo[4,5-d]pyrimidine (**4a**,**b**,**c**)

To a solution of 2.17 g (8.87 mmol) of the isomeric mixture **3a**,**b**,**c** in 60 ml of anhydrous benzene, 4.50 g (43.60 mmol) of ethyl carbazate and 3 ml of TEA were added and the mixture was heated under reflux for 12 h. The solvent was evaporated in vacuo, the residue was treated with water and stirred for 30 min, then the suspension was extracted with chloroform. The combined extracts were washed with 10% hydrochloric acid and water, dried (magnesium sulfate) and evaporated in vacuo. The residue, by trituration with ethyl acetate, gave the title mixture which was collected by filtration and crystallized from ethanol: 1.30 g, yield: 47%; m.p. 220–250 °C; IR ($cm^{-1}$): 3255 (NH), 1722 (CO). Mass (*m*/*z*): 314 ($MH^+$). *Anal*. ($C_{14}H_{15}N_7O_2$): C, H, N.

### 3.4. Mixture of 1-methyl-5-phenyl-1H-, 2-methyl-5-phenyl-2H- and 3-methyl-5-phenyl-3H-7-hydroxy-1,2,3-triazolo[4,5-e]1,2,4-triazolo[3,4-c]pyrimidine (**5a**,**b**,**c**)

A solution of 0.500 g (1.60 mmol) of **4a**,**b**,**c** mixture in 15 ml of Dowtherm was heated and stirred at 130 °C for 4 hours. After cooling the precipitated solid was collected and crystallized by DMF-water to give the title mixture: 0.320 g, yield: 75%; m.p. 320–354 °C. Mass (*m*/*z*): 268 ($MH^+$). *Anal*. ($C_{12}H_9N_7O$): C, H, N.

### 3.5. 3-Benzyl-5-phenyl-7-chloro-3H-1,2,3-triazolo[4,5-d]pyrimidine (7)

To a solution of 3-benzyl-5-phenyl-3,6-dihydro-1,2,3-triazolo[4,5-d]pyrimidin-7-one (**6**) [21] (0.650 g, 2.14 mmol) in 10 ml of chloroform and 1 ml of DMF, 2 mL of thionyl chloride were added and the mixture was heated under reflux for 4 hours. The solvent was evaporated in vacuo and the residue was treated with crushed ice. The title compound was obtained as a white solid which was collected by filtration and crystallized from benzene: 0.624 g, yield: 90%, m.p. 176–179 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 8.48 (m, 2H), 7.64–7.33 (m, 8H), 6.01 (s, 2H). Mass (*m*/*z*): 321 ($M^+$), 91 (base). UV: $\lambda_{max} = 275.8$ nm, $\log \varepsilon = 3.900$; $\lambda_{max} = 244.3$ nm, $\log \varepsilon = 4.035$. *Anal*. ($C_{17}H_{12}N_5Cl$): C, H, N.

### 3.6. 3-Benzyl-5-phenyl-7-ethoxycarbonylhydrazino-3H-1,2,3-triazolo[4,5-d]pyrimidine (**8**)

A mixture of chloroderivative **7** (0.450 g, 1.40 mmol), ethyl carbazate (0.700 g, 6.73 mmol) and TEA (0.5 ml, 3.59 mmol) in 10 ml of anhydrous benzene was heated under reflux for 19 hours. The solvent was evaporated in vacuo, the residue was treated with 10% hydrochloric acid and the aqueous phase was extracted repeatedly with chloroform. The combined extracts were washed with 10% hydrochloric acid and water, then were dried and evaporated. The solid residue, consisting of the title compound, was crystallized from methanol–water: 0.450 g, yield: 83%, m.p. 169–172 °C; IR ($cm^{-1}$): 3256, 3187 (NH), 1727 (CO).

$^1$H NMR (DMSO-$d_6$): $\delta$ 10.52 (d, NH), 9.78 (d, NH), 8.44 (m, 2H), 7.56–7.26 (m, 8H), 5.86 (s, 2H), 4.13 (q,

2H), 1.26 (t, 3H). Mass (*m/z*): 389 ($M^+$), 91 (base). *Anal*. ($C_{20}H_{19}N_7O_2$): C, H, N.

### 3.7. 3-Benzyl-5-phenyl-7-hydroxy-1,2,3-triazolo[4,5-e]1,2,4-triazolo[3,4-c]pyrimidine (**9**)

A solution of 0.200 g (0.50 mmol) of **8** in 3 ml of Dowtherm was heated under reflux ( $\approx 230$ °C) for 2.5 hours. After cooling the reaction mixture was diluted with petroleum ether and stirred for 30 min. The precipitated solid, consisting of the title compound, was crystallized from water: 0.134 g, yield: 77%, m.p. 185–189 °C. $^1$H NMR (DMSO-$d_6$): $\delta$ 12.6 (broad, OH), 7.76–7.20 (m, 10H), 5.83 (s, 2H). Mass (*m/z*): 343 ($M^+$), 91 (base). *Anal*. ($C_{18}H_{13}N_7O$): C, H, N.

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