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The 7-chloro-3-(2-chlorobenzyl)- and 7-chloro-3-(2-fluorobenzyl)-1,2,3-triazolo[4,5-*d*]pyrimidines (**1** and **4**), by nucleophilic replacement with some hydrazides, gave the corresponding 7-hydrazidoderivatives (**2a-e** and **5a-e**). These, by heating in Dowtherm, underwent an intramolecular cyclization to form the new tricyclic 7-substituted-3-(2-chlorobenzyl)- and 3-(2-fluorobenzyl)-1,2,3-triazolo[4,5-*e*]1,2,4-triazolo[4,3-*c*]pyrimidines (**3a-d** and **6a-d**). The 7-hydrazino-3-(2-chlorobenzyl)- and 7-hydrazino-3-(2-fluorobenzyl)-triazolo-pyrimidines (**9a** and **9b**) were also prepared *via* the corresponding mercapto (**7a** and **7b**) and thiomethyl (**8a** and **8b**) derivatives.

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In a previous paper [1] we have reported that the 1,2,3-triazolo[4,5-*e*]1,2,4-triazolo[4,3-*c*]pyrimidine derivatives had been relatively little studied from a chemical point of view and their biological properties were practically unknown. The new prepared compounds, bearing a lipophilic substituent (benzyl, phenethyl, *p*-methylbenzyl, *p*-methylphenyl) in the 3 position, were lacking affinity towards the A_1 and A_{2A} adenosine receptors, whilst analogous compounds bearing a hydroxyl function in the 7 position showed affinity towards the benzodiazepine receptors.

Although these derivatives had shown a low biological activity, the planar nitrogen tricyclic structure, as well as the isomeric 1,2,3-triazolo[4,5-*d*]1,2,4-triazolo[4,3-*b*]pyridazine structure [2], appeared interesting and worthy of further studies and experimentations.

Thus, as a continuation of the mentioned paper [1], we undertook the synthesis of new 1,2,3-triazolo-1,2,4-triazolo-pyrimidine derivatives bearing in the 3 position the 2-chlorobenzyl and 2-fluorobenzyl substituents and some different substituents in the 7 position. The two benzyl substituents were chosen because they resulted very effective for the biological activity of 1,2,3-triazolo[4,5-*d*]pyridazines [3,4] and 1,2,3-triazolo[4,5-*d*]pyrimidines [5,6].

The synthetic approach has been changed; in fact the 1,2,3-triazole ring was obtained starting from the 1,2,3-triazolopyrimidine pattern by intramolecular cyclization of

Table 1

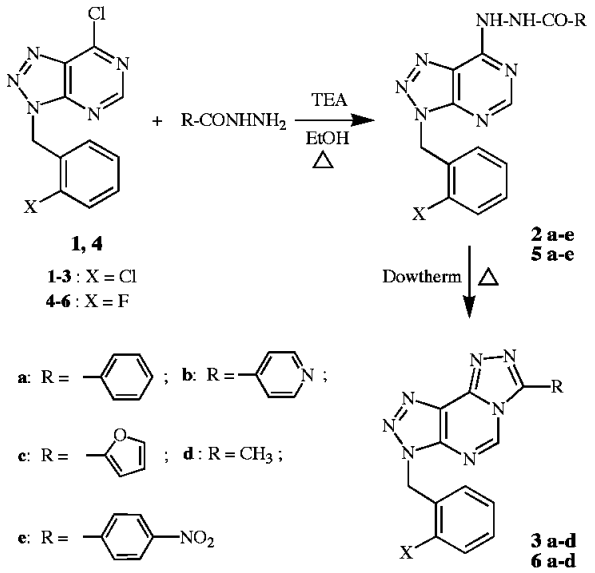
Chemical and physical properties of the prepared compounds

Comp.	Yield %	Crystall. Solvent	M.p. (°C) [a]	Formula	Mass *m/z* M^+	Mass *m/z* Base	Analyses C, H, N Calc. %	Analyses C, H, N Found %
2a	97	DMF-H_2O	297-301	$C_{18}H_{14}N_7OCl$	379	105	56.92; 3.72; 25.81	56.53; 3.41; 26.13
2b	58	DMF-H_2O	276-279	$C_{16}H_{13}N_8OCl$	380	125	52.11; 3.55; 30.38	52.49; 3.55; 29.98
2c	77	DMF	295-296	$C_{16}H_{12}N_7O_2Cl$	369	95	51.97; 3.27; 26.52	51.73; 3.46; 26.17
2d	66	EtOH	212-213	$C_{13}H_{12}N_7OCl$	317	125	49.14; 3.81; 30.86	48.87; 3.48; 31.16
2e	68	ETOH-H_2O	268-269	$C_{18}H_{13}N_8O_3Cl$	394 [e]	120	50.89; 3.08; 26.38	50.49; 3.44; 26.73
3a	52	MeOH	227-230	$C_{18}H_{12}N_7Cl$	361	125	59.76; 3.34; 27.10	59.39 ; 2.98; 27.48
3b	15.5	[b]	203-207	$C_{17}H_{11}N_8Cl$	327 [f]	125	56.28; 3.06; 30.89	56.67; 3.14; 30.89
3c	7.5	[c]	230 dec.	$C_{16}H_{10}N_7Cl$	351	125	57.24; 3.00; 29.20	56.75; 2.78; 29.56
3d	35.5	[b]	136-140	$C_{13}H_{10}N_7Cl$	264 [g]	125	52.10; 3.36; 32.71	52.47; 3.72; 32.40
5a	93.5	DMF-H_2O	285-286	$C_{18}H_{14}N_7OF$	363	105	59.50; 3.88; 26.98	59.88; 3.51; 27.35
5b	43.5	MeOH-H_2O	262-272 dec.	$C_{17}H_{13}N_8OF$	364	109	56.04; 3.60; 30.76	55.65; 3.31; 30.38
5c	77	EtOH	285-290	$C_{16}H_{12}N_7O_2F$	353	109	54.39; 3.42; 27.75	54.16; 3.56; 28.10
5d	88.5	EtOH	226-227	$C_{13}H_{12}N_7OF$	301	109	51.83; 4.01; 32.54	52.20; 4.25; 32.27
5e	79	Rid-H_2O	275-278	$C_{18}H_{13}N_8O_3F$	378 [h]	120	52.94; 3.21; 27.44	52.61; 3.54; 27.08
6a	67	MeOH-H_2O	250-253	$C_{18}H_{12}N_7F$	345	109	62.60; 3.50; 28.39	62.22; 3.13; 28.01
6b	18	[b]	193-207 dec.	$C_{17}H_{11}N_8F$	346	109	58.96; 3.20; 32.35	58.55; 3.49; 33.33
6c	11.5	[b]	244-250	$C_{16}H_{10}N_7OF$	335	109	57.31; 3.01; 29.24	57.70; 3.37; 28.95
6d	48	EtOH	170-174	$C_{13}H_{10}N_7F$	283	109	55.12; 3.56; 34.61	55.46; 3.55; 34.86
7a	81	[d]	135-137	$C_{11}H_8N_5SCl$	277	125	47.57; 2.90; 25.22	47.42; 2.81; 25.43
7b	92	[d]	148-149	$C_{11}H_8N_5SF$	261	109	50.57; 3.09; 26.80	50.19; 2.81; 27.08
8a	68	MeOH	137-140	$C_{12}H_{10}N_5SCl$	291	125	49.40; 3.45; 24.00	49.05; 3.21; 23.64
8b	90	MeOH-H_2O	100-102	$C_{12}H_{10}N_5SF$	275	109	52.35; 3.66; 25.44	52.38;3.29; 25.32
9a	87	DMF-H_2O	214-217	$C_{11}H_{10}N_7Cl$	275	125	47.92; 3.66; 35.56	48.23; 3.52; 37.25
9b	95	EtOH	216-218	$C_{11}H_{10}N_7F$	259	109	50.96; 3.89; 37.82	50.91; 3.73; 38.10

[a] Compounds **2a-d** and **5a-d** change from an amorphous to a crystalline solid at about180-230 °C; [b] Purified by flash chromatography on silica gel, eluting with AcOEt; [c] Purified by flash chromatography on silica gel, eluting with AcOEt-petroleum ether 1:1. [d] Precipitated from the sodium salt; [e] (M^+- 30); [f] (M^+- 35); [g](M^+- 35); [h] (M^+- 30).

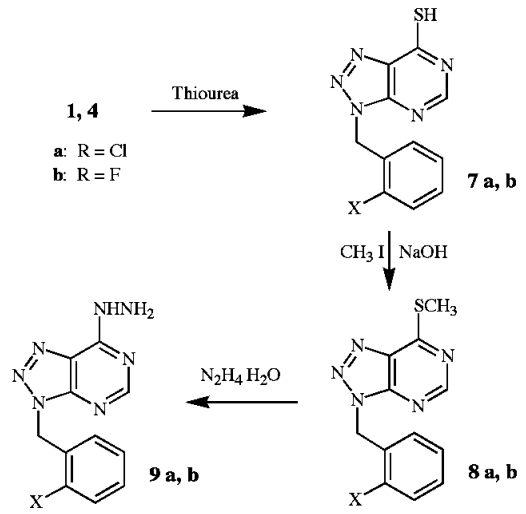
an appropriate hydrazido function in the 7 position and not by reaction of a 7-hydrazino compound with a bifunctional reagent. The hydrazido functions were introduced by a suitable nucleophilic acid hydrazide on the appropriate 7-chloro-triazolopyrimidine, so that they characterize the substituent in the 7 position of the tricyclic ring. As illustrated in Scheme 1, the 3-(2-chlorobenzyl)-7-chloro-1,2,3-triazolo[4,5-*d*]pyrimidine (**1**) [5] reacted with the appropriate acid hydrazides (benzoic, isonicotinic, 2-furoic,acetic and *p*-nitrobenzoic), prepared by reaction of the corresponding methyl or ethyl esters with 99% hydrazine hydrate. The substitution reaction was carried out in boiling ethanol in the presence of two or more equivalents of hydrazide and the expected hydrazido derivatives **2a-e** were obtained in good yield. The intramolecular cyclization with elimination of water to form the 1,2,4-triazole ring bearing the substituent corresponding to the hydrazide, was performed heating the open compounds **2a-e** at a high temperature (≈ 230 °C) in Dowtherm.

Scheme 1



However the expected tricyclic derivatives **3a-d** were isolated in low or very low yields (Table 1) and the cyclization reaction of the *p*-nitrobenzoylhydrazino derivative **2e** caused complete decomposition. A similar reaction sequence was performed starting from the 3-(2-fluorobenzyl)-7-chloro-1,2,3-triazolo[4,5-*d*]pyrimidine (**4**) [6], which was reacted with the same hydrazides in boiling ethanol in the presence of triethylamine (TEA) (Scheme 1). The hydrazido derivatives **5a-e** were isolated in high yields, except for the isonicotinoyl derivative **5b** (43.5%). By heating in Dowtherm, these compounds cyclized to form the 1,2,4-triazole ring, providing the tricyclic derivatives **6a-d**. In fact, in this case also, the *p*-nitrobenzoyl derivative **5e** decomposed.

Scheme 2



The high reactivity toward the nucleophilic substitution of the chlorine atom of the triazolopyrimidine derivatives **1** and **4**, did not allow the direct introduction of the hydrazino substituent by reaction with hydrazine hydrate, even if partially dried by heating on potassium hydroxide pellets. Therefore the 7-hydrazino derivatives, useful for further different cyclizations, were prepared with another procedure previously experimented [1] (Scheme 2).

The chloroderivatives **1** and **4** reacted with thiourea in methanol to give the corresponding mercapto derivatives **7a** and **7b** which were easily converted to the methylthio derivatives **8a** and **8b**, by treatment with methyl iodide in 5% sodium hydroxide. Finally, heating with 99% hydrazine hydrate in methanolic solution, the expected 7-hydrazino derivatives **9a** and **9b** were obtained in high yield.

The structures of all the new prepared compounds were easily assigned upon the basis of known reaction mechanisms and were confirmed by analytical and spectroscopic methods (ir, ms and ^{1}H-nmr).

The mass spectra are reported in the Table 1 as molecular peak and base peak, but fragments corresponding to the 2-chlorobenzyl (125) and 2-fluorobenzyl (109) respectively, are also present. In the infrared spectra of the compounds **2a-e** and **5a-e**, the carbonyl band at 1660-1670 cm^{-1} and NH bands at 3160-3400 cm^{-1} are clearly observed. The hydrazinoderivatives **9a** and **9b** show the NH bands at 3348-3450 cm^{-1}. The ^{1}H-nmr spectra of the tricyclic compounds **3a-d** and **6a-d** are reported in Table 2.

The open compounds **2a-e**, **5a-e**, **9a** and **9b** together with the tricyclic derivatives **3a-d** and **6a-d**, submitted to binding assays to evaluate an eventual affinity

Table 2

^{1}H-NMR Data of **3a-d** and **6a-d**

	H-5 (s, 1H)	CH_2 (s, 2H)	3-substituent (m, 4H)	7-substituent
3a	9.88	6.08	7.22-7.62	7.60 and 8.31 (m, 5H)
3b	9.95	6.10	7.28-7.59	8.20 and 8.84 (d, d, 4H)
3c	9.86	6.08	7.30-7.58	6.79, 7.36 and 7.42 (m, 3H)
3d	9.75	6.06	7.30-7.59	2.60 (s, 3H)
6a	9.89	6.05	7.16-7.52	7.60 and 8.30 (m, 5H)
6b	9.95	6.06	7.15-7.52	8.20 and 8.84 (d, d, 4H)
6c	9.85	6.04	7.17-7.51	6.78, 7.39 and 7.70 (m, 3H)
6d	9.74	6.02	7.15-7.50	2.59 (s, 3H)

towards the adenosine A_1 and A_{2A} receptors, resulted lacking in activity.

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. Mass spectra were performed with a Hewlett Packard MS/System 5988 A. ^{1}H-nmr spectra were recorded with a Varian Gemini 200 spectrometer in DMSO-d_6 in δ units, using TMS as internal standard. Elemental analyses (C,H,N) were performed on a Carlo Erba Elemental Analyzer Mod. 1106 apparatus. Petroleum ether corresponds to fraction boiling at 40-60 °C. Hydrazine hydrate 99% is a very toxic and dangerous reagent that requires an appropriate personal protection.

Hydrazides.

The employed hydrazides, all described in the literature, were prepared in the usual manner by reaction of the suitable methyl or ethyl ester with 99% hydrazine hydrate: benzoic [7], isonicotinic [8], 2-furoic [9], acetic [10] and *p*-nitrobenzoic [11].

3-(2-Chlorobenzyl)-7-hydrazido-1,2,3-triazolo[4,5-d]pyrimidines (**2a-e**).

A mixture of 1.100 g (3.93 mmol) of the chloroderivative **1**, 7.86 mmoles of the suitable hydrazide (39 mmol for **2d**) and 1.10 mL (7.86 mmol) of TEA in 35 mL of absolute ethanol, was heated under reflux for 2.5 hours (16 hours for **2d**). After cooling the title compounds precipitated and were collected by filtration (Table 1).

3-(2-Chlorobenzyl)-7-substituted-1,2,3-triazolo[4,5-*e*]1,2,4-triazolo[4,3-*c*]pyrimidines (**3a-d**).

A solution of 2.00 mmoles of the suitable hydrazido derivative (**2a**, **2b**, **2c** or **2d**) in 20 mL of Dowtherm was heated under reflux (≈ 230 °C) for 2 hours. After cooling, petroleum ether was added to the solution, which caused precipitation of a solid product. This solid, collected by filtration, was extracted with boiling petroleum ether portions. Compound **3a** was further purified by crystallization (Table 1) while compounds **3b-d** were purified by flash-chromatography through a silica gel column (Table 1).

3-(2-Fluorobenzyl)-7-hydrazido-1,2,3-triazolo[4,5-*d*]-pyrimidines (**5a-e**).

A mixture of 0.880 g (3.34 mmol) of the chloroderivative **4**, 6.68 mmoles of the suitable hydrazide and 0.93 mL (6.68 mmol) of TEA in 20-25 mL of absolute ethanol, was heated under reflux for 2.5 hours. After cooling, the title compounds precipitated and were collected by filtration (Table 1).

3-(2-Fluorobenzyl)-7-substituted-1,2,3-triazolo[4,5-*e*]1,2,4-triazolo[4,3-*c*]pyrimidines (**6a-d**).

A solution of 2.50 mmoles of the suitable hydrazido derivative (**5a**, **5b**, **5c** or **5d**) in 20 mL of Dowtherm was heated under reflux (≈ 230 °C) for 2 hours. After cooling, petroleum ether was added to the solution, which caused precipitation of a solid product. This solid, collected by filtration, was extracted with boiling petroleum ether portions. For the purification of compounds **6a** and **6d** the solid was crystallized from ethanol (Table 1) while for that of compounds **6b** and **6c** the solid was flash-chromatographed through a silica gel column (Table 1).

3-(2-Chlorobenzyl)-7-mercapto-1,2,3-triazolo[4,5-*d*] pyrimidine (**7a**) and 3-(2-Fluorobenzyl)-7-mercapto-1,2,3-triazolo[4,5-*d*] pyrimidine (**7b**).

A mixture of 7.00 mmoles of the appropriate chloroderivative (**1** or **4**) and 1.60 g (21 mmoles) of thiourea in 60 mL of methanol was heated under reflux for 25 minutes. The solution was evaporated *in vacuo* and the residue was stirred with 0.5 *N* sodium hydroxide. The insoluble material was filtered off and the filtrate was acidified (pH 4) with acetic acid to precipitate the title compounds which were collected by filtration and washed with ethanol (Table 1).

3-(2-Chlorobenzyl)-7-methylthio-1,2,3-triazolo[4,5-*d*] pyrimidine (**8a**) and 3-(2-Fluorobenzyl)-7-methylthio-1,2,3-triazolo[4,5-*d*] pyrimidine (**8b**).

To a solution of 7.20 mmoles of the suitable mercapto derivative (**7a** or **7b**) in 20 mL of 1 *N* sodium hydroxide, 0.58 mL (9.30 mmol) of methyl iodide were added and the mixture was stirred at room temperature for 20 minutes. The title compounds precipitated as solids which were collected by filtration and washed with water (Table 1).

3-(2-Chlorobenzyl)-7-hydrazino-1,2,3-triazolo[4,5-*d*]pyrimidine (**9a**) and 3-(2-Fluorobenzyl)-7-hydrazino-1,2,3-triazolo[4,5-*d*] pyrimidine (**9b**).

A suspension of 1.70 mmoles of the suitable methylthio derivative (**8a** or **8b**) in 15 mL of methanol was heated to boiling point until complete solution. Hydrazine hydrate (99%, 1.20 mL, 25 mmol) was added to the hot solution and the reaction mixture was stirred and left to cool at room temperature (≈ 30-40 minutes). The title compounds precipitated as crystalline solids which were collected and washed with methanol (Table 1).

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