

Dipartimento di Scienze Farmaceutiche, Facoltà di Farmacia,
Università di Pisa, via Bonanno 6, 56126 Pisa, Italy
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Some new 1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]pyrimidines were prepared starting from the corresponding 1,2,3-triazolo[4,5-*d*]pyrimidines *via* the formation of the 1,2,4-triazole ring. Thus suitable hydrazino derivatives **6** were condensed with triethyl orthoformate, triethyl orthoacetate and triethyl orthobenzoate to give the expected tricyclic derivatives **7**, **8** and **9**. Intramolecular cyclization of the ethoxy-carbonylhydrazino derivatives **10** gave the tricyclic compounds **11** bearing an hydroxyl group in the 3 position. The *v*-triazolo-*s*-triazolopyrimidine derivatives were tested towards the A₁ and A_{2A} adenosine receptors in binding assays, but they did not show any receptor affinity.

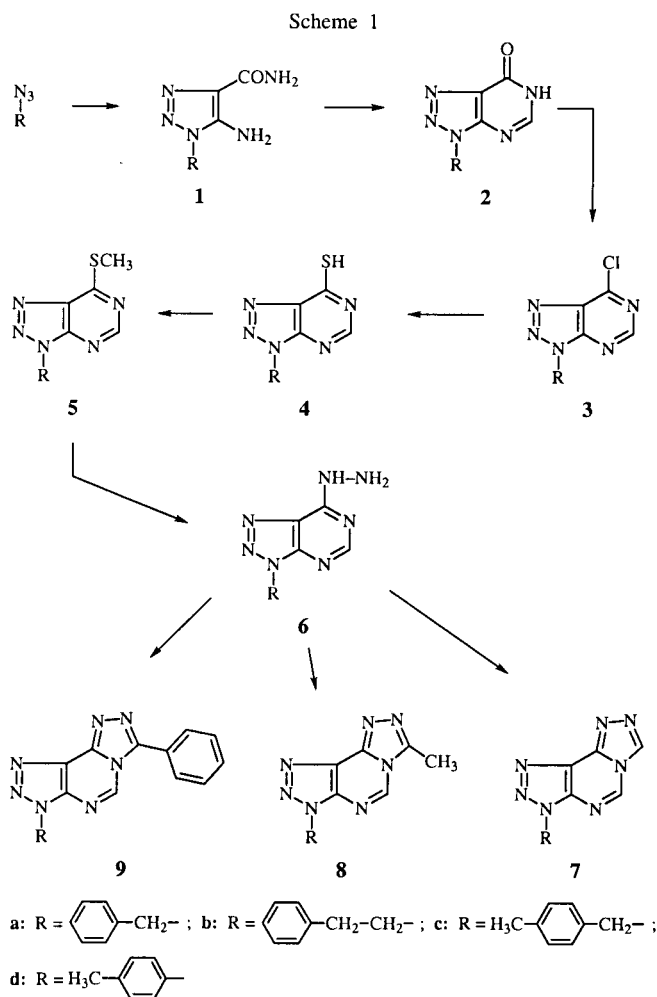
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The 1-benzoyloxy-7-phenyl-1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]pyrimidine derivative was mentioned in a short paper published in 1978, concerning the thermolysis of *N*-hetaryl-tetrazoles with the generation of nitrilimines to give competitive intramolecular 1,*x*-dipolar cyclizations [1]. In 1990, while pursuing the synthesis of novel nitrogen-rich heterocycles, Ried and Laoutidis [2] obtained some *v*-triazolo-*s*-triazolopyrimidine derivatives by the cyclization of 7-hydrazino-1*H*-1,2,3-triazolo[4,5-*d*]pyrimidines with triethyl orthoformate or triethyl orthoacetate.

Italian authors [3,4,5] have patented derivatives with the isomeric structure 1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (together with analogous derivatives with a pyrazolo or imidazole ring in place of the 1,2,3-triazole), which show a high, selective antagonistic activity towards A_{2A}-adenosine receptors. However, the 1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]pyrimidine derivatives have not been studied in detail, and the biological properties of this tricyclic structure, which can also be correlated to other similar pharmacologically active tricyclic structures [6,7], are practically unknown. For these reasons, after studying the isomeric *v*-triazolo-5-triazolopyridazine structure [8], we followed an analogous synthetic route using the 1,2,3-triazolo[4,5-*d*]pyrimidine compounds which had been the subject of our studies [9], in order to prepare 1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]pyrimidines bearing lipophilic substituents in the 3 position of the heterocyclic ring.

This synthesis was based upon the formation of the 1,2,4-triazole ring by condensation of an appropriate monocarbon fragment with the 4-hydrazino substituent, with the nitrogen atom in the 6 position of the 1,2,3-triazolo[4,5-*d*]pyrimidine ring [2].

The reaction sequence followed for the synthesis of the tricyclic derivatives is illustrated in Scheme 1: by cycloaddition of the appropriate azide [benzyl azide [10] (series a), phenethyl azide [11] (series b), *p*-methylbenzyl azide [12] (series c) and *p*-methylphenyl azide [13] (series d)] to cyanacetamide in ethanol/sodium ethoxide, the corresponding triazole derivatives **1a-d** were obtained, which were easily converted into the relative



3-substituted-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyrimidine derivatives **2a-d** by heating in formamide. Chlorination of compounds **2a-d** with thionyl chloride in chloroform/dimethylformamide provided the 7-chloro derivatives **3a-d** in 50-70% yields. The direct reaction of the chloro derivative **3a** with 99% hydrazine hydrate or partially anhydridified hydrazine gave the corresponding hydrazino

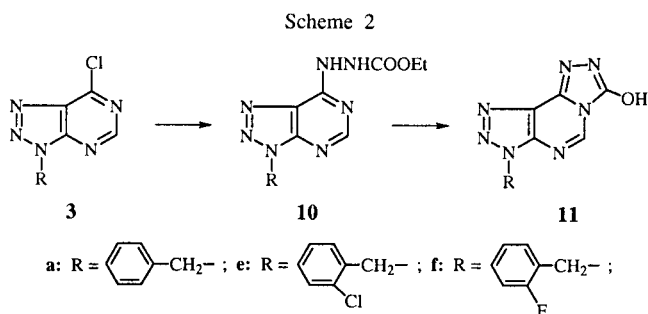
Table I
Chemical and Physical Properties of Derivatives 1-11

Compound	Yield %	Crystall. Solvent	Mp °C	Mass m/z		Elemental Analysis	Calcd./Found		
				M +	base peak		C	H	N
1c	83	EtOH	218-222			C ₁₁ H ₁₃ N ₅ O	57.13	5.67	30.28
							57.14	5.63	30.30
2b	89	EtOH	262-264	241	150	C ₁₂ H ₁₀ N ₅ O	59.99	4.20	29.15
							59.61	4.49	28.81
2c	94	EtOH	257-259	241	184	C ₁₂ H ₁₀ N ₅ O	59.99	4.20	29.15
							59.72	4.47	28.80
3b	76	60-80° petroleum ether	94-96	259	104	C ₁₂ H ₁₀ N ₅ Cl	55.50	3.88	26.97
							55.56	3.92	27.28
3c	45	60-80° petroleum ether	88-91	259	105	C ₁₂ H ₁₀ N ₅ Cl	55.50	3.88	26.97
							55.45	3.99	26.61
4b	97	-----	167-170	257	104	C ₁₂ H ₁₁ N ₅ S	56.01	4.31	27.22
							55.62	4.35	27.15
4c	98	-----	205-207	257	105	C ₁₂ H ₁₁ N ₅ S	56.01	4.31	27.22
							56.37	4.36	27.50
4d	95	-----	186-188	244	91	C ₁₁ H ₁₀ N ₅ S	54.08	4.13	28.67
							53.98	3.76	28.81
5b	95	-----	62-63	271	79	C ₁₃ H ₁₃ N ₅ S	57.55	4.83	25.83
							57.60	4.82	25.83
5c	92	-----	119-121	271	105	C ₁₃ H ₁₃ N ₅ S	57.55	4.83	25.83
							57.20	4.75	25.51
5d	99	EtOH	129-131	259	91	C ₁₂ H ₁₃ N ₅ S	55.58	5.05	27.01
							55.68	4.70	27.22
6b	77	MeOH	155-158	255	151	C ₁₂ H ₁₃ N ₇	56.46	5.13	38.41
							56.20	4.75	38.43
6c	88	MeOH	209-212	255	105	C ₁₂ H ₁₃ N ₇	56.46	5.13	38.41
							56.49	5.10	38.34
6d	86	MeOH	194-195	241	91	C ₁₁ H ₁₁ N ₇	54.76	4.60	40.64
							54.42	4.55	40.24
7b	63	EtOH	198-200	265	174	C ₁₃ H ₁₁ N ₇	58.86	4.18	36.96
							58.85	4.37	37.30
7c	77	EtOH	226-229	265	105	C ₁₃ H ₁₁ N ₇	58.86	4.18	36.96
							58.46	4.37	36.81
7d	64	EtOH	213-216	251	222	C ₁₂ H ₉ N ₇	57.37	3.61	39.02
							57.62	3.65	39.40
8b	65	EtOH	228-231	279	188	C ₁₄ H ₁₃ N ₇	60.20	4.69	35.10
							59.81	4.69	35.39
9a	70	EtOH	270-272	327	91	C ₁₈ H ₁₃ N ₇	66.05	4.00	29.95
							65.80	4.32	30.12
9b	71	EtOH	209-212	341	77	C ₁₉ H ₁₅ N ₇	66.85	4.43	28.72
							66.56	4.81	28.91
10a	95	MeOH	202-204	313	91	C ₁₄ H ₁₅ N ₇ O ₂	53.67	4.83	31.29
							53.51	5.10	31.26
10e	90	MeOH	205-207	347	125	C ₁₄ H ₁₄ N ₇ O ₂ Cl	48.35	4.06	28.19
							48.27	3.71	28.53
10f	84	MeOH	208-209	331	109	C ₁₄ H ₁₄ N ₇ O ₂ F	50.75	4.26	29.59
							50.42	3.99	29.42
11a	71	MeOH	265-270 dec	267	91	C ₁₂ H ₉ N ₇ O	53.93	3.39	36.69
							54.15	3.53	36.92
11e	82	MeOH	258-269 dec	301	125	C ₁₂ H ₈ N ₇ OCl	47.77	2.67	32.50
							47.46	2.49	32.48
11f	90	MeOH	256-266 dec	285	109	C ₁₂ H ₈ N ₇ OF	50.53	2.83	34.37
							50.87	2.56	34.72

derivative **6a** in a low yield as a result of the concurrent formation of the hydroxy derivative **2a**, which could only be separated with difficulty.

We therefore followed an alternative synthetic route described in the literature [10] for the introduction of nucleophilic substituents in the 7 position of the triazolopyrimidine ring: the chloro derivatives **3a-d** reacted with thiourea in

methanol to give the corresponding thiol derivatives **4a-d** in high yields, which, in turn, were easily converted to the methylthio derivatives **5a-d** with methyl iodide in an aqueous alkaline solution. By reaction with 99% hydrazine hydrate, these last compounds provided the expected hydrazino derivatives **6a-d** in $\approx 80\%$ yields. The reactions of the benzylic series (compounds **1a-6a**) have been already



described in literature [10] but they were repeated for biological purposes. The intermediates **1b** [11], **1c**, **2c** [14] and **3c** [15] have also been previously described. Analogously to the cyclizations carried out on the triazolopyridazine derivatives [8], the hydrazino derivative **6a** was heated with formic acid to obtain the third 1,2,4-triazole heterocyclic ring, but the reaction proved to be unsatisfactory. The tricyclic compounds **7a-d** were subsequently obtained in good yield in accordance with the preparation of **7a** [2], by heating the hydrazino derivatives **6a-d** with triethyl orthoformate under reflux. By heating **6a,b** with triethyl orthoacetate in the same manner, the expected 3-methyl derivatives **8a** [2] and **8b** were obtained, while the reaction with triethyl orthobenzoate provided the 3-phenyl-substituted tricyclic compounds **9a** and **9b**. The appropriate 3-substituted-7-chlorotriazolopyrimidines **3a** (benzyl [10]), **3e** (2-chlorobenzyl [9]) and **3f** (2-fluorobenzyl [16]) (Scheme 2) reacted with ethyl carbazate in a benzene solution in the presence of triethylamine to give in high yields the corresponding triazolopyrimidine compounds **10a, e, f**, bearing the ethoxycarbonylhydrazino substituent in the 7 position. By heating **10a, e, f** at a high temperature (Dowtherm), an elimination of ethanol took place, thus forming the 1,2,4-triazole ring, and the expected 3-substituted-7-hydroxy-1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]pyrimidines **11a, e, f** were obtained in good yields.

The structures of all the new compounds were assigned on the basis of the well-known reaction mechanism (1,3-dipolar cycloaddition of azides to activated methylenic compounds, formation of the pyrimidine ring, chlorination and nucleophilic displacement of the halogen by thiourea or hydrazine, formation of the fused 1,2,4-triazole ring) and were confirmed by analytical and spectroscopic data. Table 2 reports the ¹H-nmr spectral data of the tricyclic compounds **7, 8, 9** and **11**.

The tricyclic compounds **7, 8** and **9** were tested in radioligand binding assays for their affinity at A₁ and A_{2A} adenosine receptors in bovine brain cortical membranes and in bovine brain striatal membranes, respectively. The experiment, details of which have been reported in a previous paper [9], used [³H]R(-)-N⁶-cyclohexyl-adenosine as the A₁ radioligand and [³H]-2-[[*p*-(2-carboxyethyl)phenyl]ethyl]amino-5'-*N*-ethylcarbamoyladenosine (CGS-21680) as the A_{2A} radioligand. None of the compounds were found to possess any binding affinity.

Table II

¹H-NMR Data (δ) in Dimethyl-*d*₆ Sulfoxide of the Tricyclic Compounds

	R	R ₁ and R ₂
7a	7.32 (brs, 5H, C ₆ H ₅), 5.95 (s, 2H, CH ₂)	9.46 (s, 1H, CH), 9.45 (s, 1H, CH)
7b	7.20 (brs, 5H, C ₆ H ₅), 5.01 (t, 2H, CH ₂), 3, 38 (t, 2H, CH ₂)	9.51 (s, 1H, CH), 9.46 (s, 1H, CH)
7c	2.25 (s, 3H, CH ₃), 7.10 and 7.25 (AA'BB', 4H, C ₆ H ₄), 5.86 (s, 2H, CH ₂)	9.45 (s, 1H, CH), 9.43 (s, 1H, CH)
7d	2.44 (s, 3H, CH ₃), 7.48 and 7.95 (AA'BB', 4H, C ₆ H ₄)	9.86 (s, 1H, CH), 8.78 (s, 1H, CH)
8a	7.38 (brs, 5H, C ₆ H ₅), 5.94 (s, 2H, CH ₂)	9.66 (s, 1H, CH), 2.58 (s, 3H, CH ₃)
8b	7.15 (brs, 5H, C ₆ H ₅), 4.95 (t, 2H, CH ₂), 3.33 (t, 2H, CH ₂)	9.25 (s, 1H, CH), 2.80 (s, 3H, CH ₃)
9a	7.35 (brs, 5H, C ₆ H ₅), 5.97 (s, 2H, CH ₂)	9.81 (s, 1H, CH), 8.21 (m, 2H, Ar), 7.56 (m, 3H, Ar)
9b	7.18 (brs, 5H, C ₆ H ₅), 5.09 (t, 2H, CH ₂), 3.36 (t, 2H, CH ₂)	9.78 (s, 1H, CH), 8.24 (m, 2H, Ar), 7.56 (m, 3H, Ar)
11a	7.32 (brs, 5H, C ₆ H ₅), 5.82 (s, 2H, CH ₂)	8.75 (s, 1H, CH), 11.10 (brs, 1H, exchangeable)
11e	7.57-7.08 (m, 4H, C ₆ H ₄), 5.89 (s, 2H, CH ₂)	8.75 (s, 1H, CH), 11.12 (brs, 1H, exchangeable)
11f	7.58-6.96 (m, 4H, C ₆ H ₄), 5.86 (s, 2H, CH ₂)	8.76 (s, 1H, CH), 11.16 (brs, 1H, exchangeable)

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage and are uncorrected. The ir spectra in nujol mulls were recorded on a Perkin-Elmer Mod. 1310 spectrometer. The ¹H nmr spectra were recorded with a Varian CFT-20 spectrometer in dimethyl-*d*₆ sulfoxide in δ units, using tetramethylsilane as the internal standard. Mass spectra were performed with a Hewlett Packard MS/System 5988. The tlc data were obtained with Riedel de Haen, 37360 DC-Karten F₂₅₄, 0.2 mm, eluting with a 1:2 AcOEt/60-80° petroleum ether mixture. Elemental analyses (C,H,N) were within ± 0.4% of theoretical values and were performed on a Carlo Erba Elemental Analyzer Mod. 1106 apparatus.

1-(4-Methylbenzyl)-4-carboxamido-5-amino-1*H*-1,2,3-triazole (**1c**).

To a stirred solution of sodium ethoxide, prepared with 0.780 g (34.0 g atoms) of sodium in 37 ml of absolute ethanol, 3.14 g (34.0 mmoles) of cyanacetamide was added. After 15 minutes, a solution of 4.80 g (32.6 mmoles) of 4-methylbenzyl azide [14] in 15 ml of absolute ethanol was added to the suspension obtained. The reaction mixture was heated under reflux for 2 hours and after cooling, the solid precipitate was collected by filtration, washed with ethanol and dried (Table I).

3-Substituted-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyrimidines **2b** and **2c**.

A solution of 22.0 mmoles of the appropriate triazole derivative **1b** [11] or **1c** in 25 ml of formamide was refluxed for 2 hours. After cooling the reaction mixture was diluted with water, stirred for 3 hours and the solid precipitate was collected by filtration (Table I).

3-Substituted-7-chloro-1,2,3-triazolo[4,5-*d*]pyrimidines **3b** and **3c**.

To a suspension of 8.5 mmoles of the appropriate triazolopyrimidine **2b** or **2c** in 40 ml of boiling anhydrous chloroform, 1.5 ml of dimethylformamide and 7 ml of thionyl chloride were added. The reaction mixture was refluxed for 2 hours, the solvent was evaporated *in vacuo* (temperature $\leq 35^\circ$), and the residue, after cooling at 0° , was triturated with crushed ice. The solid formed was collected by filtration, dried and extracted repeatedly with boiling 60-80° petroleum ether. The combined extracts were evaporated *in vacuo* to give the title compounds as white solids (Table I).

3-Substituted-7-mercapto-1,2,3-triazolo[4,5-*d*]pyrimidines **4b**, **4c** and **4d**.

A mixture of 6.0 mmoles of a suitable chloro derivative **3b**, **3c** or **3d** and 1.50 g (20.0 mmoles) of thiourea in 60 ml of anhydrous methanol was heated under reflux for 20 minutes. The reaction mixture was evaporated *in vacuo*, the residue was treated with 2% sodium hydroxide and the insoluble material was filtered. The filtrate was acidified (pH 4) with acetic acid to precipitate the title compounds which were collected, washed and dried (Table I).

3-Substituted-7-methylthio-1,2,3-triazolo[4,5-*d*]pyrimidines **5b**, **5c** and **5d**.

To a stirred solution or suspension of 2.20 mmoles of the appropriate thio derivative **4b**, **4c** or **4d** in 4-6 ml of 5% sodium hydroxide, 0.5-0.6 ml (8.0-9.6 mmoles) of methyl iodide was added and stirring was continued at room temperature for 1 hour. The solid precipitate was collected by filtration, washed with water and dried (Table I).

3-Substituted-7-hydrazino-1,2,3-triazolo[4,5-*d*]pyrimidines **6b**, **6c** and **6d**.

A suspension of 2.50 mmoles of the appropriate methylthio derivative **5b**, **5c** and **5d**, in 20 ml of anhydrous methanol was heated until it boiled, and then 2.5 ml (≈ 50 mmoles) of 99% hydrazine hydrate was added. The reaction mixture was stirred at room temperature for 1 hour and the crystalline solid formed, consisting of the title compounds, was collected, washed with methanol and dried (Table I).

3-Substituted-1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]pyrimidines **7b**, **7c** and **7d**.

A solution of 0.80 mmole of **6b**, **6c** or **6d** in 4 ml of triethyl orthoformate was heated under reflux for 8 hours. After cooling, the title compounds precipitated and were collected and washed with ethanol (Table I).

3-Phenethyl-7-methyl-1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]pyrimidine (**8b**).

A solution of 0.200 g (0.78 mmole) of **6b** in 3.5 ml of triethyl orthoacetate was heated at 140° for 8 hours. After cooling, **8b** precipitated as a crystalline solid which was collected by filtration and washed with methanol (Table I).

3-Substituted-7-phenyl-1,2,3-triazolo[4,5-*e*]-1,2,4-triazolo[3,4-*c*]pyrimidines **9a** and **9b**.

A solution of 1.0 mmole of the appropriate hydrazino derivative **6a** or **6b** in 2.5 ml of triethyl orthobenzoate was heated at 160° for 8 hours. After cooling, the title compounds crystallized

from the reaction mixture and were collected by filtration and recrystallized (Table I).

3-Substituted-7-ethoxycarbonylhydrazino-1,2,3-triazolo[4,5-*d*]pyrimidines **10a**, **10e** and **10f**.

To a solution of 6.0 mmoles of the appropriate 3-substituted-7-chlorotriazolopyrimidine **3a**, **3e** or **3f** in 65 ml of anhydrous benzene, 0.80 ml (6.0 mmoles) of triethylamine and 1.25 g (12.0 mmoles) of ethyl carbazate were added and the mixture was heated under reflux for 2 hours. The solvent was evaporated *in vacuo*, the residue was triturated with 50-60 ml of 10% hydrochloric acid and the insoluble material, consisting of the title compounds, was collected by filtration and washed with water (Table I).

3-Substituted-7-hydroxy-1,2,3-triazolo[4,5-*e*]1,2,4-triazolo[3,4-*c*]pyrimidines **11a**, **11e** and **11f**.

A solution of 1.50 mmoles of the appropriate derivative **10a**, **10e** or **10f** in 15 ml of Dowtherm was heated under reflux for 3 hours. After cooling the title compounds precipitated, the suspension was diluted with petroleum ether and the solid precipitated was collected by filtration and washed with petroleum ether (Table I).

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