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Original article

New 1,2,3-triazolo[1,5-a]quinoxalines: synthesis and binding to benzodiazepine and adenosine receptors. II

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Abstract

On pursuing research about 1,2,3-triazolo[1,5-a]quinoxalines, in this paper we report synthesis and binding assays toward the benzodiazepine and A_1 and A_{2A} adenosine receptors, of a new series of derivatives, bearing some structural changes (introduction of fluorine and trifluoromethyl in the seventh position, amino substituents in the fourth position, benzyl group in the fifth position and aroyl substituents in the third position). The biological tests have shown that only the 7-fluorosubstituted compounds **3a** and **4a** and the *N*-benzyl derivative **7** have a good affinity toward the benzodiazepine receptors, while only the 7-trifluoromethyl substituted compound **3b** presents a moderate affinity with low selectivity toward the A_1 adenosine receptors. The other structural modifications strongly decreased biological activity. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: 1,2,3-triazolo[1,5-a]quinoxalines; Benzodiazepine receptor binding; Adenosine receptor binding

1. Introduction

In a previous paper [1] we reported synthesis and binding assays towards benzodiazepine and adenosine A_1 and A_{2A} receptors of two series (A and B, Fig. 1) of triazoloquinoxaline derivatives. The biological results indicated that these compounds possessed a good affinity towards the benzodiazepine receptors (Ki values included between 53 and 314 nM). The GABA ratio values suggested a prevailing inverse agonist activity for the N(5) unsubstituted compounds A, and a prevailing agonist activity for the N(5) methyl substituted compounds B. The best derivatives were A (R = Cl, Ki = 53 nM) and B (R = Cl, Ki = 54 nM) with GABA ratios 1.2 and 1.6, respectively. Some derivatives showed a good affinity also (Ki < 100 nM) towards the A_1 adenosine receptors, with a high selectivity regarding the A_{2A} receptor subtype.

The best derivatives were A (R = OCH_3, Ki = 29 nM; R = CH_3, Ki = 49 nM).

The investigation on the 1,2,3-triazolo[1,5-a]-quinoxalines was continued by the introduction of new substituents on the tricyclic ring and the biological evaluation of the new derivatives, to understand the effect of the structural changes and, therefore, the structure–activity relationships.

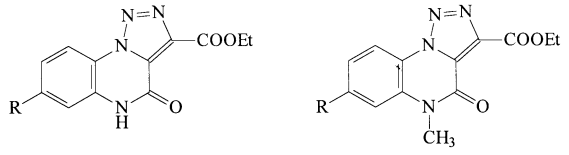

Fig. 1. Reference triazoloquinoxaline derivatives.

2. Chemistry

Two new substituents, a fluorine atom and a trifluoromethyl group, were introduced in the seventh position of the triazolo-quinoxaline ring. The fluorine atom appeared interesting for the affinity towards the

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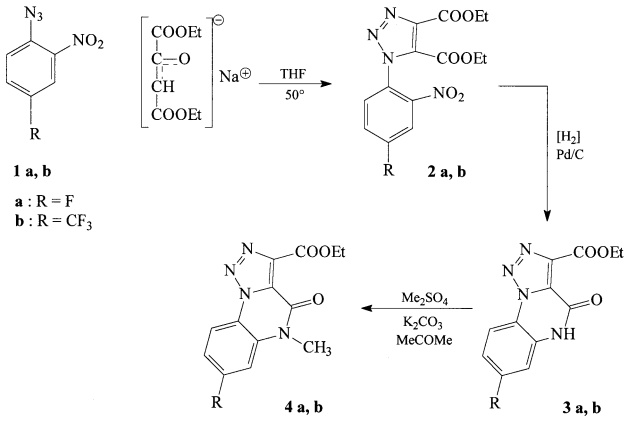


Fig. 2. Synthetic route for the preparation of compounds **4a**, **b**.

benzodiazepine receptors, because the structure of **3a** and **4a** is comparable to the competitive antagonist Ro.15-1788 (Flumazenil).

Thus starting from 2-nitro-4-fluoro-phenylazide (**1a**) [2] or 2-nitro-4-trifluoromethyl-phenylazide (**1b**) [2] (Fig. 2), by reaction with diethyl oxalacetate sodium salt in anhydrous THF at 50 °C, a mixture consisting of the expected triazole diester (**2a** or **2b**) and triazole byproducts together with the aniline corresponding to the azide and the substituted benzofurazan-*N*-oxide was obtained as previously described for analogous reactions [1].

This mixture underwent a silica gel column flash-chromatography and compounds **2a** and **2b** were isolated in 25 and 16.5% yield, respectively. The nitrogroup reduction of **2a** and **2b**, by catalytic hydrogenation, induced intramolecular condensation between the formed amino group and the ethoxycarbonyl function in the fifth position of the triazole ring, to give directly the desired tricyclic derivatives **3a** and **3b**. These compounds by treatment with dimethyl sulfate in anhydrous acetone in the presence of anhydrous potassium carbonate, provided the corresponding *N*-methyl derivatives **4a** and **4b**. Their structure was confirmed by spectroscopic data which agreed with those reported in the literature [1] for analogous *N*-methyl compounds.

A further structural change concerned synthesis of some new triazolo-quinoxaline derivatives bearing in the fourth position an alkylamino or aralkylamino substituent. These lipophilic substituents bonded to a NH

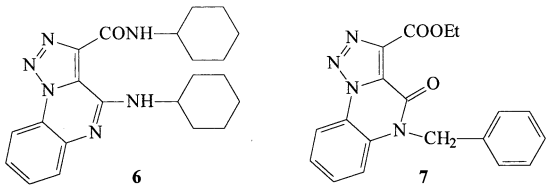


Fig. 4. Structure of compounds **6** and **7**.

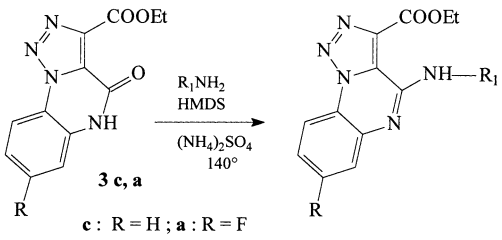
function had shown to increase the adenosine receptor binding [3,4].

Thus starting from the 3-ethoxycarbonyl-1,2,3-triazolo[1,5-a]quinoxalin-4-one (**3c**) [1], by a silylation–amination reaction with 3-pentylamine, (±)-α-methylbenzylamine and (±)-1-methyl-2-phenethylamine, the corresponding 4-substituted compounds **5a**–**c** were obtained in very low yields (Fig. 3). An analogous reaction between the fluoro substituted triazolo-quinoxaline **3a** and (±)-α-methyl-benzylamine provided the derivative **5d** in 18% yield.

The reaction of **3c** with cyclohexylamine, carried out also under different experimental conditions, allowed isolation of the only disubstituted compound **6** (Fig. 4).

Besides, as an alternate structural pattern, to compare with the previously examined *N*-methyl derivatives [1], the *N*-benzylderivative **7** (Fig. 4) was prepared by reaction of **3c** with benzyl chloride in methylethylketone, in the presence of anhydrous potassium carbonate. The *N*-benzylsubstituted structure was confirmed and discriminated from the *O*-benzyl isomer by the chemical shift value (44.9 ppm) of the benzyl carbon in the ^{13}C-NMR spectrum of **7**.

Finally, as a further structural change, triazoloquinoxaline derivatives bearing a lipophilic and bulky substituent in the third position were prepared. In fact a phenyl substituent in the third position of analogous triazolo-quinazoline structures resulted effective for binding towards the adenosine receptors [5] as well as a furoyl substituent [6]. According to the acquired synthetic procedure, 2-nitrophenylazide (**1c**) [7] and 2-nitro-4-chlorophenylazide (**1d**) [8] were reacted with the appropriate activated methylenic compound to obtain the 4-aroyl-5-ethoxycarbonyl-1,2,3-triazoles, the key intermediates for the preparation of the corresponding triazolo-quinoxaline derivatives.



5a : R = H ; R_1 = 3-pentyl
5b : R = H ; R_1 = (±)α-methyl-benzyl
5c : R = H ; R_1 = (±)α-methyl-phenetyl
5d : R = F ; R_1 = (±)α-methyl-benzyl

Fig. 3. Synthesis of compounds **5a**–**d**.

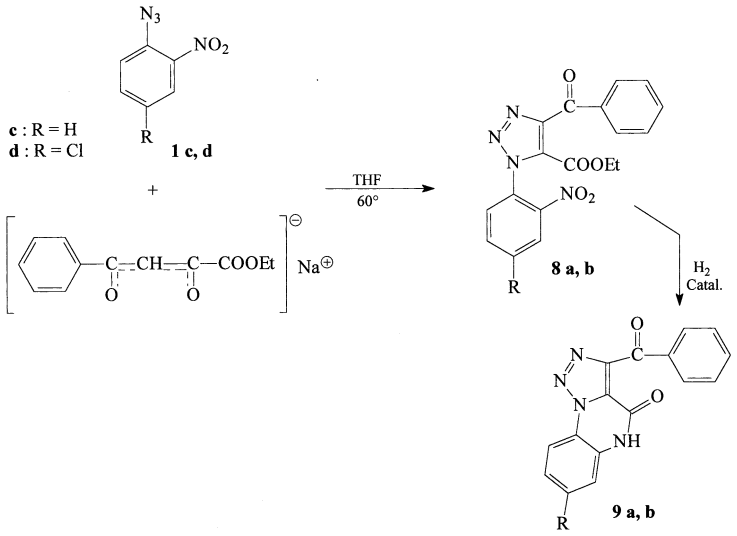


Fig. 5. Synthetic route for the preparation of compounds **9a**, **b**.

The reagents, ethyl benzoylpyruvate [9] and ethyl 2-furoylpyruvate [10] as sodium salts, were prepared starting from acetophenone and 2-acetylfuran, respectively, by a Claisen reaction with diethyl oxalate in anhydrous ethanol, in the presence of sodium ethoxide. The 1,3-dipolar cycloaddition reactions (Fig. 5) were carried out in anhydrous THF, the azide solution was added dropwise to the reagent solution at 40 °C and the mixture was heated at 60 °C for 7 h, under stirring. The expected triazolesters **8a** and **8b** were isolated in moderate yield by flash-chromatography through a silica gel column, to separate them from large amounts of 2-nitroaniline and benzofurazan *N*-oxide. From the alkaline aqueous layers little amounts of the corresponding 5-carboxy acids were also isolated. The nitrogroup reduction by catalytic hydrogenation at room temperature and pressure directly provided the 3-benzoyl- (**9a**) and 3-furoyl- (**9b**) triazolo-quinoxalines, via intramolecular cyclization with elimination of ethanol between the formed aminogroup and the ethoxycarbonyl group in the fifth position of the triazole ring.

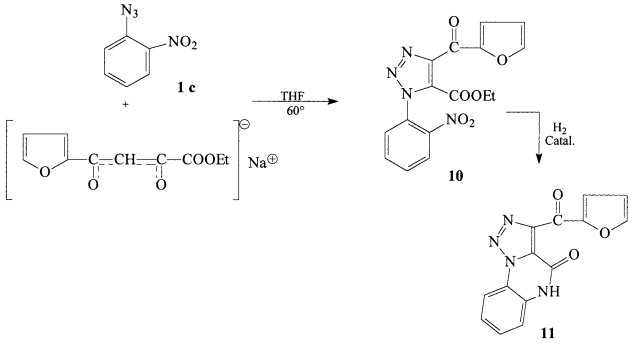


Fig. 6. Synthetic route for the preparation of compound **11**.

Under the same experimental conditions (Fig. 6), the 2-nitrophenylazide (**1c**) reacted with the 2-furoyl reagent to give the expected triazolester **10**, isolated by flash chromatography, which was cyclized to the corresponding 3-furoyl-triazolo-quinoxaline **11**, by catalytic hydrogenation.

The structures of all the new prepared compounds were assigned according to their reaction mechanisms and our previous evidence [1] and were confirmed by analytical and spectroscopic data (Table 2 and Table 3).

3. Biological results and discussion

All the triazolo-quinoxaline derivatives 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*-ethylcarbamoyl)-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 [1].

The results of the binding assays toward the adenosine receptors (Table 4) show that these triazolo-quinoxaline derivatives have a low affinity towards the two receptor subtypes. Only compound **3b**, bearing the trifluoromethyl group in the seventh position, shows a good A_1 receptor affinity (Ki = 91 nM) and selectivity.

Table 1
Physico-chemical properties

	Crystall. solvent	Yield (%)	M.p. (°C)	Analysis C,H,N
2a	[a]	25	50–53	$C_{14}H_{13}N_4O_6F$
3a	EtOH	60	244–246	$C_{12}H_9N_4O_3F$
4a	EtOH	63	184–186	$C_{13}H_{11}N_4O_3F$
2b	[a]	17	66–68	$C_{15}H_{13}N_4O_6F_3$
3b	EtOH	53	239–241	$C_{13}H_9N_4O_3F_3$
4b	EtOH	64	174–176	$C_{14}H_{11}N_4O_3F_3$
5a	EtOH	15	64–65	$C_{17}H_{21}N_5O_2$
5b	EtOAc	16	142–145	$C_{20}H_{19}N_5O_2$
5c	EtOAc	10	170–173	$C_{21}H_{21}N_5O_2$
5d	EtOAc	22	150–153	$C_{20}H_{18}N_5O_2F$
6	EtOAc	9	214–216	$C_{22}H_{28}N_6O$
7	EtOH	52	148–150	$C_{19}H_{16}N_4O_3$
8a	[a]	28	99–100	$C_{18}H_{14}N_4O_5$
9a	MeOH	66	165–168	$C_{16}H_{10}N_4O_2$
8b	[a]	26	137–138	$C_{18}H_{13}N_4O_5Cl$
9b	$CHCl_3$	62	201–203	$C_{16}H_9N_4O_2Cl$
10	[a]	18	94–95	$C_{16}H_{12}N_4O_6$
11	EtOAc	74	171–174	$C_{14}H_8N_4O_3$

[a] Isolated by flash-chromatography

Table 2
Spectroscopic data

	IR ν (cm^{-1})	Mass m/z	
		M^+	Base
2a	1727 (COOEt), 1463 and 1342 (NO_2)	–	–
3a	1740 (COOEt), 1674 (CON), 3417 (NH)	276	163
4a	1739 (COOEt), 1685 (CON)	290	177
2b	1730 (COOEt), 1470 and 1340 (NO_2)	402	69
3b	1734 (COOEt), 1694 (CON), 3462 (NH)	326	213
4b	1736 (COOEt), 1680 (CON)	340	227
5a	1694 (COOEt), 3292 (NH)	327	43
5b	1694 (COOEt), 3246 (NH)	361	105
5c	1692 (COOEt), 3290 (NH)	373	91
5d	1693 (COOEt), 3265 (NH)	379	105
6	1650 (CON), 3390 and 3255 (NH)	392	55
7	1732 (COOEt), 1685 (CON)	348	91
8a	1725 (COOEt), 1669 (CO), 1464 and 1345 (NO_2)	366	105
9a	1694 (CON, CO), 3425 (NH)	290	77
8b	1718 (COOEt), 1656 (CO), 1443 and 1340 (NO_2)	400	105
9b	1678 (CON, CO), 3214	324	105
10	1736 (COOEt), 1658 (CO), 1462 and 1341 (NO_2)	356	95
11	1684 (CON, CO), 3420 (NH)	280	95

These new derivatives have generally shown a low affinity towards the benzodiazepine receptors too (Table 4). Only compounds **4a**, **3a** and **7** present a moderate affinity with Ki values 80, 115 and 117 nM, respectively; the GABA ratio values indicate a partial agonist activity for **4a** and **7** and an antagonist activity for **3a**.

In conclusion the structural changes introduced have not induced an increase in biological activity with regard to the previous derivatives [1]. However, the trifluoromethyl group is the more effective substituent towards the A_1-adenosine receptors, whilst the fluorine atom is better toward the benzodiazepine receptors. In addition, introduction of a methyl or benzyl substituent on the nitrogen in the fifth position induced a partial agonist activity toward the benzodiazepine receptors.

4. Experimental

4.1. Chemistry

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. ^{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 an internal standard. Mass spectra were performed with a Hewlett Packard MS/System 5988 A. Elemental analyses (C, H, N) were within $\pm$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}, aluminium sheets. Petroleum ether corresponds to fraction boiling at 40–60 °C.

4.2. 1-(2-Nitro-4-fluoro-phenyl)-4,5-di-ethoxycarbonyl-1H-1,2,3-triazole (**2a**)

To a suspension of 4.25 g (20.0 mmol) of diethyl oxalacetate sodium salt in 60 mL of anhydrous THF, heated at 35 °C, a solution of 2.50 g (13.7 mmol) of 2-nitro-4-fluoro-phenylazide [2] in 50 mL of anhydrous THF was added dropwise. The reaction mixture was stirred at 50 °C for a further 7 h, then the solvent was evaporated in vacuo and the residue was treated with H_2O and extracted with $CHCl_3$. The organic layer dried ($MgSO_4$) and evaporated in vacuo, gave a solid residue (2.60 g) consisting of a mixture which was fractionated by flash-chromatography through a silica gel column, eluting with EtOAc–petroleum ether 1:2. The title compound was isolated as a pure compound (Tables 1–3).

4.3. 1-(2-Nitro-4-trifluoromethyl-phenyl)-4,5-di-ethoxycarbonyl-1H-1,2,3-triazole (**2b**)

To a suspension of 5.57 g (26.5 mmol) of diethyl oxalacetate sodium salt in 60 mL of anhydrous THF, heated at 35 °C, a solution of 4.12 g (20.0 mmol) of 2-nitro-4-trifluoromethyl-phenylazide [2] in 50 mL of anhydrous THF was added dropwise and the reaction mixture was worked up as described above. The solid

Table 3
^{1}H-NMR δ (ppm) in DMSO-d_6 or $CDCl_3$*

2a	7.97 (m, 1H), 7.55 (m, 2H), 4.47 and 4.28 (2q, 4H), 1.44 and 1.25 (2t, 6H)
3a	12.2 (br, 1H), 8.41 (m, 1H), 7.23 (m, 2H), 4.39 (q, 2H), 1.34 (t, 3H)
4a	8.50 (m, 1H), 7.75 (m, 2H), 4.40 (q, 2H), 3.60 (s, 3H), 1.35 (t, 3H)
2b*	8.56 (s, 1H), 8.13 (d, 2H), 7.79 (d, 1H), 4.51 and 4.32 (2q, 4H), 1.46 and 1.29 (2t, 6H)
3b	12.4 (br, 1H), 8.55 (d, 1H), 7.71 (m, 2H), 4.41 (q, 2H), 1.35 (t, 3H)
4b	8.66 (m, 1H), 7.98 (m, 2H), 4.42 (q, 2H), 3.69 (s, 3H), 1.36 (t, 3H)
5a	8.85 (d, 1H), 8.20 (d, 1H), 7.80–7.25 (m, 3H), 4.50 (q, 2H), 4.15 (m, 1H), 1.85–1.20 (m, 10H), 1.21 (t, 3H)
5b	9.40 (d, 1H), 8.44 (d, 1H), 7.63–7.25 (m, 8H), 5.50 (m, 1H), 4.51 (q, 2H), 1.61 (d, 3H), 1.41 (t, 3H)
5c	8.90 (d, 1H), 8.40 (m, 1H), 7.80–7.10 (m, 8H), 4.50 (m, 1H), 4.45 (q, 2H), 2.80 (m, 2H), 1.30 (d, 3H), 1.26 (t, 3H)
5d	9.55 (d, 1H), 8.42 (m, 1H), 7.55–7.42 (m, 7H), 5.50 (m, 1H), 4.51 (q, 2H), 1.61 (d, 3H), 1.41 (t, 3H)
6*	9.89 (d, 1H), 8.45 (m, 1H), 7.45–7.28 (m, 3H), 4.15 (m, 2H), 2.17–1.30 (m, 20H)
7	8.50 (d, 1H), 7.62–7.10 (m, 8H), 5.53 (s, 2H), 4.41 (q, 2H), 1.36 (t, 3H)
8a*	8.35 (m, 1H), 8.06 (m, 2H), 7.95–7.79 (m, 2H), 7.70–7.25 (m, 4H)
9a	12.2 (s, 1H), 8.32 (d, 1H), 7.60–7.18 (m, 8H)
8b*	8.47 (m, 1H), 8.19–7.40 (m, 7H), 4.22 (q, 2H), 1.00 (t, 3H)
9b	12.0 (s, 1H), 8.38 (d, 1H), 7.74 (d, 1H), 7.60–7.41 (m, 3H), 7.41–7.20 (m, 3H)
10*	8.34 (d, 1H), 7.95–7.62 (m, 5H), 6.68 (m, 1H), 4.25 (q, 2H), 1.19 (t, 3H)
11	12.2 (s, 1H), 8.35 (d, 1H), 7.65–7.35 (m, 4H), 6.42–6.24 (m, 2H)

residue from $CHCl_3$ (3.0 g) underwent flash-chromatography through a silica gel column and elution with EtOAc–petroleum ether 1:4 gave the title compound as a pure compound (Tables 1–3).

*4.4. 3-Ethoxycarbonyl-7-fluoro-1,2,3-triazolo[1,5-a]-quinoxalin-4-one (**3a**)*

To a solution of 1.10 g (3.12 mmol) of the triazole diester **2a** in 70 mL of EtOH, 10% Pd/C (0.100 g) was added and the mixture was hydrogenated at room temperature (r.t.) and pressure. When the absorption of the hydrogen volume was completed, the catalyst was filtered off and washed with hot EtOH. Filtrate and washings were combined and evaporated in vacuo to give the title compound as a solid residue which was purified by crystallisation (Tables 1–3).

*4.5. 3-Ethoxycarbonyl-7-trifluoromethyl-1,2,3-triazolo[1,5-a]quinoxalin-4-one (**3b**)*

To a solution of 1.32 g (3.28 mmol) of **2b** in 200 mL of EtOH, 10% Pd/C (0.100 g) was added and the mixture was hydrogenated and worked up as described above (Tables 1–3).

*4.6. 3-Ethoxycarbonyl-5-methyl-7-fluoro-1,2,3-triazolo-[1,5-a]quinoxalin-4-one (**4a**) and 3-Ethoxycarbonyl-5-methyl-7-trifluoromethyl-1,2,3-triazolo[1,5-a]-quinoxalin-4-one (**4b**)*

A mixture of 1.0 mmol of **3a** or **3b**, 0.60 mL (6.30 mmol) of dimethyl sulfate and 0.400 g (2.90 mmol) of anhydrous potassium carbonate in 20 mL of anhydrous acetone, was heated under reflux for 4.5 h. The inorganic material was filtered off, washed with acetone and the filtrates were combined and evaporated to give a residue consisting of crude **4a** or **4b**, which was purified by crystallisation (Tables 1–3).

Table 4
Results of the binding assays

	Benzodiazepine			A_1-adenosine		A_{2A}-adenosine	
	Inhib.% (10 μM)	Ki (nM)	GABA ratio	Inhib.% (10 μM)	Ki (nM)	Inhib.% (10 μM)	Ki (nM)
3a	97	115	0.93	80	1131	10.5	>10 000
3b	67	2900	0.96	95	91	42	>10 000
4a	98	80	1.19	31	>10 000	10	>10 000
4b	72	3900	1.30	27	>10 000	17	>10 000
5a	55	>5000	–	48	7059	21	>10 000
5b	0	>10 000	–	55	5139	15	>10 000
5c	26	>10 000	–	48	5435	0	–
5d	24	>10 000	–	49	5387	0	–
6	0	>10 000	–	29	>10 000	2	>10 000
7	99	117	1.20	50	5692	39	>10 000
9a	78	3230	1.20	47	7517	20	>10 000
9b	36	>10 000	–	10	>10 000	23	>10 000
11	0	>10 000	–	36	>10 000	13	>10 000

*4.7. 3-Ethoxycarbonyl-4-(3-pentylamino)-1,2,3-triazolo[1,5-a]quinoxaline (**5a**)*

A suspension of 3-ethoxycarbonyl-1,2,3-triazolo[1,5-a]quinoxalin-4-one (**3c**) [1] (0.350 g, 1.35 mmol) in 2.1 mL of hexamethyldisilazane (HMDS) was heated at 140 °C for 1 h; 0.132 g (1.00 mmol) of ammonium sulfate and 0.87 mL (7.50 mmol) of 3-pentylamine were added and heating was continued for 20 h. After evaporation in vacuo, the residue was extracted with $CHCl_3$ and the organic layer was washed with 5% HCl, 10% NaOH and H_2O, then dried on $MgSO_4$. Evaporation of the solvent gave a semisolid residue (0.160 g) which was crystallised to obtain the title compound (Tables 1–3).

*4.8. (±) 3-Ethoxycarbonyl-4-(1-phenylethyl)-1,2,3-triazolo[1,5-a]quinoxaline (**5b**)*

A suspension of **3c** [1] (0.250 g, 0.97 mmol) in 2.5 mL of HMDS was heated at 140 °C for 1 h; 0.044 g (0.30 mmol) of ammonium sulfate and 0.60 mL (4.70 mmol) of (±)-α-methylbenzylamine were added and heating was continued for 20 h. The reaction mixture was worked up as described to obtain **5a** (Tables 1–3).

*4.9. (±) 3-Ethoxycarbonyl-4-(1-methyl-2-phenylethyl)-1,2,3-triazolo[1,5-a]quinoxaline (**5c**)*

A suspension of **3c** [1] (0.250 g, 0.97 mmol) in 3.5 mL of HMDS was heated at 140 °C for 1 h; 0.044 g (0.30 mmol) of ammonium sulfate and 0.70 mL (4.80 mmol) of (±)-α-methylphenethylamine were added and heating was continued for 20 h. The reaction mixture was worked up as described to obtain **5a** (Tables 1–3).

*4.10. (±) 3-Ethoxycarbonyl-4-(1-phenylethyl)-7-fluoro-1,2,3-triazolo[1,5-a]quinoxaline (**5d**)*

A suspension of **3a** (0.250 g, 0.90 mmol) in 5 mL of HMDS was heated at 140 °C for 1 h; 0.044 g (0.30 mmol) of ammonium sulfate and 0.58 mL (4.50 mmol) of (±)-α-methylbenzylamine were added and heating was continued for 20 h. The reaction mixture was worked up as described to obtain **5a** (Tables 1–3).

*4.11. 3-Cyclohexylaminocarbonyl-4-cyclohexylamino-1,2,3-triazolo[1,5-a]quinoxaline (**6**)*

A suspension of **3c** [1] (0.350 g, 1.35 mmol) in 5 mL of HMDS was heated at 140 °C for 1 h; 0.058 g (0.44 mmol) of ammonium sulfate and 0.75 mL (6.50 mmol) of cyclohexylamine were added and heating was continued for 20 h. The reaction mixture was worked up as described to obtain **5a** (Tables 1–3).

*4.12. 3-Ethoxycarbonyl-5-benzyl-1,2,3-triazolo[1,5-a]-quinoxalin-4-one (**7**)*

A mixture of **3c** [1] (0.250 g, 0.97 mmol), benzyl chloride (0.17 mL, 1.47 mmol) and anhydrous potassium carbonate (0.400 g, 2.90 mmol) in 9 mL of methyl ethyl ketone was heated under reflux for 4 days. The solvent was evaporated in vacuo and the residue was treated with H_2O. The insoluble material, consisting of **7** as a white solid, was collected by filtration and crystallised (Tables 1–3).

*4.13. 1-(2-Nitrophenyl)-4-benzoyl-5-ethoxycarbonyl-1H-1,2,3-triazole (**8a**) and 1-(4-chloro-2-nitrophenyl)-4-benzoyl-5-ethoxycarbonyl-1H-1,2,3-triazole (**8b**)*

To 30 mL of anhydrous THF heated at 40 °C, 1.00 g (4.10 mmol) of ethyl benzoylpyruvate sodium salt [9] was added and the mixture was stirred until complete solution (ca. 1 h). A solution of 4.00 mmol of 2-nitrophenylazide (**1c**) or 4-chloro-2-nitrophenylazide (**1d**) in 20 mL of anhydrous THF was added dropwise. Temperature was raised to 60 °C and the mixture was stirred for 7 h. The solvent was evaporated in vacuo and the residue was treated with H_2O and extracted with $CHCl_3$.

The organic layer, dried ($MgSO_4$) and evaporated, gave a solid residue consisting essentially of the nitroaniline corresponding to the azide (ca. 35%) and of the expected triazole derivative **8a** or **8b**.

The mixture was fractionated by flash-chromatography through a silica gel column, eluting with EtOAc–petroleum ether 1:3, and the title compounds were isolated as pure crystalline solids (Tables 1–3). Acidification of the alkaline aqueous layers provided the corresponding 1,2,3-triazole-5-carboxylic acids (ca. 14% yield).

*4.14. 1-(2-Nitrophenyl)-4-(2-furoyl)-5-ethoxycarbonyl-1H-1,2,3-triazole (**10**)*

To 30 mL of anhydrous THF heated at 40 °C, 1.00 g (4.30 mmol) of ethyl 2-furoylpyruvate sodium salt [10] was added and the mixture was stirred until complete solution (ca. 1 h). A solution of 2-nitrophenylazide (**1c**) (0.710 g, 4.30 mmol) in 20 mL of anhydrous THF was added dropwise and the mixture was worked up as described above. The separation by flash-chromatography through a silica gel column,

eluting with EtOAc–petroleum ether 1:2 provided the title compound as a pure compound (Tables 1–3).

4.15. 3-Benzoyl-1,2,3-triazolo[1,5-a]quinoxalin-4-one (**9a**) and 3-(2-furoyl)-1,2,3-triazolo[1,5-a]-quinoxalin-4-one (**11**)

To a solution of 1.00 mmol of the triazolester **8a** or **10** in 60 mL of EtOH, 30–40 mg of 10% Pd/C were added and the mixture was hydrogenated at r.t. and pressure. The catalyst was filtered off and washed with hot EtOH. Filtrate and washings were combined and evaporated in vacuo to give the title compounds as solid residues which were purified by crystallisation (Tables 1–3).

4.16. 3-Benzoyl-7-chloro-1,2,3-triazolo[1,5-a]-quinoxalin-4-one (**9b**)

To a solution of the triazolester **8b** (0.360 g, 1.10 mmol) in 60 mL of EtOH, ca. 100 mg of aqueous Ni-Raney suspension were added and the mixture was hydrogenated and worked up as described above (Tables 1–3).

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