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ORIGINAL PAPER

Efficient multicomponent synthesis of highly substituted [1,2,3]triazolo[1,5-*a*]pyrimidines

Eugene S. Gladkov · Svetlana N. Sirko · Svetlana V. Shishkina · Oleg V. Shishkin · Irina V. Knyazeva · Sergey M. Desenko · Valentin A. Chebanov

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Abstract An efficient and facile multicomponent procedure for the synthesis of highly substituted [1,2,3]triazolo-[1,5-*a*]pyrimidines by reaction of equimolar amounts of aromatic aldehyde, CH-acid, and 5-amino-1,2,3-triazole in refluxing dimethylformamide is described.

Keywords Combinatorial chemistry · Cyclizations · Heterocycles · Multicomponent reactions · Triazolo[1,5-*a*]pyrimidines

Introduction

In recent years, considerable attention has been devoted to the development of new efficient methodology for the synthesis of highly substituted partially hydrogenated azolopyrimidines. These fused heterocycles belong to an important class of organic compounds due to their physiological activities, e.g., as cardiovascular vasodilators, calcium channel blocking agents, and potassium channel inhibitors and openers [1–8].

The most facile and widespread method for the synthesis of substituted azoloazines is reaction of aminoazoles with α,β-unsaturated ketones [9, 10]. In contrast to the analogous reaction with β-diketones, cyclocondensations involving α,β-unsaturated carbonyls are characterized by high regioselectivity. However, multicomponent procedures based on reactions of synthetic precursors of unsaturated ketones—aromatic aldehydes and active methylene compounds—are considered more efficient and have attracted the attention of scientists. Diverse partially hydrogenated azolopyrimidines were synthesized by the reactions of aminoazoles with aldehydes and numerous CH-acids like acetoacetic acid derivatives, β-diketones, β-ketosulfones, pyruvic acids, etc. [9, 11–17].

However, in most cases reported 3-amino-1,2,4-triazoles, 5-aminotetrazole, 2-aminoimidazoles, and 2-aminobenzimidazole have been used, whereas application of 4-amino-1,2,3-triazoles has not been described for the above-mentioned multicomponent cyclocondensations. There are only a few examples of heterocyclizations involving 4-amino-1,2,3-triazoles: with β-diketones yielding [1–3]triazolo[1,5-*a*]pyrimidines [18], with *N*-cyanomethaneimidates giving rise to 4-amino[1,2,3]triazolo[1,5-*a*]-[1,3,5]triazines [19], and with isocyanates leading to [1,2,3]triazolo[5,1-*d*][1,2,3,5]tetrazin-4-ones [20]. In addition, one of our recent publications described the treatment of chalcone derivatives with 4-amino-5-phenyl- and 4-amino-1,2,3-triazole-5-carboxamide as an efficient synthetic pathway to 4,7-dihydro-5,7-diaryl[1,2,3]triazolo-[1,5-*a*]pyrimidines [21] followed by the study of their tautomerism. In particular, it was shown that reactions with chalcone did not affect the carboxamide group though heterocyclizations despite the fact that the participation of the carboxamide had been reported in other publications [22, 23].

Results and discussion

The synthesis of highly substituted 4,7-dihydro-[1,2,3]triazolo[1,5-*a*]pyrimidines was based on the

E. S. Gladkov (✉) · S. N. Sirko · S. V. Shishkina · O. V. Shishkin · I. V. Knyazeva · S. M. Desenko · V. A. Chebanov
State Scientific Institution "Institute for Single Crystals" of National Academy of Sciences of Ukraine, Lenin Ave, 60, Kharkiv 61001, Ukraine
e-mail: gladkov@isc.kharkov.com

multicomponent reaction of 4-amino-1,2,3-triazoles **1a–1c** with aromatic aldehydes **2a–2d** and several types of CH-acids **3a**, **3b**, **4a**, and **4b**. It was established that the treatment of 4-phenyl-1*H*-1,2,3-triazol-5-amine (**1a**), 5-amino-*N*-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carboxamide (**1b**), or 5-amino-*N*-(2-methylphenyl)-1*H*-1,2,3-triazole-4-carboxamide (**1c**) with *N*-(4-methoxyphenyl) acetoacetamide (**3a**) or ethyl acetoacetate (**3b**) and aromatic aldehydes **2a–2d** in boiling DMF for 5–15 min afforded 3,5,6,7-tetrasubstituted 4,7-dihydro[1,2,3]triazolo[1,5-*a*]pyrimidines **5a–5l** in satisfactory or good yields (Scheme 1; Table 1). Longer durations of the multicomponent reaction led to resinification of the reaction mixture which resulted in drastically reduced yields. The most drastic case was the reaction of 4-phenyl-1*H*-1,2,3-triazol-5-amine (**1a**). Correspondingly, the reaction times for the treatment involving **1a** were the shortest (about 5 min), while the yields were the lowest (35–42%). For 5-amino-1,2,3-triazoles **1b** and **1c** the influence of the reaction time was not so dramatic.

The procedure works also for three-component reactions involving cyclic 1,3-diketones as CH-acid component. Refluxing of aminotriazoles **1a** and **1b** with benzaldehyde (**2a**) and dimedone (**4a**) or 1,3-cyclohexanedione (**4b**) in DMF for 10 min gave rise to 3,6,6,9-tetrasubstituted 6,7-dihydro[1,2,3]triazolo[5,1-*b*]quinazolin-8-ones **6a–6c** in good yields (Scheme 1; Table 1).

The multicomponent reactions were monitored with the help of HPLC. The target heterocycles **5** and **6** and the corresponding azomethines of aminotriazoles **1a–1c** with the aldehydes **2a–2d** could be detected by HPLC. For work-up methanol was added to the cooled reaction mixture. The precipitate formed was filtered, dried in air at room temperature and, when needed, crystallized from DMF/methanol mixture (1:2).

Because of the multicomponent character of the reaction and the high number of commercially available aldehydes, *β*-diketones, and acetoacetic acid derivatives, substituents in position 5 of the aminotriazoles can easily be varied. The reported method represents an attractive combinatorial synthesis of moderately complicated heterocycles, which can be realized in short reaction times.

The compositions and structures of the heterocycles synthesized were established with help of elemental analysis, mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy, and X-ray data. The ^{1}H NMR spectra of compounds **5a–5l** and **6a–6c** show the expected signals for the aromatic rings and terminal functional groups. Characteristic signals were: a singlet for the 7-methyne proton of the dihydropyrimidine moiety at ca. 6.55–6.86 ppm, the broad singlet of the pyrimidine NH (9.70–10.34 ppm), the signal of the carboxamide NH at 9.67–10.50 ppm (for compounds **5d–5l**, **6b**, and **6c**), and the signals of CH_2 groups of the cyclohexanone ring at 2.09–2.85 ppm.

This ^{1}H NMR spectra are compatible with several alternative structures **5–8** with different orientation of the substituents in the dihydropyrimidine ring (Fig. 1). Importantly, our earlier experience with similar compounds demonstrated a distinct dependence of the chemical shift of the amino group in the ^{1}H NMR spectrum on its position in the dihydroazine fragment [12, 24–26]. Linear structures like **5** and **6** exhibit a signal for the NH proton at 9.5–10.5 ppm, whereas in the case of structures similar to **7** and **8** this signal usually was shifted to high field by 2–3 ppm. As a further confirmation, no NOE and COSY correlations in the structures of type **5** and **6** were found

Scheme 1

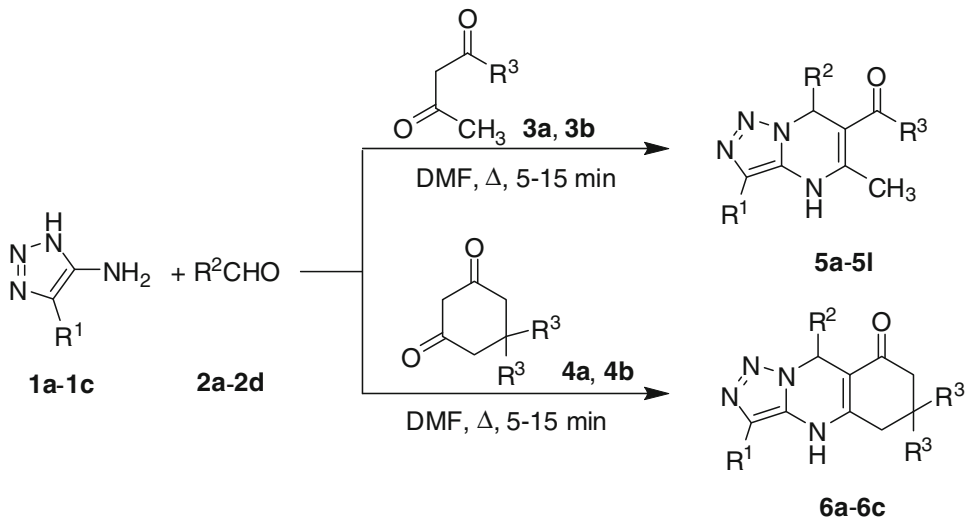
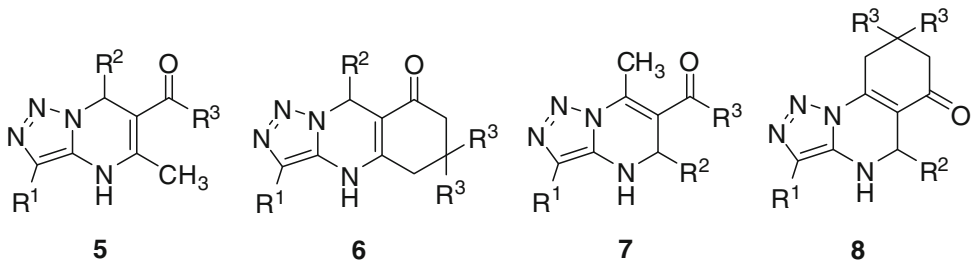


Table 1 Synthesis of 4,7-dihydro[1,2,3]triazolo[1,5-*a*]pyrimidines **5a–5l** and **6a–6c**

Building blocks						Reaction time (min)	Product	Yield (%)
Amine		Aldehyde		CH-acid				
	R^1		R^2		R^3			
1a	C_6H_5	**2a**	C_6H_5	**3a**	4-$CH_3OC_6H_4NH$	10	**5a**	37
1a	C_6H_5	**2b**	4-$CH_3OC_6H_4$	**3a**	4-$CH_3OC_6H_4NH$	10	**5b**	35
1a	C_6H_5	**2c**	4-ClC_6H_4	**3a**	4-$CH_3OC_6H_4NH$	10	**5c**	42
1a	C_6H_5	**2a**	C_6H_5	**4a**	CH_3	5	**6a**	45
1b	4-$CH_3C_6H_4NHCO$	**2a**	C_6H_5	**3a**	4-$CH_3OC_6H_4NH$	10	**5d**	47
1b	4-$CH_3C_6H_4NHCO$	**2b**	4-$CH_3OC_6H_4$	**3a**	4-$CH_3OC_6H_4NH$	10	**5e**	65
1b	4-$CH_3C_6H_4NHCO$	**2d**	4-BrC_6H_4	**3a**	4-$CH_3OC_6H_4NH$	10	**5f**	71
1b	4-$CH_3C_6H_4NHCO$	**2a**	C_6H_5	**3b**	OC_2H_5	15	**5g**	55
1b	4-$CH_3C_6H_4NHCO$	**2d**	4-BrC_6H_4	**3b**	OC_2H_5	15	**5h**	41
1b	4-$CH_3C_6H_4NHCO$	**2a**	C_6H_5	**4b**	H	5	**6b**	45
1b	4-$CH_3C_6H_4NHCO$	**2a**	C_6H_5	**4a**	CH_3	5	**6c**	65
1c	2-$CH_3C_6H_4NHCO$	**2a**	C_6H_5	**3a**	4-$CH_3OC_6H_4NH$	10	**5i**	40
1c	2-$CH_3C_6H_4NHCO$	**2b**	4-$CH_3OC_6H_4$	**3a**	4-$CH_3OC_6H_4NH$	10	**5j**	50
1c	2-$CH_3C_6H_4NHCO$	**2a**	C_6H_5	**3b**	OC_2H_5	15	**5k**	65
1c	2-$CH_3C_6H_4NHCO$	**2b**	4-$CH_3OC_6H_4$	**3b**	OC_2H_5	15	**5l**	57



5 **6** **7** **8**

Fig. 1 Possible alternative structures of the multicomponent reaction products

between the CH and the NH group in the pyrimidine moiety.

The structure of the heterocycles synthesized was confirmed by an X-ray structural analysis. Suitable crystals of compound **5h** were selected for an X-ray diffraction study. The X-ray structure confirmed that **5h** is ethyl 7-(4-bromophenyl)-4,7-dihydro-5-methyl-3-[(4-methylphenyl)-aminocarbonyl][1,2,3]triazolo[1,5-*a*]pyrimidine-6-carboxylate (Fig. 2).

The dihydropyrimidine ring of the compound **5h** adopts a sofa conformation (the puckering parameters [27] are $S = 0.29$, $\Theta = 59.8°$, $\Psi = 9.2°$). Deviation of the C3 atom from the mean plane of the remaining atoms of the ring is −0.29 Å. The *p*-bromophenyl substituent has pseudo-axial orientation and it is turned relative to the plane of the partially hydrogenated ring (the C1–N4–C3–C10 and N4–C3–C10–C15 torsion angles are 99.1(3) and 119.3(3)°). The ester substituent is coplanar to the C4–C5 endocyclic double bond (the C5–C4–C6–O1 torsion angle is 3.3(6)°), stabilized by the H3···O2 (2.32 Å) and H9c···O1 (2.28 Å) attractive interactions, which can be considered as very weak intramolecular hydrogen bonds, as the values of the angles C3–H3···O2 and C9–H9c···O1 are rather small (95° and 117°). The ethyl group of the ester substituent has the *ap*-conformation relative the C4–C6 bond (the C7–O2–C6–C4 torsion angle is 177.6(3)°) and it is disordered over two positions (A and B) with equal populations owing to the rotation around the O2–C7 bond (the C6–O2–C7–C8 torsion angle is 158.3(6)° in A and −174.6(6)° in B). The carbamide fragment of the substituent at the C2 atom is almost coplanar to the plane of the triazole ring (the C1–C2–C16–O3 torsion angle is 7.8(5)°), stabilized additionally by the H5N···N2 2.51 Å attractive interaction and the N1–H1N···O3 weak intramolecular hydrogen bond (H···O 2.45 Å N–H···O 117°). The *p*-methylphenyl group is practically coplanar to the carbamide fragment (the C16–N5–C17–C18 torsion angle is 9.0(5)°). The conformation of this group is stabilized by

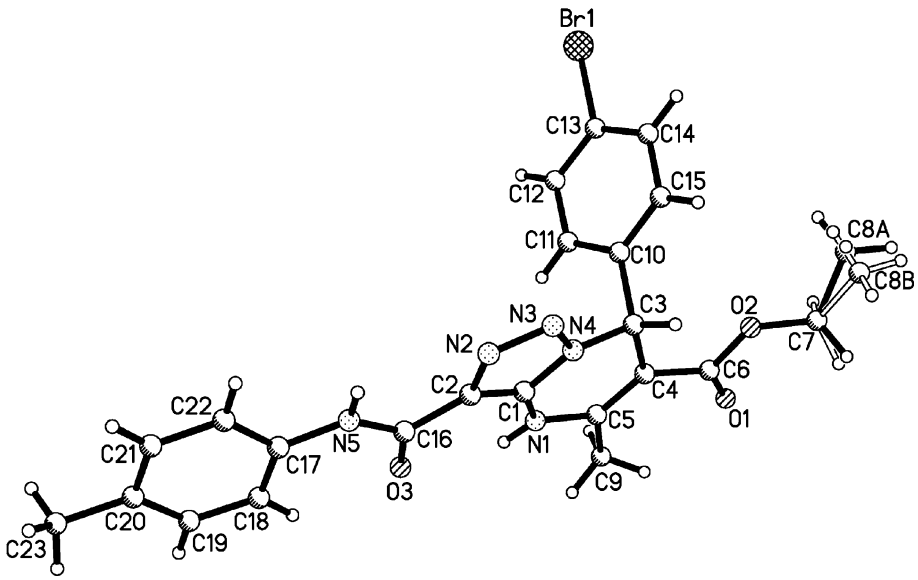


Fig. 2 Molecular structure (X-ray diffraction data) of compound **5h**

the C18–H18···O3 intramolecular hydrogen bond (H···O 2.28 Å C–H···O 121°) on the one hand and is destabilized by the repulsion between hydrogen atoms (H22···H5N 2.29 Å as compared with van der Waals radii sum [28] of 2.34 Å) on the other hand.

In the crystal of **5h** two intermolecular weak hydrogen bonds are observed: N5–H5N···N3′ H···N 2.64 Å N–H···N 156° and C3–H3···N2′ H···N 2.65 Å C–H···N 155°.

In conclusion, we developed a new facile procedure for the synthesis of diverse highly substituted dihydro[1,2,3]triazolo[1,5-*a*]pyrimidines by the multicomponent reaction of 5-amino-1,2,3-triazoles with aromatic aldehydes and CH-acids like acetoacetic acid derivatives and cyclic 1,3-diketones. The method is simple and provides the target compounds in good yields.

Experimental

Melting points of all compounds synthesized were determined with a Gallenkamp melting point apparatus. The NMR spectra were recorded in DMSO-d_6 at 400 MHz (100 MHz for ^{13}C) with Jeol Lambda 400 and at 200 MHz with Varian Mercury VX-200 spectrometers. The mass spectra were measured on a GC–MS Varian 1200L instrument (ionizing voltage 70 eV) and on a Hewlett-Packard LC/MSD 1100 series instrument in atmospheric pressure chemical ionization (positive APCI) mode. Elemental analysis was realized on EuroVector EA-3000, and results agreed with calculated values. Starting 4-phenyl-1*H*-1,2,3-triazol-5-amine (**1a**) was obtained by a known method [29].

5-Amino-N-(4-methylphenyl)-1H-1,2,3-triazole-4-carboxamide (**1b**, $C_{10}H_{11}N_5O$)

A solution of 13.3 g benzyl azide (0.1 mol) and 17.4 g 2-cyano-*N*-(4-methylphenyl)acetamide (0.1 mol) in 250 cm^3 absolute alcohol containing 0.1 mol sodium ethoxide was refluxed for 6 h. After cooling, the reaction mixture was poured into 1 dm^3 water and allowed to stand overnight. The resulting precipitate was filtered, washed with water, and dried in vacuo. Recrystallization from DMF/methanol (1:2) gave 27.3 g (89% yield) of the *N*-benzyl derivative.

5-Amino-1-benzyl-*N*-(4-methylphenyl)-1*H*-1,2,3-triazole-4-carboxamide (15.35 g, 0.05 mol) was suspended in 150 cm^3 liquid ammonia and small pieces of sodium were added with stirring until a permanent blue color was produced. The color was discharged with a small amount of ammonium chloride and the solvent was allowed to evaporate. The solid was dissolved in minimal amount of water and after filtration the solution was adjusted to pH 1 with concentrated hydrochloric acid. After cooling and crystallization from DMF/methanol (1:2) amine **1b** was obtained in 74% yield (8.03 g). M.p.: 176–177 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.24$ (s, 3H, CH_3), 5.97 (bs, 2H, NH_2), 7.07 (d, 2H), 7.65 (d, 2H), 9.86 (s, 1H, NH), 13.5 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 21.1$, 120.8, 124.7, 129.5, 132.7, 137.0, 133.2, 161.5 ppm; MS (70 eV): $m/z = 217$ (M^+), 107 (100).

5-Amino-N-(2-methylphenyl)-1H-1,2,3-triazole-4-carboxamide (**1c**, $C_{10}H_{11}N_5O$)

Compound **1c** was synthesized by an analogous method to **1b**. Yield 7.60 g (70%); m.p.: 158–159 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.23$ (s, 3H, CH_3), 6.17 (bs, 2H, NH_2), 7.16 (m, 4H, Ar), 9.29 (s, 1H, NH), 14.3 (bs, 1H,

NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 18.2$, 121.8, 124.8, 125.5, 126.7, 130.9, 131.1, 136.8, 142.0, 161.4 ppm; MS (70 eV): $m/z = 217$ (M^+), 111 (100).

4,7-Dihydro-N-(4-methoxyphenyl)-5-methyl-3,7-diphenyl[1,2,3]triazolo[1,5-a]pyrimidine-6-carboxamide (**5a**, $C_{26}H_{23}N_5O_2$)

A mixture of 1.60 g 4-phenyl-1*H*-1,2,3-triazol-5-amine (**1a**, 10 mmol), 2.07 g amide **3a** (10 mmol), and 1.06 g benzaldehyde (10 mmol) in 0.5 cm^3 DMF was refluxed for 10 min. The reaction mixture was cooled to 20 °C, mixed with 10 cm^3 methanol, and the precipitate formed was filtered and washed with methanol. Recrystallization from DMF/methanol afforded 1.62 g (37%). M.p.: 154–155 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.28$ (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 6.83 (d, 2H), 6.86 (s, 1H, 7-H), 7.33 (m, 10H), 7.76 (d, 2H), 9.37 (s, 1H, NH), 9.68 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 18.1$, 56.0, 60.1, 104.0, 114.6, 122.2, 126.6, 127.3, 127.6, 128.8, 129.1, 129.3, 131.5, 132.4, 132.9, 137.3, 141.7, 156.3, 165.2 ppm; MS (70 eV): $m/z = 437$ (M^+), 259 (100), 149, 123.

4,7-Dihydro-N,7-bis(4-methoxyphenyl)-5-methyl-3-phenyl[1,2,3]triazolo[1,5-a]pyrimidine-6-carboxamide (**5b**, $C_{27}H_{25}N_5O_3$)

Yield 1.63 g (35%); m.p.: 247–249 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.55$ (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 6.76 (s, 1H, 7-H), 6.85 (d, 2H), 6.89 (d, 2H), 7.10 (d, 2H), 7.45 (m, 5H), 7.70 (d, 2H), 9.77 (s, 1H, NH), 12.06 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 34.7$, 55.2, 94.1, 114.0, 114.3, 121.0, 124.4, 127.1, 127.6, 129.4, 130.9, 132.1, 132.2, 146.6, 155.4, 159.2, 167.4 ppm; MS (70 eV): $m/z = 467$ (M^+), 289 (100), 123, 108.

7-(4-Chlorophenyl)-4,7-dihydro-N-(4-methoxyphenyl)-5-methyl-3-phenyl[1,2,3]triazolo[1,5-a]pyrimidine-6-carboxamide (**5c**, $C_{26}H_{22}ClN_5O_2$)

Yield 1.98 g (42%); m.p.: 201–202 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.33$ (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 6.85 (s, 1H, 7-H), 6.82 (d, 2H), 7.42 (m, 9H), 8.04 (d, 2H), 9.04 (s, 1H, NH), 10.50 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 17.5$, 55.2, 64.5, 113.9, 114.1, 121.3, 127.1, 128.9, 129.0, 129.4, 130.9, 131.2, 131.5, 134.5, 135.5, 137.2, 139.8, 150.9, 156.1, 161.7, 162.0, 196.5 ppm; MS (70 eV): $m/z = 471$ (M^+), 122.

4,7-Dihydro-N6-(4-methoxyphenyl)-5-methyl-N3-(4-methylphenyl)-7-phenyl[1,2,3]triazolo[1,5-a]pyrimidine-3,6-dicarboxamide (**5d**, $C_{28}H_{26}N_6O_3$)

Yield 2.32 g (47%); m.p.: 261–262 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.23$ (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 6.82 (d, 2H), 6.84 (s, 1H, H-7), 7.10 (d, 2H), 7.28 (m, 5H), 7.39 (d, 2H), 7.70 (d, 2H), 9.49 (bs, NH), 9.72 (s, NH), 10.24 (s, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 17.2$, 20.5, 55.2, 59.3, 101.1, 113.9, 118.7, 120.2, 121.3, 122.8, 127.1, 128.5, 128.8, 129.1, 132.1, 132.5, 135.5, 136.3, 137.0, 140.6, 155.6, 160.3, 164.4 ppm; MS (70 eV): $m/z = 494$ (M^+), 149 (100).

4,7-Dihydro-N6,7-bis(4-methoxyphenyl)-5-methyl-N3-(4-methylphenyl)-[1,2,3]triazolo[1,5-a]pyrimidine-3,6-dicarboxamide (**5e**, $C_{29}H_{28}N_6O_4$)

Yield 3.41 g (65%); m.p.: 238–240 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.25$ (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.78 (s, 1H, H-7), 6.80 (d, 2H), 6.86 (d, 2H), 7.11 (d, 2H), 7.21 (d, 2H), 7.41 (d, 2H), 7.70 (d, 2H), 9.38 (bs, NH), 9.70 (s, NH), 10.22 (s, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 17.2$, 20.5, 55.1, 55.2, 58.9, 104.3, 113.9, 114.1, 120.3, 121.3, 122.8, 128.6, 129.1, 132.2, 132.5, 132.7, 135.5, 136.4, 136.9, 155.6, 159.4, 160.4, 164.5 ppm; MS (70 eV): $m/z = 524$ (M^+), 123 (100).

7-(4-Bromophenyl)-4,7-dihydro-N6-(4-methoxyphenyl)-5-methyl-N3-(4-methylphenyl)-[1,2,3]triazolo[1,5-a]-pyrimidine-3,6-dicarboxamide (**5f**, $C_{28}H_{25}BrN_6O_3$)

Yield 4.10 g (71%); m.p.: 254–256 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 2.24$ (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 6.81 (d, 2H), 6.83 (s, 1H, 7-H), 7.11 (d, 2H), 7.22 (d, 2H), 7.40 (d, 2H), 7.53 (d, 2H), 7.69 (d, 2H), 9.56 (bs, 1H, NH), 9.76 (s, 1H, NH), 10.26 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 17.8$, 55.7, 59.2, 94.5, 104.1, 114.3, 120.6, 121.8, 122.2, 123.2, 129.5, 129.8, 132.1, 132.4, 132.9, 136.2, 137.3, 140.3, 153.2, 156.0, 159.6, 164.5 ppm; MS (70 eV): $m/z = 574$ (M^+), 123 (100).

Ethyl 4,7-dihydro-5-methyl-3-[(4-methylphenyl)-aminocarbonyl]-7-phenyl[1,2,3]triazolo-[1,5-a]-pyrimidine-6-carboxylate (**5g**, $C_{23}H_{23}N_5O_3$)

Yield 2.29 g (55%); m.p.: 221–222 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 1.06$ (t, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.97 (q, 2H, CH_2), 6.67 (s, 1H, 7-H), 7.10 (d, 2H), 7.29 (m, 5H, Ar), 7.69 (d, 2H), 9.99 (bs, 1H, NH), 10.28 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 13.9$, 18.2, 20.5, 58.5, 59.7, 97.7, 120.3, 123.7, 127.1, 128.4, 128.8, 129.1, 132.6, 135.7, 136.2, 142.0, 146.6, 159.1, 165.0 ppm; MS (70 eV): $m/z = 417$(M^+), 340 (89).

Ethyl 7-(4-bromophenyl)-4,7-dihydro-5-methyl-3-[(4-methylphenyl)aminocarbonyl]-[1,2,3]-triazolo-[1,5-a]pyrimidine-6-carboxylate (**5h**, $C_{23}H_{22}BrN_5O_3$)

Yield 2.03 g (41%); m.p.: 211–212 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 1.07$ (t, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.97 (q, 2H, CH_2), 6.66 (s, 1H, 7-H), 7.10 (d, 2H), 7.25 (d, 2H), 7.53 (d, 2H), 7.68 (d,

2H), 10.0 (bs, 1H, NH), 10.32 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.6, 18.9, 21.1, 58.7, 60.4, 98.0, 121.0, 122.1, 124.3, 129.6, 129.7, 132.2, 133.3, 136.3, 136.7, 141.7, 147.2, 159.5, 165.4 ppm; MS (70 eV): m/z = 495 (M^+), 440 (41), 340 (59).

X-ray diffraction study of ***5h***

The colourless crystals of **5h** ($C_{23}H_{22}BrN_5O_3$) are orthorhombic. At 293 K a = 8.7078(4), b = 22.7737(6), c = 22.7737(6) Å, V = 4,516.2(3) Å^3, M_r = 496.37, Z = 8, space group *Pbca*, d_{calc} = 1.460 g/cm^3, μ(MoKα) = 1.855 mm^{-1}, F(000) = 2,032. Intensities of 46,884 reflections (6,579 independent, R_{int} = 0.100) were measured on the "Xcalibur-3" diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scanning, $2\Theta_{max}$ = 60°). The structure was solved by direct methods by using the SHELXTL package [30]. The absorption correction was performed by multi-scan method (T_{min} = 0.402, T_{max} = 0.964). The restraints for the bond lengths (Csp^3–Csp^3 1.54 Å) in the disordered fragment were applied during the refinement of the structure. Positions of the hydrogen atoms were located from electron density difference maps and refined by using the "riding" model with $U_{iso} = nU_{eq}$ of the carrier atom (n = 1.5 for methyl group and n = 1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 6,505 reflections was converged to wR_2 = 0.142 (R_1 = 0.044 for 1,755 reflections with $F > 4(F)$, S = 0.789). The final atomic coordinates, and crystallographic data for **5h** have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition number CCDC 768488.

4,7-Dihydro-N6-(4-methoxyphenyl)-5-methyl-N3-(2-methylphenyl)-7-phenyl[1,2,3]triazolo[1,5-a]pyrimidine-3,6-dicarboxamide (**5i**, $C_{28}H_{26}N_6O_3$)

Yield 1.98 g (40%); m.p.: 227–228 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.26 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 6.87 (d, 2H), 6.85 (s, 1H, 7-H), 7.32 (m, 10H, Ar), 7.50 (d, 1H), 9.49 (s, 1H, NH), 9.69 (s, 1H, NH), 9.72 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.9, 18.2, 56.0, 60.1, 104.9, 114.6, 122.2, 122.4, 126.6, 126.8, 127.7, 129.2, 129.4, 130.9, 132.7, 136.2, 136.6, 136.9, 141.0, 159.8, 164.9, 192.4 ppm; MS (70 eV): m/z = 494 (M^+), 345 (27), 123 (100).

4,7-Dihydro-N6,7-bis(4-methoxyphenyl)-5-methyl-N3-(2-methylphenyl)-[1,2,3]triazolo[1,5-a]pyrimidine-3,6-dicarboxamide (**5j**, $C_{29}H_{28}N_6O_4$)

Yield 2.62 g (50%); m.p.: 220–221 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.24 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.79 (s, 1H, 7-H), 6.82 (d, 2H), 6.87 (d, 2H), 7.14 (m, 5H), 7.41 (d, 2H), 7.53 (dd, 1H), 9.44 (bs, 1H, NH), 9.67 (s, 1H, NH), 9.70 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.7, 18.2, 55.6, 55.7, 59.3, 104.6, 114.3, 114.5, 121.7, 122.9, 125.3, 125.7, 126.5, 129.0, 130.8, 132.4, 132.5, 133.0, 136.0, 136.3, 137.0, 155.9, 159.6, 159.7, 164.7 ppm; MS (70 eV): m/z = 524 (M^+), 375 (25), 149 (100).

Ethyl 4,7-dihydro-5-methyl-3-[(2-methylphenyl)aminocarbonyl]-7-phenyl[1,2,3]triazolo[1,5-a]pyrimidine-6-carboxylate (**5k**, $C_{23}H_{23}N_5O_3$)

Yield 2.71 g (65%); m.p.: 90–92 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.04 (t, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.99 (q, 2H, CH_2), 6.65 (s, 1H, 7-H), 7.48 (m, 7H, Ar), 7.52 (d, 2H), 9.76 (s, 1H, NH), 10.0 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.4, 18.2, 18.6, 19.0, 56.5, 59.0, 60.1, 98.0, 123.9, 125.5, 125.8, 126.4, 127.5, 128.7, 129.1, 130.7, 132.5, 135.9, 136.2, 142.2, 146.9, 159.3, 165.3 ppm; MS (70 eV): m/z = 417 (M^+), 340 (79), 284 (42).

Ethyl 4,7-dihydro-7-(4-methoxyphenyl)-5-methyl-3-[(2-methylphenyl)aminocarbonyl]-[1,2,3]triazolo-[1,5-a]pyrimidine-6-carboxylate (**5l**, $C_{24}H_{25}N_5O_4$)

Yield 2.55 g (57%); m.p.: 100–102 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.07 (t, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 3.97 (q, 2H, CH_2), 6.60 (s, 1H, 7-H), 6.87 (d, 2H), 7.18 (m, 5H), 7.49 (d, 1H), 9.74 (s, 1H, NH), 9.95 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.4, 18.2, 18.6, 55.6, 58.4, 60.1, 98.3, 114.4, 114.9, 123.8, 125.5, 125.9, 126.4, 128.7, 130.7, 132.6, 134.5, 135.8, 136.2, 146.6, 159.3, 159.6, 165.4 ppm; MS (70 eV): m/z = 447 (M^+), 390 (100).

4a,5,6,7,8a,9-Hexahydro-6,6-dimethyl-3,9-diphenyl[1,2,3]triazolo[5,1-b]quinazolin-8(4H)-one (**6a**, $C_{23}H_{22}N_4O$)

Yield 1.67 g (45%); m.p.: 282–284 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 0.96 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.17 (q, 2H, CH_2), 2.67 (s, 2H, CH_2), 6.55 (s, 1H, 7-H), 7.25 (m, 5H, Ar), 7.45 (t, 2H), 7.75 (d, 2H), 10.3 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.6, 29.3, 40.7, 50.7, 57.7, 105.8, 127.1, 127.5, 128.0, 128.4, 129.0, 129.3, 131.0, 131.1, 142.5, 151.0, 193.4 ppm; MS (70 eV): m/z = 370 (M^+), 341 (100).

4,4a,5,6,7,8,8a,9-Octahydro-N-(4-methylphenyl)-8-oxo-9-phenyl[1,2,3]triazolo[5,1-b]quinazoline-3-carboxamide (**6b**, $C_{23}H_{21}N_5O_2$)

Yield 1.80 g (45%); m.p.: 189–190 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.09 (m, 2H), 2.25 (s, 3H, CH_3), 2.31 (m, 2H), 2.82 (m, 2H), 6.60 (s, 1H, 7-H), 7.11 (d, 2H), 7.27 (m, 5H, Ar), 7.70 (d, 2H), 10.32 (s, 1H, NH), 10.50 (bs, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6):

δ = 20.5, 20.6, 26.3, 36.4, 56.8, 106.7, 120.4, 124.1, 127.1, 128.2, 128.7, 129.1, 132.7, 135.6, 136.2, 141.5, 152.3, 159.1, 193.7 ppm; MS (70 eV): m/z = 399(M^+), 322 (38), 266 (56).

4,4a,5,6,7,8,8a,9-Octahydro-6,6-dimethyl-N-(4-methylphenyl)-8-oxo-9-phenyl[1,2,3]triazolo[5,1-b]-quinazoline-3-carboxamide (**6c**, $C_{25}H_{25}N_5O_2$)
Yield 2.78 g (65%); m.p.: 179–180 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ = 0.93 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.25 (q, 2H, CH_2), 2.72 (q, 2H, CH_2), 6.59 (s, 1H, 7-H), 7.11 (d, 2H), 7.26 (m, 5H, Ar), 7.70 (d, 2H), 10.34 (s, 1H, NH), 10.42 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.5, 20.6, 26.3, 36.4, 56.8, 106.7, 120.4, 124.1, 127.1, 128.2, 128.7, 129.1, 132.7, 135.6, 136.2, 141.5, 152.3, 159.1, 193.7 ppm; MS (70 eV): m/z = 427 (M^+), 322 (41), 294 (50).

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