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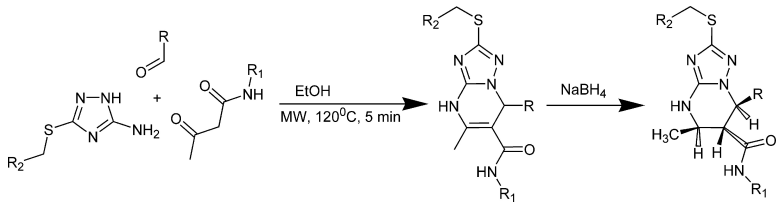

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Microwave-Assisted Three-Component Synthesis of 7-Aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]-pyrimidine-6-carboxamides and Their Selective Reduction

Valentin A. Chebanov,*[,†,‡] Elena A. Muravyova,[†] Sergey M. Desenko,[†] Vladimir I. Musatov,[†] Irina V. Knyazeva,[†] Svetlana V. Shishkina,[†] Oleg V. Shishkin,[†] and C. Oliver Kappe[‡]

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Multicomponent reactions (MCRs) and microwave-assisted organic synthesis (MAOS) have been used as key methods for the synthesis of fused dihydropyrimidine derivatives. The three-component condensation of 3-amino-5-alkylthio-1,2,4-triazoles with aromatic aldehydes and acetoacetamides under microwave irradiation was developed as a rapid and efficient solution-phase method for the high-yielding preparation of 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide libraries. In addition, the selective reduction of the formed dihydrotriazolopyrimidines to *trans-trans*-2-alkylthio-7-aryl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides was established. The described synthetic protocols provide rapid access to novel and diversely substituted dihydroazolopyrimidine libraries.

Introduction

The importance of partially hydrogenated azolopyrimidines in medicinal chemistry is widely known; many of those fused nitrogen heterocycles (Figure 1) are known as cardiovascular vasodilators, calcium channel blocking agents, and potassium channel inhibitors and openers.[1] One of the synthetic pathways to dihydroazolopyrimidines is based on the Biginelli-like cyclocondensation of aromatic aldehydes and acetoacetic acid derivatives with aminoazoles containing a guanidine fragment. There are literary data about the synthesis of fused azolopyrimidines by treatment of 3-amino-1,2,4-triazole or 5-aminotetrazole with aldehydes and ethyl acetoacetate or cyclic β-diketones.[2] The cyclocondensations were realized by heating of the starting materials in ethanol with catalytic amounts of hydrochloric acid under reflux conditions[2a−c] or using DMF as solvent.[2d−f] The use of acetoacetamides in these or similar reactions has not been described. Toward this end, the known pharmacological activity of azolopyrimidine derivatives containing both a carboxamide fragment and an alkylthioazole moiety[1g] has stimulated our interest in an efficient combinatorially oriented protocol for the preparation of compound libraries of this type.

The efficient high-throughput synthesis of organic compounds is one of the most important objectives in modern drug discovery. Today's organic reactions should preferably be facile and fast, and the resulting products should be easily and rapidly purified. Controlled microwave irradiation has proven to be a powerful tool both for speeding up reaction optimizations and for the efficient preparation of new target compounds related to drug discovery projects.[3] The use of microwave irradiation in high-speed organic synthesis has become particularly popular within the past decade as an enabling technology in heterocyclic chemistry,[3] and numerous examples of microwave-assisted multicomponent condensations for the construction of heterocycles with interesting properties have been reported in the literature.[4]

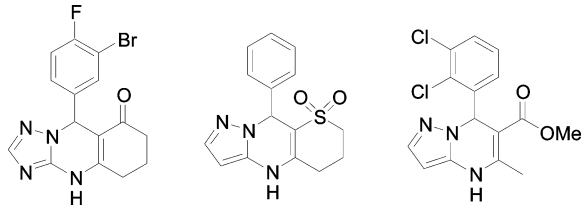

Figure 1. Selected examples of biologically active dihydroazolopyrimidines.[1g,h]

The present article is devoted to the fast microwave-assisted synthesis of 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides of type **18** by three-component condensation of 3-amino-1,2,4-triazol-5-thione derivatives with aromatic aldehydes and acetoacetamides. In addition, the selective reduction of the formed dihydrotriazolopyrimidines to *trans-trans*-2-alkylthio-7-aryl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides was carried out. Our interest in these target compounds is stimulated by their close structural relationship to molecules of known biological activity[1f−g] and the presence of three readily variable diversity points, which opens extensive possibilities for the synthesis of diverse libraries of azolopyrimidine carboxamides.

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Scheme 1

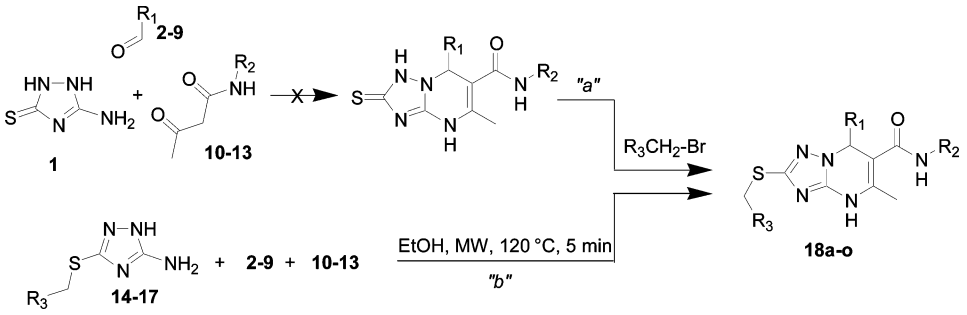


Table 1. Synthesis of 7-Aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo-[1,5-*a*]pyrimidine-6-carboxamides

building blocks								
aldehyde **2**−**9**		amide **10**−**13**		aminoazole **14**−**17**		triazolopyrimidines **18**		
entry	R_1	entry	R_2	entry	R_3	entry	yield[a]	yield[b]
2	C_6H_5	**10**	C_6H_5	**14**	H	**18a**	45	70
3	4-F−C_6H_4	**10**	C_6H_5	**14**	H	**18b**	65	87
4	4-Cl−C_6H_4	**10**	C_6H_5	**14**	H	**18c**	78	90
5	4-Br−C_6H_4	**10**	C_6H_5	**14**	H	**18d**	80	95
3	4-F−C_6H_4	**11**	4-Cl−C_6H_4	**14**	H	**18e**	65	85
7	4-CH_3O−C_6H_4	**11**	4-Cl−C_6H_4	**14**	H	**18f**	58	85
2	C_6H_5	**10**	C_6H_5	**15**	3-CH_3−C_6H_4	**18g**	47	78
7	4-CH_3O−C_6H_4	**10**	C_6H_5	**15**	3-CH_3−C_6H_4	**18h**	58	75
3	4-F−C_6H_4	**12**	2,4-$(CH_3)_2$−C_6H_3	**15**	3-CH_3−C_6H_4	**18i**	55	75
4	4-Cl−C_6H_4	**12**	2,4-$(CH_3)_2$−C_6H_3	**15**	3-CH_3−C_6H_4	**18j**	67	90
5	4-Br−C_6H_4	**12**	2,4-$(CH_3)_2$−C_6H_3	**15**	3-CH_3−C_6H_4	**18k**	70	90
6	4-CH_3−C_6H_4	**12**	2,4-$(CH_3)_2$−C_6H_3	**15**	3-CH_3−C_6H_4	**18l**	55	75
7	4-CH_3O−C_6H_4	**12**	2,4-$(CH_3)_2$−C_6H_3	**15**	3-CH_3−C_6H_4	**18m**	52	78
8	2-thienyl	**12**	2,4-$(CH_3)_2$−C_6H_3	**16**	3-Cl−C_6H_4	**18n**	50	75
9	2-CH_3CH_2O−C_6H_4	**13**	2-CH_3O−C_6H_4	**17**	CH_3	**18o**	62	76

[a] Conventional conditions. [b] Microwave irradiation (see Experimental Section for details).

Results and Discussion

Three-Component Synthesis of 7-Aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides. Two possible synthetic pathways (a and b, Scheme 1) to the target compounds, differing by the sequence of the S-alkylation step, were considered. Carrying out S-alkylation as the last step (pathway a) is more convenient for the combinatorial synthesis of 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides; however, our attempts to realize the three-component condensation of 3-amino-1,2,4-triazolo-5-thione **1** with aldehydes **2**−**9** and acetoacetamides **10**−**13** were unsuccessful. In all cases, the starting aminoazole **1** was reisolated from the reaction mixture quantitatively under microwave irradiation (range of temperature 120−170 °C in ethanol, acetic acid, or DMF) or under conventional conditions (refluxing in the same solvents).

As an alternative, initial S-alkylation of aminoazole **1** with appropriate alkylbromides (R_3CH_2Br) led to the formation of 3-amino-5-alkylthio-1,2,4-triazoles **14**−**17**, which were introduced into the reaction with aromatic aldehydes **2**−**9** and acetoacetamides **10**−**13** (pathway b). The cyclocondensations were performed under microwave irradiation in ethanol at 120 °C for 5 min. As a result, the desired 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides of type **18** were generally obtained as colorless solids in good to excellent yields. Addition of acidic catalysts, such as hydrochloric acids, or changing the solvent to acetic acid or DMF led to the significantly decreased yields of the fused heterocycles. Out of the 512 possible products, a small library of 15 triazolopyrimidine derivatives **18a**−**o** (70−95%, Table 1) was rapidly generated using a set of four 3-amino-5-alkylthio-1,2,4-triazole derivatives (**14**−**17**, diversity point R_3), eight aldehyde building blocks (**2**−**9**, diversity point R_1), and four acetoacetamides (**10**−**13**, diversity point R_2). After irradiation in the microwave reactor, the reaction mixtures were allowed to stand at room temperature overnight, and the precipitated crystalline solids were subsequently filtered, washed with ethanol, and air-dried. All triazolopyrimidines **18a**−**o** were obtained in high purity and without further purification and were fully characterized by ^{1}H NMR and MS data, in addition to elemental analysis.

Table 2. Synthesis of *trans*-*trans*-5-Methyl-2-alkylthio-7-aryl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides **21**

product	R_1	R_2	R_3	yield %
21b	4-F−C_6H_4	C_6H_5	H	85
21c	4-Cl−C_6H_4	C_6H_5	H	90
21h	4-CH_3O−C_6H_4	C_6H_5	3-CH_3−C_6H_4	85
21j	4-Cl−C_6H_4	2,4-di-CH_3−C_6H_3	3-CH_3−C_6H_4	92
21n	2-thienyl	2,4-di-CH_3−C_6H_3	3-Cl−C_6H_4	70

The same 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides **18a**−**o** could also be obtained under conventional conditions by refluxing of the starting materials in DMF for 10−20 min. However, the yields of **18a**−**o** were significantly lower, as compared to those obtained under microwave irradiation (Table 1), and the purity of the compounds was also unsatisfactory.

Scheme 2

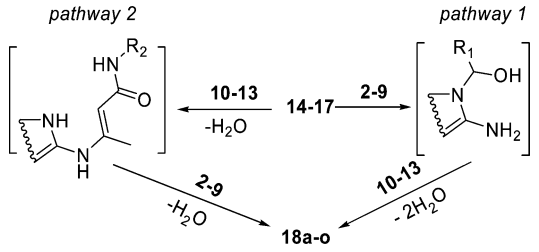
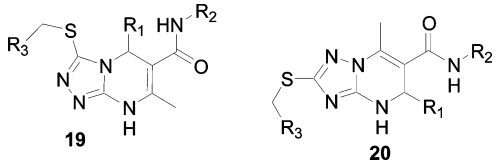


Chart 1. Possible Isomers



The reaction mechanism of this three-component condensation is probably similar to the described[5a] mechanism for the "classical" Biginelli reaction (Scheme 2, pathway 1). The first step is a nucleophilic addition of $N_{(2)}$ of the aminoazole to a carbonyl carbon of aldehyde, followed by subsequent cyclization with acetoacetamide to form the dihydropyrimidine ring. An alternate sequence is also possible and cannot be excluded[5b] (Scheme 2, pathway 2), which is the initial formation of an enamine by reaction of aminoazole with the acetoacetamide followed by cyclocondensation. The third alternative involving the formation of 2-benzylidene-*N*-aryl-3-oxobutanamide derivatives as intermediates requires the presence of a strong base[5c] and is most likely not possible for the cases described herein.

Structure Elucidations. The structures of the heterocyclic carboxamides **18a**−**o** were established by IR spectroscopy, MS spectrometry, NMR spectral data, and X-ray analysis. The generation of several isomers, for example, **18**−**20**, is possible in the transformations described above. In our opinion, the formation of structure **19** is unlikely because it is known[6] that cyclocondensation of 3-amino-1,2,4-triazole and its derivatives both with α,*β*-unsaturated carbonyl compounds and with their synthetic precursors proceeds with participation of $N_{(2)}$ of the aminoazole. Heterocyclic systems formed with participation of $N_{(4)}$, as in isomer **19**, were isolated only as minor byproducts in reactions of 3-amino-1,2,4-triazole with diaroylethylene[6] or pyruvic acid and aldehydes.[7] One of the facts indicating that isomer structure **19** was not formed in the reaction studied here are the NOE data: the close proximity of the R_3-CH_2S fragment to the *o*-H atoms of R_1 in structure **19** should lead to the appearance of a distinct NOE, which was not observed. A choice between structures **18** and **20** initially was made on the basis of the ^{1}H NMR spectra, which exhibit the following signals: characteristic signals for the aromatic rings (6.5−8.0 ppm), a singlet for the methylene H atom (∼6.4 ppm), broad singlets for the amino and amide groups (10.3 and 9.6−9.8 ppm, respectively), and doublets of diastereotopic methylene $S-CH_2$ atoms (4.1−4.3 ppm). Earlier,[2d,8] for related compounds, a dependence of the amino group signal position in the ^{1}H NMR spectra on the type of dihydropyrimidine fragment was established. Compounds such as **18** exhibited a signal for NH at 9.5−10.5 ppm, whereas in the case of structures related to **20**, this signal was strong-field-shifted by 2−3 ppm. Additionally, the COSY spectrum of **18j** did not show a correlation peak of the methylene H atom and the NH group. Hence, the spectral data of the synthesized compounds correspond to structure **18**.

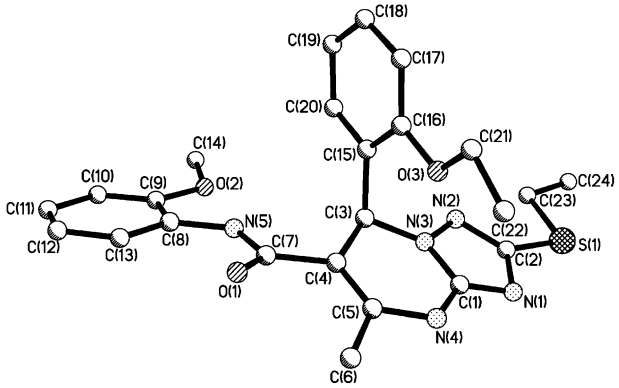
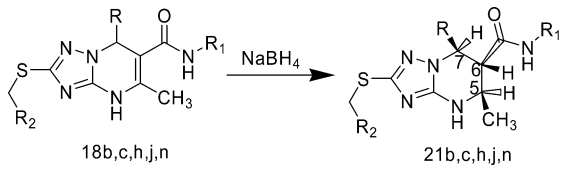


Figure 2. Molecular structure (X-ray analysis) of compound **18o**.

Scheme 3



Ultimately, the structures of the synthesized triazolopyrimidines were establishedon the basis of an X-ray analysis, which demonstrated that **18o** has the structure of 7-(2-ethoxyphenyl)-2-(ethylthio)-*N*-(2-methoxyphenyl)-5-methyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (Figure 2).

Reduction of 4,7-Dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides. The reduction of dihydroheterocycles into the corresponding tetrahydro derivatives is a facile way of increasing the structural diversity and to change the overall geometry of those heterocycles. It is known that the C═C bond in dihydropyrimidines can be reduced with several different reducing agents.[9] One of the most convenient reduction methods for dihydroazolopyrimidines is the use of sodium borohydride,[9a,b,d,e] although the reduction of dihydropyrimidines containing a carboxylic group conjugated with the C═C bond sometimes calls for high-pressure procedures[9g] and the use of special catalysts.

In that event, we found that 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides **18b**,**c**,**h**,**j**,**n** can be easily reduced with sodium borohydride using 2-propanol as solvent (Scheme 3). The ^{1}H NMR spectra of the reduced products **21** show the following: signals for aromatic protons: a doublet for the methyl group at position 5 of the heterocycle (^3J = 5.7 Hz), a doublet of doublets for $H_{(6)}$ (^3J = 9.8 and 10.4 Hz), a multiplet for $H_{(5)}$ (^3J = 5.7 and 9.8 Hz), and a doublet for $H_{(7)}$ (^3J = 10.4 Hz). In comparison with dihydroderivatives **18**, a broad singlet for the amino group in **21** strong-field-shifted by ∼3 ppm was observed, whereas the position of the amide H atom did not change.

Attempts to carry out reduction of compounds **18** under MW irradiation led to formation of **21** in low yields and purity.

The doubling of signals in the ^{1}H NMR spectra—typical for diastereomeric mixtures—for the obtained reduced compounds was not observed. It indicates stereoselectivity in the reduction and formation of only one of the possible diastereoisomers. According to the spin−spin coupling constants between the H atoms in the tetrahydropyrimidine ring, $H_{(5)}$, $H_{(6)}$, and $H_{(7)}$ have a pseudoaxial orientation. Therefore, the ^{1}H NMR data (in agreement with MS data and elemental analyses), allows us to assert that compounds **18b**,**c**,**h**,**j**,**n** were reduced with sodium borohydride into *trans-trans*-5-methyl-2-alkylthio-7-aryl-4,5,6,7-tetrahydro-1,2,4-triazolo-[1,5-*a*]pyrimidine-6-carboxamides **21b**,**c**,**h**,**j**,**n**.

Conclusions

We have developed a fast and convenient microwave-assisted procedure for the rapid generation of 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides **18** by three-component condensation of 3-amino-2-alkylthio-1,2,4-triazoles with aromatic aldehydes and acetoacetamides. All reactions were completed within 5 min of microwave irradition at 120 °C and provided the desired products in high yields and excellent purities. Further structural modification was achieved by selective reduction of the C=C double bond in dihydroazolopyrimidines to provide the corresponding tetrahydroderivatives.

Experimental Section

General. Melting points of all compounds synthesized were determined with a Kofler apparatus. The NMR spectra were recorded in DMSO-d_6 at 200 MHz (50 MHz for ^{13}C) on a suitable spectrometer. The MS spectra were measured on a GC/MS (ionizing voltage 70 eV). IR spectra were recorded in KBr pellets.

All microwave experiments were performed using the Emrys Creator EXP and Emrys Initiator synthesizers from Biotage Sweden AB (Uppsala) possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz. Experiments were carried out in sealed microwave process vials utilizing the standard absorbance level. Reaction time reflects total irradiation times.

The synthesis of 3-amino-5-alkylthio-1,2,4-triazoles **14**−**17**[10a,b] and of acetoacetamides **10**−**13**[10c] was carried out according to known methods as described in the literature.

Microwave-Assisted Synthesis of 7-Aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides 18a−o; General Procedure. A mixture of the appropriate aminoazole **14**−**17** (2.0 mmol), the aromatic aldehyde **2**−**9** (2.0 mmol), and the acetoacetamide **10**−**13** (2.0 mmol) in ethanol (1.5 mL) was irradiated under sealed vessel microwave conditions at 120 °C for 5 min in a 5-mL microwave process vial. The reaction mixture was allowed to stand overnight at room temperature and was then filtered to give the solid triazolopyrimidine products **18a**−**o**, which were washed with ethanol and dried in air. Carboxamides **18a**−**o** were obtained in high purity (> 98% by ^{1}H NMR) and did not require further purification by recrystallization. The analytical samples were dried in a drying pistol.

Conventional Synthesis of 7-Aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides 18a−o; General Procedure. A mixture of the appropriate aminoazole **14**−**17** (2.0 mmol), the aromatic aldehyde **2**−**9** (2.0 mmol), and the acetoacetamide **10**−**13** (2.0 mmol) was refluxed in 0.4 mL of DMF for 10 min. After cooling, acetone (~10 mL) was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid triazolopyrimidine products **18a**−**o**, which were crystallized from ethanol and subsequently dried in air.

Reduction of 7-Aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides 18; General Procedure. In a flask equipped with stir bar placed on a magnetic stirrer at 40−50 °C were introduced a 2.0-mmol sample of the corresponding 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides **18b**,**c**,**h**,**j**,**n** dissolved in 10 mL of 2-propanol. Sodium borohydride (10 mmol) was subsequently added in small portions to the flask within 2 h. The reaction mixture was then poured onto 50 mL of water. The formed precipitate was filtered and dried in a drying oven at 80 °C. Analytical samples were obtained by crystallization from ethanol and dried in drying pistol.

X-ray Analysis Data for 7-(2-Ethoxyphenyl)-2-(ethylthio)-*N*-(2-methoxyphenyl)-5-methyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (Compound 18o). The colorless crystals of **18o** ($C_{24}H_{27}N_5O_3S$) are triclinic. At 293 K, $a = 11.810(1)$, $b = 12.247(1)$, $c = 17.070(2)$ Å; $\alpha = 74.50(1)°$, $\beta = 78.57(1)°$, $\gamma = 86.39(1)°$, $V = 2331.8(3)$ Å^3; $M_r = 465.57$, $Z = 4$; space group $P\bar{1}$; $d_{calcd} = 1.326$ Γ/cm^3; μ(Mo Kα) = 0.175 MM^{-1}; F(000) = 984. Intensity of 20 076 reflections (8192 independent, $R_{int} = 0.063$) were measured on an Xcalibur-3 diffractometer (graphite monochromated Mo K_α radiation, CCD detector, ω-scaning, $2\Theta_{max} = 50°$). The structure was solved by direct method using SHELXTL package. Positions of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with $U_{iso} = nU_{eq}$ of non-hydrogen atom bonded with a given H atom ($n = 1.5$ for a methyl group and $n = 1.2$ for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation using 8112 reflections was converged to w$R_2 = 0.174$ ($R_1 = 0.076$ for 4734 reflections with $F > 4\sigma$(F), $S = 1.113$.

The asymmetric part of the unit cell of crystal **18o** contains two molecules (A and B) with slightly different geometrical parameters. The dihydropyrimidine ring adopts a sofa conformation. Deviation of the C(3) atom from the mean plane of the remaining atoms of the ring is 0.20 and 0.24 Å for the molecules A and B, respectively. The orthoethoxyphenyl substituent at the C(3) atom has a pseudoaxial orientation (the C(1)−N(3)−C(3)−C(15) torsion angle is 111.4(4)° for A and 108.1(4)° for B).

The carbamide and ortho-metoxyphenyl groups of the substituent at the C(4) atom are nearly coplanar (the C(7)−N(5)−C(8)−C(13) torsion angle is 5.4(7)° for A and 6.5(7)° for B). Such conformation is stabilized by the weak intramolecular hydrogen bond C(13)−H(13)···O(1) (H···O 2.31 Å, C−H···O 120° for A and B). The substituent at the C(4) atom is turned relative to the C(4)−C(5) endocyclic

double bond (the C(5)−C(4)−C(7)−O(1) torsion angle is 23.9(6)° and 19.9(6)° for molecules A and B, respectively).

The ethyl group of the substituent at the C(2) atom is not coplanar to the triazole ring (the C(23)−S(1)−C(2)−N(2) torsion angle is −9.3(4)° for A and −19.0(4)° for B). This group has *ap* conformation relative to the C(2)−S(1) bond in the molecule A and *sc* conformation in the molecule B (the C(2)−S(1)−C(23)−C(24) torsion angle is 176.5(3)° for A and −69.2(4)° for B).

The final atomic coordinates and crystallographic data for molecule **18o** have been deposited with 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 numbers CCDC).

5-Methyl-2-methylthio-*N*,7-diphenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (18a). Colorless prisms of mp 276−278 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.14 (s, 3H, CH_3), 2.39 (s, 3H, SCH_3), 6.43 (s, 1H, 7-CH), 6.4−7.8 (m, 10H$_{arom}$), 9.72 (s, 1H, CONH), 10.29 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 15.3, 18.7, 59.8, 112.8, 119.5, 120.8, 129.8, 130.5, 132.1, 134.3, 138.0, 139.9, 145.7, 156.4, 161.6, 164.4. MS (EI, 70 eV): *m*/*z* (%) = 377 (24) [M$^+$], 330 (52.3), 301 (17.6), 285 (100). IR (KBr): $\nu_{C=C}$ = 1620, $\nu_{C=O}$ = 1650, ν_{NH} = 2970, ν_{NH} = 3250. Anal. Calcd. for $C_{20}H_{19}N_5OS$ (%): C, 63.64; H, 5.07; N, 18.55; S, 8.49. Found: C, 63.67; H, 5.10; N, 18.57; S, 8.50.

7-(4-Fluorophenyl)-5-methyl-2-methylthio-*N*-phenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (18b). Colorless prisms of mp 319−321 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.14 (s, 3H, CH_3), 2.39 (s, 3H, SCH_3), 6.46 (s, 1H, 7-CH), 6.8−7.7 (m, 9H$_{arom}$), 9.73 (s, 1H, CONH), 10.29 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 395 (17) [M$^+$], 348 (50,4), 304 (17.4), 303 (100), 302 (3.8), 119 (23.5). IR (KBr): $\nu_{C=C}$ = 1610, $\nu_{C=O}$ = 1650, ν_{NH} = 2980, ν_{NH} = 3290. Anal. Calcd. for $C_{20}H_{18}FN_5OS$ (%): C, 60.74; H, 4.59; N, 17.71; S, 8.11. Found: C, 60.80; H, 4.46; N, 17.73; S, 8.09.

7-(4-Chlorophenyl)-5-methyl-2-methylthio-*N*-phenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (18c). Colorless prisms of mp 306−307 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.14 (s, 3H, CH_3), 2.39 (s, 3H, SCH_3), 6.40 (s, 1H, 7-CH), 6.4−7.8 (m, 9H$_{arom}$), 9.65 (s, 1H, CONH), 10.25 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 411 (12) [M$^+$], 366 (12.1), 364 (35.0), 321 (38.5), 320 (17.7), 319 (100). IR (KBr): $\nu_{C=C}$ = 1620, $\nu_{C=O}$ = 1650, ν_{NH} = 2980, ν_{NH} = 3290. Anal. Calcd. for $C_{20}H_{18}ClN_5OS$ (%): C, 58.32; H, 4.40; N, 17.00; S, 7.78. Found: C, 58.40; H, 4.36; N, 17.03; S, 7.81.

7-(4-Bromphenyl)-5-methyl-2-methylthio-*N*-phenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (18d). Colorless prisms of mp 318−320 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.15 (s, 3H, CH_3), 2.40 (s, 3H, SCH_3), 6.46 (s, 1H, 7-CH), 6.9−7.6 (m, 9H$_{arom}$), 9.72 (s, 1H, CONH), 10.24 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 15.4, 18.6, 59.8, 112.9, 119.7, 120.9, 124.0, 129.7, 131.7, 132.8, 138.0, 139.6, 145.8, 156.4, 161.6, 164.6. MS (EI, 70 eV): *m*/*z* (%) = 455 (14) [M$^+$], 457 (12,8), 410 (56,7), 408 (55), 365(95,9), 363 (100). IR (KBr): $\nu_{C=C}$ = 1620, $\nu_{C=O}$ = 1650, ν_{NH} = 2980, ν_{NH} = 3290. Anal. Calcd. for $C_{20}H_{18}BrN_5OS$ (%): C, 52.64; H, 3.98; N, 15.35; S, 7.03. Found: C, 52.70; H, 4.00; N, 15.4; S, 7.01.

7-(4-Fluorophenyl)-5-methyl-2-methylthio-*N*-(4-chlorophenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]-pyrimidine-6-carboxamide (18e). Colorless prisms of mp 310−312 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.15 (s, 3H, CH_3), 2.40 (s, 3H, SCH_3), 6.45 (s, 1H, 7-CH), 7.05−7.56 (m, 8H$_{arom}$), 9.76 (s, 1H, CONH), 10.23 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 429 (15) [M$^+$], 382 (10,2), 384 (8.1), 303 (100), 301 (16.4). IR (KBr): $\nu_{C=C}$ = 1620, $\nu_{C=O}$ = 1660, ν_{NH} = 2980, ν_{NH} = 3280. Anal. Calcd. for $C_{20}H_{17}FClN_5OS$ (%): C, 55.88; H, 3.99; N, 16.29; S, 7.46. Found: C, 55.90; H, 4.00; N, 16.31; S, 7.41.

7-(4-Methoxyphenyl)-5-methyl-2-methylthio-*N*-(4-chlorophenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]-pyrimidine-6-carboxamide (18f). Colorless prisms of mp 301−302 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.14 (s, 3H, CH_3), 2.39 (s, 3H, SCH_3), 3.68(s, 3H, OCH_3), 6.41 (s, 1H, 7-CH), 6.81−7.56 (m, 8H$_{arom}$), 9.82 (s, 1H, CONH), 10.26 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 441 (10) [M$^+$], 394 (16.5), 316 (17.9), 315 (100), 313 (17,6). IR (KBr): $\nu_{C=C}$ = 1610, $\nu_{C=O}$ = 1650, ν_{NH} = 2980, ν_{NH} = 3290. Anal. Calcd. for $C_{21}H_{20}ClN_5O_2S$ (%): C, 57.07; H, 4.56; N, 15.85; S, 7.26. Found: C, 57.10; H, 4.60; N, 15.87; S, 7.29.

5-Methyl-2-(3-methybenzylthio)-*N*,7-diphenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (18g). Colorless prisms of mp 280−282 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.15 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 4.15 (d, *J* = 13.2 Hz, 1H, CH), 4.16 (d, *J* = 13.2 Hz, 1H, CH), 6.41 (s, 1H, 7-CH), 6.72−7.59 (m, 14H$_{arom}$), 9.72 (s, 1H, CONH), 10.23 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 18.7, 20.9, 35.5, 59.9, 112.6, 119.6, 120.9, 126.3, 129.40, 129.7, 129.8, 129.9, 130.5, 132.1, 134.4, 135.6, 137.8, 138.1, 140.1, 145.8, 154.9, 161.6, 164.7. MS (EI, 70 eV): *m*/*z* (%) = 467 (35) [M$^+$], 391 (28.5), 348 (45.5), 330 (100), 105 (37.8). IR (KBr): $\nu_{C=C}$ = 1620, $\nu_{C=O}$ = 1650, ν_{NH} = 2980, ν_{NH} = 3280. Anal. Calcd. for $C_{27}H_{25}N_5OS$ (%): C, 69.35; H, 5.39; N, 14.98; S, 6.86. Found: C, 69.40; H, 5.40; N, 15.00; S, 6.89.

7-(4-Methoxyphenyl)-5-Methyl-2-(3-methylbenzylthio)-*N*-phenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (18h). Colorless prisms of mp 282−283 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.15 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.15 (d, *J* = 13.1 Hz, 1H, CH), 4.14 (d, *J* = 13.1 Hz, 1H, CH), 6.41 (s, 1H, 7-CH), 6.82−7.51 (m, 13H$_{arom}$), 9.72 (s, 1H, CONH), 10.23 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 497 (42) [M$^+$], 405 (86.9), 392 (51.3), 378 (45.4), 360 (100), 105 (35.6). IR (KBr): $\nu_{C=C}$ = 1620, $\nu_{C=O}$ = 1660, ν_{NH} = 2980, ν_{NH} = 3280. Anal. Calcd. for $C_{28}H_{27}N_5O_2S$ (%): C, 67.58; H, 5.47; N, 14.07; S, 6.44. Found: C, 67.60; H, 5.45; N, 14.05; S, 6.45.

7-(4-Fluorophenyl)-5-methyl-2-(3-methylbenzylthio)-*N*-(2,4-dimethylphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (18i). Colorless prisms of mp 289−290 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.79 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.21 (s, 6H, $2CH_3$), 4.16 (d, *J* = 13.4 Hz, 1H, CH), 4.14 (d, *J* = 13.4 Hz, 1H, CH), 6.42

(s, 1H, 7-CH), 6.87−7.37 (m, 11H_{arom}), 9.08 (s, 1H, CONH), 10.15 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 513 (41) [M^+], 393 (85.5), 367 (23.9), 366 (100), 333 (47.5), 121 (91.90). IR (KBr): $\nu_{C=C}$ = 1620, $\nu_{C=O}$ = 1650, ν_{NH} = 2970, ν_{NH} = 3280. Anal. Calcd. for $C_{29}H_{28}FN_5OS$ (%): C, 67.81; H, 5.49; N, 13.63; S, 6.24. Found: C, 67.80; H, 5.46; N, 13.65; S, 6.26.

7-(4-Chlorophenyl)-5-methyl-2-(3-methylbenzylthio)-*N*-(2,4-dimethylphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (18j). Colorless prisms of mp 300−301 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.80 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.21 (s, 6H, 2CH_3), 4.15 (d, *J* = 13.4 Hz, 1H, CH), 4.16 (d, *J* = 13.4 Hz, 1H, CH), 6.42 (s, 1H, 7-CH), 6.89−7.42 (m, 11H_{arom}), 9.09 (s, 1H, CONH), 10.17 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 529 (12) [M^+], 409 (33.8), 382 (33.5), 121 (100), 105 (33.3). IR (KBr): $\nu_{C=C}$ = 1620, $\nu_{C=O}$ = 1660, ν_{NH} = 2970, ν_{NH} = 3280. Anal. Calcd. for $C_{29}H_{28}ClN_5OS$ (%): C, 65.71; H, 5.32; N, 13.21; S, 6.05. Found: C, 65.75; H, 5.37; N, 13.24; S, 6.08.

7-(4-Bromphenyl)-5-Methyl-2-(3-methylbenzylthio)-*N*-(2,4-dimethylphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (18k). Colorless prisms of mp 301−302 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.80 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.21 (s, 6H, 2CH_3), 4.15 (d, *J* = 13.6 Hz, 1H, CH), 4.16 (d, *J* = 13.6 Hz, 1H, CH), 6.40 (s, 1H, 7-CH), 6.89−7.56 (m, 11H_{arom}), 9.09 (s, 1H, CONH), 10.17 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 573 (11) [M^+], 428 (37.2), 426 (38.2), 121 (100), 105 (31.1). IR (KBr): $\nu_{C=C}$ = 1620, $\nu_{C=O}$ = 1660, ν_{NH} = 2980, ν_{NH} = 3280. Anal. Calcd. for $C_{29}H_{28}BrN_5OS$ (%): C, 60.63; H, 4.91; N, 12.19; S, 5.58. Found: C, 60.65; H, 4.95; N, 12.22; S, 5.60.

7-(4-Methylphenyl)-5-methyl-2-(3-methylbenzylthio)-*N*-(2,4-dimethylphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (18l). Colorless prisms of mp 285−287 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.80 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.21 (s, 6H, 2CH_3), 2.27 (s, 3H, CH_3), 4.15 (d, *J* = 13.4 Hz, 1H, CH), 4.17 (d, *J* = 13.4 Hz, 1H, CH), 6.36 (s, 1H, 7-CH), 6.89−7.19 (m, 11H_{arom}), 9.03 (s, 1H, CONH), 10.07 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 509 (21) [M^+], 389 (100), 372 (41.3), 362 (61.0), 121 (65.1). IR (KBr): $\nu_{C=C}$ = 1620, $\nu_{C=O}$ = 1660, ν_{NH} = 2970, ν_{NH} = 3280. Anal. Calcd. for $C_{30}H_{31}N_5OS$ (%): C, 70.70; H, 6.13; N, 13.74; S, 6.29. Found: C, 70.72; H, 6.15; N, 13.73; S, 6.32.

7-(4-Methoxyphenyl)-5-methyl-2-(3-methylbenzylthio)-*N*-(2,4-dimethylphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]-pyrimidine-6-carboxamide (18m). Colorless prisms of mp 319−320 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.80 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.21 (s, 6H, 2CH_3), 3.72 (s, 3H, OCH_3), 4.15 (d, *J* = 13.3, 1H, CH), 4.16 (d, *J* = 13.3, 1H, CH), 6.36 (s, 1H, 7-CH), 6.86−7.24 (m, 11H_{arom}), 9.03 (s, 1H, CONH), 10.07 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 525 (22) [M^+], 405 (100), 388 (39.8), 378 (32.6), 121 (75.5). IR (KBr): $\nu_{C=C}$ = 1620, $\nu_{C=O}$ = 1650, ν_{NH} = 2970, ν_{NH} = 3280. Anal. Calcd. for $C_{30}H_{31}N_5O_2S$ (%): C, 68.55; H, 5.94; N, 13.32; S, 6.10. Found: C, 68.60; H, 6.00; N, 13.35; S, 6.12.

7-(2-Thienyl)-5-methyl-2-(3-chlorobenzylthio)-*N*-(2,4-dimethylphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]-pyrimidine-6-carboxamide (18n). Colorless prisms of mp 267−268 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.88 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 4.23 (d, *J* = 13.6, 1H, CH), 4.24 (d, *J* = 13.6, 1H, CH), 6.75 (s, 1H, 7-CH), 6.88−7.49 (m, 10H_{arom}), 9.07 (s, 1H, CONH), 10.25 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 17.7, 19.4, 20.7, 35.4, 55.7, 112.9, 118.4, 125.6, 127.6, 128.9, 128.9, 129.4, 129.9, 130.4, 130.6, 132.8, 134.9, 135.9, 136.0, 136.4, 136.6, 136.9, 143.9, 155.9, 161.5, 163.5. MS (EI, 70 eV): *m*/*z* (%) = 521 (10) [M^+], 376 (43.7), 374 (100), 364 (43.5), 121 (91.4). IR (KBr): $\nu_{C=C}$ = 1610, $\nu_{C=O}$ = 1650, ν_{NH} = 2970, ν_{NH} = 3280. Anal. Calcd. for $C_{26}H_{24}ClN_5OS_2$ (%): C, 59.81; H, 4.63; N, 13.41; S, 12.28. Found: C, 59.85; H, 4.65; N, 13.44; S, 12.30.

7-(2-Ethoxyphenyl)-2-(ethylthio)-*N*-(2-methoxyphenyl)-5-methyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (18o). Colorless prisms of mp 193−195 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.19 (m, 6H, 2CH_3), 2.12 (s, 3H, CH_3), 2.91 (q, *J* = 7.3 Hz, 2H, CH_2S), 3.73 (s, 3H, CH_3O), 3.90 (q, *J* = 7.1 Hz, 2H, CH_2O), 6.54 (s, 1H, 7-CH), 6.70−7.70 (m, 8H_{arom}), 8.59 (s, 1H, CONH), 10.19 (s, 1H, NH). MS (EI, 70 eV): *m*/*z* (%) = 465 (71) [M^+], 405 (21.6), 404 (91.7), 343 (74.0), 315 (22.4), 123 (100). IR (KBr): $\nu_{C=C}$ = 1621, $\nu_{C=O}$ = 1661, ν_{NH} = 2980, ν_{NH} = 3279. Anal. Calcd. for $C_{24}H_{27}N_5O_3S$ (%): C, 61.92; H, 5.85; N, 15.04; S, 6.89. Found: C, 61.97; H, 5.80; N, 15.02; S, 6.91.

7-(4-Fluorophenyl)-5-methyl-2-methylthio-*N*-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (21b). Colorless prisms of mp 313−315 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.18 (d, 6.4, 3H, CH_3), 2.32 (s, 3H, SCH_3), 2.78 (dd, ^3J = 9.8 and 10.2 Hz, 1H, 6-CH), 3.65 (m, ^3J = 5.7 and 9.8 Hz, 1H, 5-CH), 5.27 (d, *J* = 10.1 Hz, 1H, 7-CH), 6.98−7.44 (m, 9H_{arom}), 7.51 (s, 1H, NH), 9.96 (s, 1H, CONH). MS (EI, 70 eV): *m*/*z* (%) = 397 (73) [M^+], 350 (98.8), 277 (94.7), 231 (100), 164 (69.5). IR (KBr): $\nu_{C=O}$ = 1650, ν_{NH} = 2980, ν_{NH} = 3290. Anal. Calcd. for $C_{20}H_{20}FN_5OS$ (%): C, 60.44; H, 5.07; N, 17.62; S, 8.07. Found: C, 60.50; H, 5.10; N, 17.65; S, 8.10.

7-(4-Chlorophenyl)-5-methyl-2-methylthio-*N*-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (21c). Colorless prisms of mp 335−338 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.18 (d, *J* = 6.3 Hz, 3H, CH_3), 2.32 (s, 3H, SCH_3), 2.78 (dd, ^3J = 9.8 and 10.2 Hz, 1H, 6-CH), 3.65 (m, ^3J = 5.7 and 9.8 Hz, 1H, 5-CH), 5.28 (d, *J* = 10.1, 1H, 7-CH), 6.98−7.52 (m, 9H_{arom}), 7.54 (s, 1H, NH), 9.98 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 15.4, 20.9, 51.7, 58.8, 60.6, 118.4, 125.5, 129.4, 130.6, 132.4, 132.3, 134.3, 134.4, 144.1, 156.4, 161.3, 174.6. MS (EI, 70 eV): *m*/*z* (%) = 413 (57) [M^+], 415 (22.6), 368 (33.1), 366 (100), 119 (64.8). IR (KBr): $\nu_{C=O}$ = 1650, ν_{NH} = 2980, ν_{NH} = 3280. Anal. Calcd. for $C_{20}H_{20}ClN_5OS$ (%): C, 58.03; H, 4.87; N, 16.92; S, 7.75. Found: C, 58.05; H, 4.9; N, 16.95; S, 7.78.

7-(4-Methoxyphenyl)-5-Methyl-2-(3-methylbenzylthio)-*N*-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (21h). Colorless prisms of mp 326−

328 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.18 (d, J = 6.3 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.81 (dd, ^3J = 9.8 and 10.1 Hz, 1H, 6-CH), 3.61 (m, ^3J = 5.7 and 9.8 Hz, 1H, 5-CH), 3.70 (s, 3H, OCH_3), 4.06 (d, J = 13.4 Hz, 1H, CH), 4.07 (d, J = 13.4 Hz, 1H, CH), 5.22 (d, J = 10.2 Hz, 1H, 7-CH), 6.84−7.48 (m, 13H_{arom}), 7.51 (s, 1H, NH), 9.98 (s, 1H, CONH). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 21.1, 21.2, 51.7, 55.4, 58.1, 58.8, 117.1, 118.4, 125.5, 129.1, 129.3, 130.4, 130.5, 130.8, 131.9, 133.8, 134.4, 138.4, 140.1, 159.3, 159.9, 162.3, 174.8. MS (EI, 70 eV): m/z (%) = 499 (99) [M^+], 379 (93.3), 362 (100), 246 (86.8), 243 (78.6). IR (KBr): $\nu_{C=O}$ = 1660, ν_{NH} = 2980, ν_{NH} = 3280. Anal. Calcd. for $C_{28}H_{29}N_5O_2S$ (%): C, 67.31; H, 5.85; N, 14.02; S, 6.42. Found: C, 67.35; H, 5.87; N, 14.05; S, 6.45.

7-(4-Chlorophenyl)-5-methyl-2-(3-methylbenzylthio)-*N*-(2,4-dimethylphenyl)-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (21j). Colorless prisms of mp 301−302 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.27 (d, J = 6.1 Hz, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.84 (dd, ^3J = 9.8 and 10.2 Hz, 1H, 6-CH), 3.67 (m, ^3J = 5.6 and 9.8 Hz, 1H, 5-CH), 4.12 (d, J = 13.6 Hz, 1H, CH), 4.13 (d, J = 13.6 Hz, 1H, CH), 5.22 (d, J = 10.2 Hz, 1H, 7-CH), 6.89−7.53 (m, 11H_{arom}), 7.56 (s, 1H, NH), 9.34 (s, 1H, CONH). MS (EI, 70 eV): m/z (%) = 531 (56) [M^+], 351 (42.8), 533 (26.6), 246 (59.1), 213 (100). IR (KBr): $\nu_{C=O}$ = 1660, ν_{NH} = 2970, ν_{NH} = 3280. Anal. Calcd. for $C_{29}H_{30}ClN_5OS$ (%): C, 65.46; H, 5.68; N, 13.16; S, 6.03. Found: C, 65.50; H, 5.70; N, 13.18; S, 6.05.

7-(2-Thienyl)-5-methyl-2-(3-chlorobenzylthio)-*N*-(2,4-dimethylphenyl)-4,5,6,7-tetrahydro-1,2,4-triazolo-[1,5-*a*]-pyrimidine-6-carboxamide (21n). Colorless prisms of mp 258−260 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.27 (d, J = 6.3 Hz, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.94 (dd, ^3J = 9.8 and 10.2 Hz, 1H, 6-CH), 3.66 (m, ^3J = 5.7 and 9.8 Hz, 1H, 5-CH), 4.12 (d, J = 13.6 Hz, 1H, CH), 4.13 (d, J = 13.6 Hz, 1H, CH), 5.54 (d, J = 10.2 Hz, 1H, 7-CH), 6.90−7.54 (m, 10H_{arom}), 7.57 (s, 1H, NH), 9.49 (s, 1H, CONH). MS (EI, 70 eV): m/z (%) = 523 (54) [M^+], 375 (67.7), 366 (100), 125 (30.6). IR (KBr): $\nu_{C=O}$ = 1650, ν_{NH} = 2970, ν_{NH} = 3280. Anal. Calcd. for $C_{26}H_{26}ClN_5OS_2$ (%): C, 59.58; H, 5.00; N, 13.36; S, 12.24. Found: C, 59.60; H, 5.05; N, 13.38; S, 12.27.

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