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# Switchable selectivity in multicomponent heterocyclizations of acetoacetamides, aldehydes, and 3-amino-1,2,4-triazoles/5-aminopyrazoles

Elena A. Muravyova [a], Sergey M. Desenko [a,b], Roman V. Rudenko [a], Svetlana V. Shishkina [a], Oleg V. Shishkin [a,b], Yulia V. Sen'ko [a], Elena V. Vashchenko [a], Valentin A. Chebanov [a,*]

[a] State Scientific Institution 'Institute for Single Crystals' of National Academy of Sciences of Ukraine, Lenin Ave. 60, 61001 Kharkiv, Ukraine
[b] Karazin Kharkiv National University, Svobody sq., 4, 61077 Kharkiv, Ukraine

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ABSTRACT

Multicomponent heterocyclizations of 3-amino-1,2,4-triazoles/5-aminopyrazoles with acetoacetamides and aromatic aldehydes were studied in detail using conventional thermal heating, ultrasonication, and microwave irradiation. Several different synthetic pathways for these cyclocondensations occurring under either kinetic or thermodynamic control were established depending on the temperature regime and building block selection. The experimental data obtained and the procedures developed allow tuning selectivity of the multicomponent reactions studied.



## 1. Introduction

Polyfunctionalized heterocyclic compounds play an important role in the drug discovery process—an analysis of drugs on the market shows that about 70% of them are heterocycles.[1] Therefore it is not surprising that research concerning their synthesis has received special attention. For example, fused heterocycles containing pyrimidine or pyridine ring as a core unit are known to exhibit various biological and pharmaceutical activities,[2] and synthesis of these complex heterocyclic scaffolds is assigned as one of the most fertile areas for both organic and medicinal chemistry.

One of the main tasks of modern synthetic chemistry is to develop efficient approaches allowing in a minimum synthetic steps to give an opportunity of obtaining target compound in high yields from available starting reagents. Due to the simplicity, convenience, great diversity, and combinatorial potential multicomponent reactions attract an attention of chemists working in the field of both classical organic synthesis and drug discovery.[3] It leads to their widespread application for solving problems of medicinal chemistry and, in particular, for producing libraries of compounds for high-throughput biological screening. However, the problem concerning the ambiguity of direction of multicomponent reaction often appears[4] and, therefore, one of the interesting challenges is increasing selectivity for such treatments by development of the methods of tuning their direction.

This problem is also urgent for multicomponent heterocyclizations involving aminoazoles as key building-blocks.[4a] Especially it is an actual matter when aminoazole molecule contains alternative nucleophilic reaction centers making their cyclocondensations with carbonyl and active methylene compounds ambiguous from the viewpoint of chemo- and regioselectivity.[4,5] Moreover, the formation of several final compounds is caused not only by competition of the reaction centers, but also by position isomerism (different location of substituents in the heterocyclic skeleton). For example, there are literature data on the multicomponent treatment of 3-amino-1,2,4-triazole with aromatic aldehydes and acetophenone yielding sole dihydrotriazolopyrimidine as the reaction product.[6] On the other hand, a similar heterocyclization involving benzocycloalkanones instead of acetophenone led to the formation of two position isomers **I** and **II** (Scheme 1), which differed by location of cycloalkane and aldehyde fragments.[6]

The formation of mixtures of isomeric 4,5- and 4,7-dihydrotriazolopyrimidines was also observed in the reaction of 3-amino-1,2,4-triazole with methylarylketones in the presence of $ZnCl_2$[7a] while under acidic catalysis (acetic or mineral acids) the same treatment yielded only 4,5-dihydroderivatives.[7b]

There are publications concerning multicomponent heterocyclizations of aminoazoles with wide sets of aldehydes and

* Corresponding author. Tel.: +380 57 341 0191; fax: +380 57 341 0273; e-mail address: chebanov@isc.kharkov.com (V.A. Chebanov).

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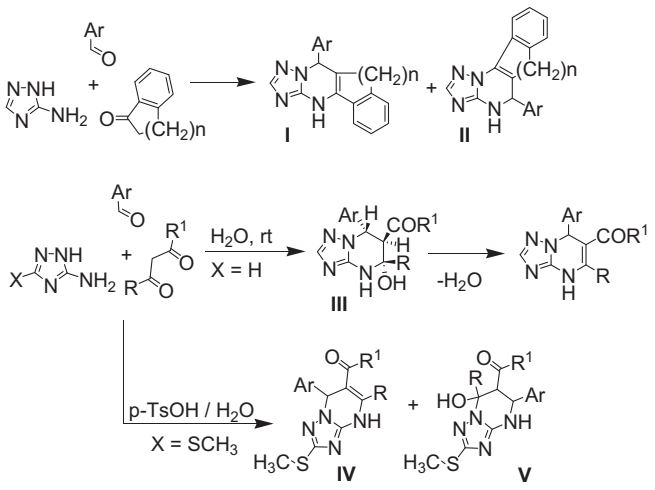
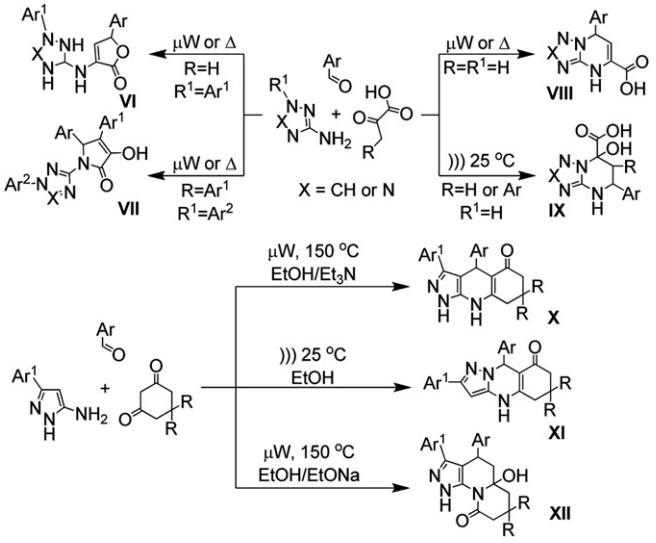



Scheme 1.




Scheme 2.

derivatives of acetoacetic acid giving diverse types of azolopyrymidines.[8] In several cases such treatments led to the unusual results from the viewpoint of selectivity. For instance, reaction of 3-amino-1,2,4-triazole with aldehydes and β-dicarbonyl CH-acids in water at room temperature without any catalyst gave tetrahydrotriazolopyrimidines **III** (Scheme 1), which further were not able to eliminate water.[8f] Formation of similar compounds was also described by Rusinov and colleagues[8c] for heterocyclizations involving fluoroalkyl derivatives of acetoacetic ester. It should be noted that in both of these articles the structure of final compounds was established only with help of $^{1}H$ and $^{13}C$ NMR data that, in our opinion, was not enough due to possibility of formation of position isomers.[8h,9]

Yang et al.[8h] declared the first example of regioselective Biginelli-like heterocyclization based on reaction of 3-alkylthio-5-amino-1,2,4-triazole, aldehydes, and acetoacetic esters in water medium. However, the heterocyclization described in this article in the most cases gave mixtures of two different compounds (**IV** and **V**, Scheme 1). Selective procedure for the synthesis of tetrahydrotriazolopyrimidine **V** were not developed at all, while highly effective method for obtaining heterocycles **IV** had already been elaborated in our earlier publication.[8d]

On the other hand, a possibility of tuning the chemo- and regioselectivity of heterocyclizations allowing their switching from one direction to another by variation of the reaction parameters was shown in several publications of our laboratory[9,10] and other authors.[11]

For example, heterocyclizations of some aminoazoles and aldehydes with derivatives of pyruvic acid proceeding under kinetic or thermodynamic control can be directed by variation of the temperature regime to the formation of four types of final compounds (**VI**–**IX**, Scheme 2).[9,10a,c,h] Combination of different activation methods (microwave or ultrasonic irradiation) and changing catalytic systems allows tuning selectivity of three-component reaction between 3-aryl-5-aminopyrazoles, aldehydes, and 1,3-cyclohexanediones, which gives a possibility to obtain three classes of heterocycles (**X**–**XII**, Scheme 2).[10b,d] Similar principles were applied to switch directions of heterocyclizations involving 5-aminopyrazoles, aldehydes and barbituric acids,[10e] 3-amino-1,2,4-triazole, *o*-salicylic aldehyde, and carbonyl-containing CH-acids.[10f]

In this article we disclose our recent results in tuning selectivity of multicomponent heterocyclization involving aromatic aldehydes, 3-amino-1,2,4-triazoles or 5-aminopyrazoles, and acetoacetamides being earlier less studied in similar treatments.

## 2. Results and discussion

### 2.1. Three-component reaction of aminoazoles, aldehydes, and acetoacetamides

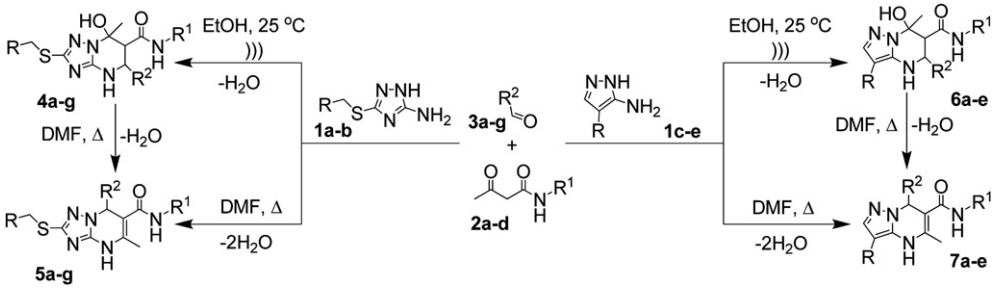
The comprehensive study of three-component reactions of aminoazoles **1a**–**m**, acetoacetamides **2a**–**d**, and aromatic aldehydes **3a**–**o** allowed us to establish a dependence of direction of the treatments on the temperature regime and structure of the starting building-blocks.

For example, proceeding the reaction involving 5-alkylthio-3-amino-1,2,4-triazoles (**1a**,**b**), anilides of acetoacetic acid **2a**–**c**, and aldehydes **3a**–**e** was successfully tuned by variation of the temperature with help of ultrasonication, conventional thermal heating or microwave irradiation.

It was established, that a three-component treatment of the starting materials in EtOH at 25 °C under ultrasonication, similar to the analogous reactions involving pyruvic acids,[9] gave only 7-hydroxy-7-methyl-2-(alkylthio)-*N*,5-diaryl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxamides (**4a**–**g**, Scheme 3) in 55–86% yields (Table 1). This procedure opens the way to high selective synthesis of heterocycles like **V** (Scheme 1), described as side products by Yang et al.[8h] On the other hand, as it had been already shown in our earlier publication,[8d] reaction of the same building-blocks under microwave irradiation (EtOH, 120 °C, 5 min) or under conventional refluxing in DMF yielded 5-methyl-2-(alkylthio)-*N*,7-diaryl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxamides (**5a**–**g**). Additionally it was found that smooth heating (~50 °C) of tetrahydropyrimidines **4a**–**g** in DMF led to their reversible decomposition into the starting compounds (NMR control), while heating at reflux for 3 h converted them into heterocycles **5a**–**g** (80–90%, Table 1).

Thus, the experimental data indicates that this three-component reaction can proceed both under kinetic and under thermodynamic control that gives an opportunity to direct it into two different ways reaching true chemoselectivity.

5-Aminopyrazoles **1c**–**e**, containing in the fourth position electron-withdrawing substituents (R=CN, $CO_2CH_3$, $CONH_2$) showed in the three-component reactions with aldehydes and acetoacetamides similar behavior: kinetically controlled treatment (ultrasonication in EtOH at 25 °C) yielded tetrahydropyrazolopyrimidines **6a**–**e**, while under thermodynamic control (refluxing in DMF) reaction switched to formation of dihydroderivatives **7a**–**e**




**Scheme 3.**

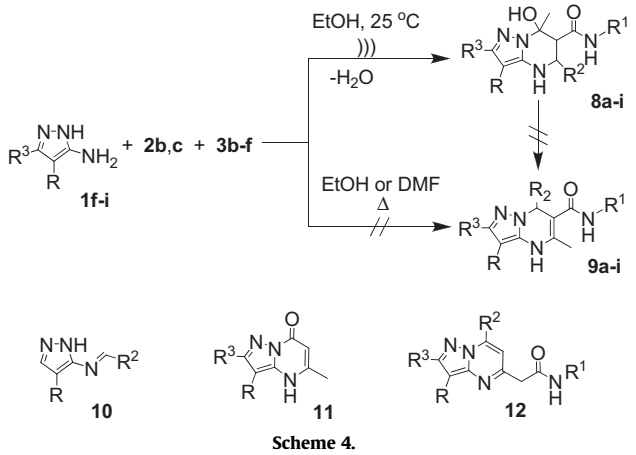
**Table 1**
Three-component synthesis of compounds **4a–g**, **5a–g**, **6a–e**, **7a–e**, **8a–i**, **13a–e**, **14a–e**, **15a–l**

| Building-blocks | | | | | | Reaction products | |
|---|---|---|---|---|---|---|---|
| Aminoazole | | Acetoacetamide | | Aldehyde | | | |
| Compound | R/R$^3$ | Compound | R$^1$ | Compound | R$^2$ | Compound | Yield, % |
| **1a** | $CH_3$ | **2a** | $C_6H_5$ | **3a** | 4-$(CH_3CH_2)C_6H_4$ | **4a** | 85 |
| **1a** | $CH_3$ | **2a** | $C_6H_5$ | **3b** | 4-$ClC_6H_4$ | **4b** | 55 |
| **1b** | $C_6H_5$ | **2a** | $C_6H_5$ | **3c** | 4-$CH_3C_6H_4$ | **4c** | 55 |
| **1b** | $C_6H_5$ | **2b** | 2-$CH_3OC_6H_4$ | **3a** | 4-$(CH_3CH_2)C_6H_4$ | **4d** | 85 |
| **1b** | $C_6H_5$ | **2b** | 2-$CH_3OC_6H_4$ | **3d** | 4-$BrC_6H_4$ | **4e** | 70 |
| **1b** | $C_6H_5$ | **2b** | 2-$CH_3OC_6H_4$ | **3e** | $C_6H_5$ | **4f** | 86 |
| **1b** | $C_6H_5$ | **2c** | 4-$CH_3OC_6H_4$ | **3a** | 4-$(CH_3CH_2)C_6H_4$ | **4g** | 65 |
| **1a** | $CH_3$ | **2b** | $C_6H_5$ | **3a** | 4-$(CH_3CH_2)C_6H_4$ | **5a** | 90, 80[a] |
| **1a** | $CH_3$ | **2a** | $C_6H_5$ | **3b** | 4-$ClC_6H_4$ | **5b** | 80, 80[a] |
| **1b** | $C_6H_5$ | **2a** | $C_6H_5$ | **3c** | 4-$CH_3C_6H_4$ | **5c** | 85, 82[a] |
| **1b** | $C_6H_5$ | **2b** | 2-$CH_3OC_6H_4$ | **3a** | 4-$(CH_3CH_2)C_6H_4$ | **5d** | 85, 85[a] |
| **1b** | $C_6H_5$ | **2b** | 2-$CH_3OC_6H_4$ | **3d** | 4-$BrC_6H_4$ | **5e** | 85, 87[a] |
| **1b** | $C_6H_5$ | **2b** | 2-$CH_3OC_6H_4$ | **3e** | $C_6H_5$ | **5f** | 90, 85[a] |
| **1b** | $C_6H_5$ | **2c** | 4-$CH_3OC_6H_4$ | **3a** | 4-$(CH_3CH_2)C_6H_4$ | **5g** | 90, 90[a] |
| **1c** | $CONH_2$ | **2a** | $C_6H_5$ | **3f** | 4-OH−3-$CH_3OC_6H_4$ | **6a** | 85 |
| **1c** | $CONH_2$ | **2d** | 2,4-$(CH_3)_2C_6H_3$ | **3g** | 3,4- $(CH_3O)_2C_6H_3$ | **6b** | 85 |
| **1d** | CN | **2b** | 2-$CH_3OC_6H_4$ | **3d** | 4-$BrC_6H_4$ | **6c** | 85 |
| **1d** | CN | **2b** | 2-$CH_3OC_6H_4$ | **3e** | $C_6H_5$ | **6d** | 85 |
| **1e** | $CO_2CH_3$ | **2b** | 2-$CH_3OC_6H_4$ | **3b** | 4-$ClC_6H_4$ | **6e** | 52 |
| **1c** | $CONH_2$ | **2a** | $C_6H_5$ | **3f** | 4-OH−3-$CH_3OC_6H_3$ | **7a** | 55, 82[a] |
| **1c** | $CONH_2$ | **2d** | 2,4-$(CH_3)_2C_6H_3$ | **3g** | 3,4-$(CH_3O)_2C_6H_3$ | **7b** | 65, 90[a] |
| **1d** | CN | **2b** | 2-$CH_3OC_6H_4$ | **3d** | 4-$BrC_6H_4$ | **7c** | 65, 85[a] |
| **1d** | CN | **2b** | 2-$CH_3OC_6H_4$ | **3e** | $C_6H_5$ | **7d** | 60, 85[a] |
| **1e** | $CO_2CH_3$ | **2b** | 2-$CH_3OC_6H_4$ | **3b** | 4-$ClC_6H_4$ | **7e** | 50, 82[a] |
| **1f** | $CH_3$/4-$ClC_6H_4$ | **2b** | 2-$CH_3OC_6H_4$ | **3c** | 4-$CH_3C_6H_4$ | **8a** | 85 |
| **1f** | $CH_3$/4-$ClC_6H_4$ | **2b** | 2-$CH_3OC_6H_4$ | **3d** | 4-$BrC_6H_4$ | **8b** | 85 |
| **1f** | $CH_3$/4-$ClC_6H_4$ | **2b** | 2-$CH_3OC_6H_4$ | **3e** | $C_6H_5$ | **8c** | 87 |
| **1g** | $C_6H_5$/H | **2b** | 2-$CH_3OC_6H_4$ | **3b** | 4-$ClC_6H_4$ | **8d** | 75 |
| **1g** | $C_6H_5$/H | **2b** | 2-$CH_3OC_6H_4$ | **3d** | 4-$BrC_6H_4$ | **8e** | 80 |
| **1g** | $C_6H_5$/H | **2c** | 4-$CH_3OC_6H_4$ | **3e** | $C_6H_5$ | **8f** | 70 |
| **1h** | 4-$ClC_6H_4$/H | **2b** | 2-$CH_3OC_6H_4$ | **3c** | 4-$CH_3C_6H_4$ | **8g** | 75 |
| **1h** | 4-$ClC_6H_4$/H | **2b** | 2-$CH_3OC_6H_4$ | **3d** | 4-$BrC_6H_4$ | **8h** | 75 |
| **1i** | 4-$FC_6H_4$/H | **2b** | 2-$CH_3OC_6H_4$ | **3f** | 4-OH−3-$CH_3OC_6H_3$ | **8i** | 80 |
| **1j** | $CH_3$ | **2a** | $C_6H_5$ | **3h** | 4-$CNC_6H_4$ | **13a** | 55 |
| **1j** | $CH_3$ | **2a** | $C_6H_5$ | **3d** | 4-$BrC_6H_4$ | **13b** | 50 |
| **1j** | $CH_3$ | **2a** | $C_6H_5$ | **3i** | 4-$NO_2$−$C_6H_4$ | **13c** | 65 |
| **1j** | $CH_3$ | **2a** | $C_6H_5$ | **3j** | 4-$CO_2HC_6H_4$ | **13d** | 50 |
| **1j** | $CH_3$ | **2e** | 4-$ClC_6H_4$ | **3i** | 4-$NO_2C_6H_4$ | **13e** | 50 |
| **1j** | $CH_3$ | **2a** | $C_6H_5$ | **3k** | 4-OH−3-$(CH_3CH_2O)C_6H_3$ | **14a** | 55 |
| **1j** | $CH_3$ | **2a** | $C_6H_5$ | **3l** | 3,4-$(OH)_2C_6H_3$ | **14b** | 35 |
| **1j** | $CH_3$ | **2a** | $C_6H_5$ | **3g** | 3,4-$(CH_3O)_2C_6H_3$ | **14c** | 45 |
| **1j** | $CH_3$ | **2a** | $C_6H_5$ | **3m** | 4-$OHC_6H_4$ | **14d** | 42 |
| **1j** | $CH_3$ | **2a** | $C_6H_5$ | **3n** | 4-$N(CH_3)_2C_6H_4$ | **14e** | 50 |
| **1k** | $C_6H_5$ | **2a** | $C_6H_5$ | **3f** | 4-OH−3-$CH_3OC_6H_3$ | **15a** | 55 |
| **1l** | 4-$ClC_6H_4$ | **2a** | $C_6H_5$ | **3j** | 4-$CO_2HC_6H_4$ | **15b** | 52 |
| **1l** | 4-$ClC_6H_4$ | **2a** | $C_6H_5$ | **3h** | 4-$CNC_6H_4$ | **15c** | 55 |
| **1l** | 4-$ClC_6H_4$ | **2a** | $C_6H_5$ | **3i** | 4-$NO_2C_6H_4$ | **15d** | 65 |
| **1l** | 4-$ClC_6H_4$ | **2a** | $C_6H_5$ | **3o** | β-$C_5H_4N$ | **15e** | 40 |
| **1l** | 4-$ClC_6H_4$ | **2b** | 2-$CH_3OC_6H_4$ | **3d** | 4-$BrC_6H_4$ | **15f** | 65 |
| **1l** | 4-$ClC_6H_4$ | **2d** | 2,4-$(CH_3)_2C_6H_3$ | **3f** | 4-OH−3-$CH_3OC_6H_3$ | **15g** | 50 |
| **1m** | 4-$CH_3OC_6H_4$ | **2a** | $C_6H_5$ | **3b** | 4-$ClC_6H_4$ | **15h** | 65 |
| **1m** | 4-$CH_3OC_6H_4$ | **2a** | $C_6H_5$ | **3f** | 4-OH−3-$CH_3OC_6H_3$ | **15i** | 52 |
| **1m** | 4-$CH_3OC_6H_4$ | **2a** | $C_6H_5$ | **3d** | 4-$BrC_6H_4$ | **15j** | 65 |
| **1m** | 4-$CH_3OC_6H_4$ | **2b** | 2-$CH_3OC_6H_4$ | **3d** | 4-$BrC_6H_4$ | **15k** | 65 |
| **1m** | 4-$CH_3OC_6H_4$ | **2d** | 2,4-$(CH_3)_2C_6H_3$ | **3d** | 4-$BrC_6H_4$ | **15l** | 55 |

[a] Yields of the transformations of compounds **4** and **6**.

having opposite location of two substituents in pyrimidine ring (Scheme 3). Compounds **6a**–**e** at reflux in DMF for 3 h can be easily transformed into heterocycles **7a**–**e** in 82–90% yields (Table 1).

The presence of a methyl or aryl substituent in the fourth position of 5-aminopyrazole changes its behavior in the multicomponent reaction with acetoacetamides and aldehydes. It was established that treatment of the starting materials **1f**–**i**, **2b**,**c**, and **3b**–**f** in EtOH at room temperature gave the expected tetrahydropyrazolopyrimidines **8a**–**i** (Scheme 4, Table 1), whereas thermodynamic controlled reactions (refluxing in EtOH or DMF) of the same compounds never yielded heterocycles **9** being 'classical' products of such treatments. Instead of them the mixtures of compounds **10**, **11**, and **12** were isolated. In order to carry out their identification analytical samples of representatives of compounds **11** (R=$CH_3$, $R^3$=4-$ClC_6H_4$) and **12** (R=4-$FC_6H_4$, $R^1$=$C_6H_5$, $R^2$=4-OH–3-$CH_3OC_6H_3$, $R^3$=H) were obtained.



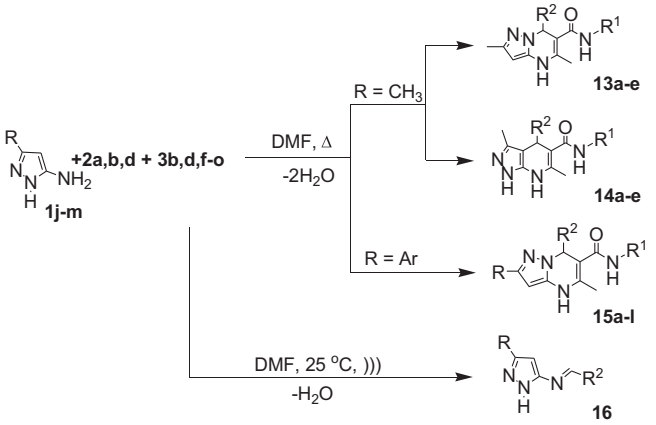

Scheme 4.

In the case of kinetic controlled reactions after isolation of the main products and evaporation of the mother liquor in the rest formed with help of $^1$H NMR a presence of target compounds (up to 7%), corresponding azomethines of aldehydes and aminozoles, starting acetoacetamides, and several undefined products in minor amounts were found. Very similar situation, excepting azomethine, was observed for the thermodynamic controlled reactions.

Our attempts to carry out dehydration of tetrahydroazolopyrimidines **4**, **6**, and **8** were unsuccessful: heating in ethanol in the presence of HCl or *p*-TsOH led to their recyclization or decomposition (in the case of **8**) while at room temperature only the starting heterocycles were quantitatively isolated from the reaction mixture.

Another situation was observed for the multicomponent reactions between aldehydes, acetoacetamides, and 3-substituted 5-aminopyrazoles. In this case direction of the treatment was strongly depended on the character of substituents in pyrazole and aldehyde while changing temperature regime did not give the expected results. It was found that three-component reaction of aminopyrazoles **1j**–**m**, amides **2a**,**b**,**d**, and aldehydes **3b**,**d**,**f**–**o** in DMF at room temperature yielded only corresponding imines **16** (Scheme 5) in 50–70% yields. On the other hand, increasing the temperature led to the formation of heterocyclized compounds, though, their structures were different.

3-Aryl-5-aminopyrazoles **1k**–**m** in their three-component reaction with aldehydes and acetoacetamides in boiling DMF gave exclusively 5-methyl-*N*,2,7-triaryl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxamides (**15a**–**l**). In the case of 5-amino-3-methylpyrazole (**1j**) proceeding the similar treatments was ambiguous and depended on the substituent in the aldehyde




Scheme 5.

component. Application of aldehydes **3d**,**h**–**j** containing electron-withdrawing groups in *para*-position led to the formation of pyrimidine ring (compounds **13a**–**e**) while a presence of π-electron-donating substituents (aldehydes **3g**,**k**–**n**) switched the direction toward 3,6-dimethyl-*N*,4-diaryl-4,7-dihydropyrazolo-[3,4-*b*]pyridine-5-carboxamides (**14a**–**e**).

Realization of the different directions in the three-component reactions involving 3-methyl- or 3-aryl-substituted 5-aminopyrazoles concerned, in our opinion, with sterical influence of the substituent: in the case of methyl-derivative both 4-CH and 1-NH centers are accessible for other reagents while 3-aryl ring due to its size prevents participation of 4-CH center in the treatment that leads to the formation of dihydropyrimidine nucleus only. A similar influence of the character of the substituents in 5-aminopyrazoles on the direction of multicomponent reactions was observed and discussed in our earlier publications.[10c,d]

## 2.2. Structure determination

Identification of all the compounds synthesized was made with help of elemental analysis, MS spectrometry, NMR spectroscopy, and X-ray study.

Physicochemical characteristics and spectra of dihydrotriazolopyrimidines **5** were in good accordance with the data described for these types of compounds in earlier publications.[8d,h] To determine structures of heterocycles **7**, **13**–**15** the algorithm used before for similar compounds[8d,9,10a] was applied. Spectra of azomethines **16** were in a good accordance with known data.[12]

The $^1$H NMR spectra of heterocycles **4**, **6**, and **8** showed duplication of some signals due to the presence of two diastereomeric pairs. $^1$H NMR spectra of the main stereoisomers of these compounds contain two doublets for the CH-protons of the pyrimidine ring at 3.08–4.97 ppm with $J$ ~11.2–11.7 Hz corresponding to their *trans*-orientation. In addition a singlet for the CH-group of the pyrazole ring (compounds **6a**–**e**, **8a**–**i**) at 7.6–7.8 ppm as well as multiplets for the aromatic rings (6.4–7.7 ppm), signals for the NH-group of the pyrimidine ring at ca. 6.3–7.0 ppm, amide NH at 8.8–9.7 ppm, OH group at 6.5–7.77 ppm, and signals for the other terminal substituents at appropriate positions were found. For the minor stereoisomers, observed in amounts up to ~5%, practically all signals were down-field shifted for 0.2–0.4 ppm while spin–spin coupling constants of CH protons of tetrahydropyrimidine ring were the same (11.4–12.0 Hz) and corresponded to *trans*-configuration of these stereogenic centers as well. It means that for minor stereoisomer relative orientation of OH–C–$CH_3$ moiety changes in comparison with major one.

The spectral data obtained for the compounds **4**, **6**, and **8** may correspond to several possible regioisomers. For example, for the

products of three-component reaction involving 5-alkylthio-3-amino-1,2,4-triazoles according to $^{1}H$ and $^{13}C$ NMR may be assigned several different structures **A**–**D** (Fig. 1).

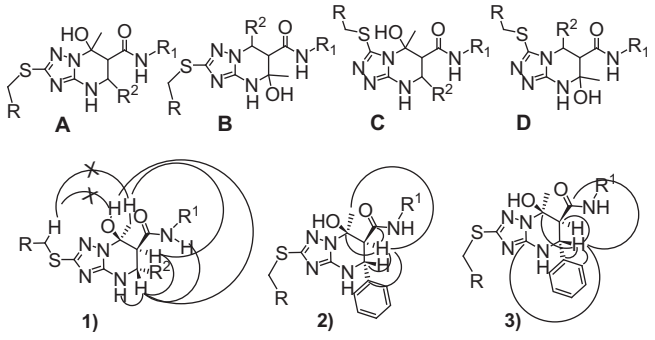



**Fig. 1.** Possible isomers (**A**–**D**), stereochemistry of main diastereomers, and some ROESY (1) and HMBC (2, 3) correlations for compounds **4**.

ROESY and HMBC experiments allowed confirming the structure of type **B** for the compounds synthesized and establishing their stereochemistry were carried out (Fig. 1). The same approach was applied for the compounds **6** and **8**. Additionally, the structures of pyrazolopyrimidines **6** were unequivocally established by X-ray diffraction analysis of a single crystal of one diastereomer of compound **6d**, which allowed assignment of the structure as 3-cyano-7-hydroxy-*N*-(2-methoxyphenyl)-7-methyl-5-phenyl-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidine-6-carboxamide (Fig. 2).

The tetrahydropyrimidine ring of the compound **6d** adopts an asymmetric half-chair conformation where the deviations of the C1 and C2 atoms from the mean plane of the remaining atoms of the ring are 0.19 Å and −0.60 Å, respectively. The hydroxyl substituent has an axial orientation while other substituents in tetrahydropyrimidine ring have an equatorial orientation (the O1–C3–N2–C4, C8–C3–N2–C4, C15–C2–C3–N2, and C9–C1–N1–C4 torsion angles are −86.2(3)°, 150.8(3)°, 176.4(2)°, and −166.9(2)°, respectively). The phenyl substituent and the amide fragment are turned almost orthogonal to the C1–C2 endocyclic bond (the C1–C2–C15–O2 and C2–C1–C9–C10 torsion angles are 94.4(2)° and 97.8(3)°, respectively). The orientation of the amide fragment is stabilized additionally by the N5–H···O1 intramolecular hydrogen bond (H···O 2.16 Å N–H···O 131°). The methoxyphenyl substituent is located in ap-conformation relatively to the C2–C15 bond (the C2–C15–N5–C16 torsion angle is −171.2(2)°) and is turned with respect to the amide fragment (the C17–C16–N5–C15 torsion angle is −62.3(3)°).

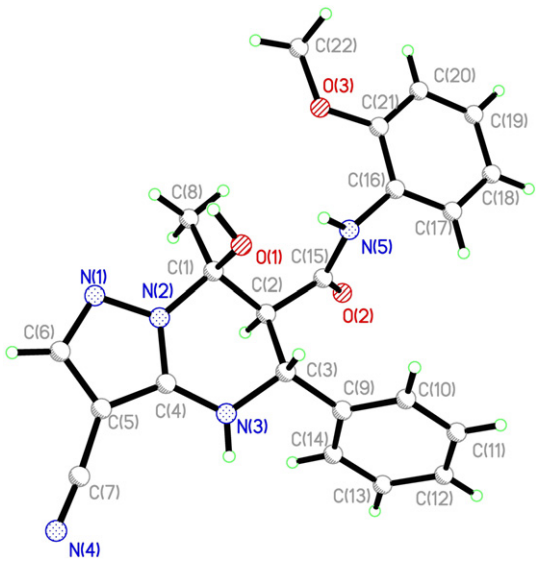



**Fig. 2.** Molecular structure of compound **6d** according to X-ray diffraction data.

## 3. Conclusions

In summary, the direction of the multicomponent reactions between aminoazoles, aldehydes, and acetoacetamides depends on the temperature regime and structure of the starting materials, which allows controlling chemoselectivity. Thus, three-component heterocyclizations involving 3-amino-1,2,4-triazoles or 4-substututed 5-aminopyrazoles can proceed under kinetic control (ultrasonication at room temperature) yielding 4,5,6,7-tetrahydrozolo[1,5-*a*]pyrimidine-6-carboxamides. Under thermodynamic control (at reflux in an appropriate solvent) 5-aminopyrazole having in the fourth position electron-withdrawing substituents (CN, $CO_2CH_3$, $CONH_2$) gives 4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxamides while in the case of methyl or aryl substituents heterocycles of this type are not formed. Direction of the treatments involving 3-substituted 5-aminopyrazoles under reflux depends on the structure both of aminoazoles and aldehydes, which allows to synthesize either pyrazolopyridine or pyrazolopyrimidine heterocyclic systems. The same treatments under ultrasonication at room temperature yields no heterocyclic compound but only corresponding azomethines.

## 4. Experimental part

### 4.1. General

The 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 $^{13}C$) and at 200 MHz (50 MHz for $^{13}C$) with a Varian Unity Plus-400 and Varian Mercury VX-200 spectrometers. The MS spectra were measured on a GC–MS Varian 1200L (ionizing voltage 70 eV) instrument. Elemental analysis was realized on EuroVector EA-3000. Analytical samples of the compounds were obtained by their recrystallization from ethanol and further drying in vacuum at room temperature.

Sonication was carried out with the help of standard ultrasonic bath producing irradiation at 44.2 kHz. Microwave experiments were performed using the Emrys™ Creator EXP from Biotage AB (Uppsala, Sweden) possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz.

The syntheses of 3-amino-5-alkylthio-1,2,4-triazoles **1a**,**b**,[13a,b] of 5-aminopyrazoles **1c**,**d**,[13c,d] **1j**–**n**,[13e] and of acetoacetamides **2a**–**d**[13f] were carried out according to known methods. Solvents, other aminoazoles, and aromatic aldehydes were commercially available and used without additional purification.

### 4.2. X-ray diffraction data

The colorless crystals of **6d** ($C_{22}H_{21}N_5O_3$) are monoclinic. At 293 K $a$=11.805(1), $b$=8.380(1), $c$=19.578(3) Å, $\beta$=91.75(1)°, $V$=1935.9(5) Å$^3$, $M_r$=403.44, $Z$=4, space group $P2_1/n$, $d_{calcd}$=1.384 g/cm$^3$, $\mu$(Mo Kα)=0.095 mm$^{-1}$, $F$(000)=848. Intensities of 12,636 reflections (3392 independent, $R_{int}$=0.110) were measured on the 'Xcalibur-3' diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scanning, $2\theta_{max}$=50°). The structure was solved by direct method using SHELXTL package.[14] Positions of the hydrogen atoms were located from electron density difference maps and refined by 'riding' model with $U_{iso}=nU_{eq}$ of the carrier atom ($n$=1.5 for methyl and hydroxy 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 3364 reflections was converged to

*w*R2=0.037 (*R*1=0.033 for 1108 reflections with $F>4\sigma(F)$, *S*=0.515). The final atomic coordinates, and crystallographic data for molecule **6d** have been deposited to 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 818957.

### 4.3. General procedure for the ultrasonic promoted synthesis of 2-alkylthio-*N*,5-diaryl-7-hydroxy-7-methyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxamides 4a–g

A mixture of aminoazole **1a**,**b** (1 mmol), acetoacetamide **2a**–**c** (1 mmol), and aromatic aldehyde **3a**–**e** (1 mmol) in 10 mL of ethanol was ultrasonicated at room temperature for 90 min in a round-bottom flask equipped with a condenser. The reaction mixture was allowed to stand up to 12 h at room temperature and then was filtered out to give the solid compounds **4a**–**g**, which were then washed with ethanol and air dried. Reaction products were obtained in high purity and did not require further purification by recrystallization.

*4.3.1. 5-(4-Ethylphenyl)-2-(ethylthio)-7-hydroxy-7-methyl-N-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**4a**).* Yield 371 mg (85%) of colorless prisms, mp 177–178 °C. [Found: C, 63.2; H, 6.2; N, 16.0. $C_{23}H_{27}N_5O_2S$ requires C, 63.13; H, 6.22; N, 16.01%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.09 (3H, t, *J* 7.1 Hz, C$H_3$), 1.28 (3H, t, *J* 7.3 Hz, C$H_3$), 1.75 (3H, s, C$H_3$), 2.54 (2H, q, *J* 7.1 Hz, C$H_2$), 2.97 (2H, q, *J* 7.3 Hz, SC$H_2$), 3.08 (1H, d, *J* 11.4 Hz, 6-C*H*), 4.98 (1H, d, *J* 11.4 Hz, 5-C*H*), 6.69 (1H, s, 4-N*H*), 6.99–7.46 (9H, m, ArH), 7.68 (1H, s, O*H*), 9.69 (1H, s, CON*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 15.1, 15.3, 26.3, 28.0, 30.7, 59.8, 113.6, 113.8, 115.6, 119.0, 119.4, 123.7, 128.4, 128.6, 128.7, 128.8, 130.0, 137.0, 138.9, 139.5, 146.7, 165.0, 165.7; MS (EI, 70 eV): *m*/*z* (%)=437 (1.0), 301 (3.5), 261 (18.8), 260 (85.5), 231 (20.3), 227 (28.2), 177 (48.7), 159 (17.5), 132 (13.7), 117 (12.6), 93 (99.9), 77 (17.2), 65 (27.8), 43 (33.7).

*4.3.2. 5-(4-Chlorophenyl)-2-(ethylthio)-7-hydroxy-7-methyl-N-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**4b**).* Yield 244 mg (55%) of colorless prisms, mp 179–180 °C. [Found: C, 56.8; H, 5.0; N, 15.8. $C_{21}H_{22}ClN_5O_2S$ requires C, 56.81; H, 4.99; N, 15.77%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.28 (3H, t, *J* 7.1 Hz, C$H_3$), 1.76 (3H, s, C$H_3$), 2.98 (2H, q, *J* 7.1 Hz, SC$H_2$), 3.08 (1H, d, *J* 11.4 Hz, 6-C*H*), 5.00 (1H, d, *J* 11.4 Hz, 5-C*H*), 6.78 (1H, s, 4-N*H*), 6.99–7.54 (9H, m, ArH), 7.78 (1H, s, O*H*), 9.72 (1H, s, CON*H*); MS (EI, 70 eV): *m*/*z* (%)=443 (1.4) [$M^+$], 267 (17.2), 266 (65.8), 265 (44.5), 235 (13.8), 234 (7.5), 233 (56.5), 177 (20.0), 173 (19.7), 167 (30.7), 166 (8.9), 165 (63.1), 139 (8.5), 138 (24.8), 137 (16.6), 77 (36.1), 43 (99.9), 42 (11.3).

*4.3.3. 2-(Benzylthio)-7-hydroxy-7-methyl-5-(4-methylphenyl)-N-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**4c**).* Yield 267 mg (55%) of colorless prisms, mp 180–181 °C. [Found: C, 66.8; H, 5.6; N, 14.4. $C_{27}H_{27}N_5O_2S$ requires C, 66.78; H, 5.60; N, 14.42%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.76 (3H, s, C$H_3$), 2.22 (3H, s, C$H_3$), 3.08 (1H, d, *J* 11.4 Hz, 6-C*H*), 4.18 (H, d, *J* 13.0 Hz, C*H*), 4.22 (H, d, *J* 13.0 Hz, C*H*), 4.96 (1H, d, *J* 11.4 Hz, 5-C*H*), 6.71 (1H, s, 4-N*H*), 6.96–7.41 (14H, m, ArH), 7.71 (1H, s, O*H*), 9.70 (1H, s, CON*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 21.3, 25.8, 35.7, 53.9, 58.4, 82.3, 120.7, 124.4, 127.7, 128.7, 129.0, 129.2, 129.3, 129.5, 137.1, 137.8, 138.8, 139.0, 154.2, 156.9, 167.1; MS (EI, 70 eV): *m*/*z* (%)=485 (1.1) [$M^+$], 399 (1.9), 309 (33.3), 308 (99.9), 275 (33.6), 177 (65.1), 145 (27.7), 105 (16.3), 93 (30.0), 91 (20.7), 77 (23.7), 43 (29.5).

*4.3.4. 2-(Benzylthio)-5-(4-ethylphenyl)-7-hydroxy-N-(2-methoxyphenyl)-**7**-methyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**4d**).* Yield 450 mg (85%) of colorless prisms, mp 163–165 °C. [Found: C, 65.8; H, 5.9; N, 13.2. $C_{29}H_{31}N_5O_3S$ requires C, 65.76; H, 5.90; N, 13.22%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.12 (3H, t, *J* 7.1 Hz, C$H_3$), 1.79 (3H, s, C$H_3$), 2.54 (2H, q, *J* 7.1 Hz, C$H_2$), 3.25 (1H, d, *J* 11.4 Hz, 6-C*H*), 3.75 (3H, s, C$H_3$O), 4.20 (1H, d, *J* 13.0 Hz, C*H*), 4.25 (1H, d, *J* 13.0 Hz, C*H*), 4.85 (1H, d, *J* 11.4 Hz, 5-C*H*), 6.98 (1H, s, 4-N*H*), 6.79–7.52 (13H, m, ArH), 7.76 (1H, s, O*H*), 9.28 (1H, s, CON*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 15.4, 24.4, 27.7, 34.6, 53.5, 55.7, 57.6, 81.1, 111.1, 120.0, 121.6, 122.3, 124.4, 126.5, 126.9, 127.3, 128.2, 128.7, 136.3, 138.1, 143.3, 149.4, 153.3, 155.9, 166.1; MS (EI, 70 eV): *m*/*z* (%)=529 (1.1) [$M^+$], 322 (99.9), 323 (56.2), 294 (26.6), 289 (31.6), 207 (37.0), 149 (27.2), 123 (97.1), 108 (87.4), 91 (71.9).

*4.3.5. 2-(Benzylthio)-5-(4-bromophenyl)-7-hydroxy-N-(2-methoxyphenyl)-7-methyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**4e**).* Yield 406 mg (70%) of colorless prisms, mp 177–178 °C. [Found: C, 55.8; H, 4.5; N, 12.0. $C_{27}H_{26}BrN_5O_3S$ requires C, 55.87; H, 4.51; N, 12.06%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.79 (3H, s, C$H_3$), 3.26 (1H, d, *J* 11.7 Hz, 6-C*H*), 3.75 (3H, s, OC$H_3$), 4.23 (1H, d, *J* 13.0 Hz, C*H*), 4.29 (1H, d, *J* 13.0 Hz, C*H*), 4.88 (1H, d, *J* 11.7 Hz, 5-C*H*), 6.99 (1H, s, 4-N*H*), 6.81–7.52 (13H, m, ArH), 7.84 (1H, s, O*H*), 9.31 (1H, s, CON*H*); MS (EI, 70 eV): *m*/*z* (%)=580 (1.0) [$M^+$], 561 (2.4), 376 (11.8), 375 (42.8), 374 (99.9), 254 (10.5), 253 (55.4), 252 (13.5), 251 (55.4), 196 (16.4), 195 (10.0), 194 (29.5), 191 (12.2), 190 (78.8), 134 (16.5), 131 (31.3), 102 (35.6), 91 (58.2), 65 (42.4), 43 (43.4).

*4.3.6. 2-(Benzylthio)-7-hydroxy-N-(2-methoxyphenyl)-7-methyl-5-phenyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**4f**).* Yield 430 mg (86%) of colorless prisms, mp 177–178 °C. [Found: C, 64.6; H, 5.4; N, 13.9. $C_{27}H_{27}N_5O_3S$ requires C, 64.65; H, 5.43; N, 13.96%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.80 (3H, s, C$H_3$), 3.27 (1H, d, *J* 11.4 Hz, 6-C*H*), 3.75 (3H, s, C$H_3$O), 4.22 (H, d, *J* 12.0 Hz, C*H*), 4.30 (H, d, *J* 12.0 Hz, C*H*), 4.89 (1H, d, *J* 11.4 Hz, 5-C*H*), 6.98 (1H, s, 4-N*H*), 6.78–7.50 (14H, m, ArH), 7.81 (1H, s, O*H*), 9.31 (1H, s, CON*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 25.3, 35.7, 54.9, 56.8, 58.8, 82.1, 112.3, 121.0, 122.5, 125.3, 127.7, 128.7, 128.8, 129.0, 129.5, 139.0, 139.8, 150.5, 154.2, 156.9, 167.0; MS (EI, 70 eV): *m*/*z* (%)=501 (1.0) [$M^+$], 294 (81.2), 261 (47.1), 207 (38.0), 173 (16.8), 149 (41.3), 131 (11.6), 123 (56.8), 108 (74.1), 91 (99.9), 43 (13.0).

*4.3.7. 2-(Benzylthio)-5-(4-ethylphenyl)-7-hydroxy-N-(4-methoxyphenyl)-7-methyl-4,5,6,7-tetrahydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**4g**).* Yield 344 mg (65%) of colorless prisms, mp 162–164 °C. [Found: C, 65.7; H, 5.9; N, 13.2. $C_{29}H_{31}N_5O_3S$ requires C, 65.76; H, 5.90; N, 13.22%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.13 (3H, t, *J* 7.1 Hz, C$H_3$), 1.79 (3H, s, C$H_3$), 2.56 (2H, q, *J* 7.1 Hz, C$H_2$), 3.25 (1H, d, *J* 11.4 Hz, 6-C*H*), 3.75 (3H, s, C$H_3$O), 4.23 (1H, d, *J* 13.4 Hz, C*H*), 4.29 (1H, d, *J* 13.4 Hz, C*H*), 4.85 (1H, d, *J* 11.4 Hz, 5-C*H*), 6.76–7.51 (13H, m, ArH), 6.98 (1H, s, 4-N*H*), 7.74 (1H, s, O*H*), 9.27 (1H, s, CON*H*); MS (EI, 70 eV): *m*/*z* (%)=529 (1.0) [$M^+$], 323 (7.1), 322 (25.0), 289 (18.0), 207 (18.5), 159 (17.0), 123 (42.6), 108 (99.9), 91 (78.7), 65 (18.3), 43 (28.7).

### 4.4. General procedure for the synthesis 2-alkylthio-*N*,7-diaryl-5-methyl-4,7-dihydro[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxamide 5a–g

A mixture of aminoazole **1a**,**b** (1 mmol), acetoacetamide **2a**–**c** (1 mmol), and aromatic aldehyde **3a**–**e** (1 mmol) in 0.1 mL of DMF was heated to reflux for 10 min. Then after cooling acetone (10 mL) was added and the precipitate formed was filtered out to give the solid compounds **5a**–**g**, which were washed with acetone and air dried.

Microwave-assisted synthesis of compounds **5a**–**g** was carried out according to the earlier described procedure.[8d]

*4.4.1. 7-(4-Ethylphenyl)-2-(ethylthio)-5-methyl-N-phenyl-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**5a**).* Yield 378 mg (90%) of colorless prisms, mp >300 °C. [Found: C, 65.9; H, 6.0; N, 16.7. $C_{23}H_{25}N_5OS$ requires C, 65.85; H, 6.01; N, 16.69%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.10 (3H, t, *J* 7.1 Hz, C$H_3$), 1.22 (3H, t, *J* 7.5 Hz, C$H_3$), 2.14 (3H, s, C$H_3$), 2.54 (2H, q, *J* 7.1 Hz, C$H_2$), 2.94 (2H, q, *J* 7.5 Hz, SC$H_2$), 6.42 (1H, s, 7-C*H*), 6.95–7.51 (9H, m, ArH), 9.71 (1H, s, CON*H*), 10.22 (1H, s, N*H*). $\delta_C$ (50 MHz, DMSO-$d_6$) 15.7, 15.8, 17.9, 26.0, 28.4, 60.8, 105.0, 120.5, 124.0, 127.6, 128.5, 129.1, 136.8, 138.7, 139.7, 144.3, 149.4, 158.4, 165.5. MS (EI, 70 eV): *m*/*z* (%)=419 (10.0) [$M^+$], 358 (15.6), 327 (46.7), 183 (10.5), 161 (21.7), 154 (12.1), 141 (32.4), 132 (18.6), 128 (25.9), 120 (36.5), 119 (35.0), 103 (21.3), 93 (99.5), 92 (99.9), 91 (70.1), 77 (63.6), 67 (37.1), 61 (35.6).

*4.4.2. 7-(4-Chlorophenyl)-2-(ethylthio)-5-methyl-N-phenyl-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**5b**).* Yield 341 mg (80%) of colorless prisms, mp >300 °C. [Found: C, 59.2; H, 4.7; N, 16.4. $C_{21}H_{20}ClN_5OS$ requires C, 59.22; H, 4.73; N, 16.44%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.21 (3H, t, *J* 7.5 Hz, C$H_3$), 2.14 (3H, s, C$H_3$), 2.93 (2H, q, *J* 7.5 Hz, SC$H_2$), 6.45 (1H, s, 7-C*H*), 6.96–7.49 (9H, m, ArH), 9.73 (1H, s, CON*H*), 10.32 (1H, s, N*H*); MS (EI, 70 eV): *m*/*z* (%)=425 (25.0) [$M^+$], 335 (22.9), 334 (12.1), 333 (51.7), 273 (16.9), 165 (21.0), 163 (11.2), 129 (18.0), 128 (62.2), 127 (98.3), 102 (11.0), 101 (14.8), 93 (38.0), 92 (22.7), 85 (34.4), 67 (99.9), 66 (44.1), 65 (57.9), 43 (13.0).

*4.4.3. 2-(Benzylthio)-5-methyl-7-(4-methylphenyl)-N-phenyl-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**5c**).* Yield 397 mg (85%) of colorless prisms, mp 290–292 °C. [Found: C, 69.4; H, 5.4; N, 15.0. $C_{27}H_{25}N_5OS$ requires C, 69.35; H, 5.39; N, 14.98%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.13 (3H, s, C$H_3$), 2.23 (3H, s, C$H_3$), 4.12 (H, d, *J* 13.4 Hz, C*H*), 4.16 (H, d, *J* 13.4 Hz, C*H*), 6.41 (1H, s, 7-C*H*), 6.95–7.51 (14H, m, ArH), 9.73 (1H, s, CON*H*), 10.24 (1H, s, N*H*). MS (EI, 70 eV): *m*/*z* (%)=467 (2.7) [$M^+$], 376 (9.4), 375 (15.9), 344 (12.9), 128 (15.7), 91 (99.9), 90 (9.7).

*4.4.4. 2-(Benzylthio)-7-(4-ethylphenyl)-N-(2-methoxyphenyl)-5-methyl-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**5d**).* Yield 435 mg (85%) of colorless prisms, mp 240–242 °C. [Found: C, 68.1; H, 5.7; N, 13.7. $C_{29}H_{29}N_5O_2S$ requires C, 68.08; H, 5.71; N, 13.69%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.14 (3H, t, *J* 7.3 Hz, C$H_3$), 2.22 (3H, s, C$H_3$), 2.55 (2H, q, *J* 7.3 Hz, C$H_2$), 3.71 (3H, s, OC$H_3$), 4.14 (H, d, *J* 13.4 Hz, C*H*), 4.16 (H, d, *J* 13.4 Hz, C*H*), 6.37 (1H, s, 7-C*H*), 6.81–7.64 (13H, m, ArH), 8.70 (1H, s, CON*H*), 10.29 (1H, s, N*H*); MS (EI, 70 eV): *m*/*z* (%)=511 (22.2) [$M^+$], 363 (12.2), 362 (42.9), 329 (23.3), 271 (10.4), 170 (14.4), 150 (13.1), 149 (99.9), 120 (20.5), 91 (28.1), 51 (12.5).

*4.4.5. 2-(Benzylthio)-7-(4-bromophenyl)-N-(2-methoxyphenyl)-5-methyl-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**5e**).* Yield 478 mg (85%) of colorless prisms, mp >300 °C. [Found: C, 57.6; H, 4.3; N, 12.4. $C_{27}H_{24}BrN_5O_2S$ requires C, 57.65; H, 4.30; N, 12.45%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.13 (3H, s, C$H_3$), 3.67 (3H, s, C$H_3$O), 4.12 (1H, d, *J* 13.2 Hz, C*H*), 4.20 (1H, d, *J* 13.2 Hz, C*H*), 6.42 (1H, s, 7-C*H*), 6.79–7.54 (13H, m, ArH), 9.62 (1H, s, CON*H*), 10.30 (1H, s, N*H*); MS (EI, 70 eV): *m*/*z* (%)=562 (10.5) [$M^+$], 414 (18.2), 149 (24.3), 124 (14.8), 123 (53.8), 91 (99.9).

*4.4.6. 2-(Benzylthio)-N-(2-methoxyphenyl)-5-methyl-7-phenyl-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**5f**).* Yield 435 mg (90%) of colorless prisms, mp 247–248 °C. [Found: C, 67.0; H, 5.2; N, 14.5. $C_{27}H_{25}N_5O_2S$ requires C, 67.06; H, 5.21; N, 14.48%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.23 (3H, s, C$H_3$), 3.71 (3H, s, C$H_3$O), 4.14 (1H, d, *J* 13.2 Hz, C*H*), 4.25 (1H, d, *J* 13.2 Hz, C*H*), 6.42 (1H, s, 7-C*H*), 6.81–7.59 (14H, m, ArH), 8.74 (1H, s, CON*H*), 10.31 (1H, s, N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 18.1, 35.8, 56.5, 61.2, 104.2, 112.1, 120.9, 123.1, 125.3, 127.6, 128.0, 128.9, 129.2, 129.4, 138.4, 138.8, 141.1, 149.2, 151.0, 158.2, 165.1; MS (EI, 70 eV): *m*/*z* (%)=483 (10.0), 392 (10.3), 361 (47.7), 360 (15.2), 334 (23.7), 241 (11.4), 149 (14.9), 123 (98.3), 122 (15.0), 91 (99.9).

*4.4.7. 2-(Benzylthio)-7-(4-ethylphenyl)-N-(4-methoxyphenyl)-5-methyl-4,7-dihydro[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (**5g**).* Yield 460 mg (90%) of colorless prisms, mp 260–262 °C. [Found: C, 68.1; H, 5.7; N, 13.7. $C_{29}H_{29}N_5O_2S$ requires C, 68.08; H, 5.71; N, 13.69%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.12 (3H, t, *J* 7.3 Hz, C$H_3$), 2.13 (3H, s, C$H_3$), 2.53 (2H, q, *J* 7.3 Hz, C$H_2$), 3.67 (3H, s, C$H_3$O), 4.14 (1H, d, *J* 13.4 Hz, C*H*), 4.16 (1H, d, *J* 13.4 Hz, C*H*), 6.42 (1H, s, 7-C*H*), 6.78–7.42 (13H, m, ArH), 9.62 (1H, s, CON*H*), 10.22 (1H, s, NH); $\delta_C$ (50 MHz, DMSO-$d_6$) 15.8, 17.8, 28.4, 35.8, 56.0, 60.9, 105.1, 114.6, 122.2, 127.7, 128.4, 128.9, 129.4, 132.9, 136.3, 138.6, 138.8, 144.3, 149.5, 156.3, 158.1, 165.2; MS (EI, 70 eV): *m*/*z* (%)=511 (4.5) [$M^+$], 389 (21.5), 362 (69.1), 330 (18.9), 329 (79.9), 172 (12.7), 170 (27.4), 157 (14.2), 149 (34.9), 142 (20.9), 141 (37.4), 128 (24.9), 115 (46.3), 91 (99.9), 80 (53.1), 78 (85.0), 65 (40.2), 52 (56.8), 51 (51.9).

### 4.5. General procedure for the synthesis *N*,5-diaryl-7-hydroxy-7-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*] pyrimidine 6a–e

A mixture of aminoazole **1c**–**e** (1 mmol), acetoacetamide **2a**,**b**,**d** (1 mmol), and aromatic aldehyde **3b**,**d**–**g** (1 mmol) in 10 mL of ethanol was ultrasonicated at room temperature for 90 min in a round-bottom flask equipped with a condenser. The reaction mixture was allowed to stand up to 12 h at room temperature and then was filtered out to give the solid compounds **6a**–**e**, which were washed with ethanol and air dried. Reaction products were obtained in high purity and did not require further purification by recrystallization.

*4.5.1. 7-Hydroxy-5-(4-hydroxy-3-methoxyphenyl)-7-methyl-N$^6$-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3,6-dicarboxamide (**6a**).* Yield 371 mg (85%) of colorless prisms, mp 164–165 °C. [Found: C, 60.4; H, 5.3; N, 16.0. $C_{22}H_{23}N_5O_5$ requires C, 60.40; H, 5.30; N, 16.01%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.82 (3H, s, C$H_3$), 3.19 (1H, d, *J* 11.7 Hz, 6-C*H*), 3.69 (3H, s, C$H_3$O), 4.94 (1H, d, *J* 11.7 Hz, 5-C*H*), 6.37 (1H, s, 4-N*H*), 6.58 (1H, s, O*H*), 6.68–7.39 (8H, m, ArH), 7.36 (2H, br s, CON$H_2$), 7.71 (1H, s, 2-CH), 8.96 (1H, s, N*H*), 9.74 (1H, s, O*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 26.8, 53.0, 56.6, 58.2, 82.5, 96.4, 112.7, 116.9, 120.1, 120.7, 124.1, 126.0, 129.3, 130.9, 140.4, 147.4, 150.3, 164.4, 166.5; MS (EI, 70 eV): *m*/*z* (%)=437 (10.1) [$M^+$], 311 (1.2), 310 (2.8), 177 (24.2), 126 (21.7), 119 (38.9), 95 (43.1), 93 (99.9), 65 (27.2).

*4.5.2. 5-(3,4-Dimethoxyphenyl)-N$^6$-(2,4-dimethylpheny)l-7-hydroxy-7-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3,6-dicarboxamide (**6b**).* Yield 408 mg (85%) of colorless prisms, mp 195–196 °C. [Found: C, 62.6; H, 6.1; N, 14.6. $C_{25}H_{29}N_5O_5$ requires C, 62.62; H, 6.10; N, 14.60%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.78 (3H, s, C$H_3$), 1.89 (3H, s, C$H_3$), 2.18 (3H, s, C$H_3$), 3.25 (1H, d, *J* 11.5 Hz, 6-C*H*), 3.72 (6H, s, 2C$H_3$O), 4.91 (1H, d, *J* 11.5 Hz, 5-C*H*), 6.43 (1H, s, 4-N*H*), 6.63 (1H, s, O*H*), 6.80–7.08 (6H, m, ArH), 7.25 (2H, br s, CON$H_2$), 7.72 (1H, s, 2-C*H*), 9.27 (1H, s, N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 17.8, 21.0, 25.5, 54.0, 56.6, 57.4, 82.5, 96.5, 113.2, 121.5, 125.8, 127.0, 131.4, 132.6, 133.6, 135.5, 138.2, 147.4, 149.8, 150.1, 166.5, 167.9; MS (EI, 70 eV): *m*/*z* (%)=479 (8.8) [$M^+$], 419 (1.0), 203 (9.5), 202 (85.7), 200 (78.9), 82 (25.2), 81 (31.0), 77 (53.6), 76 (99.3), 51 (99.9), 45 (49.0).

*4.5.3. 5-(4-Bromophenyl)-3-cyano-7-hydroxy-N-(2-methoxyphenyl)-7-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**6c**).* Yield 410 mg (85%) of colorless prisms, mp 215–216 °C. [Found: C, 54.8; H, 4.2; N, 14.5. $C_{22}H_{20}BrN_5O_3$ requires C, 54.78; H, 4.18; N, 14.52%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.84 (3H, s, C$H_3$), 3.33 (1H, d, *J* 11.7 Hz, 6-C*H*), 3.75 (3H, s, C$H_3$O), 4.88 (1H, d, *J* 11.7 Hz, 5-C*H*),

6.81–7.54 (8H, m, ArH), 7.00 (1H, s, 4-NH), 7.26 (1H, s, OH), 7.67 (1H, s, 2-CH), 8.87 (1H, s, NH); MS (EI, 70 eV): *m*/*z* (%)=482 (10.1) [$M^+$], 373 (2.8), 275 (15.6), 274 (34.9), 211 (23.5), 209 (32.4), 207 (62.3), 182 (12.1), 149 (99.9), 120 (20.7), 65 (54.0).

*4.5.4. 3-Cyano-7-hydroxy-N-(2-methoxyphenyl)-7-methyl-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**6d**).* Yield 343 mg (85%) of colorless prisms, mp 200–202 °C. [Found: C, 65.5; H, 5.2; N, 17.3. $C_{22}H_{21}N_5O_3$ requires C, 65.50; H, 5.25; N, 17.36%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.84 (3H, s, $CH_3$), 3.31 (1H, d, *J* 11.5 Hz, 6-CH), 3.75 (3H, s, $CH_3O$), 4.88 (1H, d, *J* 11.5 Hz, 5-CH), 6.74–7.50 (9H, m, ArH), 7.00 (1H, s, 4-NH), 7.26 (1H, s, OH), 7.66 (1H, s, 2-CH), 9.28 (1H, s, NH); $\delta_C$ (50 MHz, DMSO-$d_6$) 27.1, 54.7, 56.6, 56.8, 71.8, 82.6, 112.6, 121.0, 125.4, 128.7, 128.9, 129.3, 130.4, 130.8, 139.6, 141.2, 149.2, 166.9; MS (EI, 70 eV): *m*/*z* (%)=403 (10.1) [$M^+$], 294 (1.4), 196 (14.7), 131 (14.1), 123 (99.9), 120 (11.0), 108 (30.3), 80 (33.6), 78 (17.8), 64 (26.5).

*4.5.5. Methyl-5-(4-chlorophenyl)-7-hydroxy-6-{[(2-methoxyphenyl) amino]carbonyl}-7-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxylate (**6e**).* Yield 245 mg (52%) of colorless prisms, mp 207–209 °C. [Found: C, 58.6; H, 4.9; N, 11.9. $C_{23}H_{23}ClN_4O_5$ requires C, 58.66; H, 4.92; N, 11.90%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.82 (3H, s, $CH_3$), 3.30 (1H, d, *J* 11.7 Hz, 6-CH), 3.73 (3H, s, $CH_3O$), 3.75 (3H, s, $CH_3O$), 4.86 (1H, d, *J* 11.7 Hz, 5-CH), 6.83–7.55 (8H, m, ArH), 7.01 (1H, s, 4-NH), 7.27 (1H, s, OH), 7.67 (1H, s, 2-CH), 8.89 (1H, s, NH); MS (EI, 70 eV): *m*/*z* (%)=470 (1.2) [$M^+$], 469 (2.4), 330 (14.5), 261 (48.5), 209 (32.5), 150 (28.9), 139 (99.9), 111 (48.9), 59 (23.6).

### 4.6. General procedure for the synthesis of 5-methyl-*N*,7-diaryl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxamide 7a–e

A mixture of aminoazole **1c–e** (1 mmol), acetoacetamide **2a**,**b**,**d** (1 mmol), and aromatic aldehyde **3b**,**d–g** (1 mmol) in 0.1 mL of DMF was heated to reflux for 10 min. After cooling acetone (10 mL) was added. The precipitate formed was filtered out to give the solid dihydropyrimidines **7a–e**, which were washed with acetone and air dried.

*4.6.1. 7-(4-Hydroxy-3-methoxyphenyl)-5-methyl-$N^6$-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-3,6-dicarboxamide (**7a**).* Yield 230 mg (55%) of colorless prisms, mp 284–285 °C. [Found: C, 63.0; H, 5.0; N, 16.6. $C_{22}H_{21}N_5O_4$ requires C, 63.00; H, 5.05; N, 16.70%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.23 (3H, s, $CH_3$), 3.61 (3H, s, $CH_3O$), 6.36 (1H, s, 7-CH), 6.51–7.54 (8H, m, ArH), 7.01 (1H, s, $CONH_2$), 7.52 (1H, s, $CONH_2$), 7.78 (1H, s, 2-CH), 8.57 (1H, s, NH), 8.96 (1H, s, OH), 9.71 (1H, s, 4-NH); $\delta_C$ (50 MHz, DMSO-$d_6$) 18.2, 56.7, 60.4, 98.5, 105.1, 112.8, 116.2, 120.4, 120.6, 123.9, 129.1, 133.2, 135.9, 138.9, 139.8, 141.0, 147.3, 148.1, 165.6, 165.9; MS (EI, 70 eV): *m*/*z* (%)=419 (24.9) [$M^+$], 327 (99.9), 310 (32.9), 296 (2.5), 160 (31.4), 119 (16.0), 56 (9.6).

*4.6.2. 7-(3,4-Dimethoxyphenyl)-$N^6$-(2,4-dimethylphenyl)-5-methyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-3,6-dicarboxamide (**7b**).* Yield 300 mg (65%) of colorless prisms, mp 287–288 °C. [Found: C, 65.1; H, 5.9; N, 15.2. $C_{25}H_{27}N_5O_4$ requires C, 65.06; H, 5.90; N, 15.17%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.83 (3H, s, $CH_3$), 1.89 (3H, s, $CH_3$), 2.30 (3H, s, $CH_3$), 3.65 (3H, s, $CH_3O$), 3.69 (3H, s, $CH_3O$), 6.30 (1H, s, 7-CH), 6.73–7.74 (6H, m, ArH), 7.01 (1H, s, $CONH_2$), 7.44 (1H, s, $CONH_2$), 7.76 (1H, s, 2-CH), 8.58 (1H, s, NH), 8.64 (1H, s, 4-NH); MS (EI, 70 eV): *m*/*z* (%)=461 (1.9) [$M^+$], 412 (16.7), 322 (99.9), 312 (38.6), 258 (28.9), 252 (14.5), 222 (14.4), 158 (46.6), 134 (19.0), 133 (43.3), 132 (64.3), 106 (19.4), 41 (19.6).

*4.6.3. 7-(4-Bromophenyl)-3-cyano-N-(2-methoxyphenyl)-5-methyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**7c**).* Yield 302 mg (65%) of colorless prisms, mp 295–296 °C. [Found: C, 56.9; H, 3.9; N, 15.0. $C_{22}H_{18}BrN_5O_2$ requires C, 56.91; H, 3.91; N, 15.08%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.25 (3H, s, $CH_3$), 3.73 (3H, s, $CH_3O$), 6.44 (1H, s, 7-CH), 6.84–7.58 (8H, m, ArH), 7.82 (1H, s, 2-CH), 8.87 (1H, s, NH), 10.43 (1H, s, 4-NH); $\delta_C$ (50 MHz, DMSO-$d_6$) 17.8, 56.4, 60.6, 73.5, 104.3, 112.1, 114.8, 122.1, 123.5, 125.6, 127.8, 130.1, 132.1, 137.3, 140.6, 142.8, 151.2, 164.9. MS (EI, 70 eV): *m*/*z* (%)=464 (9.9) [$M^+$], 465 (44.0), 343 (22.1), 342 (18.0), 108 (99.9).

*4.6.4. 3-Cyano-N-(2-methoxyphenyl)-5-methyl-7-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**7d**).* Yield 230 mg (60%) of colorless prisms, mp 243–244 °C. [Found: C, 68.5; H, 4.9; N, 18.2. $C_{22}H_{19}N_5O_2$ requires C, 68.54; H, 4.96; N, 18.15%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.26 (3H, s, $CH_3$), 3.72 (3H, s, $CH_3O$), 6.44 (1H, s, 7-CH), 6.79–7.59 (9H, m, ArH), 7.80 (1H, s, 2-CH), 8.81 (1H, s, NH), 10.39 (1H, s, 4-NH); MS (EI, 70 eV): *m*/*z* (%)=385 (7.9) [$M^+$], 221 (12.4), 192 (13.7), 159 (78.5), 158 (45.3), 157 (21.7), 155 (40.8), 133 (25.1), 129 (43.1), 128 (80.6), 127 (99.9), 123 (42.8), 102 (26.0), 94 (25.6), 67 (45.7), 65 (69.5).

*4.6.5. Methyl-7-(4-chlorophenyl)-6-{[(2-methoxyphenyl)amino]carbonyl}-5-methyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxylate (**7e**).* Yield 230 mg (50%) of colorless prisms, mp 230–231 °C. [Found: C, 61.0; H, 4.6; N, 12.4. $C_{23}H_{21}ClN_4O_4$ requires C, 61.00; H, 4.67; N, 12.37%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.32 (3H, s, $CH_3$), 3.73 (6H, s, $2CH_3O$), 6.44 (1H, s, 7-CH), 6.84–7.55 (8H, m, ArH), 7.67 (1H, s, 2-CH), 8.89 (1H, s, NH), 8.96 (1H, s, 4-NH); $\delta_C$ (50 MHz, DMSO-$d_6$) 18.2, 51.3, 56.6, 60.3, 95.8, 104.8, 112.4, 121.0, 121.4, 125.5, 128.0, 129.1, 129.7, 133.6, 137.4, 140.5, 140.9, 141.2, 151.2, 163.3, 165.1. MS (EI, 70 eV): *m*/*z* (%)=452 (21.8) [$M^+$], 454 (7.7), 453 (6.5), 330 (18.5), 300 (39.9), 299 (21.1), 298 (99.9).

### 4.7. General procedure for the synthesis of 7-hydroxy-7-methyl-*N*,5-diaryl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine-6-carboxamides 8a–i

A mixture of aminoazole **1f–i** (1 mmol), acetoacetamides **2a–c** (1 mmol), and aromatic aldehyde **3b–f** (1 mmol) in 10 mL of ethanol was ultrasonicated at room temperature for 90 min in a round-bottom flask equipped with condenser. The reaction mixture was allowed to stand up to 12 h at room temperature and then was filtered to give the solid compounds **8a–i**, which were washed with ethanol and air dried. Reaction products were obtained in high purity and did not require further purification by recrystallization.

*4.7.1. 2-(4-Chlorophenyl)-7-hydroxy-N-(2-methoxyphenyl)-3,7-dimethyl-5-(4-methylphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**8a**).* Yield 440 mg (85%) of colorless prisms, mp 151–152 °C. [Found: C, 67.4; H, 5.6; N, 10.8. $C_{29}H_{29}ClN_4O_3$ requires C, 67.37; H, 5.65; N, 10.84%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.86 (3H, s, $CH_3$), 1.95 (3H, s, $CH_3$), 2.26 (3H, s, $CH_3$), 3.18 (1H, d, *J* 11.4 Hz, 6-CH), 3.78 (3H, s, $CH_3O$), 4.81 (1H, d, *J* 11.4 Hz, 5-CH), 6.37 (1H, s, 4-NH), 6.98 (1H, s, OH), 6.79–7.62 (12H, m, ArH), 9.41 (1H, s, NH); $\delta_C$ (50 MHz, DMSO-$d_6$) 9.0, 21.0, 25.0, 55.0, 55.9, 58.2, 88.5, 95.3, 111.1, 117.2, 120.3, 125.1, 125.5, 127.5, 127.8, 129.1, 129.7, 132.1, 133.3, 136.1, 138.0, 141.1, 146.3, 147.9, 169.0; MS (EI, 70 eV): *m*/*z* (%)=516 (1.1) [$M^+$], 514 (2.1), 316 (2.7), 276 (15.7), 275 (83.2), 274 (99.9), 260 (13.3), 207 (45.6), 172 (10.4), 149 (23.7), 130 (17.1), 123 (41.9), 115 (13.7), 108 (75.2), 104 (12.0), 91 (10.8), 80 (23.5), 77 (15.4), 43 (18.7).

*4.7.2. 5-(4-Bromophenyl)-2-(4-chlorophenyl)-7-hydroxy-N-(2-methoxyphenyl)-3,7-dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**8b**).* Yield 495 mg (85%) of colorless prisms, mp 165–166 °C. [Found: C, 57.8; H, 5.0; N, 9.6.

$C_{28}H_{26}BrClN_4O_3$ requires C, 57.80; H, 4.50; N, 9.63%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.88 (3H, s, C$H_3$), 1.96 (3H, s, C$H_3$), 3.22 (1H, d, *J* 11.7 Hz, 6-C*H*), 3.77 (3H, s, C$H_3$O), 4.85 (1H, d, *J* 11.7 Hz, 5-C*H*), 6.53 (1H, s, 4-N*H*), 7.13 (1H, s, O*H*), 6.82–7.67 (12H, m, ArH), 9.48 (1H, s, N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 8.7, 18.6, 52.3, 56.6, 60.3, 94.1, 101.5, 112.1, 121.0, 122.5, 124.7, 128.9, 129.3, 130.0, 130.8, 131.9, 132.5, 133.8, 136.3, 137.7, 138.3, 139.9, 142.1, 157.8; MS (EI, 70 eV): *m*/*z* (%)=581 (1.1) [$M^+$], 579 (1.2), 414 (7.2), 377 (20.6), 376 (32.7), 375 (94.6), 374 (99.9), 373 (85.9), 372 (70.6), 191 (21.8), 157 (16.3), 138 (13.2), 130 (29.7), 115 (26.6), 102 (9.8).

*4.7.3. 2-(4-Chlorophenyl)-7-hydroxy-N-(2-methoxyphenyl)-3,7-dimethyl-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**8c**).* Yield 435 mg (87%) of colorless prisms, mp 133–134 °C. [Found: C, 66.9; H, 5.4; N, 11.1. $C_{28}H_{27}ClN_4O_3$ requires C, 66.86; H, 5.41; N, 11.14%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.87 (3H, s, C$H_3$), 1.96 (3H, s, C$H_3$), 3.21 (1H, d, *J* 11.2 Hz, 6-C*H*), 3.77 (3H, s, C$H_3$O), 4.85 (1H, d, *J* 11.2 Hz, 5-C*H*), 6.50 (1H, s, 4-N*H*), 7.11 (s, 1H, OH), 6.78–7.65 (m, 13H, ArH), 9.43(9.27) (1H, s, NH); $\delta_C$ (50 MHz, DMSO-$d_6$) 8.9, 25.4, 52.4, 55.1, 59.5, 84.9, 92.3, 111.9, 121.0, 122.1, 125.0, 128.7, 129.0, 129.1, 129.5, 130.6, 132.0, 136.9, 139.6, 140.8, 141.0, 144.1, 149.5, 150.2, 158.8, 166.5, 167.7; MS (EI, 70 eV): *m*/*z* (%)= 502 (1.1) [$M^+$], 500 (1.0), 362 (11.5), 337 (12.9), 336 (56.9), 335 (28.3), 334 (99.9), 297 (15.8), 296 (28.4), 295 (43.4), 294 (40.2), 207 (23.1), 123 (21.0), 108 (16.1), 80 (6.4).

*4.7.4. 5-(4-Chlorophenyl)-7-hydroxy-N-(2-methoxyphenyl)-7-methyl-3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**8d**).* Yield 365 mg (75%) of colorless prisms, mp 177–178 °C. [Found: C, 66.3; H, 5.1; N, 11.4. $C_{27}H_{25}ClN_4O_3$ requires C, 66.32; H, 5.15; N, 11.46%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.88 (3H, s, C$H_3$), 3.27 (1H, d, *J* 11.5 Hz, 6-C*H*), 3.77 (3H, s, C$H_3$O), 4.90 (1H, d, *J* 11.2 Hz, 5-C*H*), 6.69 (1H, s, 4-N*H*), 7.01 (1H, s, O*H*), 6.82–7.61 (8H, m, ArH), 9.44 (1H, s, N*H*); MS (EI, 70 eV): *m*/*z* (%)=487 (1.1) [$M^+$], 485 (1.2), 329 (3.2), 281 (31.7), 280 (20.6), 207 (55.2), 159 (15.8), 149 (32.2), 123 (99.9), 92 (15.1), 89 (25.3), 63 (11.1).

*4.7.5. 5-(4-Bromophenyl)-7-hydroxy-N-(2-methoxyphenyl)-7-methyl-3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**8e**).* Yield 425 mg (80%) of colorless prisms, mp 174–175 °C. [Found: C, 60.8; H, 4.7; N, 10.5. $C_{27}H_{25}BrN_4O_3$ requires C, 60.80; H, 4.72; N, 10.50%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.87 (3H, s, C$H_3$), 3.25 (1H, d, *J* 11.7 Hz, 6-C*H*), 3.77 (3H, s, C$H_3$O), 4.87 (1H, d, *J* 11.7 Hz, 5-C*H*), 6.69 (1H, s, 4-N*H*), 6.82–7.61 (13H, m, ArH), 9.44 (1H, s, N*H*); MS (EI, 70 eV): *m*/*z* (%)=533 (1.1) [$M^+$], 366 (2.6), 328 (10.0), 327 (28.5), 326 (19.8), 325 (19.4), 324 (13.0), 211 (10.8), 209 (10.0), 207 (62.0), 170 (99.9), 149 (22.2), 123 (44.6), 108 (70.2), 89 (15.7), 80 (13.6), 43 (18.8).

*4.7.6. 7-Hydroxy-N-(4-methoxyphenyl)-7-methyl-3,5-diphenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**8f**).* Yield 317 mg (70%) of colorless prisms, mp 153–154 °C. [Found: C, 71.3; H, 5.8; N, 12.3. $C_{27}H_{26}N_4O_3$ requires C, 71.35; H, 5.77; N, 12.33%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.84 (3H, s, C$H_3$), 3.12 (1H, d, *J* 11.5 Hz, 6-C*H*), 3.66 (3H, s, C$H_3$O), 4.97 (1H, d, *J* 11.5 Hz, 5-C*H*), 6.49 (1H, s, 4-N*H*), 6.62 (1H, s, O*H*), 6.76–7.59 (14H, m, ArH), 9.59 (1H, s, NH); $\delta_C$ (50 MHz, DMSO-$d_6$) 26.0, 54.7, 56.0, 58.2, 82.4, 102.3, 114.6, 122.0, 122.7, 125.0, 125.8, 128.6, 128.8, 129.2, 131.7, 134.3, 138.0, 141.4, 142.0, 156.7, 167.9; MS (EI, 70 eV): *m*/*z* (%)=453 (1.1) [$M^+$], 294 (7.3), 207 (46.0), 171 (12.9), 170 (99.9), 149 (15.9), 143 (13.5), 142 (12.6), 170 (99.9), 149 (15.9), 143 (13.5), 108 (85.7), 80 (13.3), 77 (16.1), 51 (14.8), 43 (15.9).

*4.7.7. 3-(4-Chlorophenyl)-7-hydroxy-N-(2-methoxyphenyl)-7-methyl-5-(4-methylphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**8g**).* Yield 380 mg (75%) of colorless prisms, mp 170–171 °C. [Found: C, 66.8; H, 5.4; N, 11.1. $C_{28}H_{27}ClN_4O_3$ requires C, 66.86; H, 5.41; N, 11.14%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.86 (3H, s, C$H_3$), 2.26 (3H, s, C$H_3$), 3.24 (1H, d, *J* 11.4 Hz, 6-C*H*), 3.78 (3H, s, C$H_3$O), 4.84 (1H, d, *J* 11.4 Hz, 5-C*H*), 6.63 (1H, s, 4-N*H*), 6.80–7.62 (12H, m, ArH), 9.38 (1H, s, N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 21.8, 26.9, 30.6, 52.3, 56.8, 88.8, 112.4, 112.7, 121.1, 122.4, 125.2, 127.8, 129.0, 129.1, 129.3, 130.0, 130.2, 130.6, 132.7, 139.6, 141.0, 142.3, 150.5, 160.2, 165.7; MS (EI, 70 eV): *m*/*z* (%)=502 (1.1) [$M^+$], 500 (1.0), 297 (21.9), 296 (22.6), 295 (65.7), 294 (30.2), 207 (67.6), 206 (29.9), 205 (13.2), 204 (99.9), 149 (29.5), 123 (55.5), 108 (65.0), 80 (15.5).

*4.7.8. 5-(4-Bromophenyl)-3-(4-chlorophenyl)-7-hydroxy-N-(2-methoxyphenyl)-7-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**8h**).* Yield 425 mg (75%) of colorless prisms, mp 167–168 °C. [Found: C, 57.1; H, 4.2; N, 9.9. $C_{27}H_{24}BrClN_4O_3$ requires C, 57.11; H, 4.26; N, 9.87%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.87 (3H, s, C$H_3$), 3.25 (1H, d, *J* 11.7 Hz, 6-C*H*), 3.77 (3H, s, C$H_3$O), 4.87 (1H, d, *J* 11.7 Hz, 5-C*H*), 6.75 (1H, s, 4-N*H*), 6.82–7.63 (12H, m, ArH), 9.43 (1H, s, N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 25.5, 54.7, 56.8, 58.9, 82.2, 101.4, 112.3, 121.0, 121.6, 122.5, 125.4, 127.4, 129.1, 129.3, 131.1, 131.4, 132.4, 133.1, 138.1, 140.5, 141.9, 150.5, 167.4; MS (EI, 70 eV): *m*/*z* (%)=567 (1.1) [$M^+$], 400 (2.2), 362 (8.0), 361 (6.2), 360 (9.5), 359 (13.6), 207 (43.3), 206 (18.2), 204 (52.8), 193 (23.1), 149 (35.4), 123 (99.9), 122 (31.3), 102 (11.3), 92 (11.0), 89 (17.4), 80 (13.3), 43 (34.5).

*4.7.9. 3-(4-Fluorophenyl)-7-hydroxy-5-(4-hydroxy-3-methoxy phenyl)-N-(2-methoxyphenyl)-7-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**8i**).* Yield 415 mg (80%) of colorless prisms, mp 136–137 °C. [Found: C, 67.9; H, 5.2; N, 10.8. $C_{28}H_{27}FN_4O_3$ requires C, 67.86; H, 5.25; N, 10.80%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.82 (3H, s, C$H_3$), 3.08 (1H, d, *J* 11.4 Hz, 6-C*H*), 3.68 (3H, s, C$H_3$O), 3.69 (3H, s, C$H_3$O), 4.87 (1H, d, *J* 11.4 Hz, 5-C*H*), 6.44 (1H, s, 4-N*H*), 6.48–7.46 (11H, m, ArH), 7.56 (1H, s, O*H*), 8.85 (1H, s, O*H*), 9.59 (1H, s, N*H*); MS (EI, 70 eV): *m*/*z* (%)=518 (1.5) [$M^+$], 519 (3.5), 517(1.6), 312 (13.3), 311 (90.3), 310 (32.4), 295 (12.7), 188 (99.9), 161 (12.6), 120 (10.3).

*4.7.10. 2-(4-Chlorophenyl)-3,5-dimethylpyrazolo[1,5-a]pyrimidin-7(4H)-one (**11a**).* Yield 110 mg (40%) of colorless prisms, mp >300 °C. [Found: C, 61.4; H, 4.4; N, 15.4. $C_{14}H_{12}ClN_3O$ requires C, 61.43; H, 4.42; N, 15.35%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.25 (3H, s, C$H_3$), 2.31 (3H, s, C$H_3$), 5.55 (1H, s, 6-C*H*), 7.52–7.77 (4H, m, ArH), 11.90 (1H, s, 4-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 8.5, 20.1, 95.5, 97.0, 125.9, 126.3, 128.5, 133.0, 133.4, 147.5, 154.1, 155.0; MS (EI, 70 eV): *m*/*z* (%)=273 (88.8) [$M^+$], 275 (29.6), 204 (99.9), 206 (33.3), 162 (22.2).

*4.7.11. 2-[3-(4-Fluorophenyl)-7-(4-hydroxy-3-methoxyphenyl)-pyrazolo[1,5-a]pyrimidin-5-yl]-N-phenylacetamide (**12a**).* Yield 50 mg (11%) of yellow prisms, mp 279–280 °C. [Found: C, 69.2; H, 4.5; N, 11.9. $C_{21}H_{21}FN_4O_3$ requires C, 69.22; H, 4.52; N, 11.96%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 3.93 (3H, s, C$H_3$O), 4.36 (2H, s, C$H_2$), 6.96–8.26 (12H, m, ArH), 7.79 (1H, s, 6-C*H*), 8.66 (1H, s, 2-C*H*), 9.75 (1H, s, O*H*), 10.55 (1H, s, N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 51.1, 56.8, 97.3, 107.1, 108.8, 112.3, 115.9, 116.3, 116.8, 120.1, 121.7, 124.1, 128.0, 128.2, 128.7, 129.3, 129.7, 139.8, 142.8, 144.5, 145.0, 148.9, 150.6, 156.0, 155.4, 166.1; MS (EI, 70 eV): *m*/*z* (%)=468 (67.0) [$M^+$], 470 (3.9), 469 (21.1), 350 (25.4), 349 (99.9), 348 (19.1), 334(20.4), 306 (12.7), 77 (19.4).

### 4.8. General procedure for the synthesis of compounds 13a–e, 14a–e, and 15a–l

A mixture of aminoazole **1j**–**m** (1 mmol), acetoacetamide **2a**,**b**,**d**,**e** (1 mmol), and aromatic aldehyde **3b**,**d**,**f**,**g**,**h**–**o** (1 mmol) in

0.1 mL of DMF was heated to reflux for 10 min. After cooling acetone (10 mL) was added and the precipitate formed was filtered out to give the solid compounds **13a**–**e**, **14a**–**e** or **15a**–**l**, which were washed with acetone and air dried.

*4.8.1. 7-(4-Cyanophenyl)-2,5-dimethyl-N-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**13a**).* Yield 204 mg (55%) of colorless prisms, mp 163–164 °C. [Found: C, 71.5; H, 5.1; N, 18.9. $C_{22}H_{19}N_5O$ requires C, 71.53; H, 5.18; N, 18.96%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.01 (3H, s, C$H_3$), 2.16 (3H, s, C$H_3$), 5.42 (1H, s, 7-C*H*), 6.45 (1H, s, 3-C*H*), 6.97–7.74 (9H, m, ArH), 9.53 (1H, s, N*H*), 9.58 (1H, s, 4-N*H*); MS (EI, 70 eV): *m*/*z* (%)=370 (9.5) [$M^+$], 369 (21.7), 278 (20.2), 277 (60.6), 250 (4.6), 249 (99.9), 127 (13.0), 93 (44.6).

*4.8.2. 7-(4-Bromophenyl)-2,5-dimethyl-N-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**13b**).* Yield 212 mg (50%) of colorless prisms, mp 153–154 °C. [Found: C, 59.6; H, 4.5; N, 13.2. $C_{21}H_{19}BrN_4O$ requires C, 59.59; H, 4.52; N, 13.24%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.00 (3H, s, C$H_3$), 2.15 (3H, s, C$H_3$), 5.37 (1H, s, 7-C*H*), 6.37 (1H, s, 3-C*H*), 6.97–7.48 (9H, m, ArH), 9.43 (1H, s, N*H*), 9.55 (1H, s, 4-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 14.4, 18.3, 59.8, 87.0, 102.3, 120.5, 121.2, 123.7, 129.1, 129.6, 131.8, 137.8, 139.6, 140.0, 142.8, 148.5, 166.2; MS (EI, 70 eV): *m*/*z* (%)=423 (14.2) [$M^+$], 424 (15.6), 422 (18.7), 332 (99.9), 331 (99.1), 330 (98.7), 302 (43.6), 122 (43.0), 93 (72.9).

*4.8.3. 2,5-Dimethyl-7-(4-nitrophenyl)-N-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**13c**).* Yield 254 mg (65%) of colorless prisms, mp 169–170 °C. [Found: C, 64.8; H, 4.9; N, 17.9. $C_{21}H_{19}N_5O_3$ requires C, 64.77; H, 4.92; N, 17.98%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.00 (3H, s, C$H_3$), 2.17 (3H, s, C$H_3$), 5.43 (1H, s, 7-C*H*), 6.51 (1H, s, 3-C*H*), 6.97–8.11 (9H, m, ArH), 9.58 (1H, s, N*H*), 9.60 (1H, s, 4-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 14.4, 18.4, 59.8, 87.3, 101.7, 120.5, 123.8, 124.2, 128.6, 129.1, 138.3, 139.9, 147.6, 148.8, 150.5, 166.0; MS (EI, 70 eV): *m*/*z* (%)=389 (11.8) [$M^+$], 297 (32.6), 223 (35.4), 148 (99.9), 122 (33.5), 93 (42.0), 77 (36.9).

*4.8.4. 7-(4-Carboxyphenyl)-2,5-dimethyl-N-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**13d**).* Yield 195 mg (50%) of colorless prisms, mp 183–184 °C. [Found: C, 68.0; H, 5.2; N, 14.4. $C_{22}H_{20}N_4O_3$ requires C, 68.03; H, 5.19; N, 14.42%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.00 (3H, s, C$H_3$), 2.17 (3H, s, C$H_3$), 5.40 (1H, s, 7-C*H*), 6.48 (1H, s, 3-C*H*), 6.97–7.48 (9H, m, ArH), 9.54 (1H, s, N*H*), 9.58 (1H, s, 4-N*H*); MS (EI, 70 eV): *m*/*z* (%)=386 (5.6) [$M^+$], 295 (15.1), 294 (99.9), 250 (20.2), 154 (14.6), 97 (14.7), 92 (11.6), 65 (12.6).

*4.8.5. N-(4-Chlorophenyl)-2,5-dimethyl-7-(4-nitrophenyl)-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**13e**).* Yield 212 mg (50%) of colorless prisms, mp 158–160 °C. [Found: C, 59.5; H, 4.3; N, 16.5. $C_{21}H_{18}ClN_5O_3$ requires C, 59.51; H, 4.28; N, 16.52%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.00 (3H, s, C$H_3$), 2.17 (3H, s, C$H_3$), 5.44 (1H, s, 7-C*H*), 6.51 (1H, s, 3-C*H*), 7.29–8.12 (8H, m, ArH), 9.63 (1H, s, N*H*), 9.72 (1H, s, 4-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 14.4, 18.4, 59.8, 87.4, 101.5, 122.1, 124.1, 127.6, 128.5, 129.0, 138.8, 139.6, 147.7, 148.9, 150.4, 166.1; MS (EI, 70 eV): *m*/*z* (%)=423 (9.4) [$M^+$], 425 (3.6), 424 (3.0), 297 (99.9), 296 (31.2), 269 (32.6), 148 (39.2).

*4.8.6. 4-(3-Ethoxy-4-hydroxyphenyl)-3,6-dimethyl-N-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carboxamide (**14a**).* Yield 225 mg (50%) of colorless prisms, mp 238–240 °C. [Found: C, 68.3; H, 6.0; N, 13.8. $C_{23}H_{24}N_4O_3$ requires C, 68.30; H, 5.98; N, 13.85%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.19 (3H, t, *J* 7.1 Hz, C$H_3$), 1.81 (3H, s, C$H_3$), 2.06 (3H, s, C$H_3$), 3.80 (2H, q, *J* 7.1 Hz, C$H_2$O), 5.09 (1H, s, 4-C*H*), 6.50–7.47 (8H, m, ArH), 8.50 (1H, s, N*H*), 8.53 (1H, s, O*H*), 9.10 (1H, s, 7-N*H*), 11.48 (1H, s, 1-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 10.3, 15.4, 19.3, 40.0, 65.1, 102.8, 104.7, 115.1, 116.2, 120.1, 121.0, 123.1, 128.9, 135.4, 139.0, 139.9, 140.6, 145.9, 146.9, 148.2, 168.8; MS (EI, 70 eV): *m*/*z* (%)=404 (8.5) [$M^+$], 390 (9.1), 389 (31.3), 312 (35.2), 285 (40.2), 284 (99.9), 267 (26.7), 255 (45.7), 174 (31.3), 148 (18.1), 77 (47.9).

*4.8.7. 4-(3,4-Dihydroxyphenyl)-3,6-dimethyl-N-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carboxamide (**14b**).* Yield 132 mg (35%) of colorless prisms, mp 178–180 °C. [Found: C, 67.0; H, 5.4; N, 14.9. $C_{21}H_{20}N_4O_3$ requires C, 67.01; H, 5.36; N, 14.88%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.81 (3H, s, C$H_3$), 2.07 (3H, s, C$H_3$), 5.09 (1H, s, 4-C*H*), 6.46–7.48 (8H, m, ArH), 8.49 (1H, s, N*H*), 8.52 (1H, s, O*H*), 8.63 (1H, s, O*H*), 9.03 (1H, s, 7-N*H*), 11.47 (1H, s, 1-N*H*); MS (EI, 70 eV): *m*/*z* (%)=374 (10.5) [$M^+$], 282 (43.5), 119 (35.5), 93 (99.9), 92 (61.1), 91 (40.3), 65 (33.9), 41 (17.6).

*4.8.8. 4-(3,4-Dimethoxyphenyl)-3,6-dimethyl-N-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carboxamide (**14c**).* Yield 182 mg (45%) of colorless prisms, mp 240–242 °C. [Found: C, 68.3; H, 5.9; N, 13.8. $C_{23}H_{24}N_4O_3$ requires C, 68.30; H, 5.98; N, 13.85%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.82 (3H, s, C$H_3$), 2.07 (3H, s, C$H_3$), 3.57 (3H, s, C$H_3$O), 3.63 (3H, s, C$H_3$O), 5.17 (1H, s, 4-C*H*), 6.63–7.51 (8H, m, ArH), 8.55 (1H, s, N*H*), 9.17 (1H, s, 7-N*H*), 11.50 (1H, s, 1-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) $\delta$ 10.4, 19.3, 39.5, 56.4, 102.5, 104.5, 113.0, 120.1, 120.5, 123.1, 128.9, 129.2, 135.3, 140.0, 140.5, 140.6, 148.0, 148.3, 149.2, 168.8; MS (EI, 70 eV): *m*/*z* (%)=404 (16.2) [$M^+$], 312 (99.9), 146 (21.7), 93 (40.6), 77 (43.7).

*4.8.9. 4-(4-Hydrophenyl)-3,6-dimethyl-N-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carboxamide (**14d**).* Yield 151 mg (42%) of colorless prisms, mp 264–266 °C. [Found: C, 69.9; H, 5.6; N, 15.5. $C_{21}H_{20}N_4O_2$ requires C, 69.98; H, 5.59; N, 15.54%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.79 (3H, s, C$H_3$), 2.06 (3H, s, C$H_3$), 5.09 (1H, s, 4-C*H*), 6.53–7.44 (9H, m, ArH), 8.49 (1H, s, N*H*), 9.05 (1H, s, O*H*), 9.09 (1H, s, 7-N*H*), 11.46 (1H, s, 1-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 15.0, 23.4, 39.6, 115.3, 120.1, 120.5, 123.0, 124.3, 126.4, 128.9, 129.1, 129.2, 130.8, 139.5, 158.1, 167.3, 168.8; MS (EI, 70 eV): *m*/*z* (%)=360 (8.0) [$M^+$], 359 (11.3), 267 (99.9), 263 (28.5), 210 (25.3), 170 (32.5), 94 (43.6), 77 (28.1), 66 (78.3).

*4.8.10. 4-[4-(Dimethylamino)phenyl]-3,6-dimethyl-N-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carboxamide (**14e**).* Yield 195 mg (50%) of colorless prisms, mp 247–248 °C. [Found: C, 71.3; H, 6.5; N, 18.1. $C_{23}H_{25}N_5O$ requires C, 71.29; H, 6.50; N, 18.07%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.79 (3H, s, C$H_3$), 2.06 (3H, s, C$H_3$), 2.76 (6H, s, 2C$H_3$), 5.10 (1H, s, 4-C*H*), 6.70–7.49 (9H, m, ArH), 8.51 (1H, s, N*H*), 9.09 (1H, s, 7-N*H*), 11.50 (1H, s, 1-N*H*); MS (EI, 70 eV): *m*/*z* (%)=386 (8.9) [$M^+$], 343 (25.8), 267 (99.9), 147 (27.5), 132 (16.6), 120 (48.8), 119 (18.7), 95 (14.1), 77 (12.1).

*4.8.11. 7-(4-Hydroxy-3-methoxyphenyl)-5-methyl-N,2-diphenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**15a**).* Yield 250 mg (55%) of colorless prisms, mp 235–237 °C. [Found: C, 71.7; H, 5.3; N, 12.4. $C_{27}H_{24}N_4O_3$ requires C, 71.67; H, 5.35; N, 12.38%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.20 (3H, s, C$H_3$), 3.60 (3H, s, C$H_3$O), 5.99 (1H, s, 7-C*H*), 6.49 (1H, s, 3-C*H*), 6.55–7.69 (13H, m, ArH), 8.89 (1H, s, O*H*), 9.50 (1H, s, N*H*), 9.57 (1H, s, 4-N*H*); MS (EI, 70 eV): *m*/*z* (%)=453 (20.9) [$M^+$], 360 (16.3), 333 (64.0), 332 (99.9), 210 (23.8), 184 (22.2), 119 (46.7), 93 (27.0), 92 (22.9), 91 (29.8), 77 (22.9).

*4.8.12. 7-(4-Carboxyphenyl)-2-(4-chlorophenyl)-5-methyl-N-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**15b**).* Yield 252 mg (52%) of colorless prisms, mp 238–240 °C. [Found: C, 66.9; H, 4.5; N, 11.6. $C_{27}H_{21}ClN_4O_3$ requires C, 66.87; H, 4.36; N, 11.55%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.30 (3H, s, C$H_3$), 5.72 (1H, s, 7-C*H*), 6.99 (1H, s, 3-C*H*), 7.40–8.05 (13H, m, ArH), 8.98 (1H, s, N*H*), 9.89 (1H, s, 4-N*H*), 12.36 (1H, s, COO*H*); MS (EI, 70 eV): *m*/*z*

(%)=484 (26.0) [$M^+$], 327 (29.6), 325 (99.9), 324 (37.8), 138 (35.8), 136 (27.6), 101 (19.2), 77 (27.3), 76 (36.3), 51 (22.9).

*4.8.13. 2-(4-Chlorophenyl)-7-(4-cyanophenyl)-5-methyl-N-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**15c**).* Yield 260 mg (55%) of colorless prisms, mp 290–292 °C. [Found: C, 69.6; H, 4.3; N, 15.0. $C_{27}H_{20}ClN_5O$ requires C, 69.60; H, 4.33; N, 15.03%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.20 (3H, s, C$H_3$), 6.10 (1H, s, 7-C*H*), 6.63 (1H, s, 3-C*H*), 7.03–7.78 (13H, m, ArH), 9.68 (1H, s, N*H*), 9.78 (1H, s, 4-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 18.3, 60.4, 84.9, 111.2, 119.2, 120.5, 123.9, 127.5, 128.2, 129.2, 132.9, 133.1, 138.2, 139.8, 140.6, 148.1, 150.2, 168.9; MS (EI, 70 eV): *m*/*z* (%)=466 (5.0) [$M^+$], 371 (26.4), 345 (26.7), 111 (37.0), 93 (99.9), 77 (46.3), 64 (45.3).

*4.8.14. 2-(4-Chlorophenyl)-5-methyl-7-(4-nitrophenyl)-N-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**15d**).* Yield 320 mg (55%) of colorless prisms, mp 278–280 °C. [Found: C, 64.3; H, 4.1; N, 14.4. $C_{26}H_{20}ClN_5O_3$ requires C, 64.27; H, 4.15; N, 14.41%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.21 (3H, s, C$H_3$), 6.11 (1H, s, 7-C*H*), 6.68 (1H, s, 3-C*H*), 6.98–8.12 (13H, m, ArH), 9.69 (1H, s, N*H*), 9.82 (1H, s, 4-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 18.4, 60.3, 85.0, 102.0, 120.6, 123.9, 124.3, 127.5, 128.6, 129.1, 132.9, 138.3, 138.4, 139.8, 139.9, 140.7, 147.8, 150.0, 150.3, 165.9; MS (EI, 70 eV): *m*/*z* (%)=486 (4.4) [$M^+$], 487 (5.2), 485 (13.3), 365 (99.9), 366 (42.4), 367 (31.5), 393 (61.6), 394 (22.9), 93 (65.4), 92 (27.0), 119 (46.7), 120 (24.5), 218 (45.1), 244 (55.1), 243 (11.5), 319 (37.8), 318 (23.2).

*4.8.15. 2-(4-Chlorophenyl)-5-methyl-N-phenyl-7-pyridin-3-yl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**15e**).* Yield 175 mg (40%) of colorless prisms, mp 240–241 °C. [Found: C, 67.9; H, 4.5; N, 15.8. $C_{25}H_{20}ClN_5O$ requires C, 67.95; H, 4.56; N, 15.85%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.22 (3H, s, C$H_3$), 6.07 (1H, s, 7-C*H*), 6.58 (1H, s, 3-C*H*), 6.98–8.44 (13H, m, ArH), 9.67 (1H, s, N*H*), 9.74 (1H, s, 4-N*H*); MS (EI, 70 eV): *m*/*z* (%)=441 (24.0) [$M^+$], 324 (22.7), 323 (40.1), 322 (63.6), 321 (78.7), 244 (31.1), 136 (13.9), 119 (99.9), 93 (20.4), 91 (48.3), 64 (17.9).

*4.8.16. 7-(4-Bromophenyl)-2-(4-chlorophenyl)-N-(2-methoxyphenyl)-5-methyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**15f**).* Yield 360 mg (65%) of colorless prisms, mp 158–160 °C. [Found: C, 59.0; H, 4.0; N, 10.2. $C_{27}H_{22}BrClN_4O_2$ requires C, 58.98; H, 4.03; N, 10.19%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.30 (3H, s, C$H_3$), 3.74 (3H, s, C$H_3$O), 6.05 (1H, s, 7-C*H*), 6.46 (1H, s, 3-C*H*), 6.84–7.73 (12H, m, ArH), 8.57 (1H, s, N*H*), 9.76 (1H, s, 4-N*H*); MS (EI, 70 eV): *m*/*z* (%)=550 (11.0) [$M^+$], 426 (10.8), 244 (10.0), 150 (14.3), 149 (29.4), 136 (21.8), 135 (22.6), 128 (18.8), 123 (99.9), 80 (19.6), 77 (14.6).

*4.8.17. 2-(4-Chlorophenyl)-N-(2,4-dimethylphenyl)-7-(4-hydroxy-3-methoxyphenyl)-5-methyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**15g**).* Yield 260 mg (50%) of colorless prisms, mp 250–252 °C. [Found: C, 67.6; H, 5.3; N, 10.9. $C_{29}H_{27}ClN_4O_3$ requires C, 67.63; H, 5.28; N, 10.88%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.85 (3H, s, C$H_3$), 2.20 (3H, s, C$H_3$), 2.24 (3H, s, C$H_3$), 3.67 (3H, s, C$H_3$O), 5.98 (1H, s, 7-C*H*), 6.39 (1H, s, 3-C*H*), 6.67–7.73 (10H, m, ArH), 8.91 (1H, s, N*H*), 9.45 (1H, s, 4-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 18.3, 18.4, 21.1, 56.7, 60.6, 84.3, 102.7, 113.2, 116.1, 120.7, 126.3, 126.9, 127.4, 129.1, 131.3, 132.6, 133.2, 133.3, 133.9, 134.8, 134.9, 137.3, 140.4, 147.2, 148.1, 149.4, 166.3; MS (EI, 70 eV): *m*/*z* (%)=514 (4.9) [$M^+$], 515 (1.9), 516 (1.7), 36.6 (99.9), 368 (50.8), 367 (22.9), 369 (10.1), 394 (19.8).

*4.8.18. 7-(4-Chlorophenyl)-2-(4-methoxyphenyl)-5-methyl-N-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**15h**).* Yield 310 mg (65%) of colorless prisms, mp 143–145 °C. [Found: C, 68.8; H, 4.9; N, 11.9. $C_{27}H_{23}ClN_4O_2$ requires C, 68.86; H, 4.92; N, 11.90%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.20 (3H, s, C$H_3$), 3.73 (3H, s, C$H_3$O), 5.94 (1H, s, 7-C*H*), 6.55 (1H, s, 3-C*H*), 6.87–7.64 (13H, m, ArH), 9.62 (1H, s, N*H*), 9.64 (1H, s, 4-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 18.3, 55.9, 60.0, 84.0, 102.5, 114.7, 120.6, 123.8, 127.0, 127.1, 128.9, 129.1, 129.2, 132.9, 138.0, 140.0, 140.4, 142.1, 151.0, 159.8, 166.1; MS (EI, 70 eV): *m*/*z* (%)=470 (28.4) [$M^+$], 472 (11.0), 93 (99.9), 378 (80.2), 377 (40.3), 379 (31.6), 380 (26.1), 350 (66.6), 92 (49.5).

*4.8.19. 7-(4-Hydroxy-3-methoxyphenyl)-2-(4-methoxyphenyl)-5-methyl-N-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**15i**).* Yield 250 mg (52%) of colorless prisms, mp 240–241 °C. [Found: C, 69.7; H, 5.4; N, 11.6. $C_{28}H_{26}N_4O_4$ requires C, 69.70; H, 5.43; N, 11.61%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.19 (3H, s, C$H_3$), 3.60 (3H, s, C$H_3$O), 3.73 (3H, s, C$H_3$O), 5.90 (1H, s, 7-C*H*), 6.46 (1H, s, 3-C*H*), 6.53–7.65 (12H, m, ArH), 8.88 (1H, s, O*H*), 9.46 (1H, s, N*H*), 9.55 (1H, s, 4-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 18.2, 55.9, 56.5, 60.2, 83.8, 103.1, 112.5, 114.7, 116.1, 120.0, 120.4, 123.6, 127.0, 129.1, 134.3, 137.6, 140.1, 146.9, 148.0, 150.5, 159.6, 166.4; MS (EI, 70 eV): *m*/*z* (%)=482 (46.6) [$M^+$], 483 (12.0), 390 (99.9), 389 (55.4), 361 (18.2).

*4.8.20. 7-(4-Bromoxyphenyl)-2-(4-methoxyphenyl)-5-methyl-N-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**15j**).* Yield 335 mg (65%) of colorless prisms, mp 243–245 °C. [Found: C, 62.9; H, 4.5; N, 10.9. $C_{27}H_{23}BrN_4O_2$ requires C, 62.92; H, 4.50; N, 10.87%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.20 (3H, s, C$H_3$), 3.73 (3H, s, C$H_3$O), 5.95 (1H, s, 7-C*H*), 6.54 (1H, s, 3-C*H*), 6.86–7.60 (13H, m, ArH), 9.62 (1H, s, N*H*), 9.62 (1H, s, 4-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 18.3, 55.9, 60.1, 84.1, 102.5, 114.7, 120.6, 121.3, 123.8, 127.0, 127.1, 129.1, 129.5, 131.9, 138.0, 140.0, 140.4, 142.6, 151.0, 159.8, 166.1; MS (EI, 70 eV): *m*/*z* (%)=515 (7.5) [$M^+$], 516 (20.3), 514 (26.2), 422 (99.9), 423 (60.2), 424 (68.4), 421 (46.8), 394 (59.2), 240 (52.1).

*4.8.21. 7-(4-Bromoxyphenyl)-N-(2-methoxyphenyl)-2-(4-methoxyphenyl)-5-methyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**15k**).* Yield 355 mg (65%) of colorless prisms, mp 163–165 °C. [Found: C, 61.6; H, 4.6; N, 10.3. $C_{28}H_{25}BrN_4O_3$ requires C, 61.66; H, 4.62; N, 10.27%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 2.29 (3H, C$H_3$), 3.74 (6H, s, 2C$H_3$O), 5.93 (1H, s, 7-C*H*), 6.43 (1H, s, 3-C*H*), 6.83–7.72 (12H, m, ArH), 8.54 (1H, s, N*H*), 9.71 (1H, s, 4-N*H*); MS (EI, 70 eV): *m*/*z* (%)=546 (14.0) [$M^+$], 544 (1.9), 396 (43.8), 150 (15.5), 149 (42.8), 128 (23.6), 123 (99.9), 120 (33.2), 94 (28.6), 92 (22.7), 78 (22.5), 77 (25.1), 65 (17.9).

*4.8.22. 7-(4-Bromoxyphenyl)-N-(2,4-dimethylphenyl)-2-(4-methoxyphenyl)-5-methyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-6-carboxamide (**15l**).* Yield 300 mg (55%) of colorless prisms, mp 259–261 °C. [Found: C, 64.1; H, 5.0; N, 10.3. $C_{29}H_{27}BrN_4O_2$ requires C, 64.09; H, 5.01; N, 10.31%]; $\delta_H$ (200 MHz, DMSO-$d_6$) 1.84 (3H, s, C$H_3$), 2.20 (3H, s, C$H_3$), 2.24 (3H, s, C$H_3$), 3.73 (3H, s, C$H_3$O), 5.91 (1H, s, 7-C*H*), 6.48 (1H, s, 3-CH), 6.87–7.63 (11H, m, ArH), 9.03 (1H, s, N*H*), 9.53 (1H, s, 4-N*H*); $\delta_C$ (50 MHz, DMSO-$d_6$) 18.4, 21.1, 22.0, 55.9, 60.2, 83.9, 102.1, 114.7, 121.4, 123.0, 126.4, 126.9, 127.1, 129.9, 130.0, 131.4, 131.8, 132.5, 133.5, 134.7, 135.1, 135.7, 137.4, 140.3, 142.4, 150.9, 159.7, 166.2; MS (EI, 70 eV): *m*/*z* (%)=544 (7.8) [$M^+$], 543 (6.2), 545 (2.5), 396 (57.7), 395 (36.8), 394 (34.1), 121 (99.9), 120 (42.5).

### 4.9. General procedure of transformation of compounds 4a–g, 6a–e into 5a–g, 7a–e

Compound **4a–g** or **6a–e** (1 mmol) was refluxed in 0.1 mL of DMF for 180 min. After cooling acetone (10 mL) was added and the precipitate formed was filtered out to give the solid compounds **5a–g** or **6a–e**, which were washed with acetone and air dried.

## References and notes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