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Reaction of 2-(Ethoxymethylidene)-3-oxo Carboxylic Acid Esters with Tetrazol-5-amine

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Abstract—2-(Ethoxymethylidene)-3-oxo carboxylic acid esters reacted with tetrazol-5-amine to give ethyl 4-alkyl-2-azidopyrimidine-5-carboxylates capable of undergoing subsequent nucleophilic substitution of hydrogen on C^6 or azido group. The reaction of ethyl 2-benzoyl-3-ethoxyprop-2-enoate with tetrazol-5-amine was accompanied by partial decomposition to afford a mixture of ethyl 3-oxo-3-phenylpropanoate and ethyl 7-(1-ethoxy-1,3-dioxo-3-phenylpropan-2-yl)-5-phenyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate. Ethyl 7-hydroxytetrazolo[1,5-*a*]pyrimidine-6-carboxylate was formed as a result of cyclization of diethyl 2-(ethoxymethylidene)propanedioate with tetrazol-5-amine.

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2-(Ethoxymethylidene)-3-oxo carboxylic acid esters are generally recognized as building blocks for the synthesis of various open-chain and heterocyclic compounds, including those used in medical practice [1]. 2-(Ethoxymethylidene)-3-oxo carboxylic acid esters can be converted into pyrimidine and azolopyrimidine systems structurally related to nucleobases and therefore exhibiting a broad spectrum of biological activity [2–5].

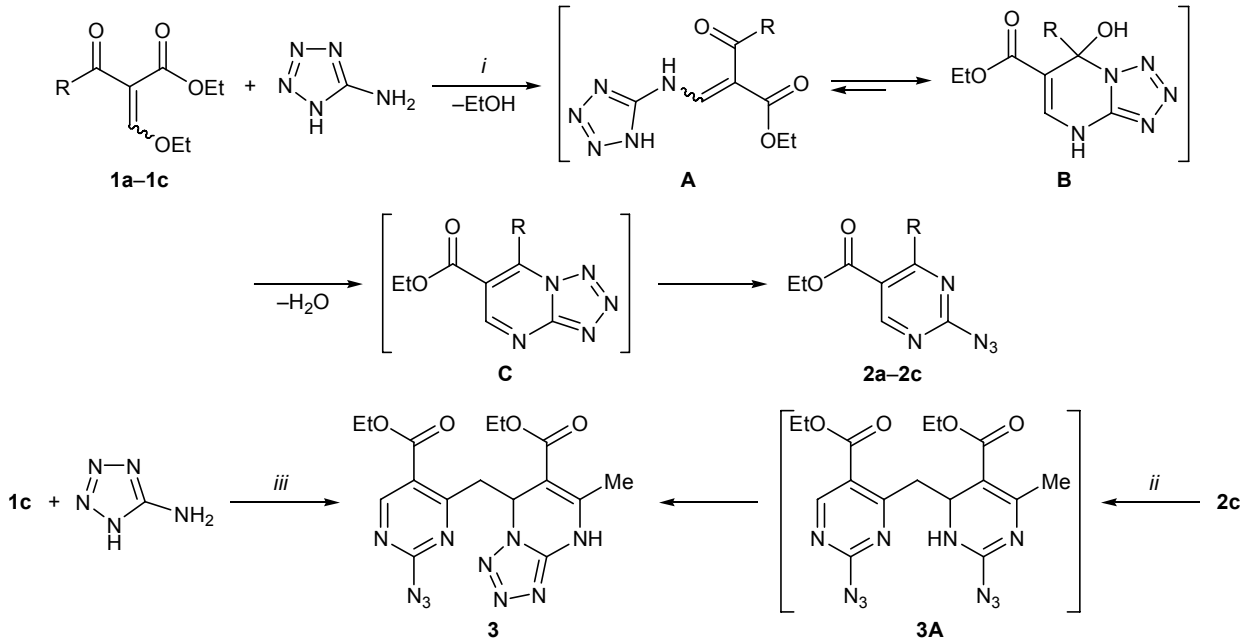
Reactions of nonfluorinated 2-(ethoxymethylidene)-3-oxo carboxylic acid esters with aminoazoles were reported to produce either open-chain 2-[(azolylamino)methylidene]-3-oxo derivatives [6] or immediately azolo[1,5-*a*]pyrimidines [7–9], depending on the reactant structure and conditions. Unlike nonfluorinated analogs, polyfluorinated 2-(ethoxymethylidene)-3-oxo carboxylates react with aminoazoles to afford stable dihydroazolo[1,5-*a*]pyrimidines with a geminal amino hydroxy fragment neighboring to the polyfluoroalkyl group [10, 11]. Due to specific features of 3-amino-1*H*-pyrazol-5-ol, reactions of that binucleophile with 2-(ethoxymethylidene)-3-oxo-3-polyfluoroalkylpropanoates lead to the formation of dihydropyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyridines [12].

We have found no published data on reactions of 2-(ethoxymethylidene)-3-oxo carboxylic acid esters with tetrazol-5-amines. However, such reactions could give rise to functionalized tetrazolo[1,5-*a*]pyrimidines as promising candidates for biological screening; in particular, compounds possessing antitumor [13], antiviral [14], antimicrobial, and antioxidant activity [15] have been found among tetrazolo[1,5-*a*]pyrimidine derivatives. Known tetrazolo[1,5-*a*]pyrimidines were prepared by cyclization of tetrazol-5-amine with 1,3-dicarbonyl compounds or their derivatives [16]. A convenient synthetic approach to the tetrazolo[1,5-*a*]pyrimidine skeleton is based on the three-component Biginelli condensation of 3-oxo esters with aldehydes and tetrazol-5-amine [17, 18] or its two-component modifications utilizing 2-benzylidene-3-oxo esters and tetrazol-5-amine [19, 20].

We anticipated that the use of tetrazol-5-amine as binucleophile in reactions with 2-(ethoxymethylidene)-3-oxo carboxylates could change the traditional cyclization pathways due to its low basicity (pK_b 12.18 [21]) relative to other aminoazoles and the ability to undergo azido–tetrazole isomerism [22, 23].

We examined the reactions of 2-(ethoxymethylidene)-3-oxo carboxylates **1a**–**1d** and diethyl 2-(ethoxymethylidene)propanedioate (**1e**) with tetrazol-5-amine. Heating of **1a**–**1c** with tetrazol-5-amine in boiling ethanol resulted in the formation of an inseparable mixture of products, whereas the reaction in

Scheme 1.



R = CF_3 (**a**), $H(CF_2)_2$ (**b**), Me (**c**); *i*: 2,2,2-trifluoroethanol, reflux, 32–38 h; *ii*: 22°C, 12 days; *iii*: EtOH, 22°C, 9 days.

1,4-dioxane, even on prolonged heating (32 h under reflux) was characterized by incomplete conversion and low selectivity. However, by heating the reactants in boiling 2,2,2-trifluoroethanol we obtained 2-azidopyrimidines **2a**–**2c** instead of expected tetrazolylaminomethylidene derivatives **A** or tetrazolo[1,5-*a*]pyrimidines like **B** and **C** (Scheme 1).

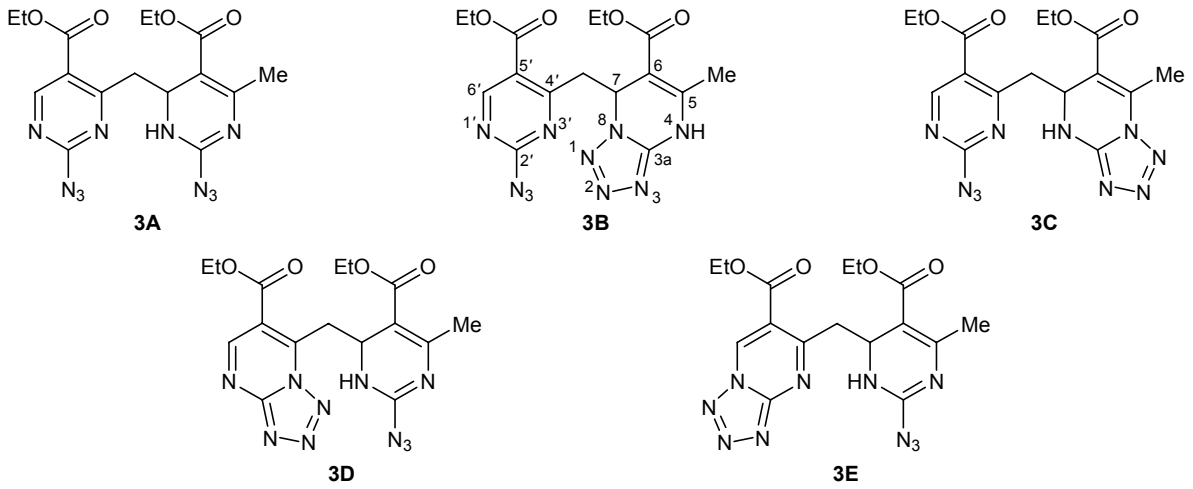
Presumably, initial condensation of **1a**–**1c** with tetrazol-5-amine yields intermediate tetrazolylaminomethylidene derivative **A** which undergo intramolecular cyclization via regioselective addition of the endocyclic NH group to the ketone carbonyl carbon atom; dihydrotetrazolo[1,5-*a*]pyrimidines **B** thus formed lose water molecule, yielding tetrazolo[1,5-*a*]pyrimidines **C**. Azido–tetrazole isomerization [24] of the latter through opening of the tetrazole ring at the N^1–N^8 leads to 2-azidopyrimidines **2a**–**2c** (Scheme 1).

The azide structure of **2a**–**2c** follows from the presence of an absorption band at 2144–2146 cm^{-1} in the IR spectra, which is typical of stretching vibrations of azido group [25]. The NMR spectra of **2a**–**2c** in chloroform-*d* also indicated the presence of only one azide isomer (6-H, δ 9.03–9.13 ppm; C^2, δ_C 163.39–163.89 ppm) [22].

Unlike 4-polyfluoroalkyl-substituted pyrimidines **2a** and **2b**, 2-azido-4-methylpyrimidine **2c** was unstable, and it transformed into compound **3** on storage in air (without a solvent). Compound **3** was also synthesized from ester **1c** and tetrazol-5-amine in ethanol at room temperature (Scheme 1). 2-Azidopyrimidine **2c** was detected by TLC in the reaction mixture as intermediate.

According to the ^{1}H NMR and IR data, five structures **3A**–**3E** are possible for compound **3** due to azido–tetrazole isomerism without taking into account annular amino–imine transformations involving the NH group. On the basis of the ^{13}C NMR spectra, including two-dimensional ^{1}H–^{13}C HSQC and HMBC experiments, compound **3** was assigned the structure of ethyl 7-{[2-azido-5-(ethoxycarbonyl)pyrimidin-4-yl]-methyl}-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate (**3B**). The C^{3a} signal in the ^{13}C NMR spectrum of **3** was observed at δ_C 149.71 ppm, which is typical of the fusion carbon atom in 4,7-dihydrotetrazolopyrimidines [20], and the $C^{2'}$ atom in the second heterocycle resonated in a weaker field, at δ_C 163.41 ppm, as in the spectra of 2-azidopyrimidines **2a**–**2c**. The difference in the chemical shifts of C^{3a} and $C^{2'}$ is determined by different hybridizations of the neighboring nitrogen atom. These data allowed us to rule out bis-azido tautomer **3A**.

Structure **3B** is confirmed by the 2D HMBC cross peaks between the NH proton (δ 10.7 ppm), on the one hand, and 5-CH_3 (δ_C 19.42 ppm), C^6 (δ_C 97.77 ppm), and C^{3a} nuclei (δ_C 149.71 ppm) of the tetrazolopyrimidine fragment, on the other, as well as between 6′-H



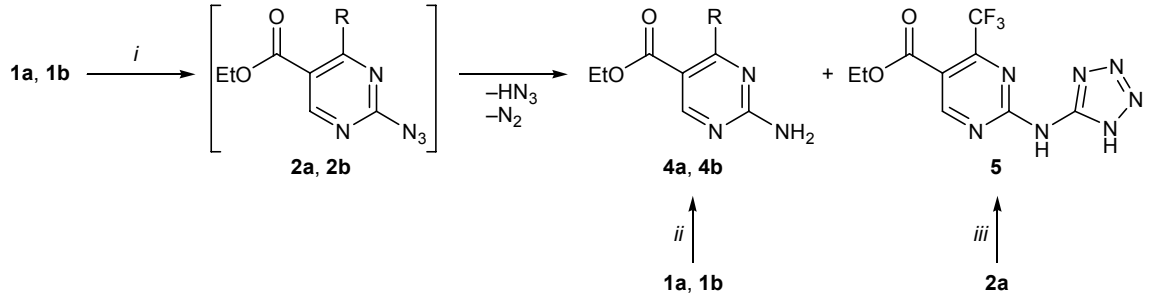
(δ 9.02 ppm) and $C^{5'}$ and $C^{2'}$ (δ_C 120.17 and 163.41 ppm, respectively) of the azidopyrimidine fragment. Nonequivalent protons in the methylene bridge (δ_C 41.01 ppm) displayed long-range couplings with carbon nuclei in both tetrazolopyrimidine (C^7, δ_C 55.28 ppm; C^6, δ_C 97.77 ppm) and azidopyrimidine fragments ($C^{5'}$, δ_C 120.17 ppm; $C^{4'}$, δ_C 169.09 ppm). Correlations were also observed between 7-H and $C^{4'}$, C^{3a}, and C^5. The signals at δ_C 163.69 and 164.71 ppm were assigned to the carbonyl carbon atoms on the basis of HMBC cross peaks with the OCH_2 protons.

Compound **3** can be formed as a result of nucleophilic addition of the methyl group of one molecule **2c** to the electrophilic C^6H atom of the other molecule, followed by azido–tetrazole isomerization of intermediate **3A** (Scheme 1).

When the reactions of fluorinated esters **1a** and **1b** with tetrazol-5-amine were carried out in boiling 1,4-dioxane in the presence of a catalytic amount of sodium acetate, the products were ethyl 2-amino-4-polyfluoroalkylpyrimidine-5-carboxylates **4a** and **4b** (Scheme 2). The reaction with **1a** was accompanied by side formation of ethyl 2-(1*H*-tetrazol-5-ylamino)-4-(trifluoromethyl)pyrimidine-5-carboxylate (**5**). Presumably, these reactions involve intermediate formation of 2-azidopyrimidines **2a** and **2b** which undergo thermal decomposition with elimination of nitrogen to give nitrenes [26], and the latter abstract hydrogen from other substrates, e.g., tetrazol-5-amine, eventually leading to **4a** and **4b**. Compound **4a** and **4b** were also synthesized by cyclization of esters **1a** and **1b** with guanidine carbonate involving the (ethoxymethylidene)acyl fragment on heating in boiling 1,4-dioxane in the presence of sodium acetate. Compound **4a** is active against herpes viruses (HSV-1); it was synthesized previously by cyclization of ethyl 2-(dimethylaminomethylidene)-4,4,4-trifluoro-3-oxobutanoate with guanidine [27]. 2-(Tetrazolylamino)pyrimidine **5** is the product of nucleophilic substitution of the azido group (which is a good nucleofuge) [28] in intermediate 2-azidopyrimidine **2a** by aminotetrazole residue. In fact, 2-(1*H*-tetrazol-5-ylamino)pyrimidine **5** was obtained in a good yield by reaction of **2a** with tetrazol-5-amine (Scheme 2).

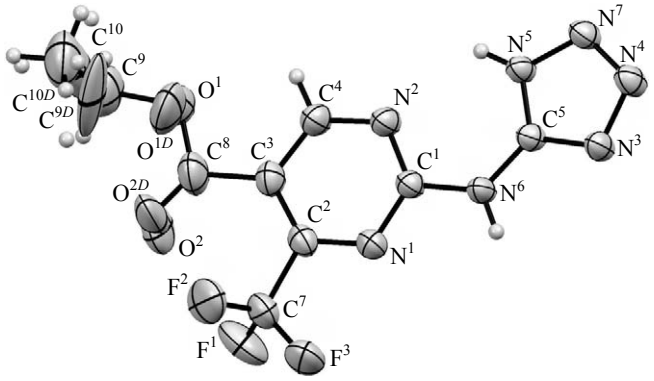
Enamine–imine tautomerism is possible for aminopyrimidine derivatives. However, compounds **4a**, **4b**,

Scheme 2.



R = CF_3 (**a**), $H(CF_2)_2$ (**b**); *i*: tetrazol-5-amine, NaOAc, 1,4-dioxane, Δ, 16–18 h; *ii*: guanidinium carbonate, NaOAc, DMF, 80°C, 24–26 h; *iii*: tetrazol-5-amine, Et_3N, 1,4-dioxane, Δ, 40 h.

and **5** in crystal and in solution exist as a single enamine tautomer. The IR spectra of **4a** and **4b** contained a doublet absorption band at 3372–3379/3336–3337 cm^{-1} due to symmetric and antisymmetric stretching vibrations of the NH_2 group, and a two-proton singlet at δ 7.95–8.04 ppm (NH_2) was observed in their ^1H NMR spectra. The structure of **5** was confirmed by X-ray analysis (see figure).



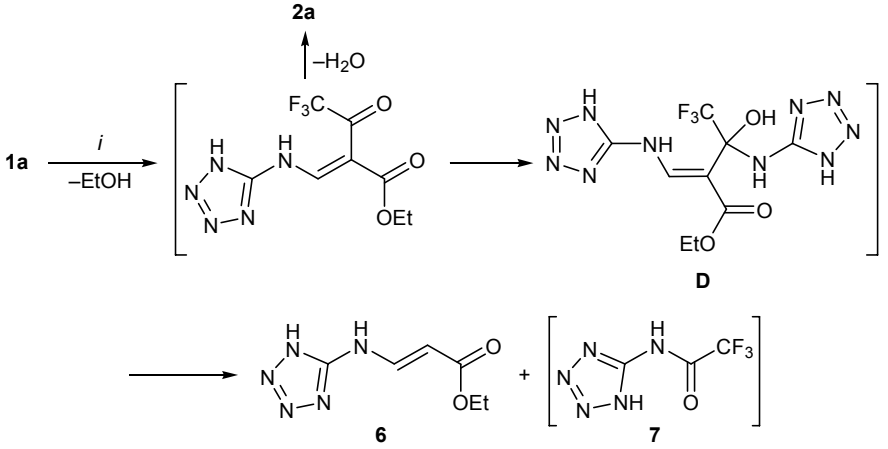
Structure of the molecule of ethyl 2-(1*H*-tetrazol-5-ylamino)-4-(trifluoromethyl)pyrimidine-5-carboxylate (**5**) according to the X-ray diffraction data.

The reaction of **1a** with tetrazol-5-amine in the presence of triethylamine in boiling ethanol has demonstrated once more the importance of the conditions. In this case, only a small amount of **2a** was formed (8%), while the major products were compounds **6** and **7** resulting from acid decomposition (Scheme 3). Ester **6** was isolated in the pure state, and trifluoroacetamide **7** was detected in the reaction mixture by GC/MS (*m*/*z* 181 $[M]^+$). Presumably, 5-aminotetrazolate anion generated by the action of base (triethylamine) reacts with **1a** both at the ethoxymethylidene group and ketone carbonyl group to give unstable intermediate **D** which decomposes into **6** and **7**.

Ethyl 2-benzoyl-3-ethoxyprop-2-enoate (**1d**) reacted with tetrazol-5-amine in boiling ethanol to produce a complex mixture of products. By column chromatography we isolated only ethyl benzoylacetate (**8**) which was likely to be formed as a result of decomposition of initial ester **1d**. The transformation of 2-(alkoxymethylidene)-3-oxo esters into the corresponding 3-oxo esters in reactions with nitrogen nucleophiles via transfer of the alkoxymethylidene group to the amine has been reported in [29, 30]. Heating of the same reactants in 2,2,2-trifluoroethanol also led to the formation of a mixture of products, from which we succeeded in isolating ester **8**, tetrazolylaminomethylidene-substituted ester **9**, and tetrazolopyrimidine **10** (Scheme 4).

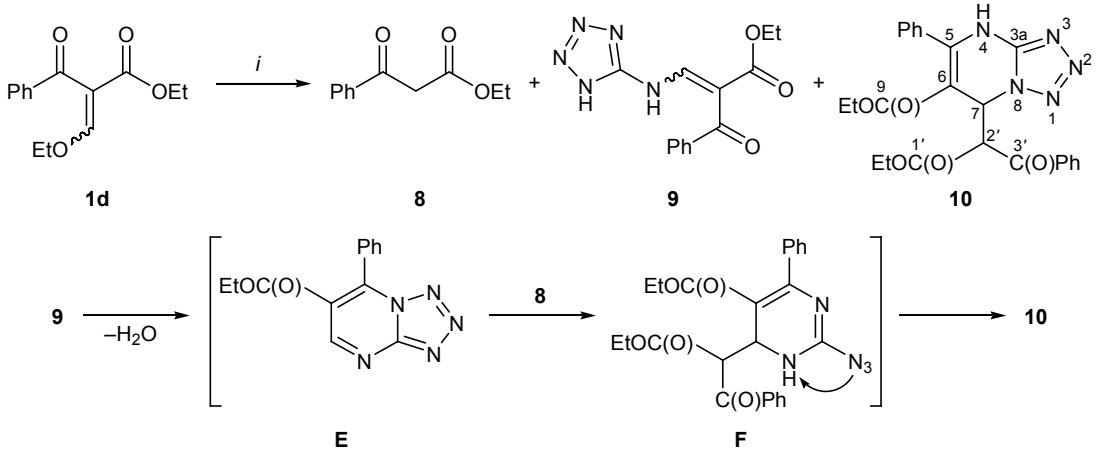
Ethyl 2-benzoyl-3-(1*H*-tetrazol-5-ylamino)prop-2-enoate (**9**) exists as a mixture of *Z* and *E* isomers stabilized by intramolecular hydrogen bond, as reported previously for 2-R-aminomethylidene-3-oxo esters [31]. The structure of **10** was determined on the basis of the ^1H and ^{13}C NMR and 2D ^1H–^{13}C HSQC/HMBC spectra ($CDCl_3$). The ^1H NMR data showed that molecule **10** contains two ethoxycarbonyl groups, two phenyl substituents, two sp^3-carbon atoms (CH, $^3J_{2',7}$ = 2.8 Hz), and an NH group (δ 10.48 ppm). Carbon atoms linked to hydrogens were unambiguously assigned using 2D HSQC experiment. The most informative cross peaks in the 2D HMBC spectrum were as follows: 2′-H was coupled with $C^{1'}$, $C^{3'}$, C^6, and C^7; 7-H was coupled with C^5, C^6, C^9, and $C^{1'}$; and NH was coupled with C^6, C^{3a}, and C^i. The carbonyl carbon signals were identified by long-range couplings with

Scheme 3.



i: Tetrazol-5-amine, EtOH, Et_3N, Δ.

Scheme 4.



i: Tetrazol-5-amine, 2,2,2-trifluoroethanol, Δ, 48 h.

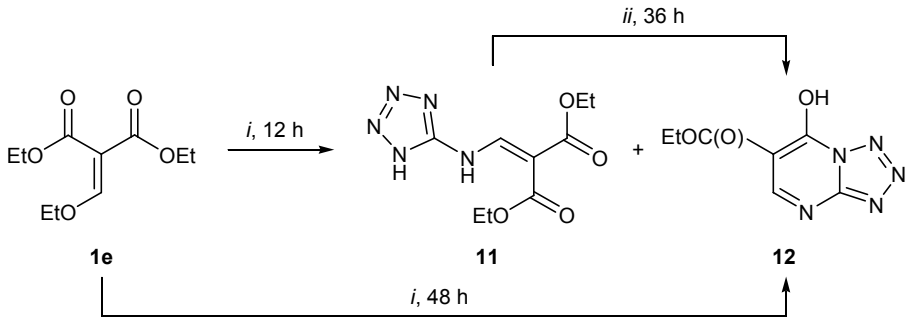
the OCH_2 (C^9, $C^{1'}$) and *o*-H protons ($C^{3'}$). Compound **10** was isolated as a single diastereoisomer, but relative configuration of its chiral centers was not determined

Presumably, heterocycle **10** is formed through intermediate tetrazolopyrimidine **E** (Scheme 5). The mass spectrum of amino derivative **9** (*m*/*z* 269 $[M - H_2O]^+$) suggests the possibility for the formation of heterocyclic structure **E** which can take up ester **8** molecule at the CH electrophilic center. The reaction is accompanied by tetrazole rearrangement through intermediate 2-azidopyrimidine **F** whose cyclization yields fused heterocycle **10**. The tetrazole structure of **10** is stabilized due to increased electron density on the N^8 fusion atom in the partly hydrogenated pyrimidine fragment. The same also applies to the tetrazolopyrimidine moiety of **3**.

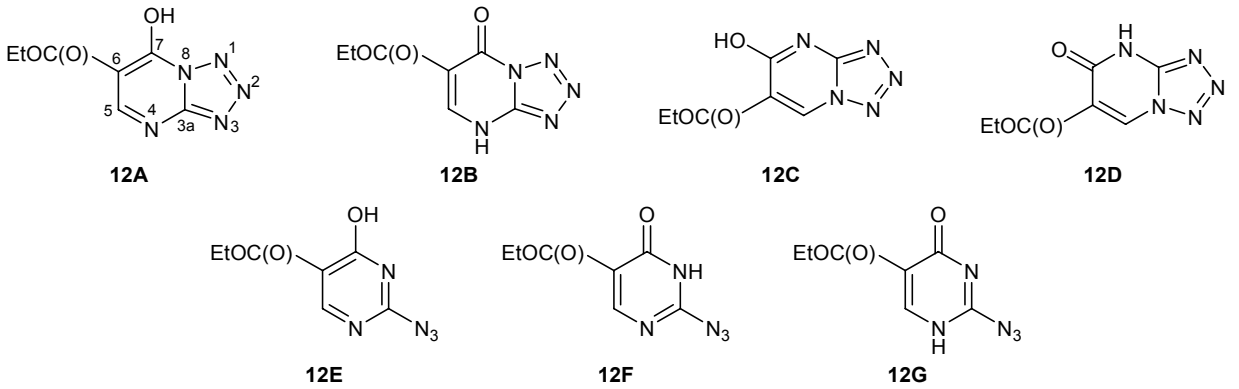
As expected, the reaction of diethyl 2-(ethoxymethylidene)propanedioate (**1e**) with tetrazol-5-amine afforded 2-(1*H*-tetrazol-5-ylaminomethylidene)propanedioate (**11**) which underwent cyclization during the process to ethyl 7-hydroxytetrazolo[1,5-*a*]pyrimidine-6-carboxylate (**12**) (Scheme 5). The optimal conditions for the formation of **12** were prolonged heating in boiling ethanol in the presence of triethylamine. If no triethylamine was added, the transformation of **1e** into **11** was not complete even after refluxing in ethanol for 48 h. Compound **11** underwent cyclization into **12** on prolonged heating in the absence of a base.

Compound **12** is potentially tautomeric: keto–enol, lactim–lactam, and azido–tetrazole transformations are possible, so that hydroxy tautomer **12A,** oxo form **12B**, azide structures **12E**–**12G**, and/or regioisomeric tetrazolo[1,5-*a*]pyrimidines **12C** and **12D** (resulting from the tetrazole rearrangement of **12A**) may be assumed. The structure of **12** was determined on the basis of the IR and ^1H and ^{13}C NMR spectra and 2D ^1H–^{13}C and 2D ^1H–^{15}N HMBC experiments. The IR spectrum of **12** lacked absorption in the region 2100–2200 cm^{-1}, which ruled out azido tautomers **12E**–**12G** in crystal. The presence of only one absorption band at 1715 cm^{-1} is rather consistent with the structures of enol tautomers **12A** and **12C** having one ester carbonyl group.

Scheme 5.



i: Tetrazol-5-amine, Et_3N, EtOH, Δ; *ii*: EtOH, Δ.



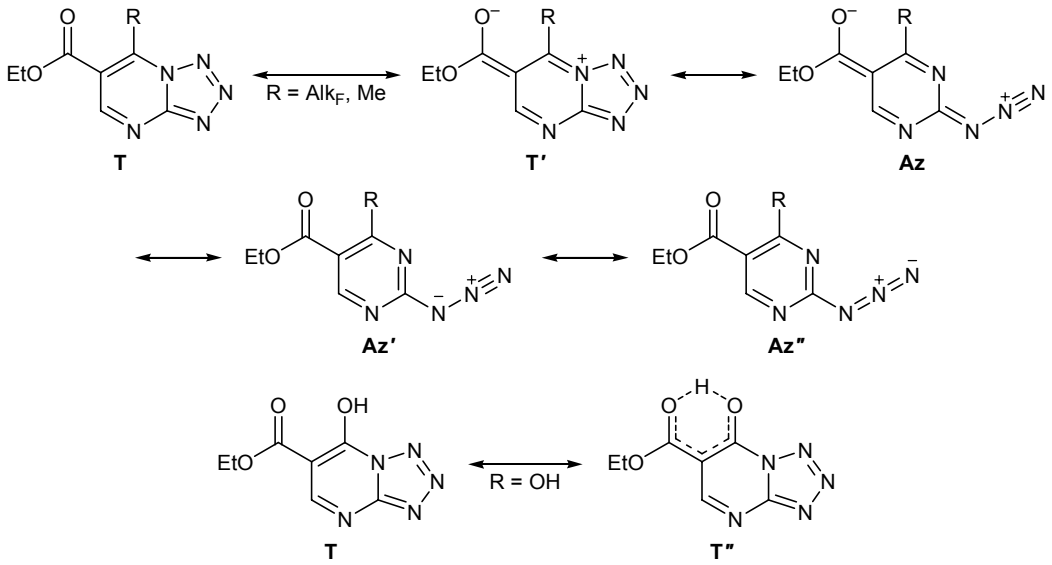
The sets of signals observed in the ^{1}H and ^{13}C NMR spectra of **12** in DMSO-d_6 also corresponded to a single tetrazole tautomer **12A** or **12C**. The two downfield signals of C^{7} and C^{3a} (δ_C 153.48 and 158.63 ppm) in the ^{13}C NMR spectrum were indistinguishable in the HMBC spectrum since both these displayed couplings with 5-H through three bonds ($^{3}J_{CH}$). However, the $^{3}J_{CH}$ value for the C^{3a} fusion atom should be larger than that for C^{7} [32, 33]. By measuring these constants in the proton-coupled ^{13}C NMR spectrum ($^{3}J_{C^{3a}-5\text{-}H}$ = 16.6, $^{3}J_{C^{7}-5\text{-}H}$ = 7.6 Hz) we unambiguously assigned the signal at δ_C 158.63 ppm to C^{3a}.

The structure of **12** was finally proved by a series of 2D ^{1}H–^{15}N HMBC experiments with variation of the pulse delay. The spectrum revealed correlations of 5-H (δ 8.7 ppm) with three ^{15}N nuclei (δ_N 210.6, 247.4, 306.3 ppm), which were assigned to N^{4}, N^{8}, and N^{3}, respectively, taking into account published data [22, 34]. The absence of a correlation between 5-H and N^{8} (δ_N 350–400 ppm), which should be observed for structure **12C**, allowed us to exclude the latter and finally choose regioisomer **12A**.

Despite structural similarity, heterocycles **2a**–**2c** and **12** are differently prone to azido–tetrazole isomerism. Electron-withdrawing substituents in the heterocycle favor opening of the fused tetrazole ring due to reduced electron density on the fusion nitrogen atom [24]. Obviously, the presence of an ethoxycarbonyl group on C^{6} and of a polyfluoroalkyl substituent on C^{7} in molecules **2a** and **2b** should considerably destabilize the fused tetrazole ring, so that the tetrazole–azide equilibrium should be displaced almost completely toward the azido isomer. On the other hand, compound **2c** with an electron-donating methyl group on C^{7} also exists solely as the azido tautomer, in contrast to tetrazolopyrimidine **12** having a hydroxy group in the same position.

The preference of the azide structure of **2c**, as well as of analogs **2a** and **2b**, may be rationalized assuming formation of unstable zwitterionic structure **T′** with the

Scheme 6.



positively charged fusion nitrogen atom (Scheme 6) and negative charge localized on the ester carbonyl oxygen atom. In this case, the electron density on N^8 is considerably reduced despite electron-donating effect of the neighboring methyl group. Opening of the tetrazole ring in **T′** leads to thermodynamically more stable azide tautomer which can be represented by a number of resonance structures (**Az**–**Az″**). Structure **T′** for compound **12** is hardly probable due to keto–enol tautomerism (tautomers **T** and **T″**; Scheme 6).

Thus, the reactions of 2-(ethoxymethylidene)-3-oxo carboxylates **1a**–**1d** with tetrazol-5-amine differ from known cyclizations with other aminoazoles [7–12]; these reactions involve formation of tetrazolopyrimidines only as intermediates due to facile isomerization of the tetrazole ring to azido group. 2-Azidopyrimidines thus obtained are promising reagents for the synthesis of biologically active pyrimidine derivatives by cross coupling at the CH electrophilic center and/or nucleophilic substitution of the azido group.

EXPERIMENTAL

The diffuse reflectance infrared Fourier transform (DRIFT) spectra were recorded on a Perkin Elmer Spectrum One spectrometer, and the attenuated total reflectance (ATR) spectra were measured on a Nicolet 6700 instrument in the range from 400 to 4000 cm^{-1}. The NMR spectra were obtained on Bruker DRX-400 and Bruker Avance-500 spectrometers using tetramethylsilane (^1H, ^{13}C) and C_6F_6 (^{19}F) as reference. All signals in the ^1H and ^{13}C NMR spectra were assigned using two-dimensional ^1H–^{13}C HSQC and HMBC techniques. The mass spectra of **2a**–**2c** and **4b** were recorded on a Thermo Scientific Trace GC Ultra DSQ II GC/MS instrument (TR-5ms column, 30 m× 0.25 mm×0.25 μm), and the mass spectra of **3**, **5**, and **9**–**12** were obtained on a Shimadzu GCMS-QP2010 Ultra instrument. The elemental compositions were determined using a Perkin Elmer PE 2400 Series II analyzer. Silica gel Merck 60 (0.063–0.200 mm) was used for column chromatography. The melting points were measured in open capillaries on a Stuart SMP3 melting point apparatus.

Ethyl 2-(ethoxymethylidene)-3-oxo-3-(polyfluoroalkyl)propanoates **1a** and **1b** [31], ethyl 2-(ethoxymethylidene)-3-oxobutanoate (**1c**) [35], and ethyl 2-benzoyl-3-ethoxyprop-2-enoate (**1d**) [36] were synthesized according to known procedures. Diethyl (ethoxymethylidene)propanedioate (**1e**) (Alfa Aesar) and tetrazol-5-amine monohydrate (Sigma–Aldrich) were commercial products.

2-Azidopyrimidines 2a–2c (*general procedure*). A mixture of 3 mmol of ester **1a**–**1c** and 0.31 g (3 mmol) of tetrazol-5-amine in 20 mL of 2,2,2-trifluoroethanol was heated for 32–38 h under reflux. When the reaction was complete (TLC), the mixture was evaporated to dryness under reduced pressure, and the residue was purified by column chromatography using chloroform as eluent.

Ethyl 2-azido-4-(trifluoromethyl)pyrimidine-5-carboxylate (2a). Yield 0.54 g (69%), yellow oily material. IR spectrum (ATR), ν, cm^{-1}: 2988 (C–H), 2144 (N_3), 1731 (C=O), 1581, 1551 (C=C–C=N), 1195–1084 (C–F). ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.41 t (3H, CH_3, J = 7.1 Hz), 4.44 q (2H, OCH_2, J = 7.1 Hz), 9.13 s (1H, 6-H). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 13.81 (CH_3), 62.90 (OCH_2), 119.57 q (CF_3, $^1J_{CF}$ = 276.6 Hz), 119.67 q (C^5, $^3J_{CF}$ = 0.9 Hz), 155.79 q (C^4, $^2J_{CF}$ = 37.8 Hz), 162.54 (C=O), 162.97 (C^6), 163.89 q (C^2, $^4J_{CF}$ = 1.2 Hz). ^{19}F NMR spectrum (470 MHz, $CDCl_3$): δ_F 95.34 ppm, s (CF_3). Mass spectrum, m/z (I_{rel}, %): 261 (20) $[M]^+$, 233 (37), 216 (33), 188 (22), 162 (17), 148 (6), 133 (10), 120 (17), 106 (11), 92 (34), 69 (81), 53 (28), 29 (100). Found, %: C 36.83; H 2.31; N 26.81. $C_8H_6F_3N_5O_2$. Calculated, %: C 36.79; H 2.32; N 26.82.

Ethyl 2-azido-4-(1,1,2,2-tetrafluoroethyl)pyrimidine-5-carboxylate (2b). Yield 0.53 g (60%), yellow oily material. IR spectrum (ATR), ν, cm^{-1}: 2989, 2940 (C–H), 2146 (N_3), 1732 (C=O), 1581, 1547 (C=C–C=N), 1130–1102 (C–F). ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.41 t (3H, CH_3, J = 7.1 Hz), 4.44 q (2H, OCH_2, J = 7.1 Hz), 6.61 t.t (1H, HCF_2, J_{HF} = 52.9, 5.7 Hz), 9.03 s (1H, 6-H). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 13.89 (CH_3), 63.02 (OCH_2), 109.38 t.t (CF_2H, J_{CF} = 252.0, 31.3 Hz), 112.19 t.t (CF_2, J_{CF} = 255.1, 26.7 Hz), 121.07 (C^5), 158.17 t (C^4, $^2J_{CF}$ = 28.4 Hz), 162.17 (C^6), 163.31 (C=O), 163.39 t (C^2, $^4J_{CF}$ = 1.5 Hz). ^{19}F NMR spectrum (375 MHz, $CDCl_3$), δ_C, ppm: 23.76 d.m (2F, CF_2H, J_{FH} = 52.9 Hz), 44.54 m (2F, CF_2). Mass spectrum, m/z (I_{rel}, %): 293 (20) $[M]^+$, 265 (17), 248 (36), 220 (23), 209 (14), 171 (9), 142 (26), 120 (21), 101 (64), 92 (46), 53 (34), 51 (58), 29 (100). Found, %: C 36.81; H 2.40; N 23.85. $C_9H_7F_4N_5O_2$. Calculated, %: C 36.87; H 2.41; N 23.89.

Ethyl 2-azido-4-methylpyrimidine-5-carboxylate (2c). Yield 0.29 g (46%), yellow oily material. IR spec-

trum (ATR), ν, cm^{-1}: 2984 (C–H), 2144 (N_3), 1725 (C=O), 1576, 1544 (C=C–C=N). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.41 t (3H, CH_3, J = 7.1 Hz), 2.80 s (Me), 4.40 q (2H, OCH_2, J = 7.1 Hz), 9.03 s (1H, 6-H). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 14.16 (CH_3), 24.42 (4-CH_3), 61.48 (OCH_2), 119.30 (C^5), 161.31 (C^6), 163.49 (C^2), 164.21 (C=O), 171.87 (C^4). Mass spectrum, m/z (I_{rel}, %): 207 (53) $[M]^+$, 162 (31), 134 (43), 109 (60), 67 (100), 53 (57), 43 (91), 29 (89). Found, %: C 46.34; H 4.22; N 33.83. $C_8H_9N_5O_2$. Calculated, %: C 46.38; H 4.38; N 33.80.

Ethyl 7-{[2-azido-5-(ethoxycarbonyl)pyrimidin-4-yl]methyl}-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]-pyrimidine-6-carboxylate (3). *a*. A mixture of 0.56 g (3 mmol) of compound **1c** and 0.31 g (3 mmol) of tetrazol-5-amine in 20 mL of ethanol was stirred for 9 days at room temperature. When the reaction was complete (TLC), the mixture was evaporated to dryness under reduced pressure, and the residue was washed with diethyl ether and recrystallized from hexane.

b. Oily compound **2c**, 0.30 g, 0.7 mmol, solidified on storage in air for 12 days at room temperature. The solid material was washed with diethyl ether and recrystallized from hexane. Yield 0.60 g (48%) (*a*), 0.26 g (86%) (*b*); yellow powder, mp 145–146°C. IR spectrum (DRIFT), ν, cm^{-1}: 3325 (N–H), 2982 (C–H), 2137 (N_3), 1705 (C=O), 1577, 1541 (C=C–C=N). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.37 m (6H, $OCH_2C\mathbf{H}_3$), 2.55 s (3H, 5-Me), 3.47 d.d (1H, CH_2, J = 13.4, 3.9 Hz), 4.16 d.d (1H, CH_2, J = 13.4, 7.0 Hz), 4.26 q (2H, OCH_2, J = 7.2 Hz), 4.24–4.35 m (2H, OCH_2'), 6.34 d.d (1H, 7-H, J = 7.0, 3.9 Hz), 9.02 s (1H, 6′-H), 10.72 s (1H, NH). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 14.10 (CH_3), 14.24 (CH_3), 19.42 (5-CH_3), 41.01 (CH_2), 55.28 (C^7), 60.73 (OCH_2), 61.84 (OCH_2'), 97.77 (C^6), 120.17 ($C^{5'}$), 147.83 (C^5), 149.71 (C^{3a}), 161.79 ($C^{6'}$), 163.41 ($C^{2'}$), 163.69 and 164.71 (C=O), 169.09 ($C^{4'}$). Mass spectrum, m/z (I_{rel}, %): 207 (69) $[M/2]^+$, 179 (3), 162 (27), 134 (48), 109 (53), 80 (45), 67 (73), 43 (100). Found, %: C 46.35; H 4.39; N 33.76. $C_{16}H_{18}N_{10}O_4$. Calculated, %: C 46.38; H 4.38; N 33.80.

Compounds 4a and 4b (*general procedure*). *a*. A mixture of 3 mmol of ester **1a** or **1b**, 0.31 g (3 mmol) of tetrazol-5-amine, and 0.20 g (1.5 mmol) of sodium acetate in 25 mL of 1,4-dioxane was heated for 16–18 h under reflux. When the reaction was complete (TLC), the mixture was poured into 100 mL of cold water. The precipitate was filtered off, dried, washed with diethyl ether, and recrystallized from ethanol. The filtrates were used to isolate compound **5**.

b. A mixture of 3 mmol of ester **1a** and **1b**, 0.27 g (3 mmol) of guanidine carbonate, and 0.40 g (3 mmol) of sodium acetate in 15 mL of DMF was stirred for 24–26 h at 80°C. When the reaction was complete (TLC), the mixture was poured into 200 mL of cold water, and the precipitate was filtered off and recrystallized from ethanol.

Ethyl 2-amino-4-(trifluoromethyl)pyrimidine-5-carboxylate (4a). Yield 0.27 g (38%) (*a*), 0.42 g (60%) (*b*); yellow powder, mp 178–179°C; published data [27]: mp 175–177°C. The ^{1}H NMR spectrum of **4a** was identical to that reported in [27].

Ethyl 2-amino-4-(1,1,2,2-tetrafluoroethyl)pyrimidine-5-carboxylate (4b). Yield 0.35 g (44%) (*a*), 0.55 g (68%) (*b*); yellow powder, mp 141–142°C. IR spectrum (DRIFT), ν, cm^{-1}: 3372, 3336, 3212 (NH, NH_2), 1716 (C=O), 1666, 1590, 1543 (C=C–C=N), 1179–1069 (C–F). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.39 t (3H, CH_3, J = 7.2 Hz), 4.37 q (2H, OCH_2, J = 7.2 Hz), 5.80 br.s (2H, NH_2), 6.68 t.t (1H, HCF_2, J_{HF} = 53.4, 5.8 Hz), 8.83 s (1H, 6-H). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 14.01 (CH_3), 62.08 (OCH_2), 109.71 t.t (CF_2H, J_{CF} = 251.6, 30.8 Hz), 112.52 t.t (CF_2, J_{CF} = 254.4, 26.1 Hz), 114.99 (C^5), 158.24 t (C^4, $^2J_{CF}$ = 26.9 Hz), 162.32 (C^6), 162.80 (C^2), 164.14 (C=O). ^{19}F NMR spectrum (470 MHz, $CDCl_3$), δ_F, ppm: 23.46 d.m (2F, CF_2H, J_{FH} = 53.4 Hz), 43.43 m (2F, CF_2). Mass spectrum, m/z (I_{rel}, %): 267 (16) $[M]^+$, 239 (13), 222 (100), 202 (11), 171 (11), 120 (10), 101 (4), 93 (7), 68 (7), 53 (6), 29 (5). Found, %: C 40.52; H 3.41; N 15.75. $C_9H_9F_4N_3O_2$. Calculated, %: C 40.46; H 3.40; N 15.73.

Ethyl 2-(1*H*-tetrazol-5-ylamino)-4-(trifluoromethyl)pyrimidine-5-carboxylate (5). *a*. The filtrates obtained after the isolation and purification of compound **4a** were combined and evaporated. The residue was washed with diethyl ether and recrystallized from ethanol.

b. A mixture of 0.13 g (0.5 mmol) of 2-azidopyrimidine **2a**, 0.05 g (0.5 mmol) of tetrazol-5-amine, and three drops of triethylamine in 15 mL of 1,4-dioxane was heated for 5 days under reflux. When the reaction was complete (TLC), the mixture was poured into 200 mL of cold water, and the precipitate was filtered off and recrystallized from ethanol. Yield 0.14 g (15%) (*a*), 0.13 g (89%) (*b*); white powder, mp 216–218°C. IR spectrum (DRIFT), ν, cm^{-1}: 3252, 3170 (NH), 2967, 2931 (C–H), 1744 (C=O), 1629,

1583, 1551 (C=C–C=N), 1205–1142 (C–F). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.33 t (3H, CH_3, J = 7.1 Hz), 4.36 q (2H, OCH_2, J = 7.1 Hz), 9.12 s (1H, 6-H), 12.50 br.s (1H, NH), 15.81 br.s (1H, 1′-H). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 13.71 (CH_3), 61.98 (OCH_2), 115.89 (C^5), 119.85 q (CF_3, $^1J_{CF}$ = 276.4 Hz), 150.78 br.s ($C^{5'}$), 154.00 q (C^4, $^2J_{CF}$ = 36.4 Hz), 158.36 (C^2), 162.37 (C^6), 162.53 (C=O). ^{19}F NMR spectrum (375 MHz, DMSO-d_6): δ_F 97.20 ppm, s (CF_3). Mass spectrum, m/z (I_{rel}, %): 303 (8) $[M]^+$, 275 (3), 258 (16), 247 (22), 220 (100), 192 (34), 152 (22), 124 (18), 77 (22), 69 (14), 53 (14), 45 (8). Found, %: C 35.62; H 2.60; N 32.25. $C_9H_8F_3N_7O_2$. Calculated, %: C 35.65; H 2.66; N 32.34.

X-Ray diffraction data for compound 5. Single crystals of **5** were grown by crystallization from acetone–ethanol (2 : 1). Monoclinic crystal system, space group $P2_1/c$; $C_9H_8F_3N_7O_2$; M 393.23; unit cell parameters: a = 13.6445(10), b = 8.2009(16), c = 12.3719(17) Å; β = 116.625(11)°; V = 1237.6(3) Å^3; Z = 4; d_{calc} = 1.627 g/cm^3; μ(MoK_α) = 0.133 mm^{-1}; F(000) = 616. Total of 8453 reflection intensities were measured on an Xcalibur 3 diffractometer at 295(2) K (MoK_α radiation, graphite monochromator, CCD detector, ω/2θ scanning); 2256 reflections were independent (R_{int} = 0.0987), and 1940 reflections were characterized by $F_o > 4\sigma(F_o)$. The structure was solved by the direct method, followed by Fourier difference syntheses, using SHELXL-97 software package [37] and was refined by the least-squares procedure in anisotropic approximation for all non-hydrogen atoms using SHELXL-97 [37]; final divergence factors R_1 = 0.0596, wR_2 = 0.1645; goodness of fit 1.004 [for reflections with $I > 2\sigma(I)$]; number of variables 227. The complete set of crystallographic data was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 918900) and is available at *http://www.ccdc.cam.ac.uk/conts/retrieving.html*.

Ethyl 3-(1*H*-tetrazol-5-ylamino)prop-2-enoate (6). A mixture of 0.72 g (3 mmol) of ethyl 3-oxo-4,4,4-trifluoro-2-(ethoxymethylidene)butanoate (**1a**), 0.31 g (3 mmol) of tetrazol-5-amine, and three drops of triethylamine in 25 mL of ethanol was heated for 4 h under reflux. When the reaction was complete (TLC), the mixture was evaporated to dryness under reduced pressure, and the precipitate was washed with diethyl ether and recrystallized from ethanol. Yield 0.24 g (44%), white powder, mp 173–174°C. IR spectrum (DRIFT), ν, cm^{-1}: 3170, 3047 (N–H), 3047, 2967 (C–H), 1692 (C=O), 1624, 1558 (C=C, C=N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.21 t (3H, CH_3, J = 7.1 Hz), 4.09 q (2H, OCH_2, J = 7.1 Hz), 5.53 d (1H, 2-H, J = 13.5 Hz), 7.78 d.d (1H, 3-H, J = 13.5, 11.0 Hz), 10.74 d (1H, NH, J = 11.0 Hz), 16.13 br.s (1H, NH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 14.33 (CH_3), 59.04 (OCH_2), 96.45 (C^2), 141.97 (C^3), 156.11 br.s ($C^{5'}$), 167.10 (C=O). Found, %: C 39.22; H 4.97; N 37.99. $C_6H_9N_5O_2$. Calculated, %: C 39.34; H 4.95; N 38.22.

Compounds 9 and 10. A mixture of 0.65 g (3 mmol) of ethyl 2-benzoyl-3-ethoxyprop-2-enoate (**1d**) and 0.31 g (3 mmol) of tetrazol-5-amine in 25 mL of 2,2,2-trifluoroethanol was heated for 48 h under reflux. When the reaction was complete (TLC), the mixture was evaporated under reduced pressure, and the residue was purified by column chromatography using chloroform as eluent. The first fraction contained ethyl 3-oxo-3-phenylpropanoate (**8**), and next fractions contained compounds **9** and **10**. The fraction containing ester **9** was evaporated under reduced pressure, and the residue was washed with diethyl ether. The fraction containing tetrazolopyrimidine **10** was evaporated to dryness under reduced pressure, and the residue was recrystallized from acetonitrile.

Ethyl 2-benzoyl-3-(1*H*-tetrazol-5-ylamino)prop-2-enoate (9). Yield 0.07 g (8%), white powder, mp 122–124°C. IR spectrum (DRIFT), ν, cm^{-1}: 3493, 3007 (N–H, O–H), 3056, 3031, 2980 (C–H), 1663 (C=O), 1612, 1584 (C=C). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: *E* isomer (60%): 0.97 t (3H, CH_3, J = 7.1 Hz), 3.97 q (2H, OCH_2, J = 7.1 Hz), 7.39–7.58 m (5H, Ph), 8.73 d (1H, 3-H, J = 13.6 Hz), 11.86 d (1H, NH, J = 13.6 Hz); *Z* isomer (40%): 0.92 t (3H, CH_3, J = 7.2 Hz), 4.03 q (2H, OCH_2, J = 7.2 Hz), 7.39–7.58 m (1H, Ph), 8.41 d (1H, 3-H, J = 13.8 Hz), 10.67 d (1H, NH, J = 13.8 Hz). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm, *E* isomer: 13.78 (CH_3), 59.37 (OCH_2), 101.28 (C^2), 127.16 (C^o), 127.58 (C^m), 130.31 (C^p), 141.49 (C^i), 152.18 (C^3), 159.25 ($C^{5'}$), 166.59 and 195.22 (C=O); *Z* isomer: 13.63 (CH_3), 59.36 (OCH_2), 101.76 (C^2), 127.86 (C^o), 128.07 (C^m), 130.99 (C^p), 140.74 (C^i), 151.95 (C^3), 159.44 ($C^{5'}$), 166.87 and 192.37 (C=O). Mass spectrum, m/z (I_{rel}, %): 269 (7) $[M - H_2O]^+$, 241 (1), 213 (2), 196 (2), 129 (6), 105 (62), 77 (24), 45 (100). Found, %: C 54.30; H 4.55; N 24.40. $C_{13}H_{13}N_5O_3$. Calculated, %: C 54.35; H 4.56; N 24.38.

Ethyl 7-(1-ethoxy-1,3-dioxo-3-phenylpropan-2-yl)-5-phenyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate (10). Yield 0.18 g (26%), white powder, mp 109–111°C. IR spectrum (DRIFT), ν, cm^{-1}: 3202, 3151 (O–H), 3073, 3034, 2980 (C–H), 1747, 1674

(C=O), 1637, 1568 (C=C). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 0.88 t (3H, CH_3, J = 7.2 Hz), 1.15 t (3H, CH'_3, J = 7.2 Hz), 3.97 d.q and 4.01 d.q (1H each, OCH_2, J = 10.7, 7.2 Hz), 4.11 q (2H, OCH'_2, J = 7.2 Hz), 5.28 d (1H, 2′-H, J = 2.8 Hz), 6.47 d (1H, 7-H, J = 2.8 Hz), 7.39 m (2H, *o*-H), 7.45–7.53 m (3H, *m*-H, *p*-H), 7.55 m (2H, *m*′-H), 7.63 m (1H, *p*′-H), 8.18 m (2H, *o*′-H), 10.48 s (1H, NH). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ_C, ppm: 13.42 (CH'_3), 13.89 (CH_3), 55.74 (C^7), 59.03 ($C^{2'}$), 60.79 (OCH'_2), 61.69 (OCH_2), 95.60 (C^6), 128.05 (C^o), 128.55 (C^m), 128.98 ($C^{o'}$, $C^{m'}$), 130.40 (C^p), 133.73 ($C^{p'}$), 134.53 (C^i), 135.62 ($C^{m'}$), 149.74 (C^{3a}), 150.39 (C^5), 165.66 (C=O), 167.53 ($C^{1'}$), 192.91 ($C^{3'}$). Mass spectrum, m/z (I_{rel}, %): 269 (10) $[M - 192]^+$, 241 (1), 213 (2), 192 (8) $[PhC(O)CH_2CO_2Et]^+$, 129 (4), 105 (100), 77 (30). Found, %: C 62.18; H 5.00; N 15.11. $C_{24}H_{23}N_5O_5$. Calculated, %: C 62.46; H 5.02; N 15.18.

Compounds 11 and 12. *a*. A mixture of 0.65 g (3 mmol) of diethyl 2-(ethoxymethylidene)propanedioate (**1e**), 0.31 g (3 mmol) of tetrazol-5-amine, and three drops of triethylamine in 25 mL of ethanol was heated for 12 h under reflux. When the reaction was complete (TLC), the mixture was evaporated to dryness under reduced pressure, the residue was ground with chloroform, and the precipitate of **11** was filtered off and recrystallized from ethanol. The filtrate was evaporated, and the residue (compound **12**) was recrystallized from acetonitrile.

b. A mixture of 0.65 g (3 mmol) of diethyl 2-(ethoxymethylidene)propanedioate (**1e**), 0.31 g (3 mmol) of tetrazol-5-amine, and three drops of triethylamine in 25 mL of ethanol was heated for 48 h under reflux. When the reaction was complete (TLC), the mixture was evaporated to dryness under reduced pressure, and the residue was recrystallized from ethanol to obtain compound **12**.

c. A mixture of 0.13 g (0.5 mmol) of ester **11** and 15 mL of ethanol was heated for 36 h under reflux. When the reaction was complete (TLC), the mixture was cooled in a refrigerator, and the precipitate of **12** was filtered off.

Diethyl 2-[(1*H*-tetrazol-5-ylamino)methylidene]-propanedioate (11). Yield 0.41 g (54%) (*a*), white powder, mp 162–164°C. IR spectrum (DRIFT), ν, cm^{-1}: 3300, 3233 (N–H), 2996, 2942 (C–H), 1702, 1649 (C=O), 1605, 1567 (C=C, C=N). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.24 t and 1.27 t (3H each, CH_3, J = 7.1 Hz), 4.16 q and 4.24 q (2H each, OCH_2, J = 7.1 Hz), 8.44 d (1H, CH, J = 13.0 Hz), 11.01 d (1H, NH, J = 13.0 Hz). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 14.02 (CH_3), 14.13 (CH_3), 60.05 (OCH_2), 60.34 (OCH_2), 98.43 (C^2), 148.70 (CH), 155.57 br.s ($C^{5'}$), 164.02 and 166.05 (C=O). Mass spectrum, m/z (I_{rel}, %): 255 (12) $[M]^+$, 227 (8), 210 (21), 198 (76), 152 (100), 124 (62), 85 (13), 53 (86). Found, %: C 42.27; H 5.12; N 27.38. $C_9H_{13}N_5O_4$. Calculated, %: C 42.35; H 5.13; N 27.44.

Ethyl 7-hydroxytetrazolo[1,5-*a*]pyrimidine-6-carboxylate (12). Yield 0.19 g (30%) (*a*), 0.48 g (76%) (*b*), 0.10 g (95%) (*c*); white powder, mp 236–238°C. IR spectrum (DRIFT), ν, cm^{-1}: 3419 (O–H), 1715 (C=O), 1633, 1534 (C=C–C=N). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.28 t (3H, CH_3, J = 7.1 Hz), 3.36 s (OH, H_2O_{solv}), 4.21 q (2H, OCH_2, J = 7.1 Hz), 8.71 s (1H, 5-H). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 14.39 q.t (CH_3, J = 126.6, 2.6 Hz), 59.14 t.q (OCH_2, J = 147.1, 4.5 Hz), 98.15 d (C^6, J = 6.2 Hz), 153.48 d (C^7, $^3J_{C7–5-H}$ = 7.6 Hz), 158.63 d (C^{3a}, $^3J_{C3a–5-H}$ = 16.6 Hz), 160.08 d (C^5, J = 177.6 Hz), 165.39 q (C=O, J = 3.2 Hz). Mass spectrum, m/z (I_{rel}, %): 209 (9) $[M]^+$, 192 (30), 165 (40), 137 (70), 124 (28), 109 (36), 95 (22), 81 (28), 69 (46), 53 (100), 44 (38), 43 (33). Found, %: C 39.99; H 3.39; N 33.30. $C_7H_7N_5O_3$. Calculated, %: C 40.20; H 3.37; N 33.48.

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