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Synthesis and transformations of 4-phenylethynyl- and 4-styrylpyrazolo[5,1-*c*][1,2,4]triazines

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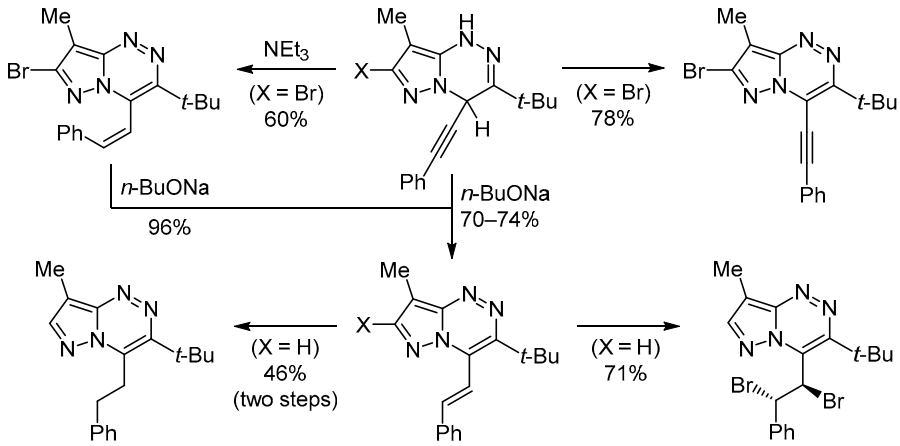


Rearrangements of 3-*tert*-butyl-8-methyl-4-phenylethynyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine derivatives by the action of bases led to the formation of aromatic (*E*)- or (*Z*)-4-styryl-functionalized compounds. At the same time, 4-styryl-1,4-dihydropyrazolotriazines did not rearrange to form the expected 4-phenylethylpyrazolo[5,1-*c*][1,2,4]triazine. The latter was obtained *via* an alternative route by the addition reaction of phenylethynylmagnesium bromide to 3-*tert*-butyl-8-methylpyrazolo[5,1-*c*][1,2,4]triazine, as well as by reduction of double bonds in the ring and side chain of the 4-styryl derivative with subsequent selective oxidation by *N*-bromosuccinimide. The spectral and X-ray structural data as well as the antimicrobial properties of the synthesized compounds are discussed.

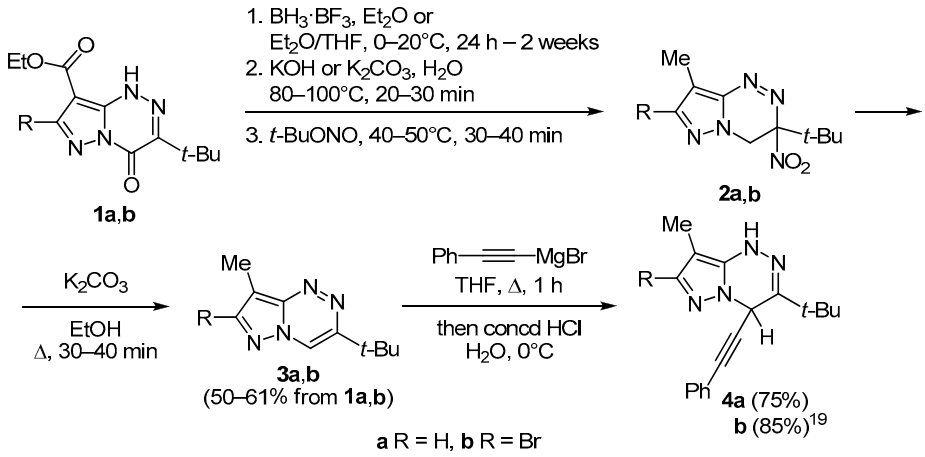
Keywords: 1,2,4-triazine, bromination, hydride shift, oxidation, rearrangement, reduction.

Today, the task of finding ways to synthesize functionalized heterocycles that can be used to create new medications remains urgent. 1,2,4-Triazines are known to exhibit a wide spectrum of biological activity.[1–5] In particular, various derivatives of azolo[1,2,4]triazines are used as effective antifungal,[6] antiviral, and antitumor drugs.[7,8] Methods for the synthesis of such systems have been systematized in a recent review.[9]

Earlier, we obtained a number of azolo[1,2,4]triazines with certain characteristics important for practical applications. In particular, 4-substituted fluoro(pyrazolo-[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)ethanones exhibit moderate antimicrobial activity and have been proposed as a novel type of acidity photogenerators.[10] 3-*tert*-Butyl-8-chalcogenylpyrazolo[5,1-*c*][1,2,4]triazines were synthesized by a metal–halogen exchange reaction followed by the action of elemental sulfur, selenium, or tellurium, and the obtained compounds were characterized.[11,12] Rearrangement of pyrazolotriazines into functionalized pyrrolotriazines was observed in reactions with alkyllithium reagents.[13] It is expected that further investigation of their chemical properties may lead to new potentially biologically active derivatives.

Earlier, the preparation of monocyclic 5,6-arylacetylenyl-1,2,4-triazines in moderate yields *via* the reactions of aromatic 1,2,4-triazines with lithium phenylacetylenides was described.[14,15] The corresponding 3,5,6-arylethynyl derivatives were obtained by adding an oxidizing agent such as DDQ to the reaction mixture.[15] In this case, σ^H-adducts were detected as unstable intermediates. In this study, the chemical properties of 4-phenylacetylenide- and stilbenyl-substituted pyrazolo[5,1-*c*][1,2,4]triazines were studied for the first time, a number of previously unknown saturated and aromatic derivatives were obtained on their

Scheme 1



basis, and the transformations, structure, and antimicrobial activity of the synthesized compounds were examined.

3-*tert*-Butyl-8-methylpyrazolo[5,1-*c*][1,2,4]triazines **3a**,**b** were synthesized by reduction of 4-oxo derivatives **1a**,**b** with borane followed by the action of *t*-BuONO in accordance with the literature data.[16–18] The aromatization of oxidative nitration products **2a**,**b** occurs upon treatment with weak bases (Scheme 1).[19] Previously, it was established on the basis of spectral data that the obtained triazines **3a**,**b** enter into the reactions of selective addition of Grignard reagents at position C-4.[19] In particular, it was shown that treatment of triazine **3b** with phenylethynylmagnesium bromide leads to the formation of compound **4b** (Scheme 1). In this work, we have synthesized for the first time 3-*tert*-butyl-8-methyl-4-phenylethynyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine (**4a**), the structure of which was reliably confirmed using X-ray structural analysis (Fig. 1).

We found that the treatment of stable azolo[1,2,4]-triazines **4a**,**b** containing the phenylethynyl moiety with a catalytic amount of sodium *n*-butylate with slight heating in THF produces (*E*)-3-*tert*-butyl-8-methyl-4-styrylpyrazolo-[5,1-*c*][1,2,4]triazines **5a**,**b** along with a small amount of oxidative degradation products, compounds **6a**,**b** (Scheme 2). The ^{1}H NMR spectra of compounds **5a**,**b** contained the expected doublets of the styryl functionality in the downfield region of 7.29–8.98 ppm with a coupling constant of 16.1–16.2 Hz. The corresponding signals of carbon atoms in the ^{13}C NMR spectra (APT, attached proton test) appeared in the 115.4–115.9 and 144.2–145.1 ppm ranges. The configuration of alkene **5b** was unambiguously established by single crystal X-ray structural analysis (Fig. 2). The spectral characteristics of oxotriazines **6a**,**b** coincided with those previously described.[16,18,19]

On the other hand, the use of a weak base such as triethylamine in reaction with acetylene **4b** led to another geometric isomer of the exocyclic double bond, (Z)-4-styrylpyrazolo[5,1-*c*][1,2,4]triazine **7** (Scheme 2). In this case, the formation of trace amounts of (*E*)-alkene **5b** was also detected (by TLC). The structure of compound **7** is convincingly confirmed by its chemical properties and

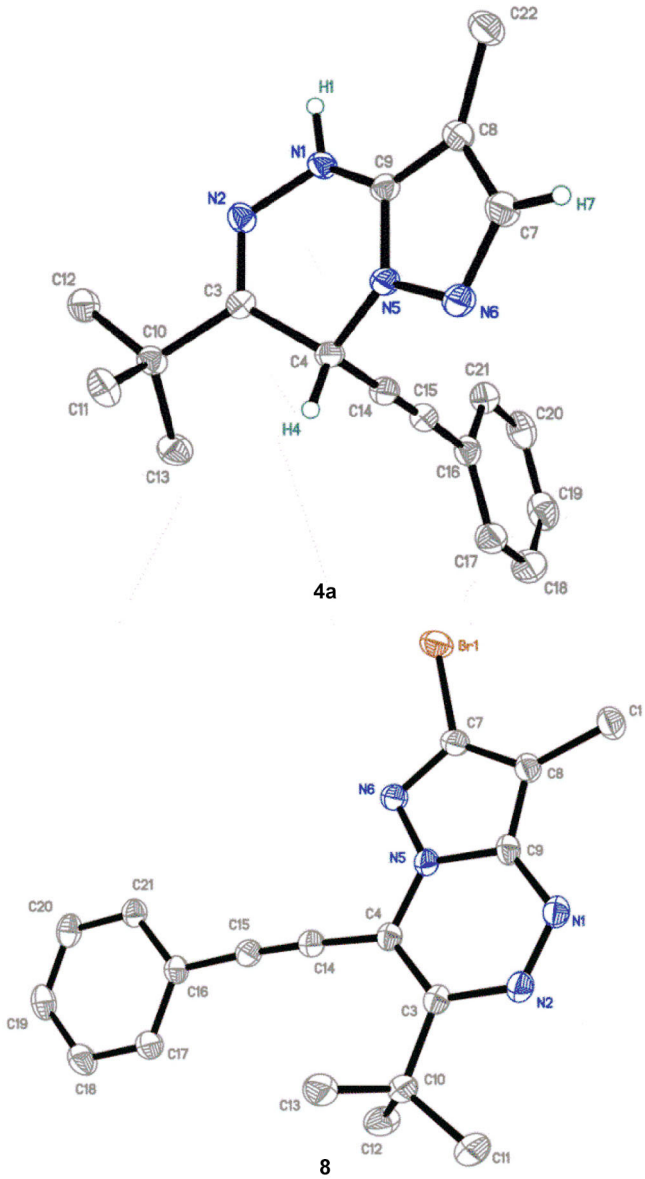
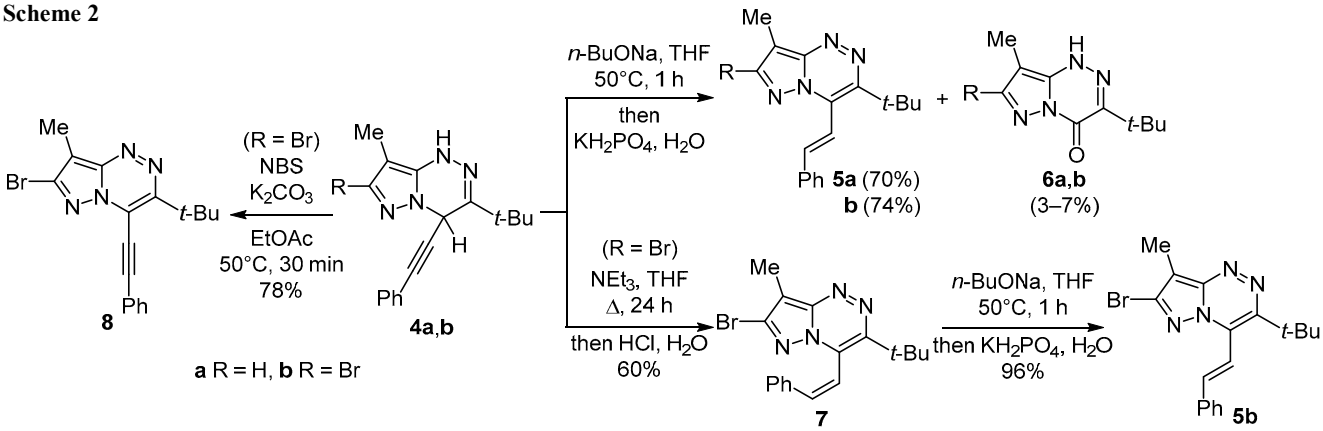


Figure 1. The molecular structure of compounds **4a** and **8** with atoms represented as thermal vibration ellipsoids of 50% probability. Hydrogen atoms of methyl and phenyl groups are not shown.

Scheme 2



spectral data. Thus, the high-resolution mass spectrum of product **7** is practically identical to the spectrum of alkene **5b**: *m*/*z* 371.0867 $[M+H]^+$. At the same time, the ^{13}C NMR spectrum (APT) of compound **7** showed signals of the Ph–CH=CH group at 115.9 and 138.7 ppm. (*Z*)-Alkene **7** is unstable; it can be isolated individually using flash chromatography, and at room temperature in the absence of a catalyst it slowly transforms into (*E*)-isomer **5b**. Similar isomerization reactions are known for substituted stilbenes.[20] Quantitative (96%) formation of (*E*)-alkene **5b** from (*Z*)-alkene **7** was observed upon addition of *n*-BuONa (Scheme 2).

The oxidation of the triazine ring of 4-phenylethynyl-1,4-dihydro derivative **4b** without affecting the triple bond was carried out using *N*-bromosuccinimide and K_2CO_3 in EtOAc. 7-Bromo-3-*tert*-butyl-8-methyl-4-(phenylethynyl)-pyrazolo[5,1-*c*][1,2,4]triazine (**8**) was isolated in good yield (78%). According to X-ray structural analysis data (Fig. 1), the Ph–C≡C–C(4) group in compound **8** lies in the plane of the heterocycle (the largest deviation was less than 4°), whereas in the partially hydrogenated analog **4a** the acetylenyl substituent is practically orthogonal to the azolo-triazine fragment. Despite the increased steric hindrance, aromatization led to a decrease in the PhCC–C(4) bond length (by about 0.06 Å).

To investigate the possibility of synthesizing 4-phenyl-ethylpyrazolotriazine **10**, we performed selective reduction of the triazine ring in alkenes **5a**,**b** using $LiBH_4$ with the isolation of 1,4-dihydro derivatives **9a**,**b** (Scheme 3). The reactions were carried out in an EtOAc–MeOH mixture in the presence of a phase-transfer catalyst. The IR spectrum of compounds **9a**,**b** shows characteristic absorption bands of the N–H groups at 3190 (compound **9a**) and 3051 cm^{-1} (compound **9b**). The ^1H NMR spectra showed the expected 4-CH and N–H signals at 5.65, 9.52 (compound **9a**) and 5.58, 9.89 ppm (compound **9b**), respectively, while the coupling constants of the protons at the double bond of the alkene fragment were 15.9–16.0 Hz. The peaks of C-4 atoms in the ^{13}C NMR spectra are localized at 54.12 (compound **9a**) and 54.11 ppm (compound **9b**). The spatial structure of compound **9b** was also confirmed by X-ray structural analysis (Fig. 2). Compound **9b** has the expected *E*-configuration at the double bond; in this case, the planar 1,2,4-triazine ring

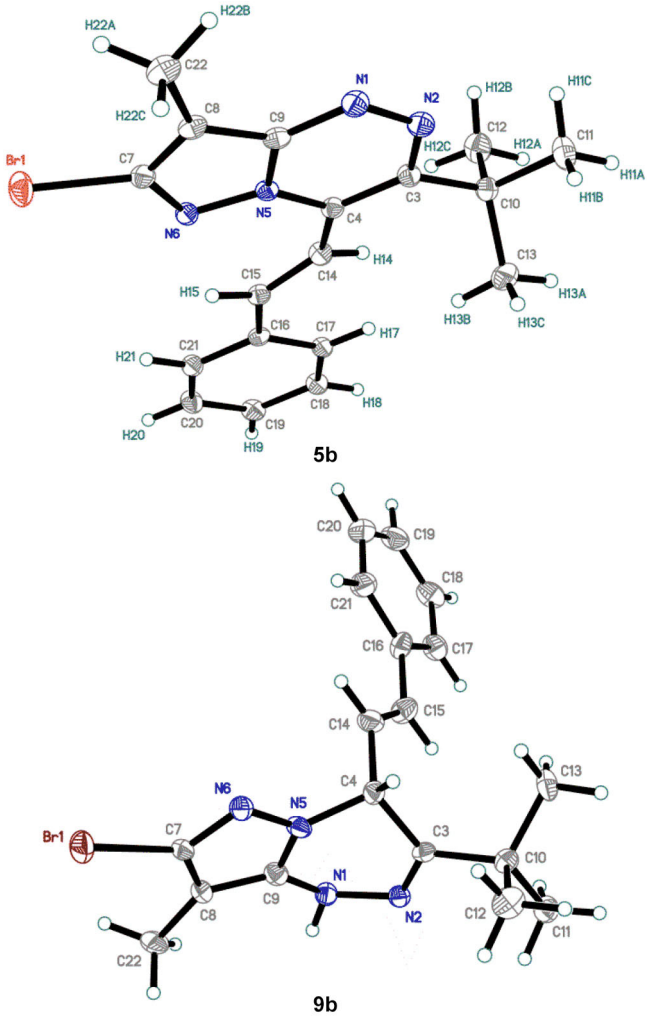
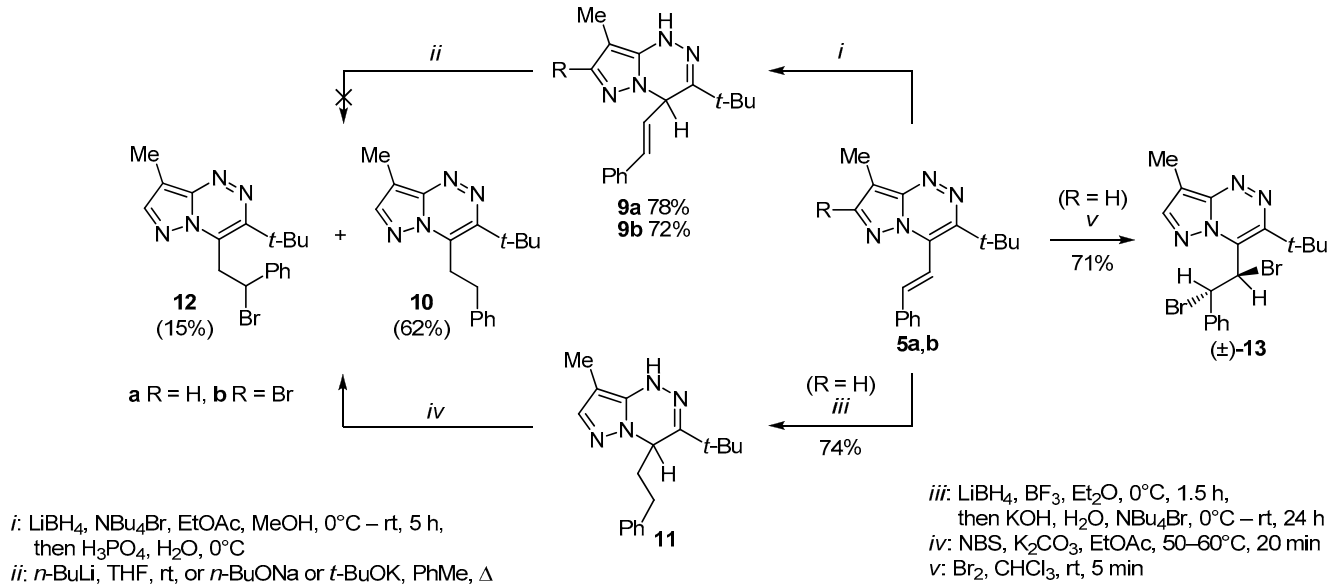


Figure 2. The molecular structure of compounds **5b** and **9b** with atoms represented as thermal vibration ellipsoids of 50% probability.

upon reduction transforms into the half-chair configuration, similar to acetylene **4a**.

It was experimentally found that derivatives **9a**,**b** are stable to the action of various bases and are not isomerized to the expected aromatic triazine **10** even under severe conditions: when compounds **9a**,**b** are treated with *n*-BuLi in THF at room temperature or with butyl anions in PhMe

Scheme 3



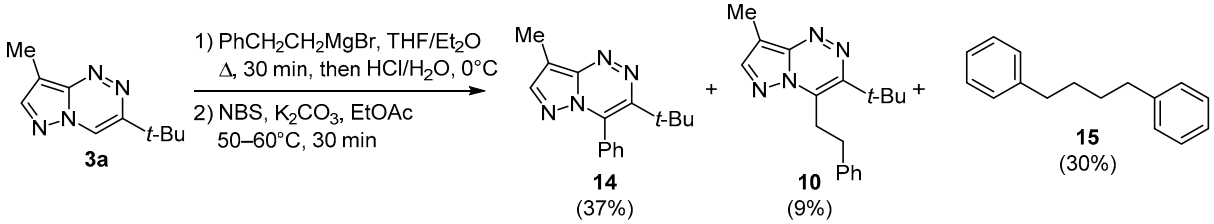
under reflux, only the starting compounds were isolated from the reaction mixture after acidification.

Compound **10** was obtained by a counter synthesis in two steps from alkene **5a**. The action of diborane generated *in situ* from $LiBH_4$ and $BF_3 \cdot Et_2O$ on triazine **5a** at low temperature led to the reduction of double bonds of the heterocycle and the side chain (Scheme 3). The ^{13}C NMR spectrum of reaction product **11** does not contain signals of the alkene fragment, while new peaks of the carbon atoms of the $PhCH_2CH_2$ fragment are observed in the aliphatic region at 34.5, 39.9 ppm. The high-resolution mass spectrum confirms the structure of compound **11** by recording the molecular ion peak with *m*/*z* 297.2078 $[M+H]^+$. An attempt to synthesize compound **11** by reduction of acetylene **4a** was unsuccessful. Treatment of pyrazolotriazine **11** with *N*-bromosuccinimide under slight heating led to the isolation of a mixture of the expected aromatization product **10** and bromo derivative **12** (Scheme 3). The formation of the latter can be explained by the simultaneous reaction of free radical bromination at the benzyl position.[21] At the same time, we obtained a diastereomerically pure product **13** by electrophilic bromination[22,23] of stilbene **5a** by the action of Br_2 (Scheme 3). Compounds **12** and **13** turned out to be unstable at room temperature, apparently due to intra- or intermolecular quaternization reactions previously described for 1,2,4-triazines.[24,25]

In the spectra of compound **10**, a downfield shift of the signals of the $PhCH_2CH_2$ group by 1.3 ppm (in the ^1H NMR spectrum) and by 4.2 ppm (in the ^{13}C NMR spectrum) in comparison with the signals of the starting hydrogenated triazine **11** was observed, which confirms the formation of an aromatic system. The ^1H NMR spectrum of the substituted benzyl bromide **12** showed a new triplet at 5.86 ppm, assigned to the Ph–C<u>H</u>Br–CH_2 proton. The spectrum of derivative **13** contained signals of the C<u>H</u>Br–C<u>H</u>Br fragment in the form of two doublets at 6.35 and 7.08 ppm with a coupling constant of 11.1 Hz. High-resolution mass spectra data for compounds **10**, **12**, and **13** were as expected.

An alternative synthesis of compound **10** can be carried out by a simpler route from compound **3a** and phenylethylmagnesium bromide with further oxidation of the intermediate addition product **11**. We have established experimentally that the reaction of compound **3a** with $PhCH_2CH_2MgBr$ (obtained from phenylethyl bromide and magnesium in diethyl ether under reflux[26]) followed by hydrolysis of the reaction mixture and oxidation with *N*-bromosuccinimide leads to 3-*tert*-butyl-8-methyl-4-phenylpyrazolo[5,1-*c*][1,2,4]triazine (**14**) as the main reaction product (Scheme 4). The expected triazine **10** (9%) and 1,4-diphenylbutane (**15**) (30%) were also isolated in low yields (the latter was characterized by X-ray structural analysis (Fig. 3)).

Scheme 4



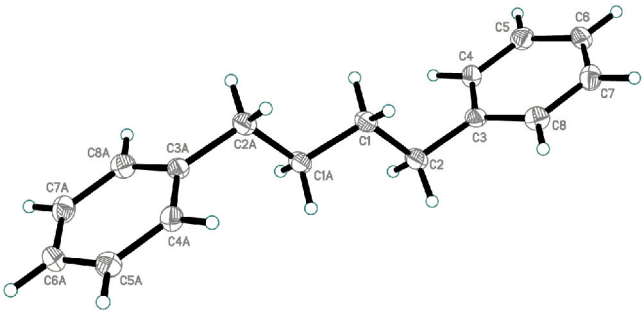


Figure 3. The molecular structure of compound **15** with atoms represented as thermal vibration ellipsoids of 50% probability.

In the spectra of phenyl-substituted triazine **14**, there were no signals in the aliphatic region except for the singlets of the C(8)–Me and *t*-Bu groups at 2.64 and 1.40 ppm, respectively. The structure of product **14** was unambiguously confirmed by X-ray structural analysis (Fig. 4). The phenyl ring is practically in antiperiplanar conformation with respect to the triazine ring, which indicates the absence of mutual π-conjugation. Apparently, the release of the ethylene molecule[27] occurs at the stage of the reaction of the starting triazine **3a** with the *in situ* generated Grignard reagent, since we did not observe the formation of product **14** in the reactions of triazine **11** with *N*-bromosuccinimide.

Compounds **3b**, **4a**, **5a**, **8**, **9a** were investigated for the presence of antibacterial activity against resistant opportunistic strains of Gram-negative bacteria *Enterobacter cloacae* sp. (clinical strain, multidrug resistance) and *Escherichia coli* (DH52 REF Amp100, recombinant ampicillin-resistant strain) (Table 1).

Compound **8** exhibited bacteriostatic activity against the *Escherichia coli* strain at a concentration of 128 μg/ml. The rest of the compounds did not possess noticeable antibacterial properties against the studied strains in the concentration range of 128–256 μg/ml. The value of the minimum inhibitory concentration of compound **8** will be clarified in subsequent experiments with lower concentrations of the substance. The experiments will continue on strains of Gram-positive bacteria (*Staphylococcus aureus*) and yeast-like fungi (*Candida albicans*).

Table 1. Antibacterial activity of compounds **3b**, **4a**, **5a**, **8**, **9a**

Compound	Solvent	Minimum inhibitory concentration, μg/ml	
		Escherichia coli (DH52 REF Amp100)*	*Enterobacter cloacae* sp.
3b	0.5% DMSO/H_2O (40°C)	>256	>256
4a	0.5% DMSO/H_2O (40°C)	>256	>256
5a	0.5% DMSO/H_2O (40°C)	>256	>256
8	0.5% DMSO/H_2O (40°C)	128	>256
9a	0.5% DMSO/H_2O (40°C)	>256	>256
Pefloxacin	–	<0.5	<0.5

* Recombinant ampicillin-resistant strain.

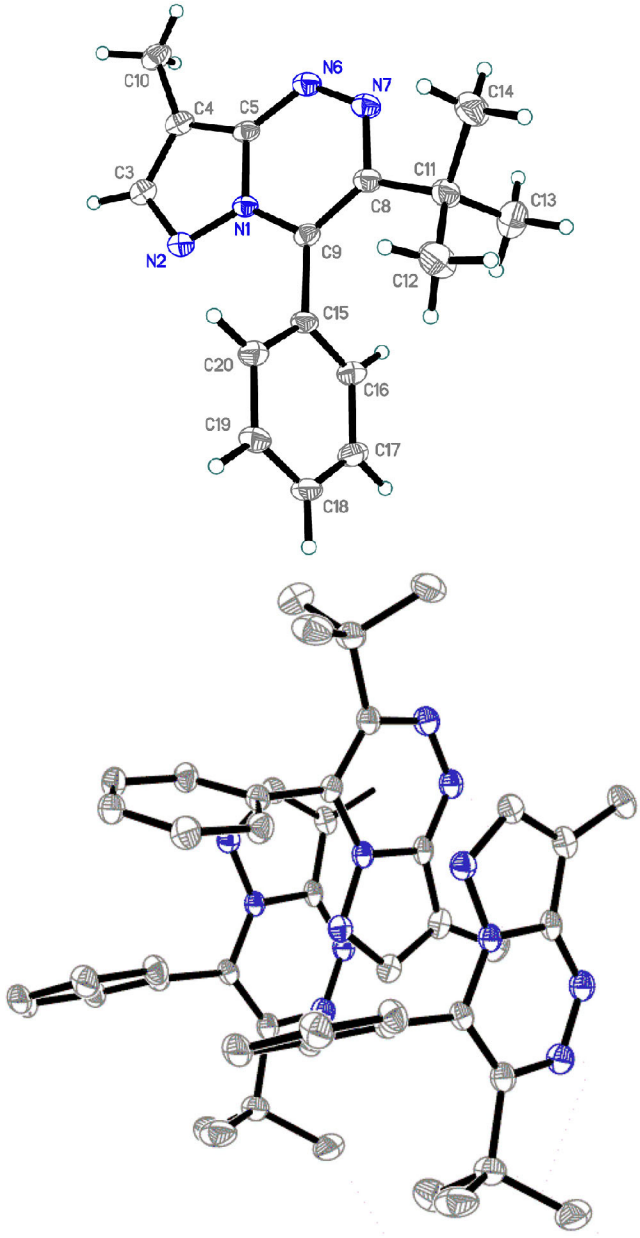


Figure 4. Molecular structure of compound **14** and its packing in the solid state with atoms represented by thermal vibration ellipsoids of 50% probability. The hydrogen atoms of the methyl and phenyl groups in the latter case are not shown.

To conclude, as a result of this work the directions of rearrangements of 3-*tert*-butyl-8-methyl-4-phenylethynyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazines were established for the first time. It was demonstrated that 4-styryl-1,4-dihydropyrazolotriazines do not enter this reaction with the formation of the expected 4-phenylethylpyrazolo[5,1-*c*]-[1,2,4]triazine. The latter was obtained by an counter synthesis, by the reduction of double bonds in the ring and the side chain of a 4-styryl derivative followed by oxidative bromination. The chemical properties, spectral, and X-ray structural characteristics of the isolated compounds were investigated. The aromatic 4-phenylethynyl derivative exhibited weak bacteriostatic activity.

Experimental

IR spectra were registered on an Agilent Cary 660 FTIR Fourier transform spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra (APT, attached proton test) were acquired on Bruker AM-300 (300 and 75 MHz, respectively) and Bruker DRX-500 (500 and 126 MHz, respectively) spectrometers in DMSO-d_6 or $CDCl_3$. The residual signals of DMSO-d_6 (2.50 ppm for ^{1}H nuclei and 39.5 ppm for ^{13}C nuclei) and $CDCl_3$ (7.26 ppm for ^{1}H nuclei and 77.2 ppm for ^{13}C nuclei) served as internal standards. High-resolution mass spectra were recorded on a Bruker micrOTOF II mass spectrometer (electrospray ionization, solvent MeOH or MeCN) in the positive ion registration mode (capillary voltage 4500 V). Melting points were determined on a STUART SMP30 apparatus. Monitoring of the reaction progress was done by TLC. Merck Silica gel, 60–200 μm was used for column chromatography. All reactions were carried out in an argon atmosphere (99.9990% purity).

THF and Et_2O were purified by distillation over K/Na in an argon atmosphere. Compounds **3a**,**b**, and **4b** were synthesized according to a previously described procedures.[16–19]

3-*tert*-Butyl-8-methyl-4-phenylethynyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine (4a). *n*-BuMgBr–Et_2O solution (27 ml, 32 mmol) was added dropwise with continuous stirring over 10 min at room temperature to a solution of phenylacetylene (3.5 ml, 32 mmol) in THF (100 ml). After the addition was complete, the mixture was stirred for another 20 min, and compound **3a** (3.0 g, 15.8 mmol) was added to the obtained phenylethynylmagnesium bromide. The reaction mixture was heated under reflux for 1 h; after cooling to room temperature, H_2O (200 ml) and concentrated HCl (20 ml) were successively added dropwise. The mixture was kept at room temperature for 24 h. After evaporation of THF, the formed precipitate was filtered and sequentially washed on filter with H_2O and EtOAc–hexane, 1:20 mixture, then air-dried. Yield 2.25 g (75%), white powder, mp 205–215°C (subl.). IR spectrum, ν, cm^{-1}: 3270, 3193, 3100 (NH), 3080, 3051, 2971, 2935, 2903, 2869 (CH), 1631, 1593, 1543, 1513, 1490, 1469, 1464, 1443, 1403, 1365, 1344, 1325, 1281, 1259, 1240, 1221, 1157, 1124, 1096, 1070, 1036, 994, 977, 906, 849, 814, 793, 757, 691, 657, 603, 534, 426. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.29 (9H, s, 3CH$_3$); 2.50 (3H, s, 8-CH$_3$); 6.29 (1H, s, 4-CH); 7.21 (1H, s, 7-CH); 7.32–7.37 (5H, m, H Ph); 10.49 (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 7.5 (CH$_3$); 28.9 (C(<u>C</u>H$_3$)$_3$); 37.5 (<u>C</u>(CH$_3$)$_3$); 44.3 (C-4); 84.2 (C(4)<u>C</u>CPh); 85.8 (C(4)C<u>C</u>Ph); 93.5 (C-8); 121.7 (C-8a); 129.2 (3,5-CH Ph); 129.5 (4-CH Ph); 131.7 (2,6-CH Ph); 136.8 (C-1 Ph); 140.9 (C-7); 145.4 (C-3). Found, *m*/*z*: 293.1761 [M+H]$^+$. $C_{18}H_{21}N_4$. Calculated, *m*/*z*: 293.1761.

Synthesis of compounds 5a,b and 6a,b (General procedure). Method I. Compound **4a** (3.0 g, 10.3 mmol) or compound **4b** (2.0 g, 5.39 mmol) (for the synthesis of compounds **5a** or **5b**, respectively) was dissolved in a mixture of THF (100 ml) and *n*-BuOH (10 ml), and NaH (60% dispersion in mineral oil; 0.5 g, 12.5 mmol) was added in one portion. The reaction mixture was heated to 50°C and stirred for 1 h at this temperature. After cooling to room temperature, saturated aqueous KH_2PO_4 (10 ml) was added dropwise and the mixture was stirred for 15 min. Then, *n*-heptane (30 ml) was added, and the resulting solution was dried over anhydrous $MgSO_4$. The organic phase was decanted and evaporated under reduced pressure at 50°C. The residue was washed with a heated (55°C) MeOH–H_2O, 1:1 mixture (3×10 ml), filtered, and air-dried to obtain compound **5a** or **5b**. The filtrate was evaporated under reduced pressure, the residue was purified by column chromatography on silica gel (eluent EtOAc–hexane, 1:40–1:2) to give compound **6a** or **6b**. Spectral characteristics and mp for compounds **6a**,**b** (yield of compound **6a** was 100–150 mg (5–7%), compound **6b** – 40–80 mg (3–5%)) correspond to the literature.[18,19]

Method II. Compound **5b** was obtained according to method I from compound **7** (0.5 g, 1.35 mmol).

3-*tert*-Butyl-8-methyl-4-((*E*)-styryl)pyrazolo[5,1-*c*]-[1,2,4]triazine (5a). Yield 2.1 g (70%, method I), yellow powder, mp 152–154°C (decomp.). IR spectrum, ν, cm^{-1}: 3065, 3027, 2991, 2965, 2920, 2871 (CH), 1610, 1576, 1496, 1476, 1455, 1384, 1368, 1318, 1293, 1248, 1216, 1192, 1152, 1114, 1033, 997, 978, 965, 926, 897, 773, 741, 717, 681, 633, 617, 593, 531, 486, 472. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.65 (9H, s, 3CH$_3$); 2.54 (3H, s, 8-CH$_3$); 7.29–7.40, 7.54–7.60 (6H, m, H Ph, C<u>H</u>CHPh); 8.00 (1H, s, 7-CH); 8.92 (1H, d, $^3J_{HH}$ = 16.1, CHC<u>H</u>Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 7.6 (8-CH$_3$); 31.8 (C(<u>C</u>H$_3$)$_3$); 37.4 (<u>C</u>(CH$_3$)$_3$); 107.7 (C-8); 115.9 (<u>C</u>HCHPh); 127.6 (3,5-CH Ph); 128.1 (C-4); 129.1 (2,6-CH Ph); 129.9 (4-CH Ph); 136.6 (C-1 Ph); 144.0 (C-7); 144.2 (CH<u>C</u>HPh); 148.7 (C-8a(3)); 149.2 (C-3(8a)). Found, *m*/*z*: 293.1752 [M+H]$^+$. $C_{18}H_{21}N_4$. Calculated, *m*/*z*: 293.1761.

7-Bromo-3-*tert*-butyl-8-methyl-4-((*E*)-styryl)pyrazolo-[5,1-*c*][1,2,4]triazine (5b). Yield 1.48 g (74%, method I), 0.48 g (96%, method II), bright-yellow crystals, mp 181–183°C (decomp.). IR spectrum, ν, cm^{-1}: 2980, 2918 (CH), 1612, 1576, 1566, 1496, 1476, 1460, 1380, 1368, 1321, 1275, 1242, 1194, 1145, 1118, 1061, 971, 772, 757, 744, 686. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.74 (9H, s, 3CH$_3$); 2.57 (3H, s, 8-CH$_3$); 7.43–7.50 (3H, m, H-3–5 Ph); 7.61 (H, d, $^3J_{HH}$ = 16.2, C<u>H</u>CHPh); 7.69 (2H, d, $^3J_{HH}$ = 6.9, H-2,6 Ph); 8.98 (H, d, $^3J_{HH}$ = 16.2, CHC<u>H</u>Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 8.0 (8-CH$_3$); 31.7 (C(<u>C</u>H$_3$)$_3$); 37.7 (<u>C</u>(CH$_3$)$_3$); 107.9 (C-8); 115.4 (<u>C</u>HCHPh); 127.6 (C-4); 127.9 (3,5-CH Ph); 129.2 (2,6-CH Ph); 130.2 (4-CH Ph); 136.2 (C-1 Ph); 136.6 (C-7); 145.1 (CH<u>C</u>HPh); 148.5 (C-8a(3)); 150.0 (C-3(8a)). Found, *m*/*z*: 371.0858 [M+H]$^+$. $C_{18}H_{20}BrN_4$. Calculated, *m*/*z*: 371.0866.

7-Bromo-3-*tert*-butyl-8-methyl-4-((*Z*)-styryl)pyrazolo-[5,1-*c*][1,2,4]triazine (7). NEt_3 (3 ml, 21.5 mmol) was added to a solution of compound **4b** (1.0 g, 2.7 mmol) in THF (10 ml), and the resulting mixture was heated under reflux for 24 h (TLC control for the disappearance of compound **4b**). The solvents were evaporated under reduced pressure, and H_2O (50 ml) and EtOAc (50 ml) were added. The organic phase was washed with 5% aqueous HCl (2×50 ml) followed by H_2O (100 ml), and

dried over anhydrous $MgSO_4$. The mixture was filtered, the filtrate was evaporated under reduced pressure at 55°C. Compound **7** was isolated by column chromatography on silica gel (eluent EtOAc–hexane, 1:20–1:10). Yield 0.6 g (60%), yellow powder, mp 88–90°C (decomp.). IR spectrum, ν, cm^{-1}: 3051, 2979, 2970, 2918, 2868 (CH), 1659, 1653, 1637, 1612, 1575, 1545, 1497, 1461, 1443, 1400, 1381, 1367, 1320, 1267, 1242, 1218, 1191, 1175, 1144, 1122, 1048, 970, 952, 786, 743, 690, 668, 651, 548, 521. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.52 (9H, s, $3CH_3$); 2.53 (3H, s, 8-CH_3); 6.74–6.78 (3H, m, H Ph, CHCHPh); 7.08–7.21 (4H, m, H Ph, CHCHPh). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 8.0 (8-CH_3); 30.5 (C(CH_3)$_3$); 37.6 (C(CH_3)$_3$); 108.4 (C-8); 115.9 (CHCHPh); 127.8 (3,5-CH Ph); 128.6 (2,6-CH Ph); 129.0 (4-CH Ph); 135.6 (C-1 Ph); 136.3 (C-7); 138.7 (CHCHPh); 147.0 (C-8a(3)); 149.9(C-3(8a)). Found, *m*/*z*: 371.0867 $[M+H]^+$. $C_{18}H_{20}BrN_4$. Calculated, *m*/*z*: 371.0866.

7-Bromo-3-*tert*-butyl-8-methyl-4-(phenylethynyl)pyrazolo[5,1-*c*][1,2,4]triazine (8). Ground K_2CO_3 (5.0 g, 36.2 mmol) followed by *N*-bromosuccinimide (0.23 g, 1.3 mmol) was added to the colorless solution of compound **4b** (0.5 g, 1.3 mmol) in EtOAc (50 ml); a change in the color of the solution to dark-orange was observed. The reaction mixture was heated to 50°C and stirred vigorously for 30 min. Upon completion of the reaction, the reaction mixture was cooled to room temperature, H_2O (100 ml) and Na_2SO_3 (2.0 g, 15.9 mmol) were added, and the mixture was stirred for 15 min. Then, the organic phase was separated, and the aqueous solution was extracted with EtOAc (3×20 ml). The combined organic phases were dried over anhydrous $MgSO_4$, the drying agent filtered off, and the filtrate was evaporated under reduced pressure. Compound **5** was isolated by column chromatography on silica gel (eluent EtOAc–hexane, 1:50–1:30). Yield 0.39 g (78%), yellow crystals, mp 141–142°C. IR spectrum, ν, cm^{-1}: 3060, 2970, 2956, 2925, 2902, 2866 (CH), 2207, 1998 (C≡C), 1686, 1658, 1653, 1607, 1622, 1571, 1528, 1502, 1472, 1458, 1444, 1422, 1363, 1383, 1336, 1313, 1250, 1268, 1208, 1160, 1178, 1142, 1115, 1050, 1067, 1022, 994, 952, 924, 840, 762, 691, 675, 649, 613, 553, 572, 525. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.76 (9H, s, $3CH_3$); 2.57 (3H, s, 8-CH_3); 7.46–7.56 (3H, m, H-3–5 Ph); 7.74–7.79 (2H, m, H-2,6 Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 8.1 (8-CH_3); 30.0 (C(CH_3)$_3$); 37.5 (C(CH_3)$_3$); 78.8 (C-1 Ph); 109.6 (C-8); 112.4 (C≡C–Ph); 116.0 (C≡C–Ph); 120.9 (C-4); 128.9 (3,5-CH Ph); 131.0 (4-CH Ph); 132.2 (2,6-CH Ph); 136.7, 147.17, 153.30 (C-3,7,8a). Found, *m*/*z*: 369.0708 $[M+H]^+$. $C_{18}H_{18}BrN_4$. Calculated, *m*/*z*: 369.0709.

Synthesis of compounds 9a,b (General method). Compound **5a** (1.0 g, 3.4 mmol) or compound **5b** (0.6 g, 1.6 mmol) was dissolved in a mixture of EtOAc (30 ml) and MeOH (5 ml), and the resulting solution was cooled to 0°C in an ice bath. $LiBH_4$ (0.8 g, 36.7 mmol) was added to the cooled solution in small portions over 10 min. Then, NBu_4Br (0.5 g, 1.5 mmol) was added, and the resulting mixture was stirred for 5 h at room temperature. Next, cooled (0°C) H_2O (100 ml) was added, followed by a dropwise addition of 85% aqueous H_3PO_4 (7 ml, 0.1 mol) with vigorous stirring. The organic phase was separated, washed successively with 5% aqueous H_3PO_4 (3×50 ml), H_2O (100 ml), dried over anhydrous $MgSO_4$, and filtered. The filtrate was evaporated under reduced pressure at 50°C. The compounds were isolated by column chromatography on silica gel (eluent EtOAc–hexane, 1:10–1:7)

3-*tert*-Butyl-8-methyl-4-((*E*)-styryl)-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine (9a). Yield 0.78 g (78%), mp 200–210°C (subl.). IR spectrum, ν, cm^{-1}: 3263, 3190 (NH), 3097, 3078, 2971, 2934, 2902, 2870 (CH), 1687, 1658, 1652, 1627, 1591, 1565, 1560, 1544, 1510, 1497, 1472, 1463, 1454, 1405, 1364, 1341, 1261, 1215, 1079, 1028, 987, 975, 927, 872, 852, 785, 744, 691. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.18 (9H, s, $3CH_3$); 1.91 (3H, s, 8-CH_3); 5.65 (1H, d, $^3J_{HH}$ = 7.2, 4-CH); 6.03 (1H, dd, $^3J_{HH}$ = 16.0, $^3J_{HH}$ = 7.2, PhCHCH); 6.33 (1H, d, $^3J_{HH}$ = 16.0, PhCHCH); 7.04–7.22 (5H, m, H Ph); 7.09 (1H, s, 7-CH); 9.52 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 6.7 (8-CH_3); 28.4 (C(CH_3)$_3$); 36.6 (C(CH_3)$_3$); 54.1 (C-4); 126.0 (3,5-CH Ph); 127.5 (4-CH Ph); 128.1 (2,6-CH Ph) (signals of some carbon atoms are not observed due to the low solubility of the sample). Found, *m*/*z*: 295.1925 $[M+H]^+$. $C_{18}H_{23}N_4$. Calculated, *m*/*z*: 295.1917.

7-Bromo-3-*tert*-butyl-8-methyl-4-((*E*)-styryl)-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine (9b). Yield 0.43 g (72%), light-yellow powder, mp 221–222°C. IR spectrum, ν, cm^{-1}: 3463, 3434, 3398, 3341, 3307, 3293, 3247, 3175, 3076, 3051 (NH), 2969, 2931, 2867, 2750 (CH), 1685, 1652, 1621, 1583, 1538, 1492, 1472, 1452, 1395, 1378, 1352, 1316, 1276, 1249, 1200, 1128, 1099, 1055, 1009, 974, 923, 905, 873, 789, 812, 753, 731, 695, 635, 608, 538, 507, 432. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.17 (9H, s, $3CH_3$); 1.86 (3H, s, 8-CH_3); 5.58 (1H, d, $^3J_{HH}$ = 7.6, 4-CH); 6.00 (1H, dd, $^3J_{HH}$ = 15.9, $^3J_{HH}$ = 7.6, PhCHCH); 6.38 (1H, d, $^3J_{HH}$ = 15.9, PhCHCH); 7.04–7.22 (5H, m, H Ph); 9.89 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 6.8 (8-CH_3); 28.3 (C(CH_3)$_3$); 36.7 (C(CH_3)$_3$); 54.1 (C-4); 93.6 (C-8); 122.0 (CHCHPh); 126.0 (3,5-CH Ph); 127.5 (4-CH Ph); 127.9 (2,6-CH Ph); 128.0 (C-1 Ph); 132.9 (CHCHPh); 135.0, 148.7, 149.9 (C-3,7,8a). Found, *m*/*z*: 373.1008 $[M+H]^+$. $C_{18}H_{22}BrN_4$. Calculated, *m*/*z*: 373.1022.

3-*tert*-Butyl-8-methyl-4-(2-phenylethyl)-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine (11). Compound **5a** (0.5 g, 1.7 mmol) was dissolved in Et_2O (40 ml), and the resulting solution was cooled to 0°C in an ice bath. $BF_3 \cdot Et_2O$ (5 ml, 40.5 mmol) was added in one portion to the cooled solution, then $LiBH_4$ (1.1 g, 50.5 mmol) was added with vigorous stirring in small portions over 30 min. The mixture was then stirred for another hour at the same temperature. Next, cooled (0°C) H_2O (10 ml) was added dropwise over 10 min and with vigorous stirring. Then, the reaction mixture was carefully poured into H_2O (300 ml) and EtOAc (50 ml), and KOH (20 g, 0.36 mol) was added to the resulting two-phase mixture in small portions with stirring over 20 min. Then, NBu_4Br (0.5 g, 1.5 mmol) was added, the mixture was stirred for 1 h and kept at room

temperature for 24 h. The precipitate formed upon evaporation of the solvents was filtered and dissolved in a $CHCl_3$–heptane, 5:1 mixture. Compound **11** was isolated by column chromatography on silica gel (eluent $CHCl_3$–heptane, 1:10). After evaporation of the solvents, the residue was washed with cooled (0°C) EtOAc–heptane, 1:10 mixture (3×5 ml). Yield 0.37 g (74%) white powder, mp 190–200°C (subl.). IR spectrum, ν, cm^{-1}: 3467, 3435, 3305, 3272 (NH), 3082, 2975 (CH), 1625, 1560, 1544, 1508, 1459, 1399, 1370, 1036, 984, 923, 670, 567, 481, 424. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.13 (9H, s, $3CH_3$); 1.86 (2H, t, $^3J_{HH}$ = 7.0, $PhC\underline{H}_2CH_2$); 1.93 (3H, s, 8-CH_3); 2.35–2.45 (2H, m, partially overlaps with the solvent signal, $PhCH_2C\underline{H}_2$); 4.99–5.03 (1H, m, 4-CH); 7.08–7.21 (6H, m, H Ph, 7-CH); 9.92 (1H, s, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 10.4 (8-CH_3); 32.1 ($C(\underline{C}H_3)_3$); 37.9 ($\underline{C}(CH_3)_3$); 34.5, 39.9 ($PhCH_2\underline{C}H_2$); 55.7 (C-4); 96.3 (C-8); 129.0 (4-CH Ph); 131.4 (3,5-CH Ph); 131.5 (2,6-CH Ph); 140.9, 142.5, 144.2, 153.1 (C-1 Ph, C-3,7,8a). Found, *m*/*z*: 297.2078 $[M+H]^+$. $C_{18}H_{25}N_4$. Calculated, *m*/*z*: 297.2074.

Synthesis of compounds 10 and 12 by oxidation of dihydro derivative 11. Method III. Compound **11** (0.5 g, 1.7 mmol) was dissolved in EtOAc (40 ml). Crystalline K_2CO_3 (5.0 g, 36.2 mmol) was added to the resulting solution. *N*-Bromosuccinimide (0.3 g, 1.7 mmol) was added in one portion with vigorous stirring; the solution turned bright-yellow. The mixture was stirred at 50–60°C for 20 min. Then, the reaction mixture was cooled to room temperature and H_2O (100 ml) and Na_2SO_3 (2.0 g, 15.9 mmol) were added. The organic phase was separated, the aqueous solution was extracted with EtOAc (2×50 ml), the combined organic phases were successively washed with 1% aqueous K_2CO_3 (50 ml) and H_2O (100 ml), dried over anhydrous $MgSO_4$, filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent EtOAc–heptane, 1:20–1:10)

Synthesis of compounds 10, 14, and 15 from 2-phenylethyl bromide and triazine 3a. Method IV. 2-Phenylethyl bromide (0.1 ml, 0.73 mmol) was added in one portion to a mixture of Mg turnings (0.2 g, 8.23 mmol), Et_2O (30 ml), and a few crystals of I_2. The mixture was heated under reflux until initiation of the reaction (3–5 min). 2-Phenylethyl bromide (1 ml, 7.32 mmol) was then added dropwise with vigorous stirring over 1 h. Then the mixture was heated under reflux for a further 1 h, cooled to room temperature, and filtered. The filtrate was added dropwise with stirring to a solution of compound **3a** (1 g, 5.26 mmol) in THF (20 ml). The resulting mixture was heated under reflux for 30 min, cooled to room temperature, and poured into cooled (0°C) 5% aqueous HCl (100 ml). After stirring for 5 min, the mixture was extracted with EtOAc (4×30 ml). The combined organic phases were washed with H_2O (100 ml), dried over $MgSO_4$, filtered, and crystalline K_2CO_3 (10 g, 72.4 mmol) was added to the filtrate. Then, *N*-Bromosuccinimide (3 g, 16.9 mmol) was added in one portion with vigorous stirring; the solution turned bright-yellow. The mixture was stirred at 50–60°C for 30 min. It was then cooled to room temperature, and H_2O (100 ml) and Na_2SO_3 (2 g, 15.9 mmol) were added. The organic phase was separated, the aqueous solution was extracted with EtOAc (2×50 ml). The combined organic phases were successively washed with 1% aqueous K_2CO_3 (50 ml) and H_2O (100 ml), dried over anhydrous $MgSO_4$, filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent EtOAc–heptane, 1:100–1:20). Spectral and X-ray structural parameters of 1,4-diphenylbutane **15** (yield 0.25 g (30%), colorless needles, mp 50–51°C) correspond to the literature data.[28,29]

3-*tert*-Butyl-8-methyl-4-(2-phenylethyl)pyrazolo[5,1-*c*]-[1,2,4]triazine (10). Yield 0.31 g (62%, method III), 0.14 g (9%, method IV), yellow powder, mp 90–91°C. IR spectrum, ν, cm^{-1}: 3079, 3024, 2969, 2921, 2872 (CH), 1603, 1585, 1515, 1493, 1478, 1457, 1367, 1332, 1285, 1272, 1254, 1215, 1203, 1165, 1146, 1126, 1030, 1005, 990, 897, 780, 761, 713, 700, 639, 556, 522. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.71 (9H, s, $3CH_3$); 2.68 (3H, s, 8-CH_3); 3.17–3.23 (2H, m, $CH_2C\underline{H}_2Ph$); 3.71–3.76 (2H, m, $C\underline{H}_2CH_2Ph$); 7.31–7.43 (5H, m, H Ph); 8.11 (1H, s, 7-CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 7.6 (8-CH_3); 30.3; 31.3 ($\underline{C}H_2\underline{C}H_2Ph$); 31.4 ($C(\underline{C}H_3)_3$); 37.2 ($\underline{C}(CH_3)_3$); 107.9 (C-8); 126.6 (4-CH Ph); 128.4; 128.8 (2,3,5,6-CH Ph); 134.0 (C-1 Ph); 144.2 (C-7); 140.6, 147.6, 148.8 (C-3,4,8a). Found, *m*/*z*: 295.1920 $[M+H]^+$. $C_{18}H_{23}N_4$. Calculated, *m*/*z*: 295.1917.

4-(2-Bromo-2-phenylethyl)-3-*tert*-butyl-8-methylpyrazolo[5,1-*c*][1,2,4]triazine (12). Yield 75 mg (15%, method IV), yellow liquid. IR spectrum, ν, cm^{-1}: 3083, 3051, 2987, 2967, 2923, 2853 (CH), 1685, 1670, 1653, 1637, 1623, 1582, 1561, 1545, 1527, 1508, 1497, 1474, 1458, 1384, 1370, 1327, 1315, 1269, 1202, 1170, 1151, 1109, 1077, 1045, 1028, 995, 963, 899, 827, 756, 714, 699, 683, 658, 637, 592, 541, 516, 497, 440, 422. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.48 (9H, s, $3CH_3$); 2.65 (3H, s, 8-CH_3); 4.00–4.04 (1H, m, $C\underline{H}_2CHBrPh$); 4.30–4.34 (1H, m, $C\underline{H}_2CHBrPh$); 5.86 (1H, t, $^3J_{HH}$ = 7.8, $CH_2C\underline{H}BrPh$); 6.88–6.90 (2H, m, H Ph); 7.16–7.20 (3H, m, H Ph); 8.20 (1H, s, 7-CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 7.7 (8-CH_3); 31.2 ($C(\underline{C}H_3)_3$); 37.2 ($\underline{C}H_2CHBrPh$); 39.3 ($\underline{C}(CH_3)_3$); 44.3 ($CH_2\underline{C}HBrPh$); 108.8 (C-8); 127.5 (4-CH Ph); 128.8; 129.0 (2,3,5,6-CH Ph); 130.6 (C-1 Ph); 144.2 (C-7); 137.1, 147.5, 148.8 (C-3,4,8a). Found, *m*/*z*: 373.1017 $[M+H]^+$. $C_{18}H_{21}BrN_4$. Calculated, *m*/*z*: 373.1022.

3-*tert*-Butyl-8-methyl-4-phenylpyrazolo[5,1-*c*][1,2,4]-triazine (14). Yield 0.52 g (37%, method IV), yellow powder, mp 137–138°C. IR spectrum, ν, cm^{-1}: 3435, 3399, 3368, 3341, 3307, 3294, 3272, 3248, 3234, 3153, 3117, 3083, 3066 (NH), 3037, 3015, 2996, 2978, 2963, 2948, 2914, 2873, 2838 (CH), 1686, 1671, 1654, 1638, 1624, 1577, 1561, 1545, 1525, 1510, 1493, 1476, 1461, 1443, 1422, 1396, 1372, 1330, 1228, 1200, 967, 869, 778, 757, 703, 673, 658, 639, 622, 583, 528, 503, 480, 427. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 (9H, s, $3CH_3$); 2.64 (3H, s, 8-CH_3); 7.39–7.42 (2H, m, H-2,6 Ph); 7.59–7.61 (3H, m, H-3–5 Ph); 7.93 (1H, s, 7-CH). ^{13}C NMR spectrum

($CDCl_3$), δ, ppm: 7.6 (8-CH_3); 32.0 (C($\underline{C}H_3)_3$); 37.7 ($\underline{C}(CH_3)_3$); 108.5 (C-8); 128.9 (3,5-CH Ph); 129.7 (2,6-CH Ph); 130.3 (4-CH Ph); 130.3 (C-1 Ph); 144.7 (C-7); 149.5, 150.8, 154.7 (C-3,4,8a). Found, *m*/*z*: 267.1604 $[M+H]^+$. $C_{16}H_{19}N_4$. Calculated, *m*/*z*: 267.1604.

(±)-4-((1*R*,2*S*)-1,2-Dibromo-2-phenylethyl)-3-*tert*-butyl-8-methylpyrazolo[5,1-*c*][1,2,4]triazine (13). Br_2 (0.1 ml, 1.95 mmol) was added in one portion with vigorous stirring in the dark to a solution of compound **5a** (0.2 g, 0.68 mmol) in $CHCl_3$ (5 ml). The reaction mixture was stirred for 5 min at room temperature, then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent EtOAc–heptane, 1:100–1:50). Yield 0.22 g (71%), orange liquid. IR spectrum, ν, cm^{-1}: 2976, 2916, 2872 (CH), 1652, 1623, 1474, 1460, 1370, 1331, 1297, 1242, 1193, 1104, 1049, 981, 956, 882, 837, 770, 695, 636, 612, 591, 550. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.84 (9H, s, $3CH_3$); 2.67 (3H, s, 8-C$\underline{H}_3$); 6.35 (1H, d, $^3J_{HH}$ = 11.1, CHBrC$\underline{H}$BrPh,); 7.08 (1H, d, $^3J_{HH}$ = 11.1, C$\underline{H}$BrCHBrPh,); 7.40–7.54 (3H, m, H Ph); 7.60–7.68 (2H, m, H Ph); 8.18 (1H, s, 7-CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 7.7 (8-CH_3); 32.0 (C($\underline{C}H_3)_3$); 37.8 ($\underline{C}(CH_3)_3$); 47.2; 50.2 ($\underline{C}$HBr$\underline{C}$HBrPh); 109.0 (C-8); 128.4; 129.2 (2,3,5,6-CH Ph); 129.52 (4-CH Ph); 129.8 (C-1 Ph); 144.4 (C-7); 138.9, 147.9, 148.8 (C-3,4,8a). Found, *m*/*z*: 453.0108 $[M+H]^+$. $C_{18}H_{20}Br_2N_4$. Calculated, *m*/*z*: 453.0108.

X-ray structural analysis of compounds 4a, 5b, 8, 9b, and 14 was carried out on a Bruker Quest D8 single crystal diffractometer (Photon-III detector, graphite monochromator, λ(MoKa) 0.71073 Å, φ- and ω-scanning) at 100K. Crystals of compounds were grown by slow evaporation of the solvent from saturated solutions in EtOAc (compounds **5b**, **8**, **9b**, and **14**) or in EtOAc–DMSO, 10:1 mixture (compound **4a**) at room temperature. The data on the reflection intensities were obtained using the SAINT program[30] and semiempirically corrected for the absorption of radiation by the crystal based on equivalent reflections using the SADABS[31] or TWINABS program (for compound **5b**, two-component twin, domain ratio 0.6509: 0.3491 (8), [1 0 0, 0 –1 0, 0 0 –1] twin law). The structures were solved by direct methods using the SHELXS/SHELXT program[32] and refined by the least squares technique in the full-matrix anisotropic (isotropic for hydrogen atoms) approximation on F^2 using the SHELXL program.[33] The position of the hydrogen atom of the NH group in compound **4a** was found from the difference electron density map. The positions of the remaining hydrogen atoms were calculated geometrically and refined using the rigid body model. Due to the low quality of the crystal **9b** (two-component twin), only the connectivity and unit cell parameters are given for it. Since the structure of compound **15** has repeatedly been investigated earlier,[28] complete X-ray structural analysis of compound **15** was not performed.

Atomic coordinates and the full set of X-ray structural data for compounds **4a**, **5b**, **8**, **9b**, and **14** were deposited at the Cambridge Crystallographic Data Center (deposits CCDC 2005376, CCDC 2005377, CCDC 2005378, CCDC 2077345, and CCDC 2046484, respectively).

The biological studies of compounds 3b, **4a**, **5a, 8, and 9a** were conducted at the Yaroslavl State Pedagogical University named after K. D. Ushinsky by the method of double serial dilutions using turbidimetric control of the growth of microorganisms in triplicate in accordance with the requirements of the guidelines MUK 4.2.1890-04 ("Opredelenie chuvstvitelnosti microorganismov k antibakterialnym preparatam") ("Determination of the sensitivity of microorganisms to antibacterial drugs") and the international standard CLSI-M07-A9-2012. Under the experimental conditions, due to the low solubility in aqueous solutions (DMSO concentration 0.5%), the compounds were studied in the form of suspensions in the concentration range of 128–256 μg/ml.

Supplementary information file containing IR spectra, ^1H and ^{13}C NMR and high-resolution mass spectra of the synthesized compounds as well as X-ray structural analysis data for compounds **4a**, **5b**, **8**, **14** is available at the journal website at http://link.springer.com/journal/10593.

X-ray structural analysis was carried out at the Department of Structural Research of the N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences.

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