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Synthesis of Polysubstituted Pyridopyrimidines, Pyrimidines, and Pyrazoles Based on 1,1-Bis(1*H*-benzotriazol-1-yl)- and 1,1-Bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dienes

I. A. Kolesnyk[a],*, S. K. Petkevich[a], A. D. Tsaryk[a], P. V. Kurman[b], and V. I. Potkin[a]

[a] *Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus, Minsk, 220072 Belarus*

[b] *Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Minsk, 220141 Belarus*

**e-mail: irynakolesnik93@gmail.com*

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Abstract—The reaction of 3,4,4-trichloro-1,1-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-nitrobuta-1,3-diene with 2-aminopyridine gave a polysubstituted pyrido[1,2-*a*]pyrimidine derivative with an aminopyridine residue in the 2-position, whereas heterocyclization of 3,4,4-trichloro-1,1-bis(1*H*-benzotriazol-1-yl)-2-nitrobuta-1,3-diene with substituted 2-aminopyridines afforded 2-(1*H*-benzotriazol-1-yl)pyrido[1,2-*a*]pyrimidines. 2-(Morpholin-4-yl), 2-amino, and 2-(2-hydroxyethylamino) derivatives of polysubstituted pyrido[1,2-*a*]pyrimidines were synthesized, and those containing a 2-hydroxyethylamino group were converted to the corresponding 4,5-dichloro-1,2-thiazole-1-carboxylates. Specific features of heterocyclizations of benzotriazolyl and dimethylpyrazolyl derivatives of trichloronitro-1,3-butadiene to pyrimidine and pyrazole systems were revealed.

Keywords: nitrodienes, pyrido[1,2-*a*]pyrimidines, pyrimidines, pyrazoles, heterocyclization, nucleophilic substitution.

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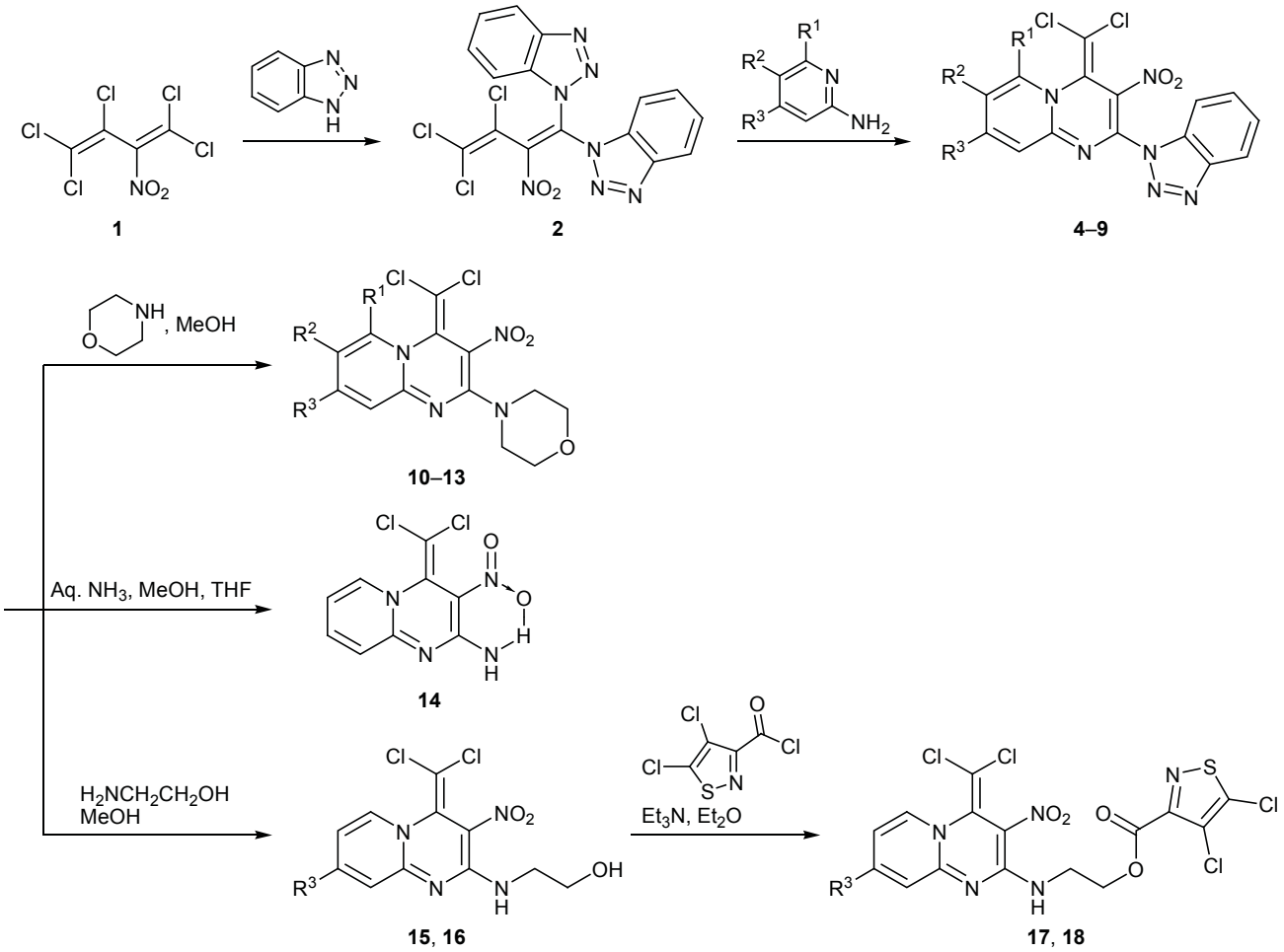
Chlorinated nitrobutadienes exhibit high reactivity and are used in organic synthesis for the preparation of various acyclic and heterocyclic compounds [1]. The presence of a conjugated bond system in combination with strong electron acceptors such as chlorine atoms and a nitro group makes polychloronitrobutadienes highly reactive toward nucleophiles [2, 3]. Pentachloro-2-nitrobutadiene (**1**) synthesized for the first time in 1975 starting from trichloroethylene is the most accessible representative of the halonitrobutadiene series. The majority of chemical reactions of nitrodiene **1** involve the dichloronitrovinyl fragment. Substitution of geminal chlorine atoms therein gave rise to various N,S,O-heterocycles; a procedure for the synthesis of benzazete derivatives was developed; and a new synthetic approach to isothiazoles was proposed on the basis of heterocyclization with participation of both chlorine atoms and nitro group [1, 4, 5]. Reactions at the trichlorovinyl fragment of **1** and its derivatives have been studied to a much lesser extent. Major studies in this field were initiated in 2000s by Kaufman and Zapol'skii who performed a number of uncommon transformations of **1** and synthesized a series of various heterocyclic derivatives with a high biological potential (see [6–8] and references therein).

In continuation of these studies, herein we report heterocyclizations of 3,4,4-trichloro-1,1-bis(1*H*-benzotriazol-1-yl)-2-nitrobuta-1,3-diene (**2**) and 3,4,4-trichloro-1,1-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-nitrobuta-1,3-diene (**3**) leading to the formation of pyridopyrimidine, pyrimidine, and pyrazole derivatives. Compounds **2** and **3** are readily available via reactions of nitrodiene **1** with benzotriazole and 3,5-dimethylpyrazole according to [1].

Bis(benzotriazolyl)butadiene **2** was reacted with 3 equiv of pyridin-2-amine and its mono- and disubstituted derivatives in tetrahydrofuran at room temperature. In the case of unsubstituted and monosubstituted pyridin-2-amines, smooth heterocyclization occurred through substitution of the internal chlorine atom and one benzotriazole residue in **2** to produce pyrido[1,2-*a*]-pyrimidines **4**–**7** in 51–70% yield (Scheme 1). This heterocyclization was similar to the only previous example reported in [7]. However, considerable tarring

Scheme 1.



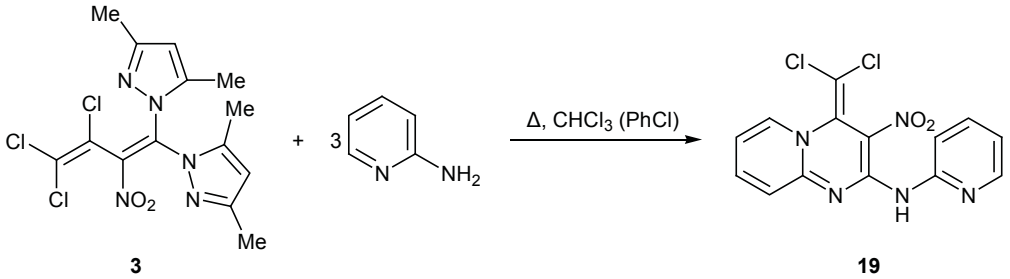
4, **10**, **15**, **17**, $R^1 = R^2 = R^3 = H$; **5**, **11**, $R^1 = R^3 = H$, $R^2 = Me$; **6**, **12**, **16**, **18**, $R^1 = R^2 = H$, $R^3 = Me$; **7**, **13**, $R^1 = R^3 = H$, $R^2 = Cl$; **8**, $R^1 = Me$, $R^2 = H$, $R^3 = OH$; **9**, $R^1 = R^3 = Me$, $R^2 = H$.

was observed in the reactions with disubstituted aminopyridines, and the expected heterocyclization products **8** and **9** were detected only by GC/MS.

Pyrido[1,2-*a*]pyrimidines **4**–**7** contain a benzotriazole fragment as a readily departing group. It was replaced by a morpholine residue by treatment of **4**–**7** with morpholine in methanol, and the corresponding morpholine derivatives **10**–**13** were isolated in 40–92% yield. The reaction of **4** with 30% aqueous ammonia in methanol containing a small amount of THF (to ensure homogeneity of the reaction medium) afforded 2-aminopyrido[1,2-*a*]pyrimidine **14**. The reactions of **4**, **6**, and **7** with 2-aminoethanol proceeded differently, depending on the substituents in the pyridine ring. Compounds **4** and **6** were converted to target substitution products **15** and **16** in about 70% yield. However, the reaction of **7** with 2-aminoethanol was not selective, strong tarring was observed, and a complex mixture of products was formed, presumably due to concurrent reactions involving chlorine atom in the pyridine ring.

Compounds **14**–**16** contain an amino or hydroxy group which can be subjected to further transformations, e.g., acylation with 4,5-dichloro-1,2-thiazole-3-carbonyl chloride. As shown previously, 4,5-dichloroisothiazole derivatives exhibit high biological activity, and some of them showed a synergistic effect with insecticides and antitumor agents, so that the dose of the latter could be reduced [9, 10]. On the other hand, pyrido[1,2-*a*]pyrimidines also display a broad spectrum of biological activity [11, 12]. Therefore, structures with a combination of fragments from different bioactive molecules are expected to possess high pharmacological potential. However, we failed to acylate amino derivative **14** with 4,5-dichloro-1,2-thiazole-3-carbonyl chloride or chloroacetyl chloride despite

Scheme 2.



variation of the conditions (prolonged heating in boiling dioxane, diethyl ether, or chloroform in the presence of triethylamine or pyridine); in all cases, there was no reaction. A probable reason is deactivation of the amino group due to intramolecular hydrogen bonding with the nitro group (N→O···H–N) to form a six-membered H-chelate ring. The acylation of 2-hydroxyethylamino derivatives **15** and **16** with 4,5-dichloro-1,2-thiazole-3-carbonyl chloride in diethyl ether in the presence of triethylamine at room temperature was fairly efficient, and esters **17** and **18** were obtained in 40 and 47% yield, respectively (Scheme 1).

We also tried to accomplish heterocyclization of 3,4,4-trichloro-1,1-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-nitrobuta-1,3-diene (**3**) to pyrido[1,2-*a*]pyrimidines. However, the reactions of **3** with aminopyridines under the conditions used for the heterocyclization of bis-benzotriazolyl analog **2** resulted in tar formation. Neither replacement of THF by ethanol, dioxane, diglyme, or acetonitrile nor addition of sodium hydride gave positive results. We succeeded in isolating a small amount of an individual compound (as yellow needles) only in the reaction of **3** with pyridin-2-amine using chlorobenzene as solvent. On the basis of the elemental analysis data and IR, ^{1}H and ^{13}C NMR, and mass spectra, the isolated compound was identified as 4-(dichloromethylidene)-3-nitropyrido[1,2-*a*]pyrimidine **19**, but the substituent on C^2 was aminopyridine residue rather than dimethylpyrazole fragment, as might be expected by analogy with compounds **4–9**. Compound **19** was formed in 95% yield when the reaction was carried out in boiling chloroform (Scheme 2). Presumably, the 3,5-dimethylpyrazolyl substituent is a better leaving group than benzotriazolyl, and it is replaced by the aminopyridine residue under the given conditions.

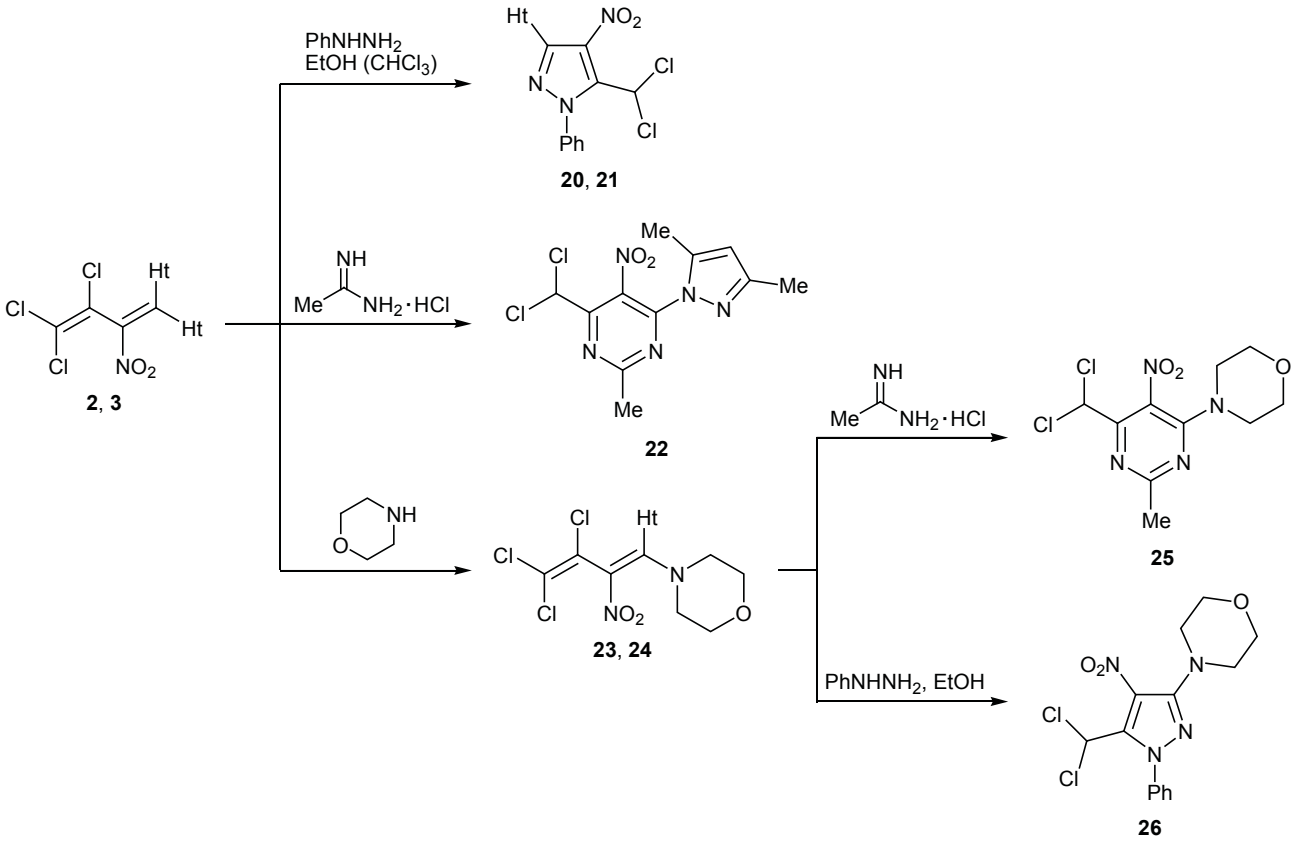
By analogy with the approaches proposed in [7], bis-hetaryl nitrodienes **2** and **3** were reacted with phenylhydrazine and acetamidine with a view to obtaining pyrazole and pyrimidine derivatives, respectively. The reaction of **2** with phenylhydrazine afforded 56% of 3-(1*H*-benzotriazol-1-yl)-5-(dichloromethyl)-4-nitro-1-phenyl-1*H*-pyrazole (**20**) (Scheme 3). In the reaction of bis(dimethylpyrazolyl) analog **3** with phenylhydrazine, a significant amount of tars was formed, and the corresponding pyrazole **21** was isolated in a poor yield (36%).

Compound **3** reacted with acetamidine (generated *in situ* from acetamidine hydrochloride by the action of sodium ethoxide) to give polysubstituted pyrimidine derivative **22** in 38% yield. We failed to isolate an analogous pyrimidine structure in the reaction of bis-benzotriazolyl butadiene **2** with acetamidine because of complete decomposition.

We also made an attempt to synthesize substituted pyrazoles and pyrimidines from aminoazolyl derivatives **23** and **24** which contained a morpholine residue instead of one of the azolyl substituent. Compounds **23** and **24** were prepared by us previously by treatment of **2** and **3**, respectively, with morpholine [13, 14]. Both compounds **23** and **24** reacted with acetamidine in anhydrous ethanol to produce 4-(morpholin-4-yl)pyrimidine **25** in 43–48% yield. The reaction of **23** with phenylhydrazine in ethanol gave 72% of pyrazole derivative **26** containing a morpholine residue on C^3 (Scheme 3). In the reaction of phenylhydrazine with dimethylpyrazolyl analog **24** only tars were obtained.

The structures of newly synthesized compounds **5–7**, **10–22**, **25**, and **26** were confirmed by elemental analyses and IR, ^{1}H and ^{13}C NMR, and mass spectra which showed the presence of the corresponding structural fragments in their molecules. The isotope ratio of the molecular ion clusters in the mass spectra of **5**, **6**, **10–22**, **25**, and **26** (100 : 65 : 1.1) indicated the presence of two chlorine atoms in their molecules. The molecular ion cluster of **7** was represented by four isotope peaks with an intensity ratio of 100 : 98 : 32 : 3.5 (three chlorine atoms) [15, 16]. The spectral and physicochemical characteristics of compound **4** were consistent with those reported previously [7].

Scheme 3.



2, **20**, **23**, Ht = 1*H*-benzotriazol-1-yl; **3**, **21**, **24**, Ht = 3,5-dimethyl-1*H*-pyrazol-1-yl.

According to the preliminary biological screening data, pyrazole derivative **26** possesses pronounced antibacterial properties against *Bacillus Subtilis* and *Aspergillus Niger*, which justifies further detailed study of biological activity of the synthesized heterocyclic compounds.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Nicolet Protégé-460 spectrometer with Fourier transform. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-500 spectrometer at 500 and 125 MHz, respectively; the chemical shifts were measured relative to the residual proton and carbon signals of the deuterated solvent ($CHCl_3$, δ 7.26 ppm, $CDCl_3$, δ_C 77.2 ppm; DMSO-d_5, δ 2.50 ppm, DMSO-d_6, δ_C 40.1 ppm). The mass spectra were obtained on an Agilent 5975 inert MSD/6890N Network GC System (electron impact, 70 eV; HP-5MS capillary column, 30 m×0.25 mm, film thickness 0.25 μm; injector temperature 250°C).

Pyridopyrimidines 5–7 (*general procedure***).** Substituted pyridin-2-amine, 10 mmol, was added to a solution of 1.45 g (3.32 mmol) of diene **2** in 30 mL of THF, and the mixture was stirred at 20°C for 6 h and left overnight at –10°C. The precipitate was filtered off, washed with 5% aqueous HCl (2×10 mL), water, and cold methanol, and dried under reduced pressure. The products required no further purification.

2-(1*H*-Benzotriazol-1-yl)-4-(dichloromethylidene)-7-methyl-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidine (5). Yield 66%, mp 178–180°C (decomp.). IR spectrum, ν, cm^{-1}: 3097, 3072, 3023, 2923, 1636, 1608, 1549, 1508, 1483, 1462, 1446, 1425, 1400, 1348, 1324, 1309, 1294, 1273, 1257, 1220, 1202, 1154, 1130, 1120, 1110, 1045, 994, 961, 933, 834, 826, 783, 760, 753, 740, 687, 626, 540, 443. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.43 s (3H, Me), 7.55 t (1H, H_{arom}, J = 7.6 Hz), 7.70 t (1H, H_{arom}, J = 7.6 Hz), 7.81 d (1H, H_{arom}, J = 8.8 Hz), 7.93 d (1H, H_{arom}, J = 8.3 Hz), 8.18 d.d (1H, H_{arom}, J = 8.8, 1.2 Hz), 8.21 d (1H, H_{arom}, J = 8.3 Hz), 8.90 s (1H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 17.66 (Me), 113.31 (CH_{arom}), 120.32 (CH_{arom}), 123.47 (CH_{arom}), 125.88 (CH_{arom}), 129.92 (CH_{arom}), 137.12 (CH_{arom}), 145.82 (CH_{arom}), 102.31, 121.53, 126.77, 130.29, 132.74, 145.99, 148.37, 150.01. Mass

spectrum: *m*/*z* 389.10 [*M* + H]$^+$. Found, %: C 49.30; H 2.45; Cl 18.19; N 21.68. $C_{16}H_{10}Cl_2N_6O_2$. Calculated, %: C 49.38; H 2.59; Cl 18.22; N 21.59. *M* 389.20.

2-(1*H*-Benzotriazol-1-yl)-4-(dichloromethylidene)-8-methyl-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidine (6). Yield 63%, mp 145–147°C (decomp.). IR spectrum, ν, cm^{-1}: 3133, 3050, 2958, 2850, 1639, 1605, 1595, 1542, 1504, 1484, 1447, 1417, 1379, 1351, 1304, 1275, 1215, 1163, 1133, 1121, 1047, 994, 941, 883, 872, 853, 812, 785, 732, 686, 666, 633, 591, 432. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.56 s (3H, Me), 7.49 d.d (1H, H_{arom}, *J* = 6.8, 1.7 Hz), 7.55 t (1H, H_{arom}, *J* = 7.7 Hz), 7.70 t (1H, H_{arom}, *J* = 7.5 Hz), 7.75 s (1H, H_{arom}), 7.95 d (1H, H_{arom}, *J* = 8.3 Hz), 8.22 d (1H, H_{arom}, *J* = 8.3 Hz), 8.88 d (1H, H_{arom}, *J* = 7.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.92 (Me), 113.36 (CH_{arom}), 120.31 (CH_{arom}), 121.32 (CH_{arom}), 123.02 (CH_{arom}), 125.89 (CH_{arom}), 129.90 (CH_{arom}), 138.13 (CH_{arom}), 102.84, 121.23, 126.63, 132.70, 145.99, 148.78, 151.04, 157.16. Mass spectrum: *m*/*z* 389.10 [*M* + H]$^+$. Found, %: C 49.14; H 2.49; Cl 18.01; N 21.62. $C_{16}H_{10}Cl_2N_6O_2$. Calculated, %: C 49.38; H 2.59; Cl 18.22; N 21.59. *M* 389.20.

2-(1*H*-Benzotriazol-1-yl)-7-chloro-4-(dichloromethylidene)-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidine (7). Yield 51%, mp 184–186°C (decomp.). IR spectrum, ν, cm^{-1}: 3134, 3085, 3012, 2925, 1624, 1614, 1536, 1513, 1486, 1442, 1389, 1348, 1302, 1280, 1216, 1148, 1132, 1093, 1047, 1003, 848, 753, 735, 709, 621, 538. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.55 t (1H, H_{arom}, *J* = 7.6 Hz), 7.70 t (1H, H_{arom}, *J* = 7.5 Hz), 7.85 d (1H, H_{arom}, *J* = 9.3 Hz), 7.92 d (1H, H_{arom}, *J* = 8.3 Hz), 8.22 d (1H, H_{arom}, *J* = 8.3 Hz), 8.34 d.d (1H, H_{arom}, *J* = 9.3, 2.2 Hz), 9.34 d (1H, H_{arom}, *J* = 2.2 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 113.34 (CH_{arom}), 120.36 (CH_{arom}), 125.06 (CH_{arom}), 125.95 (CH_{arom}), 129.98 (CH_{arom}), 137.00 (CH_{arom}), 143.48 (CH_{arom}), 103.22, 122.52, 125.16, 125.98, 132.69, 145.98, 148.10, 150.98. Mass spectrum: *m*/*z* 409 [*M* + H]$^+$. Found, %: C 43.78; H 1.70; Cl 25.99; N 20.47. $C_{15}H_7Cl_3N_6O_2$. Calculated, %: C 43.98; H 1.72; Cl 25.96; N 20.52. *M* 409.61.

2-(Morpholin-4-yl)pyrido[1,2-*a*]pyrimidines 10–14 (*general procedure*). Morpholine, 0.18 g (2.10 mmol), was added to a suspension of 1 mmol of pyridopyrimidine **4**–**7** in 30 mL of methanol, and the mixture was stirred at 40°C for 6 h and left overnight at –5°C. The precipitate was filtered off, washed with 5% aqueous HCl (2×10 mL), water, and cold methanol, and dried under reduced pressure. The products required no further purification.

4-(Dichloromethylidene)-2-(morpholin-4-yl)-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidine (10). Yield 76%, mp 158–160°C (decomp.). IR spectrum, ν, cm^{-1}: 3159, 3100, 3083, 3033, 2964, 2901, 2859, 1640, 1564, 1507, 1441, 1409, 1380, 1355, 1329, 1391, 1271, 1250, 1213, 1139, 1109, 1066, 1026, 1012, 941, 912, 886, 764, 739, 699, 602, 540, 500, 460. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.60–4.00 m (8H, CH_2), 6.82 t (1H, H_{arom}, *J* = 6.6 Hz), 7.13 d (1H, H_{arom}, *J* = 8.8 Hz), 7.66 t (1H, H_{arom}, *J* = 7.7 Hz), 8.15 d (1H, H_{arom}, *J* = 6.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 45.99 (CH_2N), 52.40 (CH_2N), 66.98 (CH_2OCH_2), 113.45 (CH_{arom}), 123.27 (CH_{arom}), 135.98 (CH_{arom}), 140.13 (CH_{arom}), 95.32, 121.83, 127.68, 152.09, 156.79. Mass spectrum: *m*/*z* 343 [*M* + H]$^+$. Found, %: C 45.72; H 3.77; Cl 20.40; N 16.32. $C_{13}H_{12}Cl_2N_4O_3$. Calculated, %: C 45.50; H 3.52; Cl 20.66; N 16.33. *M* 343.16.

4-(Dichloromethylidene)-7-methyl-2-(morpholin-4-yl)-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidine (11). Yield 93%, mp 124–126°C (decomp.). IR spectrum, ν, cm^{-1}: 3133, 3098, 3000, 2933, 2851, 1644, 1550, 1497, 1469, 1425, 1384, 1323, 1267, 1243, 1182, 1166, 1138, 1107, 1060, 1016, 956, 929, 901, 886, 817, 763, 748, 691, 665, 621, 500, 473. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.27 s (3H, Me), 3.52–4.20 m (8H, CH_2), 7.22 d (1H, H_{arom}, *J* = 9.0 Hz), 7.83 d (1H, H_{arom}, *J* = 9.0 Hz), 8.48 s (1H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 17.28 (Me), 45.91 (CH_2N), 52.38 (CH_2N), 66.76 (CH_2OCH_2), 122.53 (CH_{arom}), 135.04 (CH_{arom}), 144.62 (CH_{arom}), 95.24, 120.78, 125.07, 128.72, 150.63, 156.62. Mass spectrum: *m*/*z* 357 [*M* + H]$^+$. Found, %: C 47.01; H 4.05; Cl 19.74; N 15.77. $C_{14}H_{14}Cl_2N_4O_3$. Calculated, %: C 47.08; H 3.95; Cl 19.85; N 15.69. *M* 357.19.

4-(Dichloromethylidene)-8-methyl-2-(morpholin-4-yl)-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidine (12). Yield 85%, mp 140–142°C (decomp.). IR spectrum, ν, cm^{-1}: 3117, 3034, 2968, 2918, 2868, 1647, 1600, 1544, 1509, 1431, 1388, 1365, 1330, 1269, 1241, 1140, 1106, 1030, 1014, 942, 910, 834, 758, 747, 740, 540, 473. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.38 s (3H, Me), 3.50–4.20 m (8H, CH_2), 7.00 d (1H, H_{arom}, *J* = 6.9 Hz), 7.13 s (1H, H_{arom}), 8.49 d (1H, H_{arom}, *J* = 6.9 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.74 (Me), 45.87 (CH_2N), 52.39 (CH_2N), 66.75 (CH_2OCH_2), 117.10 (CH_{arom}), 121.61 (CH_{arom}), 136.46 (CH_{arom}), 95.54, 120.40, 128.55, 151.53, 155.04, 156.78. Mass spectrum: *m*/*z* 357.10 [*M* + H]$^+$. Found, %: C 47.20; H 4.07; Cl 19.69; N 15.60. $C_{14}H_{14}Cl_2N_4O_3$. Calculated, %: C 47.08; H 3.95; Cl 19.85; N 15.69. *M* 357.19.

7-Chloro-4-(dichloromethylidene)-2-(morpholin-4-yl)-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidine (13). Yield 93%, mp 124–126°C (decomp.). IR spectrum, ν, cm^{-1}: 3141, 3077, 3029, 2922, 2869, 1634, 1595, 1561, 1534, 1503, 1433, 1385, 1352, 1324, 1268, 1251, 1134, 1105, 1086, 1027, 938, 855, 835, 753, 713, 536. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.48–4.20 m (8H, CH_2), 7.27 d (1H, H_{arom}, J = 9.5 Hz), 7.97 d.d (1H, H_{arom}, J = 9.5, 2.0 Hz), 8.90 d (1H, H_{arom}, J = 2.0 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 46.27 (CH_2N), 52.61 (CH_2N), 66.75 (CH_2OCH_2), 124.27 (CH_{arom}), 135.10 (CH_{arom}), 142.14 (CH_{arom}), 94.97, 120.51, 121.49, 127.99, 150.75, 156.42. Mass spectrum: *m*/*z* 377.10 [M + H]$^+$. Found, %: C 41.22; H 2.91; Cl 28.25; N 14.74. $C_{13}H_{11}Cl_3N_4O_3$. Calculated, %: C 41.35; H 2.94; Cl 28.16; N 14.84. M 377.61.

4-(Dichloromethylidene)-3-nitro-4*H*-pyrido-[1,2-*a*]pyrimidin-2-amine (14). To a mixture of 0.52 g (1.5 mmol) of pyridopyrimidine **4**, 50 mL of methanol, and 5 mL of THF we added 8 mL of 30% aqueous ammonia, and the mixture was stirred for 20 h at 20°C. The precipitate was filtered off, washed with methanol and water, and dried under reduced pressure. Yield 0.26 g (64%), mp 166–168°C (decomp.). IR spectrum, ν, cm^{-1}: 3416, 3346, 3266, 3120, 1634, 1599, 1548, 1514, 1494, 1461, 1423, 1376, 1319, 1278, 1254, 1152, 1113, 1053, 1029, 976, 908, 868, 849, 756, 667, 648, 602, 536, 427. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.95 t (1H, H_{arom}, J = 6.6 Hz), 7.09 d (1H, H_{arom}, J = 8.9 Hz), 7.80 t (1H, H_{arom}, J = 7.4 Hz), 8.38 d (1H, H_{arom}, J = 6.6 Hz), 8.54 br.s (1H, NH), 8.61 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 113.12 (CH_{arom}), 121.77 (CH_{arom}), 137.29 (CH_{arom}), 141.44 (CH_{arom}), 103.05, 115.76, 127.86, 152.49, 157.34. Found, %: C 39.54; H 2.30; Cl 25.79; N 20.61. $C_9H_6Cl_2N_4O_2$. Calculated, %: C 39.59; H 2.21; Cl 25.96; N 20.52. M 273.07.

2-[(2-Hydroxyethyl)amino]pyrido[1,2-*a*]pyrimidines 15 and 16 (*general procedure*). 2-Aminoethanol, 0.13 g (2.13 mmol), was added to a suspension of 1 mmol of 2-benzotriazolyl-4*H*-pyrido[1,2-*a*]pyrimidine **4** or **6** in 30 mL of methanol. The mixture was stirred at 20°C for 12 h and evaporated under reduced pressure, and the residue was washed with diethyl ether and recrystallized from ethanol.

2-{[4-(Dichloromethylidene)-3-nitro-4*H*-pyrido-[1,2-*a*]pyrimidin-2-yl]amino}ethan-1-ol (15). Yield 65%, mp 141–143°C (decomp.). IR spectrum, ν, cm^{-1}: 3396, 3283, 3137, 3121, 2954, 2933, 2879, 1637, 1589, 1545, 1506, 1488, 1440, 1358, 1333, 1262, 1213, 1143, 1117, 1109, 1084, 1057, 980, 935, 886, 861, 762, 741, 706, 685, 632, 541, 461, 434. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.97–4.14 m (4H, CH_2), 5.36 br.s (1H, OH), 7.44 t (1H, H_{arom}, J = 6.9 Hz), 7.62 d (1H, H_{arom}, J = 8.9 Hz), 8.29 t (1H, H_{arom}, J = 7.9 Hz), 8.87 d (1H, H_{arom}, J = 6.7 Hz), 9.98 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 44.08 (CH_2N), 60.33 (CH_2O), 113.99 (CH_{arom}), 122.71 (CH_{arom}), 137.82 (CH_{arom}), 142.23 (CH_{arom}), 103.38, 116.62, 128.14, 152.69, 156.04. Found, %: C 41.87; H 3.34; Cl 22.24; N 17.55. $C_{11}H_{10}Cl_2N_4O_3$. Calculated, %: C 41.66; H 3.18; Cl 22.36; N 17.67.

2-{[4-(Dichloromethylidene)-7-methyl-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]amino}ethan-1-ol (16). Yield 70%, mp 156–158°C (decomp.). IR spectrum, ν, cm^{-1}: 3435, 3276, 3145, 3099, 3067, 2926, 2854, 1646, 1581, 1541, 1499, 1454, 1378, 1356, 1341, 1286, 1248, 1187, 1173, 1114, 1054, 1036, 1009, 978, 869, 813, 754, 703, 645, 567, 523,478, 413. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.39 s (3H, Me), 3.60–3.98 m (5H, CH_2, OH), 6.69 d.d (1H, H_{arom}, J = 7.0, 1.6 Hz), 6.96 s (1H, H_{arom}), 7.93 d (1H, H_{arom}, J = 7.0 Hz), 9.75 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.94 (Me), 44.68 (CH_2N), 63.02 (CH_2O), 115.23 (CH_{arom}), 121.12 (CH_{arom}), 135.37 (CH_{arom}), 103.75, 118.09, 126.44, 152.19, 153.49, 156.95. Found, %: C 43.70; H 3.75; Cl 21.21; N 16.98. $C_{12}H_{12}Cl_2N_4O_3$. Calculated, %: C 43.52; H 3.65; Cl 21.41; N 16.92.

4,5-Dichloro-1,2-thiazole-3-carboxylates 17 and 18 (*general procedure*). Triethylamine, 0.12 g (1.1 mmol), was added to a solution of 1 mmol of compound **15** or **16** and 1.1 mmol of 4,5-dichloro-1,2-thiazole-3-carbonyl chloride in 100 mL of anhydrous diethyl ether, and the mixture was stirred at 20–23°C for 12 h. The precipitate was filtered off, washed with diethyl ether (3×10 mL) and water (5×50 mL), and dried under reduced pressure.

2-{[4-(Dichloromethylidene)-3-nitro-4*H*-pyrido-[1,2-*a*]pyrimidin-2-yl]amino}ethyl 4,5-dichloro-1,2-thiazole-3-carboxylate (17). Yield 54%, mp 139–141°C (decomp.). IR spectrum, ν, cm^{-1}: 3299, 3141, 3125, 3058, 2967, 2925, 1723, 1640, 1581, 1546, 1508, 1482, 1379, 1348, 1237, 1149, 1133, 1097, 1020, 882, 773, 758, 706, 660, 630, 520. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.05 q (2H, CH_2N, J = 5.4 Hz), 4.60 t (2H, CH_2O, J = 4.8 Hz), 6.80 t (1H, H_{arom}, J = 6.6 Hz), 7.07 d (1H, H_{arom}, J = 8.9 Hz), 7.51 t (1H, H_{arom}, J =

7.7 Hz), 7.98 d (1H, H_{arom}, J = 6.6 Hz), 9.71 t (1H, NH, J = 5.4 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 39.77 (CH_2N), 64.91 (CH_2O), 112.49 (CH_{arom}), 122.74 (CH_{arom}), 136.11 (CH_{arom}), 139.82 (CH_{arom}), 103.53, 117.74, 125.89, 126.58, 150.86, 152.43, 154.00, 156.35, 158.98. Found, %: C 36.03; H 1.77; Cl 28.68; N 14.01; S 6.59. $C_{15}H_9Cl_4N_5O_4S$. Calculated, %: C 36.24; H 1.82; Cl 28.52; N 14.09; S 6.45.

2-{[4-(Dichloromethylidene)-7-methyl-3-nitro-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl]amino}ethyl 4,5-dichloro-1,2-thiazole-3-carboxylate (18). Yield 56%, mp 152–153°C (decomp.). IR spectrum, ν, cm^{-1}: 3264, 3125, 3086, 3058, 2987, 2966, 1731, 1645, 1581, 1539, 1501, 1484, 1461, 1421, 1364, 1348, 1272, 1254, 1222, 1180, 1121, 1113, 1092, 1023, 1006, 891, 867, 749, 645, 600, 523. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.36 s (3H, Me), 4.00–4.08 m (2H, CH_2N), 4.59 q (2H, CH_2O, J = 5.2 Hz), 6.64 d.d (1H, H_{arom}, J = 6.9, 1.2 Hz), 6.87 s (1H, H_{arom}), 7.88 d (1H, H_{arom}, J = 6.9 Hz), 9.70 t (1H, NH, J = 5.6 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.87 (Me), 39.69 (CH_2N), 64.96 (CH_2O), 114.88 (CH_{arom}), 121.25 (CH_{arom}), 135.15 (CH_{arom}), 103.70, 117.34, 125.90, 126.58, 150.82, 152.11, 152.88, 154.04, 156.60, 159.00. Found, %: C 37.45; H 2.02; Cl 27.90; N 13.71; S 6.38. $C_{16}H_{11}Cl_4N_5O_4S$. Calculated, %: C 37.60; H 2.17; Cl 27.74; N 13.70; S 6.27.

4-(Dichloromethylidene)-3-nitro-*N*-(pyridin-2-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-2-amine (19). A mixture of 0.39 g (1 mmol) of diene **3** and 0.28 g (3 mmol) of pyridin-2-amine in chloroform was refluxed for 8 h. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography (diethyl ether–methanol, 5 : 1) to isolate 0.27 g (77%) of **19**, mp 140–142°C (decomp.). IR spectrum, ν, cm^{-1}: 3129, 3096, 3052, 1663, 1631, 1577, 1561, 1540, 1485, 1436, 1397, 1364, 1342, 1397, 1275, 1243, 1206, 1172, 1140, 1085, 981, 881, 761, 717, 699, 614, 574, 513, 416. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.96 t (1H, H_{arom}, J = 6.5 Hz), 7.06 t (1H, H_{arom}, J = 6.8 Hz), 7.31 d (1H, H_{arom}, J = 8.8 Hz), 7.68–7.80 m (2H, H_{arom}), 8.10 d (1H, H_{arom}, J = 6.3 Hz), 8.37 d (1H, H_{arom}, J = 3.8 Hz), 8.41 d (1H, H_{arom}, J = 8.4 Hz), 11.66 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 113.82 (CH_{arom}), 116.59 (CH_{arom}), 120.24 (CH_{arom}), 123.18 (CH_{arom}), 136.38 (CH_{arom}), 137.99 (CH_{arom}), 140.56 (CH_{arom}), 148.52 (CH_{arom}), 102.98, 118.50, 126.32, 151.26, 152.07, 153.05. Mass spectrum: m/z 350 $[M + H]^+$. Found, %: C 48.20; H 2.65; Cl 20.11; N 19.89. $C_{14}H_9Cl_2N_5O_2$. Calculated, %: C 48.02; H 2.59; Cl 20.25; N 20.00. M 350.16.

Heterocyclization to pyrimidines (*general procedure*). Metallic sodium, 0.69 g (30 mmol), was dissolved in 80 mL of anhydrous ethanol, 2.84 g (30 mmol) of acetamidine hydrochloride was added, and the mixture was stirred for 10 min. Azolyl-substituted nitrodiene **3**, **23**, or **24**, 30 mmol, was then added, and the mixture was stirred for 18 h, poured into water, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography with ethyl acetate–hexane (1 : 5) as eluent to isolate pyrimidine derivative **22** or **25**.

4-(Dichloromethyl)-6-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-methyl-5-nitropyrimidine (22). Yield 38%, mp 141–142°C. IR spectrum, ν, cm^{-1}: 2958, 2925, 1640, 1536, 1413, 1382, 1358, 1259, 1188, 1119, 1027, 968, 942, 857, 796, 716, 587. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.04 s and 2.12 s (3H each, 3′-Me, 5′-Me), 2.18 s (3H, 2-Me), 5.72 s (1H, $CHCl_2$), 5.87 s (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.49 and 13.90 (3′-Me, 5′-Me), 21.71 (2-Me), 60.41 ($CHCl_2$), 106.40 (=CH), 121.73, 130.58, 142.97, 144.21, 150.69, 152.30. Found, %: C 41.98; H 3.66; Cl 22.25; N 22.36. $C_{11}H_{11}Cl_2N_5O_2$. Calculated, %: C 41.79; H 3.51; Cl 22.43; N 22.15.

6-(Dichloromethyl)-2-methyl-4-(morpholin-4-yl)-5-nitropyrimidine (25). Yield 48%, mp 100–101°C. IR spectrum, ν, cm^{-1}: 3031, 3002, 2977, 2954, 2924, 2861, 1577, 1530, 1510, 1434, 1405, 1373, 1338, 1307, 1281, 1267, 1209, 1175, 1114, 1063, 1022, 994, 874, 838, 826, 778, 756, 741, 672, 654, 607, 531, 473. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.61 s (3H, Me), 3.57 t (4H, CH_2NCH_2, J = 4.8 Hz), 3.75 t (4H, CH_2OCH_2, J = 4.8 Hz), 6.97 s (1H, $CHCl_2$). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 26.26 (Me), 46.83 (CH_2NCH_2), 65.38 ($CHCl_2$), 66.42 (CH_2OCH_2), 126.24, 154.69, 156.89, 168.85. Found, %: C 39.14; H 3.74; Cl 22.89; N 18.42. $C_{10}H_{12}Cl_2N_4O_3$. Calculated, %: C 39.11; H 3.94; Cl 23.08; N 18.24.

Heterocyclization to pyrazoles 20, 21, and 26 (*general procedure*). Phenylhydrazine, 0.23 g (2.13 mmol), was added with stirring to a mixture of 1 mmol of azolyl nitrodiene **2**, **3**, or **23** and 50 mL of ethanol. The mixture was refluxed for 8 h and evaporated by half, the residue was cooled to 0°C, and the

precipitate was filtered off, washed with water and ethanol, and dried under reduced pressure.

3-[5-(Dichloromethyl)-4-nitro-1-phenyl-1*H*-pyrazol-3-yl]-1*H*-benzotriazole (20). Yield 56%. IR spectrum, ν, cm^{-1}: 3100, 3066, 3020, 2921, 1573, 1524, 1495, 1458, 1449, 1409, 1379, 1330, 1296, 1287, 1243, 1210, 1176, 1077, 1034, 1000, 976, 839, 816, 778, 743, 726, 700, 533, 436. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.45 s (1H, $CHCl_2$), 7.48 t (1H, H_{arom}, J = 7.6 Hz), 7.60 t (1H, H_{arom}, J = 7.7 Hz), 7.62–7.68 m (4H, H_{arom}), 7.69–7.73 m (2H, H_{arom}), 8.17 d (1H, H_{arom}, J = 8.4 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 57.40 ($CHCl_2$), 110.79 (CH_{arom}), 120.63 (CH_{arom}), 125.16 (CH_{arom}), 126.90 (2C, CH_{arom}), 129.40 (CH_{arom}), 129.86 (2C, CH_{arom}), 131.43 (CH_{arom}), 131.05, 133.22, 137.67, 139.44, 139.73, 145.73. Found, %: C 49.49; H 2.41; Cl 18.02; N 21.67. $C_{16}H_{10}Cl_2N_6O_2$. Calculated, %: C 49.38; H 2.59; Cl 18.22; N 21.59.

5′-(Dichloromethyl)-3,5-dimethyl-4′-nitro-1′-phenyl-1′*H*-1,3′-bipyrazole (21). Yield 36%, mp 155–157°C (decomp.). IR spectrum, ν, cm^{-1}: 3333, 3142, 3112, 3067, 2975, 2924, 2850, 1674, 1610, 1572, 1491, 1481, 1456, 1427, 1332, 1295, 1223, 1178, 1072, 1043, 1026, 974, 893, 877, 846, 820, 751, 715, 683, 619, 518. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.27 s (3H, Me), 2.49 s (3H, Me), 6.00 s (1H, =CH), 7.39 t (1H, H_{arom}, J = 7.4 Hz), 7.48 t (2H, H_{arom}, J = 7.8 Hz), 7.65 d (2H, H_{arom}, J = 7.6 Hz), 8.31 (1H, $CHCl_2$). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.68 (Me), 14.40 (Me), 110.11 ($CHCl_2$), 125.13 (2C, CH_{arom}), 126.20 (C^4), 128.55 (CH_{arom}), 128.95 (2C, CH_{arom}), 139.83, 141.44, 142.02, 150.95, 154.66, 155.93. Found, %: C 49.25, H 3.69, Cl 19.21, N 19.37. $C_{15}H_{13}Cl_2N_5O_2$. Calculated, %: C 49.20, H 3.58, Cl 19.36, N 19.12.

4-[5-(Dichloromethyl)-4-nitro-1-phenyl-1*H*-pyrazol-3-yl]morpholine (26). Yield 72%. IR spectrum, ν, cm^{-1}: 3217, 3071, 3045, 2960, 2929, 2906, 2860, 2841, 1595, 1559, 1495, 1461, 1446, 1393, 1376, 1360, 1346, 1306, 1279, 1260, 1218, 1183, 1113, 1071, 1023, 928, 856, 831, 808, 782, 747, 692, 672, 643, 570, 521. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.20 t (4H, CH_2NCH_2, J = 4.6 Hz), 3.72 t (4H, CH_2OCH_2, J = 4.6 Hz), 7.60 s (1H, $CHCl_2$), 7.62 br.s (5H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 50.02 (CH_2NCH_2), 59.58 ($CHCl_2$), 66.24 (CH_2OCH_2), 127.14 (2C, CH_{arom}), 130.05 (2C, CH_{arom}), 130.97 (CH_{arom}), 123.09, 138.48, 138.99, 152.84. Found, %: C 47.25; H 4.07; Cl 19.88; N 15.55. $C_{14}H_{14}Cl_2N_4O_3$. Calculated, %: C 47.08; H 3.95; Cl 19.85; N 15.69.

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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