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Synthesis and Evaluation of Antimicrobial Activities of New Functional Derivatives of 3-[5-(4-Nitrophenyl)-2-Furyl]-4-Pyrazole-Carbaldehydes

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Abstract: The analysis of the biological potential of derivatives of 4-alkenyl- and imino functionalized pyrazoles is carried out, based on which the expediency of design of new structures with pharmacophore 5-(4-nitrophenyl)furanyl fragment is substantiated. Their synthesis method using a structural modification of 3-[5-(4-nitrophenyl)furan-2-yl]pyrazole-4-carbaldehyde to the corresponding alkenyl derivatives under the action of malononitrile, ethyl cyanoacetate, cyanoacetamide, and thioxoimidazolidine is proposed. The hydrazones, (thio)semicarbazones, and oximes were obtained by the condensation of corresponding aldehydes with hydrazides, (thio)semicarbazides, and hydroxylamine. The synthesized compounds' composition and structure were determined by elemental analysis, IR, and ^{1}H NMR spectra. The fact existence of a mixture of *E/Z*-isomers among the series of obtained hydrazones of 1-phenyl-4-pyrazolecarbaldehydes was determined, and the quantitative ratio of geometric isomers was determined using ^{1}H NMR spectroscopy data. The results of the microbiological evaluation of the synthesized pyrazole derivatives showed that they have a pronounced effect on strains of bacteria *S. aureus ATCC 25923*, *E. coli* ATCC 25922, and fungi of the genus *Candida* and are promising for the creation of effective antimicrobial agents.

Keywords: pyrazole-4-carbaldehydes; methylene active compounds; aminonucleophiles; 4-carbofunctionalized pyrazoles; *E/Z*-isomers, antimicrobial activity.

1. Introduction

The powerful synthetic and applied potential of pyrazole-containing compounds is due to the presence in their structure of a unique electron-enriched azole cycle; therefore, they are widely used in medicine [1-6], agrochemistry [7-11], and materials science [12-17]. The scope of their medical and biological use, which is based on weak non-covalent interactions with enzymes and receptors, resulting in the manifestation of a branched spectrum of pharmacological action, is particularly important [18-21]. Analysis of the literature convincingly shows that the range of therapeutic activity and affinity for various bio targets in several pyrazole derivatives is usually caused by the substituents' nature in positions 3 and 4 of

the heterocycle. It was found that the presence of exocyclic functional C=C and C=N fragments is played a significant impact on the bioactivity of the pyrazole platform. In particular, effective anticancer agents have been identified among alkenyl derivatives of 4-formylpyrazoles [22-25], compounds with antibacterial and anti-inflammatory effect were found among the hydrazones of the corresponding aldehydes [26], and compounds with antiviral [27], antihyperglycemic [28], anti-inflammatory [29] and anti-TB [30] activity were revealed in several thiosemicarbazones.

The use of imines [31], oximes [32], (heteryl)aroylhydrazones [33, 34], and thiosemicarbazones [28-30, 35] pyrazole-4-carbaldehydes as "building blocks" for the construction of bio perspective heterocyclic ensembles is no less important in the synthetic aspect.

The modification of the pyrazole scaffold by pharmacophore fragments, particularly the 5-(4-nitrophenyl)furan group, is one of the attractive options for creating bioactive compounds. Previously, its introduction into the structure of several heterocycles allowed to obtain compounds with antibacterial [36], fungicidal [37], leishmanicidal [38] action, as well as selective inhibitors of phosphodiesterase [39] and P-glucoprotein [40]. Therefore, it seemed expedient to synthesize a series of new functionalized pyrazoles with 5- (4-nitrophenyl)furyl substituent.

2. Materials and Methods

2.1. Materials.

All chemicals were of reagent grade and used without further purification. The solvents were purified according to the standard procedures [41]. The initial hydrazones of [5-(4-nitrophenylfuran-2-yl)]methyl ketones 1a,b were prepared from corresponding ketones according to the method described in [42]. Pyrazole-4-carbaldehyde 2a,b was synthesized according to the methods [43, 44].

2.2. Chemistry.

The IR spectra of the compounds in KBr tablets were recorded on a Bruker Vertex 70. ^{1}H NMR spectra were obtained on a Varian VXR-400 spectrophotometer (399.97 MHz) in DMSO-d_6 solutions, TMS as an internal standard. Chromatomas spectra were obtained on an Agilent LC\MSD SL instrument; Zorbax SB-C18 column, 4.6x15 mm, 1.8 μm (82 (C) 75-932); solvent DMSO, ionization by electro-dissolution at atmospheric pressure. Elemental analysis was performed on a Perkin Elmer CHN Analyzer 2400 series in the analytical laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. Melting points are determined on the Kofler table and uncorrected.

3-[5-(4-Nitrophenyl)furan-2-yl]-1*H*-pyrazole-4-carbaldehyde (2a).

Yield 66 %; m. p. 238-240 ºC. IR (ν/cm^{-1}): 1697 (C=O). ^{1}H NMR: δ = 7.46 (d, 1H$_{fur}$, *J* = 4.4 Hz), 7.47-5.51 (m, 1H$_{fur}$), 8.07 (d, 2H$_{ar}$, *J* = 8.8 Hz), 8.29 (d, 2H$_{ar}$, *J* = 8.8 Hz), 8.54 (s, 1H, C^{5}H$_{pyrazole}$), 8.83 (br .s, 1H, NH), 10.14 (s, 1H, CHO). LC-MS: m/z = 284 [M+1] (100%). Anal. Calcd. for $C_{14}H_9N_3O_4$, % : C 59.37; H 3.20; N 14.84. Found, % : C 59.48; H 3.16; N 14.98.

3-[5-(4-Nitrophenyl)furan-2-yl]-1-phenyl-1*H*-pyrazole-4-carbaldehyde (2b).

Yield 71%; m. p. 206-208 ºC. LC-MS: m/z = 360 [M+1] (100%). Anal. Calcd. for $C_{20}H_{13}N_3O_4$, %: C 68.85; H 3.65; N 11.69. Found, %: C 68.90; H 3.59; N 11.60.

2.2.1. General procedure of the synthesis of 4-alkenylfunctionalized 3-[5-(4-nitrophenyl)furan-2-yl]-1*H*-pyrazoles (3a-e).

An equimolar amount of the corresponding methylene active compound and 0.05 g of anhydrous sodium acetate was added to a solution (1.4 mmol) of aldehyde 2a,b in 15 ml of acetic acid. The reaction mixture was boiled for 3 hours, cooled, the precipitate formed was filtered off, washed with water, dried and crystallized from acetic acid.

2-({3-[5-(4-Nitrophenyl)-2-furyl]-1*H*-pyrazol-4-yl}methylene)malononitrile (3a).

Yield 67 %; m. p. 250-252 ºC. IR (ν/cm-1): 1642 (C=C), 2217 (C≡N), 3320 (NH). ^{1}H NMR: δ = 7.38 (br. s, 1H, H_{fur}), 7.54 (d, 1H, *J* = 4.6 Hz, H_{fur}), 8.10 (d, 2H_{ar}, *J* = 8.8 Hz), 8.31 (d, 2H_{ar}, *J* = 8.8 Hz), 8.49 (s, 1H, H5 $_{pyrazole}$), 8.54 (br. s, 1H, HC=), 11.14 (s, 1H, NH). LC-MS: m/z = 332 [M+1] (100%). Anal. Calcd. for $C_{17}H_9N_5O_3$, % : C 61.63; H 2.74; N 21.14. Found, % : C 61.77; H 2.72; N 21.29.

Ethyl(2*E*)-2-cyano-3-{3-[5-(4-nitrophenyl)-2-furyl]-1*H*-pyrazol-4-yl}acrylate (3b).

Yield 80 %; m. p. 195-197 ºC. IR (ν/cm^{-1}): 1638 (C=C), 1718 (C=O), 2228 (C≡N), 3307 (NH). ^{1}H NMR: δ = 1.31 (t, 3H, *J* = 7.6 Hz, CH_3), 4.35 (q, 2H, *J* = 7.6 Hz, CH_2), 7.12 (br. S, 1H, H_{fur}), 7.50 (d, 1H, *J* = 4.4 Hz, H_{fur}), 8.02 (d, 2H_{ar}, *J* = 8.8 Hz), 8.26 (d, 2H_{ar}, *J* 8.8 Hz), 8.71 (s, 1H, H^5 $_{pyrazole}$), 8.85 (br. s, 1H, HC=), 11.07 (s, 1H, NH). LC-MS: m/z = 379 [M+1] (100%). Anal. Calcd. for $C_{19}H_{14}N_4O_5$, % : C 60.32; H 3.73; N 14.81. Found, % : C 60.45; H 3.82; N 14.86.

(2*E*)-2-Cyano-3-{3-[5-(4-nitrophenyl)-2-furyl]-1*H*-pyrazol-4-yl}acrylamide (3c).

Yield 76 %; m. p. 210-212 ºC. IR (ν/cm^{-1}): 1640 (C=C), 1692 (C=O), 2216 (C≡N), 3313, 3407 (NH). ^{1}H NMR: δ = 7.11 (br. S, 1H, H_{furan}), 7.48 (d, 1H, *J* = 4.4 Hz, H_{furan}), 7.74-7.83 (m, 2H, NH_2), 8.6 (d, 2H_{ar}, *J* = 8.6 Hz), 8.24 (d, 2H_{ar}, *J* = 8.6 Hz), 8.64 (s, 1H, H5 $_{pyrazole}$), 8.73 (br. S, 1H, HC=), 11.07 (br. s, 1H, NH). LC-MS: m/z = 350 [M+1] (100%). Anal. Calcd. for $C_{17}H_{11}N_5O_4$, % : C 58.46; H 3.17; N 20.05. Found, % : C 58.26; H 3.16; N 20.19.

(5*Z*)-5-({3-[5-(4-Nytrophenyl)-2-furyl]-1*H*-pyrazol-4-yl}methylene)-4-thioxo-1,3-thiazolidin-2-one (3d).

Yield 78 %; m. p. 260-262 ºC. IR (ν/cm^{-1}): 1635 (C=C), 1667(C=O), 3315, 3344 (NH). ^{1}H NMR: δ = 7.04 (br. s, 1H, H_{furan}), 7.47 (d, 1H, *J* = 4.4 Hz, H_{furan}), 8.15 (d, 2H_{ar}, *J* = 8.6 Hz), 8.30 (d, 2Harom, *J* = 8.6 Hz), 8.44 (s, 1H, H5 $_{pyrazole}$), 8.73 (s, 1H, HC=), 10.15 (s, 1H, NH), 10.94 (s, 1H, NH). LC-MS: m/z = 399 [M+1] (100%). Anal. Calcd. for $C_{17}H_{10}N_4O_4S_2$, % : C 51.25; H 2.53; N 14.06. Found, % : C 51.46; H 2.44; N 14.22.

2-({3-[5-(4-Nitrophenyl)-2-furyl]-1-phenyl-1*H*-pyrazol-4-yl}methylene)malononitrile (3e).

Yield 69 %; m. p. 233-235 ºC. IR (ν/cm^{-1}): 1639 (C=C), 2220 (C≡N). ^{1}H NMR: δ = 7.38 (d, 1H, *J* = 4.8 Hz, H_{furan}), 7.44 (t, 1H_{ar}, *J* = 7.8 Hz), 7.51 (d, 1H, *J* = 4.8 Hz, H_{furan}), 7.62 (t, 2H_{ar}, *J* = 7.8 Hz), 7.93 (d, 2H_{arom}, *J* = 7.8 Hz), 8.08 (d, 2H_{arom}, *J* = 8.6 Hz), 8.31 (d, 2H_{arom}, *J* = 8.6 Hz), 8.61 (s, 1H, HC=), 9.21 (s, 1H, H^5 $_{pyrazole}$). LC-MS: m/z = [M+1] (100%). Anal. Calcd. for $C_{23}H_{13}N_5O_3$, % : C 67.81; H 3.22; N 17.19. Found, % : C 67.88; H 3.27; N 17.28.

2.2.2. General procedure of the synthesis of 4-imino-functionalized 3-[5-(4-nitrophenyl)furan-2-yl]-1*H*-pyrazoles (4a-d, f-j).

An equimolar amount of the corresponding nitrogen-containing nucleophile was added to a solution (1.4 mmol) of aldehyde 2a,b in 15 ml of acetic acid. The mixture was heated for

3 hours. The reaction mixture was cooled, the precipitate was filtered off, washed with alcohol, dried, and crystallized from acetic acid.

N´-((1*E*)-{3-[5-(4-nitrophenyl)-2-furyl]-1*H*-pyrazol-4-yl}methylene)benzohydrazide (4a).

Yield 75 %; m. p. 255-257 ºC. IR (ν/cm^{-1}): 1652 (C=N), 1680(C=O), 3343, 3369 (NH). ^{1}H NMR: δ = 7.46-7.58 (m, 5H, 3H$_{ar}$+2H$_{furan}$), 7.93 (d, 2H$_{ar}$, *J* = 8.8 Hz), 8.08-8.21 (m, 2H$_{ar}$), 8.33 (d, 2H$_{arom}$, *J* = 8.8 Hz), 8.67 (s, 1H, HC=N), 8.77 (s, 1H, H^5 $_{pyrazole}$), 11.78 (s, 1H, NH), 11.84 (s, 1H, NH). LC-MS: m/z = 402 [M+1] (100%). Anal. Calcd. for $C_{21}H_{15}N_5O_4$, % : C 62.84; H 3.77; N 17.45. Found, % : C 62.98; H 3.88; N 17.48.

N´-((1*E*)-{3-[5-(4-nitrophenyl)-2-furyl]-1*H*-pyrazol-4-yl}methylene)isonicotinohydrazide (4b).

Yield 67 %; m. p. 248-250 ºC. IR (ν/cm^{-1}): 1657 (C=N), 1682(C=O), 3336, 3352 (NH). ^{1}H NMR: δ = 7.36 (d, 1H, *J* = 3.8 Hz, H$_{furan}$), 7.52 (d, 1H, *J* = 3.8 Hz, H$_{furan}$), 7.86 (d, 2H$_{ar}$, *J* = 7.4 Hz), 8.15 (br. s, 2H$_{ar}$), 8.20 (s, 1H, HC=N), 8.31 (d, 2H$_{ar}$, *J* = 8.4 Hz), 8.79 (s, 1H, H^5 $_{pyrazole}$), 8.80 (d, 2H$_{arom}$, *J* = 8.4 Hz), NH - protons are exchanged with water molecules of deuterosolvent. LC-MS: m/z = 403 [M+1] (100%). Anal. Calcd. for $C_{20}H_{14}N_6O_4$, % : C 59.70; H 3.51; N 20.89. Found, % : C 59.81; H 3.59; N 20.78.

4-Methyl-N´-((1*E*)-{3-[5-(4-nitrophenyl)-2-furyl]-1*H*-pyrazol-4-yl}methylene)benzenesulfonohydrazide (4c).

Yield 81 %; m. p. 220-222 ºC. IR (ν/cm^{-1}): 1649 (C=N), 1673(C=O), 3329, 3360 (NH). ^{1}H NMR: δ = 2.34 (s, 3H, CH$_3$), 7.15 (d, 1H, *J* = 4.0 Hz, H$_{furan}$), 7.40 (d, 2H$_{arom}$, *J* = 7.8 Hz), 7.28 (d, 1H, *J* = 4.0 Hz, H$_{furan}$), 7.76 (d, 1H, H$_{furan}$), 8.13 (s, 1H, H^5 $_{pyrazole}$), 8.19 (d, 2H$_{arom}$, *J* = 8.6 Hz), 8.27 (s, 1H, HC=N), 8.32 (d, 2H$_{arom}$, *J* = 8.6 Hz), 11.36 (s, 1H, NH), 11.63 (s, 1H, NH). LC-MS: m/z = 452 [M+1] (100%). Anal. Calcd. for $C_{21}H_{17}N_5O_5S$, % : C 55.87; H 3.80; N 15.51. Found, % : C 55.98; H 3.89; N 15.38.

3-[5-(4-Nitrophenyl)-2-furyl]-1*H*-pyrazole-4-carbaldehyde semicarbazone (4d).

Yield 83 %; m. p. 240-242 ºC. IR (ν/cm^{-1}): 1644 (C=N), 1668(C=O), 3280, 3315, 3345 (NH). ^{1}H NMR: δ = 6.42 (br. s, 2H, NH$_2$), 7.04 (d, 1H, *J* = 4.0 Hz, H$_{furan}$), 7.48 (d, 1H, *J* = 4.0 Hz, H$_{furan}$), 8.12 (d, 2H$_{arom}$, *J* = 8.8 Hz), 8.21 (s, 1H, H^5 $_{pyrazole}$), 8.29 (d, 2H$_{ar}$, *J* = 8.8 Hz), 8.31 (s, 1H, HC=N), 10.35 (s, 1H, NH), 11.24 (s, 1H, NH). LC-MS: m/z = 341 [M+1] (100%). Anal. Calcd. for $C_{15}H_{12}N_6O_4$, % : C 52.94; H 3.55; N 24.70. Found, % : C 53.08; H 3.55; N 24.66.

N´-((1*E*)-{3-[5-(4-nitrophenyl)-2-furyl]-1-phenyl-1*H*-pyrazol-4-yl}methylene)benzohydrazide (4f).

Yield 88 %; m. p. 245-247 ºC. IR (ν/cm^{-1}): 1642 (C=N), 3364 (NH). ^{1}H NMR: δ = 7.55-8.07 (m, 12H$_{arom}$), 8.12 (d, 2H$_{ar}$, *J* = 8.8 Hz), 8.34 (d, 2H$_{ar}$, *J* = 8.8), 8.79, 9.35 (s, 1H, H^5 $_{pyrazole}$), 9.07, 10.23 (s, 1H, HC=N), 11.97 (s, 1H, NH). LC-MS: m/z = 478 [M+1] (100%). Anal. Calcd. for $C_{27}H_{19}N_5O_4$, % : C 67.92; H 4.01; N 14.67. Found, % : C 68.01; H 3.95; N 14.50.

N´-((1*E*)-{3-[5-(4-nitrophenyl)-2-furyl]-1-phenyl-1*H*-pyrazol-4-yl}methylene)isonicotinohydrazide (4g).

Yield 77 %; m. p. 237-239 ºC. IR (ν/cm^{-1}): 1647 (C=N), 3352 (NH). ^{1}H NMR: δ = 7.42 (t, 1H$_{arom}$, *J* = 7.6 Hz), 7.54 (d, 1H, *J* = 3.8 Hz, H$_{furan}$), 7.59 (t, 2H$_{ar}$, *J* = 7.6 Hz), 7.72 (d, 1H, *J* = 3.8 Hz, H$_{furan}$), 7.92 (d, 2H$_{ar}$, *J* = 7.6 Hz), 8.02 (d, 2H$_{ar}$, *J* = 7.4 Hz), 8.13 (d, 2H$_{ar}$, *J* = 7.4 Hz), 8.34 (d, 2H$_{ar}$, *J* = 8.6 Hz), 8.79, 9.36 (s, 1H, H^5 $_{pyrazole}$), 8.83 (d, 2H$_{ar}$, *J* = 8.6 Hz), 9.24, 10.13 (s, 1H, HC=N), 12.32 (s, 1H, NH). LC-MS: m/z = [M+1] (100%). Anal. Calcd. for $C_{26}H_{18}N_6O_4$, % : C 65.27; H 3.79; N 17.56. Found, % : C 65.51; H 3.88; N 17.60.

4-Methyl-N´-((1*E*)-{3-[5-(4-nitrophenyl)-2-furyl]-1-phenyl-1*H*-pyrazol-4-yl}methylene)benzenesulfonohydrazide (4h).

Yield 84 %; m. p. 212-214 ºC. IR (ν/cm^{-1}): 1653 (C=N), 3365 (NH). ^{1}H NMR: δ = 2.36 (s, 3H, CH_3), 7.21 (d, 1H, *J* = 3.8, H_{furan}), 7.34-7.55 (m, 8H_{ar}), 7.80 (d, 2H_{ar}, *J* = 7.6 Hz), 7.91 (d, 2H_{arom}, *J* = 7.6 Hz), 8.03 (d, 2H_{arom}, *J* = 8.8 Hz), 8.29 (d, 2H_{ar}, *J* = 8.8 Hz), 8.32, 9.19 (s, 1H, H^5 $_{pyrazole}$), 8.72, 10.24 (s, 1H, HC=N), 11.24 (s, 1H, NH). LC-MS: m/z = 528 [M+1] (100%). Anal. Calcd. for $C_{27}H_{21}N_5O_5S$, % : C 61.47; H 4.01; N 13.27. Found, % : C 61.61; H 4.09; N 13.41.

3-[5-(4-Nitrophenyl)-2-furyl]-1-phenyl-1*H*-pyrazole-4-carbaldehyde semicarbazone (4i).

Yield 67 %; m. p. 245-247 ºC. IR (ν/cm^{-1}): 1639 (C=N), 1657(C=O), 3269, 3344 (NH). ^{1}H NMR: δ = 6.47 (s, 2H, NH_2), 7.07 (d, 1H, *J* = 3.6 Hz, H_{furan}), 7.39-7.51 (m, 4H, 3H_{arom}+1H_{furan}), 7.89 (t, 2H_{arom}, *J* = 7.6 Hz), 8.05 (d, 2H_{arom}, *J* = 8.6 Hz), 8.23 (d, 2H_{arom}, *J* = 8.6 Hz), 8.30 (s, 1H, H^5 $_{pyrazole}$), 9.07 (s, 1H, HC=N), 10.43 (s, 1H, NH). LC-MS: m/z = 417 [M+1] (100%). Anal. Calcd. for $C_{21}H_{16}N_6O_4$, % : C 60.58; H 3.87; N 20.18. Found, % : C 60.62; H 3.79; N 20.25.

3-[5-(4-Nitrophenyl)-2-furyl]-1-phenyl-1*H*-pyrazole-4-carbaldehyde thiosemicarbazone (4j).

Yield 71 %; m. p. 238-240 ºC. IR (ν/cm^{-1}): 1645 (C=N), 1662(C=O), 3244, 3357 (NH). ^{1}H NMR: δ = 7.08 (d, 1H, *J* = 3.6 Hz, H_{furan}), 7.38-7.55 (m, 4H, 3H_{arom}+1H_{furan}), 7.86 (d, 2H_{ar}, *J* = 7.8 Hz), 7.96 (br. s, 1H, NH), 8.07 (d, 2H_{arom}, *J* = 8.6 Hz), 8.24 (d, 2H_{ar}, *J* = 8.6 Hz), 8.34 (br. s, 1H, NH), 8.48 (s, 1H, H^5 $_{pyrazole}$), 9.24 (s, 1H, HC=N), 11.71 (s, 1H, NH). LC-MS: m/z = 433 [M+1] (100%). Anal. Calcd. for $C_{21}H_{16}N_6O_3S$, % : C 58.32; H 3.73; N 19.43. Found, % : C 58.46; H 3.76; N 19.56.

2.2.3. General procedure for the synthesis of N-Hydroxy-1-{3-[5-(4-nitrophenyl)furan-2-yl]-1*H*-pyrrol-4-yl}methanimine (4e).

0.2 g (2.8 Mmol) of hydroxylamine hydrochloride and 0.25 g of sodium bicarbonate was added to a solution of 0.5 g (1.4 mmol) of aldehyde 2b in 10 ml of DMF. The reaction mixture was heated for 30 minutes, cooled, 100 ml of water was added, the precipitate formed was filtered off, washed with water, dried, and crystallized from acetic acid.

3-[5-(4-Nitrophenyl)-2-furyl]-1-phenyl-1*H*-pyrazole-4-carbaldehyde oxime (4e).

Yield 78 %; m. p. 200-202 ºC. IR (ν/cm^{-1}): 1648 (C=N), 3447 (OH). ^{1}H NMR: δ = 7.27 (d, 1H, *J* = 4.2 Hz, H_{furan}), 7.41 (t, 1H_{ar}, *J* = 7.6 Hz), 7.49 (d, 1H, *J* = 4.2 Hz, H_{furan}), 7.55 (t, 2H_{arom}, *J* = 7.6 Hz), 7.84-7.96 (m, 3H, 2H_{ar}+HC=N), 8.15 (d, 2H_{ar}, *J* = 8.8 Hz), 8.31 (d, 2H_{arom}, *J* = 8.8 Hz), 9.17 (s, 1H, H^5 $_{pyrazole}$), 11.94 (s, 1H, OH). LC-MS: m/z = 375 [M+1] (100%). Anal. Calcd. for $C_{20}H_{14}N_4O_4$, % : C 64.28; H 3.77; N 14.97. Found, % : C 64.17; H 3.77; N 14.95.

2.3. Antimicrobial activity.

Our new synthesized 4-functional pyrazole derivatives 3a-e and 4a-j were evaluated for their antimicrobial activity against reference strains of bacteria *S. aureus* ATCC 25923, *E. coli* ATCC 25922, and fungi of the genus *C. albicans* ATCC 885-653 by the value of the bacteriostatic and minimal bactericidal concentrations (MB_SC and MB_CC), minimal fungistatic and minimal fungicidal concentration (MF_SC and MF_CC) (Table 2).

The test substances' antimicrobial activity was studied by the micro method using disposable polystyrene tablets and Takachi microtiters. 0.05 Ml of working dilutions of microorganisms' culture was added in 96-well polystyrene plates (1 ml of medium contained 10^5 CFU of bacteria; dilution of microorganisms 10^2 in Saburo liquid medium was used for *C. ablicans*).

A 0.05 ml platinum basket was used to collect the test sample's matrix solution and added to the first well. The following samples were similarly introduced into the other wells of the first row. Sequentially turning the baskets received dilutions in all wells from 1: 2 to 1: 256. In the same way, an experiment with other test cultures was conducted. The plates were then placed in a humid thermostat chamber at 37ºC, incubated for 24 h (for fungi - 28ºC and 48 h, respectively). The results were estimated, taking into account the absence and presence of growth of microorganisms. The minimum static concentration was considered the dilution of the sample at which the microorganism's growth was delayed. In order to obtain reliable results, the experiment was performed three times.

The procedure of determination of minimal bactericidal and fungicidal concentrations was as follows. Microorganisms were removed from wells with a liquid nutrient medium, where their growth was practically not observed. They were transplanted to a solid nutrient medium (MPA for bacteria, Saburo agar - for fungus *C. ablicans*). Determination of MB_CC MF_CC was performed after culturing microorganisms at the optimum temperature and time. The minimum bactericidal and fungicidal concentrations were considered to be those at which the microorganism's vital activity was not restored, i.e., its growth was not observed on a solid nutrient medium.

3. Results and Discussion

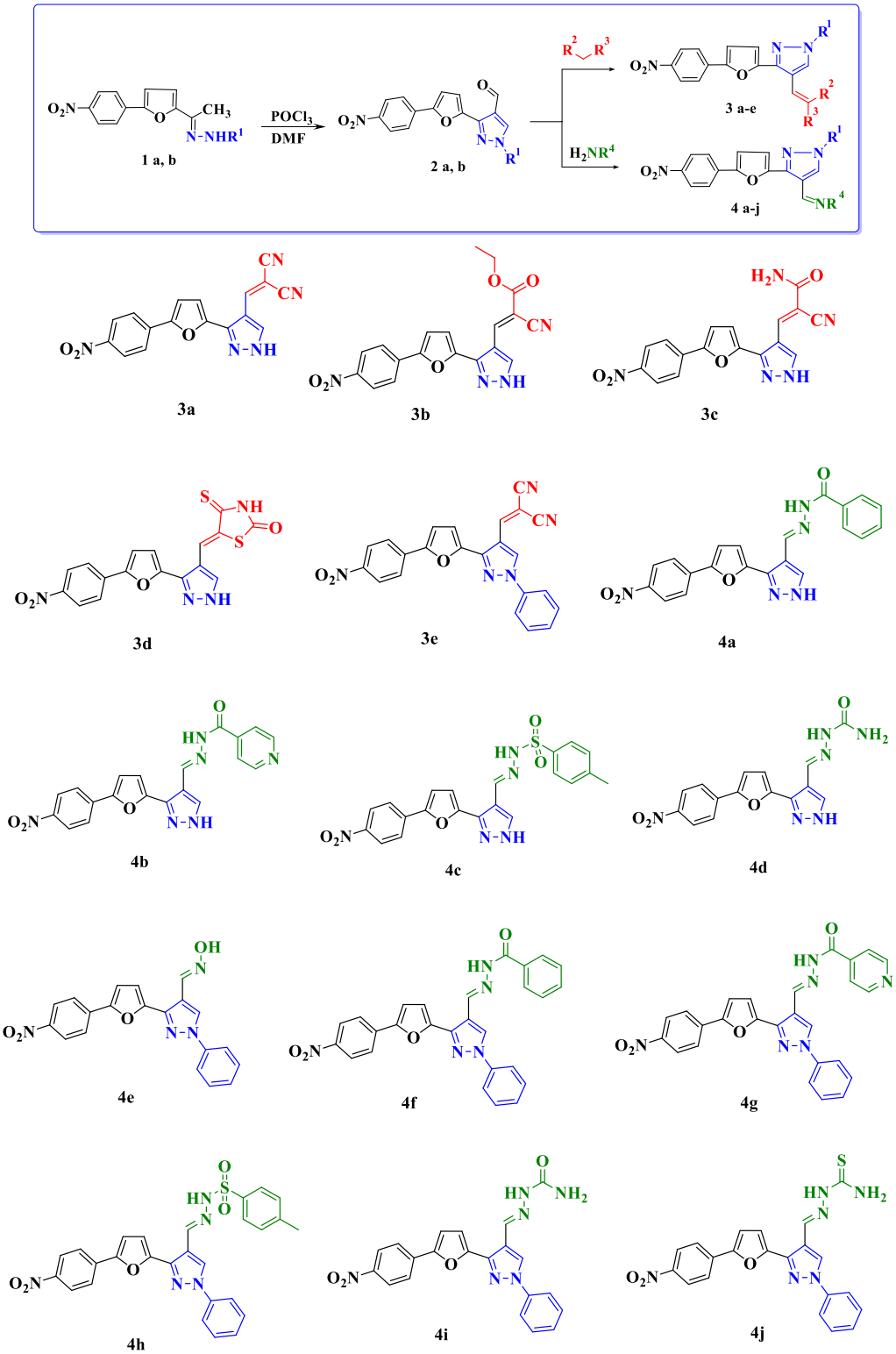
3.1. Chemistry.

The selected hydrazones [5-(4-nitrophenylfuran-2-yl)] methyl ketone 1a, b were used as base substrates to design the target compounds. They were transformed into 3-[5-(4-nitrophenyl)-furan-2-yl]pyrazole-4-carbaldehyde 2a,b under the conditions of the Vilsmeier–Haack reaction [43-45]. Their further structural functionalization with such methylene active reagents as malononitrile, ethyl cyanoacetate, cyanoacetamide, and thiooxoimidazolidin-2-one in boiling acetic acid in the presence of sodium acetate allowed them to obtain alkenyl derivatives of 3a-e with the yields of 67-80%. In turn, aldehydes 2a,b were converted into the corresponding hydrazones 4a-c, f-h, semicarbazone 4d, i, thiosemicarbazone 4j and oxime 4e with the yields of 67-88% by the condensation with hydrazides and (thio)semicarbazides in boiling acetic acid, and with hydroxylamine hydrochloride in water (see Scheme 1).

The synthesized compounds 3a-e and 4a-j are high-melting substances, low soluble in most organic solvents, except for DMSO and DMF. Their composition and structure are confirmed by the results of chromato-mass, IR, and ^{1}H NMR spectra. The latter's analysis for 1-phenyl-substituted hydrazones 4f-h revealed the fact of their existence in the form of a mixture of *E*- and *Z*-isomers. Considering the results of the authors' study [46], the percentage of each isomer was determined based on the ratio of doubled signals of protons H5 of the pyrazole cycle and H-C= hydrazone fragment (Table 1).

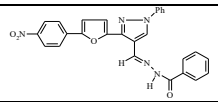
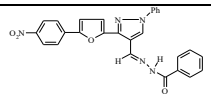
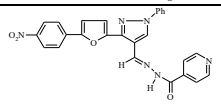
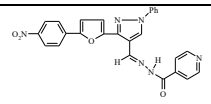
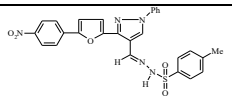
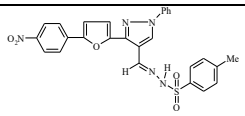
3.2. Investigation of antimicrobial activity.

It is known that over the past decades, the number of multi-resistant strains that are difficult to treat has increased [47]. This was the impetus for the discovery of several antimicrobial agents. At the same time, the issue of a narrow antimicrobial spectrum, adverse side effects, and high toxicity for many of them remain unresolved. Therefore, the development of structurally new antimicrobial agents, particularly from the class of pyrazoles with a clear therapeutic action mechanism, does not lose its relevance [48].



Scheme 1. Synthesis of pyrazole derivatives 3 a-e and 4 a-j.

Table 1. The ratio of E- and Z-isomers in hydrazones 4f-h.

Compound	*E*- isomer	Contents, %	Z- isomer	Contents, %
4f		71		29
4g		75		25
4h		73		27

Conducted microbiological studies allow characterizing 4-alkenyl-functionalized derivatives of 3a-e as substances with pronounced and moderate antimicrobial activity (Table 2). In particular, it was found that compounds 3a-d showed bacteriostatic and bactericidal action at a concentration of 12.5 μg/ml against the *S. aureus* strain. The compound 3e was less active to them in activity per dilution (25.0 μg/ml). The E. coli strain culture was sensitive to the action of the compound 3b at a concentration MBsC of 3.125 μg/ml, and the MBcC was 6.25 μg/ml. Compounds 3a, c, d disrupted the culture's viability at a concentration of 6.25 μg/ml, and compound 3e showed weaker antimicrobial activity (12.5 μg/ml).

MFsC and MFcC of compounds 3a-d, regardless of the nature of the functional substituents, were 12.5 μg/ml and caused a fungicidal effect at a concentration of 25.0 μg/ml.

The screening of the antimicrobial properties of 4-imino functionalized pyrazoles 4a-j showed bacteriostatic action in concentrations from 1.625 μg/ml to 12.5 μg/ml. The compound 4f was most active, the inhibitory effect against the *E. coli* strain was 1.625 μg/ml, and the bactericidal effect was observed at a concentration of 3.125 μg/ml. The MFsC and MFcC of the test compounds against the yeast fungus strains of the genus *Candida* were 12.5-25.0 μg/ml.

Thus, the obtained results show a wide range of antimicrobial properties of the synthesized compounds, which seem very promising for further in-depth studies, particularly the pronounced effectiveness of *N*-benzoylhydrazone 4-formylpyrazole 4f.

Table 2. Antimicrobial activity of compounds 3a-e, 4a-j.

№	*S. aureus ATCC 25923*		*E. coli ATCC 25922*		*C. albicans ATCC 885-653*	
	MBsC (μg/ml)	**MBcC (μg/ml)**	**MBsC (μg/ml)**	**MBcC (μg/ml)**	**MFsC (μg/ml)**	**MFcC (μg/ml)**
3a	12,5	12,5	6,25	6,25	12,5	12,5
3b	12,5	12,5	3,125	6,25	12,5	12,5
3c	12,5	12,5	6,25	6,25	12,5	12,5
3d	12,5	12,5	6,25	6,25	12,5	12,5
3e	25	25	12,5	12,5	25	25
4a	6,25	12,5	12,5	12,5	12,5	12,5
4b	12,5	12,5	3,125	6,25	12,5	12,5
4c	6,25	12,5	6,25	6,25	12,5	12,5
4d	12,5	12,5	6,25	6,25	12,5	12,5
4e	12,5	12,5	6,25	6,25	25	25
4f	12,5	12,5	1,625	3,125	12,5	12,5
4g	12,5	12,5	12,5	12,5	25	25
4h	12,5	12,5	12,5	12,5	12,5	12,5
4i	25	25	6,25	6,25	25	25
4j	12,5	12,5	12,5	12,5	25	25

4. Conclusions

In conclusion, the reaction of 3-[5-(4-nitrophenyl)furan-2-yl]pyrazole-4-carbaldehydes with active methylene compounds and aminonucleophiles allows to obtain new pyrazole

derivatives modified with alkenyl - and imino functional groups. In general, primary microbiological screening of the obtained functional pyrazoles revealed substances with pronounced bactericidal and fungicidal properties. It proved the expediency of their further in-depth study to search for new antimicrobial agents.

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Conflicts of Interest

The authors declare no conflict of interest.

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