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Synthesis, Antimicrobial and Anticancer Activities of 1-aryl-4-[(5-aryl-2-furyl)carbonothioyl]piperazines

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Abstract: As a result of the furfural reaction with diazonium, salts 1a-h the arylfuran-2-carbaldehydes 3a-h were synthesized. In the reaction of Wilgerodt-Kindler, arylfuran-2-carbaldehydes with sulfur and aryl piperazines was prepared 1-aryl-4-[(5-aryl-2-furyl)carbonothioyl]piperazines. The structures of target compounds 5a-l were confirmed by using ^{1}H NMR spectroscopy and elemental analysis. The antimicrobial activity of the synthesized substances was evaluated by the value of the MIC and minimum fungicidal and bactericidal concentration. The findings exhibited that the compounds possessed moderate antimicrobial potential. *In vitro* anticancer activity assessment on the full panel of about 60 human cancer cell lines showed that received compounds displayed moderate activity.

Keywords: organic synthesis; 1-aryl-4-[(5-aryl-2-furyl)carbonothioyl]piperazines; anticancer activity; antimicrobial activity.

1. Introduction

The development of effective antimicrobial agents continues to be a great challenge, particularly due to the increasing resistance of superbugs. No less interesting is the search for new anticancer drugs. The progress is seen in cancer treatment in recent decades and epidemiological data clearly indicate the need for urgent new therapeutic approaches to combat the diseases. This work is the continuation of our previous works [1-28] on the design of biologically important heterocycles. In this article, we report the synthesis of 1-aryl-4-[(5-aryl-2-furyl)carbonothioyl]piperazines for further pharmacological screening such as antimicrobic and antitumor activities.

Biological properties of 1-(2-furylcarbonothioyl)-4-phenylpiperazine have not been reported. At the same time, their bioisosteres –1-(2-furoyl)-4-phenylpiperazines have to possess various types of biological and pharmacological activities. It was described about antiviruses [29], antituberculosis [30], antiprotozoal [31], antihelmintic [32], anticonvulsant [33], antihypertensive [34] and other activities. 1-(2-Furoyl)-4-phenylpiperazines are inhibitors of human lactate dehydrogenase A [35], PARP-1 [36], dipeptidyl peptidase-4 [37] and other ferments, ligands of Nicotinic Acetylcholine [38], histamine-3 [39], urotensin-II [40], and other

receptors. About antibacterial [41-45], antifungal [46-48] and antitumor [49-51] activities were also reported.

These diverse biological applications of 1-(2-furoyl)-4-phenylpiperazines compounds have brought motivation for new efforts in search of novel hybrid derivatives with improved biological activity and diverse applications in the pharmaceutical industry

2. Materials and Methods

2.1. Materials.

The reagents used for the synthesis of target compounds were commercially available and of analytical grade. When performing the synthetic part of the work, the reagents of the company Merck (Germany) and Sigma-Aldrich (USA) were used. All solvents and reagents were used without further purification.

2.2. Chemistry.

The melting points of all the compounds were recorded in an open capillary by a Melt temp instrument. ^{1}H-NMR spectra were recorded on a Varian Mercury 500 (500 MHz for ^{1}H) instrument with TMS or deuterated solvent as an internal reference. Chemical shifts were reported as δ (ppm). Elemental analysis was performed on a Vario MICRO cube automatic CHNS analyzer. The elemental analysis data obtained experimentally for the contents of carbon, hydrogen, and nitrogen were within ±0.3% of the theoretical values.

2.2.1. General procedure of receiving 4-[(5-aryl-2-furyl)carbonothioyl]-morpholines (5a-l).

A mixture of 0.01 mol of arylfurfurals 3a-h, 0.013 mol of arylpiperazines 4a-d, and 0.32 g (0.01mol) of thin powder of sulfur in 20 ml of DMF was stirred at 100°C for 6 hours. The cooled reaction mixture was diluted with water (100 ml), and the separated precipitate was filtered off and recrystallized with ethanol-DMF.

2.2.2. 1-{[5-(3-Chlorophenyl)-2-furyl]carbonothioyl}-4-phenylpiperazine (5a).

Yield 65%; mp 198–199°C. ^{1}H NMR: δ = 7.86 (s, 1H, C_6H_4Cl), 7.75 (d, *J* = 7.6 Hz, 1H, C_6H_4Cl), 7.50 (t, *J* = 7.8 Hz, 1H, C_6H_4Cl), 7.43 (d, *J* = 7.9 Hz, 1H, C_6H_4Cl), 7.30–7.21 (m, 3H, 3-H_{Fur} and C_6H_5), 7.17 (d, *J* = 3.6 Hz, 1H, 4-H_{Fur}), 6.96 (d, *J* = 7.9 Hz, 2H, C_6H_5), 6.81 (t, *J* = 7.2 Hz, 1H, C_6H_5), 4.36 (br s, 2H, CH_2N), 4.16 (br s, 2H, CH_2N), 3.38 (br s, 4H, (CH_2)$_2$NC_6H_5). Anal. Calcd for $C_{21}H_{19}ClN_2OS$: C, 65.87; H, 5.00; N, 7.32; S, 8.37. Found: C, 65.98; H, 5.05; N, 7.28; S, 8.31.

2.2.3. 1-{[5-(2,3-Dichlorophenyl)-2-furyl]carbonothioyl}-4-phenylpiperazine (5b).

Yield 79%; mp 201–202°C. ^{1}H NMR: δ = 7.84 (d, *J* = 7.8 Hz, 1H, $C_6H_3Cl_2$), 7.69 (d, *J* = 7.7 Hz, 1H, $C_6H_3Cl_2$), 7.50 (t, *J* = 8.0 Hz, 1H, $C_6H_3Cl_2$), 7.30 (d, *J* = 3.6 Hz, 1H, 3-H_{Fur}), 7.24 (t, *J* = 7.8 Hz, 2H, C_6H_5), 7.21 (d, *J* = 3.6 Hz, 1H, 4-H_{Fur}), 6.96 (d, *J* = 8.2 Hz, 2H, C_6H_5), 6.81 (t, *J* = 7.2 Hz, 1H, C_6H_5), 4.37 (br s, 2H, CH_2N), 4.14 (br s, 2H, CH_2N), 3.38 (br s, 4H, (CH_2)$_2$NC_6H_5). Anal. Calcd for $C_{21}H_{18}Cl_2N_2OS$: C, 60.44; H, 4.35; N, 6.71; S, 7.68. Found: C, 60.52 H, 4.39; N, 6.67; S, 7.74.

2.2.4. 1-{[5-(2,4-Dichlorophenyl)-2-furyl]carbonothioyl}-4-phenylpiperazine (5c).

Yield 83%; mp 214–215°C. ^{1}H NMR: δ = 7.88 (dd, *J* = 8.5, 1,5 Hz, 1H, $C_6H_3Cl_2$), 7.78 (s, 1H, $C_6H_3Cl_2$), 7.57 (d, *J* = 8.5 Hz, 1H, $C_6H_3Cl_2$), 7.30–7.21 (m, 3H, 3-H_{Fur} and C_6H_5), 7.19 (s, 1H, 4-H_{Fur}), 6.96 (d, *J* = 7.0 Hz, 2H, C_6H_5), 6.81 (t, *J* = 7.0 Hz, 1H, C_6H_5), 4.37 (br s, 2H, CH_2N), 4.13 (br s, 2H, CH_2N), 3.37 (br s, 4H, $(CH_2)_2NC_6H_5$). Anal. Calcd for $C_{21}H_{18}Cl_2N_2OS$: C, 60.44; H, 4.35; N, 6.71; S, 7.68. Found: C, 60.37; H, 4.31; N, 6.78; S, 7.63.

2.2.5. 1-{[5-(2,4-Dichlorophenyl)-2-furyl]carbonothioyl}-4-(3-methylphenyl)piperazine (5d).

Yield 81%; mp 205–206°C. ^{1}H NMR: δ = 7.88 (d, *J* = 8.6 Hz, 1H, $C_6H_3Cl_2$), 7.78 (d, *J* = 1.7 Hz, 1H, $C_6H_3Cl_2$), 7.57 (dd, *J* = 8.5, 1,7 Hz, 1H, $C_6H_3Cl_2$), 7.26 (d, *J* = 3.6 Hz, 1H, 3-H_{Fur}), 7.19 (d, *J* = 3.6 Hz, 1H, 4-H_{Fur}), 7.12 (t, *J* = 7.8 Hz, 1H, $C_6H_4CH_3$), 6.79 (s, 1H, $C_6H_4CH_3$), 6.75 (d, *J* = 8.0 Hz, 1H, $C_6H_4CH_3$), 6.64 (d, *J* = 7.5 Hz, 1H, $C_6H_4CH_3$), 4.35 (br s, 2H, CH_2N), 4.12 (br s, 2H, CH_2N), 3.34 (br s, 4H, $(CH_2)_2NC_6H_4CH_3$), 2.26 (s, 3H, $C_6H_4CH_3$). Anal. Calcd for $C_{22}H_{20}Cl_2N_2OS$: C, 61.25; H, 4.67; N, 6.49; S, 7.43. Found: C, 61.37; H, 4.71; N, 6.55; S, 7.36.

2.2.6. 1-{[5-(3,4-Dichlorophenyl)-2-furyl]carbonothioyl}-4-phenylpiperazine (5e).

Yield 74%; mp 231–232°C. ^{1}H NMR: δ = 8.05 (s, 1H, $C_6H_3Cl_2$), 7.80–7.71 (m, 2H, $C_6H_3Cl_2$), 7.30 (d, *J* = 2.0 Hz, 1H, 3-H_{Fur}), 7.25 (t, *J* = 8.0 Hz, 2H, C_6H_5), 7.17 (d, *J* = 2.0 Hz, 1H, 4-H_{Fur}), 6.96 (d, *J* = 7.5 Hz, 2H, C_6H_5), 6.82 (t, *J* = 7.0 Hz, 1H, C_6H_5), 4.36 (br s, 2H, CH_2N), 4.15 (br s, 2H, CH_2N), 3.38 (br s, 4H, $(CH_2)_2NC_6H_5$). Anal. Calcd for $C_{21}H_{18}Cl_2N_2OS$: C, 60.44; H, 4.35; N, 6.71; S, 7.68. Found: C, 60.48; H, 4.33; N, 6.65; S, 7.77.

2.2.7. 1-Phenyl-4-({5-[3-(trifluoromethyl)phenyl]-2-furyl}carbonothioyl)piperazine (5f).

Yield 71%; mp 178–179°C. ^{1}H NMR: δ = 8.14–8.06 (m, 2H, $C_6H_4CF_3$), 7.76–7.68 (m, 2H, $C_6H_4CF_3$), 7.36 (d, *J* = 3.6 Hz, 1H, 3-H_{Fur}), 7.25 (t, *J* = 7.8 Hz, 2H, C_6H_5), 7.18 (d, *J* = 3.6 Hz, 1H, 4-H_{Fur}), 6.97 (d, *J* = 8.1 Hz, 2H, C_6H_5), 6.82 (t, *J* = 7.2 Hz, 1H, C_6H_5), 4.36 (br s, 2H, CH_2N), 4.16 (br s, 2H, CH_2N), 3.39 (br s, 4H, $(CH_2)_2NC_6H_5$). Anal. Calcd for $C_{22}H_{19}F_3N_2OS$: C, 63.45; H, 4.60; N, 6.73; S, 7.70. Found: C, 63.57; H, 4.65; N, 6.68; S, 7.64.

2.2.8. 1-{[5-(2-Nitrophenyl)-2-furyl]carbonothioyl}-4-phenylpiperazine (5g).

Yield 71%; mp 245–246°C. ^{1}H NMR: δ = 8.00–7.90 (m, 2H, $C_6H_4NO_2$), 7.79 (t, *J* = 7.0 Hz, 1H, $C_6H_4NO_2$), 7.66 (t, *J* = 7.0 Hz, 1H, $C_6H_4NO_2$), 7.25 (t, *J* = 7.0 Hz, 2H, C_6H_5), 7.21 (s, 1H, 3-H_{Fur}), 7.10 (s, 1H, 4-H_{Fur}), 6.97 (d, *J* = 7.5 Hz, 2H, C_6H_5), 6.83 (t, *J* = 6.5 Hz, 1H, C_6H_5), 4.33 (br s, 2H, CH_2N), 3.99 (br s, 2H, CH_2N), 3.34 (br s, 4H, $(CH_2)_2NC_6H_5$). Anal. Calcd for $C_{21}H_{19}N_3O_3S$: C, 64.11; H, 4.87; N, 10.68; S, 8.15. Found: C, 64.04; H, 4.81; N, 10.61; S, 8.22.

2.2.9. 1-(3-Methylphenyl)-4-{[5-(2-nitrophenyl)-2-furyl]carbonothioyl}piperazine (5h).

Yield 68%; mp 251–252°C. ^{1}H NMR: δ = 7.96 (d, *J* = 8.0 Hz, 1H, $C_6H_4NO_2$), 7.92 (d, *J* = 7.6 Hz, 1H, $C_6H_4NO_2$), 7.79 (t, *J* = 7.4 Hz, 1H, $C_6H_4NO_2$), 7.65 (t, *J* = 7.5 Hz, 1H, $C_6H_4NO_2$), 7.20 (d, *J* = 3.2 Hz, 1H, 3-H_{Fur}), 7.17–7.04 (m, 2H, 4-H_{Fur} and $C_6H_4CH_3$), 6.85–6.71 (m, 2H, $C_6H_4CH_3$), 6.65 (d, *J* = 7.2 Hz, 1H, $C_6H_4CH_3$), 4.32 (br s, 2H, CH_2N), 3.98 (br s,

2H, CH_2N), 3.32 (br s, 4H, $(CH_2)_2NC_6H_4CH_3$), 2.26 (s, 3H, $C_6H_4CH_3$). Anal. Calcd for $C_{22}H_{21}N_3O_3S$: C, 64.85; H, 5.19; N, 10.31; S, 7.87. Found: C, 64.93; H, 5.22; N, 10.37; S, 7.81

2.2.10. 1-{[5-(3-Nitrophenyl)-2-furyl]carbonothioyl}-4-phenylpiperazine (5i).

Yield 73%; mp 215–216°C. ^{1}H NMR: δ = 8.54 (s, 1H, $C_6H_4NO_2$), 8.23 (d, *J* = 8.0 Hz, 1H, $C_6H_4NO_2$), 8.20 (d, *J* = 8.5 Hz, 1H, $C_6H_4NO_2$), 7.77 (t, *J* = 7.9 Hz, 1H, $C_6H_4NO_2$), 7.42 (s, 1H, 3-H_{Fur}), 7.25 (t, *J* = 7.0 Hz, 2H, C_6H_5), 7.19 (s, 1H, 4-H_{Fur}), 6.98 (d, *J* = 7.6 Hz, 2H, C_6H_5), 6.82 (t, *J* = 7.2 Hz, 1H, C_6H_5), 4.37 (br s, 2H, CH_2N), 4.16 (br s, 2H, CH_2N), 3.40 (br s, 4H, $(CH_2)_2NC_6H_5$). Anal. Calcd for $C_{21}H_{19}N_3O_3S$: C, 64.11; H, 4.87; N, 10.68; S, 8.15. Found: C, 64.17; H, 4.84; N, 10.77; S, 8.07.

2.2.11. 1-(4-Methylphenyl)-4-{[5-(3-nitrophenyl)-2-furyl]carbonothioyl}piperazine (5j).

Yield 69%; mp 222–223°C. ^{1}H NMR: δ = 8.53 (t, *J* = 1.5 Hz, 1H, $C_6H_4NO_2$), 8.25–8.16 (m, 2H, $C_6H_4NO_2$), 7.77 (t, *J* = 8.0 Hz, 1H, $C_6H_4NO_2$), 7.41 (d, *J* = 3.5 Hz, 1H, 3-H_{Fur}), 7.18 (d, *J* = 3.5 Hz, 1H, 4-H_{Fur}), 7.06 (d, *J* = 8.0 Hz, 2H, $C_6H_4CH_3$), 6.88 (d, *J* = 8.5 Hz, 2H, $C_6H_4CH_3$), 4.37 (br s, 2H, CH_2N), 4.13 (br s, 2H, CH_2N), 3.31 (br s, 4H, $(CH_2)_2NC_6H_4CH_3$), 2.21 (s, 3H, $C_6H_4CH_3$). Anal. Calcd for $C_{22}H_{21}N_3O_3S$: C, 64.85; H, 5.19; N, 10.31; S, 7.87. Found: C, 64.72; H, 5.16; N, 10.43; S, 7.92.

2.2.12. 1-{[5-(4-Nitrophenyl)-2-furyl]carbonothioyl}-4-phenylpiperazine (5k).

Yield 83%; mp 247–248°C. ^{1}H NMR: δ = 8.31 (d, *J* = 8.7 Hz, 2H, $C_6H_4NO_2$), 8.04 (d, *J* = 8.7 Hz, 2H, $C_6H_4NO_2$), 7.45 (d, *J* = 3.6 Hz, 1H, 3-H_{Fur}), 7.25 (t, *J* = 7.7 Hz, 2H, C_6H_5), 7.21 (d, *J* = 3.6 Hz, 1H, 4-H_{Fur}), 6.98 (d, *J* = 8.3 Hz, 2H, C_6H_5), 6.82 (t, *J* = 7.2 Hz, 1H, C_6H_5), 4.37 (br s, 2H, CH_2N), 4.14 (br s, 2H, CH_2N), 3.40 (br s, 4H, $(CH_2)_2NC_6H_5$). Anal. Calcd for $C_{21}H_{19}N_3O_3S$: C, 64.11; H, 4.87; N, 10.68; S, 8.15. Found: C, 64.22; H, 4.90; N, 10.59; S, 8.09.

2.2.13. 1-(3-Chlorophenyl)-4-{[5-(4-nitrophenyl)-2-furyl]carbonothioyl}piperazine (5l).

Yield 74%; mp 252–253°C. ^{1}H NMR: δ = 8.31 (d, *J* = 8.7 Hz, 2H, $C_6H_4NO_2$), 8.04 (d, *J* = 8.7 Hz, 2H, $C_6H_4NO_2$), 7.45 (s, 1H, 3-H_{Fur}), 7.30–7.20 (m, 2H, 4-H_{Fur} and C_6H_4Cl), 6.97 (s, 1H, C_6H_4Cl), 6.91 (d, *J* = 8.5 Hz, 1H, C_6H_4Cl), 6.81 (d, *J* = 7.5 Hz, 1H, C_6H_4Cl), 4.37 (br s, 2H, CH_2N), 4.15 (br s, 2H, CH_2N), 3.47 (br s, 4H, $(CH_2)_2NC_6H_4Cl$). Anal. Calcd for $C_{21}H_{18}ClN_3O_3S$: C, 58.95; H, 4.24; N, 9.82; S, 7.49. Found: C, 58.86; H, 4.19; N, 9.91; S, 7.43.

2.3. *Pharmacology.*

2.3.1. Antimicrobial activity.

The study of the antifungal and antibacterial action of the synthesized compounds was carried out using the micro method of two-fold serial dilutions in a liquid nutrient medium. The minimum bacteriostatic or fungistatic (MIC) concentrations and the minimum bactericidal or fungicidal (MBC, MFC) concentrations of the synthesized pyrrole derivatives were determined relative to the reference bacterial strains (*S. aureus 209, B. sterothermophilus 718, S. typhimurium 441*) and the fungicidal strains (*C. albicans ATCC 885/653* and *C. krusei ATCC 6258*).

Up to 96 well polystyrene plates were added 0.05 ml of a 4-hour culture of microorganisms. For fungicidal, 10^4 CFU / ml were used in Sabouraud's liquid medium. For

bacteria, 1 ml of Mesopotamia broth contained 10^5 CFU / ml. A suspension of the studied microorganisms (inoculum) was prepared from a daily culture. Several isolated colonies of the same type were selected with a loop for inoculation. Then a small amount of material was transferred into a tube with sterile saline solution. Using a densitometer (DEN-1 Biosan), a suspension of microorganisms was obtained at a concentration of 1.5 × 108 CFU / ml. The resulting concentration corresponded to a McFarland 0.5 turbidity standard. After 15 min, the necessary working microbial suspension was obtained by tenfold dilution in a nutrient medium. Solutions of test compounds were prepared for the micro method of serial dilutions at a 1000 μg/ml concentration. DMSO was used as a solvent. The basic working solutions were stored at a temperature not exceeding 20 °C. The first well was filled with 0.05 ml of the matrix solution of the research substance. After stirring, 0.05 ml was transferred into the subsequent wells of the first row. In this way, dilutions from 500 μg/ml to 3.9 μg/ml were obtained. Studies were also carried out in the following rows of holes with other compounds. After that, the plates were placed in a thermostat; for bacteria at 37° C, incubated for 24 hours; for fungi, at 28° C, incubated for 48 hours. The minimum concentration of the test substance, at which no culture growth was observed, was taken as the bacteriostatic (fungistatic) concentration. The experiments were carried out in parallel with the control. The experiments were carried out three times to obtain reliable results, using each compound's concentration and the studied culture of microorganisms.

2.3.2. Cytotoxic activity against malignant human tumor cells.

Primary anticancer analysis of the synthesized compounds was performed on a panel of approximately 60 human tumor cell lines derived from nine neoplastic diseases, according to the Drug Evaluation Branch, National Cancer Institute, Bethesda protocol. The compounds that were studied were added to the culture in a single concentration (10^{-5} M). The cultures were incubated for 48 h. Endpoints were determined using the protein-binding dye sulforhodamine B (SRB). For each test compound, the results were reported as the percentage of growth of treated cells versus untreated control cells. The percentage of growth was assessed spectrophotometrically compared to controls not treated with the test agents. The most active compound of choice was tested in vitro on a full panel of approximately 60 human tumor cell lines. The study was conducted at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8} M. For these studies, a continuous drug exposure protocol was followed and an SRB protein assay was used to assess cell viability or growth.

Seven measurements of optical density were used [time zero, (Tz), control growth in the absence of drug, (C), and also at five concentration levels drug growth test], For each of the drug concentration levels, the percentage of growth was calculated. Percent growth inhibition was calculated as:

$$[(Ti - Tz)/(C - Tz)] \times 100 \text{ for concentrations for which } Ti \geq Tz$$
$$[(Ti - Tz)/Tz] \times 100 \text{ for concentrations for which } Ti < Tz.$$

Three dose-response parameters were calculated for each compound. In particular, 50% growth inhibition (GI50) was calculated from [(Ti - Tz) / (C - Tz)] × 100-50. This study represents the drug concentration resulting in a 50% decrease in net protein increase in treated cells (measured by SRB staining) compared to the increase in net protein observed in control cells. The resulting total inhibition of growth (TGI) drug concentration was calculated from Ti

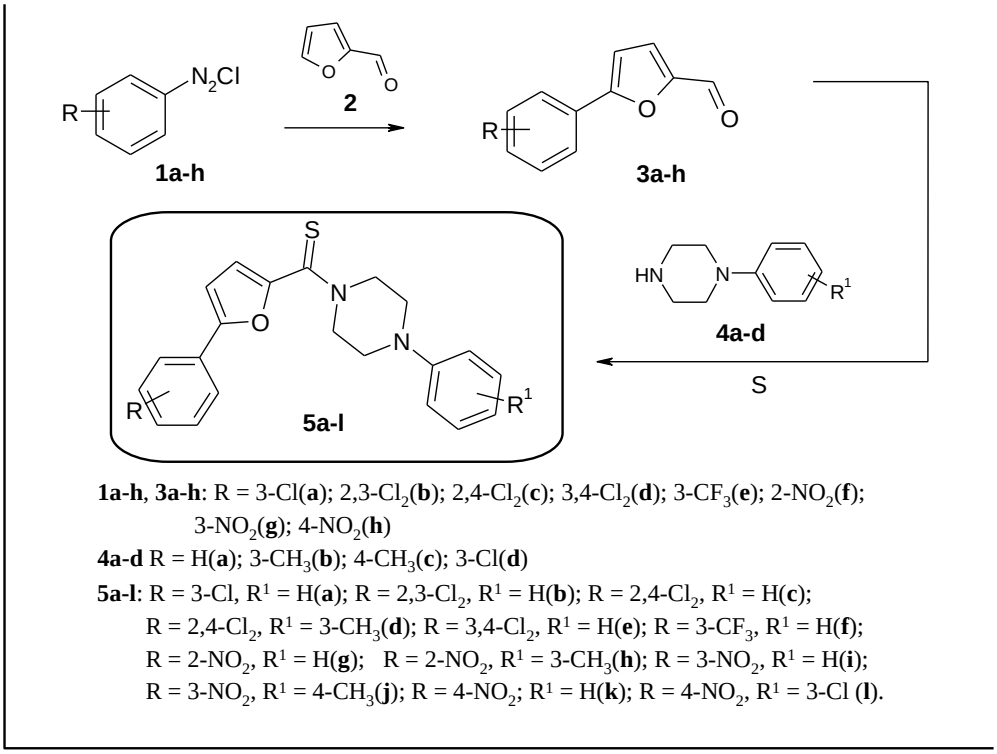
= Tz. LC50 (drug concentration resulting in a 50% decrease in measured protein at the end of drug treatment compared to the concentration at the beginning). The concentration indicating net cell loss after treatment was calculated as [(Ti - Tz) / Tz] × 100 = -50. After the level of activity was reached, the values for each of these three parameters were calculated. If the effect was not achieved or exceeded, then the value of this parameter was expressed as greater or less than the maximum or minimum tested concentration.

3. Results and Discussion

3.1. Chemistry.

Our synthesis started from aromatic diazonium salts 1a-h and furfural 2. In the first stage, compound 2 undergoes arylation in the Meerwein reaction condition [52] according to methods described in the literature [53]. As a result, arylfuran-2-carbaldehydes 3a-h were synthesized. The targeted 1-aryl-4-[(5-aryl-2-furyl)carbonothioyl]piperazines 5a-l were made by Willgerodt–Kindler reaction of arylfuran-2-carbaldehydes with sulfur and aryl piperazines 4a-d (Scheme 1).

The structures of the obtained compounds were confirmed by ^{1}H NMR spectroscopy and elemental analysis. All these new compounds gave spectroscopic data in accordance with the proposed structures. The protons of the tho ArN$(CH_2)_2$ methylene groups were observed as broad signals at δ~3,31 – 3.47 ppm. On the other hand, the protons of C(O)N$(CH_2)_2$ groups appear as two broad signals at 3.98 – 4.16 and 4.32 – 4.37 ppm. This means that the rotation around the C(S)-N bonds is restricted.



1a-h, **3a-h**: R = 3-Cl(**a**); 2,3-Cl_2(**b**); 2,4-Cl_2(**c**); 3,4-Cl_2(**d**); 3-CF_3(**e**); 2-NO_2(**f**); 3-NO_2(**g**); 4-NO_2(**h**)

4a-d R = H(**a**); 3-CH_3(**b**); 4-CH_3(**c**); 3-Cl(**d**)

5a-l: R = 3-Cl, R^1 = H(**a**); R = 2,3-Cl_2, R^1 = H(**b**); R = 2,4-Cl_2, R^1 = H(**c**); R = 2,4-Cl_2, R^1 = 3-CH_3(**d**); R = 3,4-Cl_2, R^1 = H(**e**); R = 3-CF_3, R^1 = H(**f**); R = 2-NO_2, R^1 = H(**g**); R = 2-NO_2, R^1 = 3-CH_3(**h**); R = 3-NO_2, R^1 = H(**i**); R = 3-NO_2, R^1 = 4-CH_3(**j**); R = 4-NO_2; R^1 = H(**k**); R = 4-NO_2, R^1 = 3-Cl (**l**).

Scheme 1. Synthesis of novel 1-aryl-4-[(5-aryl-2-furyl)carbonothioyl]piperazines.

3.2. Evaluation of the antimicrobial activities.

The antifungal and antibacterial activity of the synthesized substances was evaluated by the value of the MIC and minimum fungicidal and bactericidal concentration (MFC and MBC) [54]. Test cultures of microorganisms were fungi of the genus *Candida* and some gram-

positive and gram-negative bacteria. The drug "Bifonazole" was used as a control. Microbiological studies made it possible to compare that the synthesized compounds are characterized by antimicrobial action in a wide concentration range of 3.91–250 μg/ml (Table 1).

Table 1. Antimicrobial activity compounds 5a-l.

The compound or standard	Test cultures of microorganisms									
	S. aureus 209		***B. subtilis*** ATCC 6633		***M. luteus*** 4698		***C. albicans*** 669/1080		***C. krusei*** ATCC 6258	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MFC	MIC	MFC
5a	125	125	62.5	125	62.5	125	125	250	125	250
5b	62.5	125	125	250	125	125	62.5	125	62.5	125
5d	-	-	125	250	125	125	62.5	62.5	62.5	125
5g	7.81	15.62	15.62	15.62	15.62	31.25	62.5	62.5	62.5	125
5h	31.25	62.5	31.25	62.5	250	250	31.25	62.5	31.25	31.25
5i	31.25	62.5	62.5	62.5	250	250	31.25	62.5	31.25	31.25
5j	15.62	15.62	125	125	125	125	62.5	62.5	62.5	62.5
5k	15.62	31.25	125	125	125	125	62.5	125	125	250
5l	3.91	7.81	125	125	125	125	62.5	62.5	62.5	125
Bifonazole	1.95	7.81	0.97	3.9	62.5	125	15.62	62.5	7.81	7.81

Results revealed that compound 5l was the most active against *S. aureus* 209 with MIC = 3.91 μg / ml and MBC = 7.81. Also, this bacterial strain was sensitive to compound 5g (MIC = 3.91 μg / ml and MBC = 15.62. It should be noted that the compound mentioned above is somewhat inferior in its activity to the reference drug Bifonazole. The obtained compounds do not exhibit high fungicidal activity.

3.3. Evaluation of the anticancer activities.

The National Cancer Institute (NCI) Therapeutic Program Development Program (www.dtp.nci.nih.gov) selected the synthesized compounds to study their antitumor activity. This study was performed according to the NCI protocol, which is described elsewhere [55-58]. The results for each compound are reported as the percent growth (GP) (Table 2). The range of growth (%) shows the lowest and the highest growth that was found among different cancer cell lines.

Table 2. Anticancer activity of the tested compounds in the concentration 10^{-5} M against 60 cancer cell lines.

Test compounds	Average growth, %	Range of growth, %	Most sensitive cell line (cancer line/type), GP, %
5a	97.41	69.07 – 129.77	RPMI-8226 (Leukemia) 69.07 UACC-62 (Melanoma) 70.24 OVCAR-4 (Ovarian Cancer) 72.48 CCRF-CEM (Leukemia) 77.67
5b	101.24	65.89 – 149.88	HOP-92 (Non-Small Cell Lung Cancer) 65.89 SR (Leukemia) 77.16 RXF 393 (Renal Cancer) 149.88 MALME-3M (Melanoma) 147.92
5c	94.12	62.73 – 145.64	RPMI-8226 (Leukemia) 62.73 SK-MEL-5 (Melanoma) 63.58 K-562 (Leukemia) 68.94 CCRF-CEM (Leukemia) 76.31 MALME-3M (Melanoma) 145.64 RXF 393 (Renal Cancer) 144.17
5d	100.35	82.10 – 115.76	HL-60(TB) (Leukemia) 82.10 NCI-H522 (Non-Small Cell Lung Cancer) 84.27 UO-31 (Renal Cancer) 84.89
5e	97.53	79.40 – 117.31	HOP-92 (Non-Small Cell Lung Cancer) 79.40 HL-60(TB) (Leukemia) 83.63
5f	99.90	74.60 – 133.42	HL-60(TB) (Leukemia) 74.60 RPMI-8226 (Leukemia) 78.73

Test compounds	Average growth, %	Range of growth, %	Most sensitive cell line (cancer line/type), GP, %
			MOLT-4 (Leukemia) 80.00
5g	102.70	86.29 – 131.21	SR (Leukemia) 86.29
5h	91.81	70.98 – 120.86	EKVX (Non-Small Cell Lung Cancer) 70.98 K-562 (Leukemia) 70.99 OVCAR-4 (Ovarian Cancer) 73.87
5i	107.71	84.36 – 130.95	RPMI-8226 (Leukemia) 84.36
5j	***not anticancer active***		
5k	102.32	84.32 – 115.21	HL-60(TB) (Leukemia) 84.32
5l	101.10	84.55 – 124.15	EKVX (Non-Small Cell Lung Cancer) 84.55

Compounds 5a-l showed moderate activity against several cancer cell lines with mean Mean GP = 91.81 – 107.71%. The most sensitive were RPMI-8226 Leukemia cell line (GP = 62.73%), SK-MEL-5 Melanoma cell line (GP = 63.58%) to the compound 5c and HOP-92 Non-Small Cell Lung Cancer cell line (GP = 65.89%) – to the 5b. It should be noted that compounds 5b and 5c effectively promote the growth of MALME-3M Melanoma cell line and RXF 393 Renal Cancer cell line and compounds 5j – A498 Renal Cancer cell line and HS 578T Breast Cancer cell line.

4. Conclusions

A series of novel 1-aryl-4-[(5-aryl-2-furyl)carbonothioyl]piperazines possessing anticancer and antimicrobial activities were prepared by the Wilgerodt-Kindlerreaction of arylfuran-2-carbaldehydes with sulfur and arylpiperazines. Firstly identified antimicrobial and anticancer effect among 1-aryl-4-[(5-aryl-2-furyl)carbonothioyl]piperazines, making them a valuable starting point for further drug optimization.

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Conflicts of Interest

The authors declare no conflict of interest.

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