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Synthesis and Anticancer Activity of 2-Aryl-3-methylbenzofuro[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-dione and 2-Aryl-3,7,9-trimethylpyrido[3',2':4,5]thieno-[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-diones

T. I. Chaban[a],*, Y. E. Matiichuk[a], V. Ya. Horishny[a], I. G. Chaban[a], and V. S. Matiychuk[b]

[a] *Danylo Halytsky Lviv National Medical University, Lviv, 79010 Ukraine*
[b] *Ivan Franko National University of Lviv, Lviv, 79005 Ukraine*
**e-mail: chabantaras@ukr.net*

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Abstract—The reactions of ethyl 1-aryl-4-(2-bromoacetyl)-5-methyl-1*H*-pyrazolocarboxylates with *ortho*-hydroxybenzonitrile and 4,6-dimethyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile gave previously unknown 2-aryl-3-methylbenzofuro[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-diones and 2-aryl-3,7,9-trimethylpyrido[3',2':4,5]-thieno[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-diones, respectively. It was found that this reaction occurred as a tandem process. The synthesized compounds were sceened for anticancer activity and exhibited moderate activity against the most part of malignant cancer cells.

Keywords: organic synthesis, heterocyclization, tandem reactions, anticancer activity

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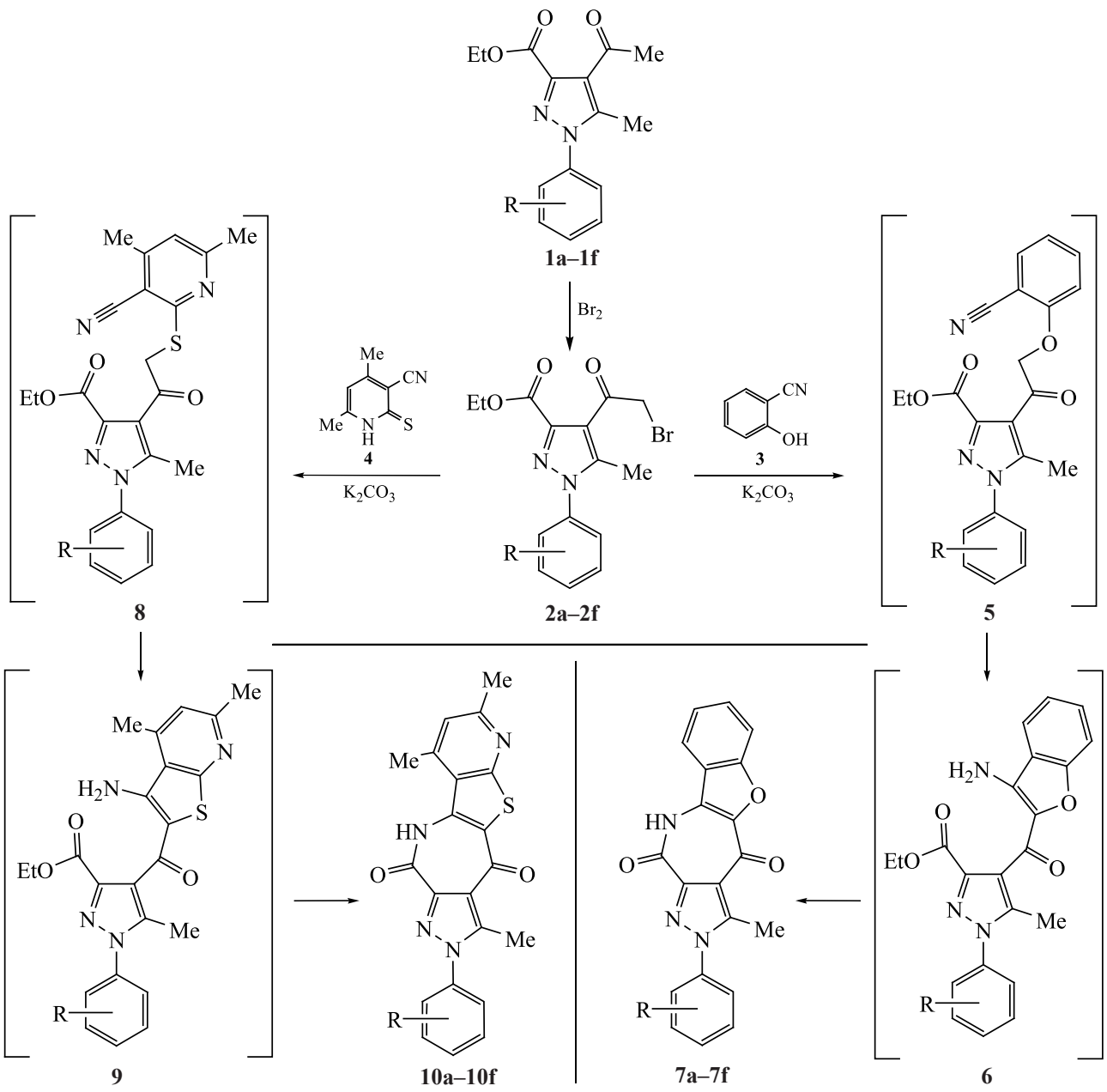
Tandem reactions are of great importance in organic chemistry, since they make it possible to obtain compounds of complex structure in one stage and high atom economy [1–4]. Such reactions are easy to perform and usually give high yields of products. Tandem reactions are widely used in the synthesis of heterocyclic compounds, drugs, as well as complete synthesis of natural compounds.

Ortho-hydroxybenzonitrile reacts with α-halocarbonyl compounds to afford 3-amino-2-acyl-1-benzofuran derivatives [5–7]. In this case, the amino group at the C^3 position of benzofuran, formed in this reaction, exhibits nucleophilic properties and can undergo, provided the starting haloketone contains an ester group, tandem lactamization reaction. In particular, benzofuro[3,2-*c*]-[2]benzoazepine-6,11-dione derivatives [8] are obtained in this way.

Proceeding with our research into the synthesis and biological activity of fused azaheterocycles [9–20], we developed a simple one-pot method of synthesis of previously unknown 2-aryl-3-methylbenzofuro[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-diones and 2-aryl-3,7,9-trimethylpyrido[3',2':4,5]thieno[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-diones. To this end, we reacted ethyl 1-aryl-4-(2-bromoacetyl)-5-methyl-1*H*-pyrazolocarboxylates **2a–2f** with *ortho*-hydroxybenzonitrile (**3**) and 4,6-dimethyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**4**). The starting bromoketones **2a–2f** were prepared by bromination of ethyl 4-acetyl-5-methyl-1-aryl-1*H*-pyrazole-3-carboxylates **1a–1f** [16] in acetic acid.

It was found that the reactions of bromoketones **2a–2f** with *ortho*-hydroxybenzonitrile (**3**) in the presence of potassium carbonate involved tandem heterocyclization with consecutive closure of the furan and azepine rings and formed 2-aryl-3-methylbenzofuro[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-diones **7a–7f**. In the same way, compounds **2a–2f** reacted with 4,6-dimethyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**4**), yelding 2-aryl-3,7,9-trimethylpyrido[3',2':4,5]thieno[3,2-*b*]-pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-diones **10a–10f** (Scheme 1).

Scheme 1.



1a–1f, **2a–2f**, **7a–7f**, **10a–10f**, R = H (**a**), 3-Cl (**b**), 4-Cl (**c**), 2,4-Cl_2 (**d**), 4-Br (**e**), 4-CH_3O (**f**).

The synthesized compounds are high-melting yellow substances readily soluble in DMF and DMSO, soluble with heating in acetic acid and alcohols, and insoluble in apolar solvents and water. The structure of compounds **2a–2f**, **7a–7f**, and **10a–10f** was proved by ^{1}H NMR spectroscopy.

Anticancer activity testing of the synthesized compounds was performed by high-throughput screening according to the National Cancer Institute Developmental Therapeutic Program international research program of the U.S. National Institute of Health [21–24] in vitro against 60 cell lines embracing almost the entire spectrum of human cancers (including leukemia, non-small cell lung cancer, epithelial colon cancer, melanoma, and ovarian and breast cancer). The concentrations of the test compounds were 10^{-5} M. The activity of the test compounds was quantified in terms the growth percentage of

Table 1. Cytotoxicity of synthesized compounds at a concentration of 10^{-5} M on 60 cancer cell lines

Compound no.	Mitotic activity on 60 lines, GP, %		The most sensitive lines (cancer line/type), GP, %
	average	range	
7a	76.16	10.25–100.91	OVCAR-4 (Ovarian cancer) 10.25 T-47D (Breast cancer) 28.89 SK-OV-3 (Ovarian cancer) 37.86 SR (Leukemia) 45.66 SNB-75 (CNS tumor) 48.76
7b	82.52	27.90–111.86	SR(Leukemia) 27.90 SF-539 (CNS tumor) 38.08
7c	94.47	53.44–110.73	SR (Leukemia) 53.44
7d	95.52	51.24–112.23	SR (Leukemia) 51.24
7e	92.78	46.78–109.77	SR (Leukemia) 46.78
7f	71.94	3.57–102.76	OVCAR-4 (Ovarian cancer) 3.57 HCT-116 (Colon cancer) 37.72 MDA-MB-231/ATCC (Breast cancer) 37.91 786-0 (Kidney cancer) 39.66 SR (Leukemia) 40.76
10a	97.60	71.93–108.12	HCT-116 (Colon cancer) 48.44 SR (Leukemia) 49.19
10b	102.93	86.53–107.76	UO-31 (Kidney cancer) 86.53
10c	98.61	75.44–122.28	SR (Leukemia) 75.44
10d	99.03	81.33–109.20	SR (Leukemia) 81.33
10e	98.09	60.89–116.11	SR (Leukemia) 60.89
10f	63.58	6.06–107.37	HOP-62 (Non-small cell lung cancer) 6.06 NCI-H226 (Non-small cell lung cancer) 16.52 SF-268 (CNS tumor) 35.13 OVCAR-4 (Ovarian cancer) 32.69 T-47D (Breast cancer) 39.03

cancer cells (GP, %) compared to control [21–24]. The resulting data are listed in the Table 1.

The synthesized compounds exhibited moderate anticancer activity. Among compounds **7a–7f**, the highest activity was found in compounds **7a** and **7f** (mean GP values 76.16 and 71.94%, respectively). The OVCAR-4 ovarian cancer cell line proved to be the most sensitive to these compounds. Among derivatives **10a–10f**, the highest activity was found in compound **10f** with respect to HOP-62 and NCI-H226 non-small cell lung cancer cell lines. It was noted that the MeO group in the test compounds had a positive effect of their anticancer activity.

Thus, the reactions of bromoketones **2a–2f** with 2-hydroxybenzonitrile or 4,6-dimethyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile, that occurred as tandem heterocyclizations, allowed us to prepare previously unknown 2-aryl-3-methylbenzofuro[3,2-*b*]pyrazolo[4,3-*e*]-azepine-4,11(2*H*,10*H*)-diones and 2-aryl-3,7,9-trimethylpyrido[3',2':4,5]thieno[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-diones. The synthesized compounds were screened for anticancer activity and exhibited moderate anticancer effect.

EXPERIMENTAL

The ^{1}H NMR spectra of DMSO-d_6 solutions were measured on a Varian Mercury VX-400 spectrometer (400 MHz), internal reference TMS. Elemental analysis

was performed on an Elementar Vario L cube analyzer. The melting points were measured in open capillaries on a Büchi B-545 apparatus.

Synthesis of 4-(bromoacetyl)-5-methyl-1-aryl-1*H*-pyrazole-3-carboxylates 2a–2f (*general procedure*). Three drops of conc. H_2SO_4 were added to a solution of 0.03 mol of acetylpyrazole **1a–1f** in 80 mL of glacial acetic acid. A solution of 1.55 mL (0.03 mol) of bromine in 20 mL of acetic acid was then added dropwise to the resulting solution. The mixture was stirred for an additional 5 h and then poured into 300 mL of water. In the case of compound **2a**, the reaction mixture was diluted with 300 mL of water and extracted with methylene chloride (3 × 300 mL). The organic layer was washed in succession with water and K_2CO_3 and NaCl solutions, dried, concentrated, and purified by column chromatography (eluent hexane–ethyl acetate, 8 : 1). In the case of compounds **2b–2f**, the precipitate that formed, dried, and recrystallized from ethanol.

Ethyl 4-(bromoacetyl)-5-methyl-1-phenyl-1*H*-pyrazole-3-carboxylate (2a). Yield 82%, mp 65–66°C. ^{1}H NMR spectrum, δ, ppm: 1.43 t (3H, CH_2CH_3, *J* 7.1 Hz), 2.43 s (3H, CH_3), 4.47 q (2H, CH_2CH_3, *J* 7.1 Hz), 4.60 s (2H, CH_2Br), 7.41–7.56 m (5H$_{arom}$). Found, %: C 51.18; H 4.39; N 7.84. $C_{15}H_{15}BrN_2O_3$. Calculated, %: C 51.30; H 4.31; N 7.98.

Ethyl 4-(bromoacetyl)-5-methyl-1-(3-chlorophenyl)-1*H*-pyrazole-3-carboxylate (2b). Yield 93%, mp 104–105°C. ^{1}H NMR spectrum, δ, ppm: 1.39 t (3H, CH_3CH_2, *J* 7.2 Hz), 2.43 s (3H, CH_3), 4.38 q (2H, CH_3CH_2O, *J* 7.2 Hz), 4.60 s (2H, CH_2Br), 7.53–7.69 m (4H$_{arom}$). Found, %: C 46.80; H 3.78; N 7.04. $C_{15}H_{14}BrClN_2O_3$. Calculated, %: C 46.72; H 3.66; N 7.26.

Ethyl 4-(bromoacetyl)-5-methyl-1-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylate (2c). Yield 95%, mp 138–139°C. ^{1}H NMR spectrum, δ, ppm: 1.38 t (3H, CH_3CH_2, *J* 7.2 Hz), 2.41 s (3H, CH_3), 4.38 q (2H, CH_3CH_2O), 4.60 s (2H, CH_2Br), 7.60 s (4H$_{arom}$). Found, %: C 46.43; H 3.74; N 7.40. $C_{15}H_{14}BrClN_2O_3$. Calculated, %: C 46.72; H 3.66; N 7.26.

Ethyl 4-(bromoacetyl)-1-(2,4-dichlorophenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (2d). Yield 77%, mp 77–78°C. ^{1}H NMR spectrum, δ, ppm: 1.43 t (3H, CH_3CH_2, *J* 7.2 Hz), 2.22 s (3H, CH_3), 4.40 s (2H, CH_2Br), 4.45 q (2H, CH_3CH_2O, *J* 7.2 Hz), 7.12–7.48 m (3H$_{arom}$). Found, %: C 42.72; H 3.24; N 6.54. $C_{15}H_{13}BrCl_2N_2O_3$. Calculated, %: C 42.89; H 3.12; N 6.67.

Ethyl 4-(bromoacetyl)-1-(4-bromophenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (2e). Yield 77%, mp 149–150°C. ^{1}H NMR spectrum, δ, ppm: 1.44 t (3H, CH_3CH_2, *J* 7.2 Hz), 2.43 s (3H, CH_3), 4.47 q (2H, CH_3CH_2O, *J* 7.2 Hz), 4.58 s (2H, CH_2Br), 7.33 d (2H$_{arom}$, *J* 8.4 Hz), 7.67 d (2H$_{arom}$, *J* 8.4 Hz). Found, %: C 41.82; H 3.31; N 6.53. $C_{15}H_{14}Br_2N_2O_3$. Calculated, %: C 41.89; H 3.28; N 6.51.

Ethyl 4-(bromoacetyl)-5-methyl-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (2f). Yield 85%, mp 81–82°C. ^{1}H NMR spectrum, δ, ppm: 1.43 t (3H, CH_3CH_2, *J* 7.1 Hz), 2.39 s (3H, CH_3), 3.87 s (3H, CH_3O), 4.46 q (2H, CH_3CH_2O, *J* 7.1 Hz), 4.60 s (2H, CH_2Br), 7.00 d (2H$_{arom}$, *J* 8.8 Hz), 7.34 d (2H$_{arom}$, *J* 8.8 Hz). Found, %: C 50.57; H 4.41; N 7.28. $C_{16}H_{17}BrN_2O_4$. Calculated, %: C 50.41; H 4.49; N 7.35.

Synthesis of 2-aryl-3-methylbenzofuro[3,2-*b*]-pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-diones and 2-aryl-3,7,9-trimethylpyrido[3',2':4,5]thieno[3,2-*b*]-pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-diones. Ethyl 4-(bromoacetyl)-5-methyl-1-aryl-1*H*-pyrazole-3-carboxylate **2a–2f** (0.001 mol) and 207 mg (0.0015 mol) of K_2CO_3 were added to a mixture of 119 mg (0.001 mol) of 2-hydroxybenzonitrile (**3**) or 164 mg (0.001 mol) of 4,6-dimethyl-2-thioxo-1,2-dihydripyridine-3-carbonitrile (**4**) in 10 mL of anhydrous acetonitrile. The mixture was refluxed for 4 h, cooled, and diluted with 20 mL of water. The precipitate that formed and recrystallized from DMF.

3-Methyl-2-phenyl-benzofuro[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-dione (7a). Yield 87%, mp > 300°C. ^{1}H NMR spectrum, δ, ppm: 2.74 s (3H, CH_3), 7.42 t (1H$_{arom}$, *J* 7.4 Hz), 7.60–7.70 m (6H$_{arom}$), 7.72 d (1H$_{arom}$, *J* 8.3 Hz), 8.50 d (1H$_{arom}$, *J* 8.0 Hz), 11.91 s (1H, NH). Found, %: C 69.83; H 3.94; N 12.11. $C_{20}H_{13}N_3O_3$. Calculated, %: C 69.97; H 3.82; N 12.24.

3-Methyl-2-(3-chlorophenyl)benzofuro[3,2-*b*]-pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-dione (7b). Yield 73%, mp > 300°C. ^{1}H NMR spectrum, δ, ppm: 2.74 s (3H, CH_3), 7.41 t (1H$_{arom}$, *J* 7.2 Hz), 7.56–7.76 m (5H$_{arom}$), 7.83 s (1H$_{arom}$), 8.48 d (1H$_{arom}$, *J* 7.2 Hz), 11.91 s (1H, NH). Found, %: C 63.42; H 3.31; N 11.25. $C_{20}H_{12}ClN_3O_3$. Calculated, %: C 63.59; H 3.20; N 11.12.

3-Methyl-2-(4-chlorophenyl)benzofuro[3,2-*b*]-pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-dione (7c). Yield 76%, mp > 300°C. ^{1}H NMR spectrum, δ, ppm: 2.73 s (3H, CH_3), 7.42 t (1H$_{arom}$, *J* 8.0 Hz), 7.64 t (1H$_{arom}$, *J* 8.0 Hz), 7.71 d (1H$_{arom}$, *J* 8.0 Hz), 7.72 s (4H$_{arom}$), 8.50 d

($1H_{arom}$, *J* 8.0 Hz), 11.92 s (1H, NH). Found, %: C 63.81; H 3.08; N 11.23. $C_{20}H_{12}ClN_3O_3$. Calculated, %: C 63.59; H 3.20; N 11.12.

2-(2,4-Dichlorophenyl)-3-methylbenzofuro[3,2-*b*]-pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-dione (7d). Yield 78%, mp > 300°C. ^1H NMR spectrum, δ, ppm: 2.57 s (3H, CH_3), 7.43 t ($1H_{arom}$, *J* 7.9 Hz), 7.65 t ($1H_{arom}$, *J* 7.9 Hz), 7.71 d ($1H_{arom}$, *J* 7.9 Hz), 7.76 d.d ($1H_{arom}$, *J* 8.6, 2.1 Hz), 7.81 d ($1H_{arom}$, *J* 8.6 Hz), 8.08 d ($1H_{arom}$, *J* 2.1 Hz), 8.51 d ($1H_{arom}$, *J* 7.9 Hz), 11.96 s (1H, NH). Found, %: C 58.02; H 2.43; N 10.25. $C_{20}H_{11}Cl_2N_3O_3$. Calculated, %: C 58.27; H 2.69; N 10.19.

2-(4-Bromophenyl)-3-methylbenzofuro[3,2-*b*]-pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-dione (7e). Yield 81%, mp > 300°C. ^1H NMR spectrum, δ, ppm: 2.74 s (3H, CH_3), 7.42 t ($1H_{arom}$, *J* 8.0 Hz), 7.62 t ($1H_{arom}$, *J* 8.0 Hz), 7.65 d ($2H_{arom}$, *J* 8.4 Hz), 7.72 d ($1H_{arom}$, *J* 8.0 Hz), 7.86 d ($2H_{arom}$, *J* 8.4 Hz), 8.49 d ($1H_{arom}$, *J* 8.0 Hz), 11.93 s (1H, NH). Found, %: C 56.65; H 2.98; N 10.12. $C_{20}H_{12}BrN_3O_3$. Calculated, %: C 56.89; H 2.86; N 9.95.

3-Methyl-2-(4-methoxyphenyl)benzofuro[3,2-*b*]-pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-dione (7f). Yield 86%, mp > 300°C. ^1H NMR spectrum, δ, ppm: 2.70 s (3H, CH_3), 3.87 s (3H, CH_3O), 7.17 d ($2H_{arom}$, *J* 8.8 Hz), 7.42 t ($1H_{arom}$, *J* 7.8 Hz), 7.58 d ($2H_{arom}$, *J* 8.8 Hz), 7.63 t ($1H_{arom}$, *J* 7.8 Hz), 7.71 d ($1H_{arom}$, *J* 7.8 Hz), 8.50 d ($1H_{arom}$, *J* 7.8 Hz), 11.89 s (1H, NH). Found, %: C 67.33; H 4.18; N 11.04. $C_{21}H_{15}N_3O_4$. Calculated, %: C 67.56; H 4.05; N 11.25.

3,7,9-Trimethyl-2-phenylpyrido[3',2':4,5]-thieno[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-dione (10a). Yield 79%, mp > 300°C. ^1H NMR spectrum, δ, ppm: 2.56 s (3H, CH_3), 2.70 s (3H, CH_3), 2.97 s (3H, CH_3), 7.21 s (1H, Py), 7.52–7.55 m ($5H_{arom}$), 10.00 s (1H, NH). Found, %: C 64.71; H 4.08; N 14.28. $C_{21}H_{16}N_4O_2S$. Calculated, %: C 64.93; H 4.15; N 14.42.

3,7,9-Trimethyl-2-(3-chlorophenyl)pyrido-[3',2':4,5]thieno[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-dione (10b). Yield 74%, mp > 300°C. ^1H NMR spectrum, δ, ppm: 2.48 s (3H, CH_3), 2.72 s (3H, CH_3), 2.97 s (3H, CH_3), 7.06 s (1H, Py), 7.62–7.70 m ($3H_{arom}$), 7.81–7.83 m ($1H_{arom}$). Found, %: C 59.43; H 3.45; N 13.34. $C_{21}H_{15}ClN_4O_2S$. Calculated, %: C 59.64; H 3.58; N 13.25.

3,7,9-Trimethyl-2-(4-chlorophenyl)pyrido-[3',2':4,5]thieno[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-dione (10c). Yield 80%, mp > 300°C. ^1H NMR spectrum, δ, ppm: 2.08 s (3H, CH_3), 2.71 s (3H, CH_3), 2.97 s (3H, CH_3), 7.16 s (1H, Py), 7.72 s ($4H_{arom}$). Found, %: C 59.43; H 3.67; N 13.38. $C_{21}H_{15}ClN_4O_2S$. Calculated, %: C 59.64; H 3.58; N 13.25.

2-(2,4-Dichlorophenyl)-3,7,9-trimethylpyrido-[3',2':4,5]thieno[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-dione (10d). Yield 74%, mp > 300°C. ^1H NMR spectrum, δ, ppm: 2.48 s (3H, CH_3), 2.52 s (3H, CH_3), 2.97 s (3H, CH_3), 6.93 s (1H, Py), 7.68–7.76 m ($2H_{arom}$), 8.01 d ($1H_{arom}$, *J* 2.1 Hz). Found, %: C 55.41; H 2.97; N 12.39. $C_{21}H_{14}Cl_4N_4O_2S$. Calculated, %: C 55.15; H 3.09; N 12.25.

2-(4-Bromophenyl)-3,7,9-trimethylpyrido-[3',2':4,5]thieno[3,2-*b*]pyrazolo[4,3-e]azepine-4,11(2*H*,10*H*)-dione (10e). Yield 76%, mp > 300°C. ^1H NMR spectrum, δ, ppm: 2.08 s (3H, CH_3), 2.71 s (3H, CH_3), 2.97 s (3H, CH_3), 7.23 s (1H, Py), 7.65 d ($2H_{arom}$, *J* 8.8 Hz), 7.86 d ($2H_{arom}$, *J* 8.8 Hz), 10.03 s (1H, NH). Found, %: C 53.86; H 3.08; N 12.14. $C_{21}H_{15}BrN_4O_2S$. Calculated, %: C 53.97; H 3.24; N 11.99.

2-(4-Methoxyphenyl)-3,7,9-trimethylpyrido-[3',2':4,5]thieno[3,2-*b*]pyrazolo[4,3-*e*]azepine-4,11(2*H*,10*H*)-dione (10f). Yield 82%, mp > 300°C. ^1H NMR spectrum, δ, ppm: 2.56 s (3H, CH_3), 2.66 s (3H, CH_3), 2.97 s (3H, CH_3), 3.87 s (3H, OCH_3), 7.17 d ($2H_{arom}$, *J* 9.0 Hz), 7.24 s (1H, Py), 7.58 d ($2H_{arom}$, *J* 9.0 Hz), 9.96 s (1H, NH). Found, %: C 63.32; H 4.20; N 13.31. $C_{22}H_{18}N_4O_3S$. Calculated, %: C 63.14; H 4.34; N 13.39.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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