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Synthesis of new antineoplastic agents based on imidazo[2,1-*a*]pyridine

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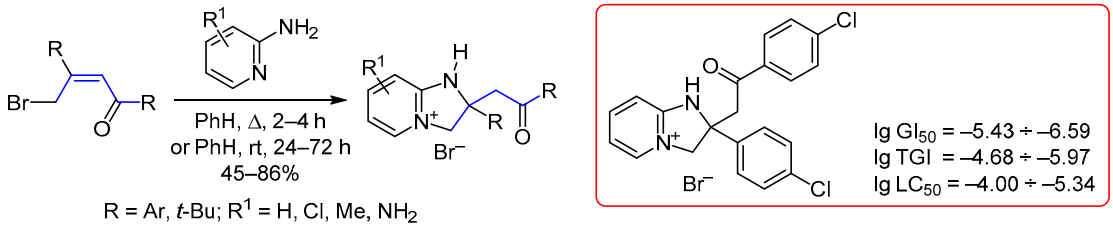


2-Aryl-2-(2-aryl-2-oxoethyl)-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyridin-4-ium bromides were obtained in the reaction of (2*Z*)-4-bromo-1,3-diphenylbut-2-en-1-one derivatives with 2-aminopyridines in benzene. The effect of the structure of the starting reagents on the results of the reactions was studied. Antitumor activity of 2-(4-chlorophenyl)-2-[2-(4-chlorophenyl)-2-oxoethyl]-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyridin-4-ium bromide was determined, which showed high antitumor potential of the test compound on 60 human cancer cell lines.

Keywords: 2-aminopyridine, γ-bromodipnone, imidazo[2,1-*a*]pyridine, antitumor activity, Michael addition.

In recent decades, imidazo[1,2-*a*]pyridine, a basic nitrogenous heterocycle, has taken leading positions in the design of biologically active compounds. Its derivatives exhibit various biological and pharmacological activity.[1] The success of this structural fragment in pharmacology is evidenced by the list of drugs that have already found their place in the clinic, for example, the neurotropic drugs alpidem and zolpidem,[2] cardiotonic olprinone,[3] the neuroleptic mosapramine.[4] A number of imidazo[1,2-*a*]-pyridine derivatives have been used as leading molecules for the creation of anticancer drugs[5,6] (Fig. 1), some of which are already undergoing clinical trials.[5c] This stimulates constant interest in the development of new synthetic methods for constructing the imidazo[1,2-*a*]-pyridine system, and to date, various synthetic strategies and approaches have been proposed.[7] Earlier,[8] we found a method for constructing the imidazole fragment to azines based on the reaction of γ-bromodipnone with 2-amino-pyridine and 2-aminopyrimidine. The method allows one to obtain partially hydrogenated derivatives. The antitumor activity of the representatives of this segment of imidazo-[1,2-*a*]pyridine derivatives has also been studied in recent years,[6] which prompted us to study the applicability of our

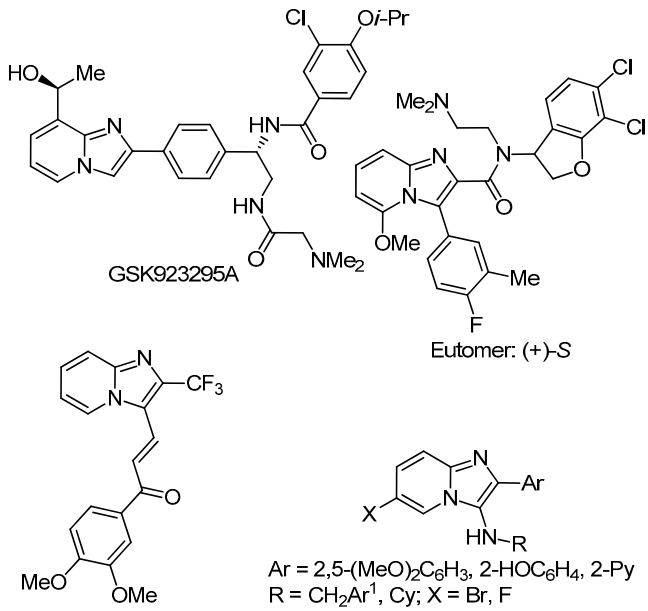
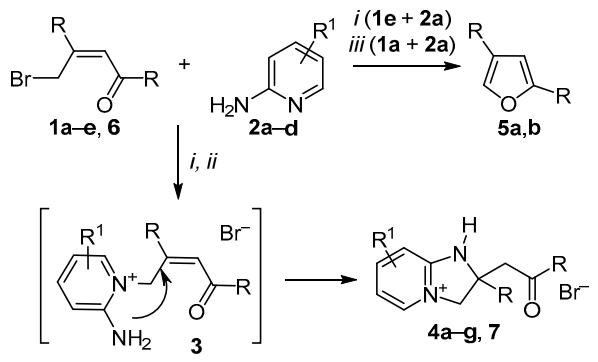


Figure 1. Antineoplastic agents based on imidazo[1,2-*a*]pyridine.

method for the synthesis of a series of compounds for further testing of their biological activity.

In this work, the number of derivatives of γ-halogen-α,β-unsaturated ketones and 2-aminopyridine was expanded. (2*Z*)-1,3-Diaryl-4-bromobut-2-en-1-one (γ-bromodipnone) derivatives **1a**–**d** readily react with 2-aminopyridines **2a**–**d** in PhH (Scheme 1). However, the resulting quaternary pyridinium salts **3** are unstable and, under the reaction conditions, easily cyclize to 2-aryl-2-(2-aryl-2-oxoethyl)-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyridin-4-ium bromides **4a**–**g** by the mechanism of the Michael addition. The use of polar solvents (Me_2CO, EtOH) directs the reaction along a different route toward the products of intramolecular cyclization 2,4-diarylfurans **5a**,**b** (according to ^{1}H NMR spectra), which is typical for bromo ketones **1a**,**e** when reacting with strong bases in the indicated solvents.[9]

Scheme 1



i: PhH, Δ, 2–4 h (45–73%); *ii*: PhH, rt, 24–72 h (58–86%)
iii: EtOH or Me_2CO, Δ, 2 h

1 a R = Ph, **b** R = 4-FC_6H_4, **c** R = 4-ClC_6H_4,
d R = 4-BrC_6H_4, **e** R = 4-$MeOC_6H_4$;
2 a R^1 = H, **b** R^1 = 5-Cl, **c** R^1 = 4-Me, **d** R^1 = 3-NH_2;
4 a R = Ph, R^1 = H; **b** R = Ph, R^1 = 6-Cl; **c** R = Ph, R^1 = 7-Me;
d R = Ph, R^1 = 8-NH_2; **e** R = 4-FC_6H_4, R^1 = H;
f R = 4-ClC_6H_4, R^1 = H; **g** R = 4-BrC_6H_4, R^1 = H;
5 a R = Ph, **b** R = 4-$MeOC_6H_4$; **6** R = *t*-Bu; **7** R = *t*-Bu, R^1 = H

The yields of salts **4a**–**g** depend on the temperature regime of the reaction in PhH and the structure of the reagents. When heated, the reaction is complete in 2–4 h. When the mixture of reagents in PhH is kept at room temperature, the reaction takes 1–3 days, but the purity and yields of the target products are higher than when heated. Only in the case of ketones **1c**,**d**, whose solubility in PhH at room temperature is low, is heating a necessary condition.

The conversion efficiency is affected by the structure of the starting pyridine **2**. The yields of bromides **4a**–**g** decrease with decreasing basicity of 2-aminopyridine **2a**–**d**. In the case of 2-amino-6-methylpyridine and 2,6-diaminopyridine, according to ^{1}H NMR spectra, only hydrobromides of the corresponding pyridines were isolated from the reaction medium (in the reaction with γ-bromodipnone **1a**). The reason for this is obviously steric hindrance to alkylation from the side of two substituents at the α-positions of these pyridines. The nature of substituents in γ-bromodipnones also affects the course of the reaction and its products. With an increase in the acceptor effect of substituents in benzene rings, the probability of an alternative reaction, the addition of a nucleophile to the β-position of bromo ketone **1**, increases, which provokes further transformations into 1,4-diketones which we previously observed in the reactions of γ-bromodipnones **1a**–**d** with hydrazine and 2-aminothiazole.[10] In the case of the reaction with 2-aminopyridines **2**, on going from ketone **1a** to ketone **1d**, both the main reaction and the side reaction accelerate, which leads to a decrease in the yield of the target imidazopyridine **4**. The electron-donating effect of the *para*-methoxyphenyl substituent in the β-position of bromo ketone **1e** significantly reduces the rate of the Michael cyclization, and as a result, the reaction with 2-aminopyridine (**2a**) leads to the formation of furan **5b**.

The cyclization *via* the Michael addition can also be prevented by the steric effect of the substituent at the β-position of the γ-halogen-α,β-unsaturated ketone. Thus, upon heating (4*Z*)-5-(bromomethyl)-2,2,6,6-tetramethylhept-4-en-3-one (**6**) with 2-aminopyridine (**2a**) in PhH, a mixture of the target imidazo[1,2-*a*]pyridinium bromide **7** with the starting pyridine hydrobromide **2a**·HBr (1:1) was obtained with a low yield of the target product (25%). However, it was not possible to isolate compound **7** because of the close solubility of the mixture components and, obviously, the low stability of salt **7**.

The structure of imidazo[1,2-*a*]pyridinium bromides **4a**–**g** and **7** was proved on the basis of their spectral data. The retention of the ketone fragment in the molecule is indicated by the signals of the carbonyl group in the IR spectra ($\nu_{C=O}$ in the range of 1675–1681 cm^{-1}) and ^{13}C NMR spectra ($\delta_{C=O}$ at 197.1 ppm). A feature of the ^{1}H NMR spectra of compounds **4a**–**g**, **7** is the presence in the 3.0–5.5 ppm range of signals of two methylene groups in the form of AB spin systems with a coupling constant of 10–19 Hz. The nonequivalence of the signals of the protons of the methylene groups is a consequence of the presence of an asymmetric center at the C-2 atom and the limitation of the conformational mobility of the phenacyl fragment, apparently due to the formation of an intramolecular hydrogen bond between the carbonyl group and the N(1)H group. The formation of a hydrogen bond is indicated by the positions of the signals of the N(1)H group in the ^{1}H NMR spectra (δ_{NH} in the range of 9.4–10.3 ppm in DMSO solution) and in the IR spectra (ν_{NH} in the range of 3070–3140 cm^{-1}).

The isolation of free bases of imidazopyridines from salts **4a**–**g**, **7** is impeded by their increased sensitivity to the action of bases, which is accompanied by cleavage of the phenacyl fragment.[8]

Compound **4f** was selected for testing antitumor activity within the framework of the international scientific program of the National Institutes of Health of the US. Screening studies were carried out *in vitro* on 60 lines of cancer cells, which cover almost the entire spectrum of human oncological diseases (lines of lung, kidney, central nervous system, ovarian, prostate, breast cancer, as well as epithelial cancer, leukemia, and melanoma), with the action

of the substance in a concentration of $1\cdot10^{-5}$ M, as a result of which the growth proportion (GP) of cancer cells in comparison with the control (control – 100%) was determined.[11] It was found that imidazo[1,2-*a*]pyridinium bromide **4f** is a potent inhibitor of the growth of all cancer cell lines: their average mitotic activity is –98.67%, the range of mitotic activity is –98.67 to 49.39%. Thus, a significant decrease in the growth of all types of ovarian (GP 4–49%) and prostate (GP ~ 27%) cancer cells was found. For all types of leukemia and melanoma cancer cells and almost all types of the colon, lung, central nervous system, kidney, and breast cancer cells, their apoptosis is on average 70%, and for some lines this figure reaches 89–99%. Taking into account the obtained result, in-depth *in vitro* screening was carried out, which consisted in the study of the antitumor effect in five concentrations at 10-fold dilution ($1\cdot10^{-4}$–10^{-8} M) on 60 human cancer cell lines, the set of which was similar before the screening stage. As a result of the experiments, three dose-dependent parameters were calculated, confirming the high antitumor potential of the tested compound **4f**: a significant level of effective inhibition (log GI_{50} from –5.43 to –6.59), as well as cytostatic (log TGI from –4.68 to –5.97) and cytotoxic (log LC_{50} –4.00 to –5.34) effects on all cancer cell lines.

To conclude, a method is proposed for the synthesis of 2-aryl-2-(2-aryl-2-oxoethyl)-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyridin-4-ium bromides, antitumor agents with a potentially high level of activity. The effectiveness of the method involving the reaction of γ-halogen-α,β-unsaturated ketones with 2-aminopyridines is determined by the structure of the starting reagents and the reaction conditions. Optimal results are provided by the combination of the high basicity of 2-aminopyridine, the absence of donor substituents at the β-position of the ketone and bulky substituents at the reaction centers of both reagents, as well as the use of aprotic nonpolar solvents.

Experimental

IR spectra were registered on a PerkinElmer Spectrum BX spectrometer in KBr pellets. ^{1}H NMR spectra were acquired on a Varian VXR-400 spectrometer (400 MHz) in DMSO-d_6 (compounds **4d**,**g**) or DMSO-d_6–CCl_4, 1:1 (compounds **4b**,**c**,**e**,**f** and the mixture of compounds **7** + **2a**·HBr). ^{13}C NMR spectra were acquired on a Varian VXR-400 spectrometer (100 MHz) in DMSO-d_6–CCl_4, 1:1. TMS was used as internal standard. The ^{13}C signals of the atoms (methyl, methylene, methine, and quaternary carbon atoms) were assigned using the APT method taking into account the known range of chemical shifts of carbon atoms contained in the functional groups. The assay of the purity of the synthesized compounds was performed by HPLC-MS on an Agilent 1100 system with an Agilent LC/MSDSL selective detector (sample injection in a CF_3CO_2H matrix, EI ionization, 70 eV). Elemental analysis was performed on a vario MICRO cube CHNS-analyzer, the content of halogens was determined using the Schöniger method. Melting points were determined in Pyrex capillaries in a Thiele tube and are uncorrected.

The starting (2*Z*)-1,3-diaryl-4-bromobut-2-en-1-ones **1a**–**e** were obtained according to known methods,[9,12] (4*Z*)-5-(bromomethyl)-2,2,6,6-tetramethylhept-4-en-3-one (**6**) was obtained according to a literature method[13] from 3,3-dimethylbutan-2-one supplied by Enamine Ltd.

Synthesis of 2-aryl-2-(2-aryl-2-oxoethyl)-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyridin-4-ium bromides 4a–**g** (General procedure). Method I. 2-Aminopyridine **2a**–**d** (3.55 mmol) was added to a solution of γ-bromodipnone **1a**–**d** (3.55 mmol) in PhH (40 ml). The mixture was boiled for 2–4 h. After cooling, the formed precipitate was filtered off, washed with PhH and Me_2CO. It was recrystallized from MeCN or AcOH.

Method II. The reaction was performed according to method I, stirring the mixture of reagents in PhH at room temperature for 1–3 days. The formed precipitate was filtered off, washed with PhH and Me_2CO. It was recrystallized from MeCN or AcOH.

2-(2-Oxo-2-phenylethyl)-2-phenyl-1*H*,2*H*,3*H*-imidazo-[1,2-*a*]pyridin-4-ium bromide (4a). Yield 1.19 g (85%, method II), 1.05 g (75%, method I[8]), colorless crystals, mp 137–138°C (MeCN) (mp 136–137°C (MeCN)[8]).

6-Chloro-2-(2-oxo-2-phenylethyl)-2-phenyl-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyridin-4-ium bromide (4b). Yield 0.69 g (45%, method I), 0.88 g (58%, method II), colorless crystals, mp 246–247°C (AcOH). IR spectrum, ν, cm^{-1}: 696, 761, 827, 1295, 1345, 1527, 1645, 1684 (C=O), 2952, 3059, 3081 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.14 (1H, d, ^2J = 18.0, 3-CH_2); 4.43 (1H, d, ^2J = 18.0, 3-CH_2); 4.79 (1H, d, ^2J = 13.5, CH_2CO); 5.29 (1H, d, ^2J = 13.5, CH_2CO); 7.27–7.32 (2H, m, H-8,4'); 7.39 (2H, t, ^3J = 8.0, H-3',5'); 7.49 (2H, t, ^3J = 8.0, H-3",5"); 7.57–7.62 (3H, m, H-2',6',4"); 7.96 (2H, d, ^3J = 8.0, H-2",6"); 8.00 (1H, d, ^3J = 9.5, H-7); 8.67 (1H, s, H-5); 10.45 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 48.0 (2-CH_2); 62.9 (C-3); 65.7 (C-2); 110.3; 118.3; 125.0 (2C); 127.3; 127.8 (2C); 128.2 (2C); 128.3 (2C); 133.1; 135.1; 136.0; 142.7; 144.3; 153.5; 196.2 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 351 $[M–Br]^+$ (19), 349 $[M–Br]^+$ (65), 105 (100). Found, %: C 58.75; H 4.20; Br 18.54; Cl 8.29; N 6.58. $C_{21}H_{18}BrClN_2O$. Calculated, %: C 58.69; H 4.22; Br 18.59; Cl 8.25; N 6.52.

7-Methyl-2-(2-oxo-2-phenylethyl)-2-phenyl-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyridin-4-ium bromide (4c). Yield 1.06 g (73%, method I), 1.25 g (86%, method II), colorless crystals, mp 136–138°C (MeCN). IR spectrum, ν, cm^{-1}: 699, 1222, 1572, 1656, 1687 (C=O), 2879, 3047, 3137 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.45 (3H, s, CH_3); 4.06 (1H, d, ^2J = 18.5, 3-CH_2); 4.40 (1H, d, ^2J = 18.5, 3-CH_2); 4.75 (1H, d, ^2J = 12.5, CH_2CO); 5.25 (1H, d, ^2J = 12.5, CH_2CO); 6.81 (1H, d, ^3J = 6.5, H-6); 7.04 (1H, s, H-8); 7.27 (1H, t, ^3J = 8.0, H-4'); 7.38 (2H, t, ^3J = 8.0, H-3',5'); 7.47 (2H, t, ^3J = 8.0, H-3",5"); 7.57–7.60 (3H, m, H-2',6',4"); 7.96 (2H, d, ^3J = 8.0, H-2",6"); 8.26 (1H, d, ^3J = 6.5, H-5); 10.09 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 21.6 (CH_3); 48.0 (2-CH_2); 62.1 (C-3); 65.3 (C-2); 108.0; 115.1; 125.0 (2C); 127.2; 127.8 (2C); 128.2 (2C); 128.3 (2C); 133.0; 135.9; 136.0; 143.0; 154.2; 156.5; 196.2 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 329 $[M–Br]^+$ (83), 105 (100). Found, %: C 64.50; H 5.20; Br 19.58; N 6.80.

$C_{22}H_{21}BrN_2O$. Calculated, %: C 64.55; H 5.17; Br 19.52; N 6.84.

8-Amino-2-(2-oxo-2-phenylethyl)-2-phenyl-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyridin-4-ium bromide (4d). Yield 1.00 g (69%, method I), 1.19 g (82%, method II), colorless crystals, mp 259–261°C (MeCN). IR spectrum, ν, cm^{-1}: 685, 727, 755, 1440, 1550, 1589, 1639, 1687 (C=O), 3064, 3188 (NH), 3311 (NH_2), 3345 (NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.06 (1H, d, ^2J = 18.5, 3-CH_2); 4.36 (1H, d, ^2J = 18.5, 3-CH_2); 4.80 (1H, d, ^2J = 13.2, CH_2CO); 5.16 (1H, d, ^2J = 13.2, CH_2CO); 6.15 (2H, br. s, NH_2); 6.77 (1H, t, ^3J = 7.5, H-6); 7.07 (1H, d, ^3J = 8.0, H-7); 7.28 (1H, t, ^3J = 8.0, H-4'); 7.38 (2H, t, ^3J = 8.0, H-3',5'); 7.45–7.50 (3H, m, H-5,3",5"); 7.57–7.60 (3H, m, H-2',6',4"); 7.94 (2H, d, ^3J = 8.0, H-2",6"); 9.42 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 47.9 (2-CH_2); 63.2 (C-3); 64.9 (C-2); 115.0; 119.6; 122.4; 125.1 (2C); 127.5; 127.9 (2C); 128.5 (2C); 128.6 (2C); 131.6; 133.5; 143.1; 145.6; 149.5; 196.5 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 330 $[M–Br]^+$ (74), 77 (100). Found, %: C 61.51; H 4.95; Br 19.46; N 10.28. $C_{21}H_{20}BrN_3O$. Calculated, %: C 61.47; H 4.91; Br 19.47; N 10.24.

2-(4-Fluorophenyl)-2-[2-(4-fluorophenyl)-2-oxoethyl]-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyridin-4-ium bromide (4e). Yield 1.09 g (71%, method I), 1.18 g (77%, method II), colorless crystals, mp 238–240°C (AcOH). IR spectrum, ν, cm^{-1}: 778, 836, 1158, 1231, 1513, 1575, 1594, 1659, 1681 (C=O), 2980, 3070 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.09 (1H, d, ^2J = 18.5, 3-CH_2); 4.49 (1H, d, ^2J = 18.5, 3-CH_2); 4.82 (1H, d, ^2J = 13.0, CH_2CO); 5.29 (1H, d, ^2J = 13.0, CH_2CO); 6.97 (1H, t, ^3J = 6.5, H-6); 7.12 (2H, t, ^3J = 8.0, H-3',5'); 7.19–7.27 (3H, m, H-8,2',6'); 7.66 (2H, dd, ^3J = 8.0, $^3J_{HF}$ = 6.0, H-3",5"); 7.99 (1H, t, ^3J = 7.6, H-7); 8.05 (2H, dd, ^3J = 8.0, $^3J_{HF}$ = 6.0, H-2",6"); 8.38 (1H, d, ^3J = 5.5, H-5); 10.20 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 48.1 (2-CH_2); 62.6 (C-3); 64.8 (C-2); 109.2; 113.3; 115.0 (d, $^3J_{CF}$ = 21.0, C-3",5"); 115.3 (d, $^3J_{CF}$ = 21.0, C-3',5'); 127.3 (d, $^4J_{CF}$ = 8.0, C-2',6'); 130.8 (d, $^4J_{CF}$ = 10.0, C-2",6"); 132.6; 136.9; 138.9; 144.2; 154.3; 161.3 (d, $^1J_{CF}$ = 245.0, C-4"); 165.2 (d, $^1J_{CF}$ = 252.0, C-4'); 194.8 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 351 $[M–Br]^+$ (78), 123 (100). Found, %: C 58.52; H 4.00; Br 18.50; N 6.52. $C_{21}H_{17}BrF_2N_2O$. Calculated, %: C 58.48; H 3.95; Br 18.53; N 6.50.

2-(4-Chlorophenyl)-2-[2-(4-chlorophenyl)-2-oxoethyl]-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyridin-4-ium bromide (4f). Yield 1.02 g (62%, method I), colorless crystals, mp 223–225°C (AcOH). IR spectrum, ν, cm^{-1}: 769, 998, 1094, 1401, 1527, 1583, 1653, 1681 (C=O), 2975, 3014, 3081 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.12 (1H, d, ^2J = 18.5, 3-CH_2); 4.54 (1H, d, ^2J = 18.5, 3-CH_2); 4.81 (1H, d, ^2J = 13.2, CH_2CO); 5.29 (1H, d, ^2J = 13.2, CH_2CO); 6.97 (1H, t, ^3J = 7.0, H-6); 7.25 (1H, d, ^3J = 8.0, H-8); 7.37 (2H, d, ^3J = 8.5, H-3',5'); 7.49 (2H, d, ^3J = 8.5, H-2',6'); 7.65 (2H, d, ^3J = 8.5, H-3",5"); 7.98–7.80 (3H, m, H-2",6",7); 8.39 (1H, d, ^3J = 6.5, H-5); 10.20 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 48.2 (2-CH_2); 62.4 (C-3); 64.8 (C-2); 109.2; 113.3; 127.1 (2C); 128.2 (2C); 128.4 (2C); 129.6 (2C); 132.6; 134.5; 137.0; 138.8; 141.7; 144.2; 154.4; 195.2 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 385 $[M–Br]^+$ (30), 383 $[M–Br]^+$ (62), 139 (100). Found, %: C 54.40; H 3.71; Br 17.19; Cl 15.29; N 6.09. $C_{21}H_{17}BrCl_2N_2O$. Calculated, %: C 54.34; H 3.69; Br 17.21; Cl 15.28; N 6.04.

2-(4-Bromophenyl)-2-[2-(4-bromophenyl)-2-oxoethyl]-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyridin-4-ium bromide (4g). Yield 1.14 g (58%, method I), colorless crystals, mp 253–255°C (AcOH). IR spectrum, ν, cm^{-1}: 752, 817, 997, 1071, 1399, 1544, 1581, 1655, 1678 (C=O), 3023, 3100 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.09 (1H, d, ^2J = 18.5, 3-CH_2); 4.46 (1H, d, ^2J = 18.5, 3-CH_2); 4.79 (1H, d, ^2J = 13.0, CH_2CO); 5.18 (1H, d, ^2J = 13.0, CH_2CO); 6.98 (1H, t, ^3J = 7.0, H-6); 7.22 (1H, d, ^3J = 8.0, H-8); 7.52–7.57 (4H, m, H-2',3',5',6'); 7.67 (2H, d, ^3J = 9.0, H-3",5"); 7.89 (2H, d, ^3J = 9.0, H-2",6"); 8.01 (1H, t, ^3J = 8.0, H-7); 8.32 (1H, d, ^3J = 6.5, H-5); 10.09 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 48.2 (2-CH_2); 62.3 (C-3); 64.9 (C-2); 109.2; 113.3; 121.0; 127.4 (2C); 127.8; 129.7 (2C); 131.1 (2C); 131.4 (2C); 134.8; 136.9; 142.2; 144.2; 154.4; 195.5 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 475 $[M–Br]^+$ (19), 473 $[M–Br]^+$ (42), 471 $[M–Br]^+$ (20), 156 (100). Found, %: C 45.55; H 3.12; Br 43.39; N 5.07. $C_{21}H_{17}Br_3N_2O$. Calculated, %: C 45.60; H 3.10; Br 43.34; N 5.06.

2,4-Diphenylfuran (5a).[14] 2-Aminopyridine (**2a**) (0.33 g, 3.55 mmol) was added to a solution of γ-bromodipnone (**1a**) (1.07 g, 3.55 mmol) in EtOH (30 ml). The mixture was refluxed for 2 h. After cooling, the formed precipitate was filtered off and washed with EtOH. Yield 0.39 g (50%), colorless crystals, mp 110.5–111°C (MeOH) (mp 110–111°C (EtOH)[14]).

2,4-Bis(4-methoxyphenyl)furan (5b)[9] was obtained following the method for the synthesis of compounds **4a**–**g** (method I) from (2*Z*)-4-bromo-1,3-bis(4-methoxyphenyl)-but-2-en-1-one (**1e**) and 2-aminopyridine (**2a**). Yield 0.47 g (47%), colorless crystals, mp 191–192°C (EtOH) (mp 190–192°C (EtOH)[9]).

2-(*tert*-Butyl)-2-(3,3-dimethyl-2-oxobutyl)-1*H*,2*H*,3*H*-imidazo[1,2-*a*]pyridin-4-ium bromide (**7**) (50% in a mixture with compound **2a**·HBr) was obtained following the method for the synthesis of compounds **4a**–**g** (method I) from (4*Z*)-5-(bromomethyl)-2,2,6,6-tetramethylhept-4-en-3-one (**6**) and 2-aminopyridine (**2a**). Yield of the mixture of compounds **7** + **2a**·HBr (1:1) 0.63 g (25% of compound **7**). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.98 (9H, s, 2-$C(CH_3)_3$); 1.09 (9H, s, $COC(CH_3)_3$); 3.00 (1H, d, ^2J = 18.5, 3-CH_2); 3.22 (1H, d, ^2J = 18.5, 3-CH_2); 4.49 (1H, d, ^2J = 13.2, CH_2CO); 4.74 (1H, d, ^2J = 13.2, CH_2CO); 6.90 (1H, t, ^3J = 7.0, H-6); 7.02 (1H, d, ^3J = 8.0, H-8); 7.91 (1H, t, ^3J = 8.0, H-7); 8.20 (1H, d, ^3J = 6.0, H-5); 9.54 (1H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 275 $[M–Br]^+$ (81), 85 (100).

Study of the antitumor activity of compound 4f *in vitro* and the interpretation of the obtained data were carried out according to the method described on the website of the therapy development program of the National Cancer Institute (USA).[15]

Supplementary information file containing the ^{1}H and ^{13}C NMR spectra of all the synthesized compounds as well as antitumor activity data of compound **4f** is available at the journal website at http://link.springer.com/journal/10593.

References

1. (a) Enguehard-Gueiffier, C.; Gueiffier, A. *Mini-Rev. Med. Chem*. **2007**, *7*, 888. (b) Devi, N.; Singh, D.; Rawal, R. K.; Bariwal, J.; Singh, V. *Curr. Top. Med. Chem*. **2016**, *16*, 2963. (c) Poormirzaei, N.; Pordel, M.; Yaghoobi, E.; Shojaee, S.; Aminiyanfar, M.; Gonabadi, A. *J. Chem. Res*. **2020**, *44*, 167. (d) Achouche-Bouzroura, S.; Dunach, E.; Merazig, H.; Nechak, R.; Nedjar-Kolli, B.; Poulain-Martini, S.; Rabia, Ch.; Salhi, L. *Synth. Commun*. **2020**, *50*, 412. (e) Gudmundsson, K. S.; Johns, B. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2735. (f) Chitti, S.; Singireddi, S.; Santosh K.; Reddy, P.; Trivedi, P.; Bobde, Y.; Kumar, C.; Rangan, K.; Ghosh, B.; Sekhar, K. V. G. C. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 2551.
2. (a) Wang, Y.; Zhang, B.; Zheng, Y.; Ma, Q.; Sui, Q.; Lei, X. *Tetrahedron* **2019**, *75*, 1064. (b) Siddiqui, I. R.; Rai, P.; Rahila; Srivastava, A.; Shamim, S. *Tetrahedron Lett.* **2014**, *55*, 1159.
3. Uemura, Y.; Tanaka, S.; Ida, S.; Yuzuriha, T. *J. Pharm. Pharmacol*.**1993**, *45*(12), 1077.
4. Tashiro, C.; Yuasa, S.; Demisu, K. *Yakugaku Zasshi* **1992**, *112*, 108.
5. (a) Deep, A.; Bhatia, R. K.; Kaur, R.; Kumar, S.; Jain, U. K.; Singh, H.; Batra, S.; Kaushik, D.; Deb, P. K. *Curr. Top. Med. Chem*. **2017**, *17*, 238. (b) Goel, R.; Luxami, V.; Paul, K. *Curr. Top. Med. Chem*. **2016**, *16*, 3590. (c) Hirayama, T.; Okaniwa, M.; Banno H, Kakei, H.; Ohashi, A.; Iwai, K.; Ohori, M.; Mori, K.; Gotou, M.; Kawamoto, T.; Yokota, A.; Ishikawa, T. *J. Med. Chem.* **2015**, *58*, 8036. (d) Nurit, D. F.; Langley, C.; Rousseau, A. L.; Yadav, D. B.; Davids, H.; de Koning, C. B. *Eur. J. Med. Chem.* **2011**, *46*, 4573. (e) Kamal, A.; Reddy, J. S.; Ramaiah, M. J.; Dastagiri, D.; Bharathi, E. V.; Sagar, M. V. P.; Pushpavalli, S. N. C. V. L.; Ray, P.; Pal-Bharda, M. *Med. Chem. Commun.* **2010**, *1*, 355. (f) Koning, D.; Bernard, C. WO Patent 2017178992.
6. (a) Anwer, K. E.; Sayed, G. H.; Hassan, H. H.; Azab, M. E. *Egypt. J. Chem*. **2019**, *62*, 707. (b) Brehmer, D.; Beke, L.; Boeckx, A.; Diels, G. S. M.; Lawson, E. C.; Meerpoel, L.; Pande, V.; Parade, M. C. B. C.; Schepens, W. B. G.; Sun, W.; Thuring, J. W. J. F.; Viellevoye, M. WO Patent 201865365.
7. (a) Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A. *Chem. Commun*. **2015**, *51*, 1555. (b) Pericherla, K.; Kaswan, P.; Pandey, K.; Kumar, A. *Synthesis* **2015**, 887. (c) Bagdi, A. K.; Hajra, A. *Chem. Rec.* **2016**, *16*, 1868.
8. Kovtunenko, V.; Potikha, L.; Turov, A. *Synth. Commun*. **2004**, *34*, 3609.
9. Potikha, L. M.; Turelyk, A. R.; Kovtunenko, V. A. *Chem. Heterocycl. Compd.* **2009**, *45*, 1184. [*Khim. Geterotsikl. Soedin.* **2009**, 1478.]
10. (a) Potikha, L. M. *Fr.-Ukr. J. Chem*. **2018**, *6*(1), 56. (b) Potikha, L. M.; Brovarec, V. S. *Chem. Heterocycl. Compd.* **2020**, *56*, 1073. [*Khim. Geterotsikl. Soedin.* **2020**, *56*, 1073.]
11. (a) Alley, M. C.; Scudiero, D. A.; Monks, A.; Hursey, M. L.; Czerwinski, M. J.; Fine, D. L.; Abbott, B. J.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 589. (b) Grever, M. R.; Schepartz, S. A.; Chabner, B. A. *Semin. Oncol*. **1992**, *19*, 622. (c) Boyd, M. R.; Paull, K. D. *Drug Dev. Res.* **1995**, *34*, 91. (d) Shoemaker, R. H. *Nat. Rev. Cancer* **2006**, *6*, 813.
12. Wassermann, H. H.; Aubrey, N. E. *J. Am. Chem. Soc.* **1953**, *75*, 96.
13. van Tamalen, E. E.; Whitesides, T. H. *J. Am. Chem. Soc*. **1968**, *90*, 3894.
14. Faragher, R.; Gilchrist, T. L. *J. Chem. Soc*., *Perkin Trans. 1* **1976**, 336.
15. *NCI-60 Human Tumor Cell Lines Screen. DTP Developmental Therapeutics Program*, *NIH website*: https://dtp.cancer.gov/discovery_development/nci-60/default.htm.