PHARMACIA

Pharmacia 71: 1–10
DOI 10.3897/pharmacia.71.e135992

Research Article

Syntheses and evaluation of novel 3-hydroxy-1,3-diaryl-2,3,5,6,7,8-hexahydro-imidazo[1,2-a] pyridine-1-ium bromides as potential anticancer agents

Sergii Demchenko[1], Sergii Yarmoluk[1], Volodymyr Sukhovieiev[2,3], Oleksandr Golovchenko[3], Oleksandr Sukhovieiev[3], Anatolii Demchenko[2,4]

1 *Institute of Molecular Biology and Genetics of National Academy of Sciences Ukraine, Kyiv, Ukraine*
2 *Department of Chemistry and Pharmacy, Nizhyn Mykola Gogol State University, Nizhyn, Ukraine*
3 *V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry of the National Academy of Sciences of Ukraine, Kyiv, Ukraine*
4 *Institute of Pharmacology and Toxicology, National Academy of Medical Sciences, Kyiv, Ukraine*

Corresponding author: Sergii Demchenko (demcha.chem@gmail.com)

Received 11 September 2024 ♦ **Accepted** 2 November 2024 ♦ **Published** 27 November 2024

Citation: Demchenko S, Yarmoluk S, Sukhovieiev V, Golovchenko O, Sukhovieiev O, Demchenko A (2024) Syntheses and evaluation of novel 3-hydroxy-1,3-diaryl-2,3,5,6,7,8-hexahydro-imidazo[1,2-a]pyridine-1-ium bromides as potential anticancer agents. Pharmacia 71: 1–10. https://doi.org/10.3897/pharmacia.71.e135992

Abstract

New 3-hydroxy-1,3-diaryl-2,3,5,6,7,8-hexahydro-imidazo[1,2-a]pyridine-1-ium bromides have been designed, synthesized, and characterized by ^{1}H NMR, ^{13}C NMR, and LCMS. The cyclic structure of the condensation products of aryl-(3,4,5,6-tetahydropyridin-2-yl)amines with α-bromoketones has been proven. It has been shown that heating 3-hydroxy-1,3-bis-(4^{1}-methoxyphenyl)-2,3,5,6,7,8-hexahydro-imidazo[1,2-a]pyridine-1-ium bromide in acetic anhydride accompanied by elimination of water to form 1,3-bis-(4^{1}-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridine-1-ium bromide. Antitumor activity of 1,3-bis-(4^{1}-ethoxyphenyl)-3-hydroxy-2,3,5,6,7,8-hexahydro-imidazo[1,2-a]pyridine-1-ium bromide and 1,3-bis-(4^{1}-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridine-1-ium bromide have been studied. The fully aromatic imidazo[1,2-a]pyridine-1-ium bromide system was shown to have a higher antitumor effect. According to the screening results, the tested compound showed a significant level of anticancer effect on cancer cells of colon COLO 205 (lgGI50 = -5.35, lgTGI = –4.70 and lgLC50 = –4.19) and melanoma SK-MEL-5 (lgGI50 = –5.57, lgTGI = –4.81 and lgLC50 = –4.17).

Keywords

arylamidines, 1,3-diaryl-3-hydroxy-2,3,5,6,7,8-hexahydro-imidazo[1,2-a]pyridine-1-ium bromides, anticancer activity

Introduction

The heterocyclic system of imidazo[1,2-a]pyridine is a part of a number of natural biologically active substances and drugs (Nisha et al. 2016). This group reveals a wide range of pharmacological activity (Fig. 1). Thus, for example, Olprinone, which contains the fragment of imidazo[1,2-a]pyridine, is a cardiotonic (Mizushige et al. 2002); Fadrozol has antitumor activity against breast cancer cells (Bonnefoi et al. 1996); Zolpidem has hypnotic properties

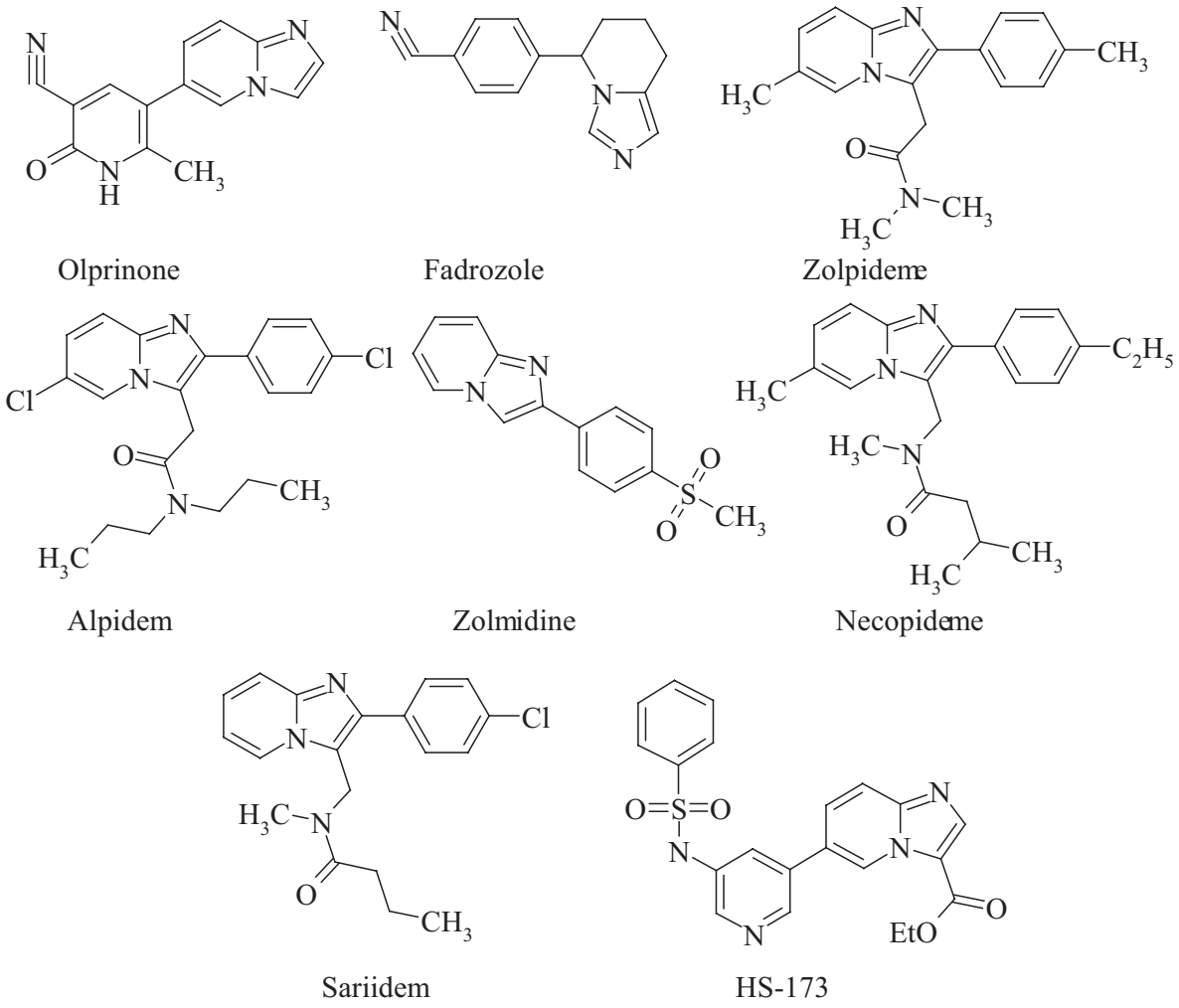


Figure 1. Some selected models of imidazo[1,2-a]pyridine derivatives possessing different biological activity.

(Arbilla et al. 1986; Crestani et al. 2000); Alpidem has anxiolytic properties (Sanger and Zivkovic 1994; Zivkovic et al. 1996); Miroprofen is an analgesic and NSAID (Sakaizumi et al. 1983); Zolmidine has antiulcer properties (Belohlavek and Malfertheiner 1979); Necopidem and Saripidem have sedative, anxiolytic properties (Santos et al. 2019). Compound HS-173 on the proliferation of human non-small cell lung cancer (NSCLC) cells. The cytotoxic effects of HS-173 on human NSCLC cell lines (A549, H1299, and NCI-H596) (Lee et al. 2013).

Thus, the synthesis of new derivatives of imidazo[1,2-a] pyridine and the search for antitumor agents among them has not only theoretical but also practical interest.

Materials and methods

Chemicals and anticancer activity

All solvents were purified before use.

The reactions were monitored by thin-layer chromatography (TLC) using Fluka silica gel (60 F 254) plates (0.25 mm). The visualization was made with UV light. Melting points of the compounds synthesized were taken on a melting point tube. Elemental analysis was performed on a EuroEA 3000 elemental analyzer. The mass spectra were recorded on an Agilent LC/MSD SL 1100 instrument (USA).

1H NMR spectra were recorded on a Varian Gemini device with 400 MHz (Germany) in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm units using the d scale.

All the chemicals used were of analytical grade (AR). The melting points of the synthesized compounds were determined by open capillaries and are uncorrected. ^{1}H NMR spectra in DMSO-d_6 on a Varian NMR mercury-300 instrument,

The structures of all the synthesized derivatives were elucidated by ^{1}H NMR and ^{13}CNMR spectroscopical analysis. The steps included in the synthesis are described below.

Chemistry

The general procedure for the synthesis of 1,3-diaryl-3-hydroxy-2,3,5,6,7,8-hexahydro-imidazo[1,2-a]pyridine-1-ium bromides 10 a–k and 11 a–f, i, l

A mixture of (0.01 mol) (4-methoxyphenyl)-(3,4,5,6-tetrahydropyridin-2-yl)amine 7 or (0.01 mol) (4-ethoxyphenyl)-(3,4,5,6-tetrahydropyridin-2-yl)amine 8 and appropriate 2-bromo-1-arylethanones 9 a–k or 9 a–f, i, l

were placed in a round bottom flask. Further add 50 ml of ethyl acetate and reflux it in a water bath for 2 h at ambient temperature for a specified time. After completion of the reaction, the solid separates out; this was then filtered, dried, and recrystallized by propanol-2.

10 a. 3-Hydroxy-1-(4¹-methoxyphenyl)-3-phenyl-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide

Yield 69%. M.p. = 236–238 °C. ^{1}H NMR (DMSO-d_6): 1.76–1.81 (m, 4H, CH_2CH_2), 2.65 and 2.71 (m+m, 2H, 8-CH_2), 2.89 and 3.37 (m+m, 2H, 5-CH_2), 3.81 (s, 3H, OCH_3), 4.31 and 4.39 (d-d, 2H, 2-CH_2, J=12.6 Hertz), 7.11 and 7.60 (d-d, 4H, C_6H_4, J=9.3 Hertz), 7.46–7.54 (m, 3H, C_6H_3), 7.72–7.74 (m, 2H, C_6H_2), 7.99 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.97, 21.05, 23.61, 56.10, 66.29, 92.57, 115.4, 126.9, 128.0, 128.3, 129.1, 129.6, 138.5, 159.9, 164.7. Anal. calcd. for $C_{20}H_{23}BrN_2O_2$: N, 6.94; Br, 19.8. Found: N, 7.09; Br, 19.6. MS m/z: 323.2 [(M+H)$^+$].

10 b. 3-Hydroxy-1-(4¹-methoxyphenyl)-3-(3²-nitrophenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a] pyridine-1-ium bromide

Yield 84%. M.p.= 233–234 °C. ^{1}H NMR (DMSO-d_6): 1.78–1.82 (m, 4H, CH_2CH_2), 2.68 and 2.72 (m+m, 2H, 8-CH_2), 2.91 and 3.37 (m+m, 2H, 5-CH_2), 3.82 (s, 3H, OCH_3), 4.35 and 4.47 (d-d, 2H, 2-CH_2, J=13.0 Hertz), 7.13 and 7.62 (d-d, 4H, C_6H_4, J=9.1 Hertz), 8.35 (s, 1H, OH), 7.81–8.56 (m, 4H, C_6H_4). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.92, 21.06, 23.80, 56.11, 65.84, 91.84, 115.4, 122.0, 124.7, 128.0, 131.0, 134.0, 140.6, 148.5, 160.0, 165.4. Anal. calcd. for $C_{20}H_{22}BrN_3O_4$: N, 9.37; Br, 17.8. Found: N, 9.53; Br, 17.6. MS m/z: 369.2 [(M+H)$^+$].

10 c. 3-Hydroxy-1,3-bis-(4¹-methoxyphenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a] pyridine-1-ium

Yield 65%. M.p. = 211–212 °C. ^{1}H NMR (DMSO-d_6): 1.79 (m, 4H, CH_2CH_2), 2.63 and 2.71 (m+m, 2H, 8-CH_2), 2.88 and 3.32 (m+m, 2H, 5-CH_2), 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.28 and 4.36 (d-d, 2H, 2-CH_2, J=12.6 Hertz), 7.04 and 7.64 (d-d, 4H, C_6H_4, J=8.7 Hertz), 7.11 and 7.67 (d-d, 4H, C_6H_4, J=9.0 Hertz), 7.92 (c, 1H, OH). Anal. calcd. for $C_{21}H_{25}BrN_2O_3$: N, 6.46; Br, 18.5. Found: N, 6.37; Br, 18.3.

10 d. 3-Hydroxy-1-(4¹-methoxyphenyl)-3-(4²-fluorophenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a] pyridine-1-ium bromide

Yield 72%. M.p. = 231–233 °C. ^{1}H NMR (DMSO-d_6): 1.88–1.97 (m, 4H, CH_2CH_2), 2.62 and 2.80 (m+m, 2H, 8-CH_2), 2.95 and 3.50 (m+m, 2H, 5-CH_2), 3.83 (s, 3H, OCH_3), 4.27 and 4.37 (d-d, 2H, 2-CH_2, J=12.2 Hertz), 7.00 and 7.81 (d-d, 4H, C_6H_4, J=8.6 Hertz), 7.15–7.89 (m+m, 4H, C_6H_4), 8.02 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.94, 21.04, 23.65, 56.10, 66.16, 92.20, 115.4, 115.8, 116.0, 128.1, 128.2, 129.4, 129.5, 134.8, 160.0, 162.0, 163.9, 164.8. Anal. calcd. for $C_{20}H_{22}BrFN_2O_2$: N, 6.65. Found: N, 6.77. MS m/z: 341.2 [(M+H)$^+$].

10 e. 3-Hydroxy-1-(4¹-methoxyphenyl)-3-(4²-difluoromethoxyphenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide

Yield 76%. M.p. = 193–194 °C. ^{1}H NMR (DMSO-d_6): 1.78–1.82 (m, 4H, CH_2CH_2), 2.64 and 2.71 (m+m, 2H, 8-CH_2), 2.89 and 3.33 (m+m, 2H, 5-CH_2), 3.82 (s, 3H, OCH_3), 4.31 and 4.39 (d-d, 2H, 2-CH_2, J=12.7 Hertz), 7.11 and 7.64 (d-d, 4H, C_6H_4, J=9.0 Hertz), 7.31 and 7.82 (d-d, 4H, C_6H_4, J=8.7 Hertz), 7.36 (t, 1H, $OCHF_2$, J=73.8 Hertz), 8.06 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.95, 21.05, 23.64, 56.10, 66.11, 92.23, 114.6, 115.4, 116.7, 118.7, 119.1, 128.0, 128.2, 129.0, 135.3, 160.0, 164.8. Anal. calcd. for $C_{21}H_{23}BrF_2N_2O_3$: N, 5.97. Found: N, 6.12. MS m/z: 389.2 [(M+H)$^+$].

10 f. 3-Hydroxy-1-(4¹-methoxyphenyl)-3-(3²,4²-dimethoxyphenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide

Yield 60%. M.p. = 223–225 °C. ^{1}H NMR (DMSO-d_6): 1.75–1.80 (m, 4H, CH_2CH_2), 2.67 and 2.72 (m+m, 2H, 8-CH_2), 2.93 and 3.33 (m+m, 2H, 5-CH_2), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.25 and 4.40 (d-d, 2H, 2-CH_2, J=12.8 Hertz), 7.04 - 7.27 (m, 3H, C_6H_3), 7.12 and 7.57 (d-d, 4H, C_6H_4, J=9.1 Hertz), 7.92 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 18.00, 21.07, 23.69, 56.10, 56.45, 66.12, 92.46, 110.7, 112.0, 115.3, 119.6, 128.0, 128.4, 130.5, 149.2, 149.8, 159.9, 165.4. Anal. calcd. For. $C_{22}H_{27}BrN_2O_2$: N, 6.04; Br, 17.2. Found: N, 6.21; Br, 17.5. MS m/z: 383.2 [(M+H)$^+$].

10 g. 3-Hydroxy-1-(4¹-methoxyphenyl)-3-(4²-diphenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a] pyridine-1-ium bromide

Yield 78%. M.p. = 273–275 °C. ^{1}H NMR (DMSO-d_6): 1.80–1.84 (m, 4H, CH_2CH_2), 2.66 and 2.74 (m+m, 2H, 8-CH_2), 2.97 and 3.41 (m+m, 2H, 5-CH_2), 3.83 (s, 3H, OCH_3), 4.35 and 4.44 (d-d, 2H, 2-CH_2, J=12.8 Hertz), 7.12 and 7.64 (d-d, 4H, C_6H_4, J=9.0 Hertz), 7.79 and 7.84 (d-d, 4H, C_6H_4, J=8.4 Hertz), 7.41-7.73 (m, 5H, C_6H_5), 8.04 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.9, 26.8, 27.3, 30.0, 44.4, 55.7, 67.8, 92.5, 115.3, 126.2, 127.1, 127.6, 127.9, 128.2, 128.8, 129.0, 138.4, 140.0, 142.3, 160.5, 169.6. Anal. calcd. for $C_{26}H_{27}BrN_2O_2$: N, 5.84; Br, 16.7. Found: N, 5.71; Br, 16.9. MS m/z: 400.2 [(M+H)$^+$].

10 h. 3-Hydroxy-1-(4¹-methoxyphenyl)-3-(4²-bromophenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a] pyridine-1-ium bromide

Yield 81%. M.p. = 245–246 °C. ^{1}H NMR (DMSO-d_6): 1.75–1.80 (m, 4H, CH_2CH_2), 2.64 and 2.69 (m+m, 2H, 8-CH_2), 2.90 and 3.33 (m+m, 2H, 5-CH_2), 3.81 (s, 3H, OCH_3), 4.30 and 4.39 (d-d, 2H, 2-CH_2, J=13.1 Hertz), 7.11 and 7.57 (d-d, 4H, C_6H_4, J=9.3 Hertz), 7.67 and 7.77 (d-d, 4H, C_6H_4, J=9.0 Hertz), 8.10 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.93, 21.06, 23.64, 56.10, 65.98, 92.25, 115.4, 123.2, 128.0, 128.2, 129.4, 132.0, 138.0, 160.0, 164.9. Anal. calcd. for $C_{20}H_{22}Br_2N_2O_2$: N, 5.81; Br, 33.1. Found: N, 5.94; Br, 29.8. MS m/z: 389.2 [(M+H)$^+$].

10 i. 3-Hydroxy-1-(4¹-methoxyphenyl)-3-(4²-ethoxyphenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide

Yield 73%. M.p. = 211–213 °C. ^{1}H NMR (DMSO-d_6): 1.34 (t, 3H, OCH_2CH_3), 1.74–1.79 (m, 4H, CH_2CH_2), 2.63 and 2.70 (m+m, 2H, 8-CH_2), 2.9 and 3.32 (m+m, 2H, 5-CH_2), 3.81 (s, 3H, OCH_3), 4.01 (q, 2H, OCH_2CH_3), 4.26 and 4.36 (d-d, 2H, 2-CH_2, J=12.8 Hertz), 7.03 and 7.57 (d-d, 4H, C_6H_4, J=8.7 Hertz), 7.11 and 7.63 (d-d, 4H, C_6H_4, J=8.7 Hertz), 7.90 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.13, 17.99, 21.07, 23.57, 56.09, 63.73, 66.18, 92.49, 114.8, 115.4, 128.0, 128.4, 130.1, 159.5, 159.9, 164.4. Anal. calcd. for $C_{22}H_{27}BrN_2O_3$: N, 5.36; Br, 17.9. Found: N, 5.51; Br, 18.2. MS m/z: 367.9 [(M+H)$^+$].

10 j. 3-Hydroxy-1-(4¹-methoxyphenyl)-3-(2²-fluoro-4²-methoxyphenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide

Yield 70%. M.p. = 195–196 °C. ^{1}H NMR (DMSO-d_6): 1.72–1.82 (m, 4H, CH_2CH_2), 2.69 and 2.72 (m+m, 2H, 8-CH_2), 2.87 and 3.41 (m+m, 2H, 5-CH_2), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.31 and 4.48 (d-d, 2H, 2-CH_2, J=13.0 Hertz), 6.91-7.71 (m, 3H, C_6H_3), 7.12 and 7.51 (d-d, 4H, C_6H_4, J=9.0 Hertz), 8.16 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.99, 21.07, 23.20, 56.14, 56.45, 64.77, 90.08, 103.0, 103.2, 110.6, 115.6, 117.1, 117.2, 127.8, 128.0, 129.7, 159.7, 160.1, 161.6, 162.4, 162.5, 163.7. Anal. calcd. for $C_{21}H_{24}BrFN_2O_3$: N, 6.20. Found: N, 6.05. MS m/z: 371.2 [(M+H)$^+$].

10 k. 3-Hydroxy-1-(4¹-methoxyphenyl)-3-(2²,3²-dihydrobenzo[1,4]dioxin-6-yl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide

Yield 79%. M.p. = 226–228 °C. ^{1}H NMR (DMSO-d_6): 1.76–1.81 (m, 4H, CH_2CH_2), 2.62 and 2.68 (m+m, 2H, 8-CH_2), 2.92 and 3.33 (m+m, 2H, 5-CH_2), 3.81 (s, 3H, OCH_3), 4.28 (m, 6H, 2-CH_2 + -OCH_2CH_2O-), 6.95-7.24 (m, 3H, C_6H_3), 7.11 and 7.60 (d-d, 4H, C_6H_4, J=8.1 Hertz), 7.90 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 17.94, 21.03, 23.49, 56.04, 64.56, 66.07, 92.23, 115.3, 115.9, 117.5, 119.8, 127.8, 128.3, 131.3, 143.8, 144.5, 159.8, 164.4. Anal. calcd. for $C_{22}H_{25}BrN_2O_4$: N, 6.07; Br, 17.3. Found: N, 6.21; Br, 17.0. MS m/z: 381.2 [(M+H)$^+$].

11 a. 3-Hydroxy-1-(4¹-ethoxyphenyl)-3-phenyl-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide

Yield 65%. M.p. = 177–179 °C. ^{1}H NMR (DMSO-d_6): 1.35 (t, 3H, OCH_2CH_3), 1.76–1.80 (m, 4H, CH_2CH_2), 2.65 and 2.71 (m+m, 2H, 8-CH_2), 2.89 and 3.33 (m+m, 2H, 5-CH_2), 4.09 (q, 2H, OCH_2CH_3), 4.30 and 4.38 (d-d, 2H, 2-CH_2, J=12.8 Hertz), 7.09 and 7.58 (d-d, 4H, C_6H_4, J=8.7 Hertz), 7.46-7.55 (m, 3H, C_6H_3), 7.72-7.75 (m, 2H, C_6H_2), 8.00 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.07, 17.97, 21.04, 23.62, 64.06, 66.32, 95.55, 115.8, 126.9, 128.0, 128.1, 129.1, 129.6, 138.5, 159.2, 164.8. Anal. calcd. for $C_{21}H_{24}BrN_2O_2$: N, 6.71; Br, 19.1. Found: N, 6.84; Br, 19.4. MS m/z: 338.2 [(M+H)$^+$].

11 b. 3-Hydroxy-1-(4¹-ethoxyphenyl)-3-(3²-nitrophenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide

Yield 80%. M.p. = 163–164 °C. ^{1}H NMR (DMSO-d_6): 1.35 (t, 3H, OCH_2CH_3), 1.77–1.81 (m, 4H, CH_2CH_2), 2.67 and 2.70 (m+m, 2H, 8-CH_2), 2.90 and 3.34 (m+m, 2H, 5-CH_2), 4.09 (q, 2H, OCH_2CH_3), 4.34 and 4.48 (d-d, 2H, 2-CH_2, J=13.0 Hertz), 7.11 and 7.58 (d-d, 4H, C_6H_4, J=8.7 Hertz), 8.35 (s, 1H, OH), 7.81-8.56 (m, 4H, C_6H_4). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.06 17.92 21.06 23.79, 64.07, 65.81, 91.84, 115.8, 122.0, 124.7, 128.0, 131.0, 134.0, 140.6, 148.5, 159.3, 165.3. Anal. calcd. for $C_{21}H_{24}BrN_3O_4$: N, 9.09; Br, 17.3. Found: N, 9.31; Br, 17.0. MS m/z: 383.1 [(M+H)$^+$].

11 c. 3-Hydroxy-1-(4¹-ethoxyphenyl)-3-(4²-methoxyphenyl)-2,3,5,6,7,8-hexahydro-imidazo[1,2-a]pyridine-1-ium bromide

Yield 65%. M.p.=197–199 °C. ^{1}H NMR (DMSO-d_6): 1.35 (t, 3H, OCH_2CH_3), 1.74–1.79 (m, 4H, CH_2CH_2), 2.64 and 2.69 (m+m, 2H, 8-CH_2), 2.88 and 3.31 (m+m, 2H, 5-CH_2), 3.80 (s, 3H, OCH_3), 4.08 (q, 2H, OCH_2CH_3), 4.27 and 4.35 (d-d, 2H, 2-CH_2, J=13.0 Hertz), 7.04 and 7.56 (d-d, 4H, C_6H_4, J=8.7 Hertz), 7.09 and 7.64 (d-d, 4H, C_6H_4, J=9.0 Hertz), 7.90 (c, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.07, 17.98, 21.04, 23.59, 55.81, 64.05, 66.22, 92.44, 114.4, 115.7, 128.0, 128.2, 128.4, 130.3, 159.2, 160.2, 164.5. Anal. calcd. for $C_{22}H_{27}BrN_2O_3$: N, 6.26; Br, 17.9. Found: N, 6.09; Br, 17.5. MS m/z: 367.2 [(M+H)$^+$].

11 d. 3-Hydroxy-1-(4¹-ethoxyphenyl)-3-(4²-fluorophenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide

Yield 72%. M.p. = 183–185 °C. ^{1}H NMR (DMSO-d_6): 1.35 (t, 3H, OCH_2CH_3), 1.76–1.80 (m, 4H, CH_2CH_2), 2.64 and 2.69 (m+m, 2H, 8-CH_2), 2.88 and 3.32 (m+m, 2H, 5-CH_2), 4.09 (q, 2H, OCH_2CH_3), 4.30 and 4.39 (d-d, 2H, 2-CH_2, J=13.1 Hertz), 7.10 and 7.57 (d-d, 4H, C_6H_4, J=9.0 Hertz), 7.32-7.82 (m, 4H, C_6H_4), 8.05 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.06, 17.93, 21.02, 23.64, 64.06, 66.14, 92.19, 115.7, 115.8, 116.0, 128.0, 128.1, 129.4, 129.5, 134.8, 159.2, 161.9, 163.9, 164.8. Anal. calcd. for $C_{21}H_{24}BrFN_2O_2$: N, 6.43. Found: N, 6.57. MS m/z: 355.2 [(M+H)$^+$].

11 e. 3-Hydroxy-1-(4¹-ethoxyphenyl)-3-(4²-difluoromethoxyphenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide

Yield 77%. M.p. = 197–198 °C. ^{1}H NMR (DMSO-d_6): 1.35 (t, 3H, OCH_2CH_3), 1.75–1.80 (m, 4H, CH_2CH_2), 2.65 and 2.69 (m+m, 2H, 8-CH_2), 2.88 and 3.32 (m+m, 2H, 5-CH_2), 4.08 (q, 2H, OCH_2CH_3), 4.29 and 4.39 (d-d, 2H, 2-CH_2, J=12.8 Hertz), 7.09 and 7.56 (d-d, 4H, C_6H_4, J=9.0 Hertz), 7.31 and 7.79 (d-d, 4H, C_6H_4, J=8.8 Hertz), 7.35 (t, 1H, $OCHF_2$, J=73.7 Hertz), 8.05 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.06, 17.94, 21.03, 23.67, 64.06, 66.16, 92.19, 114.6, 115.8, 116.7, 118.7, 119.0, 128.1, 129.0, 135.3, 151.9, 159.2, 164.8. Anal. calcd. for $C_{22}H_{25}BrF_2N_2O_3$: N, 5.79. Found: N, 5.92. MS m/z: 404.1 [(M+H)$^+$].

11 f. 3-Hydroxy-1-(4¹-ethoxyphenyl)-3-(3²,4²-dimethoxyphenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide

Yield 61%. M.p. = 229–231 °C. ^{1}H NMR (DMSO-d_6): 1.35 (t, 3H, OCH_2CH_3), 1.75–1.80 (m, 4H, CH_2CH_2), 2.67 and 2.70 (m+m, 2H, 8-CH_2), 2.92 and 3.32 (m+m, 2H, 5-CH_2), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.08 (q, 2H, OCH_2CH_3), 4.25 and 4.40 (d-d, 2H, 2-CH_2, J=12.8 Hertz), 7.09 and 7.56 (d-d, 4H, C_6H_4, J=9.1 Hertz), 7.04–7.27 (m, 3H, C_6H_3), 7.91 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.07, 18.00, 21.07, 23.69, 56.14, 56.44, 64.05, 66.07, 92.46, 110.7, 112.0, 115.7, 119.6, 127.9, 128.2, 130.5, 149.2, 149.9, 159.1, 164.4. Anal. calcd. for $C_{23}H_{29}BrN_2O_4$: N, 5.87; Br, 16.7. Found: N, 5.95; Br, 16.9. MS m/z: 397.2 [(M+H)$^+$].

11 i. 3-Hydroxy-1,3-bis-(4¹-ethoxyphenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a]-pyridine-1-ium bromide

Yield 71%. M.p. = 203–205 °C. 1H NMR (DMSO-d_6): 1.35 (t, 6H, $2OCH_2CH_3$), 1.75–1.79 (m, 4H, CH_2CH_2), 2.64 and 2.68 (m+m, 2H, 8-CH_2), 2.87 and 3.30 (m+m, 2H, 5-CH_2), 4.08 (q+q, 4H, $2OCH_2CH_3$), 4.26 and 4.36 (d-d, 2H, 2-CH_2, J=12.8 Hertz), 7.02 and 7.55 (d-d, 4H, C_6H_4, J=9.1 Hertz), 7.09 and 7.62 (d-d, 4H, C_6H_4, J=9.1 Hertz), 7.89 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.08, 17.94, 21.02, 23.51, 63.67, 64.00, 66.09, 92.43, 92.85, 114.8, 115.7, 127.9, 128.0, 128.3, 130.0, 159.1, 159.5, 164.4. Anal. calcd. for $C_{23}H_{29}BrN_2O_3$: N, 6.07; Br, 17.3. Found: N, 5.94; Br, 17.4. MS m/z: 381.3 [(M+H)$^+$].

11 l. 3-Hydroxy-1-(4¹-ethoxyphenyl)-3-(4²-chlorophenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a] pyridine-1-ium bromide

Yield 79%. M.p. = 211–213 °C. ^{1}H NMR (DMSO-d_6): 1.35 (t, 3H, OCH_2CH_3), 1.75–1.80 (m, 4H, CH_2CH_2), 2.64 and 2.69 (m+m, 2H, 8-CH_2), 2.88 and 3.32 (m+m, 2H, 5-CH_2), 4.08 (q, 2H, OCH_2CH_3), 4.30 and 4.38 (d-d, 2H, 2-CH_2, J=13.1 Hertz), 7.09 and 7.56 (d-d, 4H, C_6H_4, J=9.0 Hertz), 7.59 and 7.77 (d-d, 4H, C_6H_4, J=8.7 Hertz), 8.09 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.06, 17.93, 21.03, 23.68, 64.06, 66.08, 92.15, 115.8, 128.7, 129.1, 134.5, 137.6, 159.2, 164.9. Anal. calcd. for $C_{21}H_{24}BrClN_2O_2$: N, 6.20. Found: N, 6.38. MS m/z: 371.1 [(M+H)$^+$].

Synthesis of 1,3-bis-(4¹-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a] pyridine-1-ium bromide 12 c

0.01 mole of 3-hydroxy-1,3-bis-(4¹-methoxyphenyl)-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide 11 c was refluxed in acetic anhydride (20 ml) for 5 h and left overnight at room temperature. The obtained solution was concentrated under reduced pressure, and the purified by recrystallized from the propanol-2.

12 c. 1,3-bis-(4¹-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridine-1-ium bromide

Yield 85%. M.p. = 233–234 °C. ^{1}H NMR (DMSO-d_6): 1.90-2.80 (m, 4H, CH_2CH_2), 2.94 (m, 2H, CH_2), 2.88 and 3.32 (m+m, 2H, 5-CH_2), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.13 (s, 2H, CH_2), 7.13 and 7.59 (d-d, 4H, C_6H_4, J=8.7 Hertz), 7.18 and 7.62 (d-d, 4H, C_6H_4, J=8.8 Hertz), 8.04 (s, 1H, 2-CH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 18.01, 21.40, 22.30, 45.70, 55.92, 56.22, 115.1, 115.5, 118.0, 120.0, 127.4, 127.5, 131.2, 133.2, 145.3, 160.7, 160.9. Anal. calcd. for $C_{21}H_{23}BrN_2O_2$: N, 6.72. Found: N, 6.68. MS m/z: 336.2 [(M+H)$^+$].

Results

The synthesis of oxime cyclopentanone 2 as starting material from commercially available cyclopentanone 1 was achieved by simply grinding these hydroxylamine hydrochloride and sodium hydroxide without solvent by method (Damljanovice et al. 2006) (95% yields). 2-Piperidone (valerolactam) 3 was achieved by Beckmann rearrangement of oxime cyclopentanone 2 neat no solvent 6 hours, T = 120 °C by method (Mona et al. 2011) (80% yields). 6-Methoxy-2,3,4,5-tetrahydropyridine 4 was obtained by alkylation of valerolactam 3 with dimethyl sulfate using the method (Granik 1992) (Fig. 2). A mixture of 4-methoxyphenylamine 5 or 4-ethoxyphenylamine 6 and O-methylvalerolactim 4 was heated at 140–150 °C for 3 h under the simultaneous distillation of methanol. After cooling the mixture to room temperature, crystalline products 7 or 8 were obtained (Javorsky et al. 1992). Compounds 10 a–k and 11 a–f, i, l were obtained by condensation of equimolar amounts of (4-methoxyphenyl or 4-ethoxyphenyl)-3,4,5,6-tetrahydro-pyridin-2-yl)-amines 7 or 8 with different α-bromoketones 9 a–k or 9 a–f, l in ethyl acetate. The conclusion about the direction of alkylation of (4-methoxyphenyl or 4-ethoxyphenyl)-3,4,5,6-tetrahydro-pyridin-2-yl)-amines 7 or 8 and the structure of the resulting products 10 a–k and 11 a–f, i, l (Fig. 3) were made based on results of our previous works (Demchenko 2000; Demchenko et al. 2001, 2003, 2020, 2021; Demchenko and Lozinskii 2002). Refluxing of salt 10 c in acetic anhydride yields elimination of water molecules and formation of the corresponding 1,3-di(4-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-1-ium bromide 12 c (Fig. 4).

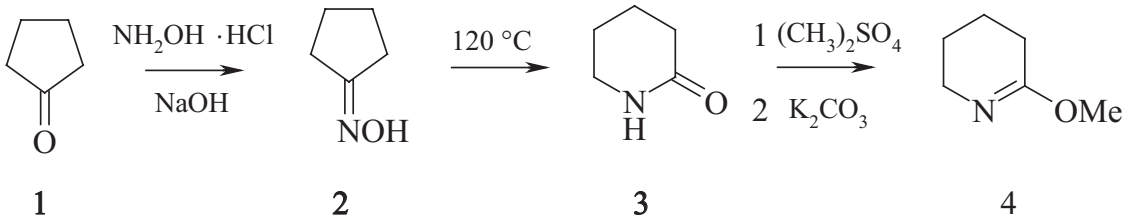
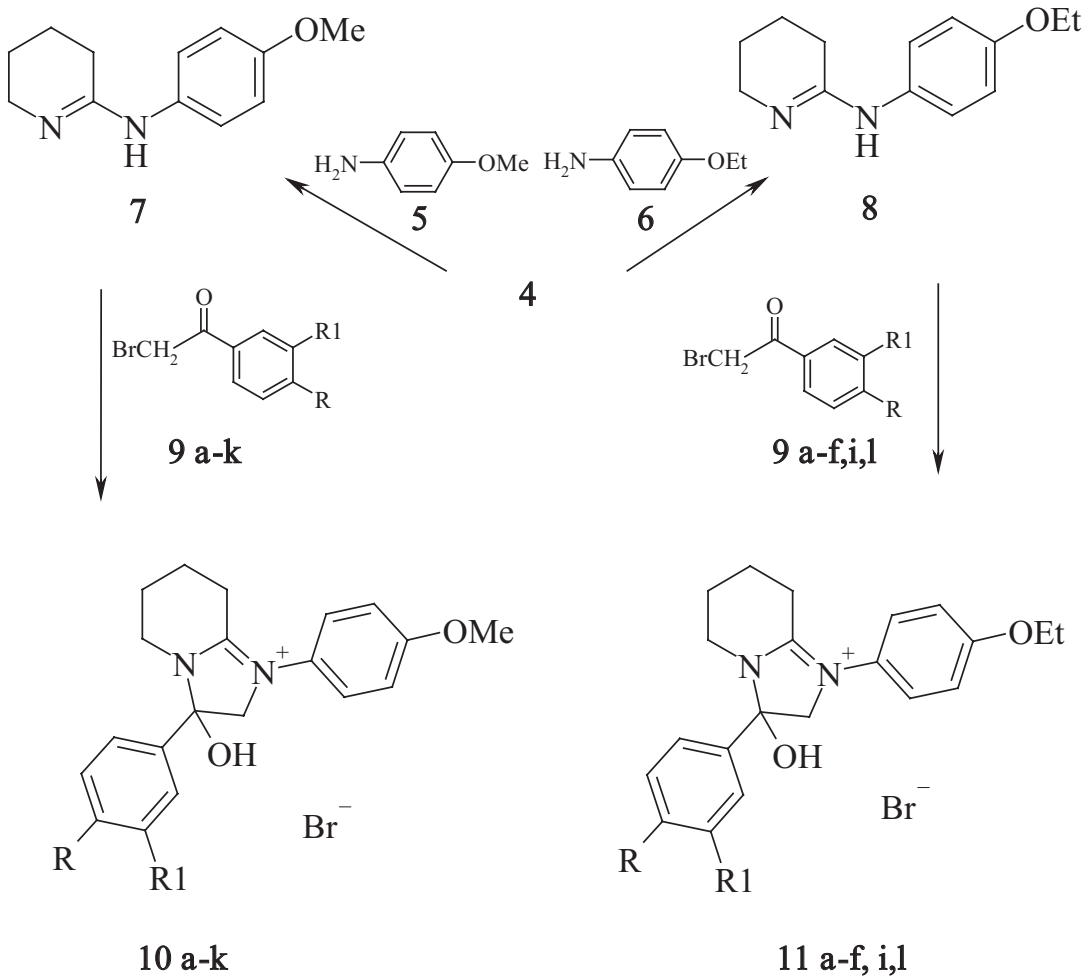


Figure 2. Schematic representation of the reaction process for the synthesis of O-methylvalerolactim 4.



9-11 a) R,R_1=H; **b)** R=H, R_1=3-NO_2; **c)** R_1=H, R=OCH_3; **d)** R_1=H, R=F; **e)** R_1=H, R=$OCHF_2$; **f)** R =OCH_3, R_1 =3-OCH_3; **g)** R_1=H, R=C_6H_5; **h)** R_1=H, R=Br; **i)** R_1=H, R=OC_2H_5; **j)** R =OCH_3, R_1 =2-F; **k)** RR_1= 3,4-OCH_2-CH_2O-; **l)** R_1=H, R=Cl.

Figure 3. Schematic representation of the reaction process for the synthesis of 3-hydroxy-1-(4[1]-methoxyphenyl)-3-aryl-2,3,5,6,7,8-hexahydro-imidazo[1,2-a]pyridine-1-ium bromides 10 a-k and 11 a-f, i, l.

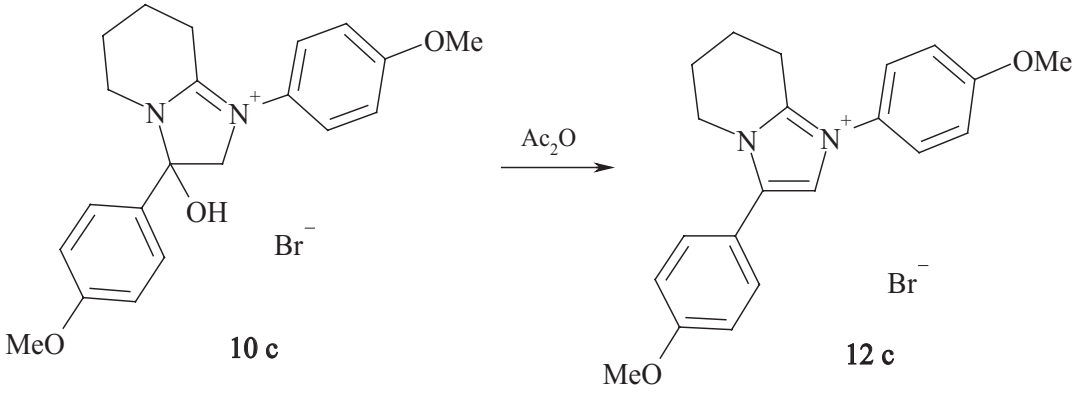


Figure 4. Schematic representation of the reaction process for the synthesis 1,3-bis-(4[1]-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridine-1-ium bromide 12 c.

Anticancer effect of 1,3-bis-(4[1]-ethoxyphenyl)-3-hydroxy-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide 11 i and 1,3-bis-(4[1]-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-1-ium bromide 12 c was investigated in the National Cancer Institute (National Cancer Institute of Health, USA) within the Therapeutic Development Program.

The first stage of the pharmacological screening (pre-screening) was aimed to analyze the antitumor effect of compounds *in vitro* within cancer cell lines (leukemia,

melanoma, lung, colon, CNS, ovarian, kidney, prostate, and breast cancer). The substance operated in the concentration of 10^{-5} mol/l according to the standard procedure (Alley et al. 1988; Teicher and Andrews 2004) of mitotic activity evaluation of new potential biologically active compounds by fluorescent staining (the stainer is sulforhodamine B). The research results are compared with the control, 5-fluorouracil; the growth of cancer cells is expressed in percent. The table indexes show how much the studied compounds are more effective in inhibiting cancer cell growth in comparison with the control.

Calculation was carried out by the high-resolution fluorometric method, quantitatively evaluating the color intensity of fluorescent light (the stainer is sulforodamin B) in 48 hours of irradiation of the cell with the tested compound. The selection and study system of potential antitumor activity compounds *in vitro* is based on the percentage of tumor cell growth (PG) under the test compound influence.

In the experiment, the compounds 11 i and 12 c in the concentration of 10^{-5} M were able to inhibit the growth of cancer cells, covering virtually the entire spectrum of human cancers (Table 1).

Discussion

According to Table 1, the compound 12 c exceeds the standard within 55 cancer cell lines out of 60 surveyed. The most effective it was relatively leukemia cells HL-60 (TB) and RPMI-8226 (higher than the effect of 5-fluorouracil up to 83.29% and 77.73%, respectively), small cell lung cancer NCI-H23 (higher than the effect of 5-fluorouracil up to 60,28%), colon cancer COLO 205 (exceeds the standard up to 50.22%), melanoma SK-MEL-5 and UACC-257 (exceed the effect of 5-fluorouracil up to 71.03% and 64.49%, respectively), and breast cancer cells MCF7, T47D, and MDA-MB-468 exceed the effect of 5-fluorouracil up to 62.22%, 70.72%, and 89.74%, respectively.

At the second phase of the research, or *in vitro* in-depth screening, the compound 12 c was tested at five concentrations and at 10-fold dilution (100 μM, 10 μM, 1 μM, 0.1 μM, and 01 μM) within the listed lines of human cancer cells. In the experiment, three dose-dependent parameters were calculated, namely: GI_{50} – concentration of the compound that causes growth inhibition of up to 50% cells within the line; TGI-concentration causes a complete

Table 1. Antitumor activity of the compounds 11 i and 12 c *in vitro* within cancer cell lines, reagent concentration of 10^{-5} M, and in-depth *in vitro* screening in the concentration gradient 10^{-4}–10^{-8} M.

Cancer Types	Cancer Cell Lines	Parameters of Antitumor Activity				
		12 c				11 i
		Mitotic Activity, %	$lgGI_{50}$	lg TGI	$lg\ LC_{50}$	Mitotic Activity, %
Leukemia	CCRF-CEM	63.76	–5.02	> –4.00	> –4.00	99.89
	HL-60(TB)	16.71	–5.77	–4.68	> –4.00	92.65
	K-562	40.17	–5.58	–4.00	> –4.00	90.44
	MOLT-4	58.43	–4.92	–4.00	> –4.00	73.47
	RPMI-8226	22.27	–6.00	–4.22	> –4.00	101.56
	SR	61.13	–5.38	–4.00	> –4.00	97.16
Small Cell Lung Cancer	A549/ATCC	55.40	–5.22	–4.00	> –4.00	96.90
	HOP-62	91.75	–4.32	–4.00	> –4.00	97.49
	HOP-92	74.28	–6.07	–4.74	> –4.00	92.49
	NCI-H226	80.12	–4.63	–4.00	> –4.00	99.48
	NCI-H23	39.72	–5.48	–4.00	> –4.00	105.00
	NCI-H322M	97.79	–4.53	–4.00	> –4.00	95.31
	NCI-H460	82.24	–4.92	–4.00	> –4.00	105.18
	NCI-H522	53.46	–5.09	–4.02	> –4.00	102.87
Colon Cancer	COLO 205	49.78	–5.35	–4.70	–4.19	106.47
	HCC2998	69.09	–5.55	> –4.00	> –4.00	106.67
	HCT-116	57.59	–5.32	> –4.00	> –4.00	102.16
	HCT-15	102.64	> –4.00	> –4.00	> –4.00	95.22
	HT-29	70.38	–4.87	> –4.00	> –4.00	92.37
	KM12	51.76	–5.53	> –4.00	> –4.00	100.66
	SW-620	100.11	–4.73	> –4.00	> –4.00	102.87
Brain Cancer	SF-268	81.05	–4.76	> –4.00	> –4.00	90.37
	SF-295	–	–4.81	–4.21	> –4.00	–
	SF-539	89.65	–4.96	> –4.00	> –4.00	109.92
	SNB-19	–	–5.04	> –4.00	> –4.00	–
	SNB-75	64.15	–5.24	> –4.00	> –4.00	95.70
	U251	54.82	–5.38	> –4.00	> –4.00	96.84
Melanoma	LOX IMVI	71.52	–4.95	> –4.00	> –4.00	95.97
	MALME-3M	–	–5.11	–4.08	> –4.00	–
	M14	84.05	–4.74	> –4.00	> –4.00	105.14
	MDA-MB-435	65.49	–5.42	–4.26	> –4.00	102.56
	SK-MEL-2	64.50	–4.92	–4.22	> –4.00	98.73
	SK-MEL-28	68.92	–4.69	> –4.00	> –4.00	105.57
	SK-MEL-5	28.97	–5.57	–4.81	–4.17	100.05
	UACC-257	35.51	–5.67	–4.72	> –4.00	108.90
	UACC-62	61.82	–5.31	> –4.00	> –4.00	108.46

Cancer Types	Cancer Cell Lines	Parameters of Antitumor Activity				
		12 c				11 i
		Mitotic Activity, %	$lgGI_{50}$	lg TGI	lg LC_{50}	Mitotic Activity, %
Ovarian Cancer	IGROV1	67.55	–4.96	> –4.00	> –4.00	93.82
	OVCAR-3	51.07	–5.43	> –4.00	> –4.00	104.04
	OVCAR-4	66.30	–5.84	> –4.00	> –4.00	104.44
	OVCAR-5	99.10	–4.36	> –4.00	> –4.00	87.30
	OVCAR-8	83.71	–4.96	> –4.00	> –4.00	105.28
	NCI/ADR-RES	106.01	> –4.00	> –4.00	> –4.00	111.06
	SK-OV-3	82.78	–4.48	> –4.00	> –4.00	95.46
Kidney Cancer	786-0	87.41	–4.38	> –4.00	> –4.00	96.68
	A498	83.28	–5.20	> –4.00	> –4.00	91.95
	ACHN	91.92	–4.15	> –4.00	> –4.00	95.73
	CAKI-1	103.09	> –4.00	> –4.00	> –4.00	95.14
	RXF 393	107.39	–4.71	> –4.00	> –4.00	115.53
	SN12C	73.35	–4.89	> –4.00	> –4.00	90.06
	TK-10	93.68	–4.37	> –4.00	> –4.00	100.73
	UO-31	98.55	> –4.00	> –4.00	> –4.00	80.97
Prostate Cancer	PC-3	74.87	–5.09	> –4.00	> –4.00	97.74
	DU-145	95.77	–5.54	> –4.00	> –4.00	118.96
Breast Cancer	MCF7	37.78	–5.38	> –4.00	> –4.00	96.00
	MDA-MB-231/ATCC	86.26	–4.73	> –4.00	> –4.00	104.55
	HS 578T	90.51	–4.58	> –4.00	> –4.00	109.99
	BT-549	57.61	–5.36	> –4.00	> –4.00	99.79
	T47D	29.28	–5.59	> –4.00	> –4.00	84.72
	MDA-MB-468	10.26	–6.44	–5.16	> –4.00	94.35

inhibition of cell growth; LC_{50}-concentration causes death in 50% of tumor cells. GI_{50} is interpreted as an effective level of inhibition; TGI makes a cytostatic effect; and LC_{50} is the lethal concentration that characterizes a cytotoxic action. If logarithmic values of researched parameters (lgGI50, lgTGI, and lgLC50) are under -4.00, the compound is considered active (Grever et al. 1998; Carter et al. 2001).

According to the screening results, the tested compound showed a significant level of anticancer effect on cancer cells of colon COLO 205 (lgGI50 = -5.35, lgTGI = –4.70 and lgLC50 = –4.19) and melanoma SK-MEL-5 (lgGI50 = –5.57, lgTGI, = –4.81 and lgLC50 = –4.17).

Conclusion

The synthesis of 19 compounds of 1,3-diaryl-3-hydroxy-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromides 10 a–k and 11 a–f, i, l was carried out. Their cyclic structure was proved using ^{1}H NMR and ^{13}C NMR spectroscopical analysis. It was demonstrated that refluxing of salt 10 c in acetic anhydride yields elimination of water molecules and formation of the corresponding 1,3-di(4-methoxyphenyl)-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridin-1-ium bromide 12 c. The antitumor activity of compounds 1,3-bis-(4^{1}-ethoxyphenyl)-3-hydroxy-2,3,5,6,7,8-hexahydroimidazo[1,2-a]pyridine-1-ium bromide 11 i and 1,3-bis-(4^{1}-methoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-1-ium bromide 12 c was studied. It was demonstrated that compound 12 c with a fully aromatized imidazolium ring is more active than compound 11 i.

Acknowledgements

The authors would like to thank all the brave defenders of Ukraine who made the finalization of this article possible.

The authors sincerely thank the Krzysztof Skubiszewski Foundation for financial support of this study.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

This study does not involve experiments on animals or human subjects.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Funding

No funding was reported.

Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal;

gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

Author ORCIDs

Sergii Demchenko https://orcid.org/0000-0003-2242-0471
Sergii Yarmoluk https://orcid.org/0000-0002-5898-6103
Volodymyr Sukhovieiev https://orcid.org/0000-0002-1590-1675
Oleksandr Golovchenko https://orcid.org/0000-0001-7756-6019
Oleksandr Sukhovieiev https://orcid.org/0000-0001-9949-2188
Anatolii Demchenko https://orcid.org/0000-0002-2173-3356

Data availability

All data generated and analyzed are included within this research article.

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