Med Chem Res (2015) 24:3912–3919
DOI 10.1007/s00044-015-1438-1

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, antiviral, and cytotoxic investigation of imidazo[4,5-*a*]acridones

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Received: 24 February 2015 / Accepted: 17 August 2015 / Published online: 27 August 2015

Abstract The importance of virus infections and the early successes with some antiviral drugs have prompted the search for new agents, and it has been focused on compounds that are active against herpesviruses, retroviruses, and rhinoviruses. In this paper, 3*H*-imidazo[4,5-*a*]acridones are introduced as new antiviral agents against a panel of DNA and RNA viruses, including herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), vaccinia virus, vesicular stomatitis virus, and herpes simplex virus-1 TK-KOS ACV ^{r}. Also, these compounds were cytostatic in the higher micromolar range. 3*H*-imidazo[4,5-*a*]acridones were synthesized by Tanasescu reaction of 3*H*-imidazo[4′,5′:3,4]benzo [*c*]isoxazoles in concentrated sulfuric acid containing nitrous acid in excellent yields. The advanced compounds were obtained from the reaction of N-alkyl-5-nitrobenzimidazoles with different aryl acetonitriles under basic conditions. Structures of all newly synthesized compounds were confirmed by IR, ^{1}H NMR, and mass spectral data. The results indicated that the title compounds have mild-to-potent activities in comparison with their appropriate reference standards.

Keywords 5-Nitrobenzimidazoles · 3*H*-imidazo[4′,5′:3,4]benzo [*c*] isoxazole · Imidazo[4,5-*a*]acridone · Cytotoxic · Antiviral

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Introduction

An intensive search for drugs effective in chemotherapy of viral infections and/or various cancers has been underway for decades. Nitrogen-containing heterocycles have diverse applications, from drugs used as antitumor agents and enzyme inhibitors (Dell'Erba *et al.*, 1992; De Angelis *et al.*, 2005; Iida *et al.*, 2005) to optical materials used in light-emitting diodes and conducting polymers (Cornil *et al.*, 2001). For example, benzo[*c*]isoxazole derivatives are prescribed as antipsychotic risperidone drugs (Szarfman *et al.*, 2006) and play a key role in many organic reactions (Loudon and Tennant, 1964), notably those leading to anthranilic acids. Also, acridine derivatives, such as acridones, pyridoacridines, and imidazoacridines, are one of the oldest classes of bioactive compounds that are widely used as antibacterial (Mitra *et al.*, 2014), antiprion (Kukowska-Kaszuba and Dzierzbicka 2007), antimalarial (Joshi and Viswanathan, 2006; Winter *et al.*, 2008) anticancer (Kamal *et al.*, 2004; Belmont *et al.*, 2007), and antitumor (Qiao *et al.*, 2012; Lang *et al.*, 2013) agents. Recently, various derivatives of the acridine series also demonstrated significant inhibitory activities toward *Plasmodium* (Girault *et al.*, 2000, 2001), *Trypanosoma* (Gamage *et al.*, 1997) and *Leishmania* (Werbovetz *et al.*, 1994; Di Giorgio *et al.*, 2003) parasites, as well as potent antiviral properties (Lowden and Bastow, 2003; Goodell *et al.*, 2006).

Recently, we reported synthesis of new derivatives of imidazo[4,5-*a*]acridines as very effective antibacterial agents (Sadeghian *et al.*, 2012; Rahimizadeh *et al.*, 2009). In continuation of our research work on the synthesis of bioactive nitrogen heterocyclic compounds (Rahimizadeh *et al.*, 2009, 2010; Sadeghian *et al.*, 2010; Bakavoli *et al.*, 2010; Pordel *et al.*, 2013), in this study, we explored the

preparation and investigation of some imidazo[4,5-*a*]acridones as potential antiviral agents against different viral strains. Furthermore, the cytotoxic activity of these compounds was also determined.

Experimental

Materials, methods, and instruments

Methanol, N,N-dimethylformamide (DMF), methyl iodide, *n*-propyl bromide, *n*-butyl bromide, isobutyl bromide, phenyl acetonitrile, 2-(4-chlorophenyl)acetonitrile, and 2-(4-bromophenyl)acetonitrile were purchased from Merck. Potassium hydroxide was purchased from Sigma–Aldrich. All solvents were dried according to standard procedures. Compounds **1a–d** were synthesized as described in the literature (Preston, 2009).

Melting points were measured on an electrothermal type-9100 melting-point apparatus. The IR (as KBr disks) spectra were obtained on a Tensor 27 spectrometer, and only noteworthy absorptions are listed. The ^{13}C NMR (100 MHz) and ^{1}H NMR (400 MHz) spectra were recorded on a Bruker Avance DRX-400 FT spectrometer in $CDCl_3$ and DMSO-d_6. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constant *J* is given in Hz. The mass spectra were recorded on a Varian Mat, CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer. All measurements were carried out at room temperature.

General procedure for the synthesis of compounds 3a–j

With stirring to a solution of KOH (13 g, 231 mmol) in methanol (50 mL), 1-alkyl-5-nitrobenzimidazole **1a–d** (10 mmol) and aryl acetonitriles **2a–c** (12 mmol) were added. The mixture was refluxed for 4 h and then poured into water. The precipitate was collected by filtration, washed with water, and air-dried to give **3a–j**. Further purification was achieved by crystallization from suitable solvent such as EtOH.

3-Methyl-8-phenyl-3*H*-imidazo[4′,5′:3,4]benzo[*c*]isoxazole (**3a**) Pale yellow crystals (methanol); m.p.: 267–269 °C [lit.(Rahimizadeh *et al.*, 2009) m.p.: 266–268 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.43 (s, 3H, N–CH_3), 7.41 (d, J = 8.0 Hz, 1H, Ar H), 7.55–7.81 (m, 7H, Ar H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4 (C, C-5), 159.7 (C, C-8), 153.6 (C, C-2), 149.4 (CH, C-7), 132.5 (C, C-9), 130.9 (CH, C-14), 129.3 (CH, C-12, C-13), 128.4 (CH, C-10, C-11), 125.8 (C, C-1), 120.5 (CH, C-4), 115.6 (CH, C-6), 103.1 (C, C-3), 35.1 (CH_3, N–CH_3).

8-(4-Chlorophenyl)-3-methyl-3*H*-imidazo[4′,5′:3,4]benzo[*c*]isoxazole (**3b**) Pale yellow crystals (methanol); m.p.: 293–295 °C (lit. [Rahimizadeh *et al.*, 2009] m.p.: 292–294 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H, N-CH_3), 7.42 (d, J = 9.5 Hz, 1H, Ar H), 7.58 (d, J = 9.5 Hz, 1H, Ar H), 7.67 (d, J = 8.8 Hz, 2H, Ar H), 7.89 (s, 1H, Ar H), 8.87 (d, J = 8.8 Hz, 2H, Ar H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9 (C, C-5), 157.3 (C, C-8), 153.2 (C, C-2), 149.0 (CH, C-7), 135.3 (CH, C-14), 133.9 (C, C-9), 131.2 (CH, C-12, C-13), 129.9 (CH, C-10, C-11), 125.6 (C, C-1), 120.2 (CH, C-4), 115.5 (CH, C-6), 102.8 (C, C-3), 35.6 (CH_3, N–CH_3).

8-Phenyl-3-propyl-3*H*-imidazo[4′,5′:3,4]benzo[*c*]isoxazole (**3c**) Pale yellow crystals (methanol); m.p.: 121–122 °C [lit.(Rahimizadeh *et al.*, 2009) m.p.: 119–122 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.0 Hz, 3H, CH_2–CH_3), 1.77–2.12 (m, 2H, CH_2–CH_3), 4.21 (t, J = 7.0 Hz, 2H, N–CH_2), 7.47–7.69 (m, 6H, Ar H), 7.89 (s, 1H, Ar H), 8.89 (d, J = 8.0 Hz, 1H, Ar H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7 (C, C-8), 162.7 (C, C-5), 148.4 (CH, C-7), 147.3 (C, C-2), 133.8 (C, C-9), 130.3 (CH, C-14), 129.5 (CH, C-12, C-13), 127.9 (CH, C-10, C-11), 123.0 (C, C-1), 120.4 (CH, C-4), 111.2 (CH, C-6), 102.8 (C, C-3), 49.3 (CH_2, N–CH_2), 21.9 (CH_2, CH_2–CH_3), 13.0 (CH_3, CH_2–CH_3).

8-(4-Chlorophenyl)-3-propyl-3*H*-imidazo[4′,5′:3,4]benzo[*c*]isoxazole (**3d**) Pale yellow crystals (methanol); m.p.: 160–163 °C [lit.(Rahimizadeh *et al.*, 2009) m.p.: 158–160 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, J = 7.3 Hz, 3H, CH_2–CH_3), 1.85–2.21 (m, 2H, CH_2–CH_2–CH_3), 4.18 (t, J = 7.3 Hz, 2H, N–CH_2), 7.40 (d, J = 9.5 Hz, 1H, Ar H), 7.56 (d, J = 9.5 Hz, 1H, Ar H), 7.62 (d, J = 8.6 Hz, 2H, Ar H), 7.86 (s, 1H, Ar H), 8.89 (d, J = 8.6 Hz, 2H, Ar H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7 (C, C-5), 158.73 (C, C-8), 148.9 (CH, C-7), 147.1 (C, C-2), 133.4 (CH, C-14), 130.5 (CH, C-12, C-13), 129.7 (CH, C-10, C-11), 129.5 (C, C-9), 122.7 (C, C-1), 120.4 (CH, C-4), 112.0 (CH, C-6), 103.3 (C, C-3), 49.5 (CH_2, N–CH_2), 22.3(CH_2, CH_2–CH_3), 13.1 (CH_3, CH_2–CH_3).

3-Butyl-8-phenyl-3*H*-imidazo[4′,5′:3,4]benzo[*c*]isoxazole (**3e**) Pale yellow crystals (methanol); m.p.: 113–115 °C [lit.(Rahimizadeh *et al.*, 2009) m.p.: 110–112 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.0 Hz, 3H, CH_2–CH_3), 1.21–1.56 (m, 2H, CH_2–CH_2–CH_3), 1.81–2.09 (m, 2H, CH_2–CH_2–CH_2–CH_3), 4.23 (t, J = 7.0 Hz, 2H, N–CH_2), 7.47–7.69 (m, 6H, Ar H), 7.88 (s, 1H, Ar H), 8.89 (d, J = 8.0 Hz, 1H, Ar H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3 (C, C-5), 159.6 (C, C-8), 148.6 (C, C-2), 146.0 (CH, C-7), 132.5 (C, C-9), 131.2 (CH, C-14), 129.2 (CH, C-12, C-13), 128.6 (CH, C-10, C-11), 121.1 (CH, C-4),

123.5 (C, C-1), 113.9 (CH, C-6), 103.2 (C, C-3), 48.3 (CH_2, N–CH_2), 31.0(CH_2, CH_2–CH_2), 21.9 (CH_2, CH_2–CH_2), 13.8 (CH_3, CH_2–CH_3).

3-Butyl-8-(4-chlorophenyl)-3*H*-imidazo[4′,5′:3,4]benzo[*c*] isoxazole (**3f**) Pale yellow crystals(methanol); m.p.: 155–157 °C [lit.(Rahimizadeh *et al.*, 2009) m.p.: 157–159 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, $J = 7.0$ Hz, 3H, CH_2–C*H*$_3$), 1.23–1.58 (m, 2H, CH_2–C*H*$_2$–CH_3), 1.82–2.10 (m, 2H, CH_2–C*H*$_2$–CH_2–CH_3), 4.24 (t, $J = 7.0$ Hz, 2H, N–CH_2), 7.41 (d, $J = 9.5$ Hz, 1H, Ar H), 7.56 (d, $J = 9.5$ Hz, 1H, Ar H), 7.61 (d, $J = 8.6$ Hz, 2H, Ar H), 7.90 (s, 1H, Ar H), 8.87 (d, $J = 8.6$ Hz, 2H, Ar H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.8$ (C, C-5), 157.5 (C, C-8), 155.0 (C, C-2), 149.8 (CH, C-7), 134.1 (CH, C-14), 132.0 (C, C-9), 131.0 (CH, C-12, C-13), 129.9 (CH, C-10, C-11), 122.7 (CH, C-4), 123.7 (C, C-1), 114.8 (CH, C-6), 103.2 (C, C-3), 48.7 (CH_2, N–CH_2), 31.5(CH_2, CH_2–CH_2), 22.0 (CH_2, CH_2–CH_2), 13.9 (CH_3, CH_2–CH_3).

8-(4-Bromophenyl)-3-methyl-3*H*-imidazo[4′,5′:3,4]benzo [*c*]isoxazole (**3g**) Pale yellow crystals (ethanol); yield (79 %), m.p.: 277–280 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H, N–CH_3), 7.40 (d, $J = 9.0$ Hz, 1H, Ar H), 7.53 (d, $J = 9.0$ Hz, 1H, Ar H), 7.7 (d, $J = 8.0$ Hz, 2H, Ar H), 7.83 (s, 1H, Ar H), 8.75 (d, $J = 8.0$ Hz, 2H, Ar H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.8$ (C, C-5), 153.5 (C, C-2), 153.2 (C, C-8), 149.7 (CH, C-7), 134.1 (CH, C-12, C-13), 130.7 (CH, C-10, C-11), 130.1 (C, C-9), 126.0 (C, C-1), 124.6 (CH, C-14), 120.1 (CH, C-4), 115.0 (CH, C-6), 100.8 (C, C-3), 35.3 (CH_3, N–CH_3). MS (70 eV): m/z 330 [M + 2] + (7), 91 (100). Anal. Calcd for $C_{15}H_{10}BrN_3O$ (328.2): C, 54.90; H, 3.07; N, 12.80. Found: C, 54.60; H, 3.02; N, 13.01.

8-(4-Bromophenyl)-3-propyl-3*H*-imidazo[4′,5′:3,4]benzo[*c*] isoxazole (**3h**) Pale yellow crystals (ethanol); yield (72 %), m.p.: 170–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, $J = 7.2$ Hz, 3H, CH_2–C*H*$_3$), 1.95 (m, 2H, CH_2–C*H*$_2$–CH_3), 4.18 (t, $J = 7.2$ Hz, 2H, N–CH_2), 7.43 (d, $J = 9.0$ Hz, 1H, Ar H), 7.55 (d, $J = 9.0$ Hz, 1H, Ar H), 7.75 (d, $J = 8.8$ Hz, 2H, Ar H), 7.85 (s, 1H, Ar H), 8.75 (d, $J = 8.8$ Hz, 2H, Ar H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.5$ (C, C-5), 156.1 (C, C-8), 148.1 (CH, C-7), 146.9 (C, C-2), 134.7 (CH, C-12, C-13), 130.8 (CH, C-10, C-11), 130.5 (C, C-9), 126.1 (C, C-1), 124.9 (CH, C-14), 120.1 (CH, C-4), 115.7 (CH, C-6), 100.5 (C, C-3), 49.3 (CH_2, N–CH_2), 22.1 (CH_2, CH_2–CH_3), 13.3 (CH_3, CH_2–CH_3). MS (70 eV): m/z 358 [M + 2] + (5), 91 (100). Anal. Calcd for $C_{17}H_{14}BrN_3O$ (356.2): C, 57.32; H, 3.96; N, 11.80. Found: C, 56.96; H, 3.93; N, 11.65.

8-(4-Bromophenyl)-3-butyl-3*H*-imidazo[4′,5′:3,4]benzo[*c*] isoxazole (**3i**) Pale yellow crystals (ethanol); yield (75 %), m.p.: 155–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, $J = 7.0$ Hz, 3H, CH_2–C*H*$_3$), 1.4 (m, 2H, CH_2–C*H*$_2$–CH_3), 1.95 (m, 2H, CH_2–C*H*$_2$–CH_2–CH_3), 4.23 (t, $J = 7.0$ Hz, 2H, N–CH_2), 7.44 (d, $J = 9.0$ Hz, 1H, Ar H), 7.57 (d, $J = 9.0$ Hz, 1H, Ar H), 7.71 (d, $J = 9.0$ Hz, 2H, Ar H), 7.83 (s, 1H, Ar H), 8.78 (d, $J = 9.0$ Hz, 2H, Ar H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.3$ (C, C-5), 156.3 (C, C-8), 148.0 (CH, C-7), 146.1 (C, C-2), 134.5 (CH, C-12, C-13), 131.1 (CH, C-10, C-11), 130.4 (C, C-9), 126.2 (C, C-1), 125.4 (CH, C-14), 120.3 (CH, C-4), 115.9 (CH, C-6), 100.3 (C, C-3), 49.0 (CH_2, N–CH_2), 31.4 (CH_2, CH_2–CH_2), 22.5 (CH_2, CH_2–CH_2), 13.7 (CH_3, CH_2–CH_3). MS (70 eV): m/z 372 [M + 2] + (3), 91 (100). Anal. Calcd for $C_{18}H_{16}BrN_3O$ (370.2): C, 58.39; H, 4.36; N, 11.35. Found: C, 58.12; H, 4.32; N, 11.23.

8-(4-Bromophenyl)-3-isobutyl-3*H*-imidazo [4′,5′:3,4] benzo [*c*] isoxazole (**3j**) Pale yellow crystals (ethanol); yield (78 %), m.p.: 153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (d, J = 7.2 Hz, 6H, CH(*CH*$_3$)$_2$), 2.22 (m, 1H, *CH*(CH_3)$_2$), 4.04 (d, $J = 7.2$ Hz, 2H, N–CH_2), 7.46 (d, $J = 9.2$ Hz, 1H, Ar H), 7.57 (d, $J_2 = 9.2$ Hz, 1H, Ar H), 7.75 (d, $J = 8.8$ Hz, 2H, Ar H), 7.86 (s, 1H, Ar H), 8.81 (d, $J = 8.8$ Hz, 2H, Ar H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.6$ (C, C-5), 156.3 (C, C-8), 148.1 (CH, C-7), 146.3 (C, C-2), 134.7 (CH, C-12, C-13), 131.3 (CH, C-10, C-11), 130.5 (C, C-9), 126.7 (C, C-1), 125.0 (CH, C-14), 120.9 (CH, C-4), 116.3 (CH, C-6), 99.8 (C, C-3), 53.8 (CH_2, N–CH_2), 28.8 (CH, $CH(CH_3)_2$), 18.6 (CH_3, $CH(CH_3)_2$). MS (70 eV): m/z 372 [M + 2] + (1), 91 (100). Anal. Calcd for $C_{18}H_{16}BrN_3O$ (370.2): C, 58.39; H, 4.36; N, 11.35. Found: C, 58.18; H, 4.31; N, 11.12.

General procedure for the synthesis of 4a–j

To a solution of **3a–j** (10 mmol) in concentrated sulfuric acid (100 mL) maintained at −10 °C, sodium nitrite (5 g, 150 mmol) was added with stirring over a half-hour period. After the addition was completed, the mixture was allowed to warm to room temperature and to stand at room temperature for 48 h. After pouring this mixture into crushed ice and water (500 mL), the solid which precipitated was removed by filtration, was washed with water and then acetone, and dried to give **4a–j**.

3-Methyl-6,11-dihydro-3*H*-imidazo[4,5-*a*]acridin-11-one (**4a**) Yellowish needles (EtOH + CH_3CN); m.p.: >300 °C [lit.(Rahimizadeh *et al.*, 2009) m.p.: >300 °C]; IR (KBr): 3420 cm^{-1} (NH), 1660 cm^{-1} (C=O). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 3.92 (s, 3H, N–CH_3), 7.41 (d, $J = 8.9$ Hz, 1H, Ar H), 7.45–7.85 (m, 5H, Ar H), 8.33 (s, 1H, Ar H), 11.79 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-*d*6): $\delta = 175.1$ (C = O, C_9), 141.6 (C, C-11), 140.3 (CH, C-7), 140.6 (C, C-1), 129.1 (CH, C-12), 127.7 (C, C-10), 126.7 (CH, C-15), 122.4 (C, C-2), 120.0 (CH,

C-13), 119.3 (CH, C-6), 117.9 (CH, C-4), 117.5 (CH, C-14), 117.0 (CH, C-5), 107.7 (CH, C-3), 33.3 (CH_3, N–CH_3). MS (70 eV): m/z 249 [M] + (3), 91 (100); Anal. Calcd for $C_{15}H_{11}N_3O$ (249.3): C, 72.28; H, 4.45; N, 16.86. Found: C, 72.01; H, 4.42; N, 17.04.

8-Chloro-3-methyl-6,11-dihydro-3*H*-imidazo[4,5-*a*]acridin-11-one (**4b**) Yellowish needles (EtOH + CH_3CN); m.p.: >300 °C (decomp) [lit.(Rahimizadeh *et al.*, 2009) m.p.: >300 °C]; IR (KBr): 3415 cm^{-1} (NH), 1660 cm^{-1} (C = O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.04 (s, 3H, N–CH_3), 7.32 (dd, J = 9.5 Hz, J = 2.1 Hz, 1H, Ar H), 7.78 (d, J = 9.4 Hz, 1H, Ar H), 7.85 (d, J = 9.4 Hz, 1H, Ar H), 8.12 (d, J = 2.1 Hz, 1H, Ar H), 8.25 (d, J = 9.5 Hz, 1H, Ar H) 8.45 (s, 1H, Ar H), 11.83 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 175.1 (C = O, C_9), 141.9 (C, C-11), 141.4 (CH, C-7), 140.6 (C, C-1), 138.2 (CH, C-12), 127.0 (C, C-10), 126.4 (CH, C-15), 122.2 (C, C-2), 119.9 (CH, C-13), 119.2 (CH, C-6), 117.9 (CH, C-4), 117.3 (CH, C-14), 117.0 (CH, C-5), 107.4 (CH, C-3), 33.4 (CH_3, N–CH_3). MS (70 eV): m/z 285 [M + 2] + (1), 91 (100); Anal. Calcd for $C_{15}H_{10}ClN_3O$ (283.7): C, 63.50; H, 3.55; N, 14.81. Found: C, 63.43; H, 3.52; N, 14.89.

3-Propyl-6,11-dihydro-3*H*-imidazo[4,5-*a*]acridin-11-one (**4c**) Yellowish needles (EtOH + CH_3CN); m.p.: >300 °C (decomp) [lit.(Rahimizadeh *et al.*, 2009) m.p.: >300 °C]; IR (KBr): 3415 cm^{-1} (NH), 1660 cm^{-1} (C=O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.79 (t, J = 7.0 Hz, 3H, CH_2–CH_3), 1.71–2.06 (m, 2H, CH_2–CH_2–CH_3), 4.26 (t, J = 7.0 Hz, 2H, N–CH_2), 7.15–8.15 (m, 6H, Ar H), 8.30 (s, 1H, Ar H), 11.86 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 175.0 (C = O, C_9), 140.2 (C, C-11), 139.4 (CH, C-7), 138.5 (C, C-1), 129.3 (CH, C-12), 127.1 (C, C-10), 126.1 (CH, C-15), 122.1 (C, C-2), 119.5 (CH, C-13), 118.8 (CH, C-6), 117.2 (CH, C-4), 117.0 (CH, C-14), 116.6 (CH, C-5), 106.9 (CH, C-3), 52.5 (CH_2, N–CH_2), 21.6 (CH_2, CH_2–CH_3), 10.0 (CH_3, CH_2–CH_3). MS (70 eV): m/z 277 [M] + (3), 91 (100); Anal. Calcd for $C_{17}H_{15}N_3O$ (277.3): C, 73.63; H, 5.45; N, 15.15. Found: C, 73.49; H, 5.41; N, 15.41.

8-Chloro-3-propyl-6,11-dihydro-3*H*-imidazo[4,5-*a*]acridin-11-one (**4d**) Yellowish needles (EtOH + CH_3CN); m.p.: >300 °C (decomp) [lit.(Rahimizadeh *et al.*, 2009) m.p.: >300 °C]; IR (KBr): 3415 cm^{-1} (NH), 1660 cm^{-1} (C=O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83 (t, J = 7.1 Hz, 3H, CH_2–CH_3), 1.69–1.95 (m, 2H, CH_2–CH_2–CH_3), 4.29 (t, J = 7.1 Hz, 2H, N–CH_2), 7.25 (dd, J = 9.5 Hz, J = 2.1 Hz, 1H, Ar H), 7.68 (d, J = 9.4 Hz, 1H, Ar H), 7.75 (d, J = 9.4 Hz, 1H, Ar H), 8.17 (d, J = 2.1 Hz, 1H, Ar H), 8.25 (d, J = 9.5 Hz, 1H, Ar H), 8.35 (s, 1H, Ar H), 11.80 (br s, 1H, NH);. ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 175.1 (C = O, C_9), 140.2 (C, C-11), 140.0 (CH, C-7), 139.6 (C, C-1), 137.4 (CH, C-12), 128.4 (C, C-10), 126.1 (CH, C-15), 121.9 (C, C-2), 119.1 (CH, C-13), 119.0 (CH, C-6), 117.7 (CH, C-4), 117.1 (CH, C-14), 115.2 (CH, C-5), 106.7 (CH, C-3), 52.8 (CH_2, N–CH_2), 21.6 (CH_2, CH_2–CH_3), 10.1 (CH_3, CH_2–CH_3). MS (70 eV): m/z 313 [M + 2] + (1), 91 (100); Anal. Calcd for $C_{17}H_{14}ClN_3O$ (311.8): C, 65.49; H, 4.53; N, 13.48. Found: C, 65.23; H, 4.51; N, 13.69.

3-Butyl-6,11-dihydro-3*H*-imidazo[4,5-*a*]acridin-11-one (**4e**) Yellowish needles (EtOH + CH_3CN); m.p.: >300 °C (decomp) [lit.(Rahimizadeh *et al.*, 2009) m.p.: >300 °C]; IR (KBr): 3415 cm^{-1} (NH), 1660 cm^{-1} (C=O). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.87 (t, J = 7.0 Hz, 3H, CH_2–CH_3), 1.16–1.51 (m, 2H, CH_2–CH_2–CH_3), 1.75–2.03 (m, 2H, CH_2–CH_2–CH_2–CH_3), 4.30 (t, J = 7.0 Hz, 2H, N–CH_2), 7.10–8.10 (m, 6H, Ar H), 8.31 (s, 1H, Ar H), 11.81 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ = 175.1 (C = O, C_9), 140.3 (C, C-11), 138.9 (CH, C-7), 138.0 (C, C-1), 129.3 (CH, C-12), 127.2 (C, C-10), 126.2 (CH, C-15), 122.1 (C, C-2), 119.5 (CH, C-13), 118.9 (CH, C-6), 117.3 (CH, C-4), 117.0 (CH, C-14), 116.6 (CH, C-5), 107.0 (CH, C-3), 49.7 (CH_2, N–CH_2), 30.8 (CH_2, CH_2–CH_2), 20.4 (CH_2, CH_2–CH_2), 11.1 (CH_3, CH_2–CH_3). MS (70 eV): m/z 291 [M] + (5), 91 (100); Anal. Calcd for $C_{18}H_{17}N_3O$ (291.3): C, 74.21; H, 5.88; N, 14.42. Found: C, 73.97; H, 5.85; N, 14.50.

3-Butyl-8-chloro-6,11-dihydro-3*H*-imidazo[4,5-*a*]acridin-11-one (**4f**) Yellowish needles (EtOH + CH_3CN); m.p.: >300 °C (decomp) [lit.(Rahimizadeh *et al.*, 2009) m.p.: >300 °C]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (t, J = 6.5 Hz, 3H, CH_2–CH_3), 1.13–1.48 (m, 2H, CH_2–CH_2–CH_3), 1.73–2.01 (m, 2H, CH_2–CH_2–CH_2–CH_3), 4.33 (t, J = 6.5 Hz, 2H, N–CH_2), 7.21(dd, J = 9.5 Hz, J = 2.1 Hz, 1H, Ar H), 7.58 (d, J = 9.4 Hz, 1H, Ar H), 7.65 (d, J = 9.4 Hz, 1H, Ar H), 8.15 (d, J = 2.1 Hz, 1H, Ar H), 8.25 (d, J = 9.5 Hz, 1H, Ar H) 8.30 (s, 1H, Ar H), 11.91 (br s, 1H, NH); IR (KBr): 3415 cm^{-1} (NH), 1660 cm^{-1} (C = O).);^{13}C NMR (100 MHz, DMSO-*d6*): δ = 175.1 (C = O, C_9), 140.3 (C, C-11), 139.7 (CH, C-7), 139.1 (C, C-1), 137.4 (CH, C-12), 128.4 (C, C-10), 126.2 (CH, C-15), 121.9 (C, C-2), 119.2 (CH, C-13), 119.0 (CH, C-6), 117.7 (CH, C-4), 117.2 (CH, C-14), 115.2 (CH, C-5), 107.4 (CH, C-3), 49.9 (CH_2, N–CH_2), 30.7 (CH_2, CH_2–CH_2), 20.4 (CH_2, CH_2–CH_2), 11.1 (CH_3, CH_2–CH_3). MS (70 eV): m/z 327 [M + 2] + (2), 91 (100); Anal. Calcd for $C_{18}H_{16}ClN_3O$ (325.8): C, 66.36; H, 4.95; N, 12.90. Found: C, 66.03; H, 4.94; N, 13.09.

8-Bromo-3-methyl-3*H*-imidazo[4,5-*a*]acridin-11(6*H*)-one (**4g**) Yellowish needles (EtOH + CH_3CN); yield (70 %), m.p.: >300 °C (decomp); IR(KBr): 3400 cm^{-1} (NH), 1632 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.93 (s,

3H, N–CH_3), 7.24 (dd, $J = 8.4$ Hz, $J' = 1.2$ Hz, 1H, Ar H), 7.66 (d, $J = 9.2$ Hz, 1H, Ar H), 7.85 (d, $J = 9.2$ Hz, 1H, Ar H), 7.94(s, 1H, Ar H), 8.05 (d, $J = 1.2$ Hz, 1H, Ar H), 8.43 (d, $J = 8.4$ Hz, 1H, Ar H), 11.8 (br s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-*d6*): $\delta = 175.1$ (C=O, C_9), 148.7 (CH, C-10), 143.4 (C, C-11), 141.9 (CH, C-7), 140.2 (C, C-1), 138.8 (CH, C-12), 129.5 (C, C-14), 125.1 (CH, C-15), 124.2 (C, C-2), 117.1 (CH, C-13), 119.0 (CH, C-6), 117.1 (CH, C-4), 117.6 (CH, C-5), 107.8 (CH, C-3), 33.9 (CH_3, N–CH_3). MS (70 eV): m/z 330 [M + 2] + (5), 91 (100). Anal. Calcd for $C_{15}H_{10}BrN_3O$ (328.2): C, 54.90; H, 3.07; N, 12.80. Found: C, 54.70; H, 3.02; N, 12.69.

8-Bromo-3-propyl-3*H*-imidazo [4,5-*a*]acridin-11(6*H*)-one (**4h**) Yellowish needles (EtOH + CH_3CN); yield (65 %), m.p.: >300 °C (decomp); IR(KBr): 3392 cm^{-1} (NH), 1633 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.86 (t, $J = 6.8$ Hz, 3H, CH_2–CH_3), 1.84 (m, 2H, CH_2–CH_2–CH_3), 4.31 (t, $J = 6.8$ Hz, 2H, N–CH_2), 7.38 (d, $J = 8.8$ Hz, 1H, Ar H), 7.41 (d, $J = 8.8$ Hz, 1H, Ar H), 7.74 (s, 1H, Ar H), 8.08 (dd, $J = 8.4$ Hz, $J' = 1.2$ Hz, 1H, Ar H), 8.18 (d, $J = 8.4$ Hz, 1H, Ar H), 8.35 (d, $J = 1.2$ Hz, 1H, Ar H), 11.8 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-*d6*): $\delta = 175.3$ (C=O, C_9), 148.5 (CH, C-10), 143.7 (C, C-11), 141.9 (CH, C-7), 140.5 (C, C-1), 138.4 (CH, C-12), 129.7 (C, C-14), 125.3 (CH, C-15), 124.4 (C, C-2), 117.4 (CH, C-13), 119.1 (CH, C-6), 117.2 (CH, C-4), 117.9 (CH, C-5), 107.8 (CH, C-3), 53.5 (CH_2, N–CH_2), 21.7 (CH_2, CH_2–CH_3), 10.0 (CH_3, CH_2–CH_3). MS (70 eV): m/z 358 [M + 2] + (4), 91 (100); Anal. Calcd for $C_{17}H_{14}BrN_3O$ (356.2): C, 57.32; H, 3.96; N, 11.80. Found: C, 57.70; H, 4.05; N, 11.56.

8-Bromo-3-butyl-3*H*-imidazo [4,5-*a*]acridin-11(6*H*)-one (**4i**) Yellowish needles (EtOH + CH_3CN); yield (67 %), m.p.: >300 °C (decomp); IR(KBr): 3423 cm^{-1} (NH), 1636 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.90 (t, $J = 6.7$ Hz, 3H, CH_2–CH_3), 1.26 (m, 2H, CH_2–CH_2–CH_3), 1.83 (m, 2H, CH_2–CH_2–CH_2–CH_3), 4.41 (t, $J = 6.7$ Hz, 2H, N–CH_2), 7.43 (d, $J = 7.0$ Hz, 1H, Ar H), 7.53 (d, $J = 7.0$ Hz, 1H, Ar H), 7.8 (s, 1H, Ar H), 8.15 (dd, $J = 8.4$ Hz, $J' = 1.2$ Hz, 1H, Ar H), 8.25 (d, $J = 8.4$ Hz, 1H, Ar H), 8.86 (d, $J = 1.2$ Hz, 1H, Ar H), 12.06 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-*d6*): $\delta = 175.4$ (C=O, C_9), 148.6 (CH, C-10), 143.9 (C, C-11), 142.3 (CH, C-7), 140.6 (C, C-1), 138.3 (CH, C-12), 129.7 (C, C-14), 125.4 (CH, C-15), 124.6 (C, C-2), 117.8 (CH, C-13), 119.3 (CH, C-6), 117.1 (CH, C-4), 117.4 (CH, C-5), 107.0 (CH, C-3), 49.5 (CH_2, N–CH_2), 30.5 (CH_2, CH_2–CH_2), 20.3 (CH_2, CH_2–CH_2), 11.0 (CH_3, CH_2–CH_3). MS (70 eV): m/z 372 [M + 2] + (3), 91 (100); Anal. Calcd for $C_{18}H_{16}BrN_3O$ (370.2): C, 58.39; H, 4.36; N, 11.35. Found: C, 58.67; H, 4.39; N, 11.25.

8-Bromo-3-isobutyl-3*H*-imidazo [4,5-*a*]acridin-11(6*H*)-one (**4j**) Yellowish needles (EtOH + CH_3CN); yield (72 %), m.p.: >300 °C (decomp); IR(KBr): 3391 cm^{-1} (NH), 1633 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.67 (d, $J = 7.0$ Hz, 6H, $CH(CH_3)_2$), 1.98 (m, 1H, $CH(CH_3)_2$), 4.14 (d, $J = 7.0$ Hz, 2H, N–CH_2), 7.27 (d, $J = 8.8$ Hz, 1H, Ar H), 7.31 (d, $J = 8.8$ Hz, 1H, Ar H), 7.62 (s, 1H, Ar H), 7.95 (dd, $J = 8.4$ Hz, $J' = 1.2$ Hz, 1H, Ar H), 8.2 (d, $J = 8.4$ Hz, 1H, Ar H), 8.37 (d, $J = 1.2$ Hz, 1H, Ar H), 11.81 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-*d6*): $\delta = 175.3$ (C=O, C_9), 148.5 (CH, C-10), 143.8 (C, C-11), 142.0 (CH, C-7), 140.4 (C, C-1), 138.7 (CH, C-12), 129.7 (C, C-14), 125.6 (CH, C-15), 124.9 (C, C-2), 117.8 (CH, C-13), 119.3 (CH, C-6), 117.0 (CH, C-4), 117.2 (CH, C-5), 107.4 (CH, C-3), 54.6 (CH_2, N–CH_2), 29.5 (CH, $CH(CH_3)_2$), 18.5 (CH_3, $CH(CH_3)_2$). MS (70 eV): m/z 372 [M + 2] + (2), 91 (100); Anal. Calcd for $C_{18}H_{16}BrN_3O$ (370.2): C, 58.39; H, 4.36; N, 11.35. Found: C, 58.21; H, 4.33; N, 11.19.

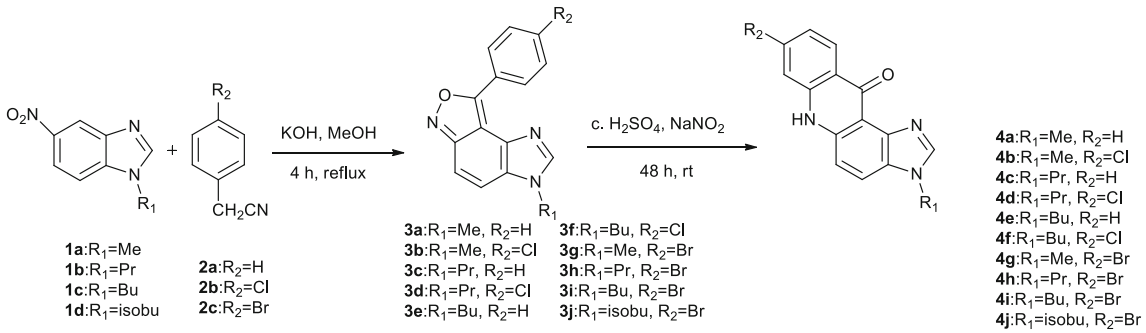
Biological evaluations

Antiviral assay (MIC or EC_{50}) (Clercq et al., 1980, 1987)

Confluent cell cultures in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus, one $CCID_{50}$ being the virus dose required to infect 50 % of the cell cultures. After 1–2 h of virus adsorption period, residual virus was removed, and the cell cultures were incubated at 37 °C in the presence of varying concentrations of the test compounds (dilutions were made based upon CTC_{50}). Viral cytopathogenicity was recorded as soon as it reached completion in the control virus infected cell cultures that were not treated with the test compounds after 4–5 days of post infection, microscopically. The antiviral activity of the compounds **4a–j** was expressed as the effective concentration required for inhibiting the viral cytopathic effect by 50 % (MIC or EC_{50}). The CTC_{50} and MIC of the test compounds were compared with the standard drugs brivudine (BVDU), cidofovir, acyclovir, and ribavirin under similar conditions. By adopting the above procedure, the MIC or EC_{50} for all the compounds **4a–j** was determined.

Cytotoxicity activity assay (Piotrowska et al., 2012)

Murine leukemia L1210, human T-lymphocyte CEM, human cervix carcinoma (HeLa), and human lung fibroblast (HEL) cells were suspended at 300,000–500,000 cells/mL of culture medium, and 100 µL of a cell suspension was added to 100 µL of an appropriate dilution of the test compounds in wells of 96-well microtiter plates. After incubation at 37 °C for two (L1210) or three (CEM, HeLa,



Scheme 1 Synthesis of compounds **3a–j** and **4a–j**

Table 1 Antiviral activity of compounds **4a–j** in E_6SM cell cultures

Compound	Minimum inhibitory concentration[a] (μM)				
	Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Vaccinia virus	Vesicular stomatitis virus	Herpes simplex virus-1 TK-KOS ACV^r
4a	>80[b]	>80[b]	>150[b]	>80[b]	>80[b]
4b	35.0	35.0	45.0	80.0	35.0
4c	19.0	19.0	26.0	45.0	23.0
4d	15.1	13.2	25.0	45.0	23.0
4e	20.0	20.0	25.0	45.0	23.0
4f	12.0	8.0	15.0	45.0	23.0
4g	>100[b]	>100[b]	>100[b]	>100[b]	>100[b]
4h	55.0	50.0	75.0	>100	60
4i	35.0	30.0	40.1	>100	45.0
4j	40.0	40.0	40.0	>100	40.0
Brivudine	0.04	150	12	>300	45
Cidofovir	1.5	3	25	>300	1.5
Acyclovir	0.5	0.5	>300	>300	70
Ribavirin	180	180	30	180	180

[a] Required to reduce virus-induced cytopathogenicity by 50 %

[b] Compound precipitated out under assay conditions

HEL) days, the cell number was determined using a Coulter counter. The IC_{50} was defined as the compound concentration required to inhibit cell proliferation by 50 %.

Results and discussion

Chemistry

Initially, N-alkyl-5-nitrobenzimidazoles **1a–d** were obtained from 5-nitrobenzimidazole using different alkyl halides treatment in DMF and KOH as previously described (Preston, 2009). 3*H*-imidazo[4′,5′:3,4]benzo [*c*] isoxazoles **3a–j** were accessed through the nucleophilic substitution of hydrogen of N-alkyl-5-nitrobenzimidazoles **1a–d** with aryl acetonitriles **2a–c** under basic conditions (Rahimizadeh *et al.*, 2009; Sahraei *et al.*, 2013; Pordel 2012) (Scheme 1). Derivatives of **3a–j** were converted to 3*H*-imidazo[4,5-*a*]acridones **4a–j** in concentrated sulfuric acid containing nitrous acid at room temperature by Tanasescu reaction (Tanasescu 1927) in fairly good yields (Scheme 1). Compounds **3g–j** and **4g–j** are new heterocyclic compounds. The structures of compounds **3g–j** and **4g–j** were unambiguously characterized on the basis of their IR, ^{1}H NMR and mass spectra.

Antiviral and cytostatic evaluation

Compounds **4a–j** were evaluated for antiviral and cytostatic activity using the method described in experimental section. The results of antiviral screening of compounds **4a–j** against herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), vaccinia virus, vesicular stomatitis virus, and herpes simplex virus-1 TK-KOS ACV ^{r} are shown in

Table 2 Cytostatic activity of compounds **4a–j**

Compound	CC_{50}^{a} (μM)			
	L1210	CEM	HeLa	HEL
4a	135	180	150	85
4b	120	179	130	60
4c	110	190	150	75
4d	85	100	100	60
4e	95	140	95	75
4f	75	110	90	60
4g	120	190	200	100
4h	120	180	180	90
4i	110	150	150	85
4j	90	145	125	65

[a] 50 % inhibitory concentration or compound concentration required to inhibit cell proliferation by 50 %

Table 1. The results of assay indicate that all the compounds have shown varying degree of cytotoxicity (i.e., from 90 to 200 μM). Based on the CTC_{50} non-toxic concentrations, all the synthesized compounds were subjected for antiviral activity determination against different viral strains. The results of antiviral activity (Table 1) indicated that all 3*H*-imidazo[4,5-*a*]acridones **4a–j** exhibited good-to-moderate antiviral activity against mentioned organisms from approximately 8 to 150 μM which is comparable with the reference drug Ribavirin.

Also, the results revealed that compounds **4b**, **4d**, and **4f** in which the R_2 substituent is a chlorine function displayed greater antiviral activity than did others. Compound **4f** (R_2 = Cl and R_1 = Bu) was the most potent of the tested compounds against viral strains. It might be due to the chain lengths and chlorine substituent that change the binding characteristics of ligands to their respective receptors and, thereby, improve the biological activities.

The cytotoxicity of the tested compounds toward the uninfected host cells was defined as the minimum compound concentration (MCC) that caused a microscopically detectable alteration of normal cell morphology. The 50 % cytostatic concentration (CC_{50}), causing a 50 % decrease in cell proliferation, was determined against murine leukemia L1210, human lymphocyte CEM, human cervix carcinoma HeLa, and human lung fibroblast HEL cells. All of the tested compounds affected cell morphology of HEL, HeLa, Vero, MDCK, and CrFK cells at concentrations ranging from 60 to 200 μM for HeLa cells, L1210, CEM, and HEL cells (Table 2).

In conclusion, we synthesized a series of 3-alkyl-6,11-dihydro-3*H*-imidazo[4,5-*a*]acridin-11-one, 8-chloro-3-propyl-6,11-dihydro-3*H*-imidazo[4,5-*a*]acridin-11-one, and new 8-bromo-3-propyl-6,11-dihydro-3*H*-imidazo[4,5-*a*]acridin-11-one, which were structurally confirmed by IR, ^{1}H NMR, ^{13}C NMR, elemental, and MS spectral analysis. The antiviral screening for all 3*H*-imidazo[4,5-*a*]acridones (**4a–j**) against a broad panel of DNA and RNA viral strains indicated that these compounds emerged as promising antiviral activity against different viral strains. Additionally, compounds **4a–j** proved slightly cytostatic (middle to higher micromolar range: 60–200 μM).

Such compounds could be selected as lead compounds for the development of novel antiviral agents active against herpes simplex virus, vaccinia virus, and vesicular stomatitis virus.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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