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Design, synthesis and anticancer activity evaluation of aziridine-1,2,3-triazole hybrid derivatives

<https://doi.org/10.1515/hc-2017-0144>

Received August 1, 2017; accepted December 19, 2017; previously published online March 30, 2018

Abstract: New 1-aryl-4-[(aziridine-1-yl)diarylmethyl]-5-methyl-1*H*-1,2,3-triazole derivatives **7a–i** were synthesized by a one-pot reaction of diaryl-(1-aryl-5-methyl-1*H*-1,2,3-triazol-4-yl)methanols **6a–i** derived from 1-aryl-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acids **4a–c**. Structures of compounds **7a–i** were confirmed by analysis of proton nuclear magnetic resonance (¹H NMR) and carbon-13 nuclear magnetic resonance (¹³C NMR), mass spectrometry (MS) and infrared (IR) data. The structure of compound **7f** was studied by X-ray diffraction analysis. The anticancer activities of compounds **7a–i** against human leukemia HL-60 cells and human hepatoma G2 cells were evaluated. Some of the compounds are highly active.

Keywords: anticancer; aziridine; human hepatoma G2; human leukemia HL-60; 1*H*-1,2,3-triazole.

Introduction

A vast majority of biologically important molecules are heterocyclic compounds [1–3]. The biological properties of aziridine-containing compounds such as azicemicins [4], miraziridine [5, 6], azinomycins [7], ficellomycin [8], FR-900482 [9] and mitomycins [10] are of significant interest (Figure 1). In particular, mitomycin C has a broad activity against a range of tumors and has been applied clinically since the 1960s. 1,2,3-Triazoles are also pharmacologically important molecules that show anticancer [11–13], antibacterial [14, 15], antifungal [16], antiviral [17], anti-inflammatory and analgesic activities [18] (Figure 2). However, there is little information describing compounds containing aziridine and 1,2,3-triazole moieties in one molecule. Such compounds are the subject of this report.

Results and discussion

1-Aryl-4-[(aziridin-1-yl)diaryl-methyl]-5-methyl-1*H*-1,2,3-triazoles **7a–i** were synthesized from diaryl-1*H*-1,2,3-triazol-4-yl)methanols **6a–i**. The synthetic route is shown in Scheme 1. Details of the synthesis of compounds **6a–i** starting with anilines **1** through intermediaries **4** and **5** were described in our previous report [19]. Structures of products **7a–i** were deduced by spectral methods. In particular, a strong absorption at 3320–3520 cm^{−1} for a hydroxy group, observed in the infrared (IR) spectra of substrates **6a–i**, is absent in the IR spectra of products **7a–i**. The proton nuclear magnetic resonance (¹H NMR) spectra of compounds **7a–i** show signals of the aziridine protons at δ 1.80–1.88 and δ 1.15–1.33, as expected. The structure of compound **7f** was additionally determined by X-ray diffraction analysis (Figure 3). Compound **7f** (CCDC deposit No 775599), C₂₅H₂₄N₄, MW 380.48, crystallizes in the triclinic space group *P* $\bar{1}$ with unit cell parameters *a*=9.3100(7), *b*=13.8263(11), *c*=17.4605(15) Å, α=107.402(4), β=92.607(4), γ=92.829(4)°, *V*=2137.8(3) Å³, *Z*=4, *D*_x=1.182 mg/cm³. The final *R* value was 0.0558.

Conclusions

New 1-aryl-4-[(aziridin-1-yl)diaryl-methyl]-5-methyl-1*H*-1,2,3-triazoles **7a–i** were synthesized and their anticancer activities were evaluated. The anticancer activity was investigated under our previously reported conditions [20, 21] using the MTT assay. Compounds **7b,c** and **7i** are highly active against human leukemia cells and compounds **7c,d**, **7f,g** inhibit human hepatoma G2 cells.

Experimental

¹H NMR spectra were obtained in deuterated chloroform (CDCl₃) at 300 MHz. Starting materials **4–6** were synthesized as previously reported [19].

Synthesis of compounds **7a–i**

Dry hydrogen chloride was bubbled through a hot solution of compounds **6a–i** (0.04 mol) in benzene (20 mL) in a 50-mL flask equipped

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Figure 1 Fused aziridine-containing natural products.

Figure 2 Anticancer compounds containing 1,2,3-triazole.

with an automatic water separator, a reflux condenser and a calcium chloride guard-tube. After 1 h, the solution was concentrated to 10 mL and treated with aziridine (0.06 mol) with rapid stirring followed by the addition of triethylamine (0.08 mol). After the mixture was stirred at 45°C for an additional 1 h, the solvent was evaporated and the residue was crystallized from ethyl acetate or purified by column chromatography on silica gel and eluted with ethyl acetate/petroleum ether.

4-[(Aziridin-1-yl)-bis(4-chlorophenyl)methyl]-5-methyl-1-(4-chlorophenyl)-1H-1,2,3-triazole (7a) White flakes; yield 86%; mp 90–92°C; ¹H NMR: δ 7.52 (d, 1H, *J* = 3 Hz), 7.50 (d, 1H, *J* = 3 Hz), 7.48 (d, 2H, *J* = 3 Hz), 7.45 (d, 2H, *J* = 3 Hz), 7.40 (d, 1H, *J* = 3.6 Hz), 7.37 (d, 1H, *J* = 3 Hz), 7.29 (d, 2H, *J* = 3 Hz), 7.26 (d, 2H, *J* = 3.6 Hz), 2.10 (s, 3H), 1.81 (s, 2H), 1.15 (s, 2H); ¹³C NMR (CDCl₃-d₁), δ 145.7, 141.6, 135.6, 134.7, 133.1, 132.9, 130.4, 129.6, 127.8, 126.8, 69.3, 21.7, 10.6; MS: *m/z* 468 (M⁺,

0.39), 428 (6), 426 (6), 154 (32), 152 (100); IR: 3425, 3061, 2987, 2926, 2844, 1734, 1496, 1442, 1422, 1400, 1264, 1117, 1092, 1010, 922, 867, 829, 818 cm⁻¹. HRMS (ESI). Calcd for C₂₄H₁₉Cl₃N₄, [M+H]⁺: *m/z* 469.0748. Found: *m/z* 469.0755.

4-[(Aziridin-1-yl)-bis(3-chlorophenyl)methyl]-5-methyl-1-(4-chlorophenyl)-1H-1,2,3-triazole (7b) White flakes; yield 65%; mp 96–98°C; ¹H NMR: δ 7.61 (s, 2H), 7.52 (q, 2H, *J* = 2.4 Hz), 7.38 (m, 4H), 7.23 (m, 4H), 2.04 (s, 3H), 1.84 (d, 2H, *J* = 2 Hz), 1.17 (d, 2H, *J* = 2 Hz); ¹³C NMR (CDCl₃-d₁), δ 145.3, 144.8, 135.6, 134.7, 133.7, 133.2, 129.6, 128.9, 128.8, 127.4, 127.3, 126.8, 69.5, 21.8, 10.6; MS: *m/z* 468 (M⁺, 0.71), 428 (5), 154 (27), 152 (100), 111 (29), 75 (12); IR: 3449, 3088, 3063, 2990, 2931, 2869, 1734, 1590, 1572, 1496, 1469, 1422, 1368, 1256, 1202, 1148, 1120, 1091, 1049, 1006, 978, 940, 893, 875, 845, 785, 753, 728, 699, 681 cm⁻¹; HRMS (ESI). Calcd for C₂₄H₁₉Cl₃N₄, [M+H]⁺: *m/z* 469.0748. Found: *m/z* 469.0751.

Scheme 1

Figure 3 View of the molecular structure of **7f** (CCDC, 2005).

4-[(Aziridin-1-yl)diphenylmethyl]-5-methyl-1-(4-chlorophenyl)-1H-1,2,3-triazole (7c) White needles; yield 90%; mp 92–94°C; ^1H NMR: δ 7.50 (m, 6H), 7.50 (m, 2H), 7.26 (m, 6H), 2.08 (s, 3H), 1.80 (s, 2H), 1.19 (d, 2H, $J=2$ Hz); ^{13}C NMR ($\text{CDCl}_3\text{-d}_1$), δ 146.6, 143.3, 135.3, 134.9, 132.8, 129.5, 129.2, 127.4, 126.8, 126.7, 69.9, 21.7, 10.5; MS: m/z 400 (M^+ , 1.2), 358 (11), 178 (5), 154 (32), 152 (100), 11 (26), 77 (8), 75 (11), 51 (5), 43 (7); IR: 3459, 3088, 3059, 2987, 2928, 1738, 1594, 1495, 1445, 1422, 1402, 1371, 1262, 1235, 1202, 1177, 1120, 1090, 1042, 1004, 938, 902, 848, 821, 765, 744, 700, 639 cm^{-1} . HRMS (ESI). Calcd for $\text{C}_{24}\text{H}_{21}\text{ClN}_4$, $[\text{M}+\text{H}]^+$: m/z 401.1528. Found: m/z 401.1532.

4-[(Aziridin-1-yl)-bis(4-chlorophenyl)methyl]-5-methyl-1-*p*-tolyl-1H-1,2,3-triazole (7d) White flakes; yield 89%; mp 86–88°C; ^1H NMR: δ 7.48 (m, 4H), 7.28 (m, 8H), 2.43 (s, 3H), 2.00 (s, 3H), 1.80 (d, 2H, $J=2$ Hz), 1.15 (d, 2H, $J=2$ Hz); ^{13}C NMR ($\text{CDCl}_3\text{-d}_1$), δ 144.8, 142.1, 139.6, 133.7, 133.1, 132.8, 130.3, 129.9, 127.8, 125.4, 69.2, 21.7, 21.1, 10.5; MS: m/z 448 (M^+ , 0.52), 406 (8), 152 (22), 133 (11), 132 (100), 125 (7), 111 (12), 97 (8), 91 (11), 83 (12), 74 (11), 55 (15); IR: 3429, 3060, 2987, 2923, 2856, 1517, 1486, 1443, 1421, 1400, 1264, 1205, 1180, 1094, 1011, 923, 867, 819, 559 cm^{-1} . HRMS (ESI). Calcd for $\text{C}_{25}\text{H}_{22}\text{Cl}_2\text{N}_4$, $[\text{M}+\text{H}]^+$: m/z 449.1294. Found: m/z 449.1299.

4-[(Aziridin-1-yl)-bis(3-chlorophenyl)methyl]-5-methyl-1-*p*-tolyl-1H-1,2,3-triazole (7e) White needles; yield 82%; mp 103–105°C; ^1H NMR: δ 7.65 (s, 2H), 7.42 (m, 2H), 7.30 (s, 4H), 7.22 (m, 4H), 2.42 (s, 3H), 1.95 (s, 3H), 1.85 (d, 2H, $J=2$ Hz), 1.18 (d, 2H, $J=2$ Hz); ^{13}C NMR ($\text{CDCl}_3\text{-d}_1$), δ 145.8, 143.8, 139.7, 133.8, 133.7, 133.3, 129.9, 128.9, 128.7, 127.3, 127.2, 125.4, 69.4, 21.8, 21.2, 10.6; MS: m/z 448 (M^+ , 0.54), 406 (5), 133 (10), 132 (100), 91 (30), 65 (13); IR: 3449, 3062, 2990, 2923, 2865, 1735, 1590, 1571, 1515, 1469, 1420, 1368, 1256, 1235, 1203, 1179, 1147, 1121, 1102, 1078, 1048, 1010, 939, 883, 826, 785, 754, 729, 698, 682 cm^{-1} ; HRMS (ESI). Calcd for $\text{C}_{25}\text{H}_{22}\text{Cl}_2\text{N}_4$, $[\text{M}+\text{H}]^+$: m/z 449.1294. Found: m/z 449.1301.

4-[(Aziridin-1-yl)-diphenylmethyl]-5-methyl-1-*p*-tolyl-1H-1,2,3-triazole (7f) White needles; yield 91%; mp 151–152°C; ^1H NMR: δ 7.57 (m, 4H), 7.37 (m, 10H), 2.42 (s, 3H), 1.98 (s, 3H), 1.82 (d, 2H, $J=2$ Hz), 1.22 (d, 2H, $J=2$ Hz); ^{13}C NMR ($\text{CDCl}_3\text{-d}_1$), δ 145.7, 143.8, 139.4, 133.9, 132.9, 129.8, 129.1, 127.4, 126.8, 125.5, 69.9, 21.8, 21.2, 10.5; MS: m/z 380 (M^+ , 1.0), 33 (13), 178 (6), 133 (10), 132 (100), 91 (34), 77 (6), 65 (14); IR: 3430, 3055, 3021, 2983, 2926, 2864, 1594, 1516, 1488, 1444, 1420, 1387, 1259, 1208, 1181, 1120, 1104, 1031, 1006, 987, 935, 898, 859, 838, 818, 798, 767, 748, 700, 662, 640, 553, 529 cm^{-1} . HRMS (ESI). Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_4$, $[\text{M}+\text{H}]^+$: m/z 381.2074. Found: m/z 381.2079.

4-[(Aziridin-1-yl)-bis(4-chlorophenyl)methyl]-5-methyl-1-phenyl-1H-1,2,3-triazole (7g) White flakes; yield 90%; mp 83–85°C; ^1H NMR: δ 7.52 (m, 5H), 7.47 (m, 2H), 7.42 (m, 2H), 7.29 (m, 2H), 7.26 (s, 2H), 2.05 (s, 3H), 1.82 (d, 2H, $J=3$ Hz), 1.16 (d, 2H, $J=3$ Hz); ^{13}C NMR ($\text{CDCl}_3\text{-d}_1$), δ 145.1, 141.9, 136.2, 133.0, 132.9, 130.4, 129.5, 129.4, 127.8, 125.6, 69.3, 21.7, 10.6; MS: m/z 434 (M^+ , 0.7), 394 (5), 392 (9), 332 (11), 129 (11), 119 (11), 118 (100), 104 (10), 91 (13), 77 (21), 57 (11); IR: 3429, 3060, 2987, 2955, 2924, 2854, 1595, 1485, 1416, 1398, 1264, 1113, 1092, 1072, 1011, 921, 867, 817, 763, 694, 565, 531 cm^{-1} . HRMS (ESI). Calcd for $\text{C}_{24}\text{H}_{20}\text{Cl}_2\text{N}_4$, $[\text{M}+\text{H}]^+$: m/z 435.1138. Found: m/z 435.1144.

4-[(Aziridin-1-yl)-bis(3-chlorophenyl)methyl]-5-methyl-1-phenyl-1H-1,2,3-triazole (7h) White flakes; yield 40%; mp 141–143°C; ^1H NMR: δ 7.65 (s, 2H), 7.52 (m, 3H), 7.40 (m, 4H), 7.23 (m, 4H), 1.99 (s, 3H), 1.85 (t, 2H, $J=2$ Hz), 1.19 (t, 2H, $J=2$ Hz); ^{13}C NMR ($\text{CDCl}_3\text{-d}_1$), δ 145.7, 144.1, 136.2, 133.8, 133.3, 129.5, 129.4, 128.9, 128.7, 127.3, 127.2, 125.6, 69.4, 21.8, 10.5; MS: m/z 434 (M^+ , 0.3), 176 (5), 118 (100), 77 (69), 51 (16); IR: 3429, 3058, 2985, 2926, 2844, 1592, 1571, 1501, 1471, 1265, 1119, 1144, 1120, 1100, 1015, 976, 940, 893, 813, 784, 761, 747, 713, 695 cm^{-1} . HRMS (ESI). Calcd for $\text{C}_{24}\text{H}_{20}\text{Cl}_2\text{N}_4$, $[\text{M}+\text{H}]^+$: m/z 435.1138. Found: m/z 435.1145.

4-[(Aziridin-1-yl)-diphenylmethyl]-5-methyl-1-phenyl-1H-1,2,3-triazole (7i) White needles; yield 89%; mp 203–206°C; ^1H NMR: δ 7.56 (m, 4H), 7.51 (m, 3H), 7.43 (m, 2H), 7.26 (m, 6H), 2.03 (s, 3H), 1.81 (s, 2H), 1.21 (s, 2H); ^{13}C NMR ($\text{CDCl}_3\text{-d}_1$), δ 145.9, 143.6, 136.4, 132.9, 129.3, 129.1, 127.4, 126.8, 125.6, 69.9, 21.7, 10.5; MS: m/z 366 (M^+ , 0.4), 324 (8), 178 (5), 119 (8), 118 (100), 77 (46); IR: 3424, 3070, 3051, 3022, 2988, 2925, 2890, 1594, 1496, 1444, 1416, 1387, 1261, 1207, 1077, 1033, 993, 937, 903, 854, 767, 747, 697, 646, 561 cm^{-1} . HRMS (ESI). Calcd for $\text{C}_{24}\text{H}_{22}\text{N}_4$, $[\text{M}+\text{H}]^+$: m/z 367.1917. Found: m/z 367.1924.

Biological evaluation

The effects of the synthesized compounds on cell viability were investigated under previously reported conditions with human leukemia cells and human hepatoma G2 cells [20, 21] using the MTT assay.

Acknowledgments: The authors wish to acknowledge the funding support by the Education Department of Gansu Province (grant 2016B-124) and by the Lanzhou University of Arts and Science (grant 2015GSP05).

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