Research Article

Synthesis and Anticancer Activity of 1-(1*H*-Indol-3-yl)-2-(4-diarylmethylpiperazine-1-yl)ethane-1,2-dione Derivatives

Jun-Rong Jiang, Feng Xu, and Han-Gui Wu

Chemical Pharmaceutical Research Institute, Taizhou Vocational & Technical College, Zhejiang, Taizhou 318000, China

Correspondence should be addressed to Jun-Rong Jiang; jjrqikan@qq.com and Han-Gui Wu; taizhihaiyangkeji@126.com

Received 12 April 2016; Revised 9 May 2016; Accepted 26 May 2016

Academic Editor: Xinyong Liu

Copyright © 2016 Jun-Rong Jiang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Several new 1-(4-diarylmethylpiperazine-1-yl)-2-(1*H*-indol-3-yl)ethane-1,2-dione derivatives were synthesized by acylation of 1-diarylmethylpiperazine with 2-(1*H*-indol-3-yl)-2-oxoacetyl chloride. Their structures were confirmed by ¹H NMR, IR, mass spectra, and elemental analysis. These compounds were further evaluated for their anticancer activity, and most of them were found to have moderate-to-potent antiproliferative activities against Hela, A-549, and ECA-109 cancer cell lines *in vitro*.

1. Introduction

Compounds containing the 1-(1*H*-indol-3-yl)ethane-1,2-dione have antiviral [1], antimicrobial [2], and anticancer [3] activities. For example, compound **1**, named BMS-378806, has been found to have good HIV-1 attachment inhibitory activity in preventing entry to the host cell by binding to the viral envelope gp120 [1]; compound **2**, an indolylglyoxamide derivative, has good antibacterial activity against Gram-positive pathogens [2]; compound **3** exhibited good ATP-β binding cassette (ABC) transporter modulatory activity and can be used as a potential anticancer agent [3].

Until now, the N⁴-substituent of the piperazine ring of the above-reported compounds contains only an aryl group (Figure 1) [4–6], and there have been few reports on diaryl-substituted compounds. Herein, we adopted a skeleton splicing method to design a new class of compounds, 1-(1*H*-indol-3-yl)-2-(4-diarylmethylpiperazine-1-yl)ethane-1,2-dione derivatives, which not only contain the skeleton of 1-(piperazine-1-yl)-2-(1*H*-indol-3-yl)ethane-1,2-dione (from compounds **1** and **2**) but also contain the skeleton of a diaryl methyl group (from compound **3**).

2. Results and Discussion

The reactions for synthesis of 1-(1*H*-indol-3-yl)-2-(4-diarylmethylpiperazine-1-yl)ethane-1,2-dione derivatives (**19–30**)

are summarised in Scheme 1. Compounds **4–6** were prepared from indole and oxalyl chloride in anhydrous ether at 0~5°C under the protection of nitrogen [7]. Compounds **7–10** were obtained from diaryl ketones in the presence of sodium borohydride in methanol at reflux [8]. A following chlorination of **7–10** with a stoichiometric amount of thionyl chloride in dichloromethane at room temperature afforded **11–14** [9]. Compounds **11–14** were then treated with piperazine in DMF at 80°C to yield **15–18** [9], acylation of which with **1** in the presence of triethylamine in dry THF, and then gave compounds **19–30** [10].

In the infrared (IR) spectra of **19–30**, the most characteristic absorptions are at 3154–3225 cm⁻¹ (NH) and 1612–1652 cm⁻¹ ((C=O)₂ broad peaks). In the ¹H NMR spectra, for compounds **19–30**, characteristic signals due to the (NH) protons appeared at 12.22–12.46 ppm, and signals due to the (CH) protons attached to the diaryl moiety appeared at 4.37–4.43 ppm.

Compounds **19–30** were tested *in vitro* for anticancer activity by MTT assays against cervix uterus cancer cell Hela, human lung adenocarcinoma cell A-549, and human esophageal carcinoma cancer cell ECA-109. Cisplatin (DDP) was employed as a positive control in the assay. The results are presented in Table 1.

According to Table 1, most of the title compounds **19–30** exhibited moderate-to-potent antiproliferative activities against Hela, A-549, and ECA-109 cancer cell lines *in vitro*.

FIGURE 1: Some reported 1-(1*H*-indol-3-yl)ethane-1,2-dione derivatives.

19	20	21	22	23	24	25	26	27	28	29	30
R^1 : H	H	H	H	Br	Br	Br	Br	H	H	H	H
R^2 : H	H	H	H	H	H	H	H	CH ₃	CH ₃	CH ₃	CH ₃
R^3 : H	Cl	F	Br	H	Cl	F	Br	H	Cl	F	Br

Reagents and conditions

(i) Anhydrous ether, N₂, 0~5°C(ii) NaBH₄, MeOH, 0 ~ rt(iii) SOCl₂, CH₂Cl₂, rt

(iv) Piperazine, DMF

(v) Compound 1, THF, Et₃N, 0 ~ rt

SCHEME 1: Synthesis of the compounds (19–30).

TABLE 1: Antiproliferative activities (IC_{50}) of compounds **19–30** against human cancer cell lines.

Compd.	Cell lines (IC_{50} , μM) ^a		
	Hela	A-549	ECA-109
19	6.75 $\pm$ 0.40	11.29 $\pm$ 1.60	16.65 $\pm$ 1.98
20	4.06 $\pm$ 0.06	14.74 $\pm$ 2.68	8.23 $\pm$ 1.46
21	7.22 $\pm$ 1.72	16.72 $\pm$ 1.56	9.51 $\pm$ 1.22
22	11.58 $\pm$ 1.05	12.92 $\pm$ 1.17	12.26 $\pm$ 0.99
23	4.78 $\pm$ 0.67	13.34 $\pm$ 2.05	2.13 $\pm$ 0.35
24	15.03 $\pm$ 2.01	33.28 $\pm$ 4.35	8.74 $\pm$ 1.22
25	8.99 $\pm$ 1.21	20.00 $\pm$ 2.05	8.19 $\pm$ 0.75
26	5.21 $\pm$ 0.70	70.89 $\pm$ 5.33	2.60 $\pm$ 0.36
27	93.17 $\pm$ 5.00	97.42 $\pm$ 9.21	12.80 $\pm$ 1.98
28	>212	74.56 $\pm$ 8.73	153.35 $\pm$ 14.36
29	61.12 $\pm$ 6.85	28.19 $\pm$ 2.26	162.90 $\pm$ 11.78
30	>194	>194	>194
DDP	17.50 $\pm$ 0.83	30.89 $\pm$ 1.44	12.73 $\pm$ 0.70

^aValues presented are means of three experiments.

It was noteworthy that the antiproliferative effects of compounds **19–30** were more pronounced against *Hela* and *ECA-109* cells compared with A-549 cancer cells; some of them displayed higher activities (e.g., **19–26** with IC_{50} 4.06–15.03 μM for *Hela* and **20–26** with IC_{50} 2.13–12.26 μM for *ECA-109*) in comparison with cisplatin (IC_{50} 17.50 μM for *Hela* and 12.73 μM for *ECA-109*). When the different substituents R_2 were introduced to the title compounds, the antiproliferative activities varied greatly. Compounds **27–30** were less effective than **19–26** on all cell lines and this result may be caused by the introduction of the CH_3 group of R_2 , which might lead to **27–30** having a different conformation by comparison with **19–26**. Compounds **20** and **23** showed the most effective activity on *Hela* and *ECA-109* and were 4-fold and 6-fold more active than DDP, respectively, which deserves further research.

3. Experimental

Melting points were carried out on a XRC-1 apparatus and are uncorrected (Beijing Technical Instrument Co.). Infrared spectra were recorded, from KBr discs of solid materials, on a Nicolex FI-IR-170 instrument. The 1H NMR spectra were run on a Bruker AC500 (500 MHz). Compounds were dissolved in d_6 -DMSO, and chemical shifts were referenced to TMS. Mass spectra were obtained on a Agilent 1260 Ion Trap LC/MS 500 analysis system. Elemental analyses were performed on a Thermo-Finnigan Flash EA 1112 instrument. TCL was carried out on silica gel UV-254 plates.

3.1. Synthesis of Compounds (15–18). Compounds **15–18** were synthesized from **7–10** via **11–14** according to literature methods [9], respectively. Compounds **7–10** were obtained from diaryl ketones in the presence of sodium borohydride in methanol at reflux [8]. Compounds, **11** [11], **12** [8], **13** [12], **14** [13], **15** [11], **16** [8], and **17** [12], were reported in literatures.

But the characterized data of compound **18** had not been reported.

1-[(4-Bromophenyl)(phenyl)methyl]piperazine (18). 1H NMR ($CDCl_3$, 400 MHz): δ 7.80 (t, 2H, J = 4.2 Hz, Ar), 7.56–7.66 (m, 5H, Ar), 7.47 (t, 2H, J = 7.6 Hz, Ar), 3.70 (m, 1H, CH), 2.94 (brs, 4H, NCH_2), 2.88 (brs, 4H, NCH_2).

3.2. Synthesis of Compounds (19–30): General Procedure. Triethylamine was added to the mixture of 1-diarylmethylpiperazine compounds **15–18** (9.5 mmol) and compounds **4–6** (10 mmol) in THF (50 mL) with acyl chloride (10 mmol) at 0°C; the mixture was kept under magnetic stirring for 30 min and then was warmed up to room temperature for 10–20 h at which time the progress of the reaction was monitored by thin-layer chromatography (ethyl acetate : alcohol = 9 : 1). The reaction mixture was then concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: 2% EtOH in EtOAc) to obtain title compounds **19–30**.

1-(4-Benzhydrylpiperazine-1-yl)-2-(1H-indol-3-yl)ethane-1,2-dione (19). A light gray solid (55%, mp 225–227°C). IR 3157, 3081, 3062, 2984, 1652, 1519, 1436, 1241, 957, 775 cm^{-1} ; 1H NMR (d_6 -DMSO, 500 MHz): δ 12.30 (s, 1H, NH), 8.13 (s, 1H, CH), 8.08 (d, 1H, J = 7.6 Hz, Ar), 7.53 (d, 1H, J = 7.8 Hz, Ar), 7.42 (d, 4H, J = 7.8 Hz, Ar), 7.17–7.31 (m, 8H, Ar), 4.37 (s, 1H, CH), 3.66 (t, 2H, J = 4.6 Hz, NCH_2), 3.37 (t, 2H, J = 4.6 Hz, NCH_2), 2.43 (t, 2H, J = 4.6 Hz, NCH_2), 2.27 (t, 2H, J = 4.6 Hz, NCH_2); ESI-MS, m/z (%): 424.4 [(M+H)⁺, 100]; Anal. calcd for $C_{27}H_{25}N_3O_2$: C, 76.57; H, 5.95; N, 9.92; O, 7.56; Found: C, 76.55; H, 5.94; N, 9.93; O, 7.57.

1-(4-((4-Chlorophenyl)(phenyl)methyl)piperazine-1-yl)-2-(1H-indol-3-yl)ethane-1,2-dione (20). A white solid (60%, mp 241–243°C); IR 3156, 3099, 3063, 2983, 1617, 1523, 1463, 1242, 1001, 806 cm^{-1} ; 1H NMR (d_6 -DMSO, 500 MHz): δ 12.29 (s, 1H, NH), 8.13 (s, 1H, CH), 8.08 (d, 1H, J = 7.7 Hz, Ar), 7.53 (d, 1H, J = 7.8 Hz, Ar), 7.17–7.45 (m, 11H, Ar), 4.43 (s, 1H, CH), 3.46 (t, 2H, J = 4.6 Hz, NCH_2), 3.37 (t, 2H, J = 4.6 Hz, NCH_2), 2.42 (t, 2H, J = 4.6 Hz, NCH_2), 2.26 (t, 2H, J = 4.6 Hz, NCH_2); ESI-MS, m/z (%): 460.4 [(M+2)⁺, 50], 458.4 [(M+H)⁺, 100]; Anal. calcd for $C_{27}H_{24}ClN_3O_2$: C, 70.81; H, 5.28; N, 9.18; O, 6.99 Found: C, 70.80; H, 5.28; N, 9.17; O, 7.00.

1-(4-((4-Fluorophenyl)(phenyl)methyl)piperazine-1-yl)-2-(1H-indol-3-yl)ethane-1,2-dione (21). A white solid (59%, mp 246–248°C); IR 3159, 3099, 3063, 2982, 1610, 1506, 1446, 1244, 999, 800 cm^{-1} ; 1H NMR (d_6 -DMSO, 500 MHz): δ 12.28 (s, 1H, NH), 8.13 (s, 1H, CH), 8.08 (d, 1H, J = 7.5 Hz, Ar), 7.53 (d, 1H, J = 7.9 Hz, Ar), 7.10–7.46 (m, 11H, Ar), 4.42 (s, 1H, CH), 3.65 (s, 2H, NCH_2), 3.37 (s, 2H, NCH_2), 2.42 (s, 2H, NCH_2), 2.26 (s, 2H, NCH_2); ESI-MS, m/z (%): 442.4 [(M+H)⁺, 100]; Anal. calcd for $C_{27}H_{24}FN_3O_2$: C, 73.45; H, 5.48; N, 9.52; O, 7.25; Found: C, 73.48; H, 5.47; N, 9.53; O, 7.24.

1-(4-((4-Bromophenyl)(phenyl)methyl)piperazine-1-yl)-2-(1H-indol-3-yl)ethane-1,2-dione (22). A pale white solid (62%, mp 227–229°C); IR 3225, 3060, 2980, 1617, 1491, 1444, 1244, 997,

775 cm⁻¹; ¹H NMR (d₆-DMSO, 500 MHz): δ 12.28 (s, 1H, NH), 8.13 (s, 1H, CH), 8.10 (d, 1H, *J* = 7.7 Hz, Ar), 7.53 (d, 1H, *J* = 7.8 Hz, Ar), 7.17–7.50 (m, 11H, Ar), 4.41 (s, 1H, CH), 3.66 (s, 2H, NCH₂), 3.36 (t, 2H, *J* = 4.5 Hz, NCH₂), 2.43 (t, 2H, *J* = 4.7 Hz, NCH₂), 2.26 (s, 2H, NCH₂); ESI-MS, *m/z*(%): 504.4 [(M+2)⁺, 100], 502.4 [(M+H)⁺, 100]; Anal. calcd for C₂₇H₂₄BrN₃O₂: C, 64.55; H, 4.81; N, 8.36; O, 6.37; Found: C, 64.53; H, 4.82; N, 8.35; O, 6.38.

1-(4-Benzhydrylpiperazine-1-yl)-2-(5-bromo-1H-indol-3-yl)ethane-1,2-dione (23). A pale white solid (53%, mp 238–240°C); IR 3154, 3083, 3061, 2970, 1617, 1477, 1438, 1232, 998, 807 cm⁻¹; ¹H NMR (d₆-DMSO, 500 MHz): δ 12.46 (s, 1H, NH), 8.19–8.21 (m, 2H, Ar+CH), 7.50 (d, 1H, *J* = 8.6 Hz, Ar), 7.18–7.43 (m, 11H, Ar), 4.38 (s, 1H, CH), 3.65 (s, 2H, NCH₂), 3.37 (t, 2H, *J* = 4.7 Hz, NCH₂), 2.43 (t, 2H, *J* = 4.7 Hz, NCH₂), 2.27 (s, 2H, NCH₂); ESI-MS, *m/z*(%): 504.4 [(M+2)⁺, 100], 502.4 [(M+H)⁺, 100]; Anal. calcd for C₂₇H₂₄BrN₃O₂: C, 64.55; H, 4.81; N, 8.36; O, 6.37; Found: C, 64.57; H, 4.80; N, 8.34; O, 6.38.

1-(5-Bromo-1H-indol-3-yl)-2-(4-((4-chlorophenyl)(phenyl)methyl)piperazine-1-yl)ethane-1,2-dione (24). A white solid (81%, mp 240–242°C); IR 3164, 3061, 3028, 2922, 1620, 1489, 1447, 1234, 954, 804 cm⁻¹; ¹H NMR (d₆-DMSO, 500 MHz): δ 12.46 (s, 1H, NH), 8.19–8.21 (m, 2H, Ar+CH), 7.50 (d, 1H, *J* = 8.6 Hz, Ar), 7.19–7.46 (m, 11H, Ar), 4.43 (s, 1H, CH), 3.65 (s, 2H, NCH₂), 3.37 (s, 2H, NCH₂), 2.42 (s, 2H, NCH₂), 2.26 (s, 2H, NCH₂); ESI-MS, *m/z*(%): 540.3 [(M+4)⁺, 30], 538.3 [(M+2)⁺, 100], 536.3 [(M+H)⁺, 70]; Anal. calcd for C₂₇H₂₃BrClN₃O₂: C, 60.41; H, 4.32; N, 7.83; O, 5.96; Found: C, 60.44; H, 4.31; N, 7.84; O, 5.95.

1-(5-Bromo-1H-indol-3-yl)-2-(4-((4-fluorophenyl)(phenyl)methyl)piperazine-1-yl)ethane-1,2-dione (25). A white solid (82%, mp 251–253°C); IR 3156, 3064, 3031, 2964, 1624, 1478, 1437, 1232, 999, 806 cm⁻¹; ¹H NMR (d₆-DMSO, 500 MHz): δ 12.46 (s, 1H), 8.20–8.21 (m, 2H, Ar+CH), 7.50 (d, 1H, *J* = 8.6 Hz, Ar), 7.11–7.47 (m, 11H, Ar), 4.42 (s, 1H, CH), 3.65 (s, 2H, NCH₂), 3.36 (s, 2H, NCH₂), 2.42 (s, 2H, NCH₂), 2.26 (s, 2H, NCH₂); ESI-MS, *m/z*(%): 522.4 [(M+2)⁺, 100], 520.4 [(M+H)⁺, 100]; Anal. calcd for C₂₇H₂₃BrFN₃O₂: C, 62.32; H, 4.45; N, 8.07; O, 6.15; Found: C, 62.33; H, 4.45; N, 8.08; O, 6.14.

1-(5-Bromo-1H-indol-3-yl)-2-(4-((4-bromophenyl)(phenyl)methyl)piperazine-1-yl)ethane-1,2-dione (26). A white solid (78%, mp 227–229°C); IR 3158, 3082, 3060, 2970, 1617, 1477, 1437, 1233, 998, 807 cm⁻¹; ¹H NMR (d₆-DMSO, 500 MHz): δ 12.46 (s, 1H, NH), 8.20–8.21 (m, 2H, Ar), 7.51 (d, 1H, *J* = 8.6 Hz, Ar), 7.18–7.49 (m, 11H, Ar), 4.41 (s, 1H, CH), 3.65 (s, 2H, NCH₂), 3.37 (t, 2H, *J* = 4.5 Hz, NCH₂), 2.42 (t, 2H, *J* = 4.6 Hz, NCH₂), 2.27 (s, 2H, NCH₂); ESI-MS, *m/z*(%): 584.2 [(M+4)⁺, 50], 582.3 [(M+2)⁺, 100], 580.3 [(M+H)⁺, 50]. Anal. calcd for C₂₇H₂₃Br₂N₃O₂: C, 55.79; H, 3.99; N, 7.23; O, 5.50; Found: C, 55.81; H, 4.00; N, 7.22; O, 5.51.

1-(4-Benzhydrylpiperazine-1-yl)-2-(2-methyl-1H-indol-3-yl)ethane-1,2-dione (27). A gray solid (78%, mp 199–201°C); IR 3180, 3103, 3058, 2974, 1610, 1492, 1457, 1246, 986, 790 cm⁻¹;

¹H NMR (d₆-DMSO, 500 MHz): δ 12.22 (s, 1H, NH), 7.88 (s, 1H, Ar), 7.15–7.44 (m, 13H, Ar), 4.38 (s, 1H, CH), 3.66 (s, 2H, NCH₂), 3.33 (s, 2H, NCH₂), 2.59 (s, 3H, CH₃), 2.41 (s, 2H, NCH₂), 2.22 (s, 2H, NCH₂); ESI-MS, *m/z*(%): 438.2 [(M+H)⁺, 100]; Anal. calcd for C₂₈H₂₇N₃O₂: C, 76.86; H, 6.22; N, 9.60; O, 7.31; Found: C, 76.89; H, 6.21; N, 9.62; O, 7.30.

1-(4-((4-Chlorophenyl)(phenyl)methyl)piperazine-1-yl)-2-(2-methyl-1H-indol-3-yl)ethane-1,2-dione (28). A gray solid (85%, mp 180–182°C); IR 3180, 3103, 3058, 2974, 1610, 1492, 1457, 1247, 986, 790 cm⁻¹; ¹H NMR (d₆-DMSO, 500 MHz): δ 12.22 (s, 1H, NH), 7.87 (s, 1H, Ar), 7.14–7.44 (m, 12H, Ar), 4.43 (s, 1H, CH), 3.66 (s, 2H, NCH₂), 3.33 (s, 2H, NCH₂), 2.59 (s, 3H, NCH₂), 2.42 (s, 2H, NCH₂), 2.24 (s, 2H, NCH₂); ESI-MS, *m/z*(%): 474.3 [(M+2)⁺, 40], 472.5 [(M+H)⁺, 100]; Anal. calcd for C₂₈H₂₆ClN₃O₂: C, 71.25; H, 5.55; N, 8.90; O, 6.78; Found: C, 71.26; H, 5.54; N, 8.89; O, 6.79.

1-(4-((4-Fluorophenyl)(phenyl)methyl)piperazine-1-yl)-2-(2-methyl-1H-indol-3-yl)ethane-1,2-dione (29). A gray solid (79%, mp >300°C); IR 3185, 3085, 3057, 2973, 1616, 1508, 1437, 1245, 986, 800 cm⁻¹; ¹H NMR (d₆-DMSO, 500 MHz): δ 12.22 (s, 1H, NH), 7.88 (s, 1H, Ar), 7.11–7.46 (m, 12H, Ar), 4.39 (s, 1H, CH), 3.66 (s, 2H, NCH₂), 3.33 (s, 2H, NCH₂), 2.59 (s, 3H, CH₃), 2.41 (s, 2H, NCH₂), 2.22 (s, 2H, NCH₂); ESI-MS, *m/z*(%): 456.5 [(M+2)⁺, 60], 457.4 [(M+2)⁺, 100]; Anal. calcd for C₂₈H₂₆FN₃O₂: C, 73.83; H, 5.75; N, 9.22; O, 7.02; Found: C, 73.81; H, 5.75; N, 9.21; O, 7.03.

1-(4-((4-Bromophenyl)(phenyl)methyl)piperazine-1-yl)-2-(2-methyl-1H-indol-3-yl)ethane-1,2-dione (30). A gray solid (79%, mp 181–183°C); IR 3182, 3085, 3057, 2970, 1612, 1491, 1453, 1246, 986, 789 cm⁻¹; ¹H NMR (d₆-DMSO, 500 MHz): δ 12.22 (s, 1H, NH), 7.87 (s, 1H, Ar), 7.15–7.49 (m, 12H, Ar), 4.39 (s, 1H, CH), 3.66 (s, 2H, NCH₂), 3.38 (s, 2H, NCH₂), 2.58 (s, 3H, CH₃), 2.42 (s, 2H, NCH₂), 2.24 (s, 2H, NCH₂); ESI-MS, *m/z*(%): 518.4 [(M+2)⁺, 50], 516.4 [(M+H)⁺, 100]; Anal. calcd for C₂₈H₂₆BrN₃O₂: C, 65.12; H, 5.07; N, 8.14; O, 6.20; Found: C, 65.15; H, 5.06; N, 8.15; O, 6.19.

3.3. Treatment of Tumor Cell Lines. The antiproliferative activity of compounds **19–30** against several human cancer cell lines was assayed by standard MTT assay procedures. Cells were cultured in DMEM medium at 37°C with 5% CO₂ and 95% air, supplemented with 10% (V/V) bovine calf serum [14]. Cells were plated in 96-well plates at the density of 10,000 cells per well. After 24 h, the cells were treated with various concentrations of compounds from 1.0 to 100.0 μg/mL. Wells containing culture medium without cells were used as blanks and cisplatin was assayed at the same time as a positive control. The cells were further incubated for 72 h. The cytotoxicity was measured by adding 5 mg/mL of MTT to each well and incubated for another 4 h. The formazan crystals were dissolved by adding 150 μL of DMSO to each well. The optical density of each well was then measured on a microplate spectrophotometer at a wavelength of 570 nm. The IC₅₀ value (μg/mL) was determined from plots of % viability against dose of compound added.

The calculation formula of IC_{50} values has been revised as follows:

$$IC_{50} = \lg^{-1} [Xm - i(\Sigma P - 0.5)], \quad (1)$$

where Xm is the log value of the designed maximum concentration, i is the log value of dilution ratio, and ΣP is the sum of growth inhibition rate of each group:

$$I(\%) = 100\% \left(1 - \frac{E}{C}\right), \quad (2)$$

where $I(\%)$ is the growth inhibition rate, E are the mean OD values for experimental groups, and C are the mean OD values for control groups.

4. Conclusion

A series of indoleoxoacetic piperazine derivatives **19**~**30** were synthesized and characterized. The *in vitro* antitumor activities of these compounds against Hela, A-549, and ECA-109 cells were evaluated. The effects of compounds **19**~**26** are all superior to DDP against all tested cancer cell lines, and compounds **20**, **19**, and **23** showed the best antiproliferative effect on Hela, A-549, and ECA-109 cells, respectively. These results encourage us to synthesize additional new indoleoxoacetic piperazine derivatives with the expected more potent antitumor activity.

Competing Interests

The authors have declared that there are no competing interests regarding the publication of this paper.

Acknowledgments

The authors are indebted to the Program of Marine Biological Resources Exploitation and Utilization of Science and Technology Innovation Team of Taizhou (Document of CPC Taizhou Municipal Committee Office of Zhejiang Province no. (2012) 58), Biopharmaceutical R & D Center, Taizhou Vocational & Technical College.

References

- [1] K.-S. Yeung, Z. Qiu, Z. Yang et al., "Inhibitors of HIV-1 attachment—part 9: an assessment of oral prodrug approaches to improve the plasma exposure of a tetrazole-containing derivative," *Bioorganic and Medicinal Chemistry Letters*, vol. 23, no. 1, pp. 209–212, 2013.
- [2] M. Takhi, G. Singh, C. Murugan et al., "Novel and potent oxazolidinone antibacterials featuring 3-indolylglyoxamide substituents," *Bioorganic & Medicinal Chemistry Letters*, vol. 18, no. 18, pp. 5150–5155, 2008.
- [3] H. R. Sara and A. Hazlewood, "Modulators of ATP-binding cassette transporters," WO Patent 2007044560, 2007.
- [4] D. K. Leahy and S. K. Pack, "Preparation of phosphonoxy-methyl prodrugs of HIV-1 attachment inhibitors," *Organic Process Research and Development*, vol. 17, no. 11, pp. 1440–1444, 2013.
- [5] T. Wang, Z. Yin, Z. Zhang et al., "Inhibitors of human immunodeficiency virus type 1 (HIV-1) attachment. 5. An evolution from indole to azaindoles leading to the discovery of 1-(4-benzoylpiperazin-1-yl)-2-(4,7-dimethoxy-1H-pyrrolo[2,3-c]pyridin-3-yl)ethane-1,2-dione (BMS-488043), a drug candidate that demonstrates antiviral activity in HIV-1-infected subjects," *Journal of Medicinal Chemistry*, vol. 52, no. 23, pp. 7778–7787, 2009.
- [6] J. Wang, N. Le, A. Heredia, H. Song, R. Redfield, and L.-X. Wang, "Modification and structure-activity relationship of a small molecule HIV-1 inhibitor targeting the viral envelope glycoprotein gp120," *Organic and Biomolecular Chemistry*, vol. 3, no. 9, pp. 1781–1786, 2005.
- [7] C. Aubry, A. J. Wilson, D. Emmerson et al., "Fascaplysin-inspired diindolyls as selective inhibitors of CDK4/cyclin D1," *Bioorganic & Medicinal Chemistry*, vol. 17, no. 16, pp. 6073–6084, 2009.
- [8] A. V. Narsaiah and P. Narsimha, "Efficient synthesis of anti-histamines clocinazine and chlorcyclizine," *Medicinal Chemistry Research*, vol. 21, no. 4, pp. 538–541, 2012.
- [9] P. Srivastava, S. S. Razi, R. Ali et al., "Selective naked-eye detection of Hg^{2+} through an efficient turn-on photoinduced electron transfer fluorescent probe and its real applications," *Analytical Chemistry*, vol. 86, no. 17, pp. 8693–8699, 2014.
- [10] G. Spadoni, A. Bedini, S. Bartolucci et al., "Towards the development of 5-HT7 ligands combining serotonin-like and arylpiperazine moieties," *European Journal of Medicinal Chemistry*, vol. 80, no. 2, pp. 8–35, 2014.
- [11] P. Srivastava, R. Ali, S. S. Razi, M. Shahid, S. Patnaik, and A. Misra, "A simple blue fluorescent probe to detect Hg^{2+} in semi-aqueous environment by intramolecular charge transfer mechanism," *Tetrahedron Letters*, vol. 54, no. 28, pp. 3688–3693, 2013.
- [12] O. Makoto, H. Koichi, N. Takahiro et al., "Heterocyclic ring compound and H1 receptor antagonist," WO Patent 2011148888, 2011.
- [13] G. A. Holloway, J. P. Parisot, P. M. Novello et al., "Discovery of novel and potent benzhydryl-tropane trypanocides highly selective for *Trypanosoma cruzi*," *Bioorganic & Medicinal Chemistry Letters*, vol. 20, no. 6, pp. 1816–1818, 2010.
- [14] M. Ohno and T. Abe, "Rapid colorimetric assay for the quantification of leukemia inhibitory factor (LIF) and interleukin-6 (IL-6)," *Journal of Immunological Methods*, vol. 145, no. 1-2, pp. 199–203, 1991.