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Synthesis and Antibacterial Activity of 1,5-Disubstituted Indolin-2-one Derivatives Containing Sulfonamides

QIU-XIAN LIANG[1], LING LIAO[2], JUAN LUO[3], SHUAI PU[3], YU-LIANG WANG[1,3,*] and TIAN CHEN[2,*]

[1]College of Life Science, Sichuan University, Chengdu 610064, P.R. China
[2]Department of Pathogenic Biology, School of Biomedical Science, Chengdu Medical College, Chengdu 610083, P.R. China
[3]Faculty of Chemistry, Sichuan University, Chengdu 610065, P.R. China

*Corresponding authors: Tel: +86 15378195811; E-mail: chemwang2008@163.com; tianchen66@gmail.com

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A series of novel 1,5-disubstituted indolin-2-one derivatives containing sulfonamides as potential antibacterial agent were synthesized and the antibacterial activity was preliminary evaluated against two Gram-positive bacteria *S. aureus* ATCC26112, *S. aureus* SC and Gram-negative bacteria *P. vulgaris in vitro*. The results indicated that most of the target compounds exhibited promising antibacterial potency. Compounds **7b**, **7d** and **8b** showed notable antimicrobial activity with corresponding inhibition zone (IZ = 19 mm, 21 mm and 23.5 mm, respectively) at the concentration of 100 µg/mL against *S. aureus* ATCC26112.

Keywords: 1,5-Disubstituted Indolin-2-one, Sulfonamides, Synthesis, Antibacterial.

INTRODUCTION

Heterocyclic systems carrying indolin-2-one moiety have drawn tremendous interest of researchers in the area of synthetic organic and medicinal chemistry, since they were widely existed in natural products (*e.g.*, rhyncophylline, horsfiline)[1,2] and synthetic pharmaceuticals which have various biological properties such as antiinflammatory[3], antitubercular[4], anti-bacterial[5], anti-HIV[6] and antitumor[7] *etc*.

During past decades, modifications mainly been made at the C-3 position of indolin-2-one and numerous compounds have been reported as drugs for treating various kinds of diseases[8-11]. Derivatives of 3-benzylidene indolin-2-one have been marketed owing to their excellent medicinal value, such as Sunitinib A (Fig. 1), Toceranib B (Fig. 1), Tenidap C (Fig. 1) *etc*.

Futhermore, indolin-2-one compounds with a sulfonamide group on the 5-position were found to be associated with diverse biological activities: SU1127412 (Fig. 2, D) and SU665613 (Fig. 2, E) which have been demonstrated as inhibitors of Met and Src kinase. Kiran *et al.*[14,15] reported that 2,3-dioxo-N-*p*-tolylindoline-5-sulfonamide F (Fig. 2) analogues showed antioxidant activity and anticonvulsant activity. Lee and co-workers[16,17] identified the highly potent 5-(2-phenoxy-methyl-pyrrolidine-1-sulfonyl) indolin-2-one derivatives G (Fig. 2) as an inhibitor of caspase 3, the group of Chu[18-20], Limpachayaporn[21,22] and other groups[23-25] have made a series of modifications based on the lead compound G to extend the structure-activity relationship study and improve the inhibit activity of caspase-3.

Herein, novel derivatives of indolin-2-one, twelve compounds **6a-6f**, **7a-7d**, **8a-8b** (Fig. 3), were designed and synthesized (**Scheme-I**) with a sulfonamide group on the 5-position. Various functional groups including electron-withdrawing, electron-donating, aralkyl and alkyl with different chain lengths were introduced into the target compounds to investigate their bioactivities. The antimicrobial activities of the target compounds against three bacterial strains were preliminary evaluated *in vitro*. Compounds **7b**, **7d** and **8b** showed significant antibacterial activity at the concentration of 100 and 50 µg/mL against *S. aureus* ATCC26112.

EXPERIMENTAL

All the reagents and solvents used in this study were acquired from commercial sources without further purification. Analytical thin layer chromatography was performed on silica gel GF254 and spots were visualized with ultraviolet (UV) light. Melting point was recorded on XRC-1 apparatus without corrected. The IR spectra were recorded on a Perkin-Elemer 16PC-FT spectrometer. Mass spectra (MS) were acquired with the Agilent 6210 (DOF-MAS) spectrometer (Agilent Inc., Santa Clara, CA, USA) using the electrospray ionisation (ESI) method. ^{1}H NMR spectra were recorded on a varian Unity Inova-400 spectrometer (Varian Inc., Palo Alto, CA, USA)

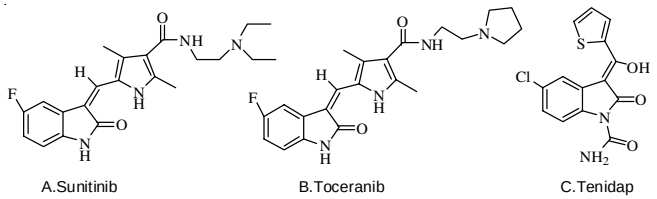


Fig. 1. Structure of 3-benzylidene indolin-2-one derivatives A-C

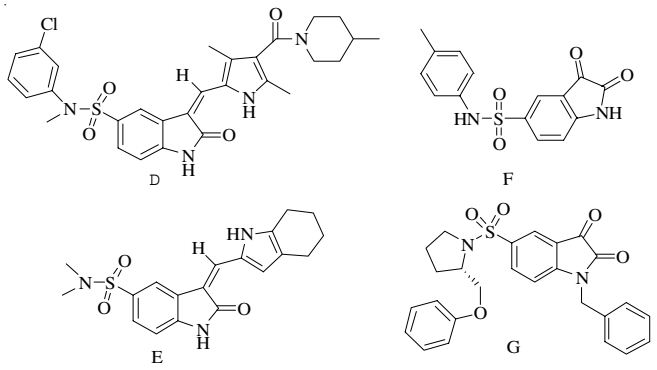


Fig. 2. Structure of 5-sulfonamide indolin-2-one derivatives D-G

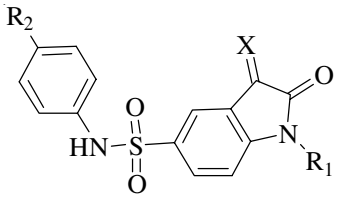


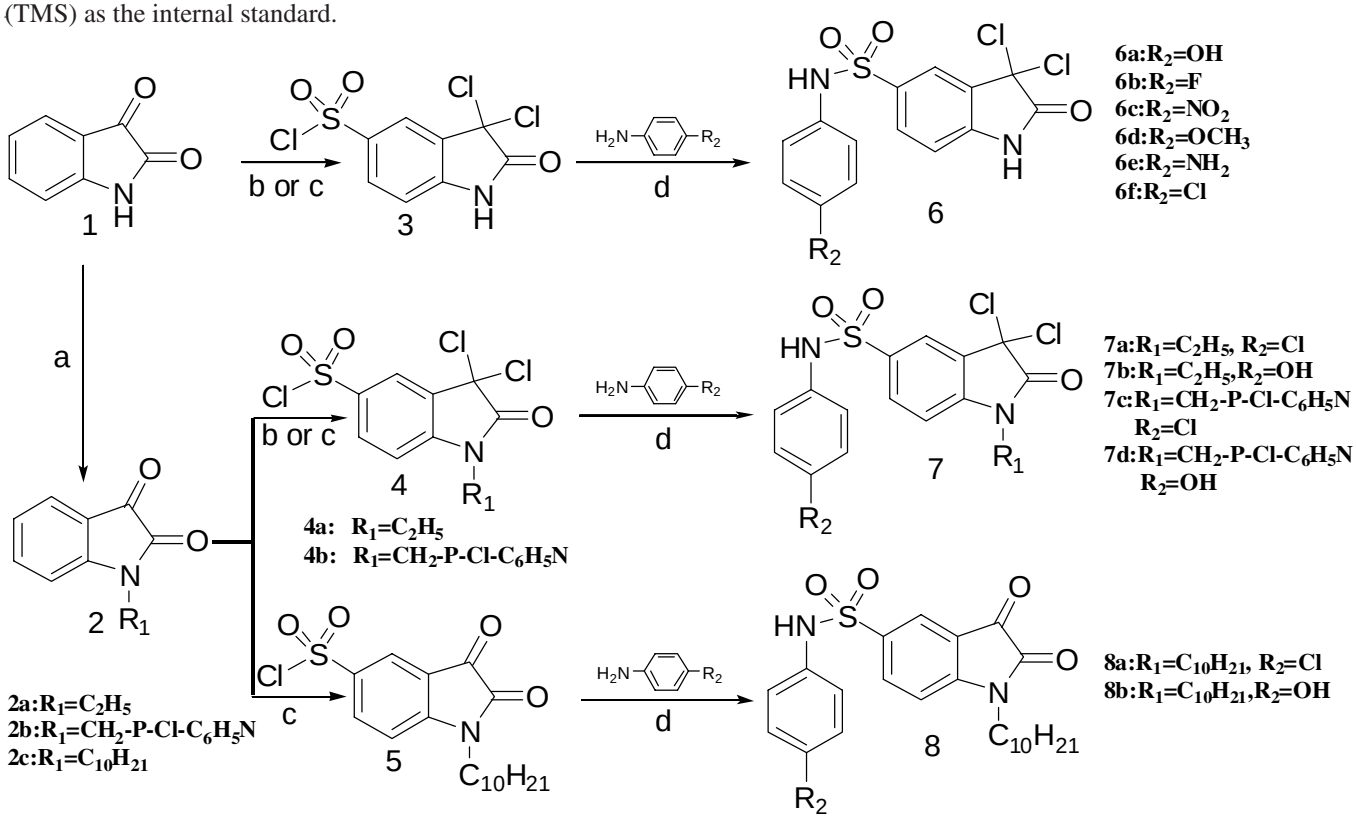
Fig. 3. Structure of target compounds

with d_6-DMSO, $CDCl_3$ or $(CD_3)_2CO$ as the solvent. Chemical shifts are given in δ values (ppm), using tetramethylsilane (TMS) as the internal standard.

Synthesis of 3,3-dichloro-2-oxoindoline-5-sulfonyl chloride (3): 1*H*-indole-2,3-dione (4.41 g, 30 mmol) was added in portions into chlorosulfonic acid (34.8 g, 300 mmol) below 5 °C. The reaction mixture was stirred for another 0.5 h at the same temperature and then the reaction temperature was slowly raised to 70 °C and maintained for 3 h. The mixture was cooled and poured into ice, standed still 0.5 h in the ice water, filtrated and the solid was washed with cold water, dried in vacuum oven to afford compound **3** (6.34 g, 70 %). White solid, m.p.: 165-166 °C. ^{1}H NMR (400 MHz, CD_3COCD_3, TMS): δ 8.39 (d, *J* = 2.0 Hz, 1H), 8.23 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 3.29 (s, 1H). IR (KBr, ν_{max}, cm^{-1}): 3363, 2963, 1767, 1615, 1475, 1359, 1296, 1167, 1124, 1067, 960, 838, 714, 595, 511. HR-MS (ESI): Calcd for $C_8H_4NO_3SCl_3$ [M-H]$^-$: 297.8899; found: 297.8897.

3,3-Dichloro-1-ethyl-2-oxoindoline-5-sulfonyl chloride (4a): Synthesize as compound **3**, Yellowish solid, yield: 78.5 %; m.p.: 136-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.30 (d, *J* = 1.9 Hz, 1H), 8.15 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 3.90 (q, *J* = 7.3 Hz, 2H), 1.38 (t, *J* = 7.3 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3480, 3085, 3043, 2986, 1750, 1606, 1479, 1380, 1334, 1230, 1170, 1113, 1058, 952, 842, 810, 707, 673, 606, 512. HR-MS (ESI): Calcd for $C_{10}H_8NO_3SCl_3$ [M-H]$^-$: 325.9212; found: 325.9210.

3,3-Dichloro-1-((6-chloropyridin-3-yl)methyl)-2-oxoindoline-5-sulfonyl chloride (4b): Synthesize as compound **3**, Yellowish solid, yield: 68.8 %; mp: 173-174 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.45 (d, *J* = 2.2 Hz, 1H), 8.32 (d, *J* = 1.9 Hz, 1H), 8.08 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.62 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 5.03 (s, 2H). IR (KBr, ν_{max}, cm^{-1}): 3481, 3059, 1752, 1612,



Scheme-1: Synthetic route of compound **6a-6f**, **7a-7d**, **8a-8b**; Reagents and conditions: a. R_1X, DMF, K_2CO_3, 80 °C, 4 h; b. $ClSO_2OH$, 70 °C, 3h; c. $ClSO_2OH$, CH_2Cl_2, reflux, 3h; d. 2.1eq.p-R_2-$C_6H_4NH_2$, THF, reflux, 3 h

1484, 1378, 1335, 1170, 1128, 1106, 1026, 953, 932, 837, 810, 599, 513. HR-MS (ESI): Calcd for $C_{14}H_8N_2O_3SCl_4$ [M-H]$^-$: 424.8903; found: 424.8905.

Synthesis of 1-decyl-2,3-dioxoindoline-5-sulfonyl chloride (5): 1-Decylindoline-2,3-dione (5.74 g, 20 mmol) was added in portions into chlorosulfonic acid (23.2 g, 200 mmol) in CH_2Cl_2 (20 mL) below 5 °C. The reaction mixture was stirred for another 0.5 h at the same temperature and then the reaction temperature was slowly raised to reflux and maintained for 3 h. After recycled the solvent, the mixture was cooled and poured into ice, standed still 0.5 h in the ice water, filtrated and the solid was washed with cold water, dried in vacuum oven to afford **5** (6.34 g, 86.6 %). Yellow solid, m.p.: 103-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 8.29 (dd, *J* = 8.4, 2.1 Hz, 1H), 8.27 (d, *J* = 1.8 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 3.83 (t, *J* = 7.6, 2H), 1.78-1.70 (m, 2H), 1.40-1.19 (m, 14H), 0.90 (t, *J* = 6.8 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3484, 3098, 2921, 2850, 1748, 1604, 1478, 1374, 1336, 1177, 1128, 1064, 842, 727, 635, 607, 534, 510. HR-MS (ESI): Calcd for $C_{18}H_{24}NO_4SCl$ [M + Na]$^+$: 408.1013; found: 408.1015.

Synthesis of 3,3-dichloro-N-(4-hydroxyphenyl)-2-oxoindoline-5-sulfonamide (6a): 4-Aminophenol (0.92 g, 8.40 mmol) was added to the solution of 3,3-dichloro-2-oxoindoline-5-sulfuryl chloride (1.20 g, 4 mmol) in THF (20 mL) at room temperature. The reaction mixture was heated to reflux and maintained for 3 h, then cooled to room temperature and evaporated under reduced pressure to remove the excess solvent, After acidification with 50 mL 10 % cold hydrochloric acid, the mixture was extracted with ethyl acetate. The organic layer was washed with 10 % hydrochloric acid, brine, dried and evaporated to give crude product. The crude product was chromatographed using petroleum ether and ethyl acetate as eluent to afford the target products **6a**, yellowish solid, yield: 73 %; m.p.: 195-196 °C. ^{1}H NMR (400 MHz, *d*$_6$-DMSO, TMS): δ = 11.78 (s, 1H), 9.71 (s, 1H), 9.35 (s, 1H), 7.79 (d, *J* = 1.6 Hz, 1H), 7.66 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H). IR (KBr, ν_{max}, cm^{-1}): 3375, 3193(w) , 1765, 1739, 1615, 1509, 1474, 1386, 1324, 1209, 1147, 1124, 1071, 962, 841, 714, 591, 523. HR-MS (ESI): Calcd for $C_{14}H_{10}N_2O_4SCl_2$ [M-H]$^-$: 370.9660; found: 370.9660.

3,3-Dichloro-N-(4-fluorophenyl)-2-oxoindoline-5-sulfonamide (6b): Synthesize as compound **6a**, yellowish solid, yield: 93 %; m.p.: 207-208 °C. ^{1}H NMR (400 MHz, CD_3COCD_3, TMS): δ = 10.50 (s, 1H), 8.98 (s, 1H), 7.90 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.25 -7.17 (m, 3H), 7.07 (t, *J* = 8.6 Hz, 2H). IR (KBr, ν_{max}, cm^{-1}): 3271, 1747 , 1614, 1504, 1471, 1391, 1345, 1144, 1127, 1074, 838, 723, 602, 504. HR-MS (ESI): Calcd for $C_{14}H_9N_2O_3SCl_2F$ [M-H]$^-$: 372.9617; found: 372.9615.

3,3-Dichloro-N-(4-nitrophenyl)-2-oxoindoline-5-sulfonamide (6c): Synthesize as compound **6a**, yellowish solid, yield: 30 %; m.p.: 201-202 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) : δ = 9.72 (s, 1H), 8.12-8.03 (m, 2H), 7.97 (d, *J* = 10.0 Hz, 1H), 7.87 (t, *J* = 7.7 Hz, 2H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H). IR (KBr, ν_{max}, cm^{-1}): 3369, 3266, 1764, 1603, 1531, 1481, 1388, 1340, 1265, 1147, 1070, 957, 914, 844, 631, 594. HR-MS (ESI): Calcd for $C_{14}H_9N_3O_5SCl_2$ [M-H]$^-$: 399.9562; found: 399.9564.

3,3-Dichloro-N-(4-methoxyphenyl))-2-oxoindoline-5-sulfonamide (6d): Synthesize as compound **6a**, yellowish solid, yield: 88 %; m.p.: 188-189 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) : δ = 9.17 (s, 1H), 7.87 (d, *J* = 1.1 Hz, 1H), 7.73 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.02 (m, 4H), 6.78 (d, *J* = 8.9 Hz, 2H), 3.74 (s, 3H). IR (KBr, ν_{max}, cm^{-1}): 3252, 1759, 1614, 1506, 1341, 1238, 1155, 836, 723, 521. HR-MS (ESI): Calcd for $C_{15}H_{12}N_2O_4SCl_2$ [M-H]$^-$: 384.9817; found: 384.9811.

N-(4-Aminophenyl)-3,3-dichloro-2-oxoindoline-5-sulfonamide (6e): Synthesize as compound **6a**, deep yellow solid, yield: 18 %; m.p.: > 260 °C. ^{1}H NMR (400 MHz, *d*$_6$-DMSO, TMS): δ = 11.81 (s, 1H), 9.74 (s, 1H), 7.82 (d, *J* = 1.7 Hz, 1H), 7.68 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.63 (s, 2H). IR (KBr, ν_{max}, cm^{-1}): 3431, 2928, 1748, 1618, 1509, 1468, 1403, 1150, 1118, 1079, 844, 617, 514. HR-MS (ESI): Calcd for $C_{14}H_{11}N_3O_3SCl_2$ [M-H]$^-$: 369.9820; found: 369.9816.

3,3-Dichloro-N-(4-chlorophenyl)-2-oxoindoline-5-sulfonamide (6f): Synthesize as compound **6a**, pale yellow solid, yield: 92 %; m.p.: 205-206 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.63 (s, 1H), 7.94 (s, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.25 (d, *J* = 9.0 Hz, 2H), 7.08-6.99 (m, 3H), 6.90 (s, 1H). IR (KBr, ν_{max}, cm^{-1}): 3219 , 1741, 1620, 1491, 1388, 1314, 1294, 1141, 1076, 949, 840, 711, 514. HR-MS (ESI): Calcd for $C_{14}H_9N_2O_3SCl_3$ [M-H]$^-$: 388.9321; found: 388.9328.

3,3-Dichloro-N-(4-chlorophenyl)-1-ethyl-2-oxoindoline-5-sulfonamide (7a): Synthesize as compound **6a**, yellowish solid, two step yield: 66 %; m.p.: 193-194 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.94 (d, *J* = 1.3 Hz, 1H), 7.77 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.27 (d, *J* = 1.4 Hz, 1H), 7.25 (s, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.50 (s, 1H), 3.80 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3310 , 1738, 1606, 1488, 1335, 1155, 1111,1064, 917, 831, 614, 590, 522. HR-MS (ESI): Calcd for $C_{16}H_{13}N_2O_3SCl_3$ [M-H]$^-$: 416.9634; found: 416.9634.

3,3-Dichloro-1-ethyl-N-(4-hydroxyphenyl)-2-oxoindoline-5-sulfonamide (7b): Synthesize as compound **6a**, yellowish solid, two step yield: 30 %; m.p.: 203-204 °C. ^{1}H NMR (400 MHz, *d*$_6$-DMSO, TMS): δ = 9.76 (s, 1H), 9.35 (s, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.74 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 3.79 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3514 , 3296, 1736, 1609, 1506, 1409, 1333, 1150, 1112, 1071, 841, 611, 520. HR-MS (ESI): Calcd for $C_{16}H_{14}N_2O_4SCl_2$ [M-H]$^-$: 398.9973, found: 398.9965.

3,3-Dichloro-N-(4-chlorophenyl)-1-[(2-chloropyridin-4-yl)methyl]-2-oxoindoline-5-sulfonamide (7c): Synthesize as compound **6a**, yellowish solid, two step yield: 40 %; m.p.: 205-206 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.41 (d, *J* = 2.3 Hz, 1H), 7.98 (d, *J* = 1.7 Hz, 1H), 7.74 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.60 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.69 (s, 1H), 4.95 (s, 2H). IR (KBr, ν_{max}, cm^{-1}): 3440(w) , 3211, 1739, 1612, 1486, 1339, 1150, 912, 835, 720, 597, 523. HR-MS (ESI): Calcd for $C_{20}H_{13}N_2O_4SCl_4$ [M-H]$^-$: 515,9324; found: 515,9324.

3,3-Dichloro-1-[(2-chloropyridin-4-yl)methyl]-N-(4-hydroxyphenyl)-2-oxoindoline-5-sulfonamide (7d): Synthesize as compound **6a**, yellowish solid, two step yield: 46 %;

m.p.: 109-110 °C. ^{1}H NMR (400 MHz, d_6-DMSO, TMS) : δ = 9.77 (s, 1H), 9.36 (s, 1H), 8.44 (d, *J* = 2.3 Hz, 1H), 7.88 (d, *J* = 1.8 Hz, 1H), 7.72 (td, *J* = 8.7, 2.2 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 5.07 (s, 2H). IR (KBr, ν_{max}, cm^{-1}): 3428(w), 3255, 1754, 1609, 1509, 1474, 1333, 1153, 832, 606, 520. HR-MS (ESI): Calcd for $C_{20}H_{14}N_3O_4SCl_3$ $[M + H]^+$: 497.9849; found: 497.9851.

N-(4-Chlorophenyl)-1-decyl-2,3-dioxoindoline-5-sulfonamide (8a): Synthesize as compound **6a**, yellowish solid, two step yield: 50 %; m.p.: 212-213 °C. ^{1}H NMR (400 MHz, CD_3COCD_3, TMS): δ = 9.18 (s, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.87 (s, 1H), 7.29 (m, 5H), 3.78 (t, *J* = 6.9 Hz, 2H), 1.74-1.64 (m,2H), 1.27 (m,14H), 0.87 (s, 3H). IR (KBr, ν_{max}, cm^{-1}): 3434(w), 3378, 3231, 2919, 2849, 1751, 1609, 1492, 1330, 1153, 1068, 921, 823, 632, 467. HR-MS (ESI): Calcd for $C_{24}H_{29}N_2O_4SCl$ $[M-H]^-$: 475.1459; found: 475.1460

1-Decyl-N-(4-hydroxyphenyl)-2,3-dioxoindoline-5-sulfonamide (8b): Synthesize as compound **6a**, yellow solid, two step yield: 45 %; m.p.: 163-164 °C. ^{1}H NMR (400 MHz, d_6-DMSO, TMS): δ = 9.77 (s, 1H), 9.33 (s, 1H), 7.83 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.68 (d, *J* = 1.9 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.87 (t, *J* = 6.0 Hz, 2H), 6.65-6.55 (m, 2H), 3.63 (t, *J* = 7.1 Hz, 2H), 1.61-1.48 (m, 2H), 1.35-1.20 (m, 14H), 0.85 (t, *J* = 6.8 Hz, 3H). IR (KBr, ν_{max}, cm^{-1}): 3405, 3278, 3231, 2922, 2852, 1756, 1727, 1603, 1512, 1471, 1347, 1212, 1159, 1124, 1065, 918, 829, 635, 511. HR-MS (ESI): Calcd for $C_{24}H_{30}N_2O_5S$ $[M-H]^-$: 457.1797; found: 457.1790.

Antibacterial assays: Antimicrobial activity of the synthesized compounds was determined *in vitro* using the disc diffusion method against pathogenic microorganisms: *Staphylococcus aureus* ATCC, *Staphylococcus aureus* SC and *Pinguicula vulgaris*. Every sample (1000 μg) was dissolved with 5 % DMSO of ethanol (1 mL) and diluted to 100 μg/mL with ethanol. The solution was carried out against bacteria species by cup-plate method using nutrient agar as medium. The holes of 6 mm diameter were punched and filled with test solution (100 μg/mL in 5 % DMSO of ethanol) and 5 % DMSO of ethanol as the negative control. The inhibition zones (IZ) of the tested compounds were measured after 24 h incubation at 37 °C. The results of average diameters of the inhibition zone were listed in Table-1.

RESULTS AND DISCUSSION

The general strategy for the synthesis of target compounds was summarized in **Scheme-I**. 1*H*-indole-2,3-dione (**1**) was prepared using aniline as the initial agent according to the reported procedure[26], 1-substituted indole-2,3-dione **(2a-2c)** were synthesized by the reaction of 1*H*-indole-2,3-dione (**1**) with R_1X in the presence of K_2CO_3[27]. Heating indole-2,3-dione derivatives **1**, **2a** and **2b** in chlorosulfonic acid at 70 °C, the product of chlorosulfonation was consistently the mixture of 3,3-dichloro and 3-keto 5-chlorosulfonyl indole-2-one in the presence of dichloromethane or not[27] and the former one was the major product.

While the reaction of chlorosulfonic acid with **2c** in which R_1 was a long alkyl chain decyl at 70 °C giving no product, lowering the temperature and adding methylene chloride as a solvent resulted in product **5** with a high yield.

TABLE-1
ANTIBACTERIAL ACTIVITY OF THE TARGET COMPOUNDS **6a-6f, 7a-7d, 8a-8b** AT THE CONCENTRATION OF 100 μg/mL *in vitro*

Compound	Diameter of inhibition zone (mm)		
	S. aureus ATCC26112	*P. vulgaris*	*S. aureus SC*
6a	7.5	8.5	10
6b	8.5	9	9
6c	8.5	9.5	9.5
6d	7	7	7.5
6e	8	8	7
6f	9	8.5	9
7a	8	9	10
7b	19	8	7
7c	8.5	9.5	9.5
7d	23.5	9.5	7.5
8a	8.5	9.5	9.5
8b	21	8.5	9
5 % DMSO of ethanol [a]	7	7	7

[a] Negative control: 5 % DMSO of ethanol; Diameter of the cup in each plate: 6 mm

The synthesis of the target compounds **6a-6f**, **7a-7d**, **8a-8b** involved the process of condensing *p*-substitued anilines with 5-chlorosulfonyl indole-2-one at reflux for 3 h in tetrahydrofuran (THF). The molar ratio of 5-chlorosulfonyl indole-2-one and *p*-substitued anilines was 1:2.1. The target compounds were acquired smoothly in this condition. The structures of compounds were confirmed by ^{1}H NMR spectrum, IR spectrum and HR-MS. All spectroscopic data were in accordance with the assigned structures.

Biological activity: The synthesized compounds were screened by disc diffusion method for their antibacterial activity against two Gram-positive bacteria *S. aureus* ATCC-26112, *S. aureus* SC and one Gram-negative bacteria *P. vulgaris*, the results were summarized in Table-1. The results showed that most of the target compounds exhibited activity at the concentration of 100 μg/mL. It was observed that hydroxy or nitro group at *p*-position of phenyl ring showed better activity against *S. aureus* SC than the group of fluorine, methoxy *etc*; compounds with different electronic effect groups on *p*-position of phenyl ring displayed no significant antibacterial activities against *S. aureus* ATCC26112 and *P. vulgaris*. The introduction of aralkyl and alkyl types groups on the indolin-2-one nitrogen atom resulted in improvement in potency for antibacterial activities: Compounds **7a**, **7c** and **8a** that have electron-withdrawing group chlorine atom on the phenyl ring showed moderate activity (IZ ≥ 9 mm) against *S. aureus* SC and *P. vulgaris*, while derivatives **7b**, **7d** and **8b** with electron-donating group hydroxy showed notable antibacterial activity (IZ ≥ 19 mm) against *S. aureus* ATCC26112.

Considering the compound **7b**, **7d** and **8b** displayed excellent antibacterial activities against *S. aureus* ATCC-26112 at the concentration of 100 μg/mL, we measured the activity of the compounds **7b**, **7d** and **8b** at different concentrations and the results were shown in Table-2. Three compounds still have obvious inhibitory effects at 50 and 20 μg/mL.

TABLE-2
in vitro ANTIBACTERIAL ACTIVITY OF COMPOUND **7b**, **7d** AND **8b** AGAINST *S. aureus* ATCC26112 AT DIFFERENT CONCENTRATION

Concentration	Diameter of inhibition zone (mm)			
	7b	**7d**	**8b**	5 % DMSO of ethanol[a]
100 µg/mL	19	23.5	21	7
50 µg/mL	15	18	19	7
20 µg/mL	8.5	7.5	8	7

[a]Negative control: 5 % DMSO of ethanol; Diameter of the cup in each plate: 6 mm

Conclusion

A novel class of indolin-2-one derivatives possessing sulfonamides at the C-5 position was prepared and their antibacterial activities were preliminary evaluated *in vitro*. The results of antibacterial activities showed that most of the synthesized compounds exhibited antibacterial activity at the concentration of 100 µg/mL, some of which had significant antibacterial activities and they might be selected for further investigation. The results of this work might be helpful for the design and synthesis of new antibacterial agents.

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