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ORIGINAL PAPER

Microwave-assisted synthesis and antibacterial activity of derivatives of 3-[1-(4-fluorobenzyl)-1*H*-indol-3-yl]-5-(4-fluorobenzylthio)-4*H*-1,2,4-triazol-4-amine

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Herein, an excellent method for the synthesis of twelve novel Schiff base derivatives containing indole and triazole assisted by microwave irradiation is reported. Compared with the conventional method, the yields increased from 59–84 % to 85–96 % and the reaction time was reduced from 24–30 h to 4–8 min. Moreover, all series of the newly synthesized Schiff bases were evaluated for their antibacterial activity. The values of minimum inhibitory concentration (MIC) and IC_{50} indicated that many target compounds possessed excellent antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacillus subtilis*.

Keywords: microwave synthesis, indole, triazole, Schiff base, antibacterial activity

Introduction

Due to the universality and resistance of pathogenic bacteria, the contest between human and pathogenic bacteria exists along the whole course of human development (Giske & Cornaglia, 2010). Unfortunately, billions of people are infected by pathogenic bacteria every year, which brings great pain and loss to mankind. Therefore, the research of antibacterial drugs has become an urgent task for our existence.

In recent years, indole has attracted significant attention because of its good antimicrobial activity. Many derivatives of indole-2-ones were reported to possess good antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis*, etc. (Reddy et al., 2011; Akhaja & Raval, 2011, 2012). Some derivatives of 1-(1*H*-indol-3-yl) ethanamine were found to strongly inhibit the growth of *Staphylococcus strains* (Burchak et al., 2011).

1,2,4-Triazole derivatives are reported frequently for their good antimicrobial activity (Patil et al., 2010; Pardeshi & Bobade, 2011). Quinoline derivatives carrying 1,2,4-triazole (Eswaran et al., 2009), 1,2,4-triazole fused macrocyclic crown compounds (Khalil, 2010), and sulfonamide-1,2,4-triazoles (Zoumpoulakis et al., 2012) were confirmed to have good antimicrobial activity against *S. aureus*, *E. coli*, and *B. subtilis*, etc.

Schiff bases have also received attention owing to their good antimicrobial activity (da Silva et al., 2011). Many Schiff bases with good inhibition activity against both Gram-positive and Gram-negative bacterial strains were explored (Bharti et al., 2010; Negm et al., 2010); e.g. pyrazole based Schiff bases (Singh et al., 2012) and Schiff bases containing the thiourea structure (Zhang et al., 2011) were reported to possess good inhibition activity against *E. coli*, and *B. subtilis*, etc.

From the above facts results that indole, 1,2,4-triazole and Schiff bases possess good antimicrobial activity. However, to our knowledge, Schiff bases containing both 1,2,4-triazole and indole have been reported only rarely.

In addition, due to the environmental pollution and waste of resources, traditional chemical industry processes have also brought serious harm to the environment (Nadal et al., 2011). To improve chemical processes and reduce environmental pollution

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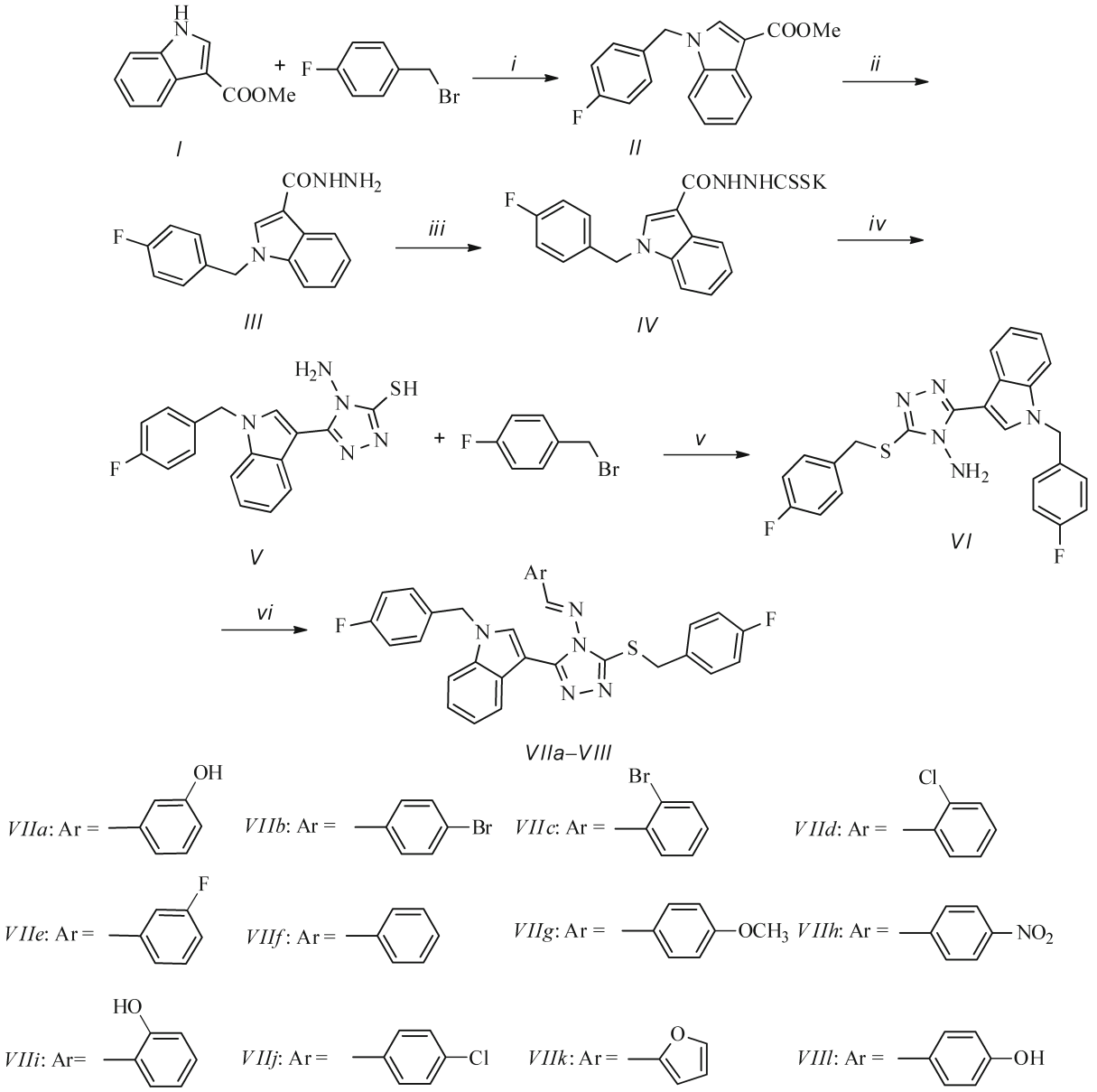

Fig. 1. Reagents and conditions: *i*) K_2CO_3; *ii*) $NH_2NH_2 \cdot H_2O$, microwave irradiation; *iii*) CS_2, KOH, ethanol; *iv*) $NH_2NH_2 \cdot H_2O$, microwave irradiation; *v*) K_2CO_3; *vi*) ArCHO, AcOH, microwave irradiation.

has become an urgent task for chemical researchers. Microwave-assisted synthesis as a novel green chemical process shows distinct advantages over the traditional process, such as energy conservation, short reaction times, good conversions, and solvent-free mechanism (Appukkuttan et al., 2009). Further study is required to broaden its range of application.

Based on the above research information and our efforts on pharmaceutical synthesis (Zhao et al., 2010; Shi et al., 2011), a series of novel Schiff bases containing indole, triazole structures was designed and synthesized under microwave irradiation for the purpose of broadening the application range of microwave-assisted synthesis and discovering new antibacterial compounds. The synthetic route is shown in Fig. 1.

Experimental

General

Melting point was measured on a WRS-1B micro-melting point apparatus (China) without thermometer correction. Infrared spectra were determined on a 1700 Perkin–Elmer FTIR (USA) using KBr disks. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were taken on a Varian INOVA (USA) spectrometer with TMS as the internal standard, DMSO-d_6 or $CDCl_3$ as the solvent. Chemical shift is given in δ relative to TMS. Mass spectra were obtained at 70 eV on a Finnigan LCQDECA (USA) instrument. Elemental analyses were carried out on a Carlo Erba-

1106 autoanalyzer (USA). All microwave-assisted reactions were run in a commercial microwave reactor (XH-100A, 100–1000 W, Beijing Xianghu Science and Technology Development, China). Sterilization of equipment and reagents used in the in vitro antimicrobial activity tests was carried out in a portable stainless steel pressure steam sterilizer (YX280A, Shanghai Sanshen Medical Instrument, China). Aseptic operation was carried out in a super clean bench (DL-CJ-1N, Donglian Elactronic & Technology Develepment, China). Bacterial culture was processed in a biological constant temperature incubator (ECA-9272, Beijing ECOA Science & Development, China). All solvents (Beijing Chemical Reagent Factory, China) were purified before use. Petroleum ether, boiling point range 30–60 °C was used. Intermediates *II*, *III*, *IV*, and *V* were prepared by the reported procedure (Farghaly, 2004; Shi et al., 2011).

Synthesis of compound VI

Compound *V* (2 g, 5.89 mmol), 1-(bromomethyl)-4-fluorobenzene (1.1 g, 5.89 mmol), K_2CO_3 (0.81 g, 11.78 mmol), and *N*,*N*-dimethylformamide (DMF; 20 mL) were stirred in a 50 mL round bottom flask at room temperature for 2 h. TLC (ethyl acetate/petroleum ether; $\varphi_r = 1 : 1$) indicated that the reaction was completed. Then, the solvent was removed by reduced pressure distillation. The mixture was purified by silica gel column chromatography using a mixture of ethyl acetate/petroleum ether ($\varphi_r = 1 : 1$; $R_f = 0.4$) to get pure compound *VI*.

Conventional method for the preparation of compounds VIIa–VIIl

Compound *VI* (0.045 g, 0.1 mmol), aromatic aldehyde (0.1 mmol), and acetic acid (100 %, 4 mL) were placed in a round bottom flask assembled with a condenser pipe, and heated to reflux for 24–30 h. The reaction was monitored by TLC (ethyl acetate/petroleum ether; $\varphi_r = 1 : 1$) until it was completed. Acetic acid was removed by reduced pressure distillation and co-evaporated with toluene. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate/petroleum ether ($\varphi_r = 1 : 1$) ($R_f = 0.5$–0.7) to get pure compounds *VIIa–VIIl*.

Microwave method for the preparation of compounds VIIa–VIIl

Compound *VI* (0.045 g, 0.1 mmol), aromatic aldehyde (0.1 mmol), and one drop of acetic acid (100 %,

Table 1. Characterization data of newly prepared compounds

Compound	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p.
			C	H	N	%	°C
VI	$C_{24}H_{19}F_2N_5S$	447.50	64.41 64.44	4.28 4.31	15.65 15.63	91	173–175
VIIa	$C_{31}H_{23}F_2N_5OS$	551.61	67.50 67.57	4.20 4.15	12.70 12.56	85	199–201
VIIb	$C_{31}H_{22}BrF_2N_5S$	614.51	60.59 60.64	3.61 3.65	11.40 11.44	85	137–139
VIIc	$C_{31}H_{22}BrF_2N_5S$	614.51	60.59 60.66	3.61 3.64	11.40 11.38	91	132–134
VIId	$C_{31}H_{22}ClF_2N_5S$	570.05	65.32 65.36	3.89 3.85	12.29 12.33	89	175–177
VIIe	$C_{31}H_{22}F_3N_5S$	553.60	67.26 67.29	4.01 4.08	12.65 12.64	86	156–158
VIIf	$C_{31}H_{23}F_2N_5S$	535.61	69.52 69.59	4.33 4.38	13.08 13.04	95	147–149
VIIg	$C_{32}H_{25}F_2N_5OS$	565.64	67.95 67.89	4.45 4.42	12.38 12.42	87	110–112
VIIh	$C_{31}H_{22}F_2N_6O_2S$	580.61	64.13 64.20	3.82 3.84	14.47 14.44	88	108–110
VIIi	$C_{31}H_{23}F_2N_5S$	551.61	67.50 67.58	4.20 4.24	12.70 12.68	86	210–212
VIIj	$C_{31}H_{22}ClF_2N_5S$	570.05	65.32 65.38	3.89 3.95	12.29 12.23	87	148–150
VIIk	$C_{29}H_{21}F_2N_5OS$	525.57	66.27 66.35	4.03 4.09	13.33 13.23	84	149–151
VIIl	$C_{31}H_{23}F_2N_5OS$	551.61	67.50 67.57	4.20 4.22	12.70 12.68	85	234–236

Table 2. Spectral data of newly prepared compounds

Compound	Spectral data
VI	IR, $\tilde{\nu}$/cm^{-1}: 1221 (C—S), 1447 (C—N), 1597 (C═N), 3353 (NH_2) ^{1}H NMR ($CDCl_3$), δ: 4.24 (s, 2H, $ArCH_2S$), 4.32 (s, 2H, $ArCH_2N$), 5.28 (s, 2H, NH_2), 6.94–7.00 (m, 4H, ArH), 7.09–7.10 (m, 2H, ArH), 7.28–7.31 (m, 5H, ArH), 7.97 (s, 1H, ArH), 8.48–8.50 (m, 1H, ArH) ^{13}C NMR (DMSO-d_6), δ: 34.8, 49.1, 102.2, 110.9, 111.1, 115.7, 121.0, 122.3, 122.9, 126.4, 129.6, 131.5, 134.3, 134.5, 134.6, 135.9, 151.2, 152.0, 160.6, 160.8, 163.2 ESI–MS, m/z (I_r/%): 448.14 (100) $(M + 1)^+$
VIIa	IR, $\tilde{\nu}$/cm^{-1}: 1226 (C—S), 1438 (C—N), 1575 (C═N), 3419 (PhOH) ^{1}H NMR (DMSO-d_6), δ: 4.40 (s, 2H, $ArCH_2S$), 5.47 (s, 2H, $ArCH_2N$), 7.06–7.32 (m, 11H, ArH), 7.37–7.40 (m, 3H, ArH), 7.61 (d, 1H, J = 8.0 Hz, ArH), 7.88 (s, 1H, ArH), 8.26 (d, 1H, J = 8.0 Hz, ArH), 8.74 (s, 1H, N═CHAr), 10.02 (s, 1H, ArOH) ^{13}C NMR (DMSO-d_6), δ: 36.9, 49.0, 101.7, 111.0, 111.3, 115.2, 115.7, 115.9, 121.0, 121.5, 122.0, 123.0, 123.3, 126.1, 129.7, 129.9, 130.1, 130.7, 130.9, 131.3, 131.6, 133.3, 133.9, 136.1, 144.4, 148.9, 158.4, 160.8, 163.1, 168.4 ESI–MS, m/z (I_r/%): 552.15 (100) $(M + 1)^+$
VIIb	IR, $\tilde{\nu}$/cm^{-1}: 1226 (C—S), 1428 (C—N), 1590 (C═N) ^{1}H NMR ($CDCl_3$), δ: 4.46 (s, 2H, $ArCH_2S$), 5.28 (s, 2H, $ArCH_2N$), 6.95–6.97 (m, 4H, ArH), 7.26–7.34 (m, 7H, ArH), 7.53 (d, 3H, J = 7.2 Hz, ArH), 7.62 (d, 2H, J = 6.8 Hz, ArH), 8.36 (s, 1H, N═CHAr), 8.49–8.51 (m, 1H, ArH) ^{13}C NMR (DMSO-d_6), δ: 37.2, 48.9, 101.6, 111.0, 111.3, 115.7, 115.9, 121.2, 121.5, 122.0, 123.0, 123.3, 126.1, 127.5, 129.8, 130.0, 130.2, 131.2, 131.6, 132.7, 132.9, 133.8, 136.2, 144.3, 149.0, 160.7, 163.1, 166.6, 166.9 ESI–MS, m/z (I_r/%): 616.01 (100) $(M + 1)^+$
VIIc	IR, $\tilde{\nu}$/cm^{-1}: 1229 (C—S), 1438 (C—N), 1587 (C═N) ^{1}H NMR ($CDCl_3$), δ: 4.50 (s, 2H, $ArCH_2S$), 5.30 (s, 2H, $ArCH_2N$), 6.95–6.99 (m, 4H, ArH), 7.13–7.14 (m, 2H, ArH), 7.29–7.38 (m, 7H, ArH), 7.58 (s, 1H, ArH), 7.63 (d, 1H, J = 7.2 Hz, ArH), 7.90 (d, 1H, J = 6.4 Hz, ArH), 8.41 (d, 1H, J = 6.4 Hz, ArH), 8.94 (s, 1H, N═CHAr) ^{13}C NMR (DMSO-d_6), δ: 37.2, 49.0, 101.6, 111.1, 111.3, 115.7, 115.9, 121.2, 121.5, 121.9, 123.3, 126.1, 129.0, 130.0, 130.2, 131.0, 131.3, 131.6, 133.7, 134.0, 134.9, 135.1, 136.2, 144.4, 149.2, 160.8, 163.2, 163.7, 163.9 ESI–MS, m/z (I_r/%): 614.09 (100) $(M + 1)^+$
VIId	IR, $\tilde{\nu}$/cm^{-1}: 1215 (C—S), 1430 (C—N), 1575 (C═N) ^{1}H NMR ($CDCl_3$), δ: 4.50 (s, 2H, $ArCH_2S$), 5.30 (s, 2H, $ArCH_2N$), 6.94–6.99 (m, 4H, ArH), 7.12–7.13 (m, 2H, ArH), 7.29–7.37 (m, 7H, ArH), 7.59 (s, 1H, ArH), 7.91 (d, 1H, J = 7.6 Hz, ArH), 7.99 (d, 1H, J = 7.6 Hz, ArH), 8.39 (d, 1H, J = 7.6 Hz, ArH), 8.97 (s, 1H, N═CHAr) ^{13}C NMR (DMSO-d_6), δ: 37.3, 49.0, 101.6, 111.1, 115.8, 121.4, 121.9, 123.2, 126.1, 127.7, 128.5, 128.7, 130.0, 131.3, 131.9, 132.0, 133.0, 133.8, 134.0, 134.8, 135.7, 136.2, 144.3, 149.2, 160.7, 161.8, 161.9, 163.1, 163.2, 167.2 ESI–MS, m/z (I_r/%): 570.05 (100) $(M + 1)^+$
VIIe	IR, $\tilde{\nu}$/cm^{-1}: 1221 (C—S), 1437 (C—N), 1577 (C═N) ^{1}H NMR ($CDCl_3$), δ: 4.47 (s, 2H, $ArCH_2S$), 5.29 (s, 2H, $ArCH_2N$), 6.93–6.99 (m, 4H, ArH), 7.12–7.15 (m, 2H, ArH), 7.29–7.34 (m, 6H, ArH), 7.41–7.46 (m, 3H, ArH), 7.54 (s, 1H, ArH), 8.40 (s, 1H, N═CHAr), 8.50–8.51 (m, 1H, ArH) ^{13}C NMR (DMSO-d_6), δ: 37.3, 48.9, 101.5, 111.1, 111.2, 115.1, 115.4, 115.7, 120.6, 121.4, 122.0, 123.2, 126.1, 126.3, 130.0, 131.5, 131.9, 133.8, 133.9, 134.3, 134.4, 136.2, 144.3, 149.1, 160.8, 161.5, 163.1, 164.0, 166.4 ESI–MS, m/z (I_r/%): 554.22 (100) $(M + 1)^+$
VIIf	IR, $\tilde{\nu}$/cm^{-1}: 1222 (C—S), 1434 (C—N), 1585 (C═N) ^{1}H NMR ($CDCl_3$), δ: 4.45 (s, 2H, $ArCH_2S$), 5.28 (s, 2H, $ArCH_2N$), 6.95–6.97 (m, 4H, ArH), 7.12–7.15 (m, 2H, ArH), 7.31–7.33 (m, 5H, ArH), 7.49–7.50 (m, 2H, ArH), 7.57–7.58 (m, 2H, ArH), 7.69 (d, 2H, J = 7.6 Hz, ArH), 8.40 (s, 1H, N═CHAr), 8.54 (d, 1H, J = 7.2 Hz, ArH) ^{13}C NMR (DMSO-d_6), δ: 37.1, 48.9, 101.7, 111.1, 115.6, 115.8, 116.0, 121.3, 122.0, 123.2, 126.1, 129.5, 129.8, 130.1, 131.5, 132.0, 133.6, 133.9, 136.2, 144.3, 149.0, 160.7, 160.8, 163.1, 163.2, 167.9 ESI–MS, m/z (I_r/%): 536.15 (100) $(M + 1)^+$
VIIg	IR, $\tilde{\nu}$/cm^{-1}: 1226 (C—S), 1427 (C—N), 1596 (C═N) ^{1}H NMR ($CDCl_3$), δ: 3.91 (s, 3H, OCH_3), 4.43 (s, 2H, $ArCH_2S$), 5.26 (s, 2H, $ArCH_2N$), 6.92–6.97 (m, 6H, ArH), 7.10–7.12 (m, 2H, ArH), 7.30–7.34 (m, 5H, ArH), 7.53 (s, 1H, ArH), 7.63 (d, 2H, J = 7.2 Hz, ArH), 8.28 (s, 1H, N═CHAr), 8.55 (d, 1H, J = 6.4 Hz, ArH) ^{13}C NMR (DMSO-d_6), δ: 36.9, 48.9, 56.1, 101.8, 111.2, 115.1, 115.3, 115.7, 115.9, 116.1, 121.2, 121.4, 122.1, 123.0, 123.3, 124.5, 126.1, 129.5, 129.7, 130.2, 131.5, 131.7, 133.8, 136.2, 144.4, 148.9, 160.8, 163.1, 163.8, 167.9 ESI–MS, m/z (I_r/%): 1130.25 (100) $(2M + 1)^+$
VIIh	IR, $\tilde{\nu}$/cm^{-1}: 1222 (C—S), 1430 (C—N), 1589 (C═N) ^{1}H NMR ($CDCl_3$), δ: 4.50 (s, 2H, $ArCH_2S$), 5.30 (s, 2H, $ArCH_2N$), 6.96–6.99 (m, 4H, ArH), 7.13–7.14 (m, 2H, ArH), 7.29–7.34 (m, 5H, ArH), 7.53 (s, 1H, ArH), 7.80 (d, 2H, J = 8.4 Hz, ArH), 8.30–8.32 (m, 2H, ArH), 8.42 (d, J = 7.2 Hz, 1H, ArH), 8.54 (s, 1H, N═CHAr) ^{13}C NMR (DMSO-d_6), δ: 37.5, 49.0, 101.4, 111.1, 111.3, 115.7, 115.9, 121.6, 122.1, 123.1, 123.3, 124.8, 126.1, 130.0, 130.2, 130.6, 131.3, 131.6, 132.1, 133.7, 136.2, 137.7, 144.3, 149.3, 150.2, 160.7, 163.1, 164.8, 165.0, 167.4 ESI–MS, m/z (I_r/%): 581.08 (100) $(M + 1)^+$

Table 2. (continued)

Compound	Spectral data
VIIi	IR, $\tilde{\nu}$/cm^{-1}: 1223 (C—S), 1435 (C—N), 1594 (C═N), 3427 (PhOH) ^{1}H NMR ($CDCl_3$), δ: 4.42 (s, 2H, $ArCH_2S$), 5.25 (s, 2H, $ArCH_2N$), 6.89–6.95 (m, 4H, ArH), 6.97–7.01 (m, 1H, ArH), 7.05–7.11 (m, 3H, ArH), 7.17–7.19 (m, 1H, ArH), 7.29–7.32 (m, 5H, ArH), 7.39 (s, 1H, ArH), 7.49–7.52 (m, 2H, ArH), 8.41 (s, 1H, N═CHAr), 10.26 (s, 1H, ArOH) ^{13}C NMR (DMSO-d_6), δ: 36.8, 49.0, 101.8, 111.1, 115.5, 115.8, 115.9, 117.1, 118.3, 120.2, 121.3, 122.0, 123.1, 126.1, 127.9, 129.1, 130.0, 131.5, 132.0, 132.1, 133.7, 133.9, 135.3, 136.2, 144.2, 149.1, 159.1, 160.7, 163.3, 167.4 ESI–MS, m/z (I_r/%): 552.15 (100) $(M + 1)^+$
VIIj	IR, $\tilde{\nu}$/cm^{-1}: 1219 (C—S), 1418 (C—N), 1589 (C═N) ^{1}H NMR ($CDCl_3$), δ: 4.45 (s, 2H, $ArCH_2S$), 5.28 (s, 2H, $ArCH_2N$), 6.92–6.99 (m, 4H, ArH), 7.10–7.13 (m, 2H, ArH), 7.27–7.33 (m, 5H, ArH), 7.46 (d, 2H, $J = 6.8$ Hz, ArH), 7.51 (s, 1H, ArH), 7.60–7.61 (m, 2H, ArH), 8.37 (s, 1H, N═CHAr), 8.49 (d, 1H, $J = 8.0$ Hz, ArH) ^{13}C NMR (DMSO-d_6), δ: 37.3, 49.0, 101.6, 111.1, 111.3, 115.7, 115.9, 121.5, 121.9, 123.2, 126.1, 128.3, 128.6, 129.5, 130.0, 130.2, 130.3, 130.7, 130.9, 131.3, 131.5, 133.8, 134.0, 134.8, 135.7, 136.2 ESI–MS, m/z (I_r/%): 570.07 (100) $(M + 1)^+$
VIIk	IR, $\tilde{\nu}$/cm^{-1}: 1221 (C—S), 1431 (C—N), 1586 (C═N) ^{1}H NMR ($CDCl_3$), δ: 4.47 (s, 2H, $ArCH_2S$), 5.31 (s, 2H, $ArCH_2N$), 6.63 (s, 1H, ArH), 7.00–6.94 (m, 6H, ArH), 7.12–7.15 (m, 2H, ArH), 7.28–7.29 (m, 3H, ArH), 7.36–7.33 (m, 1H, ArH), 7.68–7.70 (m, 2H, ArH), 8.24 (s, 1H, N═CHAr), 8.54–8.55 (m, 1H, ArH) ^{13}C NMR (DMSO-d_6), δ: 36.9, 49.0, 101.6, 111.2, 113.6, 115.7, 115.9, 121.2, 121.5, 121.8, 122.1, 123.2, 126.1, 129.7, 130.1, 131.3, 131.6, 133.8, 133.9, 136.2, 144.4, 147.6, 148.9, 149.2, 155.8, 155.9, 160.7, 163.2 ESI–MS, m/z (I_r/%): 526.08 (100) $(M + 1)^+$
VIIl	IR, $\tilde{\nu}$/cm^{-1}: 1226 (C—S), 1429 (C—N), 1595 (C═N), 3440 (PhOH) ^{1}H NMR (DMSO-d_6), δ: 4.38 (s, 2H, $ArCH_2S$), 5.46 (s, 2H, $ArCH_2N$), 6.88–6.90 (d, 2H, $J = 7.6$ Hz, ArH), 7.05–7.13 (m, 4H, ArH), 7.20–7.26 (m, 4H, ArH), 7.37–7.39 (m, 2H, ArH), 7.59 (d, 1H, $J = 8.0$ Hz, ArH), 7.72 (d, 2H, $J = 8.0$ Hz, ArH), 7.86 (s, 1H, ArH), 8.29 (d, 1H, $J = 7.6$ Hz, ArH), 8.57 (s, 1H, N═CHAr), 10.02 (s, 1H, ArOH) ^{13}C NMR (DMSO-d_6), δ: 36.7, 48.9, 101.9, 111.1, 115.7, 116.9, 121.2, 122.1, 123.1, 126.1, 129.5, 130.0, 131.4, 132.0, 133.9, 134.9, 136.1, 140.5, 144.4, 148.9, 160.7, 163.2, 164.0, 168.3 ESI–MS, m/z (I_r/%): 552.10 (100) $(M + 1)^+$

catalyst) were mixed thoroughly by grinding in a porcelain mortar. The mixture was transferred into a 10 mL specialized tube placed in a microwave oven and irradiated with the MW power of 300 W at 125 ℃ and the pressure of 413–552 kPa for 4–6 min. The reaction was monitored by TLC (ethyl acetate/petroleum ether; $\varphi_r = 1 : 1$) until it was completed. The mixture was extracted with DMF (3 × 5 mL). Then, ethanol (10 mL) was added to the DMF mixture. Solid was formed and collected by filtration, it was purified by silica gel column chromatography using a mixture of ethyl acetate/petroleum ether ($\varphi_r = 1 : 1$) ($R_f = 0.5$–0.7) to get pure compounds *VIIa*–*VIIl*. The operational procedure was referred to a published article (Ju & Varma, 2005).

Biological activity test for MIC and IC_{50} values

Two Gram-positive bacteria (*S. aureus* ATCC6538, *B. subtilis* ATCC 6633) and two Gram-negative bacteria (*E. coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853; Agricultural University of Sichuan, China) were used in the biological activity tests (in vitro). Amoxicillin (Shanghai medical company, China) was used as positive control and DMF was used as negative control. The experimental procedure was referred to the standard broth microdilution technique described by NCCLS (National Committee for Clinical Laboratory Standards, 2000).

Results and discussion

Spectral characterization

Purity of the compounds was checked by the physical properties and elemental analyses (Table 1), and the structures of compounds were identified using spectral data (Table 2). The elemental analysis results were within ± 0.4 % of the theoretical values. The mass spectra showed the expected molecular peaks at high intensity. In the IR spectra of *V*, the absorption band at about 2640 cm^{-1} assigned to the SH group which was absent in the IR spectra of *VI* can be observed. The strong bands at about 3353 cm^{-1} ascribed to the NH_2 group disappeared in IR spectra of *VIIa*–*VIIl*. The strong bands at 1596–1575 cm^{-1} were attributed to the absorption of C═N. In the ^{1}H NMR spectra, compound *V* showed a singlet peak at δ 13.72 due to the SH group which was not observed in the spectra of compound *VI*. The singlet peak at δ 5.28 (*VI*) was assigned to the NH_2 group and that at δ 8.96–8.28 was assigned to N═CHAr. Protons of ArH appeared at δ 8.56–6.88. The singlet peak in *VIIa*–*VIIl* at δ 5.26–5.45 was assigned to $ArCH_2N$ and that at δ 4.38–4.50 (*VI* and *VIIa*–*VIIl*) was attributed to

Table 3. Comparison of syntheses under microwave irradiation and conventional heating

Compounds	Traditional method		Microwave method		Time ratio[a]
	Time/h	Yield/%	Time/min	Yield/%	
III	21	75	6	93	210
V	25	43	8	86	188
VIIa	30	65	4	85	450
VIIb	26	59	5	88	312
VIIc	28	72	5	89	336
VIId	27	73	6	91	270
VIIe	26	68	5	86	312
VIIf	24	70	4	95	360
VIIg	25	64	6	87	250
VIIh	28	67	6	88	280
VIIi	26	66	5	86	312
VIIj	26.5	75	4	87	398
VIIk	28.5	84	4	96	428
VIIl	24.5	68	5	85	294

a) Ratio between time needed for the conventional and microwave method.

Table 4. MIC and IC_{50} values of Schiff bases *VIIa–VIIl* and Amoxicillin

Compounds	Inhibitory concentration/(μg mL^{-1})							
	Gram-positive bacteria				Gram-negative bacteria			
	S. aureus		*B. subtilis*		*E. coli*		*P. aeruginosa*	
	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}
VIIa	> 128	> 64	> 128	> 64	> 128	> 64	> 128	> 64
VIIb	8	5.3	2	1.4	8	7	2	1.5
VIIc	16	7.5	32	14.6	16	9.8	16	8.3
VIId	32	14.9	8	5.7	8	6.2	4	3.1
VIIe	8	4.1	4	2.8	8	5.2	8	3.9
VIIf	> 128	> 64	> 128	> 64	> 128	> 64	> 128	> 64
VIIg	32	26.9	> 128	> 64	> 128	> 64	> 128	> 64
VIIh	8	4.9	4	2.4	4	2.8	8	5.2
VIIi	> 128	> 64	> 128	> 64	> 128	> 64	> 128	> 64
VIIj	8	6.4	8	4.6	4	3.3	4	3.3
VIIk	32	25.4	> 128	> 64	64	33.3	> 128	> 64
VIIl	> 128	> 64	> 128	> 64	> 128	> 64	> 128	> 64
Amoxicillin	16	6.4	8	2.7	16	7.3	8	2.5

SCH_2Ar. In the ^{13}C NMR spectra, the peak at δ 34.8–37.4 (*VI* and *VIIa–VIIl*) was assigned to SCH_2Ar, that at δ 48.9–49.1 (*VI* and *VIIa–VIIl*) to $ArCH_2N$, and that at δ 163.2–168.4 (*VIIa–VIIl*) to N=CHAr. Carbon atoms of the aromatic ring in *VI* and *VIIa–VIIl* showed their peaks at δ 101.4–166.6.

Comparison of syntheses under microwave irradiation and conventional heating

Using methyl 1*H*-indole-3-carboxylate as the initial material, the target Schiff bases were synthesized in six steps, three of which were completed via microwave radiation. Compared with the traditional heating method, microwave synthesis showed many advantages (Table 3). From Table 3, it can be seen that the microwave synthesis has significantly shorter reaction time and visibly higher yields compared to the traditional method.

In the synthesis of *III*, the reaction time decreased from 21 h to 6 min and the yield increased from 75 % to 93 % in the microwave method. In the synthesis of *V*, the reaction time was decreased from 25 h to 8 min, and the yield was increased from 43 % to 86 %. Moreover, *VIIa–VIIl* were synthesized without using any solvent under microwave radiation. A typical aromatic aldehyde (*VI*) and a drop of acetic acid were thoroughly mixed together and irradiated by microwave radiation for a few minutes. To our amazement, the reaction time decreased from 24–30 h to 4–6 min and the yield increased from 59 % (84 %) to 84 % (96 %).

Biological screening

MIC and IC_{50} values of these newly synthesized target compounds to four tested microorganisms are

presented in Table 4. According to the data in Table 4 it can be concluded that compounds *VIIb*, *VIIe*, *VIIh*, and *VIIj* possess antibacterial activity equivalent to or even higher than Amoxicillin. Compared with Amoxicillin, *VIIc* and *VIId* are a little weaker in the inhibition of Gram-positive bacteria and a little stronger in the inhibition of Gram-negative bacteria. Compounds *VIIg* and *VIIk* showed poor antibacterial activity, and *VIIa*, *VIIf*, *VIIi*, and *VIIl* no antibacterial activity at all.

It can thus be concluded that the aromatic substituent of these Schiff bases plays an important part in their antibacterial activity. Halogen and nitro groups enhance the antibacterial activity significantly while hydroxy and methoxy groups have no such function.

Conclusions

In summary, a facile, efficient and eco-friendly method for the synthesis of twelve novel Schiff bases via microwave irradiation has been introduced. The presented method has some distinct advantages compared with the conventional method, such as shorter reaction times, good conversions, and it also meets the requirements of the green chemistry protocols. Antibacterial activity of these newly synthesized compounds was evaluated by biological activity tests in vitro. Based on the activity data, compounds *VIIb*, *VIIe*, *VIIh*, and *VIIj* were proved to possess strong antibacterial activity which can be possibly used in antibacterial drugs. Studies on their efficiency and safety in vitro are planned.

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