Microwave-assisted synthesis and antibacterial activity of methyl 1-{2-[4-amino-5-(naphthalen-1-yl)-4H-1,2,4-triazol-3-ylthio]ethyl}-1H-indole-3-carboxylate derivatives

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Twelve new Schiff bases containing a disubstituted 1,2,4-triazole and a monosubstituted indole linked by a thioethyl group were efficiently synthesised via a method employing microwave irradiation. Compared with a conventional method of heating at 100 °C, yields were increased from 46–48 to 82–92% and the reaction times were reduced from 20–25 h to 4–7 min. The structures of these novel hexacyclic Schiff bases were characterised by their spectral data and elemental analysis. Evaluation of their antibacterial activity showed that many of them possess excellent activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacillus subtilis*.

Keywords: microwave-synthesis, antibacterial activity, Schiff base, indole, 1, 2, 4-triazole

Antimicrobial agents have been used to treat patients since the 1940s, greatly reducing pain and death from infectious diseases.[1] However, these drugs have been used so widely and for so long that they are no longer so effective.[2] During the past several decades, the number of new antibiotics being brought to the market has shown a precipitous decline.[3] As a result, developing new antibacterials is quite urgent to keep human beings healthy. The latest research shows that compounds containing a Schiff base,[4–6] an indole[7–9] or a 1,2,4-triazole[10–12] possess good antibacterial activity. Building on the achievements our team have made,[13–14] we have designed and synthesised a series of novel Schiff bases containing an indole and a 1,2,4-triazole for the purpose of finding new compounds which can intensively inhibit the growth of bacteria.

Microwave-synthesis is a well-established technique in green chemistry and has many advantages compared with traditional methods, such as faster reaction times, higher yields and is solvent-free.[15–17] It has been applied in many organic syntheses.[18] Accordingly, as a further development of our green agenda,[19,20] we hoped microwave-synthesis could be used successfully in the synthesis of our newly designed Schiff bases.

Results and discussion

Synthesis

The synthetic route used is shown in Scheme 1. The trisubstituted 1,2,4-triazole **5** was prepared in four steps from 1-naphthoic acid **1a** via compounds **2**, **3** and **4** as described previously.[21,22] Methyl 1-(2-bromoethyl)-1H-indole-3-carboxylate **6** was prepared by treatment of methyl 1H-indole-3-carboxylate **1b** with 1,2-dibromoethane according to a literature method.[22] Tricyclic **5** was reacted with bicyclic **6** in the presence of potassium carbonate to give the pentacyclic amine **7**, condensation of which with a series of araldehydes in acetic acid, either at 100 °C or under microwave irradiation, gave the hexacyclic imines **8a–l**.

Comparison of microwave irradiation and conventional heating

Compared with the traditional heating method, microwave synthesis showed a lot of advantages such as solvent-free, shorter reaction times and higher yields, as shown in Table 1. When compounds **8a–l** were synthesised without any solvent under microwave irradiation, the reaction time was reduced from 20–25 h to 4–7 min, and the yield was increased from 46–68 to 82–92%.

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Spectroscopic studies

The structures of compounds **7** and **8a–l** were characterised by their IR spectra, ^{1}H NMR spectra, ESI-MS and elemental analyses. In the IR spectra of **7**, the absorption band at 3336 cm^{-1} was assigned to the NH_2 group which was absent, as expected, in the IR spectra of **8a–l**. The strong bands at 1596–1575 cm^{-1} in the IR spectra of **8a–l** were attributed to the absorption of C=N which did not appear in the IR spectrum of **7**. The singlet at 4.39 ppm in the ^{1}H NMR spectra of **7** was assigned to the NH_2 group and a similar signal was absent in the ^{1}H NMR spectra of **8a–l**. The singlet at 7.97–7.64 ppm in **8a–l** was assigned to the ArCHN. The aromatic protons appeared at 8.38–6.43 ppm. The triplet at 4.82 ppm was assigned to the indole-1-CH_2. The singlet at 4.39 ppm was assigned to the OCH_3 group. The triplet at about 3.79 ppm was attributed to the SCH_2 group. Their ESI-MS spectra showed the correct molecular ion peaks with high intensity. Moreover, their elemental analyses further confirmed their structures.

Biological activity

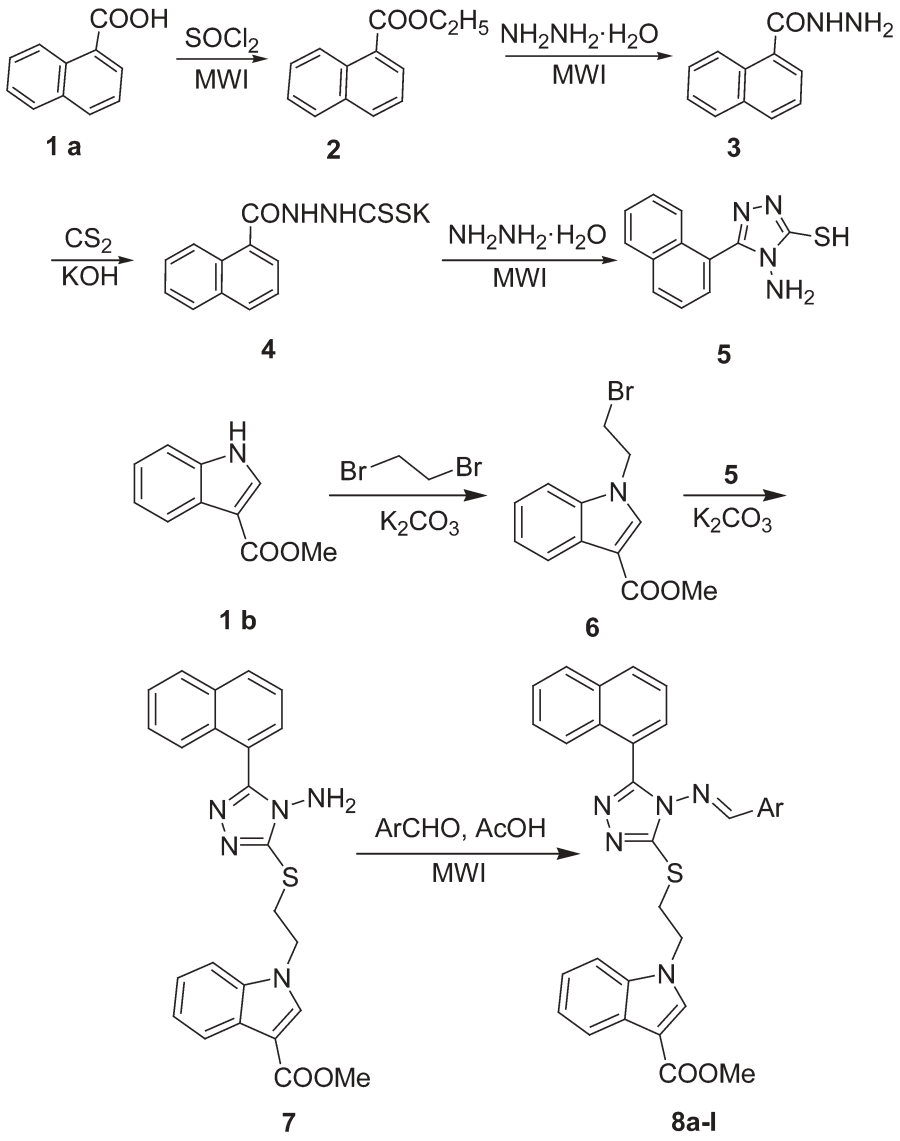
To evaluate the antimicrobial activity of these novel Schiff bases, the values of MIC and IC_{50} were determined via *in vitro* biological activity tests. Two Gram-positive bacteria (*Staphylococcus aureus* ATCC6538, *Bacillus subtilis* ATCC 6633) and two Gram-negative bacteria (*Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853) were used as test strains. Amoxicillin was used as a positive control and dimethyl sulfoxide was used as a negative control.

The MIC and IC_{50} values of these newly synthesised Schiff bases are shown in Table 2. From Table 2, we can conclude that compounds **8b**, **8c**, **8e**, **8f**, **8h and 8k** possess good antibacterial activity to the four test strains. Indeed compounds **8b**, **8c**, **8e**, **8f** and **8k** showed better inhibition to *S. aureus* than did Amoxicillin, as did compounds **8c**, **8e**, **8f** and **8k** towards *E. coli* and compounds **8f**, **8h** and **8k** towards *P. aeruginosa.*

According to the antibacterial activity conclusions above, we can recognise that the aromatic substituents play an important role in the antibacterial activity, halogen and nitro groups effecting enhancement of the antibacterial activity of these Schiff bases, whereas hydroxy and methoxy did not do so.

Experimental

Melting points were measured via a micro-melting point apparatus and are uncorrected. IR spectra were determined on a 1700 Perkin-Elmer FTIR using KBr disks. ^{1}H NMR spectra were obtained on a Varian INOVA 400 MHz spectrometer using TMS as the internal standard, in DMSO-d_6 or $CDCl_3$. Mass spectra were obtained on Finnigan LCQDECA instrument. Elemental analyses was obtained on



Scheme 1 Synthetic route for the target compounds.

Table 1 Comparison of microwave irradiation with conventional heating for the efficiency of synthesis of hexacyclic imines **8a–l** by condensation of araldehydes with pentacyclic amine **7** (Scheme 1)

Compd	Ar	Microwave method		Conventional method		t_C/t_{MW}[a]
		Time /min	Yield /%	Time /min	Yield /%	
8a	3-HO-C_6H_4	5	86	1260	57	252
8b	4-Br-C_6H_4	4	88	1380	62	345
8c	4-NO_2-C_6H_4	6	85	1440	46	240
8d	4-HO-C_6H_4	5	87	1260	54	252
8e	4-F-C_6H_4	4	90	1500	65	375
8f	2-Cl-C_6H_4	7	88	1380	56	197
8g	2-furyl	5	88	1320	60	264
8h	4-Cl-C_6H_4	4	86	1200	53	300
8i	4-CH_3O-C_6H_4	6	82	1440	63	240
8j	2-HO-C_6H_4	6	85	1380	58	230
8k	3-F-C_6H_4	4	88	1260	55	315
8l	phenyl	5	92	1320	68	264

[a] t_C = conventional method time; t_{MW} = microwave method time.

a Carlo-Erba-1106 autoanalyser. Microwave-assisted reactions were processed in a microwave reactor (XH-100A, 100-1000 W, Beijing Xianghu Science and Technology Development Co. Ltd, Beijing, P. R. China). The sterilisation of equipment and reagents was carried out in a portable stainless steel pressure steam steriliser (YX280A, Shanghai Sanshen Medical Instrument Co.,Ltd, Shanghai, P.R. China). All aseptic operations were performed on a super clean bench (DL-CJ-1N, Donglian Elactronic & Technology Develepment Co.Ltd, Beijing, P.R. China). The bacteria were grown in a constant temperature incubator (ECA-9272, Beijing ECOA Science & Development Co., Ltd, Beijing, P.R. China). All solvents were purified before use. 1-Naphthoic acid **1a** and methyl 1H-indole-3-carboxylate **1b** were supplied by Tokyo Chemical Industry Co., Ltd.

Synthesis of intermediate **7**

Compound **5** (0.86 g, 3.54 mmoL), compound **6** (1 g, 3.54 mmoL) and K_2CO_3 (0.98 g, 7.01 mmoL) were dissolved in DMF (15 mL) in a 50 mL round bottomed flask and stirred at room temperature until TLC indicated that the reaction was completed. Then DMF was removed by reduced pressure distillation. The residue was recrystallised in MeOH to give compound **7** as a grey solid (85%), m.p. 171–173 °C; IR, v: 3350, 3018, 2970, 1735, 1603, 1433, 1281, 1224, 834, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.19–8.17 (m, 1H, ArH), 8.05–8.03 (d, *J* = 8.4 Hz, 1H, ArH), 7.97–7.95 (m, 1H, ArH), 7.92 (s, 1H, ArH),

Table 2 Antibacterial activity of hexacyclic imines **8a–l** and a positive control (amoxicillin)

Compd	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}
8a	>128	>64	>128	>64	>128	>64	>128	>64
8b	8	5.2	16	8.1	16	6.9	8	4
8c	8	6.8	8	6.5	8	3.5	8	4.1
8d	>128	>64	>128	>64	>128	>64	>128	>64
8e	8	4.2	8	38	4	2.3	8	5
8f	8	4.1	8	3.9	8	3.9	4	2.4
8g	64	29.7	>128	>64	32	23.4	>128	>64
8h	16	9.1	8	64	16	7.9	4	2.8
8i	64	35.9	>128	>64	>128	>64	32	24.1
8j	>128	>64	>128	>64	>128	>64	>128	>64
8k	4	3	8	3.3	8	4	4	1.8
8l	>128	>64	>128	>64	>128	>64	>128	>64
Amoxicillin	16	6.4	8	2.7	16	7.3	8	2.5

7.76–7.74 (m, 1H, ArH), 7.69–7.67 (d, J = 6 Hz, 1H, ArH), 7.63–7.32 (m, 4H, ArH), 7.32–7.28 (m, 2H, ArH), 4.78 (t, J = 6.8 Hz, 2H, indole-CH_2), 4.39 (s, 2H, NH_2), 3.88 (s, 2H, OCH_3), 3.74 (t, J = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 908.80 [(2M+23)$^+$, 100]. Anal. Calcd for $C_{24}H_{21}N_5O_2S$: C, 64.99; H, 4.77; N, 15.79. Found: C, 65.07; H, 4.75; N, 15.76%.

Synthesis of compounds **8a–l***; conventional method*

Compound **7** (66.4 mg, 0.15 mmoL) and an aromatic aldehyde (0.15 mmoL) were dissolved in acetic acid (2 mL) in a 10 mL round bottom flask and stirred and heated to 100 °C. The reaction was monitored by TLC to ensure that it was completed. Then the solvent was removed by reduced pressure distillation. The residue was recrystallised in MeOH or EtOH to give compounds **8^a–l** (46–68%) as solids of various colours.

Synthesis of compounds **8a–l***; microwave method*

Compound **7** (66.4 mg, 0.15 mmoL), an aromatic aldehyde (0.15 mmoL) and two drops of acetic acid (catalyst) were mixed thoroughly by grinding in a porcelain mortar. The mixture was added into a specialised vessel which was placed in a microwave oven and irradiated at 300 W for 4–7 min. The reaction was monitored by TLC until it was completed. The mixture was recrystallised in MeOH or EtOH to obtain the pure products **8a–l** (82–92%) as solids of various colours. The physical and spectra data of the compounds **8a–l** are as follows.

8a: White solid (86%), m.p. 182–184 °C (MeOH); IR, ν: 3560, 3053, 2946, 2830, 2720, 1688, 1574, 1539, 1438, 1399, 1290, 1271, 770, 746 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.78 (s, 1H, OH), 8.38 (s, 1H, ArH), 8.23 (s, 1H, ArH), 8.13 (d, J = 7.6 Hz, 1H, ArH), 8.03 (d, J = 7.2 Hz, 2H, ArH), 7.87 (s, 1H, ArH), 7.74 (t, J = 6.4 Hz, 2H, ArH), 7.66 (t, J = 8.0 Hz, 1H, ArH),7.60–7.58 (m, 2H, ArH), 7.29–7.19 (m, 3H, ArH), 6.94 (t, J = 8.0 Hz, 3H, ArH), 4.77 (t, J = 6.8 Hz, 2H, indole–CH_2), 3.79 (s, 3H, OCH_3), 3.76 (t, J = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 547.89 [(M+1)$^+$, 100]. Anal. Calcd for $C_{31}H_{25}N_5O_3S$: C, 67.99; H, 4.60; N, 12.79. Found: C, 68.06; H, 4.58; N, 12.76%.

8b: White solid (88%), m.p. 126–128 °C (MeOH); IR, ν: 3052, 2945, 2361, 2354, 1698, 1587, 1532, 1464, 1436, 1395, 1280, 1222, 1160, 774, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20 (t, J = 6.8 Hz, 1H, ArH), 8.03 (d, J = 8.4 Hz, 1H, ArH), 7.95 (s, 1H, ArH), 7.93–7.89 (m, 2H, ArH), 7.79 (s, 1H, ArH), 7.70 (d, J = 6.8 Hz, 1H, ArH), 7.59–7.53 (m, 4H, ArH), 7.45 (d, J = 8.0 Hz, 2H, ArH), 7.33–7.28 (m, 2H, ArH), 7.25 (d, J = 8.8 Hz, 2H, ArH), 4.83 (t, J = 6.8 Hz, 2H, indole-CH_2), 3.90 (s, 3H, OCH_3), 3.79–3.75 (t, J = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 611.96 [(M+1)$^+$, 100]. Anal. Calcd for $C_{31}H_{24}BrN_5O_2S$: C, 60.99; H, 3.96; N, 11.47. Found: C, 61.06; H, 3.94; N, 11.45%.

8c: Yellow solid (85%), m.p. 148–150 °C (EtOH); IR, ν: 3110, 3050, 2948, 1694, 1523, 1346, 1226, 1162, 846, 777, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 6.8 Hz, 1H, ArH), 8.15 (d, J = 8.8 Hz, 2H, ArH), 8.07 (d, J = 8.4 Hz, 1H, ArH), 7.95 (d, J = 8.0 Hz, 1H, ArH), 7.87 (s, 1H, ArH), 7.83 (t, J = 5.6 Hz, 2H, ArH), 7.73 (d, J = 6.8 Hz, 1H, ArH), 7.62–7.49 (m, 6H, ArH), 7.31–7.27 (m, 2H, ArH), 4.84 (t, J = 6.8 Hz, 2H, indole-CH_2), 3.89 (s, 3H, OCH_3), 3.82 (t, J = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 576.98 [(M+1)$^+$, 100]. Anal. Calcd for $C_{31}H_{24}N_6O_4S$: C, 64.57; H, 4.20; N, 14.57. Found: C, 64.60; H, 4.18; N, 14.55%.

8d: White solid (87%), m.p. 198–200 °C (MeOH); IR, ν: 3419, 3058, 2959, 1721, 1688, 1597, 1438, 1293, 1229, 802, 744 738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.41 (s, 1H, OH), 8.30 (s, 1H, ArH), 8.22 (s, 1H, ArH), 8.10 (d, J = 8.0 Hz, 1H, ArH), 8.02 (s, 2H, ArH), 7.91 (m, 1H, ArH), 7.77–7.67 (m, 3H, ArH), 7.64–7.62 (m, 3H, ArH), 7.41 (d, J = 8.8 Hz, 1H, ArH), 7.28–7.22 (m, 2H, ArH), 6.77 (d, J = 8.4 Hz, 2H, ArH), 4.76–4.72 (t, J = 6.8 Hz, 2H, indole-CH_2), 3.79 (s, 3H, OCH_3), 3.74 (t, J = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 547.97 [(M+1)$^+$, 100]. Anal. Calcd for $C_{31}H_{25}N_5O_3S$: C, 67.99; H, 4.60; N, 12.79. Found: C, 68.05; H, 4.58; N, 12.75%.

8e: Yellow solid (90%), m.p. 212–214 °C (EtOH); IR, ν: 3054, 2934, 2357, 1697, 1533, 1435, 1395, 1261, 1223, 1160, 775, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1H, ArH), 8.20 (d, J = 8.0 Hz, 1H, ArH), 8.04 (d, J = 8.0 Hz, 1H, ArH), 7.97 (s, 1H, ArH), 7.94–7.92 (m, 1H, ArH), 7.89 (d, J = 7.6 Hz, 1H, ArH), 7.76 (d, J = 6.8 Hz, 2H, ArH), 7.64–7.60 (m, 2H, ArH), 7.55–7.53 (m, 2H, ArH), 7.38–7.21 (m, 5H, ArH), 4.85 (t, J = 6.8 Hz, 2H, indole-CH_2), 3.90 (s, 3H, OCH_3), 3.80 (t, J = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 1242.41 [(2M+23)$^+$, 100]. Anal. Calcd for $C_{31}H_{24}BrN_5O_2S$: C, 60.99; H, 3.96; N, 11.47. Found: C, 61.05; H, 3.93; N, 11.44%.

8f: Yellow solid (88%), m.p. 160–162 °C (MeOH); IR, ν: 3058, 2942, 2365, 2341, 1697, 1533, 1436, 1395, 1261, 1223, 1160, 775, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1H, ArH), 8.20 (d, J = 7.6 Hz, 1H, ArH), 8.05 (d, J = 8.0 Hz, 1H, ArH), 7.97 (s, 1H, ArH), 7.95–7.92 (m, 1H, ArH), 7.89 (d, J = 7.6 Hz, 1H, ArH), 7.78–7.74 (m, 2H, ArH), 7.64–7.59 (m, 2H, ArH), 7.55–7.53 (m, 2H, ArH), 7.34–7.28 (m, 3H, ArH), 7.23–7.18 (m, 2H, ArH), 4.85 (t, J = 6.8 Hz, 2H, indole-CH_2), 3.90 (s, 3H, OCH_3), 3.80 (t, J = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 1152.53 [(2M+23)$^+$, 100]. Anal. Calcd for $C_{31}H_{24}ClN_5O_2S$: C, 65.77; H, 4.27; N, 12.37. Found: C, 65.81; H, 4.24; N, 12.34%.

8g: Yellow solid (88%), m.p. 212–214 °C (EtOH); IR, ν: 3112, 3054, 2946, 2361, 1698, 1533, 1395, 1224, 1161, 1090, 775, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, J = 7.6 Hz, 1H, ArH), 8.02 (d, J = 8.4 Hz, 1H, ArH), 7.96–7.91 (m, 2H, ArH), 7.69 (d, J = 7.2 Hz, 1H, ArH), 7.64 (s, 1H, ArH), 7.61–7.53 (m, 5H, ArH), 7.33–7.28 (m, 3H, ArH), 6.68–6.67 (d, J = 3.2 Hz, 1H, ArH), 6.43 (s, 1H, ArH), 4.83 (t, J = 6.8 Hz, 2H, indole-CH_2), 3.90 (s, 3H, OCH_3), 3.76 (t, J = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 1064.75 [(2M+23)$^+$, 100]. Anal. Calcd for $C_{29}H_{23}N_5O_3S$: C, 66.78; H, 4.44; N, 13.43. Found: C, 66.82; H, 4.41; N, 13.45%.

8h: Yellow solid (86%); m.p. 152–154 °C (MeOH); IR, ν: 3050, 2938, 1697, 1588, 1395, 1223, 1161, 1090, 775, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.20–8.18 (m, 1H, ArH), 8.03 (d, J = 8.4 Hz, 1H, ArH), 7.96 (s, 1H, ArH), 7.93–7.90 (m, 2H, ArH), 7.81 (s, 1H, ArH), 7.71–7.69 (d, J = 6.8 Hz, 1H, ArH), 7.60–7.57 (m, 2H, ArH), 7.55–7.53 (m, 3H, ArH), 7.33–7.28 (m, 5H, ArH), 4.84 (t, J = 6.8 Hz, 2H, indole-CH_2), 3.90 (s, 3H, OCH_3), 3.79 (t, J = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 565.90 [(M+1)$^+$, 100]. Anal. Calcd for $C_{31}H_{24}ClN_5O_2S$: C, 65.77; H, 4.27; N, 12.37. Found: C, 65.82; H, 4.25; N, 12.35%.

8i: White solid (82%), m.p. 117–119 °C (EtOH); IR, ν: 3054, 2942, 1698, 1597, 1258, 1166, 1089, 775, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.21 (d, *J* = 6.8 Hz, 1H, ArH), 8.02–7.96 (m, 3H, ArH), 7.91 (t, *J* = 6.8 Hz, 1H, ArH), 7.81 (s, 1H, ArH), 7.71 (d, *J* = 7.2 Hz, 1H, ArH), 7.61–7.53 (m, 4H, ArH), 7.38 (d, *J* = 8.8 Hz, 2H, ArH), 7.33–7.28 (m, 2H, ArH), 6.82 (d, *J* = 8.8 Hz, 2H, ArH), 4.84 (t, *J* = 6.8 Hz, 2H, indole-CH_2), 3.90 (s, 3H, $COOCH_3$), 3.79 (s, 3H, $ArOCH_3$), 3.77 (t, *J* = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 561.98 [$(M+1)^+$, 100]. Anal. Calcd for $C_{32}H_{27}N_5O_3S$: C, 68.43; H, 4.85; N, 12.47. Found: C, 68.49; H, 4.82; N, 12.45%.

8j: White solid (85%), m.p. 190–192 °C (MeOH); IR, ν: 3390, 3052, 2944, 2360, 2342, 1698, 1603, 1533, 1463, 1396, 1262, 1224, 1158, 1090, 776, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.85 (s, 1H, OH), 8.20–8.19 (d, *J* = 7.2 Hz, 1H, ArH), 8.04 (d, *J* = 8.4 Hz, 1H, ArH), 7.97 (s, 1H, ArH), 7.94 (d, *J* = 8.0 Hz, 3H, ArH), 7.69 (d, *J* = 7.2 Hz, 1H, ArH), 7.60 (t, *J* = 7.6 Hz, 4H, ArH), 7.36–7.28 (m, 3H, ArH), 6.92 (d, *J* = 8.4 Hz, 1H, ArH), 6.81–6.73 (m, 2H, ArH), 4.85 (t, *J* = 6.8 Hz, 2H, indole-CH_2), 3.89 (s, 3H, OCH_3), 3.81 (t, *J* = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 1116.32 [$(2M+23)^+$, 100]. Anal. Calcd for $C_{31}H_{25}N_5O_3S$: C, 67.99; H, 4.60; N, 12.79. Found: C, 68.05; H, 4.57; N, 12.75%.

8k: Yellow solid (88%), m.p. 149–151 °C (EtOH); IR, ν: 3054, 2946, 2361, 2344, 1697, 1533, 1448, 1396, 1380, 1261, 1224, 1161, 1090, 776, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (t, *J* = 7.2 Hz, 1H, ArH), 8.04 (d, *J* = 8.4 Hz, 1H, ArH), 7.96 (s, 1H, ArH), 7.94–7.89 (m, 2H, ArH), 7.82 (s, 1H, ArH), 7.72 (d, *J* = 6.8 Hz, 1H, ArH), 7.60–7.54 (m, 4H, ArH), 7.33–7.28 (m, 3H, ArH), 7.19 (d, *J* = 9.6 Hz, 1H, ArH), 7.14–7.10 (m, 1H, ArH), 7.07 (d, *J* = 7.6 Hz, 1H, ArH), 4.84 (t, *J* = 6.8 Hz, 2H, indole-CH_2), 3.90 (s, 3H, OCH_3), 3.80 (t, *J* = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 1120.56 [$(2M+23)^+$, 100]. Anal. Calcd for $C_{31}H_{24}FN_5O_2S$: C, 67.74; H, 4.40; N, 12.74. Found: C, 67.80; H, 4.37; N, 12.70%.

8l: Pale solid (92%), m.p. 94–96 °C (EtOH); IR, ν: 3053, 2945, 2361, 2328, 1698, 1533, 1396, 1374, 1261, 1224, 1161, 1090, 776, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (t, *J* = 6.4 Hz, 1H, ArH), 8.02 (d, *J* = 8.4 Hz, 1H, ArH), 7.96 (s, 2H, ArH), 7.93–7.90 (m, 1H, ArH), 7.88 (s, 1H, ArH), 7.71 (d, *J* = 7.2 Hz, 1H, ArH), 7.61–7.53 (m, 4H, ArH), 7.45–7.39 (m, 3H, ArH), 7.33–7.28 (m, 4H, ArH), 4.84 (t, *J* = 6.8 Hz, 2H, indole-CH_2), 3.89 (s, 3H, OCH_3), 3.78 (t, *J* = 6.8 Hz, 2H, SCH_2); ESI–MS (*m/z*, %): 530.01 [$(M+1)^+$, 100]. Anal. Calcd for $C_{31}H_{25}N_5O_2S$: C, 70.04; H, 4.74; N, 13.17. Found: C, 70.09; H, 4.71; N, 13.14%.

*Antibacterial activity test for the MIC values (*in vitro*):* The MIC was evaluated by the double dilution method in tubes employing standard inoculums of 10^5 CFU mL^{-1}. Successive dilutions of the test compounds dissolved in DMSO (1 mL) were prepared to final concentrations of 256, 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25 μg mL^{-1}. Bacterial fluid of 0.5 McFarland standards (1 mL) was added into each test solution. The MIC values were visually determined by inhibition of the visible bacterial growth after incubation for 16 h at 37 °C.

*Antibacterial activity test for the IC_{50} values (*in vitro*):* The IC_{50} evaluation was performed by the inhibition zone test. Serial dilutions of the test compounds dissolved in DMSO were prepared to final concentrations of 640, 320, 160, 80, 40, 20, 10, 5 μg mL^{-1}. Bacteria fluids of 0.5 McFarland standards were painted on bouillon medium and then filter papers (diameter of 6 mm) saturated with compound dilutions above were placed on top of the growing bacteria. The diameter of the inhibition zone was obtained after incubation at 37 °C for 16 h.

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