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SYNTHESIS AND BIOLOGICAL ACTIVITY OF AMINOISOQUINOLINE SCHIFF BASES

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Abstract – Twelve new isoquinoline Schiff bases were prepared in excellent yields by the condensation reaction of different aromatic aldehydes with 1-chloro-5-aminoisoquinoline. The structures of the synthesized compounds were confirmed by nuclear magnetic resonance and mass spectrometry. All new compounds were tested against 3 microorganisms: *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*. The results showed that compounds **3d**, **3k** and **3l** exhibited excellent antibacterial activity against *E. coli* with diameters of 16.9, 16.7 and 15.5 mm, respectively. The antibacterial diameter of compound **3e** against *S. aureus* was 14.5 mm, and it demonstrated good antibacterial action.

Isoquinoline alkaloids are an important class of common heterocyclic compounds, with isoquinoline or tetrahydroisoquinoline as the basic nucleus, which exist in many natural products. Since the first biologically active isoquinoline alkaloid, morphine, was isolated from the opium plant in the early 19th century,[1] this class of compounds has attracted extensive scientific attention. Increasing numbers of isoquinoline alkaloids have been isolated and identified from natural sources, and various studies have reported their antitumor,[2] antimalarial,[3] antibacterial,[4] antifungal,[5] antiparasitic and insecticidal,[6] antiviral,[7] antiinflammatory,[8] antiplatelet and other activities.[9] Berberine (Figure 1) extracted from rhizomes of *Coptis chinensis* and other plants is used as an antibacterial agent to treat gastroenteritis, bacillary dysentery and other intestinal infections. As lead compounds in the drug discovery and development process, isoquinoline alkaloids have a high probability of success,[10] reflected by several revolutionary drugs, such as the analgesic morphine, the antibacterial berberine, the antitussive codeine,

the antirheumatic sinomenine, and the acetylcholinesterase inhibitor galantamine.[11] Derivatives containing isoquinoline backbones have become the focus of research in the scientific community due to their wide range of biological properties. Many isoquinoline derivative drugs are currently in clinical application or preclinical stage for the treatment of a wide range of diseases, such as tumors, respiratory diseases, infections, neurological diseases, cardiovascular and cerebrovascular diseases, endocrine and metabolic diseases.[12] The research on the use of isoquinoline skeletons to design active structural groups in drug molecules is becoming more and more active.

Schiff bases are key intermediates in organic synthesis and common ligands in coordination chemistry. Synthesis, characterization and structure-activity relationship of Schiff bases have been studied worldwide as it is proven that C=N linkage in Schiff bases is an essential feature for bioactivity.[13] Schiff bases have been reported to possess noteworthy antibacterial,[14] antifungal,[15] anticancer,[16] urease inhibition,[17] antioxidant,[18] and antiglycation activities.[19] The antibacterial mechanism of Schiff base is to interfere with microbial cellular activities by forming hydrogen bonds with the active centers of cellular constituents through azomethine (-C=N-) linkage.[20] Schiff base can also achieve antibacterial effect by destroying microbial cell wall morphology,[21] regulating gene expression associated with metabolism, hemolysis, and virulence,[22] etc. Schiff bases derived from the prodrug abacavir (Ziagen) have been reported to exhibit good antiviral activity and have been shown to be potent lead molecules for further clinical use as anti-HIV therapy.[23] Furthermore, Schiff bases of 2-phenylquinazolin-4(3*H*)-one have been reported to show antiviral activity against some strains of viruses like feline corona virus, influenza viruses, and herpes simplex virus types 1 and 2.[24] Imran's research group[25] designed and synthesized a series of bisindolylmethane Schiff bases (Figure 1), demonstrating the potential of this series of compounds as antimicrobial agents. Gao's group discovered in their research on the antibacterial activity of berberine Schiff base derivatives that the introduction of a chlorine atom significantly improves the antibacterial effect,[26] and the side chain of the isoquinoline benzene ring is another important area to construct novel compounds with better activity.

Isoquinoline and Schiff base structures have been widely used in drug design. However, there is little research on derivatives of isoquinoline Schiff base. Therefore, we designed and synthesized a series of isoquinoline Schiff base derivatives based on the structure combination principle of drug design, and carried out in vitro biological activity research, hoping to get better bioactive structures (Figure 1).

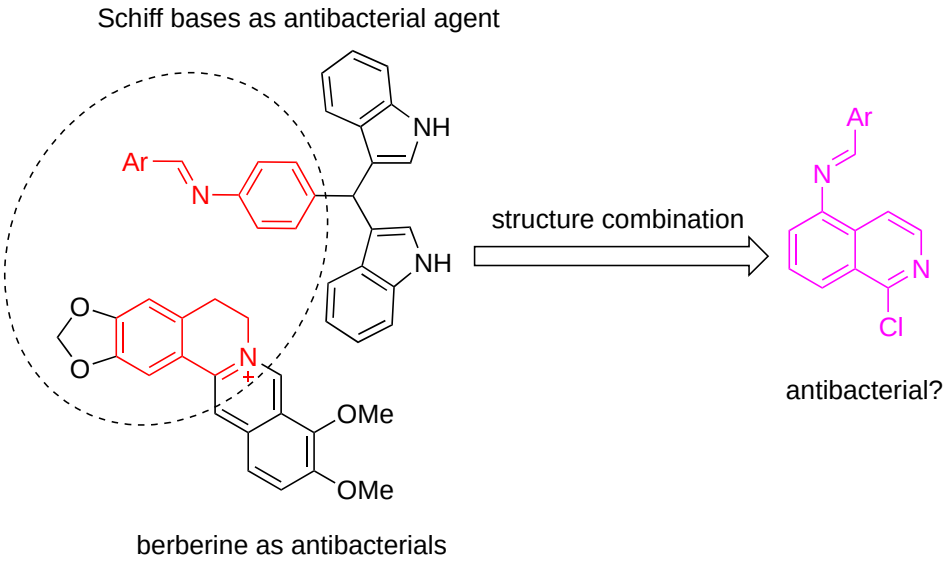


Figure 1. Structural combination of aminoisoquinoline Schiff bases

CHEMISTRY

A series of aminoisoquinoline Schiff bases (**3a–3l**) were prepared by treatment of 1-chloro-5-aminoisoquinoline (**2**) with the corresponding aldehydes in toluene. The general synthesis route of aminoisoquinoline Schiff base is shown in Figure 2. *p*-Hydroxybenzaldehyde and **2** were chosen as the model substrates for the optimization reaction procedure. The yield of Schiff base is highest only in toluene (Table 1, Entries 1–4). Because the solubility of Schiff base in toluene is lower than that in methanol and ethanol, solid products will be separated easily by filtration. In order to increase the reaction rate and yield, we added an appropriate amount of catalyst during the reaction. Both acetic acid (AcOH) and *p*-toluenesulfonic acid (TsOH) were tested (Table 1, Entries 4–5, 10), and the results showed that the catalytic effect of acetic acid was better than that of *p*-toluenesulfonic acid. Then we further investigated the effect of temperature on the reaction yield. The findings indicated that the yield of Schiff base increased slightly with the increase of temperature (Table 1, Entries 5–9). The yield is the highest at the reflux temperature. The best reaction procedure was endowed by Entry 9 with such conditions: the solvent was toluene, the catalyst was acetic acid, and the temperature was 110 °C. With the optimized conditions in hand, we systematically investigated the scope of the aromatic aldehydes access to Schiff bases (Table 2).

Table 1. Optimization of reaction conditions

Entry	Solvent	Temp. (°C)	Catalyst	Yield(%)
1	MeOH	65	TsOH	45
2	EtOH	65	TsOH	60
3	benzene	65	TsOH	65
4	toluene	65	TsOH	75
5	toluene	65	AcOH	85
6	toluene	75	AcOH	88
7	toluene	85	AcOH	90
8	toluene	95	AcOH	90
9	toluene	110	AcOH	95
10	toluene	110	TsOH	86

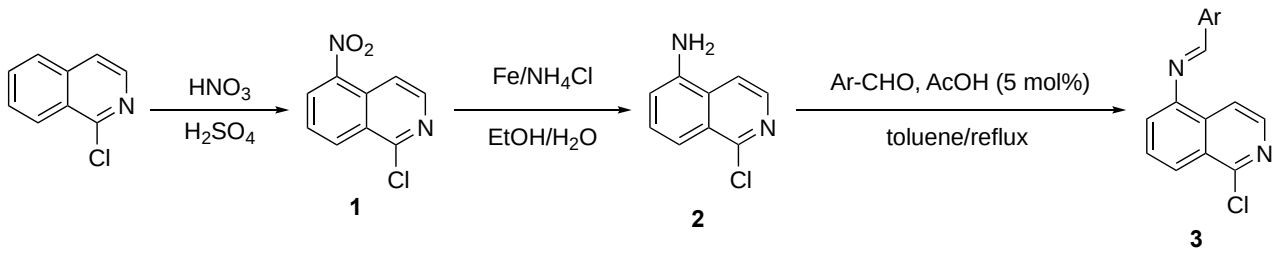
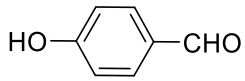
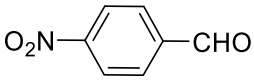
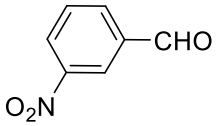
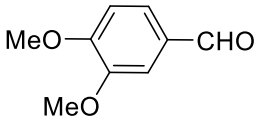
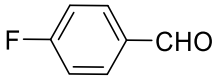
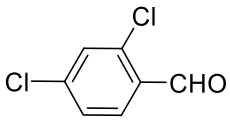
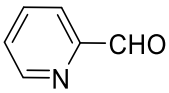
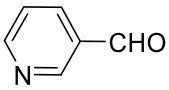
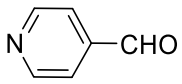
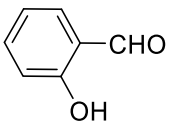
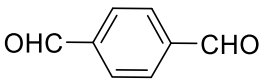
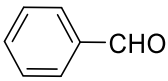


Figure 2. General synthetic route for aminoisoquinoline Schiff bases

Twelve novel aminoisoquinoline Schiff bases were successfully synthesized under our optimized conditions with a high yield. We discovered that aromatic aldehydes that bear electron-withdrawing groups are more reactive than those with electron-donating groups. For example, obtaining compounds **3b** and **3c** takes less time than acquiring compound **3d** (Table 2). This is because the strong electron-withdrawing property of nitro group, which increases the electropositivity of the electrophilic center on aromatic aldehydes. As a result, aromatic aldehydes containing nitro group have better activity, and can react well without the participation of catalyst. In addition, for compounds **3a** and **3j** with the same substituent, **3a** has better reactivity than **3j**. This may be due to the steric parameters of *ortho* hydroxyl group, which reduces the reactivity of the compound.

Table 2. Synthesis of aminoisoquinoline Schiff base by substrates expansion

Substrates	Compounds	Time	Yield(%)
	**3a**	3 h	95
	**3b**	2 h[a]	95
	**3c**	2 h[a]	95
	**3d**	8 h	88
	**3e**	3 h	85
	**3f**	6 h	90
	**3g**	4 h	95
	**3h**	6 h	92
	**3i**	6 h	92
	**3j**	4 h	95
	**3k**	2 h	60
	**3l**	3 h	92

[a] indicates that no catalyst is required for the reaction

^{1}H NMR, ^{13}C NMR and mass spectrometry were used to confirm the formation of the final Schiff bases **3a**–**3l**. We found a strong singlet peak at 8.50–8.98 ppm in the ^{1}H NMR spectrum, and a carbon signal was detected at 157.13–164.13 ppm in the ^{13}C NMR spectrum, which was consistent with the chemical shift values of azomethine (-CH=N-) reported in the literature.[27] Among them, the carbon signal of compound **3e** was split at 132.27 (d, J = 3.0 Hz) and 131.25 (d, J = 8.9 Hz) ppm, which may be caused by carbon-fluorine dipole coupling. The carbon signal splitting caused by fluorine nuclei can be confirmed by the research of Magnuson research group.[28] The mass spectral data were coherent with their molecular weight.

ANTIBACTERIAL BIOASSAY

The inhibitory ability of the newly prepared compounds against *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans* was evaluated by the Oxford cup method. The results are shown in Table 3. In the Oxford Cup method, a diameter of the inhibition zone is 20 mm or more indicates that the drug has a very strong antibacterial effect on the strain; the inhibition zone of 15–20 mm is categorized as strong antibacterial effect; diameter of 10–15 mm indicates a moderate antibacterial effect; and diameter of 10 mm or less indicates that there is little or no antibacterial effect of the compound on the strain. The results listed in Table 3 show that these derivatives have moderate to strong inhibitory activity against the Gram-negative bacteria *E. coli*, weak to moderate inhibitory activity against the Gram-positive bacteria *S. aureus*, and weak inhibitory activity against the fungal *C. albicans*. Most of the Schiff base derivatives showed better antibacterial activity than the substrates 1-chloroisoquinoline and benzaldehyde. It is worth mentioning that for compounds having the same substituents at different positions, the Schiff base with substituents at the *para* position shows better inhibitory activity. Among them, the compounds having methoxy, nitro and halogen display excellent inhibitory activity against *E. coli*, and the compounds with hydroxyl have weak inhibitory activity, which may be that the lipophilicity of hydroxyl is not as good as methoxy, nitro and halogen. According to Overtone's concept of cell permeability, lipid solubility plays an important role in regulating antibacterial activity based on the ability of cell membranes to allow only lipid-soluble substances to pass through. Therefore, compounds with higher lipophilicity, such as those with methoxy, nitro, and halogen groups, have a greater ability to diffuse into bacteria and lead to increased antibacterial activity of these compounds. The charge distribution of the compounds has close relations with biological activity. If the distribution of charge density of drug is just suited with the specific receptor, the interaction between drug and receptor would increase, and then drug and receptor are apt to form complexes and increase the activity. The weak antibacterial activity of compound **3g** compared to compounds **3h** and **3i** may be explained by their charge distribution. These derivatives generally showed poor inhibitory activity against *C. albicans*, which may be related to the structural

differences between fungi and bacteria. The tested compounds selectively showed good antibacterial effects against bacteria.

Table 3. Screening results of compounds **3a–3l** using the Oxford cup method (zones of inhibition in mm)

Compounds	Inhibition Zone (mm)		
	Candida albicans	***Staphylococcus aureus***	***Escherichia coli***
3a	11.5	8.7	9.4
3b	9.3	10.6	14.3
3c	–	8.5	13.5
3d	–	9.1	16.9
3e	10.3	14.5	14.9
3f	11.3	8.3	13.7
3g	–	–	–
3h	10.5	9.3	14.3
3i	11.4	10.2	13.8
3j	–	9.8	10.6
3k	12	11.5	16.7
3l	–	9.3	15.5
1-chloroisoquinoline	9.8	8.8	11.3
benzaldehyde	–	8.3	9.5

"–" represents sample no inhibitory effect on the strain

CONCLUSION

In this work, 12 new aminoisoquinoline Schiff bases were synthesized in excellent yields through optimization of reaction conditions, and their structures were confirmed by spectroscopic studies. The antimicrobial activities of the synthesized compounds against *S. aureus, C. albicans* and *E. coli* were evaluated by Oxford cup method. Among them, compounds **3d**, **3k** and **3l** showed excellent antimicrobial activity against *E. coli* and compound **3e** showed good antimicrobial activity against *S. aureus*. These data lay a foundation for the study of Schiff base derivatives of aminoisoquinoline as potential antibacterial agents.

EXPERIMENTAL

General: Reagents were purchased from commercial sources and used as received. All anhydrous solvents were analytical grade and were used without further purification. The Gram-negative bacteria *E. coli*, the Gram-positive bacteria *S. aureus* and the fungus *C. albicans* used in the antibacterial experiments were all from Jiangsu Ocean University. Reaction progress was monitored by thin-layer chromatography on silica gel GF-254 with detection by UV. Melting points were determined on an SGWX-4 microscope melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCEIII 500MHz spectrometer. MS spectra were recorded by a ThermoFinnigan LCQ Advantage (USA) mass spectrometer.

Compounds **1** and **2** were synthesized according to methodologies described in the literature.[29]

General procedure for the synthesis of aminoisoquinoline Schiff bases 3a–3l

1-Chloro-5-aminoisoquinoline (2.100 mg, 0.56 mmol) and aromatic aldehyde (1 mmol) were dissolved in a mixed solution of toluene (15 mL) and acetic acid (5 mol%). The reaction mixture was stirred and refluxed at 110 °C for 2–8 h. The completion of the reaction was detected by TLC (5% *n*-hexane/$CHCl_3$), and the reaction mixture was cooled to room temperature. The resulting solid was filtered, washed with toluene, and recrystallized to give the desired aminoisoquinoline Schiff base.

1-Chloro-5-nitroisoquinoline (1)

Milky yellow solid; yield, 99%; mp 181–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, *J* = 8.5 Hz, 1H), 8.58 (dd, *J* = 7.7, 1.1 Hz, 1H), 8.52 (d, *J* = 6.1 Hz, 1H), 8.43 (dd, *J* = 6.1, 0.7 Hz, 1H), 7.87–7.80 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.61, 145.35, 144.76, 133.26, 130.32, 128.88, 127.50, 126.99, 115.80. HPLC-MS (*m/z*): Calcd for $C_9H_6N_2O_2Cl$ $[M+H]^+$: 209.0118. Found: 209.0124.

1-Chloroisoquinolin-5-amine (2)

Orange flaky crystals recrystallized from a solution of $CHCl_3$/*n*-hexane (1/20); yield, 92%; mp 176–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 5.9 Hz, 1H), 7.79–7.74 (m, 1H), 7.53 (dd, *J* = 5.9, 0.8 Hz, 1H), 7.49–7.44 (m, 1H), 6.99 (dd, *J* = 7.6, 0.8 Hz, 1H), 4.25 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.24, 141.90, 140.17, 128.93, 127.76, 127.73, 116.64, 114.29, 114.10. HPLC-MS (*m/z*): Calcd for $C_9H_8N_2Cl$ $[M+H]^+$: 179.0376. Found: 179.0383.

4-(((1-Chloroisoquinolin-5-yl)imino)methyl)phenol (3a)

Orange-red flaky crystals recrystallized from EtOAc; yield, 95%; mp 228–229 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.60 (s, 1H), 8.30 (d, *J* = 5.7 Hz, 1H), 8.15 (d, *J* = 5.8 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.83–7.74 (m, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.60, 161.75, 150.58, 148.85, 141.68, 133.87, 131.77, 130.12, 127.79, 126.99, 122.62, 118.67, 117.72, 116.28. HPLC-MS (*m/z*): Calcd for $C_{16}H_{12}N_2OCl$ $[M+H]^+$: 283.0638. Found: 283.0640.

***N*-(1-Chloroisoquinolin-5-yl)-1-(4-nitrophenyl)methanimine (3b)**

Yellow flaky crystals recrystallized from $CHCl_3$; yield, 95%; mp 238–239 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.44 (d, *J* = 8.8 Hz, 2H), 8.37 (dd, *J* = 11.9, 7.3 Hz, 3H), 8.27–8.20 (m, 2H), 7.89 (t, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.81, 150.72, 149.72, 147.47, 142.17, 141.62, 133.82, 130.68, 130.11, 126.99, 124.57, 124.31, 119.23, 117.60. HPLC-MS (*m/z*): Calcd for $C_{16}H_{11}N_3O_2Cl$ $[M+H]^+$: 312.0540. Found: 312.0542.

***N*-(1-Chloroisoquinolin-5-yl)-1-(3-nitrophenyl)methanimine (3c)**

Yellow flaky crystals recrystallized from $CHCl_3$; yield, 95%; mp 227 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.96–8.83 (m, 1H), 8.55 (d, *J* = 7.7 Hz, 1H), 8.45 (ddd, *J* = 8.2, 2.4, 1.0 Hz, 1H), 8.38 (d, *J* = 5.7 Hz, 1H), 8.23 (dd, *J* = 9.9, 4.5 Hz, 2H), 7.96–7.83 (m, 2H), 7.79–7.68 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.79, 150.70, 148.77, 147.55, 142.15, 137.73, 135.45, 133.72, 131.13, 130.12, 126.98, 126.74, 124.08, 123.87, 119.26, 117.63. HPLC-MS (*m/z*): Calcd for $C_{16}H_{11}N_3O_2Cl$ $[M+H]^+$: 312.0540. Found: 312.0547.

***N*-(1-Chloroisoquinolin-5-yl)-1-(3,4-dimethoxyphenyl)methanimine (3d)**

Orange crystals recrystallized from EtOAc; yield, 88%; mp 143–144 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.33 (d, *J* = 5.7 Hz, 1H), 8.21 (dd, *J* = 5.7, 0.7 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.83 (dd, *J* = 8.4, 7.5 Hz, 1H), 7.72 (d, *J* = 1.8 Hz, 1H), 7.59 (ddd, *J* = 10.3, 7.9, 1.3 Hz, 2H), 7.18–7.12 (m, 1H), 3.89 (d, *J* = 9.2 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.78, 152.91, 150.60, 149.61, 148.66, 141.78, 133.82, 130.15, 129.29, 127.00, 125.19, 122.86, 118.81, 117.79, 111.86, 110.40, 56.22, 56.04. HPLC-MS (*m/z*): Calcd for $C_{18}H_{16}N_2O_2Cl$ $[M+H]^+$: 327.0900. Found: 327.0898.

***N*-(1-Chloroisoquinolin-5-yl)-1-(4-fluorophenyl)methanimine (3e)**

Orange needles recrystallized from EtOAc; yield, 85%; mp 176–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.28 (d, *J* = 5.8 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 5.7 Hz, 1H), 8.05–7.97 (m, 2H), 7.65 (dd, *J* = 8.4, 7.5 Hz, 1H), 7.31 (dd, *J* = 7.4, 0.7 Hz, 1H), 7.25–7.17 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.15, 164.13, 160.26, 151.37, 148.38, 141.38, 133.77, 132.27 (d, *J* = 3.0 Hz), 131.25 (d, *J* = 8.9 Hz), 128.63, 127.40, 123.84, 117.47, 117.07, 116.29, 116.11. HPLC-MS (*m/z*): Calcd for $C_{16}H_{11}N_2ClF$ $[M+H]^+$: 285.0595. Found: 285.0601.

***N*-(1-Chloroisoquinolin-5-yl)-1-(2,4-dichlorophenyl)methanimine (3f)**

Orange-red needles recrystallized from EtOAc; yield, 90%; mp 181–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.35 (dd, *J* = 19.3, 7.1 Hz, 2H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 5.7 Hz, 1H), 7.70 (t, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 1.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.13, 151.44, 147.98, 141.54, 138.47, 136.88, 133.81, 131.47, 129.99, 129.81, 128.61, 127.89, 127.41, 124.50, 117.73, 116.95. HPLC-MS (*m/z*): Calcd for $C_{16}H_{10}N_2Cl_3$ $[M+H]^+$: 334.9910. Found: 334.9915.

***N*-(1-Chloroisoquinolin-5-yl)-1-(pyridin-2-yl)methanimine (3g)**

Brown needle-like crystals precipitated from the reaction solution; yield, 95%; mp 163–164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80–8.76 (m, 1H), 8.71 (d, *J* = 4.6 Hz, 1H), 8.38 (d, *J* = 7.9 Hz, 1H), 8.32 (d, *J* = 5.8 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 8.14 (dd, *J* = 5.8, 0.6 Hz, 1H), 7.91 (td, *J* = 7.6, 1.4 Hz, 1H), 7.71 (dd, *J* = 8.4, 7.5 Hz, 1H), 7.48–7.41 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.42, 154.19, 151.41, 149.90, 147.54, 141.49, 136.82, 133.74, 128.65, 127.41, 125.68, 124.56, 122.15, 117.68, 116.98. HPLC-MS (*m/z*): Calcd for $C_{15}H_{11}N_3Cl$ $[M+H]^+$: 268.0642. Found: 268.0645.

***N*-(1-Chloroisoquinolin-5-yl)-1-(pyridin-3-yl)methanimine (3h)**

Tawny solid recrystallized from a solution of $CHCl_3$/EtOAc (1/20); yield, 92%; mp 186–187 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.80 (d, *J* = 3.8 Hz, 1H), 8.62 (s, 1H), 8.41 (dt, *J* = 7.9, 1.7 Hz, 1H), 8.31 (d, *J* = 5.8 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 8.09 (dd, *J* = 5.8, 0.6 Hz, 1H), 7.68 (dd, *J* = 8.4, 7.5 Hz, 1H), 7.50 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.36 (dd, *J* = 7.4, 0.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.87, 152.62, 151.39, 151.17, 147.89, 141.53, 135.26, 133.70, 131.51, 128.57, 127.37, 124.42, 124.01, 117.45, 116.92. HPLC-MS (*m/z*): Calcd for $C_{15}H_{11}N_3Cl$ $[M+H]^+$: 268.0642. Found: 268.0649.

***N*-(1-Chloroisoquinolin-5-yl)-1-(pyridin-4-yl)methanimine (3i)**

Yellow solid recrystallized from EtOAc; yield, 92%; mp 199–200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (d, *J* = 5.8 Hz, 2H), 8.58 (s, 1H), 8.30 (dd, *J* = 26.4, 7.2 Hz, 2H), 8.09 (dd, *J* = 5.8, 0.6 Hz, 1H), 7.87 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.70 (dd, *J* = 8.4, 7.5 Hz, 1H), 7.38 (dd, *J* = 7.4, 0.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.65, 151.43, 150.81, 147.41, 142.24, 141.67, 133.66, 128.52, 127.38, 124.91, 122.43, 117.48, 116.84. HPLC-MS (*m/z*): Calcd for $C_{15}H_{11}N_3Cl$ $[M+H]^+$: 268.0642. Found: 268.0645.

2-(((1-Chloroisoquinolin-5-yl)imino)methyl)phenol (3j)

Orange flaky crystals recrystallized from a solution of $CHCl_3$/*n*-hexane (1/20); yield, 95%; mp 140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.86 (s, 1H), 8.71 (s, 1H), 8.33 (d, *J* = 5.8 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.99 (dd, *J* = 5.8, 0.7 Hz, 1H), 7.71 (dd, *J* = 8.5, 7.5 Hz, 1H), 7.51–7.42 (m, 3H), 7.11 (dd, *J* = 8.8, 0.5 Hz, 1H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.10, 161.25, 151.70, 145.76, 142.00, 134.17, 133.13, 132.79, 128.58, 127.41, 124.82, 119.54, 119.16, 118.85, 117.47, 116.33. HPLC-MS (*m/z*): Calcd for $C_{16}H_{12}N_2OCl$ $[M+H]^+$: 283.0638. Found: 283.0640.

1,1'-(1,4-Phenylene)bis(*N*-(1-chloroisoquinolin-5-yl)methanimine) (3k)

Orange solid recrystallized from $CHCl_3$; yield, 60%; mp 287–289 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 2H), 8.36 (d, *J* = 5.8 Hz, 2H), 8.29 (d, *J* = 8.5 Hz, 2H), 8.25–8.15 (m, 6H), 7.73 (dd, *J* = 8.5, 7.5 Hz, 2H), 7.43 (dd, *J* = 7.4, 0.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.69, 152.34, 148.18, 141.54, 133.84, 129.64, 128.61, 127.46, 124.34, 117.47, 117.04. HPLC-MS (*m/z*): Calcd for $C_{26}H_{17}N_4Cl_2$ $[M+H]^+$: 455.0830. Found: 455.0826.

***N*-(1-Chloroisoquinolin-5-yl)-1-phenylmethanimine (3l)**

Creamy yellow solid recrystallized from a solution of $CHCl_3$/*n*-hexane (1/20); yield, 92%; mp 120–121 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.32 (d, *J* = 5.8 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 8.14 (dd, *J* = 5.8, 0.7 Hz, 1H), 8.04 (dt, *J* = 3.8, 2.2 Hz, 2H), 7.69 (dd, *J* = 8.5, 7.4 Hz, 1H), 7.61–7.54 (m, 3H), 7.35 (dd, *J* = 7.4, 0.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.84, 151.33, 148.63, 141.35, 135.88, 133.77, 132.09, 129.20, 128.96, 128.64, 127.39, 123.74, 117.49, 117.14. HPLC-MS (*m/z*): Calcd for $C_{16}H_{12}N_2Cl$ $[M+H]^+$: 267.0689. Found: 267.0693.

Antibacterial activity

The inhibitory ability of the newly prepared compounds against *E. coli*, *S. aureus* and *C. albicans* was evaluated by the Oxford cup method. Under sterile conditions, *E. coli*, *S. aureus* and *C. albicans* were added to beef extract peptone agar medium, respectively, and cultured in a 37 °C incubator for 24 h. Take several identical colonies and place them in 2 mL sterile water to prepare bacterial suspension. Dilute the bacterial suspension to 10^6 cfu/mL, draw 0.2 mL of the diluted bacterial suspension and evenly distribute it on the surface of the sterile agar plate. Then three Oxford cups (inner diameter 6 mm, outer diameter 7.8 mm, and height 10 mm) were placed vertically on the surface of the medium. The obtained compounds were respectively dissolved in a DMSO solution to prepare a solution to be tested at a concentration of 1 mg/mL. 0.1 mL of the solution to be tested was put into an Oxford cup with a pipette, and the diameter of the inhibition zone was measured after incubating at 37 °C for 48 h. All tests were repeated three times and the final reading was determined by using the recorded average diameter.

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