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Green synthesis and antibacterial/fungal studies of two new Schiff base derived from 4-(imidazol-1-yl)benzaldehyde

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This study synthesizes two new Schiff bases, (E)-1-(4-1*H*-imidazol-1-yl)phenyl)-N-(*o*-tolyl)methanimine and (E)-1-(4-(1*H*-imidazol-1-yl)phenyl)-N-(*m*-tolyl)methanimine through condensation reaction between 4-(imidazol-1-yl)benzaldehyde and 2-toluidine/*o*-toluidine, respectively. FT-IR, X-ray diffraction and ^{1}H NMR spectroscopy have been carried out to characterize the structure of the products. Through antibacterial/ antifungal activity tests performed using 8 kinds of bacteria/fungus, it is found that the both of the two Schiff bases can suppress the growth of *Staphylococcus*, *Bacillus subtilis* and *Salmonella*, showing good potential as antibacterial drug.

Keywords: Schiff base, antibacterial activity, crystal structure

Schiff base is a group of compound with the structure of $R_1C{=}NR_2$, where R_1 and R_2 are aryl or alkyl group, are synthesized form the condensation of primary amines and carbonyl groups[1-5]. They have been widely used in many fields such as medicine, analysis, catalysis, anti-corrosion and so on[6-12]. In the field of medicine, many Schiff bases have been proved to have antibacterial, antifungal, antiviral and antitumor activities[6,13]. It is important to develop new Schiff base to broaden their applications[11,13-15].

4-(Imidazol-1-yl)benzaldehyde, as an imidazole derivative, can be used as reactant and intermediate to synthesize some important drugs. Its aldehyde group and imidazole ring make it possible to react with oxidant, alkyl group and metal ions. Particularly, it can be used to synthesize Schiff bases due to the active aldehyde group. However, few reports have reported the Schiff bases derived from 4-(Imidazol-1-yl) benzaldehyde. In this work, two new Schiff base are synthesized through condensation of 4-(imidazol-1-yl)benzaldehyde and 2-toluidine/o-toluidine. The results may contributes to the development of new antimicrobial agents and the understanding of the antimicrobial activity of Schiff base compounds.

Results and Discussion

FTIR spectra

IR spectra of 4-(imidazol-1-yl)benzaldehyde and S1 sample, which has quite different peaks, are shown in Figure 1. The peak at 1679 cm^{-1} in the spectra of raw material that can be ascribed to aromatic aldehyde cannot be observed anymore in the spectra of the product, showing the complete reaction of the raw materials. The peaks of the spectra of the product locate at 3100 cm^{-1} (m), 2360cm^{-1} (w), 1650 cm^{-1}(m), 1630 cm^{-1}(m), 1593 cm^{-1}(s), 1573 cm^{-1}(s), 1520 cm^{-1}(s), 1500 cm^{-1}(s), 1487 cm^{-1}(m), 1457 cm^{-1}(m), 1425 cm^{-1}(m), 1388 cm^{-1}(m), 1301 cm^{-1}(s), 1264 cm^{-1}(s), 1219 cm^{-1}(m), 1176 cm^{-1}(m), 1057 cm^{-1}(s), 968 cm^{-1}(s), 906 cm^{-1}(s), 841 cm^{-1}(s), 828 cm^{-1}(s), 786 cm^{-1}(s), 723 cm^{-1}(s), 710 cm^{-1}(s), 669 cm^{-1}(s), 538 cm^{-1}(s). S2 sample has almost the same peaks as S1 sample due to their similar molecular structure.

Therein, the weak peak at 1630 cm^{-1} can be attributed to the stretching mode of C=N bond, which cannot be found in the IR spectra of raw materials. The intensity of the peak was weaken due to the conjugation. The strong peaks at 841, 828, 723 and 710 cm^{-1} can be attributed to the stretching mode of C-H groups in benzene rings. Moreover, the peaks at

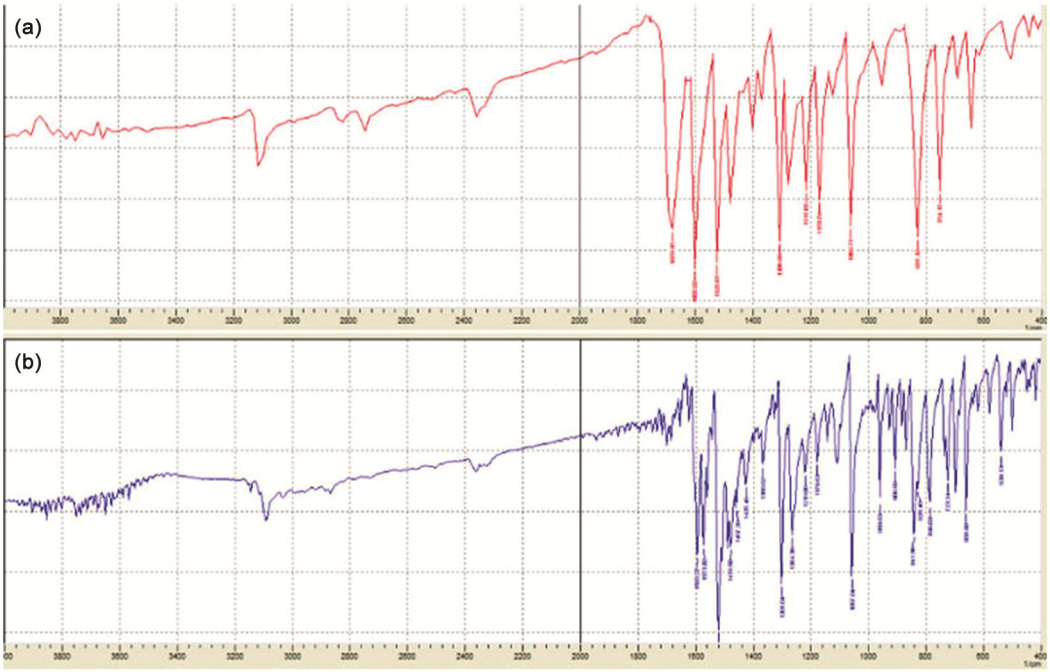

Figure 1 — IR spectra of 4-(imidazol-1-yl)benzaldehyde (a) and S1 sample (b)

1593, 1573, 1487 and 1457 cm^{-1} are the stretching mode of C=C in benzene rings. Besides, the moderately strong peaks at 1425 and 1388 correspond to the asymmetric bending vibration and the symmetric bending vibration of $–CH_3$ groups on benzene ring.

^{1}H NMR spectra

The ^{1}H NMR spectra of S1 sample has been shown in Figure 2. The integral area of the peaks are marked on the spectra. The three singlets at δ 7.287, δ 7.979, and δ 7.390 can be assignable to the hydrogens on imidazolyl ring. Besides, the two doublets at δ 7.553, δ 7.533 and δ 8.088, δ 8.086 can be assigned to the benzene ring connected to the imidazolyl ring. The hydrogen on the C=N group has a singlet at δ 8.435. The highest peak at δ 2.418 can be attributed to the three hydrogens on methyl. The hydrogen on the carbon next to the methyl has doublets at δ 6.996 and δ 6.977. The next hydrogen has triplets at δ 7.208, δ 7.190 and δ 7.172. The other two hydrogens have overlapped peaks, one of which possesses triplets at δ 7.296, 7.271 and δ 7.246, and the other one has doublets locates at about δ 7.271.

The ^{1}H NMR spectra of S2 sample has some distinct differences compared with that of S1. The hydrogens on the methyl shows one singlet at δ 2.4023. The hydrogen between the methyl and -C=N- has singlet at δ 7.0521 and its *para*-position hydrogen has triplets at δ 7.3136, δ 7.2947 and δ 7.2758. Besides, the hydrogen next to the methyl has doublets at δ 7.0858 and 7.0657. The rest hydrogen on the tolyl has doublets at δ 7.0303 and 7.4937. The other peaks are quite similar to that of S1 sample. The two doublets at δ 8.03201, δ 8.0108 as well as δ 7.5149, δ 7.4937 can be assigned to the hydrogens on the benzene ring. Moreover, the three singlets at δ 7.9692, δ 7.3548 and δ 7.2584 should be ascribed to the three hydrogens on imidazolyl ring.

Crystal structure

The resolved molecular structures of S1 and S2 are shown in Figure 3. The bond angles and bond lengths of S1 and S2 are shown in Table I and Table II. For S1 sample, the atoms in imidazole ring almost locate in the same plane. The same situation also happens in the two benzene rings. The torsion angle of C1-N2-C4-C9 and C1-N2-C4-C5 are -164.76(17) and 15.3(3)°. Thus the angle between the planes of imidazole ring and the C4/C5/C6/C7/C8/C9 benzene ring is about 15.3°. The torsion angle of C10-C7-C8-C9 is 177.96(16) which means C10 atom almost locate in the plane of C4/C5/C6/C7/C8/C9 benzene ring. Nevertheless, the torsion angle of C6-C7-C10-N3 is 5.2(3) representing that N3 atom is slightly off the plane. Besides, the torsion angle of C10-N3-C11-

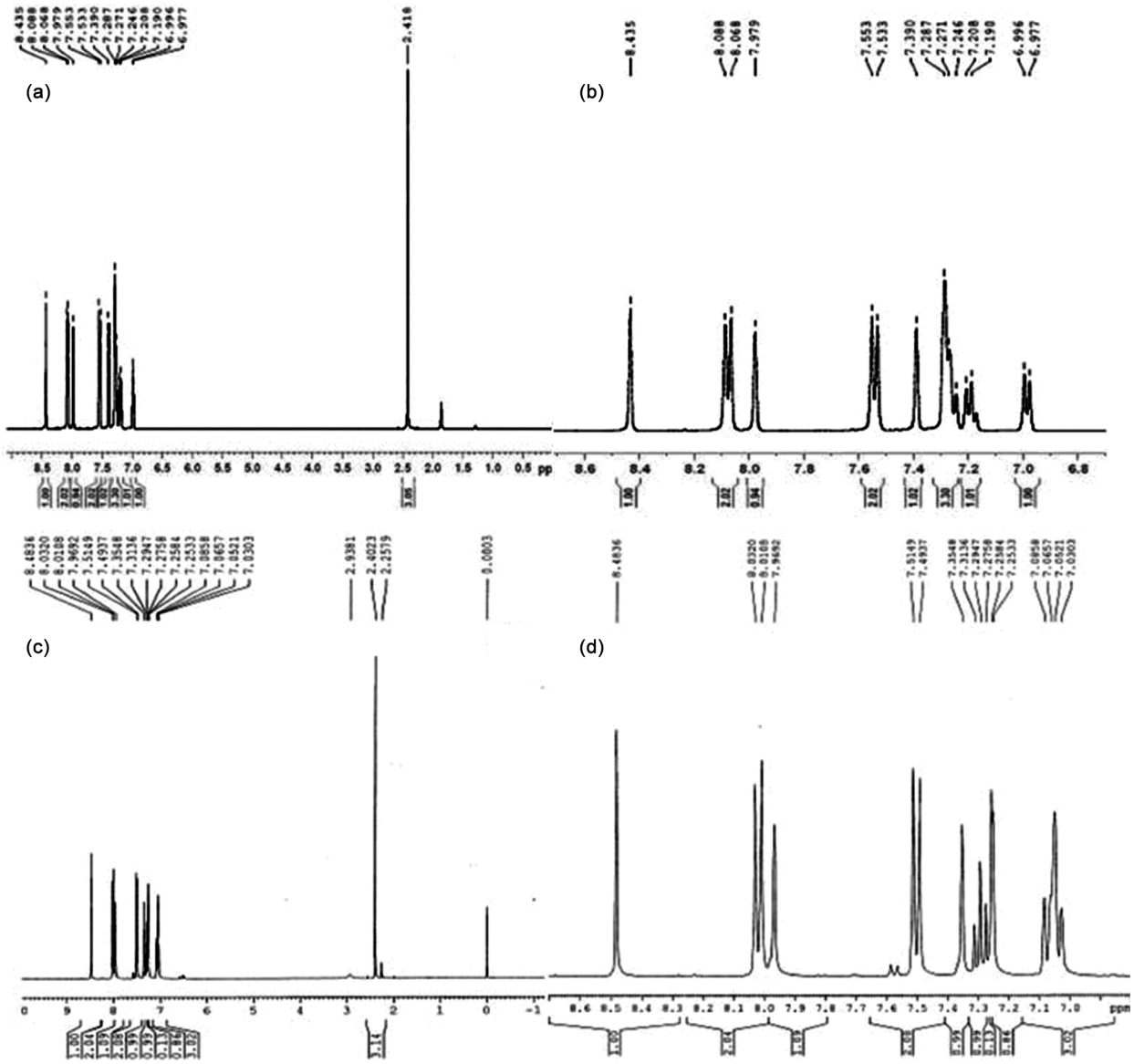

Figure 2 — Whole (a) and part (b) of H NMR spectra of S1 sample, whole (c) and part (d) of H NMR spectra of S2 sample

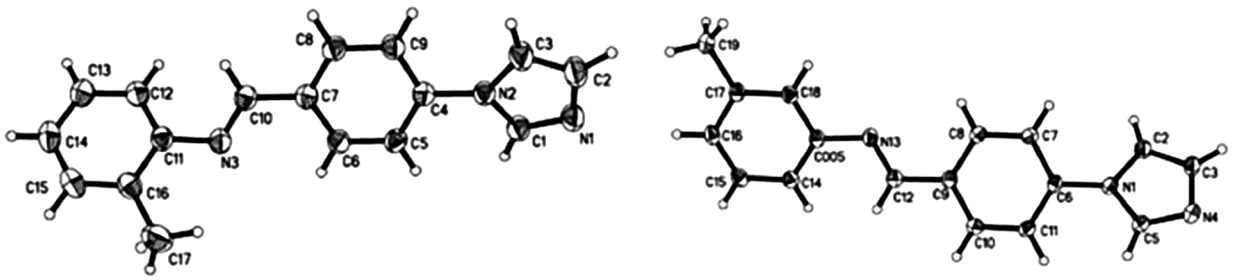

Figure 3 — The molecular structure of S1 (left) and S2 sample (right)

Table I — Bond angles of S1 and S2 sample

Bond of S1	Angle(°)	Bond of S2	Angle(°)
C1 N1 C2	104.12	C2N1C6	127.4(2)
C1 N2 C3	105.32	C5N1C2	106.4(2)
C1 N2 C4	127.43	C5N1C6	126.1(2)
C3 N2 C4	127.24	C5N4C3	104.9(2)
C10 N3 C11	119.12	C12N13C005	119.4(2)
N1 C1 N2	113.04	N1C2H2	127.2
C3 C2 N1	111.32	C3C2N1	105.6(2)
C2 C3 N2	106.19	C3C2H2	127.2
C9 C4 C5	119.69	N4C3H3	124.4
C9 C4 N2	120.34	C2C3N4	111.1(3)
C5 C4 N2	119.96	C2C3H3	124.4
C6 C5 C4	119.68	N1C5H5	124
C7 C6 C5	121.43	N4C5N1	112.0(2)
C6 C7 C8	117.93	N4C5H5	124
C6 C7 C10	121.61	C14C005N13	124.3(2)
C8 C7 C10	120.45	C18C005N13	116.8(2)
C7 C8 C9	121.25	C18C005C14	118.9(2)
C4 C9 C8	120.00	C7C6N1	119.3(2)
N3 C10 C7	122.77	C11C6N1	120.4(2)
C16 C11 C12	120.00	C11C6C7	120.3(2)
C16 C11 N3	118.03	C6C7H7	120.3
C12 C11 N3	121.89	C8C7C6	119.5(2)
C13 C12 C11	120.81	C8C7H7	120.3
C12 C13 C14	119.8	C7C8H8	119.5
C15 C14 C13	119.53	C7C8C9	120.9(2)
C14 C15 C16	122.10	C9C8H8	119.5
C11 C16 C15	117.69	C8C9C12	121.7(2)
C11 C16 C17	120.32	C10C9C8	118.6(2)
C15 C16 C17	121.98	C10C9C12	119.6(2)

C12 and C10-N3-C11-C16 are 43.9(2) and -139.21(17), respectively. Thus, there is a distinct angle between the planes of the two benzene rings. Similarly, C17 atom nearly situates in the plane of the benzene ring it connects.

For S2 sample, the atoms in imidazole ring also situate in the same plane and so do the atoms in two benzene rings according to the torsion angles between those atoms. The angle between the planes of imidazole ring and the C6/C7/C8/C9/C10/C11 benzene ring is about 15.3° is about 33° due to the torsion angle of C2-N1-C6-C7 and C5-N1-C6-C11 are -31.3° and -34.6° respectively. C12 atom has small deviation from the plane of C6/C7/C8/C9/C10/C11 benzene ring. N13 atom almost locate in the plane of C14/C15/C16/C17/C18/C005 benzene ring. However, the two planes of benzene rings has an obvious angle between each other because the torsion angle of C8-C9-C12-N13 is 8.2°.

The crystal structure and related crystal parameters are presented in Figure 4 and Table III respectively. The S1 sample belongs to monoclinic system and

Table II — Bond length of S1 and S2 sample

Bond of S1	Length (Å)	Bond of S2	Length (Å)
N1C1	1.300(2)	N1C2	1.378(4)
N1C2	1.350(3)	N1C5	1.367(3)
N2C1	1.349(2)	N1C6	1.420(3)
N2C3	1.360(2)	N4C3	1.372(4)
N2C4	1.417(2)	N4C5	1.314(4)
N3C10	1.264(2)	N13C005	1.421(3)
N3C11	1.414(2)	N13C12	1.274(4)
C1H1A	0.93	C2H2	0.93
C2C3	1.339(3)	C2C3	1.356(4)
C2H2A	0.93	C3H3	0.93
C2H3A	0.93	C5H5	0.93
C4C9	1.372(2)	C005C14	1.398(4)
C4C5	1.383(2)	C005C18	1.398(4)
C5C6	1.369(2)	C6C7	1.400(3)
C5H5A	0.93	C6C11	1.387(4)
C6C7	1.383(2)	C7H7	0.93
C6H6A	0.93	C7C8	1.379(4)
C7C8	1.381(2)	C8H8	0.93
C7C10	1.455(2)	C8C9	1.397(4)
C8C9	1.373(2)	C9C10	1.394(4)
C8H8A	0.93	C9C12	1.464(3)
C9H9A	0.93	C10H10	0.93
C10H10A	0.93	C10C11	1.381(4)
C11C16	1.392(2)	C11H11	0.93
C11C12	1.377(3)	C12H12	0.93
C12C13	1.373(3)	C14H14	0.93
C12H12A	0.93	C14C15	1.384(4)
C13C14	1.364(3)	C15H15	0.93
C13H13A	0.93	C15C16	1.390(4)
C14C15	1.371	C16H16	0.93
C14H14A	0.93	C16C17	1.397(4)
C15C16	1.38	C17C18	1.386(4)
C15H15A	0.93	C17C19	1.502(4)
C16C17	1.497	C18H18	0.93
C17H17A	0.96	C19H19A	0.96
C17H17B	0.96	C19H19B	0.96
C17H17C	0.96	C19H19C	0.96

Table III — Crystal data and structure refinement for the product

Parameter	S1	S2
Temperature (K)	296	296
Measurement range	2.68-27.82°	5.2-73.1°
Molecular formula	$C_{17}H_{15}N_3$	$C_{17}H_{15}N_3$
Molecular weight	261.32	261.32
a, b, c (nm)	1.3066, 8.9210, 1.4041	33.0827, 27.5151, 5.9315
α, β, γ (°)	90.00, 111.788, 90.00	90.0, 90.0, 90.0
Crystal system	Monoclinic	Orthorhombic
Space group	P2(1)/n	Fdd2
Cell volume (nm^3)	1.3987	5.399
Formula units (Z)	4	4
Density ($g\ cm^{-3}$)	1.241	1.286

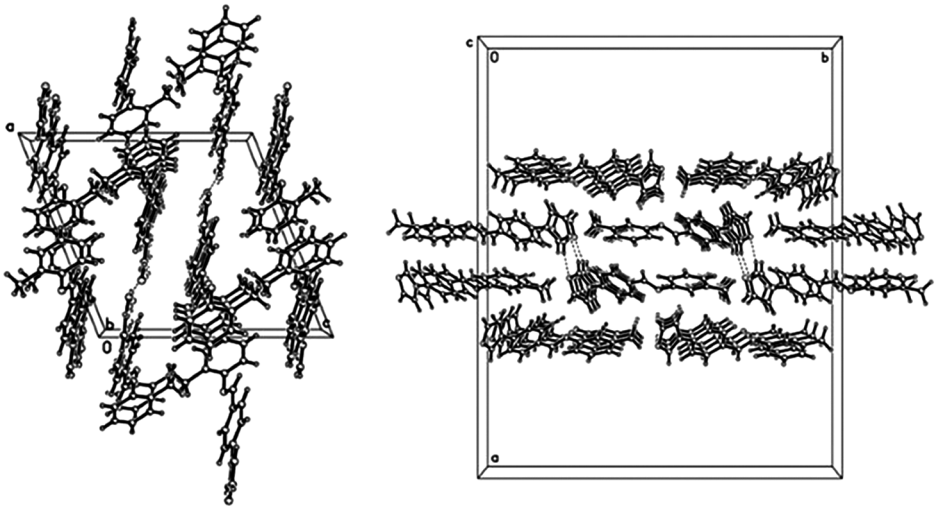

Figure 4 — Crystal structure of S1 (left) and S2 sample (right)

Table IV — Antibacterial/antifungal activity of the product

Bacteria/fungal	S1					S2					4-(imidazol-1-yl)benzaldehyde					control				
Typhoid bacillus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Staphylococcus	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
Pseudomonas aeruginosa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bacillus subtilis	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
Salmonella	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
Escherichia coli	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Saccharomyces	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Aspergillus niger	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

P2(1)/n space group. The value of a, b, and c axis are 1.3066, 8.9210, 1.4041 nm respectively. The value of β is 111.788°.The S2 sample belongs to Orthorhombic system and Fdd2 space group. Its value of a, b, and c axis are 33.0827, 27.5151, 5.9315 nm respectively. Besides, S1 possess intermolecular hydrogen bonds between N1 atom and hydrogen atom on C1 atom, and S2 has intermolecular hydrogen bonds between N4 and hydrogen on C5 atom as shown in Figure 3.

Antibacterial/antifungal activity

All the circular paper cultured in agar medium were took out after 24 hours and observed whether the inhibition zone exist or not around the paper. The results are exhibited in Table IV. The positive results represent the inhibition zone exist and the negative result it does not. It can be seen that the control group and raw material 4-(imidazol-1-yl)benzaldehyde both show no anti-bacterial/fungal activity. Both the two product are active against *Staphylococcus*, *Bacillus subtilis* and *Salmonella*, but shows no activity to suppress the growth of fungus including *Saccharomyces* and *Aspergillus niger*.

Experimental Section

Compound synthesis

All the chemical were analytical pure and used without any purification. The synthesis route is shown in Figure 5. The raw materials 4-(imidazol-1-yl) benzaldehyde was prepared according to our previous paper. Firstly, 3.4g imidazole (0.05 mol) and 5.0 g K_2CO_3 were added into 30 mL DMF in a flask under stirring. Then, three drop of aliquat336 was added into the flask as catalyst. The mixture was heated to 90°C gradually and keep for 5 min. Then 4.5 mL *p*-fluorobenzaldehyde was dropped into the mixture for three times. The solution would become yellow. Afterwards, the temperature was adjusted into 80°C and remained for 10 h. After that the cooled mixture was poured into 150 mL ice water under stirring. Large amounts of yellow precipitate could be observed. Much precipitate could be obtained when the mixture was

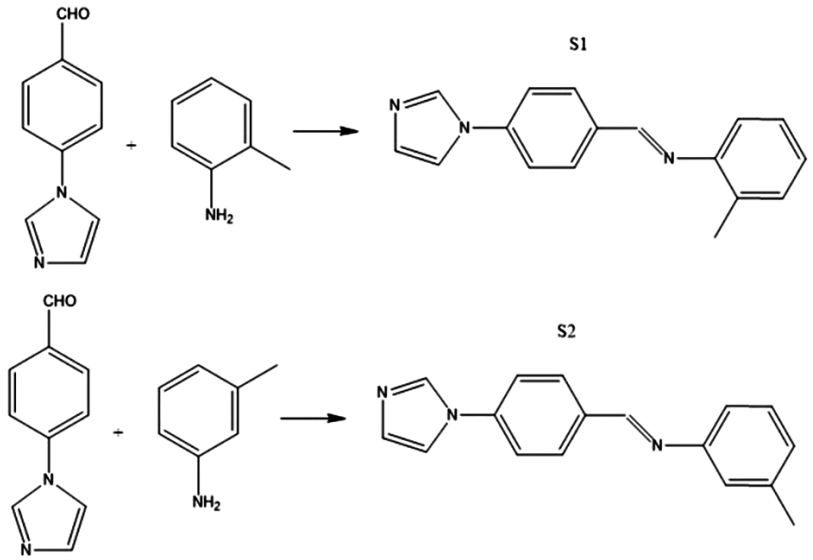

Figure 5 — Synthetic route for Schiff base S1 and S2

put into a refrigerator for 30 min. The precipitate was vaccum filtered and washed for several times and dried in vaccum chamber for using. The yield can reach about 96%.

Two Schiff base owns the same preparation procedures. Same molar mass of 4-(imidazol-1-yl) benzaldehyde and 2-toluidine/o-toluidine were dissolved in alcohol and mixed in a flask under stirring. Then the mixture was maintained steady at RT for 4 weeks. The precipitated light yellow crystals/white crystals would be the product. (It can not be obtained if the mixture is heated.).

Characterization

Infrared spectra (4000-400 cm^{-1}) was obtained using a SHIMADZU IR Affinity FTIR spectrophotometer on KBr disks. Proton nuclear magnetic resonance spectroscopy of S1 and S2 were acquired using a Bruker 300 spectrometer using DMSO-d6 and $CDCl_3$ as solvent respectively, and MS as internal standard.

X–ray diffraction was carried out on a CrysAlisPro Agilent Technologies diffractometer with graphite monochromator and MoKα radiation (λ = 0.71073 nm). The test was performed ranging from 2.68-27.82° with the increment 0.02° and the scanning rate 4°/min. The crystal structure was resolved by direct methods and refined with full matrix least squares using SHELXL 97 program. The factor R_1=0.058, ωR_2=0.1383, $\omega=1/[S^2(F_o)^2+(0.0758P)^2+(0.2385P)^2]$, where $P=(F_o^2+2F_c^2)/3$, S=1.041.

Antibacterial/ antifungal activity tests

The method of antibacterial/ antifungal activity tests was similar with our previous work[16]. Microbial strains were purchased from Agricultural Culture Collection of China (ACCC). All the tools and utensils used in this experiment were sterilized by autoclave and the procedures are finished in sterile laminar hood. S1 and S2 were grounded into powder and then dissolved in CH_2Cl_2 respectively. After that, sterilized filter papers (circular, diameter 0.5 cm) was soaked into the two solution for 10 min and then dried in air for use. The circular papers was placed in the petri dish infused with nutrient agar medium containing the corresponding bacteria, and cultured for 24 hours at 37 °C. Five paralleled samples were applied for every kind of bacteria. For comparison, the raw materials 4-(imidazol-1-yl)benzaldehyde was also tested with the same procedures mentioned above. The control group had sterilized papers soaked with pure CH_2Cl_2 and treated with other procedures as other groups.

Conclusion

Two new Schiff bases were synthesized through condensation reaction between 4-(imidazol-1-yl) benzaldehyde and 2-toluidine/*o*-toluidine. FT-IR and H NMR prove the successful synthesis of the target product. Single-crystal X-ray diffraction studies showed the molecular and crystal structures of the products. The new Schiff bases both show good antibacterial activity which can suppress the growth

of several bacteria including *Staphylococcus*, *Bacillus subtilis* and *Salmonella*.

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