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Synthesis, Characterization and Antimicrobial Activities of Schiff bases of 2-amino-4-(O-chloroanilino)-1, 3-thiazole

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ABSTRACT

A novel series of schiff bases of 2-amino-4-(o-chloro anilino)-1, 3-thiazole (**3a-3j**) were synthesized and screened for their antibacterial and antifungal activities. The structures of these compounds were ascertained by UV, IR, ^{1}H NMR, mass spectra and elemental analysis. The antibacterial activity of the synthesized schiff bases were evaluated against Gram positive bacteria such as *Staphylococcus aureus, Bacillus subtilis* and Gram negative bacteria like *Escherichia coli* and *Klebsiella pneumonia*. All the compounds had shown moderate to significant antibacterial activity amongst them; compound **3e** exhibited more significant activity against the tested bacteria. The antifungal activity was screened against two strains of fungi such as *Candida albicans* and *Aspergillus niger*. Similar to antibacterial activity compound **3e** exhibited significant antifungal activity. The standard drugs Amoxycillin and Amphotericin B were used to screen antibacterial and antifungal activity at 10µg/ml respectively. Interestingly compound **3e** had shown more prominent inhibitory activity against the tested bacteria and fungi.

INTRODUCTION

Schiff bases are an important class of organic compounds due to their flexibility, structural similarities with natural biological substances and also due to presence of imine (-N=CH-) which imparts in elucidating the mechanism of transformation and racemization reaction in biological system (Rajavel *et al.,* 2008). Schiff bases are considered as a very important class of organic compounds which have wide range of pharmacological activities (Pawar *et al.,* 1999). Many schiff bases are reported to possess a wide spectrum of biological importance, such as antibacterial (Vijesh *et al.,* 2010; Bhusare *et al.,* 2003; Shridhar *et al.,* 2001), antifungal (Rajendran *et al.,* 2002; Calais *et al.,* 2002), antimicrobial (Sheikh *et al.,* 2001; Karia *et al.,* 1999) anti HIV (Shridhar *et al.,* 2001) anti-inflammatory (Sridhar *et al.,* 2001), antitumor (Desai *et al.,* 2001; Pathak *et al.,* 2000; Tarafder *et al.,* 2002; Mohamed *et al.,* 2006) etc. These compounds could also act as valuable ligands whose biological activity has been shown to increase on complexation (Barry *et al.,* 1975). Due to rapid development of microbial resistance towards the existing drug, new chemical entities have been synthesized by condensing thiazole with different aromatic aldehydes which have attracted considerable attention as they are endowed with a wide range of diverse biological activities. In view of this, it was of considerable interest to synthesize the title compound with a hope to obtain potent biologically active antimicrobial agents. This paper represents a series of novel Schiff bases with a potent antimicrobial activity against some selected bacteria and fungi resulting from condensation of 2-amino-4-(2-chloroanilino)-1, 3-thiazole with different aromatic aldehydes.

MATERIALS AND METHODS

The commercially available AR and LR grade chemicals were used without further purification. Chemical reagents and solvents were purchased from Merck; Loba and S.D.-Fine Chem. Ltd. Melting points were determined in open capillary method and are uncorrected. IR spectra were recorded on FT-IR8400S, Fourier Transform (Shimadzu) Infrared spectrophotometer using KBr disc method. ^{1}H-NMR was recordedon PerkinElmer Spectrophotometer-300MHz. in DMSO- δ using TMS as an internal standard. Mass spectra were recorded on Micro mass Q-TOF and Shimadzu LCMS 2010A Mass spectrometer. Elemental analyses were performed on Thermo Finnigam FLASH EA1122CHNS Analyzer.

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Step-1: Synthesis of α-chloro-o-chloro acetanilide (1)

A mixture of 2-chloro aniline (0.12 M), chloro acetyl chloride (0.15M) and dry benzene (25 ml) was refluxed for 1 hour and excess of benzene was distilled off. The concentrated reaction mixture was cooled to obtain α-chloro-o-chloro acetanilide and recrystallized from ethanol. (Yield; 92.4%, m.p.; 68-70 ^{0}C).

Step-2: Synthesis of 2-amino-4-(o-chloro anilino)-1, 3-thiazole (2)

An equimolar mixture of α-chloro-o-chloro acetanilide, and thiourea was refluxed for 5 hours in presence of alcoholic potassium hydroxide. The excess of ethanol was removed under reduced pressure and concentrated solution was cooled. The precipitate obtained was filtered, washed with ice cold water and recrystallized from ethanol. (Yield; 61.3%, m.p.; 130^{0}C).

Step-3: Synthesis of N-(4-(o-chloro anilino)-1, 3-thiazol-2yl) benzaldimine derivatives 3(a-f)

Compound **2** was treated with various substituted aromatic aldehydes in presence of sodium methoxide. Then the reaction mixture was refluxed for 4 hours and neutralized with dilute HCl. The resulting precipitate was filtered and recrystallized from ethanol.

Spectral data

3a Yield: 91%; m.p.: 180-182 ^{0}C; IR (KBr): υ (cm^{-1}), 3286 (NH str), 1660 (C=N str), 1593, 1519 (Ar C-C str), 752 (C-Cl str), 663 (C-S-C str); ^{1}H NMR ($CDCl_3$, δ ppm): 9.1 (s, 1H, NH), 7.75 (s, 1H, CH of thiazole), 8.35 (s, 1H, -N=CH-), 6.78 -8.01(m, 8H, Ar-H); MS (EI): 358 (M^+); (Found: C, 53.59 H, 3.19 N, 15.83, $C_{16}H_{11}N_4O_2ClS$ requires C, 53.56 H, 3.09 N, 15.61)

3b Yield: 75.3%; m.p.: 177-179 ^{0}C; IR (KBr): υ (cm^{-1}), 3269 (NH str), 1658 (C=N str), 1591, 1519 (Ar C-C str) ,752 (C-Cl str), 692 (C-S-C str); ^{1}H NMR ($CDCl_3$, δ ppm); 9.28 (s, 1H, NH), 7.78 (s, 1H, CH of thiazole), 8.31 (s, 1H, -N=CH-), 6.93 - 7.98 (m, 8H, Ar-H); MS (EI): 358 (M^+); (Found: C, 53.89, H, 3.31, N, 15.47 $C_{16}H_{11}N_4O_2ClS$ requires C, 53.56, H, 3.09, N, 15.61)

3c Yield: 59.2%; m.p.:160-163 ^{0}C; IR (KBr): υ (cm^{-1}), 3230 (NH str), 1654 (C=N str), 1514 (Ar C-C str), 753 (C-Cl str), 678 (C-S-C str). MS (EI): 349 (M^++1), 348 (M^+); ^{1}H NMR ($CDCl_3$, δ ppm): 9.31 (s, 1H, NH), 7.76 (s, 1H, CH of thiazole), 8.36 (s, 1H, -N=CH-), 7.08- 8.26 (m, 8H, Ar-H); (Found: C, 55.37, H, 3.41, N, 12.35 $C_{16}H_{11}N_3Cl_2S$ requires C, 55.18, H, 3.18, N, 12.07)

3d Yield: 52.7%; m.p.: 152-154^{0}C IR (KBr): υ (cm^{-1}), 3330 (NH str), 1656 (C=N str), 1585, 1517 (Ar C-C str), 754 (C-Cl str), 665 (C-S-C str). MS (EI): 348 (M^+); ^{1}H NMR ($CDCl_3$, δ ppm); 8.97 (s, 1H, NH), 7.81 (s, 1H, CH of thiazole), 8.31 (s, 1H, -N=CH-), 6.92 -7.94 (m, 8H, Ar-H); (Found: C, 55.31, H, 3.38, N, 11.86 $C_{16}H_{11}N_3Cl_2S$ requires C, 55.18, H, 3.18, N, 12.07)

3e Yield: 61.9%; m.p.: 260-262 ^{0}C; IR (KBr): υ (cm^{-1}), 3201 (NH str), 1668 (C=N str), 1598, 1504 (Ar C-C str), 759 (C-Cl str), 719 (C-S-C str). MS (EI): 331 (M^+); ^{1}H NMR ($CDCl_3$, δ ppm); 9.35 (s, 1H, NH), 7.87 (s, 1H, CH of thiazole), 8.33 (s, 1H, -N=CH-), 7.00-8.38 (m, 8H, Ar-H); (Found: C, 57.81, H, 3.16, N, 12.73 $C_{16}H_{11}N_3FClS$ requires C, 57.92, H, 3.34, N, 12.66)

3f Yield: 50.2%; m.p.: 172-173 ^{0}C; IR (KBr): υ (cm^{-1}), 3315 (NH str), 1655 (C=N str), 1585, 1517 (Ar C-C str), 754 (C-Cl str), 665 (C-S-C str), 3556 (OH str). MS (EI): 329 (M^+); ^{1}H NMR ($CDCl_3$, δ ppm); 9.1 (s, 1H, NH), 7.85 (s, 1H, CH of thiazole), 8.35 (s, 1H, -N=CH-), 7.03-7.98 (m, 8H, Ar-H), 5.6 (s, 1H, OH); (Found: C, 58.56, H, 3.68, N, 12.83 $C_{16}H_{12}N_3OClS$ requires C, 58.27, H, 3.67, N, 12.74)

3g Yield: 43.2%; m.p.: 205-207 ^{0}C; IR (KBr): υ (cm^{-1}), 3328 (NH str), 1660 (C=N str), 1591, 1521 (Ar C-C str), 752 (C-Cl str), 680 (C-S-C str); MS (EI): 403 (M^+); ^{1}H NMR ($CDCl_3$, δ ppm); 9.13 (s, 1H, NH), 7.79 (s, 1H, CH of thiazole), 8.46 (s, 1H, -N=CH-), 7.03-7.84 (m, 6H, Ar-H), 3.82 (s, 9H, 3 × OCH_3); (Found: C, 56.72, H, 4.57, N, 10.57 $C_{19}H_{18}N_3O_3ClS$ requires C, 56.50, H, 4.49, N, 10.40)

3h Yield: 59.7%; m.p.: 225-226 ^{0}C; IR (KBr): υ (cm^{-1}), 3267 (NH str), 1664 (C=N str), 1589, 1533 (Ar C-C str), 758 (C-Cl str), 677 (C-S-C str); MS (EI): 405 (M^++2), 403 (M^+); ^{1}H NMR ($CDCl_3$, δ ppm); 9.21 (s, 1H, NH), 7.82 (s, 1H, CH of thiazole), 8.39 (s, 1H, -N=CH-), 7.03-8.27 (m, 6H, Ar-H) 3.79 (s, 9H, 3×OCH_3); (Found: C, 56.59, H, 4.41, N, 10.53 $C_{19}H_{18}N_3O_3ClS$ requires C, 56.50, H, 4.49, N, 10.40)

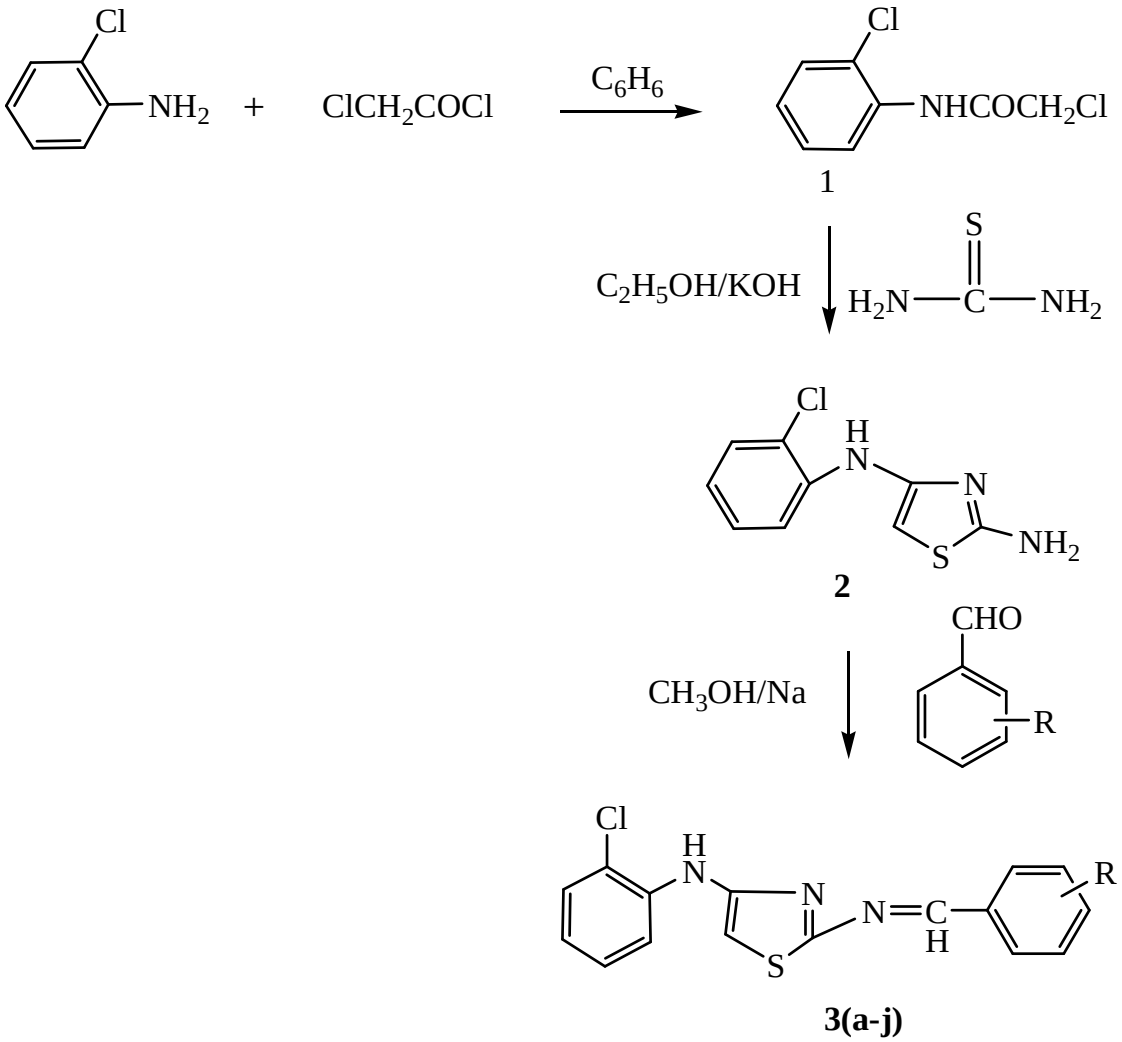
3i Yield: 62.3%; m.p.: 178-179 ^{0}C; IR (KBr): υ (cm^{-1}), 3300 (NH str), 1629 (C=N str), 1589, 1527 (Ar C-C str), 750 (C-Cl str), 665 (C-S-C str); MS (EI): 355 (M^+); ^{1}H NMR ($CDCl_3$, δ ppm); 9.17 (s, 1H, NH), 7.81 (s, 1H, CH of thiazole), 8.31 (s, 1H, -N=CH-), 6.53-8.18 (m, 8H, Ar-H), 2.7 (septet, 1H, CH), 1.0 (d, 6H, 2×CH_3); (Found: C, 64.32, H, 5.34, N, 11.61 $C_{19}H_{18}N_3ClS$ requires C, 64.12, H, 5.10, N, 11.81)

3j Yield 47.8%; m.p.: 155-157 ^{0}C; IR (KBr): υ (cm^{-1}), 3315 (NH str), 1656 (C=N str), 1585, 1517 (Ar C-C str), 754 (C-Cl str), 665 (C-S-C str); MS (EI): 373 (M^+); ^{1}H NMR ($CDCl_3$, δ ppm); 9.41 (s, 1H, NH), 7.79 (s, 1H, CH of thiazole), 8.45 (s, 1H, -N=CH-), 7.03-8.11 (m, 7H, Ar-H), 3.76 (s, 6H, OCH_3); (Found: C, 57.94, H, 4.55, N, 11.09 $C_{18}H_{16}N_3O_2ClS$ requires C, 57.83, H, 4.31, N, 11.24).

Antimicrobial activity

The compounds were screened for their antibacterial activity against four strains of bacteria *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Klebsiella pneumonia* and their antifungal activity against *Candida albicans* and *Aspergillus niger* using paper disc technique (Barry et al.,1975). The zone of inhibition against all the microorganisms was measured in millimeter.

The minimum inhibitory concentration (MIC) was determined and DMSO was used as a solvent with appropriate controls. Compound **3e** exhibited the maximum activity against both bacteria and fungi, comparable to standard whereas rest of the compounds exhibited moderate activity. Amoxycillin and Amphotericin B were used as standard against bacteria and fungi respectively.



Scheme-1 Synthesis of schiff bases

Compound code	R	Compound code	R
3a	4-NO_2	3f	4-OH
3b	2-NO_2	3g	2,3,4-$(OCH_3)_3$
3c	4-Cl	3h	3,4,5-$(OCH_3)_3$
3d	2-Cl	3i	4-$CH(CH_3)_2$
3e	4-F	3j	3,4-$(OCH_3)_2$

Table. 1: Antibacterial & Antifungal activities of synthesized compounds **3(a-j).**

Sl. No.	Compd code	Antibacterial activity Zone of inhibition (mm)				Antifungal activity Zone of inhibition (mm)	
		S.a.	B.s.	E.c.	K.p.	C. a.	A. n.
1	3a	15	15	18	21	12	15
2	3b	09	12	Nil	08	09	14
3	3c	18	20	19	20	12	16
4	3d	08	11	08	09	09	12
5	3e	18	17	19	20	14	16
6	3f	14	16	08	Nil	08	11
7	3g	09	12	10	09	08	10
8	3h	08	12	08	07	07	08
9	3i	Nil	08	Nil	Nil	Nil	Nil
10	3j	10	13	10	12	Nil	Nil
Cont.	DMSO	–	–	–	–	–	–
STD	Amoxycillin*	26	27	26	28	-	-
	Amphotericin B**					19	18

*Standard antibacterial drug, **Standard antifungal drug S.a. – *Staphylococcus aureus* B.s. – *Bacillus subtilis*, *E*.c. –*Escherichia coli,* K.p. – *Klebsiella pneumonia*, C.a. – *Candida albicans* A.n. – *Aspergillus niger*

RESULT AND DISCUSSION

A new series of Schiff bases were synthesized and the synthetic scheme is presented in scheme-1. All the synthesized compounds were in conformity with the structure envisaged. The structures were confirmed on the basis of physical and spectral data viz. IR, ^{1}H NMR, Mass spectroscopy. In IR spectra, all the compounds displayed the characteristic peaks in the region 1440-1514 cm^{-1} indicated the formation of Schiff bases (-CH=N). The appearance peaks in the region 1550-1687 cm^{-1} confirmed the presence of C=O in all the synthesized compounds. The structural assignments were further supported by their ^{1}H NMR spectra. The appearance of signal for imine proton at 7-8 ppm confirmed the formation of Schiff bases. The multiplets at 6- 9 ppm also ascertained the presence of aromatic protons in the synthesized compounds. Thus it could be confirmed that the compounds resulted were Schiff bases of thiazole derivatives. All the compounds were evaluated for antibacterial and antifungal screening (Table-1) using defined bacterial and fungal cell culture. They have shown promising antibacterial activity with moderate antifungal activity. Among all, the compounds **3c** and **3e** showed highest antibacterial activity against all the four strains of bacteria. Compound **3e** showed maximum antibacterial activity within the series. Compounds **3f** and **3i** showed least activity against all the organisms where as other analogues showed moderate antibacterial activity. The maximum antifungal activity was shown by 4-fluoro substituted derivative **3e** followed by 4-chloro substituted derivative **3c**. Compounds **3a, 3b** and **3d** showed moderate antifungal activity where as compound **3f, 3g** and **3h** showed minimum activity. Isopropyl analogue **3i** & **3j** showed no activity against both strains of fungi.

CONCLUSION

Antimicrobial activities of synthesized compounds were evaluated against different strains of bacteria and fungi. Most of the compounds showed good antibacterial activity against Gram positive and Gram negative bacteria. It was interesting to note that the presence of halogen group at the para position showed better activity in tested series of compounds. It shows that the electron withdrawing groups contributed more inhibitory activity rather than electron donating groups. None of the compounds synthesized showed considerable antifungal activity when compared to that of the standard Amphotericin B.

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