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Synthesis and Antibacterial Screening of Cefradine Schiff Bases and Their Metal Salts

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Abstract

A series of Schiff bases(3-8) were synthesized by the reaction of cefradine with six different aldehydes/ketones. These Schiff bases(3-8) were treated with different bases/salt (NaOH, KOH, $Ca(OH)_2$, $Ba(OH)_2$, $Ag(NO)_3$) to get their metal salts. Structures of the products were ascertained by spectroscopic data. The synthesized compounds were tested for biological activities against *Staphylococcus aureus*(gram positive bacterium) and *Escherichia coli*(gram negative bacterium). In general low activities of most of the synthesized compounds were observed in comparison to cefradine which can be linked to unavailability of free amino group of cefradine by its involvement in synthesis of imine derivatives.

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Introduction

Compounds with azomethine functional group (CH=N) are typically known as Schiff base[1]. The presence of a lone pair of electron in the sp^2 hybridized orbital of nitrogen atom of the azomethine group presents good chelating ability on Schiff base mainly when combined with one or more donor atoms close to the azomethine group. This chelating ability of the

Schiff base combined with the ease of separation and flexibility in varying the chemical environment about the C=N group, makes Schiff base interesting ligands in coordination chemistry [2][3][4][5]. Schiff base and its complexes represent an important class of organic compounds, having a broad range of applications especially in the biological, analytical, medicinal and pharmaceutical field [6][7][8][9]. Schiff bases are biologically active and exhibit antiviral, anti-malarial, antipyretic, anti-proliferative, anticonvulsant, antifungal, anticancer, anti-hypertensive, anti-inflammatory, antibacterial and hypnotic activities[10][11][12].

In pediatrics, wide use of antibiotics has resulted in serious issues of drug resistance and public health concern[13][14]. It has become necessary to prepare new synthetic derivatives of antibiotics with enhanced activities in order to overcome drug resistance[15]. Cefradine is a first generation cephalosporin antibiotic which was isolated for the first time in 1948 and is active against both gram-positive and gram-negative bacteria [16]. It helps to cure respiratory and urinary tract infections[17]. Cefradine derivatives may exhibit enhanced antibacterial activity compared to the pure cefradine. Therefore in order to search for compounds possessing enhanced biological activities, we converted cefradine into its Schiff bases and their metal salts which were further evaluated for their antibacterial potential.

Experimental

Pure chemicals obtained from Merk/ Aldrich/ Reidal-de-Haen/ Fluka were used. Synthesized products were analyzed through IR and NMR techniques. SHIMADZU FTIR-8900 was used for IR analysis and NMR spectra were processed on Bruker AC 300-MHz instrument.

General procedure for the preparation of Schiff bases of cefradine (3-8)

1.5 g (0.0043 mole) of cefradine was treated separately with equimolar benzaldehyde (0.45g), 3-chlorobenzaldehyde (0.60g), 4-dimethylaminobenzaldehyde (0.64g), 4-methoxybenzaldehyde (0.58g), acetophenone (0.51g) and benzophenone (0.78g). Mixture was re-fluxed for 2-6 hours in methanol solvent, in the presence of acetic acid(few drops) as a catalyst. Completion of reaction was monitored by TLC. The products were coloured Schiff bases of cefradine. Solvent was evaporated and product was washed with n-hexane. Characterization was carried out by using IR and ^{1}H NMR spectroscopy.

Compound (4)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 13.02(s, 1H, COOH), 8.30-8.26(m, 2H, NH/ imine CH), 7.74(d, 1H, J=1.2 Hz, Ar-H), 7.48(dd, 1H, J=7.5,1.2 Hz, Ar-H), 7.26-7.20(m, 2H, Ar-H), 5.29(br.s, 1H, CH), 5.01-4.95(m, 3H, olefenic H), 4.79(s, 1H, CH), 3.50(d, 1H, J=6.6Hz, CH), 3.26-3.19(m, 2H, S-CH_2), 2.53-2.46(m, 4H, CH_2), 1.66(s, 3H, CH_3).

Compound (5)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 13.23(s, 1H, COOH), 8.50-8.47(m, 2H, NH/imine CH), 7.71(td, 2H, Ar-H, J=8.7,

2.2Hz), 6.90(td, 2H, Ar-H, J=8.7, 2.2Hz), 5.29(br.s, 1H, CH), 5.14-5.06(m, 3H, olefinic CH), 4.78-4.72(m, 1H, CH), 3.58(d, 1H, J=6.6Hz, CH), 3.16-3.09(m, 2H, S-CH_2), 3.04(s, 6H, 2CH_3), 2.60-2.53(m, 4H, 2CH_2), 1.69(s, 3H, CH_3).

Compound (6)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 13.04(s, 1H, COOH), 8.47-8.36(m, 2H, NH/imine CH), 7.84(td, 2H, Ar-H, J=8.7, 2.1Hz), 7.10(td, 2H, Ar-H, J=8.7, 2.1Hz), 5.27(s, 1H, CH), 5.11-5.02(m, 3H, olefinic CH), 4.61-4.57(m, 1H, CH), 3.86(s, 3H, OCH_3), 3.52(d, 1H, J=6.3Hz, CH), 3.08-3.00(m, 2H, S-CH_2), 2.49-2.44(m, 4H, 2CH_2), 1.69(s, 3H, CH_3).

Compound (7)

^{1}H NMR(300 MHz, DMSO-d_6,, δppm): 12.87(s, 1H, COOH), 8.16(s, 1H, NH), 7.63(dd, 2H, J=7.2,1.2 Hz, Ar-H), 7.44-7.36(m, 2H, Ar-H), 7.22(t, 1H, J=7.2, 1.2 Hz, Ar-H), 5.26(br.s, 1H, CH), 5.11-5.02(m, 3H, olefenic CH), 4.81-4.77(m, 1H, CH), 3.65(d, 1H, J=6.3Hz, CH), 3.22-3.18(m, 2H, S-CH_2), 2.58-2.51(m, 4H, 2CH_2), 2.00(s, 3H, CH_3), 1.71(s, 3H, CH_3).

Compound (8)

^{1}HNMR(300 MHz, DMSO-d_6, δppm): 13.11(s, 1H, COOH), 8.06(s, 1H, NH), 7.70-7.62(m, 4H, Ar-H), 7.50-7.44(m, 6H, Ar-H), 5.33(br.s, 1H, CH), 5.09-5.01(m, 3H, olefenic CH), 4.74-4.69(m, 1H, CH), 3.64(d, 1H, J=6.6Hz, CH), 3.26-2.18(m, 2H, S-CH_2), 2.56-2.49(m, 4H, CH_2), 1.68(s,3H,CH_3).

Table 1. IR data for compounds 3-8

Functional Group		OH	N-H	C=O (Carboxylic)	C=O (Amidic)	C=N	C=C (Aliphatic)	C=C (Aromatic)	C-O	C-N
Wavenumber (cm^{-1})	**Compound 3 (Yield 81%)**	3276	3240	1708-1678	-	1658	-	-	1335	1275
	Compound 4 (Yield 91%)	3265	-	1695	1670	1640	1575	1560	1350	1280
	Compound 5 (Yield 89%)	3249	3235	1710-1685	-	1653	-	-	1342	1282
	Compound 6 (Yield 90%)	3345	3246	1700-1685	-	1656	-	-	1324	1241
	Compound 7 (Yield 78%)	3237	-	1696	1670	1652	1583	1552	1326	1282
	Compound 8 (Yield 71%)	3277	-	1695	1665	1650	1540	1530	1315	1284

General procedure for the preparation of salts of cefradine Schiff bases (9-35)

1mmol of NaOH, KOH, $AgNO_3$ while 0.5 mmol of $Ca(OH)_2$ and $Ba(OH)_2$ were treated with 1mmol of each Schiff base. Metal hydroxides/ $AgNO_3$ were dissolved in water and Schiff bases were dissolved in methanol separately. For each product both solutions were then mixed and stirred on hot plate for 30 minutes at 60°C. Solvent was evaporated and the coloured salts obtained were characterized by IR and NMR spectroscopy. Silver salts were purified by re-crystallization using methanol.

Compound (9)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.45-8.37(m, 2H, NH/imine CH), 7.78(dd, 2H, J=7.5, 1.5Hz, ArH), 7.39-7.25(m, 3H, Ar-H), 5.31(br.s, 1H, CH), 5.14-5.08(m, 3H, olefinic CH), 4.74-4.71(m, 1H, CH), 3.53(d, 1H, J=6.6Hz, CH), 3.14-3.05(m,2H, S-CH_2), 2.60-2.52(m, 4H, 2CH_2), 1.62(s, 3H, CH_3).

Compound (10)

^{1}HNMR(300 MHz, DMSO-d_6, δppm): 8.44-8.35(m, 2H, NH/imine CH), 7.76(dd, 2H, J=7.2, 1.5Hz, ArH), 7.38-7.26(m, 3H, Ar-H), 5.32(br.s, 1H, CH), 5.15-5.09(m, 3H, olefinic CH), 4.75-4.70(m, 1H, CH), 3.55(d, 1H, J=6.3Hz, CH), 3.14-3.07(m,

2H, S-CH_2), 2.60-2.55(m, 4H, 2CH_2), 1.64(s, 3H, CH_3).

Compound (11)

^{1}HNMR(300 MHz, DMSO-d_6, δppm): 8.46-8.38(m, 2H, NH/imine CH), 7.78(dd, 2H, J=7.2, 1.5Hz, ArH), 7.39-7.28(m, 3H, Ar-H), 5.33(br.s, 1H, CH), 5.16-5.09(m, 3H, olefinic CH), 4.75-4.72(m, 1H, CH), 3.54(d,1H, J=6.6Hz, CH), 3.16-3.08(m, 2H, S-CH_2), 2.61-2.54(m, 4H, 2CH_2), 1.63(s, 3H, CH_3).

Compound (12)

^{1}HNMR(300 MHz, DMSO-d_6, δppm): 8.45-8.37(m, 2H, NH/imine CH), 7.79(dd, 2H, J=7.2, 1.2Hz, ArH), 7.39-7.27(m, 3H, Ar-H), 5.30(br.s, 1H, CH), 5.14-5.08(m, 3H, olefinic CH), 4.74-4.69(m, 1H, CH), 3.53(d, 1H, J=6.6Hz, CH), 3.14-3.06(m, 2H, S-CH_2), 2.59-2.53(m, 4H, 2CH_2), 1.63(s, 3H, CH_3).

Compound (13)

^{1}HNMR(300 MHz, DMSO-d_6, δppm): 8.45-8.36(m, 2H, NH/imine CH), 7.77(dd, 2H, J=7.5, 1.5Hz, ArH), 7.38-7.27(m, 3H, Ar-H), 5.32(br.s, 1H, CH), 5.16-5.09(m, 3H, olefinic CH), 4.73-4.69(m, 1H, CH), 3.54(d, 1H, J=6.6Hz, CH), 3.15-3.06(m, 2H, S-CH_2), 2.59-2.53(m, 4H, 2CH_2), 1.63(s, 3H, CH_3).

Compound (14)

^{1}HNMR(300 MHz, DMSO-d_6, δppm): 8.28-8.24(m, 2H, NH/ imine CH), 7.70(d, 1H, J=1.2 Hz, Ar-H), 7.44(dd, 1H, J=7.5,1.5 Hz, Ar-H), 7.23-7.18(m, 2H, Ar-H), 5.27(br.s, 1H, CH), 5.00-4.94(m, 3H, olefenic H), 4.76(s, 1H, CH), 3.48(d, 1H, J=6.9Hz, CH), 3.23-3.16(m, 2H, S-CH_2), 2.51-2.44(m, 4H, CH_2), 1.65(s, 3H, CH_3).

Compound (15)

^{1}HNMR(300 MHz, DMSO-d_6, δppm): 8.29-8.27(m, 2H, NH/ imine CH), 7.73(d, 1H, J=1.2 Hz, Ar-H), 7.47(dd, 1H, J=7.5,1.2 Hz, Ar-H), 7.25-7.20(m, 2H, Ar-H), 5.27(br.s, 1H, CH), 4.99-4.94(m, 3H, olefenic H), 4.78(s, 1H, CH), 3.48(d, 1H, J=6.9Hz, CH), 3.25-3.17(m, 2H, S-CH_2), 2.52-2.47(m, 4H, CH_2), 1.67(s, 3H, CH_3).

Compound (16)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.27-8.21(m, 2H, NH/ imine CH), 7.71(d, 1H, J=1.2 Hz, Ar-H), 7.52(dd, 1H, J=7.5,1.2 Hz, Ar-H), 7.26-7.22(m, 2H, Ar-H), 5.32(br.s, 1H, CH), 5.03-4.98(m, 3H, olefenic H), 4.77(s, 1H, CH), 3.49(d, 1H, J=6.9Hz, CH), 3.25-3.18(m, 2H, S-CH_2), 2.56-2.49(m, 4H, CH_2), 1.69(s, 3H, CH_3).

Compound (17)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.30-8.27(m, 2H, NH/ imine CH), 7.71(d, 1H, J=1.2 Hz, Ar-H), 7.48(dd, 1H, J=7.8,1.5 Hz, Ar-H), 7.24-7.20(m, 2H, Ar-H), 5.27(br.s, 1H, CH), 5.00-4.94(m, 3H, olefenic H), 4.77(s, 1H, CH), 3.51(d, 1H, J=6.9Hz, CH), 3.25-3.18(m, 2H, S-CH_2), 2.51-2.45(m, 4H, CH_2), 1.68(s, 3H, CH_3).

Compound (18)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.47-8.43(m, 2H, NH/imine CH), 7.69(td, 2H, Ar-H, J=8.4, 2.2Hz), 6.86(td, 2H, Ar-H, J=8.7, 2.2Hz), 5.26(br.s, 1H, CH), 5.12-5.04(m, 3H, olefinic CH), 4.75-4.70(m, 1H, CH), 3.55(d, 1H, J=6.9Hz, CH), 3.14-3.05(m, 2H, S-CH_2), 3.03(s, 6H, 2CH_3), 2.57-2.52(m, 4H, 2CH_2), 1.67(s, 3H, CH_3).

Compound (19)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.48-8.45(m, 2H, NH/imine CH), 7.69(td, 2H, Ar-H, J=8.7, 2.2Hz), 6.88(td, 2H, Ar-H, J=8.4, 2.2Hz), 5.27(br.s, 1H, CH), 5.13-5.05(m, 3H, olefinic CH), 4.77-4.70(m, 1H, CH), 3.56(d, 1H, J=6.6Hz, CH), 3.15-3.08(m, 2H, S-CH_2), 3.00(s, 6H, 2CH_3), 2.56-2.50(m, 4H, 2CH_2), 1.67(s, 3H, CH_3).

Compound (20)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.49-8.45(m, 2H, NH/imine CH), 7.69(td, 2H, Ar-H, J=8.4, 2.2Hz), 6.86(td, 2H, Ar-H, J=8.7, 2.2Hz), 5.27(br.s, 1H, CH), 5.13-5.06(m, 3H, olefinic CH), 4.76-4.71(m, 1H, CH), 3.55(d, 1H, J=6.6Hz, CH), 3.12-3.05(m, 2H, S-CH_2), 3.02(s, 6H, 2CH_3), 2.58-2.53(m, 4H, 2CH_2), 1.66(s, 3H, CH_3).

Compound (21)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.47-8.44(m, 2H, NH/imine CH), 7.65(td, 2H, Ar-H, J=8.7, 2.2Hz), 6.88(td, 2H, Ar-H, J=8.7, 2.2 Hz), 5.27(br.s, 1H, CH), 5.13-5.04(m, 3H, olefinic CH), 4.76-4.70(m, 1H, CH), 3.55(d, 1H, J=6.6Hz, CH), 3.13-3.07(m, 2H, S-CH_2), 3.02(s, 6H, 2CH_3), 2.56-2.52(m, 4H, 2CH_2), 1.66(s, 3H, CH_3).

Compound (22)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.49-8.45(m, 2H, NH/imine CH), 7.68(td, 2H, Ar-H, J=8.7, 2.2Hz), 6.89(td, 2H, Ar-H, J=8.4, 2.2Hz), 5.26(br.s, 1H, CH), 5.12-5.02(m, 3H, olefinic CH), 4.76-4.70(m, 1H, CH), 3.55(d, 1H, J=6.9Hz, CH), 3.14-3.06(m, 2H, S-CH_2), 3.01(s, 6H, 2CH_3), 2.59-2.54(m, 4H, 2CH_2), 1.66(s, 3H, CH_3).

Compound (23)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.44-8.35(m, 2H, NH/imine CH), 7.82(td, 2H, Ar-H, J=8.7, 2.4Hz), 7.08(td, 2H, Ar-H, J=8.7, 2.1Hz), 5.24(s, 1H, CH), 5.09-5.01(m, 3H, olefinic CH), 4.59-4.54(m, 1H, CH), 3.84(s, 3H, OCH_3), 3.50(d, 1H, J=6.3Hz, CH), 3.05-2.97(m, 2H, S-CH_2), 2.45-2.42(m, 4H, 2CH_2), 1.66(s,3H, CH_3).

Compound (24)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.44-8.36(m, 2H, NH/imine CH), 7.81(td, 2H, Ar-H, J=8.7, 2.1Hz), 7.07(td, 2H, Ar-H, J=8.4, 2.1Hz), 5.25(s, 1H, CH), 5.08-5.01(m, 3H, olefinic CH), 4.59-4.54(m, 1H, CH), 3.84(s, 3H, OCH_3), 3.49(d, 1H, J=6.6Hz, CH), 3.06-2.97(m, 2H, S-CH_2), 2.46-2.42(m, 4H, 2CH_2), 1.67(s,3H, CH_3).

Compound (25)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.44-8.38(m, 2H, NH/imine CH), 7.81(td, 2H, Ar-H, J=8.4, 2.1Hz), 7.06(td, 2H, Ar-H, J=8.7, 2.1Hz), 5.25(s, 1H, CH), 5.08-4.99(m, 3H, olefinic CH), 4.57-4.52(m, 1H, CH), 3.84(s, 3H, OCH_3), 3.49(d, 1H, J=6.3Hz, CH), 3.06-2.96(m, 2H, S-CH_2), 2.47-2.43(m, 4H, 2CH_2), 1.68(s,3H, CH_3).

Compound (26)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.44-8.36(m, 2H, NH/imine CH), 7.83(td, 2H, Ar-H, J=8.7, 2.1Hz), 7.07(td, 2H, Ar-H, J=8.4, 2.1Hz), 5.26(s, 1H, CH), 5.08-5.00(m, 3H, olefinic CH), 4.57-4.54(m, 1H, CH), 3.83(s, 3H, OCH_3), 3.49(d, 1H, J=6.6Hz, CH), 3.06-2.98(m, 2H, S-CH_2), 2.46-2.42(m, 4H, 2CH_2), 1.67(s,3H, CH_3).

Compound (27)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.45-8.34(m, 2H, NH/imine CH), 7.82(td, 2H, Ar-H, J=8.4, 2.1Hz), 7.08(td, 2H, Ar-H, J=8.7, 2.4Hz), 5.24(s, 1H, CH), 5.09-4.98(m, 3H, olefinic CH), 4.58-4.54(m, 1H, CH), 3.85(s, 3H, OCH_3), 3.48(d, 1H, J=6.3Hz, CH), 3.05-2.97(m, 2H, S-CH_2), 2.46-2.43(m, 4H, 2CH_2), 1.66(s,3H, CH_3).

Compound (28)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.29-8.25(m, 2H, NH/ imine CH), 7.72(d, 1H, J=1.5 Hz, Ar-H), 7.47(dd, 1H, J=7.5,1.2 Hz, Ar-H), 7.24-7.18(m, 2H, Ar-H), 5.27(br.s, 1H, CH), 5.00-4.93(m, 3H, olefenic H), 4.76(s, 1H, CH), 3.49(d, 1H, J=6.9Hz, CH), 3.24-3.17(m, 2H, S-CH_2), 2.52-2.45(m, 4H, CH_2), 1.67(s, 3H, CH_3).

Compound (29)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.14(s, 1H, NH), 7.62(dd, 2H, J=7.2,1.2 Hz, Ar-H), 7.42-7.34(m, 2H, Ar-H), 7.21(t, 1H, J=7.5, 1.2 Hz, Ar-H), 5.23(br.s, 1H, CH), 5.09-5.01(m, 3H, olefenic CH), 4.80-4.75(m, 1H, CH), 3.63(d, 1H, J=6.6Hz, CH), 3.20-3.15(m, 2H, S-CH_2), 2.55-2.50(m, 4H, 2CH_2), 1.98(s, 3H, CH_3), 1.69(s, 3H, CH_3).

Compound (30)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.15(s, 1H, NH), 7.62(dd, 2H, J=7.2,1.2 Hz, Ar-H), 7.42-7.35(m, 2H, Ar-H), 7.21(t,

1H, J=7.2, 1.5 Hz, Ar-H), 5.24(br.s, 1H, CH), 5.10-5.00(m, 3H, olefenic CH), 4.80-4.76(m, 1H, CH), 3.64(d, 1H, J=6.6Hz, CH), 3.21-3.18(m, 2H, S-CH_2), 2.55-2.50(m, 4H, 2CH_2), 1.99(s, 3H, CH_3), 1.69(s, 3H, CH_3).

Compound (31)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.15(s, 1H, NH), 7.60(dd, 2H, J=7.2,1.2 Hz, Ar-H), 7.41-7.34(m, 2H, Ar-H), 7.20(t, 1H, J=7.5, 1.2 Hz, Ar-H), 5.24(br.s, 1H, CH), 5.09-5.01(m, 3H, olefenic CH), 4.79-4.75(m, 1H, CH), 3.62(d, 1H, J=6.6Hz, CH), 3.19-3.16(m, 2H, S-CH_2), 2.55-2.49(m, 4H, 2CH_2), 1.98(s, 3H, CH_3), 1.70(s, 3H, CH_3).

Compound (32)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.04(s, 1H, NH), 7.68-7.61(m, 4H, Ar-H), 7.49-7.42(m, 6H, Ar-H), 5.31(br.s, 1H, CH), 5.07-5.00(m, 3H, olefenic CH), 4.72-4.67(m, 1H, CH), 3.62(d, 1H, J=6.6Hz, CH), 3.24-2.14(m, 2H, S-CH_2), 2.55-2.47(m, 4H, CH_2), 1.67(s, 3H, CH_3).

Compound (33)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.04(s, 1H, NH), 7.69-7.61(m, 4H, Ar-H), 7.48-7.43(m, 6H, Ar-H), 5.31(br.s, 1H, CH), 5.07-4.99(m, 3H, olefenic CH), 4.71-4.67(m, 1H, CH), 3.63(d, 1H, J=6.9Hz, CH), 3.24-2.16(m, 2H, S-CH_2), 2.54-2.48(m, 4H, CH_2), 1.69(s, 3H, CH_3).

Compound (34)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.05(s, 1H, NH), 7.69-7.62(m, 4H, Ar-H), 7.49-7.43(m, 6H, Ar-H), 5.32(br.s, 1H, CH), 5.06-5.00(m, 3H, olefenic CH), 4.73-4.68(m, 1H, CH), 3.61(d, 1H, J=6.9Hz, CH), 3.23-2.16(m, 2H, S-CH_2), 2.55-2.47(m, 4H, CH_2), 1.70(s, 3H, CH_3).

Compound (35)

^{1}H NMR(300 MHz, DMSO-d_6, δppm): 8.03(s, 1H, NH), 7.66-7.59(m, 4H, Ar-H), 7.47-7.41(m, 6H, Ar-H), 5.30(br.s, 1H, CH), 5.06-4.98(m, 3H, olefenic CH), 4.70-4.66(m, 1H, CH), 3.61(d, 1H, J=6.6Hz, CH), 3.24-2.14(m, 2H, S-CH_2), 2.53-2.46(m, 4H, CH_2), 1.66(s, 3H, CH_3).

Table 2. IR data for compounds 9-35

Functional Group		N-H	C=O (Carboxylic)	C=O (Amidic)	C=N	C=C (Aliphatic)	C=C (Aromatic)	C-O	C-N
	Compound 9	3242	1704-1679	-	1654	-	-	1337	1278
	Compound 10	3245	1709-1676	-	1655	-	-	1338	1276
	Compound	3239	1706-1677	-	1654	-	-	1331	1275

	11								
	Compound 12	3243	1709-1677	-	1655	-	-	1332	1277
	Compound 13	3244	1711-1676	-	1656	-	-	1333	1276
	Compound 14	-	1680	1665	1650	1590	1546	1420	1388
	Compound 15	-	1684	1665	1650	1590	1560	1430	1380
	Compound 16	-	1700	1680	1664	1587	1551	1425	1371
	Compound 17	-	1695	1670	1640	1575	1560	1450	1380
	Compound 18	3231	1705-1681	-	1650	-	-	1340	1278
	Compound 19	3232	1712-1684	-	1651	-	-	1344	1281
	Compound 20	3233	1707-1684	-	1655	-	-	1340	1279
	Compound 21	3233	1713-1686	-	1652	-	-	1343	1277
Wavenumber (cm^{-1})	Compound 22	3234	1711-1683	-	1652	-	-	1343	1281
	Compound 23	3248	1703-1686	-	1655	-	-	1322	1239
	Compound 24	3243	1702-1683	-	1652	-	-	1321	1238
	Compound 25	3242	1698-1680	-	1657	-	-	1320	1242
	Compound 26	3244	1701-1683	-	1652	-	-	1327	1244
	Compound 27	3244	1698-1678	-	1653	-	-	1321	1238
	Compound 28	-	1695	1665	1645	1575	1554	1408	1382
	Compound 29	-	1680	1670	1650	1589	1560	1382	1382
	Compound 30	-	1696	1671	1650	1585	1551	1425	1382
	Compound 31	-	1696	1670	1652	1583	1552	1426	1382
	Compound 32	-	1695	1665	1650	1574	1551	1400	1382
	Compound 33	-	1685	1678	1646	1585	1551	1440	1382
	Compound 34	-	1690	1665	1649	1585	1551	1450	1382
	Compound 35	-	1695	1665	1650	1540	1530	1415	1384

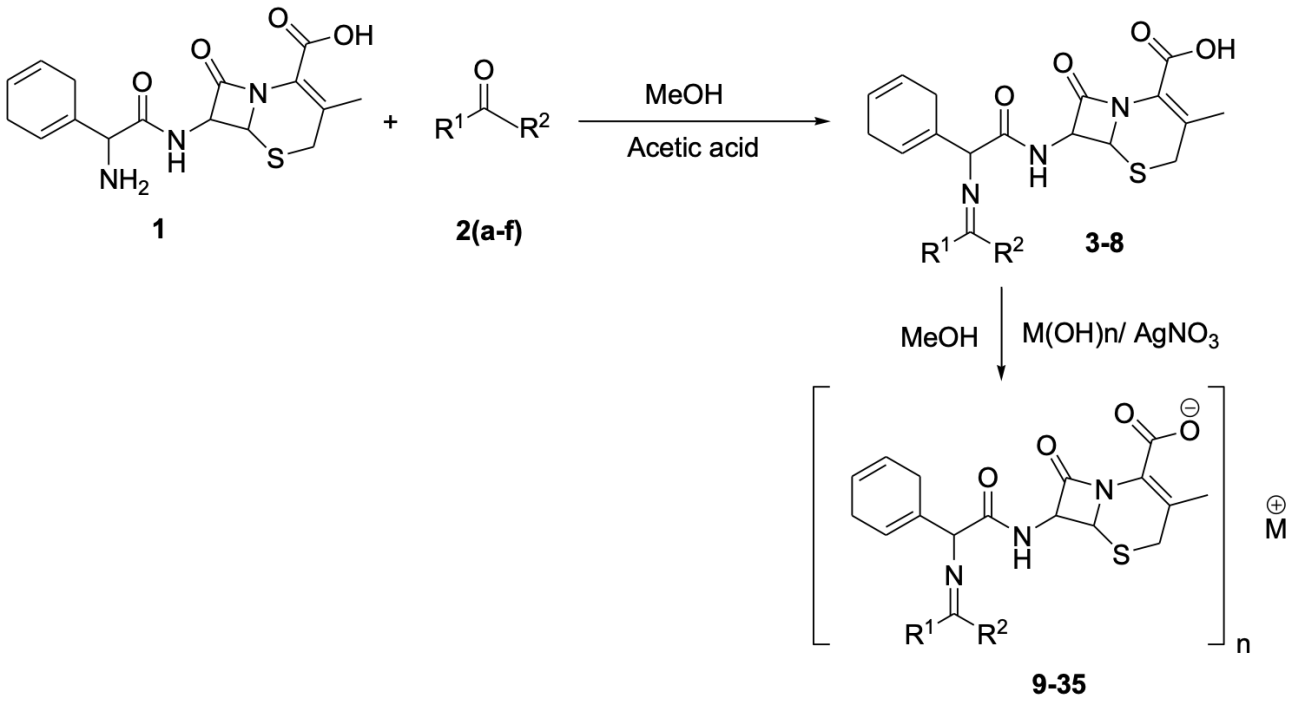
Antibacterial activities

Antibacterial activities were investigated using agar well diffusion method. The analysis was carried out against *Staphylococcus aureus*(gram positive bacteria) and *Escherichia coli*(gram negative bacteria). Bacterial culture was injected into nutrient broth and then it was incubated for 24 hours at 37 °C. Melting of soft agar tube was carried out and then after cooling it to 47 °C bacterial culture(10 µL) was added and tube was gently shaken. The culture was then transferred to nutrient agar plate and solidified. Holes were made in the agar plate with the help of borer. The test samples were injected into the holes. The samples were incubated for 24 hours at 37 °C. Zones of inhibition were measured in millimetre in each case. Pure cefradine was used as standard.

Results and Discussion

Chemistry

The present work comprises of the synthesis of **33** new compounds including Schiff bases of cefradine and their salts (**3-35**). Cefradine was reacted with various aldehydes and ketones to give Schiff bases (**3-8**). These Schiff bases (**3-8**) were characterized through IR and ^{1}H NMR techniques. The absence of characteristic bands for C=O(carbonyl) of aldehyde/ketone and NH_2(amine) of cefradine, and appearance of imine stretch in the range 1665-1640 cm^{-1} indicated product synthesis. In ^{1}H NMR presence of imine CH in range of 8.50-8.26, absence of NH_2 protons of cefradine and presence of all other relevant in their relevant ranges confirms synthesis of Schiff bases. The synthesized Schiff bases (**3-8**) were then reacted with various metal hydroxides and silver nitrate to form their respective salts (**9-35**). Synthesis of salts was indicated by IR spectra by the disappearance of OH band, and confirmed by disappearance of acidic H peak in ^{1}H NMR spectra. The synthetic pathway is illustrated in **Scheme 1**



Scheme 1: Preparation of salts of cefradine Schiff base (**9-35)**

Metal bases $M(OH)_n$: NaOH, KOH, $Ca(OH)_2$, $Ba(OH)_2$, $Ag(NO)_3$

Table 3. Structures of synthesized compounds

Code	R_1	R_2	M	n	Code	R_1	R_2	M	n
3	H	C_6H_5	--	--	**20**	H	4-$N(CH_3)_2C_6H_4$	Ag	1
4	H	3-ClC_6H_4	--	--	**21**	H	4-$N(CH_3)_2C_6H_4$	Ca	2
5	H	4-$N(CH_3)_2C_6H_4$	--	--	**22**	H	4-$N(CH_3)_2C_6H_4$	Ba	2
6	H	4-$OCH_3C_6H_4$	--	--	**23**	H	4-$OCH_3C_6H_4$	Na	1
7	CH_3	C_6H_5	--	--	**24**	H	4-$OCH_3C_6H_4$	K	1
8	C_6H_5	C_6H_5	--	--	**25**	H	4-$OCH_3C_6H_4$	Ag	1
9	H	C_6H_5	Na	1	**26**	H	4-$OCH_3C_6H_4$	Ca	2
10	H	C_6H_5	K	1	**27**	H	4-$OCH_3C_6H_4$	Ba	2
11	H	C_6H_5	Ag	1	**28**	CH_3	C_6H_5	Ca	2
12	H	C_6H_5	Ca	2	**29**	CH_3	C_6H_5	Na	1
13	H	C_6H_5	Ba	2	**30**	CH_3	C_6H_5	K	1
14	H	3-ClC_6H_4	Ca	2	**31**	CH_3	C_6H_5	Ag	1
15	H	3-ClC_6H_4	Na	1	**32**	C_6H_5	C_6H_5	Ca	2
16	H	3-ClC_6H_4	K	1	**33**	C_6H_5	C_6H_5	Na	1
17	H	3-ClC_6H_4	Ag	1	**34**	C_6H_5	C_6H_5	K	1
18	H	4-$N(CH_3)_2C_6H_4$	Na	1	**35**	C_6H_5	C_6H_5	Ba	1
19	H	4-$N(CH_3)_2C_6H_4$	K	1					

Biological Activity

The synthesized compounds were tested for biological activities against *Staphylococcus aureus*(gram positive bacterium) and *Escherichia coli*(gram negative bacterium) by using agar well diffusion method. Cefradine was used as the standard and concentration of each tested sample was 1mg/ml of dimethyl sulfoxide.

The antibacterial analysis of the synthesized compounds shows that the compound**23** exhibits best activity against both the strains *S. aureus* and *E.coli*. Compounds **18, 5, 11** and **27** show good activity against S. aureus while compounds **5, 26, 27, 3, 13, 18, 19**show good activity against E. coli. All of the above mentioned active compounds have H as R_1, Phenyl or Phenyl with NMe_2/OMe groups as R_2, so their activity might be attributed to lesser steric hindrance and increased availability of electrons at imine linkage. In addition most of these active compounds have Na or Ba as metal component.

Rest of the compounds have moderate to weak or no activity. It is observed that all compounds having R_1 as CH_3 or Ph(other than H) exhibit very low or no activity, this might be linked with steric hindrance closer to imine linkage. Reduced activities of most of the synthesized derivatives in comparison to cefradine can be linked to unavailability of free NH_2 group of cefradine for any interaction by its involvement in derivatization.

Table 4. Antibacterial activity of salts of Cefradine Schiff base

Code	*Staphylococcus aureus*	*Escherichia coli*	code	*Staphylococcus aureus*	*Escherichia coli*
	Zone of Inhibition (diameter in mm)			Zone of Inhibition (diameter in mm)	
3	15	16	**20**	15	14
4	12	14	**21**	-	-
5	16	17	**22**	-	-
6	-	-	**23**	18	18
7	11	13	**24**	-	-
8	-	-	**25**	14	13
9	-	-	**26**	13	17
10	-	-	**27**	16	17
11	16	15	**28**	-	9
12	-	-	**29**	-	-
13	15	16	**30**	7	7
14	8	-	**31**	8	-
15	7	7	**32**	7	7
16	9	-	**33**	7	11
17	13	13	**34**	-	-
18	17	16	**35**	-	14
19	14	16	Cefradine	24	21

Conclusion

Cefradine derivatives(Schiff bases 3-8 and their salts 9-35) were synthesized and characterized by ^{1}H NMR and IR spectroscopy. All the synthesized compounds were evaluated for anti-bacterial activity against two bacterial strains *S.aureus* and *E.coli.* Compound **23** shows the best activity against both the strains*S. aureus* and *E.coli*. Compounds **18, 5, 11** and **27** show good activity against *S. aureus* while compounds **5, 26, 27, 3, 13, 18, 19**show good activity against *E. coli*. However a general reduction in activities of most of the synthesized compounds in comparison to cefradine can be linked to unavailability of free NH_2 group of cefradine for any interaction by its involvement in derivatization.

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Conflict of interest

The authors declare that there is no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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