Review of: "Synthesis and Antibacterial Screening of Cefradine Schiff Bases and Their Metal Salts"

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

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Declarations

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

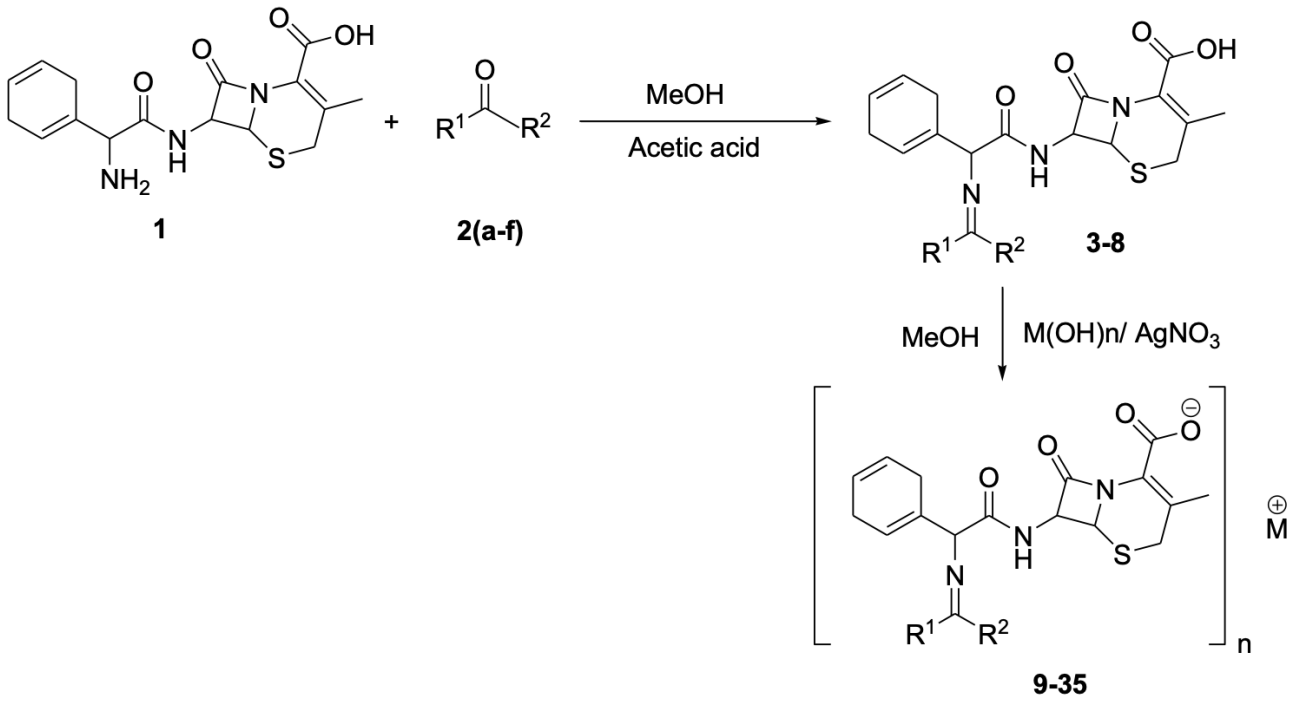
Antibacterial activities

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.

Acknowledgments

The authors are thankful to the Higher Education Commission of Pakistan.

Funding

No funding source is available.

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.

Open Peer Review

Review this Article

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PM

Prof. Venkata Basaveswararao Mandava posted a **Review**

December 5, 2023

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https://doi.org/10.32388/8S9Z7P

accept the manuscript for publication

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Comment

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AA

Ali Thoulfikar Abdul Imeer posted a **Review**

December 5, 2023

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https://doi.org/10.32388/YIVDMH

Recommend for publicatio

0 0

Comment

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MM

Mohamed Moumou posted a **Review**

December 4, 2023

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https://doi.org/10.32388/SXAMIW

Dear Editor

I have gone through the manuscript and I am of the opinion that the manuscript needs to undergo major revision before it

can be accepted for publication. My comments are given below. Authors are advised to go through these comments, and respond to them in detail and make necessary changes in the manuscript.

1. The usage of English needs improvement.
2. The NMR ^{13}C spectra of the compounds are missing in the paper and need not be omitted
3. The authors write: Completion of the reaction was monitored by TLC, how??? Add eluent: percent, and which technical tool was used to visualize the spots?
4. The conformations of all the rings in the structure must be quantified. The molecular structure especially the conformations, stereochemistry etc needs some explanation.
5. Include the obtained yields in scheme 1
6. Add the yields and color of each product to the physical information data in the manuscript.
7. It is important to include IR data in the characterization section, not in a table format.
8. In order to have antibacterial activity, it is crucial to specify the references or origin of the strains used.
9. Examine the activity of the most potent derivatives against the cefradine parent in dose response analyses that include multiple concentrations.

I hope the following suggestion would be helpful to the authors to improve their work

See more

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Comment

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RD

Ruaa M. Dhedan posted a **Review**

December 4, 2023

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https://doi.org/10.32388/ZOGHC6

I have posted my comments in the text body regarding the scientific and linguistic issues

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Comment

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AA

Ahmed N. Ayyash posted a **Review**

December 3, 2023

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https://doi.org/10.32388/HNNL5X

Dear Editor,

Thank you for your opportunity to read and review the manuscript entitled**"Synthesis and Antibacterial Screening of Cefradine Schiff Bases and Their Metal Salts".**

Our comments are given below.

The manuscript may be accepted for publication after the following corrections:

1. The manuscript title may be re-write to become more informative.
2. The aim of the article should be more clearly.
3. The introduction section is poor scientifically. Other and new reports are required.
4. For synthesized compounds characterization, full characterization is required. (The ^{13}C NMR and Mass spectra /or microanalysis for C.H.N should be provided).
5. References need to be more newly.

Best Regards…

Asist. prof. Dr Ahmed Neamah Ayyash

See more

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Comment

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MB

Mahesh Bhat posted a **Review**

December 3, 2023

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https://doi.org/10.32388/LHXGXJ

The author has carried out routine work by taking most bioactive compound and end up with less bioactive compounds as author said. The manuscript becomes sounds if single crystal data included in characterization techniques.

My comments to the author

1. Revise the abstract with spectroscopic and results.
2. Write the NMR range for doublet peak
3. IR data should be include in characterization section not in table format.
4. MIC should be determine in antibacterial study.

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Comment

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DA

Dr Khalil Ahmad posted a **Review**

December 3, 2023

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https://doi.org/10.32388/ORIIKU

1. In abstract add brief findings of characterization techniques.

2. In abstract also give ZOI for bacterial strains using synthesized compounds as well as for standard medicine.

3. Also discuss in abstract which bacterial strains give more ZOI for which type of bacteria (gram positive or negative) and why?

4. Add state of the art study gap in introduction.

5. As you discussed that your synthesized compounds showed less activities than cefradine. Then what was your purpose to carry out study.

6. In scheme 1 also give mechanism used for catalyst.

7. You have given only 17 references. Also add more references.

See more

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Comment

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DG

Daniel Tadeu Gomes Gonzaga posted a **Review**

December 3, 2023

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https://doi.org/10.32388/GYZNOL

page 2 - Put examples of cefradine derivatives with enhanced antibacterial activity

In the experimental, make a generic text for all aldehydes and ketones

It would be nice to do at least NMR 13C

Compound 3 is missing

page 4 - Some IR bands do not appear, why does this happen?

in procedure for the preparation of salts of cefradine Schiff bases, again use a generic text for all compounds

page 8 - The yield of compounds 10-35 was missing

page 10 - Would it be important to do the IC50?

page 13 - Talk about income at the conclusion

See more

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Comment

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AS

Aamer Saeed posted a **Review**

December 3, 2023

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https://doi.org/10.32388/DFNS7J

Reviewers Decision:

Revision for improvement the quality of manuscript.

Overall the manuscript is very weak and needs improvement in different parts of the work that have been highlighted as reviewer comments for consideration.

Reviewer Comments:

please first note disparity in the numbers and letters used manuscript authors list and the affiliations

1. Why the washing of crude product was done with n-hexane and not with mild polar solvent. Please provide the reason.

2. Specify the color of each product formed as part of physical info data input to the manuscript.

3. Spacing should be added which is missing in case of experimental data section.

4. J of coupling constant be provided in italics.

5. C-13 data is missing which should be added.

6. It is recommended to add mass spectral data.

7. Results and discussion section is very weak and needs a lot of improvement. It is important to mention the effect of substitutions on the Schiff base yield and ultimately on the bioactivity carried out.

8. The manuscript lacks discussion in terms of comparative effect of various metals for formation of their corresponding

complexes and its ultimate effect on the bioactivity.

9. Why the metal complexes were chosen for bioactivity and not their neutral azomethine complexes.

See more

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Comment

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HA

Heba Alshater posted a **Review**

December 2, 2023

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https://doi.org/10.32388/WVPPHD

Authors should add more details in abstract and introduction. references are old.more details are highlighted in the attached pdf file

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1 comment

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MH

Mostafa Hussien posted a **Review**

December 2, 2023

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https://doi.org/10.32388/JXL2EZ

The manuscript deal with synthesizing and characterizing some cefradine derivatives(Schiff bases 3-8 and their salts 9-35) by 1H NMR and IR spectroscopy. All the synthesized compounds were evaluated for anti-bacterial activity against two

bacterial strains S.aureus and E.coli.is qualified to be accepted in its form and the result and discussion is explained correctly.

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Comment

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ZD

Zeleke Digafie posted a **Review**

December 2, 2023

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https://doi.org/10.32388/VZMESH

Date 02/12/2023

To editor

I have thoroughly seen a manuscript entitled as" Synthesis and Antibacterial Screening of Cefradine Schiff Bases and Their Metal Salts" which attempted to search for compounds possessing enhanced biological activities based on converting cefradine into its Schiff base and their metal salts.

1. The researchers used methanol solvent with acetic acid catalyst to prepare the Schiff bases and methanolic aqueous basic solutions to prepare the salts of the Schiff bases. Unfortunately, Cefradine is β-lactam bioactive substance. The main bioactive structure feature β-lactam drugs are the β-lactam ring. The β-lactam is highly strained ring and will be opened when it comes in contact with nucleophilic solvents. The researchers used protonic nucleophilic solvents to conduct the reactions. Thus, this reaction conditions completely destroy β-lactam ring. As any β-lactam drugs, once β-lactam rings of the derivatives were opened, they would lose any bioactivity as it was evidenced in *table 4* of this manuscript.

Most probably the procedures followed by researchers would result in the following amide Schiff bases rather than what have been asserted by researchers as Cefradine Schiff Bases:

1. The researchers attempted to use ^{1}H NMR and IR data to approve the structure of the Schiff bases and their salts. However, these spectroscopic techniques are not enough to indicate the structure of the compounds unambiguously. Especially to indicate the presence or absence of the β-lactam ring in the products.
2. Even the ^{1}H NMR data were not clearly correlated to structure of compounds by identifying the carbons or hydrogens

in structure with numbers.

3. Even though most synthetic reactions procedures including preparation of Schiff bases introduces some impurities and byproducts, the researchers didn't use any purification procedures.
4. Any of the spectroscopic spectrum results were not included as supplementary data with manuscript. This created difficulties to assure if the synthesis were achieved with acceptable degree of purity.
5. The result of antibacterial activity reported in manuscript was against premises of the researchers themselves and low bioactivity may be mainly due to destruction of β-lactam ring due to the preparation procedures rather than what have been suggested as steric interference.

Thus, in my opinion, **the current manuscript is not appropriate to be published** in Qeios,

See more

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1 comment

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YD

Yogesh Deswal posted a **Review**

December 1, 2023

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https://doi.org/10.32388/MEX8F0

Dear Editor,

Recommendations: Reject

The work is a routine one of marginal interest and i think the work is not suitable for publication. Also before resubmitting it elsewhere the authors address the following points:

1. What is the main purpose of the study? Synthesis or Biological applications. All these things should be present in a understandable manner.
2. The work lacks discussion of many spectroscopic and physico-analytical techniques necessary to characterize the compounds.

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Comment

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BM

Bencela M posted a **Review**

December 1, 2023

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https://doi.org/10.32388/RC6VFF

1. The authors should explicitly justify their choice of preparing metal salts of Schiff bases rather than coordination complexes. A thorough explanation of the anticipated impact of these metal salts on antimicrobial activity compared to their respective Schiff bases is necessary. Highlight any specific properties or mechanisms believed to enhance antibacterial properties in the metal salt form.

2. The discussion of obtained results needs to be more comprehensive. Consider delving into the specific trends observed in antibacterial activity among different metal salts and Schiff bases. Discuss the possible reasons behind variations in activity and relate these findings to existing literature. A more detailed analysis of the results will contribute to a deeper understanding of the study's implications.

3. To address concerns about structural confirmation, it is essential to include additional spectroscopic analyses, such as mass spectrometry /CHN analysis. These techniques can provide valuable information for confirming the molecular structures of the synthesized compounds.

4. Need in depth discussion in introduction, result and discussion & conclusion

5. Pay attention to the clarity of language and overall structure of the article, making it accessible to a broad scientific audience.

See more

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Comment

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SE

Safae Er Raouan posted a **Review**

November 30, 2023

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https://doi.org/10.32388/1QT3VW

REVISION OF The ARTICLE: Synthesis and Antibacterial Screening of Cefradine Schiff Bases and Their Metal Salts

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