

SYNTHESIS AND CHARACTERIZATION OF SCHIFF BASES DERIVED FROM 7-[[2-(2-AMINO-1,3-THIAZOL-4-YL)-2-(CARBOXYMETHOXYIMINO)ACETYL]AMINO]-3-ETHENYL-8-OXO-5-THIA-1-AZABICYCLO[4.2.0]OCT-2-ENE-2-CARBOXYLIC ACID

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ABSTRACT

The Schiff bases (**8-13**) were synthesized by the reaction of cefixime (**1**) with aldehydes (**2-7**). The characterization of Schiff bases were carried out by using spectroscopic techniques including IR, ¹H-NMR, EI-MS along with elemental analyses.

Keywords: Schiff Base, Cefixime, Transamination, Rasemination, Cephalosporins.

INTRODUCTION

A number of reports are available on structural, chemical and biological aspects of Schiff bases and related compounds. The -N=CH- (imine) group is the major characteristic of Schiff bases elucidation of the mechanism of transamination and rasemination reaction in biological system is based on this group¹⁻². The work on Schiff bases has been reported extensively in the scientific literature. The clear stability of Schiff bases synthesized from aromatic aldehydes or aromatic ketones is quite evident from the literature. The frightening problem of microbial resistance to antibiotics can be minimized³, by the extensive discovery of novel active compounds against new targets⁴. A variety of crude types of drugs, which can be used as the source of medicine preparations at some later stage, are still being discovered from wild plants. Anyhow, the life span of material sources has been shortened by the use of plant based drugs. The efforts are still underway to search or locate more potent and cheaper raw materials for fulfilling requirements of industry. The treatment of bacterial infections is carried out by using cephalosporins, which have exhibited broad antibacterial activities with little toxicity and are employed extensively⁵. Most of antimicrobial agents with improved spectra of activity and β -lactamase stability are obtained by structural modifications in cephem⁶. Cefixime belongs to cephalosporin i.e. third generation of antibiotics. The first and second generations of cephalosporins have lesser activity against gram-negative bacteria as compared with the third generation.

As in continuation of our group on the Schiff bases⁷, in the present work, six Schiff bases (**8-13**) of cefixime have been synthesized. The spectral ¹H-NMR, IR, EI-MS and microbial analysis was used for confirmation of structures of synthesized compounds.

MATERIALS AND METHODS

Reagent grade solvents and chemicals were purchased from Merck which were used without further purification. Washing of all the glassware during the reaction was accomplished by using distilled water and drying was carried out at 110 °C.

Physical measurements

The melting points of the synthesized compounds were determined by Gallenkamp melting point apparatus and are uncorrected. Elemental composition was determined by Perkin-Elmer 2400 Series II elemental analyzer. For IR spectra, Thermo Nicolet Avatar 320 FT-IR spectrometer within 400-4000 cm⁻¹ range was used by employing KBr disc method. The recording of EI-MS spectra was conducted by electron impact mode on Finnigan MAT-112 spectrometer (Finnigan, Waltham, MA, USA) and *m/z* (%) of [M]⁺

ions reported. Pre-coated silica gel G-25-UV₂₅₄ plates (E-Merck) were utilized for checking the purity of compounds by TLC method. The compounds were dissolved in DMSO-*d*₆ for the measurement of ¹H-NMR spectra on Bruker AMX-400 spectrometer. The values for chemical shift (δ) are given in ppm, while employing TMS as internal standard and the data of scalar coupling constants (*J*) is presented in Hertz.

Preparation of Schiff bases (8-13)

The aldehydes (**2-7**) (0.01 mmol) dissolved in MeOH (25 mL) were mixed with a stirred solution of cefixime (**1**) (0.01 mmol) in MeOH (30 mL). KOH (0.1% in MeOH) was added to this solution and pH of the solution was adjusted at 7-8 and solution was refluxed for about 45 minutes. The solution, thus obtained, was clear. TLC was employed for monitoring the completion of reaction. The pH was adjusted to 7 by adding a few drops of acetic acid. The solution was cooled after condensing on rotary evaporator. Washing of solid residue was performed with cold ethanol after filtration and then the solid was dried. The Schiff base was obtained by recrystallization with a mixture of MeOH and ethyl acetate (50:50)⁸.

Schiff base (8): Color: brown; Yield: 38.91%; IR (KBr, cm⁻¹): 1615 (HC=N); ¹H-NMR (DMSO-*d*₆, δ , ppm): 8.31 (s, 1H, HC=N); Anal. Calcd. for C₂₃H₁₈N₆O₉S₂ (%): C 47.10, H 3.09, N 14.33; Found: C 47.32, H 3.18, N 14.19; Mass spectrum (EI-MS) [M]⁺ 586.18.

Schiff base (9): Color: brown; Yield: 43.91%; IR (KBr, cm⁻¹): 1647 (HC=N); ¹H-NMR (DMSO-*d*₆, δ , ppm): 8.40 (s, 1H, HC=N); Anal. Calcd. for C₂₃H₁₈N₆O₉S₂ (%): C 47.10, H 3.09, N 14.33; Found: C 47.37, H 3.23, N 14.41; Mass spectrum (EI-MS) [M]⁺ 586.21.

Schiff base (10): Color: yellow; Yield: 86.01%; IR (KBr, cm⁻¹): 1687 (HC=N); ¹H-NMR (DMSO-*d*₆, δ , ppm): 8.01 (s, 1H, HC=N); Anal. Calcd. for C₂₅H₂₀BrN₅O₇S₂ (%): C 46.45, H 3.12, N 10.83; Found: C 46.31, H 3.19, N 11.14; Mass spectrum (EI-MS) [M]⁺ 644.91.

Schiff base (11): Color: peru; Yield: 63.32%; IR (KBr, cm⁻¹): 1668 (HC=N); ¹H-NMR (DMSO-*d*₆, δ , ppm): 8.30 (s, 1H, HC=N); Anal. Calcd. for C₂₃H₁₉N₅O₈S₂ (%): C 49.55, H 3.43, N 12.56; Found: C 50.02, H 3.57, N 12.74; Mass spectrum (EI-MS) [M]⁺ 557.31.

Schiff base (12): Color: crimson; Yield: 57.82%; IR (KBr, cm⁻¹): 1649 (HC=N); ¹H-NMR (DMSO-*d*₆, δ , ppm): 8.28 (s, 1H, HC=N); Anal. Calcd. for C₂₃H₁₇ClN₆O₉S₂ (%): C 44.48, H 2.76, N 13.53; Found: C 44.63, H 2.67, N 13.42; Mass spectrum (EI-MS) [M]⁺ 620.43.

Schiff base (13): Color: khaki; Yield: 75.68%; IR (KBr, cm⁻¹): 1672 (HC=N); ¹H-NMR (DMSO-*d*₆, δ , ppm): 8.05 (s, 1H, HC=N); Anal. Calcd. for C₂₃H₁₇Br₂N₅O₈S₂ (%): C 38.62, H 2.40, N 9.79; Found: C 38.77, H 2.53, N 9.58; Mass spectrum (EI-MS) [M]⁺ 712.77.

RESULTS AND DISCUSSION

Chemistry and characterization

The Schiff bases (**8-13**) were prepared by refluxing the appropriate amount of cefixime (**1**) with the corresponding aldehydes (**2-7**), in methanol (Fig. 1). The completion of reaction for Schiff bases (**8-13**) was estimated by a direct comparison of reactants and reaction mixtures spot on TLC. The structures of synthesized Schiff-base (**8-13**) were established by EI-MS, IR, NMR and micro-analytical data.

Elemental analyses of the Schiff bases (**8-13**) (Table 2) are compatible with the structures shown in Fig. 1. IR spectra of the

Schiff bases (**8-13**) showed the absence of bands at 1735 and 3420 cm^{-1} due to $\nu(\text{C}=\text{O})$ and $\nu(\text{NH}_2)$ stretching vibrations and instead, new bands appeared at in the range 1615-1687 cm^{-1} (Table 3). These are assigned to azomethine $\nu(\text{HC}=\text{N})$ linkage.

This suggested that amino and aldehyde moieties of the starting reagents have been converted into the corresponding Schiff bases (Fig. 1). $^1\text{H-NMR}$ spectra of the Schiff bases (**8-13**) displayed the azomethine proton ($\text{CH}=\text{N}$) at δ 8.01-8.40 as a singlet (Table 3). The molecular ion peaks $[\text{M}]^+$ for the Schiff bases (**8-13**) were observed in the EI-MS spectra of respective Schiff base which is a supportive evidence for successful synthesis (Fig. 1).

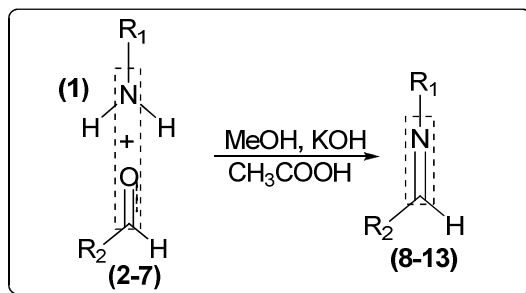


Fig. 1: Proposed structure of Schiff bases (**8-13**).

Table 1: Synthesis of Schiff bases (**8-13**).

Compound	R ₂	Compound	R ₂
2, 8		5, 11	
3, 9		6, 12	
4, 10		7, 13	

Table 2: Analytical data of the Schiff bases (**8-13**).

Entry	Empirical formula	Color	Yield (%)	Found (Calcd.) (%)		
				C	H	N
8	C ₂₃ H ₁₈ N ₆ O ₉ S ₂	Brown	38.91	47.32 (47.10)	3.18 (3.09)	14.19 (14.33)
9	C ₂₃ H ₁₈ N ₆ O ₉ S ₂	Brown	43.91	47.37 (47.10)	3.23 (3.09)	14.41 (14.33)
10	C ₂₅ H ₂₀ BrN ₅ O ₇ S ₂	Yellow	86.01	46.31 (46.45)	3.19 (3.12)	11.14 (10.83)
11	C ₂₃ H ₁₉ N ₅ O ₈ S ₂	Peru	63.32	50.02 (49.55)	3.57 (3.43)	12.74 (12.56)
12	C ₂₃ H ₁₇ ClN ₆ O ₉ S ₂	Crimson	57.82	44.63 (44.48)	2.67 (2.76)	13.42 (13.53)
13	C ₂₃ H ₁₇ Br ₂ N ₅ O ₈ S ₂	Khaki	75.68	38.77 (38.62)	2.53 (2.40)	9.58 (9.79)

Table 3: Spectral data of the Schiff bases (8-13).

Entry	¹ H-NMR (s*, HC=N) ppm	IR (HC=N) cm ⁻¹	EI-MS m/z %
8	8.31	1615	586.18
9	8.40	1647	586.21
10	8.01	1687	644.91
11	8.30	1668	557.31
12	8.28	1649	620.43
13	8.05	1672	712.77

(*s: singlet)

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