Conventional and microwave irradiated syntheses of new symmetric double Schiff bases of 1,1'-bis(4-amino phenyl)cyclohexane, their spectral characterization and microbial activity

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ABSTRACT. Symmetric double Schiff bases of 1,1'-bis(4-amino phenyl)cyclohexane and substituted aromatic benzaldehydes were synthesized by thermal and microwave irradiated green chemistry techniques. The purity of Schiff bases was checked by TLC. The structure of Schiff bases were supported by UV, FTIR, ¹H NMR and MS techniques. The antibacterial and antifungal activities of Schiff bases were checked against gram positive and gram negative microbes. Schiff bases showed moderate antibacterial activity but they showed good comparable antifungal activity against chosen microbes and standard drugs.

1. INTRODUCTION

Schiff bases are widely used as analytical reagents, fine chemicals, medical substrates and ligands for metal complexes [1, 2] having industrial importance as antifungal and biological applications [3-6]. The Schiff bases derived from aromatic diamines and salicyaldehyde or bis salicyaldehyde possess unique characteristics of improving both antiwear and corrosion inhibition of synthetic lubricants. Schiff bases are added in lubricants and lubricating oil greases up to 5 % of total composition [7]. They are also useful as a starting materials for the synthesis of drugs like antibiotics, antiallergic, antiphlogistic and antitumor [8-10]. Kuzmin et. al [11] have reported anticancer activity of a set of macrocyclic Schiff bases based on 2,6-bis(2 and 4 formyl arylosy methyl) pyridines. They have derived correlation equation between the anticancer activity and structural parameters of the molecules studied. Lozitsky et. al [12] have reported 4D-QSAR study and anticancer activity of Schiff bases synthesized by the condensation of various aliphatic and aromatic diamines with 2,6-bis(2 and 4 formyl arylosy methyl) pyridine derivatives. The results of biological activities showed that Schiff bases are active towards cell growth of the nine cell culture of human malignant tumors like leukemia, CNS cancer, colon cancer, ovarian cancer and renal cancer. They claimed that pyridine ring has a negative influence on anticancer activity, while the presence of the C=N group with different substitutions promotes anticancer activity.

Most widely Schiff bases are synthesized by classical method catalyzed by acid at reflux temperature. Recently stoichiometric reaction of aldehyde and diamine in a suitable solvent is employed successfully for the synthesis of Schiff bases [13]. In conventional method solvent removal is a problem especially when dipolar high boiling solvents are used or isolation of product through liquid-liquid extraction. The solvent free syntheses in a microwave oven reduce the risk of hazardous explosion [14]. Solvent free microwave irradiated synthesis [15, 16] has become popular over usual homogeneous and heterogeneous reaction [17-19] due to environment friendly, economic and rapid reaction rate [20-25]. This technique provides pure product in quantitative yields and structural parameters of the molecules studied. Zheng et.al [26] have reported two novel porphyrionogen like macrocyclic Schiff base ligands by different internal cavities and characterized by elemental analysis, ¹H NMR, FAB-MS and IR methods. They have synthesized Schiff base ligands by thermal method.
In present work we have reported conventional and microwave irradiated synthesis of new symmetric double Schiff bases, their spectral and microbial study.

2. MATERIALS AND METHODS

Solvents and chemicals used in the present investigation were of LR grade and used either as received or purified by fractional distillation. 1, 1’ Bis (4-aminophenyl) cyclohexane [Scheme-1] was synthesized and recrystallized according to reported work [27, 28]. Symmetric double Schiff base [Scheme-2] were synthesized by conventional and microwave irradiated techniques [29] and crystallized from appropriated solvent system as shown in Table 1. Analytical and physical data of Schiff bases (SDSB-1 to SDSB-4) are presented in Table 2.

Scheme 1: Syntheses of 1,1’- bis (4-amino phenyl)cyclohexane

Scheme 2: Syntheses of symmetric double Schiff base

3. MEASUREMENTS

Melting points were determined in open capillary tubes and were uncorrected. Purity of the compounds was checked by TLC in appropriate solvent systems. IR spectra (KBr pellets) were scanned on a Shimadzu FTIR- 8400 spectrophotometer. The ¹HNMR spectra of Schiff bases were scanned on a Brucker FTNMR (300 MHz) spectrometer by using CDCl₃ as a solvent and TMS as an internal standard. Mass spectra of the compounds were scanned on a Shimadzu GC-MS-QP 2010 spectrometer by using E.I. (0.7 kV) detector. The ion source temperature was 220°C and interface temperature was 240°C. UV spectra were scanned on a Shimadzu UV-1700 spectrophotometer by using CHCl₃ and DMSO as solvents. Microbial activity of the compounds was checked by cup-plate technique [30].

4. RESULTS AND DISCUSSION:

From Table-1 it is observed that reaction time for conventional method is pretty long (7-8h) while it is much smaller for microwave irradiation method (7-8min). UV absorption of SDSB-1 to SDSB-4 was studied in chloroform and dimethyl formamide solvents at room temperature. Schiff bases showed longer wave length of absorption in DMSO system as compared to chloroform system. Thus, DMSO solution displayed blue shift and solvent polarity affect UV absorption. IR, ¹HNMR and MS data of SDSB-1 to SDSB-4 are as follow.
Table 1: Experimental detail for the synthesis of SDSB-1 to SDSB-4

| Schiff base | Conventional method | Microwave irradiation method | Crystallization solvent system |
|-------------|---------------------|-----------------------------|-------------------------------|
|             | Time, h | % Yield | Time, min | % Yield |                                |
| SDSB-1      | 7.5     | 68     | 8         | 90      | Chloroform – n Hexane          |
| SDSB-2      | 8.0     | 72     | 7         | 95      | Ethyl acetate – n-Hexane       |
| SDSB-3      | 8.0     | 74     | 7         | 95      | Ethyl acetate – n-Hexane       |
| SDSB-4      | 7.0     | 70     | 8         | 94      | Chloroform – n Hexane          |

Table 2: Physical and analytical data of SDSB-1 to SDSB-4

| Schiff bases | M.F. | M.W. | m. p., °C | Color  | Rf value |
|--------------|------|------|-----------|--------|----------|
| SDSB-1       | C_{36}H_{34}N_{2} | 494  | 232       | Light brown | c-0.59 |
| SDSB-2       | C_{32}H_{28}N_{4}O_{4} | 532  | 258       | Yellow    | a-0.68 |
| SDSB-3       | C_{32}H_{28}N_{4}O_{4} | 532  | 260       | Yellow    | a-0.71 |
| SDSB-4       | C_{36}H_{40}N_{4}  | 528  | 248       | Light brown | b-0.56 |

a: Ethyl acetate – n-Hexane (65:35 V/V)  
b: Ethyl acetate – n-Hexane (80:20 V/V)  
c: Ethyl acetate – n-Hexane (75:25 V/V)

4.1 Characterizations of the Schiff bases

SDSB-1:  
UV (λ_{max}, nm): CHCl$_3$ 255.4, DMSO 263.4  
IR (cm$^{-1}$): CH=N 1626.8, V$_{C\cdot N}$ 1362.6, V$_{C\cdot C}$ 1609.6, 1577.7, V$_{CH}$ 2929.7, 2854.5, V$_{CH}$ (-oopd) 814.9, V$_{CH}$ (-ipd) 1106.1, 1075.2  
MS: 490

SDSB-2:  
UV (λ_{max}, nm): CHCl$_3$ 246.0, DMSO 261.4  
IR (cm$^{-1}$): CH=N 1614.3, V$_{C\cdot N}$ 1305.7, V$_{C\cdot C}$ 1568.0, 1519.8, V$_{CH}$ 2931.6, 2856.4, V$_{CH}$ (-oopd) 829.3, V$_{CH}$ (-ipd) 1174.6, 1109.0  
$^1$H NMR (ppm): 1.611 (6H, s, β + γ, -CH$_2$), 2.329 (4H, s, α, -CH$_2$), 7.294 - 7.286 (4H, d, Ar-H$_b$, J= 8.5)  
7.244 (CDCl$_3$), 7.373-7.344 (2H, d, Ar- H$_a$, J= 8.5), 7.617-7.561 (2H, m, Ar-H$_a$, J=8.4), 7.738-7.688 (2H, m, Ar-H$_a$, J=7.5), 8.066 -8.035 (2H, d, Ar-H$_g$, J=9.4), 8.298 -8.270 (2H, d, Ar-H$_d$, J=8.5), 8.942 (2H, s, -CH=N-)  
MS: 532
SDSB-3:
UV (λ_max, nm): CHCl₃ 245.2, DMSO 266.4
IR (cm⁻¹): CH=N 1626.8, ν_C=N 1352.0, ν_C=C 1573.8,1498.6 ν_C-H (-oopd) 813.9, ν_C-H (-ipd) 1171.7,1074.3
¹H NMR (ppm): 1.599 (6H, s, β + γ, -CH₂-), 2.329 (4H, s, α, -CH₂-), 7.211-7.183 (4H,d, Ar-H₆, J= 8.4)
7.292 (CDCl₃), 7.372-7.343 (4H, d, Ar- H₆, J= 8.6 ), 7.647-7.597(2H, t,Ar-H₆, J=7.4,7.7 ), 8.224 - 8.196 (2H, d, Ar-H₈, J=8.3 )8.296- 8.267 (2H, d, Ar-H₈, J=7.9 ), 8.529 (2H, s, Ar-H₈, J= 8.4) , 8.705 (2H, s, -CH=N-)
MS: 532

SDSB-4:
UV (λ_max, nm): CHCl₃ 361.4, DMSO 363.4
IR (cm⁻¹): CH=N 1606.6, ν_C=N 1312.5, ν_C=C 1606.6, ν_C-H₂ 2930.6, 2853.5, ν_C-H (-oopd) 814.9, ν_C-H (-ipd) 1165.9,1123.5
¹H NMR (ppm): 1.575 (6H, s, β + γ, -CH₂-), 2.291 (4H, s, α, -CH₂-), 3.019 (12H, s, H₆), 6.722-6.693 (4H, d, Ar-H₆ J=8.7), 7.137-7.109 (4H, d, Ar-H₆, J=8.5), 7.238 (CDCl₃), 7.291-7.263 (4H, d, Ar-H₆, J=8.4), 7.766-7.737 (4H, d, Ar-H₆, J=8.7), 8.314 (2H, s, -CH=N-) 
MS: 528

Pyrolysis of compounds is a complex process and involves a variety of reactions such as ionization, decomposition, branching, cross-linking and rearrangement. Mass spectral fragmentation of the Schiff base is shown in Scheme-3. Important fragments are presented Tables-3. Loss of electron results in to molecular ion, while loss of azomethine proton gives (M-1)⁺ ion peak in the mass spectrum. (M-1)⁺ ion undergoes further fragmentation to give fragments 1 and 2. Fragment - 1 further undergoes fragmentation to give fragments 3 and 4. Similarly fragment - 2 produces fragments - 4 and 6, while fragment - 3 produces fragments 5, 6 and 7. In case of main fragments, many more fragments are possible due to above mentioned possible reactions. At the end all fragments are converted into low molecular mass gaseous products.
Table 3: Molecular ion (M$^+$), (M-1)$^+$ peaks and some important Fragments of SDSB-1 to SDSB-4.

| Schiff base | M$^+$ | (M-1)$^+$ | F-1 | F-2 | F-3 | F-4 | F-5 | F-6 | F-7 |
|-------------|------|----------|-----|-----|-----|-----|-----|-----|-----|
| SDSB-1      | 490  | -        | 448 | 130 | 360 | 318 | 91  | 77  | 178 |
| SDSB-2      | 532  | 531      | 490 | 149 | 383 | 341 | 91  | 77  | 178 |
| SDSB-3      | 532  | 531      | 490 | 149 | 383 | 341 | 91  | 77  | 178 |
| SDSB-4      | 528  | 527      | 486 | 147 | 381 | 339 | 91  | 77  | 178 |

5. ANTIMICROBIAL ACTIVITY

Schiff bases, standard drugs (amoxicillin, ampicillin, ciprofloxacin and erythromycin) and solvent DMF were screened for their microbial activity against Escherichia coli (E.coli), Bacillus megaterium (B. mega), Proteus Vulgeris (P.vulgeris), Staphylococcus aureus (S.aureus) and Aspergillus niger (A. niger) by cup plate method at 37°C. The sample volume was 0.1ml (50µg). The plates were incubated for 24h at 37°C and zones of inhibition for each microbial growth were measured relative to control (DMF) and are reported in Table 4, from which it is observed that SDSB-1 to SDSB-4 showed moderate antibacterial activity in comparison with standard drugs. SDSB-1 showed moderate antifungal activity against A. niger and erythromycin but SDSB-2 to SDSB-4 showed comparable activity. The significant antifungal activity is due to presence of nitro groups and N, N -dimethyl groups in the Schiff bases.

Table 4: A comparative zone of inhibition for standard drugs and Schiff bases

| Sample       | Zone of inhibition, mm |
|--------------|------------------------|
|              | E. coli MTCC-443 | B. mega MTCC-244 | B. sub. MTCC-441 | P. vulgaris MTCC-744 | A. niger MTCC-282 |
| SDSB-1       | 7               | 9               | 8               | 9               | 12              |
| SDSB-2       | 9               | 9               | 11              | 10              | 15              |
| SDSB-3       | 9               | 9               | 10              | 11              | 16              |
| SDSB-4       | 8               | 10              | 9               | 10              | 16              |
| Amoxicillin  | 18              | 19              | 22              | 22              | -               |
| Amoxicillin  | 17              | 21              | 19              | 23              | -               |
| Ciprofloxacin| 22              | 20              | 21              | 24              | -               |
| Erythromycin | 19              | 20              | 22              | 24              | 18              |

6. CONCLUSIONS

As compared to conventional method microwave irradiated method led to shorter reaction time and improved reaction yields. Schiff bases showed moderate antibacterial activity and moderate to comparable antifungal activity against chosen microbes and standard drugs.

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