SYNTHESIS OF SOME NOVEL TRIAZOLE DERIVATIVES AS SCHIFF BASES AND THEIR ANTIMICROBIAL EVALUATION

VAIBHAV SHARMA$^{a,b}$, DINESH KUMAR MEHTA*, RINA DAS, PREET KAWAL KAUR

$^{a}$M. M. College of Pharmacy, MM University, Mullana, Ambala, Haryana, India, $^{b}$Assistant Professor, IEC School of Pharmacy, IEC University, Kalujhanda, Solan, Baddi, Himachal Pradesh, India
Email: dkmehtamumu@gmail.com

Received: 15 Feb 2016 Revised and Accepted: 22 Jul 2016

ABSTRACT

Objective: This work involves the synthesis of some novel Schiff base derivatives synthesized from p-amino benzoic acid.

Methods: A series of 4-[4-(arylidene amino)-5-mercapto-4H-[1, 2, 4] triazol-3-yl]-benzoic acid complexes were synthesized from 4-(4-amino-5-mercapto-4H-[1, 2, 4] triazol-3-yl)-benzoic acid by reaction with different aromatic aldehydes. All the synthesized Schiff base derivatives were characterized by using analytical techniques (FT-IR, $^1$H NMR and Mass spectroscopy). The title compounds were evaluated for antibacterial activity against Gram-positive bacteria (Staphylococcus aureus and Streptococcus pneumoniae) and Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa) and anti-fungal activity against (Candida albicans and Aspergillus niger).

Results: Schiff base derivatives 5(a-h) were synthesized in good yields and showed antimicrobial activity, among them, compounds 5c, 5d, 5e and 5f were significantly active against gram positive, gram negative bacterial and fungal strains and rest of compounds showed moderate to weak activity.

Conclusion: The Schiff base obtained showed variation in the antimicrobial and antifungal activity, based on the structure of the substituted aromatic aldehydes.

Keywords: Anti-bacterial, Anti-fungal, Aldehyde, Schiff base

INTRODUCTION

Schiff bases are the product of primary amines and carbonyl compounds, named after Hugo Schiff, who discovered it in 1864. The common structural feature of these compounds is the azomethine group with a general formula RNC=N-R$_2$, where R and R$_2$ are alkyl, aryl, cycloalkyl or heterocyclic groups which may be variously substituted. These compounds are also known as anilines, imines or azomethines. Schiff bases are also synthesized by some researchers using solvent free and environmentally friendly methods [1]. The general reaction for the synthesis of Schiff bases is given as

$$\text{RNH}_2 + \text{RCHO} \rightarrow \text{R}=\text{CH}-\text{R} + \text{H}_2\text{O}$$

The presence of a lone pair of electrons in a sp$^2$ hybridized orbital of the nitrogen atom of the azomethine group is of considerable chemical and biological importance. Because of the relative ease of preparation, synthetic flexibility and the special property of C=N group, Schiff bases are generally excellent chelating agents, especially when a functional group like–OH or–SH is present close to the azomethine group so as to form a five or six-membered rings with the metal ion [2]. Their metal complexes such as copper, nickel and zinc complexes have been widely studied and proved as competent anticancer agents [3]. Further some complexes such as copper, nickel and zinc complexes have been studied and proved as competent anticancer agents [3].

Now a day, in the research field, dealing with Schiff base coordination chemistry has expanded enormously. Schiff bases are characterized by the-N=CH-(imine) group which imports in elucidating the mechanism of transamination and racemization reaction in the biological system. Schiff bases have been reported for their biological properties, such as, anti-inflammatory agents, anti-cancer agents, various metal complexes as antimicrobial agents [5-8], anti-convulsant [9], analgesic, anti-inflammatory agents [10-11] and anti-tubercular agents [12]. They serve as models for biologically important species. In this research article, we have synthesized some novel Schiff base derivatives from p-amino benzoic acid, and all the newly synthesized compounds were tested against the anti-microbial action.

MATERIALS AND METHODS

General

All the chemicals and solvents used in synthesis were purchased from the Himedia, Nice and Merck. The progress of reaction and purity of the synthesized compounds were checked by thin layer chromatography (TLC) with silica gel plates.

The melting points were determined by a capillary method using Thermoscientific melting point apparatus and found to be uncorrected. The FT-IR spectra (nujol) were recorded on Shimadzu FT-IR spectrophotometer. The $^1$H NMR spectra were recorded (in DMSO) on a BRUKER AVANCE-400 (400 MHZ) spectrometer using TMS as an internal standard. Mass spectra were recorded on Water, Q-TOF Micro mass (LC-MS).

Chemical synthesis

General procedure

Synthesis of Thiocarbohydrazide (3)

Schiff bases derivatives were prepared according to reported literature [13]. Hydrazine hydrate (1) (1.0 mol) was placed in a round bottom flask, 0.2 mol of carbon disulphide (2) (CS$_2$) (15.2 g, 12.1 ml) was added dropwise into the flask while maintaining the temperature below 15 °C and the temperature was gradually raised for 1.5 hr. The completion of the reaction was confirmed by TLC. The reaction mixture was cooled down; the precipitate was filtered and washed with water. The product was recrystallized with ethanol.

Synthesis of 4-(4-Amino-5-mercapto-4H-[1, 2, 4] triazol-3-yl)-benzoic acid (4)

A mixture of p-amino benzoic acid (0.01 mol) and thiocarbohydrazide (3) (0.015 mol) were taken in a round bottomed flask.
The completion of the reaction was confirmed by TLC. The reaction mixture was cooled; the precipitate was filtered and washed with water. The product was recrystallized with ethanol.

**Synthesis of 4-[4-(arylidene amino)-5-mercapto-4H-[1,2,4]triazol-3-yl]-benzoic acid (5a-h)**

Suspension of 4-[4-amino-5-mercapto-4H-[1, 2, 4]triazol-3-yl]-benzoic acid (4) (0.2 mol) and equimolar amount of the corresponding substituted benzaldehyde with 3 to 4 drops of sulphuric acid was added. The reaction mixture was refluxed for 2-3 h. The completion of reaction was confirmed by TLC. The reaction mixture was cooled; precipitate was filtered and washed with water. The product was recrystallized with ethanol. Various substituted aldehyde used in the reaction are mentioned in Table 1.

**5a: Synthesis of: 4-[[Benzyldiene-amino]-5-mercapto-4H-[1,2,4]triazol-3-yl]-benzoic acid**

Yield (80%); m. p. 188 °C; FT-IR (NaCl, λ\text{max} cm\text{−1}): 3022 (C-H, Ar str), 1570 (C=C), 1543 (C=N), 1512 (N-O), 937 (C-S); 1H NMR: 10.70 (s, 1H, COOH), 10.15 (s, 1H, C-SH), 8.42-7.50 (m, 9H, Ar-H); MS (m/z): 357.1 (M\text{+}^+).

**5b: Synthesis of 4-[[5-Mercapto-4-[[4-nitro-benzylidene-amino]-4H-[1,2,4]triazol-3-yl]-benzoic acid**

Yield (75%); m. p. 217 °C; FT-IR (NaCl, λ\text{max} cm\text{−1}): 3020 (C-H, Ar str), 2788 (C=C str), 1700 (C=O in COOH gpp), 1681 (C=C in Ar str), 1585 (CH=N), 1409 (N-O), 937 (C-S); 1H NMR: 11.62 (s, 1H, COOH), 10.07 (s, 1H, C-SH), 8.41-7.53 (m, 9H, Ar-H); MS (m/z): 357.1 (M\text{+}^+).

**5c: Synthesis of 4-[5-Mercapto-4-[3-(nitro-benzylidene)-amino]-4H-[1,2,4]triazol-3-yl]-benzoic acid**

Yield (75%); m. p. 214 °C; FT-IR (NaCl, λ\text{max} cm\text{−1}): 3035 (C-H, Ar str), 2772 (C=C str), 1716 (C=O str), 1572 (CH=N), 1533 (C=C), 1512 (N-O ortho); 1H NMR: 10.70 (s, 1H, COOH), 10.15 (s, 1H, C-SH), 8.42-7.50 (m, 9H, Ar-H); MS (m/z): 357.1 (M\text{+}^+).

**Scheme**

![Scheme](image)

**Antimicrobial activity testing**

**General procedure**

The anti-microbial activities of the test compound 5(a-h) were evaluated by using cup plate method [14]. The synthesized compounds were screened for antibacterial activity against Gram-positive (S. aureus and B. subtilis) and Gram-negative strains (E. coli and P. aeruginosa). Antifungal activity was done against C. albicans and A. niger. Muller Hinton agar medium was used for the evaluation of antibacterial activity. Screening of antifungal activity was done using Sabouraud’s dextrose agar medium. Stock solutions of the compounds were first prepared by dissolving them in a solution of 30% DMF in water. 20 ml sterilized dehydrated nutrient agar medium was poured in each petri dish and was allowed to set. Eight cups were then made by punching the agar surface with a sterile cork bore (6 mm). The Petri plates were placed at 37 °C for 24 h.

At the end of the period the inhibition zones formed on media were measured with a zone reader in millimeters. 30% of Dimethyl formamide (DMF) was used as blank. Ciprofloxacin was used as a standard for anti-bacterial activity. Fluconazole used as a standard for anti-fungal activity. The experiment was conducted in triplicate (n=3), and the average values were calculated.
RESULTS AND DISCUSSION

A novel series of 4-[4-(Arylidene amino)-5-mercapto-4H-[1, 2, 4]triazolo-3-yl]-benzoic acid complexes from p-amino benzoic acid and thiocarboxyhydrate was synthesized and characterized using analytical methods like TLC, IR, H-NMR and Mass spectroscopy. The structures of newly synthesized compounds were characterized on the basis of spectral data and elemental analysis. The physicochemical factors of the above-synthesized compounds were mentioned in table 2. The synthesized compounds were soluble in chloroform and methanol. All the synthesized Schiff bases were screened for in vitro antibacterial and antifungal activities. The antimicrobial activity of the synthesized compounds was evaluated by using Cup Plate method. The Schiff base complexes synthesized from p-amino benzoic acid were characterized by using FT-IR technique. The range of 3035-3020 cm\(^{-1}\) indicates the presence of (C-H) aromatic group. The IR spectra of Schiff base complexes synthesized from p-amino benzoic acid mainly characterized by absorption width at the range 1588-1570 cm\(^{-1}\) which attribute the presence of CH=N group in derivatives. Observation of singlet peak on \(\delta\) scale observed on \(\delta\) scale between 9.98-9.62 ppm indicate the presence of the aromatic ring in compound 5(a-h). Similarly, a single peak was observed on \(\delta\) scale between 8.4-6.8 ppm which showed the presence of the aromatic ring in compound 5(a-h). A multiple peak was confirmed the presence of C-SH group in the complexes. The MS spectrum suggested that all the synthesized compounds are in given range.

Anti-microbial activity

The anti-microbial activities of the newly synthesized Schiff base 5(a-h) were assessed against Gram-positive (Staphylococcus aureus, Streptococcus pneumonia) and Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa) using the cup-plate method and antifungal activity against Candida albicans and Aspergillus niger. Ciprofloxacin and fluconazole were used as a standard.

It was found that Compounds 5(c), 5(d) and 5(e) showed significant activity against S. aureus, S. pneumoniae, E. coli, P. aeruginosa, whereas compounds 5(c), 5(d) and 5(f) showed significant antifungal activity against C. albicans and A. niger. Whilst, 5(a), 5(b) showed moderate activity against bacterial strains. Anti-microbial data of all the synthesized compounds were shown in table 3. The presence of chloride atom at para position in 5(d) has increased the antimicrobial activity of the compound [15]. The similarly presence of nitro group at meta position increased the antibacterial activity of 5(c), whereas, the remarkable antifungal activity of 5(e) observed due to the presence of hydroxyl group at ortho position. Similarly, the good anti-bacterial activity of 5(d) was also reported due to the presence of hydroxyl group at para position [15]. Antimicrobial activity depends on the nature of bacterial strain, the solvent and chelating ability of the Schiff base. It is believed that Schiff bases act by forming a chelate with the bacterial strain.

This may involve hydrogen bonding through the azomethine group with the active centers of cell constituents thus resulting in an interference with normal cell process [16]. Hence, stronger the hydrogen bonding, more will be activity. Compounds 5(c), 5(d), 5(e) and 5(f) showed a wider zone of inhibition as compared to other synthesized compounds. The reason for the enhanced anti-microbial activity in these compounds was the-1 effect of their substituents. Electron withdrawing ability of chlorine yielded a compound with significant anti-bacterial activity. Similarly, the activity of 5(e) and 5(f) was also increased due to the presence of hydroxyl group and its electron withdrawing effect [17]. In my present work some compounds like 5b (containing nitro group) and 5d (containing a hydroxyl group) showed better performance as an anti-microbial agent as compared to the compounds which were reported in previous literature containing same group [15].

### Table 1: Various substituted aldehyde used are

| Compound | R          | Compound | R          |
|----------|------------|----------|------------|
| 5a       |            | 5e       |            |
| 5b       |            | 5f       |            |
| 5c       |            | 5g       |            |
| 5d       |            | 5h       |            |

### Table 2: Physicochemical data of 4-[4-(arylidene amino)-5-mercapto-4H-[1, 2, 4]triazolo-3-yl]-benzoic acid complexes

| S. No. | Molecular formula | Mol. Wt. | Melting point | Yield | Physical state | Solubility | \(R_t\) |
|--------|-------------------|----------|---------------|-------|----------------|------------|--------|
| 5a     | \(C_7H_7O_2N_5S\) | 312.0    | 188           | 80    | Yellowish amorphous | CHCl\(_2\),CH\(_3\)OH | 0.45   |
| 5b     | \(C_7H_7O_2N_5S\) | 357.0    | 217           | 75    | Light orange amorphous | CHCl\(_2\),CH\(_3\)OH | 0.57   |
| 5c     | \(C_7H_7O_2N_5S\) | 37.9     | 214           | 75    | Dark orange | CHCl\(_2\),CH\(_3\)OH | 0.53   |
| 5d     | \(C_7H_7O_2N_5S\) | 346.5    | 240           | 85    | Yellow crystalline | CHCl\(_2\),CH\(_3\)OH | 0.70   |
| 5e     | \(C_7H_7O_2N_5S\) | 328.0    | 162           | 80    | Crystalline orange | CHCl\(_2\),CH\(_3\)OH | 0.63   |
| 5f     | \(C_7H_7O_2N_5S\) | 328.0    | 245           | 85    | Creamish, fluffy | CHCl\(_2\),CH\(_3\)OH | 0.61   |
| 5g     | \(C_7H_7O_2N_5S\) | 342.0    | 275           | 70    | Whitish Yellow | CHCl\(_2\),CH\(_3\)OH | 0.65   |
| 5h     | \(C_7H_7O_2N_5S\) | 326.0    | 219           | 80    | Creamish, Amorphous | CHCl\(_2\),CH\(_3\)OH | 0.53   |
CONCLUSION

The Schiff base compounds were synthesized by using thioicarboxyhydradize, p-amino benzoic acid and aromatic aldehydes. Due to the presence of different substituted aldehydes, novel Schiff base derivatives were synthesized. All the compounds were subjected to antimicrobial activity, and mostly compounds showed significant to moderate activity. The purpose of this paper is to throw light on the fact that substitution on Schiff base compounds synthesized from the same precursor leads to the formation of novel Schiff base derivatives, which showed good antimicrobial activity. Compounds containing chlorine group and nitro exhibited significant antimicrobial activity. Whereas, other derivatives containing other groups like methoxy and methyl group showed moderate to weak anti-microbial activity.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Padil S, Jadhav SD, Padil UP. Natural acid-catalyzed synthesis of Schiff base under the solvent-free condition: as a green approach. Arch Appl Sci Res 2012;4:1074-8.
2. Nandi J, Sankar VK. Synthesis and docking of the Schiff base derived from 4-amino pyridine. J Pharm Sci Innovation; 2012; p. 9-11.
3. Raman N, Raja JD, Sakthivel A. Synthesis, spectral characterization of Schiff base transition metal complexes: DNA cleavage and antimicrobial activity studies. J Chem Soc 2007;11:303-10.
4. Singh K, Kumar Y, Puri P, Sharma C, Aneja KR. Metal-based biologically active compounds: synthesis, spectral and antimicrobial studies of cobalt, nickel, copper, and zinc complexes of triazole-derived Schiff bases. Bioinorg Chem Appl 2011;1:10. Doi.org/10.1155/2011/901716.
5. Bhagyalakshmi N, Udupi RH, Niranjan MS. Design, synthesis, and evaluation of biological activity of certain novel triazole Schiff bases. Int J Pharm Chem Sci 2012;1:287-94.
6. Wahi AK, Singh AK. Singh A. Design and synthesis of novel Schiff bases having N-(4H-1,2,4-triazole-4-yl)benzamide moiety as antimicrobial and anti-inflammatory agents. Pharm Chem 2011;3:46-54.
7. Chandramouli, Shivanand MR, Navinbhai TB, Bheemacharaya, Udupi RH. Synthesis and biological screening of certain new triazole Schiff bases and their derivatives bearing substituted benzothiazole moiety. J Chem Pharm Res 2012;4:1151-9.
8. Thai M, Webster ER, Wilson R, Nithinchandra, Kalluraya B, Aamir S, et al. Regioslective reaction: synthesis, characterization and pharmacological activity of some new Mannich and Schiff bases containing sydnone. Eur J Med Chem 2012;54:597-604.
9. Sondhi SM, Singh N, Kumar A, Loazache O, Meijer L. Synthesis, anti-inflammatory, analgesic and kinase (CDK-1, CDK-5 and GSK-3) inhibition activity evaluation of benzimidazole/ benzoxazole derivatives and some Schiff bases. Bioorg Med Chem 2006;14:375-85.
10. Bhandari VS, Bothara KG, Raut MK, Patil AA, Sarkate PA, Mokal VJ. Design, synthesis, and evaluation of anti-inflammatory, analgesic and ulcerogenicity studies of novel s-substituted phenacetyl-1,3,4-oxadiazole-2-thiol and Schiff bases of dicyofenac acid as nonulcerogenic derivatives. Bioorg Med Chem 2008;16:1822-31.
11. Sondhi SM, Dinodia M, Kumar A. Synthesis, anti-inflammatory and analgesic activity evaluation of some amidine and hydrazine derivatives. Bioorg Med Chem 2006;14:4657-63.
12. Khedr AM, Marwani HM. Synthesis, spectral, thermal analyses and molecular modeling of bioactive Cu (II)-complexes with 1,3,4-thiadiazole Schiff base derivatives. Their catalytic effect on the cathodic reduction of oxygen. Int J Electrochem Sci 2012;7:10074-93.
13. Gupta AK, Prachand S, Patel A, Jain S. Synthesis of some 4-amino-5-(substituted-phenyl)-4H-[1, 2, 4] triazole-3-thiol derivatives and antifungal activity. Int J Pharm Life Sci 2012;3:1849-57.
14. Mehta D, Das R, Dua K. Synthesis, anti-inflammatory and antimicrobial activity of some new 1,3,4-oxadiazoles and 1,3,4-oxadiazoles-2-thione derivatives as mannnich bases containing furan moiety. Int J Chem Soc 2009;2:225-34.
15. Desai NC, Makwana AH, Sena RD. Synthesis, characterization and antimicrobial activity of some novel 4-(4-(aryl amino)-6-(piperidin-1-yl)-1,3,5-triazine-2-ylamino)-N-(pyrimidin-2-yl)benzenesulfonylamides. J Chem Soc 2015;1-9. Doi:10.1016/J.Jscs.2015.01.004.
16. Kumari G, Kumari D, Singh C, Kumari A, VBR. Synthesis, physical characterization and antimicrobial activity of trivalent metal Schiff base complexes. J Serb Chem Soc 2010;75:629-37.
17. Holla BS, Udupa KV. Synthesis, studies and biological activities of some N-bridge heterocycles derived from 3-aryl aminomethyl-4-amino-5-mercapto-1,2,4-triazoles. Farmaco 1992;47:305-18.

How to cite this article

- Vaibhav Sharma, Dinesh Kumar Mehta, Rina Das, Preet Kawal Kaur. Synthesis of some novel triazole derivatives as Schiff bases and their antimicrobial evaluation. Int J Pharm Pharm Sci 2016;8(9):28-31.

Table 3: Antimicrobial activity of synthesized Schiff base derivatives

| Compound | Zone of inhibition (in mm) | E. coli | P. aeruginosa | S. aureus | S. pneumoniae | C. albicans | A. niger |
|----------|-----------------------------|--------|--------------|-----------|--------------|-------------|---------|
| 5a       | 14.76±0.45                  | 16.22±0.23 | 13.23±0.23  | 14.05±0.12 | 12.91±0.21  | 14.16±0.16  |
| 5b       | 15.97±0.82                  | 15.35±0.32  | 13.24±0.26  | 12.12±0.11 | 10.30±0.28  | 8.03±0.13   |
| 5c       | 17.47±0.47                  | 17.98±0.15  | 17.26±0.23  | 17.15±0.17 | 17.23±0.23  | 16.22±0.21  |
| 5d       | 19.16±0.17                  | 18.99±0.16  | 18.01±0.21  | 16.16±0.18 | 17.21±0.20  | 16.21±0.21  |
| 5e       | 19.05±0.25                  | 20.96±0.20  | 18.08±0.11  | 16.18±0.17 | 14.17±0.26  | 12.33±0.28  |
| 5f       | 10.2±0.24                   | 9.31±0.48   | 12.05±0.16  | 11.28±0.25 | 18.0±0.13   | 17.42±0.21  |
| 5g       | 11.07±0.39                  | 13.99±0.58  | 9.99±0.16   | 11.08±0.38 | 12.19±0.21  | 11.31±0.16  |
| 5h       | 13.80±0.22                  | 13.41±0.37  | 15.13±0.13  | 16.16±0.18 | 14.51±0.16  | 13.32±0.17  |
| Ciprofloxacin (Std) | 19.67±0.58 | 21.75±0.22 | 20.12±0.11 | 20.18±0.16 | -            | -        |
| DMP      | -                           | -            | -            | -          | 20.33±0.58  | 20.31±0.13  |

Values are expressed as mean±SEM. (n=3). SEM (Standard error mean)