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# Synthesis and Antimicrobial Activity of some Salicylaldehyde Schiff bases of 2-aminopyridine

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## Abstract

*Schiff bases particularly (1) N-(2-hydroxylbenzylidene) pyridin-2-amine, (2) N-(5-nitro-2- hydroxylbenzylidene) pyridin-2-amine, (3) N-(5-bromo-2- hydroxylbenzylidene) pyridin-2-amine, (4) N- (5-methoxy-2-hydroxylbenzylidene) pyridin-2-amine are prepared from 2- aminopyridine and substituted benzyaldehydes. The synthesized compounds are characterized by elemental analysis, IR and $^1$HNMR. The result shows that the compounds are capable to prevent the growth of S. aureus and E. coli in diverse concentrations. The growth prevention capability was affected by the solvent and substitute group on the salicyldene part.*

**Keywords:** 2-Aminopyridine, Schiff base, and Growth prevention capability.

## Introduction

Early time, the severe infectious diseases caused by gram positive and gram negative pathogenic bacteria have inflated to threat level around the world. This increase as well as emergence of bacteria immune to ordinarily used antibiotics has resulted in the need to devolve new categories of antibacterial agents to conflict infections. The chemistry of biological science has produced a number of compounds that are now employed as antibacterial agents. Such type of compounds revealed great promise in this area is the Schiff bases[1]. A Schiff base is the nitrogen analogue of aldehyde in which the C=O group is replaced by a C=N group.

The reported Schiff bases exhibits antibacterial[2-5], antifungal[6] and antitumor activity[7]. In addition, the compounds and their metal complexes reveal remarkable photo physical properties[8]. The spectra behaviour of Schiff bases has been investigated for structure explanation[9-12]. Salicylidimines show important photochromism where light absorption causes interconversion between enol-imine and keto-amine tautomers through intramolecular hydrogen transfer. They also exhibit a variety of biological activities with substituted salicylaldehyde compounds possessing higher activities[13]. This has led to concentrate deep research on this class of compounds[14] and their metal complexes[15-16]. Similarly, the presence of hetero-atoms in the Schiff bases enhances activity [17].

Our hard work to understand the role of fine electronic variations on molecular activity and the effect of substituent location in salicylidene- 2-aminopyridine Schiff bases on the absorption spectra in organic solvents of changeable polarities and their antibacterial activity against some common pathogens namely *Staphylococcus aureus*, *Entercoccus feacalis*, *Pseudomonas aeruginosa and Escherichia coli*.

## Material and Methods

DMF (N, N-dimethylformamide), 1, 4-dioxane and hexane and ethanol, were of AR grade and used as supplied. Elemental analyses were carried out with a Perkin-Elmer 2400 CHNS/O analyzer. Melting Points of the compounds are determined by using Gallenkemp England melting point apparatus.

**Synthesis of Schiff bases: N-(2-hydroxylbenzylidene) pyridin-2-amine:** Take (10 ml.) ethanol in round bottom flask and add a solution of 2-hydroxybenzaldehyde (2.45 g, 20 m mol.) two drops of formic acid were added to a stirred solution of 2-aminopyridine (1.88 g, 20 m mol.) Thereafter, the reaction mixture was refluxed for 6 hr, the precipitate collected by filtration and recrystallized from ethanol-hexane (1:1).

Yellow-orange crystal; yield 33%; mp 60-62$^0$C. IR (cm$^{-1}$): 3434, 1615, 1591, 1281, 1257, 1151, 996, 916, 846, 792, 736, 581. $^1$HNMR ($CDCl_3$, 400 MHz): 6.91-8.51(m, 8H), 9.41(s, 1H), 13.41(s, 1H). Anal.calcd. for $C_{12}H_{10}N_2O$: C, 72.72, H, 5.02, N, 14.10.Found: C, 72.38, H, 5.00, N, 14.08.

**N-(5-nitro-2-hydroxylbenzylidene) pyridin-2-amine:** Yellow solid; yield 44%; mp 178-180$^0$C. IR (cm$^{-1}$): 3050, 1612, 1582, 152\57, 1430, 1291, 1105, 1090, 990, 892, 830, 784, 705, 640. $^1$HNMR ($CDCl_3$, 400 MHZ): 7.11 to 8.55 (m, 7H), 9.50(s, 1H), 14.53(s, 1H). Anal.calcd. for $C_{12}H_9N_3O_3$: C, 59.24, H, 3.68, N, 17.25. Found: C, 59.18, H, 3.60, N, 17.08.

**N-(5-bromo-2-hydroxylbenzylidene) pyridin-2-amine:** Light-orange crystal; yield 78 %; mp 135-137$^0$C; IR (cm$^{-1}$): 1604, 1580, 1430, 1340, 1270, 1180, 1070, 990, 915, 870, 810, 782, 740, 698, 625. $^1$HNMR ($CDCl_3$, 400 MHZ): 6.88-8.48(m, 7H), 9.35(s, 1H), 13.43(s, 1H). Anal.calcd. for $C_{12}H_9N_2OBr$: C, 51.98, H, 3.21, N, 10.07. Found: C, 51.95, H, 3.18, N, 9.98

**N-(5-methoxy-2-hydroxylbenzylidene) pyridin-2-amine:** Dark-orange crystals; yield 73%; mp 80-82$^0$C. IR (cm$^{-1}$)*:* 1610, 1572, 1550, 1485, 1324, 1270, 1141, 1025, 990,890, 832, 773, 622. $^1$HNMR ($CDCl_3$, 400 MHZ): 3.74(s, 3H), 6.92 to 8.45(m, 7H), 9.35(s, 1H), 12.91(s, 1H). Anal.calcd. for $C_{13}H_{10}N_2O_2$: C, 68.42, H, 5.24, N, 12.25. Found: C, 68.32, H, 5.22, N, 12.18.

**Biological activity:** In vitro the results of compounds (1) to (4) were screened against *S. aureus*, *E.feacalis*, *P.aeruginosa* and *E.coli*. The stock solution from that two- fold serial dilutions were used was prepared by dissolving 40 mg of each compound in 1 ml. of N,N dimethylformamide (DMF) and 1,4-dioxane, respectively.

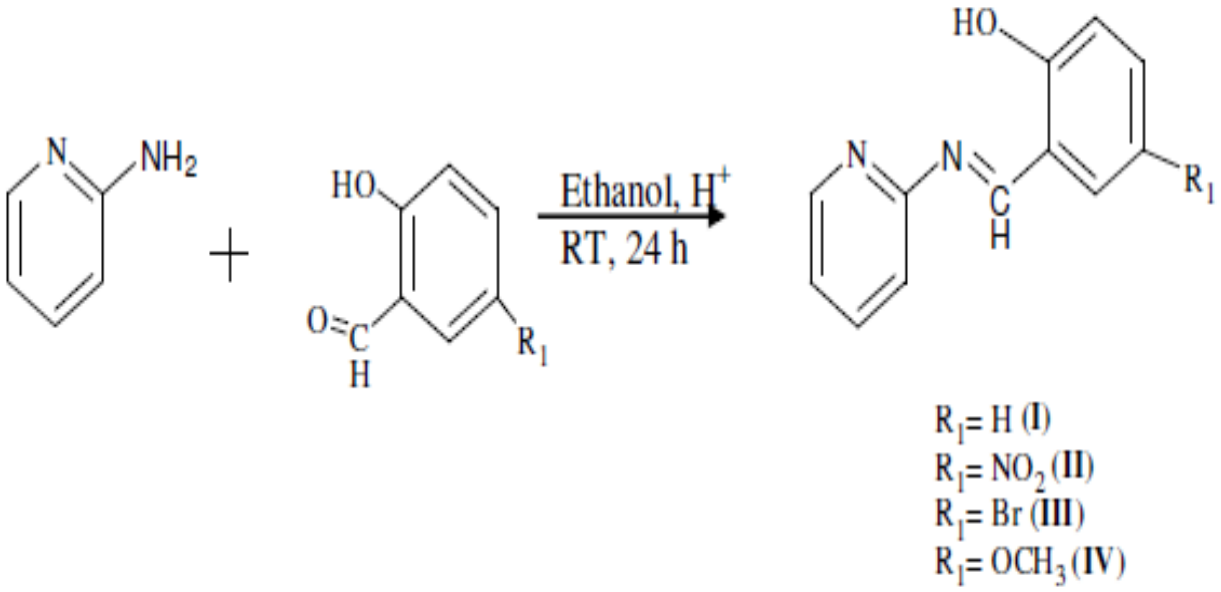
A double layered Muller Hinton agar plate was aseptically prepared. The plate was flooded with standardized (0.5 McFarland) test microorganism and allowed for two minutes to regulate the environment. A sterilized cork borer was used to make five wells radially. The wells were filled with the test compounds using a micropipette and incubated at 37°C for 24 to 48 hr. During this period, the test compounds subtle and therefore the growth of the inoculated being was affected.. The diameter of the zone of prevention surrounding each well was measured and recorded. In order to clarify any participating role of the solvent in the biological screening, control test was included using the solvent alone to fill the control well.

## Results and Discussion

**Synthesis:** The Condensation of 2-aminopyridine with the corresponding aldehyde promptly give corresponding Schiff bases (1) N-(2- hydroxylbenzylidene) pyridine-2-amine (2) N-(5-nitro-2- hydroxylbenzylidene) pyridin-2-amine (3) N-(5-bromo-2- hydroxylbenzylidene) pyridin-2-amine (4) N-(5-methoxy-2-hydroxylbenzylidene) pyridin-2-amine (figure 1).

All compounds are stable and have sharp melting points that indicate the purity of the compounds. The elemental analyses of the compounds are co-operating with the composition suggested for the compounds. The IR of each compound confirms the formation of imine bond (–C=N-) and absence of the original aldehydic bond (-C=O). A band at 1608-1614 cm$^{-1}$ is assigned to stretching vibration of the imine group ν (C=N). All the compounds displayed a band at 1270-1288 cm$^{-1}$ which is assigned to ν(C-O) stretching vibration of the Phenolic – OH, respectively. The *ν* (OH) band at 3435-3438 cm$^{-1}$ was observed only in compounds I and II. Proton NMR showed sharp singlet at 9.34-9.53 ppm which further confirmed the formation of –C=N-bonds.

**Antimicrobial activity:** Antimicrobial activity of the compounds in DMF and 1, 4-dioxane is shown in Tables 1. and 2. The morphology of the cell membrane may be a main issue that affects the activity of antimicrobial agents. The cell membrane of the bacteria consists of peptidoglycan which is thicker in the gram positive bacteria and is usually posses a barrier to the degree of diffusion of antimicrobial agents into the enzyme[18]. Four standard bacteria strains screened were gram positive *S. aureus, E. feacalis* and gram negative *E. coli, P. aeruginosa*.




**Scheme-1**
**Synthesis of Schiff bases 1 to 4. (Reaction scheme)**

**Table-1**
**Antimicrobial activity of the Schiff bases in DMF**

| Compounds | Concentration (mg/ml) | *S. aureus* | | | | | | *E. feacalis* | *E. coli* | | | | | | *P. aeruginosa* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **40** | **20** | **10** | **5** | **2.5** | **1.25** | **40-1.25** | **40** | **20** | **10** | **5** | **2.5** | **1.25** | **40-1.25** |
| 1 | | 3+ | 3+ | 1+ | 0 | 0 | 0 | 0-0 | 2+ | 2+ | 1+ | 0 | 0 | 0 | 0-0 |
| 2 | | 3+ | 3+ | 3+ | 3+ | 3+ | 2+ | 0-0 | 3+ | 2+ | 0 | 0 | 0 | 0 | 0-0 |
| 3 | | 3+ | 3+ | 3+ | 3+ | 3+ | 2+ | 0-0 | 3+ | 3+ | 3+ | 2+ | 1+ | 0 | 0-0 |
| 4 | | 3+ | 2+ | 2+ | 1+ | 0 | 0 | 0-0 | 3+ | 2+ | 0 | 0 | 0 | 0 | 0-0 |

Prevention values = 1 - 5 mm = 1+ (less active); 6 - 11 mm = 2+ (moderate active); >12 mm = 3+ (highly active), 0 = not detected.

**Table-2**
**Antimicrobial activity of the Schiff bases in 1, 4-dioxane**

| Compounds | Concentration (mg/ml) | *S. aureus* | | | | | | *E. feacalis* | *E. coli* | | | | | | *P. aeruginosa* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **40** | **20** | **10** | **5** | **2.5** | **1.25** | **40-1.25** | **40** | **20** | **10** | **5** | **2.5** | **1.25** | **40-1.25** |
| 1 | | 3+ | 2+ | 0 | 0 | 0 | 0 | 0-0 | 3+ | 2+ | 2+ | 0 | 0 | 0 | 0-0 |
| 2 | | 3+ | 3+ | 3+ | 3+ | 3+ | 3+ | 0-0 | 3+ | 2+ | 1+ | 1+ | 0 | 0 | 0-0 |
| 3 | | 2+ | 2+ | 0 | 0 | 0 | 0 | 0-0 | 3+ | 3+ | 3+ | 3+ | 2+ | 0 | 0-0 |
| 4 | | 3+ | 3+ | 3+ | 2+ | 0 | 0 | 0-0 | 3+ | 3+ | 2+ | 1+ | 0 | 0 | 0-0 |

Prevention values = 1 - 5 mm = 1+ (less active); 6 - 11 mm = 2+ (moderate active); >12 mm = 3+ (highly active), 0 = not detected.

All compounds were inactive against *E. feacalis* and *P.aeruginosa* and active against *S. aureus* and *E. coli* . The unsubstituted salicylaldehyde Schiff base (1) had least activity against bacteria studied in each solvent. Prevention studies of *S. aureus* in DMF revealed that (3) containing the bromo substituent exhibited activity at lowest concentration studied (0.625 mg/ml) with the electron-donating OMe Schiff base (4) having the least activity at the highest concentration (5 mg/ml). The electron-withdrawing $NO_2$ compound, (2) was moderately active at (1.25 mg/ml). Solvent change to less polar dioxane reported a higher activity with the minimum prevent concentration unaffected, except for (3) which showed lower activity. This, coupled with the electronic absorption suggests that the keto-amine form which exists in DMF is less active compared to the enolimine tautomer that exists in dioxane. Screening against the gram negative *E. coli* in DMF revealed that (3) showed activity at concentration of 2.5 mg/ml and both (2) and (4) were active at 20 mg/ml. The change of solvent to less polar dioxane, (2) and (4) were active at lower concentrations of 5 mg/ml. respectively. The higher activity reported in less polar solvent may be due to easier diffusion across the cell wall.

## Conclusion

In conclusion, the compounds have the ability to preventing metabolic growth of *S. aureus* and *E. coli* to different extent. The antimicrobial activity of the compounds depends on the nature of substituent present on the aldehyde. The importance of this lies within the potential use of the compounds as narrow spectrum antibiotics in treatment of some common diseases.

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