SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF SCHIFF’S BASE AND ARYL AMINOMETHYL DERIVATIVES.

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ABSTRACT. Schiff’s bases are obtained on heating an aldehydes with aromatic amine in presence of glacial acetic acid. These are the compounds containing characteristic –HC=N– group. Aryl amino methyl derivatives of heterocyclic compounds to synthesize by selective reduction of schiff’s bases (imine group) with sodiumborohydride in controlled experimental condition. Schiff’s base of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanamines & Aryl amines of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanamines were prepared. Their chemical structures were confirmed by means of IR, NMR, Mass data and by elemental analysis. All of the synthesized compounds were tested for their antibacterial and antifungal activity.

INTRODUCTION

Literature study revealed that schiff’s bases derivatives have a wide variety of uses such as antiviral1, antifungal2, antiparasitic3, antibacterial4, antipyretic5, anti-inflammatory6, plant hormone activity7, and antitubercular8. Aryl amines exhibit a wide range of biological activities such as P2X7 receptor antagonists9, HDMI-p53 protein-protein antagonists10, MCH1 receptor antagonist11, NPY5 antagonists12, dual Atk1/2 inhibitors13. This inspired us to synthesize schiff’s base of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanamines (1a-l) & Aryl amines of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanamines (2a-l).

The structure of synthesized compounds were assigned based on Elemental analysis, I.R.1H-NMR and Mass spectral data. The antimicrobial activity was assayed by using the cup-plate agar diffusion method14 by measuring the zone of inhibition in mm. All the compounds were screened in vitro for their antimicrobial activities15 against varieties of bacterial strains such Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Escherichia coli and Fungi Aspergillus niger using Dimethylformamide solvent at 40 μg/ml concentration. Standard drugs like Amoxicillin, Benzyl penicillin, Ciprofloxacin, Erythromycin and Griseofulvin were used for comparison purpose. (Table-1).

RESULTS AND DISCUSSION:

The synthesis of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3- yl]methanamines (1a-l) was prepared by reaction of 2-(4-Methylphenyl)imidazo[1,2-a]pyridin-3-carbaldehyde (Type-I) and Amine derivatives in presence of glacial acetic acid & N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanamines (2a-l) have been prepared by
the reduction of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanimines with sodiumborohydride in methanol at ambient temperature (Scheme-1).

The formulas of the selected compounds were confirmed by the elemental analysis and their structures were determined by IR, \(^1\)H-NMR, and mass spectral data.

**ANTIBACTERIAL ACTIVITY:**

It has been observed from the microbiological data that all compounds (1a-l) and (2a-l) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains. However the maximum activity was observed in compounds (1d),(1k),(2b),(2d) against *S.aureus*. The significant activity was observed in compounds (1e),(1k),(2j),(2l) against *B.subtilis*. The maximum activity was displayed by the compounds (1i),(1k),(2b),(2k), against *E.coli*. The compounds (1h),(1l),(2a), and (2l) were comparatively more effective against *P. aeruginosa*.

**ANTIFUNGAL ACTIVITY:**

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds (1c),(1d),(1j),(2c),(2g),(2h), against *A. niger*. The antibacterial activity was compared with standard drug viz. Amoxicillin, Benzyl Penicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Griseofulvin.

**EXPERIMENTAL SECTION:**

Melting points were taken in open capillary tubes are uncorrected. IR spectra (cm\(^{-1}\)) were recorded on Shimadzu-435-IR Spectrophotometer and, \(^1\)H-NMR spectra on Bruker spectrometer(300MHz) using TMS as an internal standard, chemical shift in δ ppm.

**General procedure for the preparation of 2-(4-Methylphenyl)imidazo[1,2-a]pyridin-3-carbaldehyde (Type-I):**

Align 2.0 lit 4/N RBF equipped with over head stirrer with condenser on water bath. Charged 84 ml DMF and 1.0 lit CHCl\(_3\) into RBF. It was cooled at 0 - 5 °C temperature. Slowly added 165 ml POCl\(_3\) within 1.0 h. During addition the exothermicity was controlled. Temperature raised at 10-15 °C and stirred for 30 minutes. 50g (0.225 mol) of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine was added slowly, temp. raises, refluxed for 6 hrs. CHCl\(_3\) was removed by vacuum distillation and reaction mass cooled at room temperature, poured into 2.0 lit ice cold water. Neutral pH adjusted bellow room temperature with the help of mild caustic solution. The solid mass was collected by filtration, washed with water, dried and crystallized from the methanol. Yield 80%, m.p. 152 °C.

**General procedure for the preparation of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanimines (1a-l):**

A mixture of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-carbaldehyde 2.5g (0.01mol), p-anisidine 1.23g (0.01mol) and catalytic amount of glacial acetic acid in 20 ml methanol was refluxed for 16 hrs. The contents was cooled and product isolated by filtration and
N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanimines have been prepared. The physical data are recorded in table no.1.

**N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanimines (1a-l):**

Yield 75%, m.p. 178°C; IR(KBr): ν 2958, 2852, 1444, 1398 (Alkane, -CH₃), 1585 (Imidazo[1,2-a], C=N str.), 1244 (pyridine, C-N str.); 1608 (schiff base, C=N str.), 3026, 1481, 1107, 1029, 829 (Aromatic), cm⁻¹; ¹H-NMR (CDCl₃): δ 3.82 (s, 3H, -OCH₃), 2.43 (s, 6H, -CH₃), 8.78 (s, 1H, -CH=N-Ar), 6.90-7.69 (m, 11H, Ar-H), Mass: m/z = 357 M.F.: C₂₃H₂₃N₃O.

**General procedure for the preparation of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanamines (2a-I):**

3.55g (0.01mol) N-(4-Methoxyphenyl)-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanimine was taken in 25 ml methanol and cooled at 5-10°C temperature. Sodiumborohydride 0.57g (0.15mol) was added over a period of 30 min. The reaction mixture stirred over night at room temperature. Reaction mass was then poured in ice water and excess of sodiumborohydride was neutralized by adding dil.HCl. The product was extracted with ether and washed with water. Dried over anhydrous Na₂SO₄ and finally the ether was evaporated to give amino methyl derivatives. Yield, 56%, m.p. 165°C, Elemental analysis calculated for C₂₃H₂₃N₃O; Found: C-77.98%; H-6.48%; N-11.99%; Requires: C-77.28%, H-6.49%, N-11.76%. Similarly, other N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanamines were prepared. The physical data are recorded in table no.1.

**N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methanamines (2a-I):**

Yield 56%, m.p. 165°C; IR(KBr): ν 2942, 2899, 1463, 1388 (Alkane, -CH₃), 1604 (Imidazo[1,2-a], C=N str.), 1232 (pyridine, C-N str.), 3288 (Amine, N-H str.), 3020, 1520, 1114, 1035, 823 (Aromatic), cm⁻¹; ¹H-NMR (CDCl₃): δ 3.64 (s, 3H, -OCH₃), 2.31 & 2.33 (s, 6H, -CH₃), 4.52 (s, 2H, Ar-N-CH₂-), 5.70 (s, 1H, Ar-NH-) 6.60-7.68 (m, 11H, Ar-H), Mass: m/z = 357 M.F.: C₂₃H₂₃N₃O.
### Table-1

Characterization data of the compounds (1a-l) and (2a-l):

| compd no. | R                      | Molecular formula | Mole. Wt. | M.P. (°C) | Nitrogen % Calcd. | Found |
|-----------|------------------------|-------------------|-----------|-----------|-------------------|-------|
| 1a        | 4-OCH₃-C₆H₄-          | C₂H₅NO            | 355       | 178       | 11.82             | 11.75 |
| 1b        | 4-OH-C₆H₄-           | C₂H₁₀NO₂          | 341       | 186       | 12.31             | 12.25 |
| 1c        | C₆H₄-                 | C₂H₁₀N₁          | 325       | 222       | 12.92             | 12.89 |
| 1d        | 4-Cl-C₆H₄-           | C₂H₁₀ClN₁        | 359.5     | 236       | 11.68             | 11.75 |
| 1e        | 3-Cl-C₆H₄-           | C₂H₁₀ClN₁        | 359.5     | 148       | 11.68             | 11.67 |
| 1f        | 2,5-(Cl)_2-C₆H₄-     | C₂H₁₂Cl₂N₁       | 394       | 108       | 10.65             | 10.67 |
| 1g        | 3,4-(Cl)_2-C₆H₄-     | C₂H₁₂Cl₂N₁       | 394       | 225       | 10.65             | 10.59 |
| 1h        | 4-F-C₆H₄-            | C₂H₁₀FN₃          | 343       | 184       | 12.24             | 12.27 |
| 1i        | 3-NO₂-C₆H₄           | C₂H₁₀N₂O₂        | 370       | 166       | 15.13             | 15.20 |
| 1j        | 4-NO₂-C₆H₄           | C₂H₁₀N₂O₂        | 370       | 120       | 15.13             | 15.10 |
| 1k        | 1-C₆H₄-              | C₂H₁₂N₁          | 375       | dec.176   | 11.20             | 11.19 |
| 1l        | 3-CH₃-C₆H₄           | C₂H₁₂N₁          | 339       | 118       | 12.38             | 12.41 |
| 2a        | 4-OCH₃-C₆H₄-         | C₂H₁₂NO₂          | 357      | 165       | 11.76             | 11.99 |
| 2b        | 4-OH-C₆H₄-           | C₂H₁₀NO₂          | 343      | dec.195   | 12.24             | 12.22 |
| 2c        | C₆H₄-                 | C₂H₁₂N₁          | 327       | 176       | 12.84             | 12.80 |
| 2d        | 4-Cl-C₆H₄-           | C₂H₁₀ClN₁        | 361.5     | dec.180   | 11.61             | 11.65 |
| 2e        | 3-Cl-C₆H₄-           | C₂H₁₀ClN₁        | 361.5     | 178       | 11.61             | 11.68 |
| 2f        | 2,5-(Cl)_2-C₆H₄-     | C₂H₁₂Cl₂N₁       | 396       | 194       | 10.60             | 10.56 |
| 2g        | 3,4-(Cl)_2-C₆H₄-     | C₂H₁₂Cl₂N₁       | 396       | dec.260   | 10.60             | 10.61 |
| 2h        | 4-F-C₆H₄-            | C₂H₁₀FN₃          | 345       | 138       | 12.17             | 12.15 |
| 2i        | 3-NO₂-C₆H₄           | C₂H₁₂N₂O₂        | 372       | 165       | 15.05             | 15.03 |
| 2j        | 4-NO₂-C₆H₄           | C₂H₁₂N₂O₂        | 372       | 136       | 15.05             | 15.06 |
| 2k        | 1-C₁₀H₁₇-            | C₂H₂₀N₁          | 377       | 175       | 11.14             | 11.11 |
| 2l        | 3-CH₃-C₆H₄           | C₂H₁₂N₁          | 341       | dec.204   | 12.41             | 12.40 |

### Table-2

| compd no. | Antibacterial activity (zone of inhibition in mm) | Antifungal activity |
|-----------|-------------------------------------------------|--------------------|
|           | S. aureus | B. subtilis | E. coli | P. aeruginosa | A. niger |
| 1a        | 13        | 18         | 16      | 11           | 10      |
| 1b        | 16        | 19         | 17      | 12           | 13      |
| 1c        | 11        | 13         | 16      | 17           | 21      |
| 1d        | 20        | 10         | 15      | 11           | 17      |
| 1e        | 10        | 20         | 12      | 8            | 15      |
| 1f        | 14        | 17         | 13      | 19           | 14      |
| 1g        | 11        | 15         | 9       | 18           | 11      |
| 1h        | 12        | 16         | 11      | 21           | 16      |
| 1i        | 11        | 12         | 18      | 13           | 15      |
| 1j        | 15        | 19         | 15      | 12           | 17      |
| 1k        | 18        | 20         | 21      | 10           | 8       |
| 1l        | 7         | 11         | 18      | 19           | 10      |
| 2a        | 13        | 17         | 11      | 19           | 9       |
| 2b        | 20        | 17         | 18      | 15           | 12      |
CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of new compounds. Which show significant antibacterial and antifungal activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

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