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Synthesis and Biological Evaluation of Some New CYANOPYRIDINE Derivatives of IMIDAZO [1,2-A]PYRIDINE Nucleus

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Abstract: Like other heterocyclic compounds, pyridines with different functional groups exhibit wide range of applications in the field of pharmaceutical and agriculture. Cyanopyridine derivatives like some new 2-Amino-6-aryl-4-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]nicotinonitriles derivatives of type (2a-l) have been prepared by the cyclocondensation of 1-Aryl-3-[6-methyl-2-(4-methylphenyl)imidazo [1,2-a] pyridin-3-yl]prop-2-ene-1-ones derivatives of type (1a-l) with malononitrile in presence of ammonium acetate. All the prepared compounds were characterized by their spectral (I.R., N.M.R., Mass) data and screened for their antimicrobial activities.

Keywords: Chalcones, cyanopyridines, antimicrobial activities.

I. INTRODUCTION

Cyanopyridine have attracted considerable attention as they appeared of interest to possess antibacterial¹, antihistamic², fungicidal & insecticidal³, antihypertensive⁴⁻⁶ analgesic⁷ and anti-inflammatory⁸, anticancer⁹ activities. However the simple pyridine compounds are prepared¹⁰⁻¹¹ by the cyclization of aliphatic raw materials. In our continuation work in the chemistry of pyridine nucleus, we have undertaken the synthesis of imidazo[1,2-a]pyridine derivatives.

The structure of synthesized compounds were assigned based on Elemental analysis, I.R. ¹H-NMR and Mass spectral data. The antimicrobial¹² activity was assayed by using the cup-plate agar diffusion method¹³ by measuring the zone of inhibition in mm. All the compounds were screened in vitro for their antimicrobial activities²⁶ against varieties of bacterial strains such Staphylococcus aureus, Bacillus subtilis, Escherichia coli, P. aeruginosa and fungi Aspergillus niger at 40 µg concentration. Standard drugs like Ampicillin, Benzyl penicillin, Ciprofloxacin, Erythromycin and Griseofulvin were used for comparison purpose (Table-1).

II. EXPERIMENTAL SECTION

Melting points were taken in open capillary tubes are uncorrected. IR spectra (cm⁻¹) were recorded on SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm⁻¹ (KBr disc) and ¹H-NMR spectra on Bruker spectrometer (200MHz) using TMS as an internal standard, chemical shift in δ ppm.

A. General procedure for the preparation of 1-Aryl-3-[6-methyl-2-(4-methylphenyl)imidazo [1,2-a] pyridin-3-yl]prop-2-ene-1-ones (1a-l)

6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde 2.5g (0.01mol) was dissolved in 25 ml methanol at room temperature. P-Methoxy acetophenone 1.40g (0.01mol) and 0.2 ml 40% sodium hydroxide solution was added. Stirred the content at room temperature for 24 hrs then filtered it and washed with chilled methanol. Yield 76 %, m. p. 200 oC, Elemental Analysis Calcd for C₂₅H₂₂N₂O₂ Requires: C-78.51%, H-5.80%, N-7.32%, Found : C-78.40%, H-5.72%, O-7.35%.

B. 1-Aryl-3-[6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones (1a-l)

Yield 76 %, m.p. 200⁰C; IR(KBr) : v Alkane C-H str. (asym.) 2966, -CH₃ C-H str. (sym.)2876, C-H def.(asym.) 1453 , C-H def. (sym.) 1352, C=C str. 1503, C-H o.o.p.(def) 1352, Aromatic C-Hstr. 3061, Amine NH str. 3372 , Ether C-O-C str. 1206, Pyridine C=C str. 1503 , C=N str. 1610 , un satd.C=O str. 1682, Imidazo[1,2-*a*] C=N str. 1610, pyridine C-N str. 1110 , vinyl C=C str. 1536, cm⁻¹; ¹H-NMR (CDCl₃) : δ 2.41 & 2.43, (s,6H, Ar-CH₃) , 3.85 (s, 3H,-OCH₃), 7.40 & 8.10 (d-d, 2H, CH=CH) , 6.91-8.25 (m,13 H, Ar-H) , .Mass m/z 382 .M.F.:C₂₅H₂₂N₂O₂ .

C. General procedure for the preparation of 2-Amino-6-aryl-4-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]nicotinonitriles (2a-l)

A mixture of 1-(4-Methoxyphenyl)-3-[6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one 3.82gm (0.01mol), malononitrile 0.66 gm (0.01 mol) and ammonium acetate 6.16gm (0.08 mol) dissolved in methanol was refluxed for 12 hrs. The reaction mixture was poured into crushed ice and kept overnight. Solid separated was filtered and recrystallized from ethanol. Yield, 68%, m.p. 245⁰C. Elemental Analysis Calculated for C₂₈H₂₃N₅O ; Requires : C-75.49%, H-5.20%, N-15.72 %; Found : C-75.41%, H-5.15, N-15.73%. Similarly, other 2-Amino-6-aryl-4-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]nicotinonitriles were synthesized.

D. 2-Amino-6-aryl-4-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]nicotinonitriles (2a-l) :

Yield 68 %, m.p. 245 ⁰C; IR(KBr) : Alkane C-H str. (asym.) 2917, -CH₃ C-H str. (sym.)2857, C-H def.(asym.) 1453 , C-H def. (sym.) 1323, C=C str. 1513, C-H o.o.p.(def) 800, Aromatic C-Hstr. 3061, Amine NH str. 3372 , Ether C-O-C str. 1206, Pyridine C=C str. 1513 , C=N str. 1590 , amine NH str. 3372, Imidazo[1,2-*a*] C=N str. 1556, pyridine C=N str. 1590 ,Nitrile str. 2257, pyridine C-N str. 1039 , cm⁻¹; ¹H-NMR (CDCl₃) : δ 2.31 & 2.34, (s,6H, Ar-CH₃) , 3.91 (s, 3H,-OCH₃), 3.91 (s, 2H, -NH₂) , 6.92 (s, 1H, pyr.) 7.12-8.16 (m,16 H, Ar-H).Mass m/z 445 . M.F.: C₂₈H₂₃N₅O.

Scheme-1

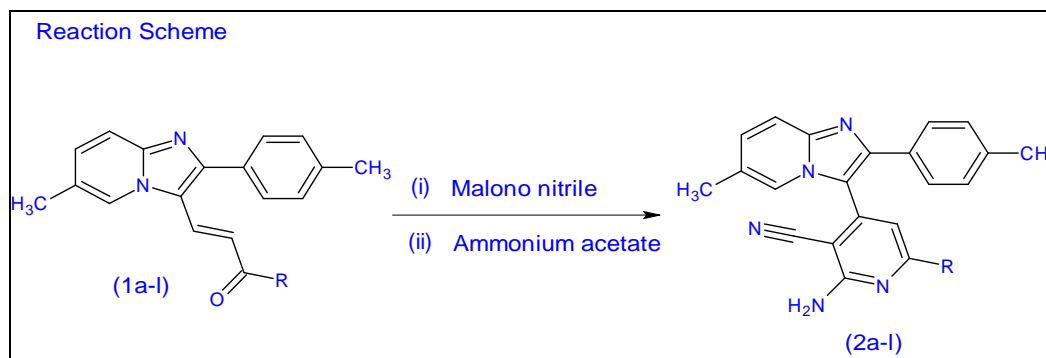


Table-1

| Characterization data of the compounds (2a-l) | | | | | | |
|-----------------------------------------------|----------------------------------------------------------|----------------------------------------------------------------|----------|-----------|------------|-------|
| compd no. | R | Molecular Formula | Mole.Wt. | M.P. (°C) | Nitrogen % | |
| | | | | | Found | Calcd |
| 2a | -C ₆ H ₅ | C ₂₇ H ₂₁ N ₅ | 415 | 158 | 16.81 | 16.86 |
| 2b | -4-Cl-C ₆ H ₄ | C ₂₇ H ₂₀ ClN ₅ | 449.5 | 240 | 15.59 | 15.57 |
| 2c | -2,4-(Cl ₂)- C ₆ H ₃ | C ₂₇ H ₁₉ Cl ₂ N ₅ | 484 | dec.200 | 14.54 | 14.46 |
| 2d | -4-NO ₂ - C ₆ H ₄ | C ₂₇ H ₂₀ N ₆ O ₂ | 460 | 144 | 18.31 | 18.25 |
| 2e | -4-OCH ₃ - C ₆ H ₄ | C ₂₈ H ₂₃ N ₅ O | 445 | 245 | 15.79 | 15.72 |
| 2f | -4-CH ₃ - C ₆ H ₄ | C ₂₈ H ₂₃ N ₅ | 429 | 189 | 16.27 | 16.31 |
| 2g | -4-OH-3-OCH ₃ - C ₆ H ₄ | C ₂₈ H ₂₃ N ₅ O ₂ | 461 | 226 | 15.27 | 15.17 |
| 2h | -4-Br-C ₆ H ₄ | C ₂₇ H ₂₀ BrN ₅ | 494 | 196 | 14.12 | 14.17 |
| 2i | -2-OH- C ₆ H ₄ | C ₂₇ H ₂₁ N ₅ O | 431 | 190 | 16.28 | 16.23 |
| 2j | -4-OH- C ₆ H ₄ | C ₂₇ H ₂₁ N ₅ O | 431 | 145 | 16.31 | 16.23 |
| 2k | -4-NH ₂ -C ₆ H ₄ | C ₂₇ H ₂₂ N ₆ | 430 | 230 | 19.47 | 19.52 |
| 2l | -2-C ₄ H ₃ S- | C ₂₅ H ₁₉ N ₅ S | 421 | 110 | 16.54 | 16.61 |

E. Antibacterial activity

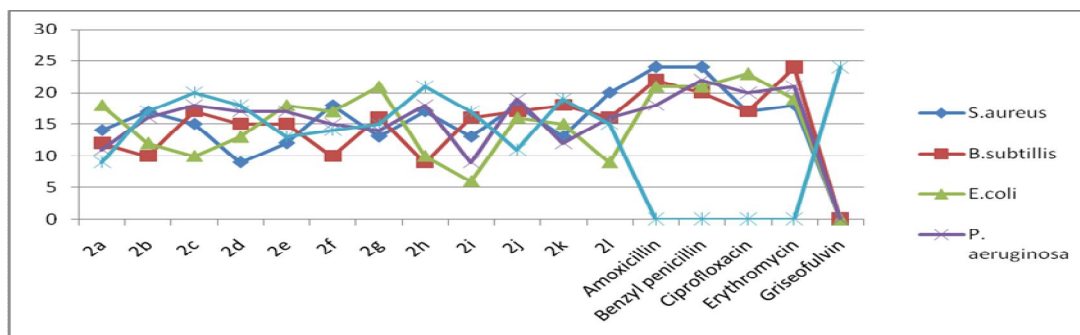
It has been observed from the microbiological data that all compounds (2a-l) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains. However the maximum activity was observed in compounds (2j), (2l) against S.aureus. The significant activity was observed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

F. Antifungal activity

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds (2c), (2h) against A.niger.

The antibacterial activity was compared with standard drug viz. Ampicillin, Benzyl penicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Griseofulvin.

Table-2 Antimicrobial activity : (zone of inhibition in mm) :



III. RESULTS AND DISCUSSION

Cyanopyridines play a vital role owing to their range of biological and physiological activities. In the light of these biological activities and variety of industrial applications, some new 2-Amino-6-aryl-4-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl] nicotinonitriles derivatives of type (2a-1) have been prepared by the cyclocondensation of 1-Aryl-3-[6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones of type (1a-1) with malononitrile in presence of ammonium acetate. The formulas of the selected compounds were confirmed by the elemental analysis and their structures were determined by IR, ¹H-NMR, and mass spectral data.

IV. 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.

V. ACKNOWLEDGMENT

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