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ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)
Vol. 1: (2), 2011, 146-152

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NOVEL 2-AMINO-3-CYANOPYRIDINES

Y.Siva Bharathi[a], T.Apparao[b] and Prof. S.Venkata Naidu[a*]

[a]Department of Polymer science and Technology,
Sri Krishnadevaraya University,
Anantapur – 515055,
Andhra.Pradesh., India.
Email: challaninaidu@yahoo.com
[b]Centre for Environment, Institute of Science and Technology,
Jawaharlal Nehru Technological University Hyderabad,
Hyderabad-500072, Andhra Pradesh, India

Abstract
6-Arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-ones **3a-l** obtained by the condensation of 2,3-dimethyl/3-methyl benzocyclohepten-5-one **1** with appropriate aromatic aldehydes, on condensation with malanonitrile and ammonium acetate in ethyl alcohol yield 2-amino-3-cyanopyridine derivatives **4a-l** respectively and the structures of these compounds were confirmed by IR, ^{1}H NMR & Mass spectral analysis. The newly synthesized compounds were evaluated for antimicrobial activity against variety of bacterial and fungal strains some of these compounds have shown significant antibacterial and antifungal activities.

Keywords: Benzocycloheptene, aromatic aldehydes, chalcones, malanonitrile, pyridine derivatives, antimicrobial activity.

Introduction

Many natural occurring and synthetic compounds containing the pyridine scaffold possess interesting pharmacological properties[1]. Among them, 2-amino-3-cyanopyridines have been identified as IKK-β-inhibitors[2]. Besides, they are important and useful intermediates in preparing variety of heterocyclic compounds[3-7]. Chalcone derivatives[8,9] play a vital role largely due to the wide range of biological activities. Much attention was directed towards the synthesis of cyanopyridenes derivatives due to their unique properties and hence their ability for application in various fields such as antimicrobial[10], antiviral[11,12], antibacterial[13]. antifungal[14], herbicidal[15,16], antitumour[17], anti-inflammatory[18,19] as well as antihypertensive[21] properties. Therefore, the synthesis of 2-amino-3-cyanopyridine derivatives continues to attract much interest in organic chemistry. The search of new heterocyclic compounds and for novel methods of their synthesis of major areas in contemporary organic chemistry.

Antimicrobial activity

The minimum inhibition concentration (MIC) was determined using the streak plate and cup plate method by measuring the zone of inhibition according to a standard procedure[20]. All the synthesized compounds were screened in vitro for their antimicrobial activity against a variety of bacterial strains such as *Staphylococcus aureus, Salmonella paratyphi, Escherichia coli, Shigella flexneri, Pseudomonas auregenosa, Bacillus subtilis,* and fungi such as *Cerevesae vitae, Candida albicans, Aspergillus niger* (**Table-1**). The MIC of the compounds was defined, as the lowest concentration at which there was 80% inhibition of growth compared with the growth for a drug free control[21]. Standard inhibition of zone size for Ciprofloxacin, Cloxacillin and for Gentamycin[21] is (++++) at ≤ 50 μgm/mL against all microbes.

Results and Discussions

6-Arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one **3a** is a useful intermediate for conversion into new heterocycles. 6-Arylidene-2,3-dimethyl/3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-ones **3a** were obtained by the condensation of 2,3-dimethyl benzocycloheptene-5-one **1a** with appropriate aldehydes **(Scheme I)**. In the enone **3a,b** the olefinic proton =CH-Ar appeared at δ 7.75 –7.80 in the ^{1}H NMR spectra. The 6-aryl methylene derivatives **3a** reacted with malanonitrile and ammonium acetate in ethanol gave 2-Amino-4-(4-bromo-phenyl)-9,10-dimethyl-6,7-dihydro-5*H*-benzo[6,7] cyclohepta[1,2-b]pyridine-3-carbonitrile **4a,b.** The mass spectra and ^{1}H NMR spectral data gave strong evidence in favour of the structure **4a**. The mass spectrum of **4a** (taken as a representative example) had the molecular ion $C_{23}H_{20}BrN_3$ at *m/z* 418, consistent with the molecular formula. The ^{1}H NMR spectrum of **4a** showed the presence of a doublet at δ 4.90 NH_2 protons, two methyl group protons at 2.15 and 2.30. Further, the spectrum had signals for 3-methylene groups between δ 1.45 and 2.95. Besides these the aromatic protons appeared as a multiplet at δ 6.70 – 7.75. The IR spectrum also showed the disappearance of the carbonyl absorption band and the presence of C=N group in the region 1600-1610 cm^{-1} indicating that cyclization has been taken place, NH_2 group in the region at 3325-3335 **(Scheme I)**. Under analogous conditions the reaction of 6-arylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one **3b** with malanonitrile in ethyl alcohol afforded 2-amino-3-cyanopyridine derivatives **4b (Scheme I)**.

Experimental Section

Melting points were determined using Gallenkamp apparatus and uncorrected. IR spectra were recorded on a FT-IR 1605 Perkin-Elmer machine; ^{1}H NMR in $CDCl_3$ on a Varian FT-80A spectrometer with TMS as an internal standard and mass spectra on a VG-Micromass 7070H mass spectrometer. TLC was run on silica gel G coated plates with iodine vapour as visualizing agent.

General procedure for the synthesis of 3a-l

Synthesis of 6-arylidene-2,3-dimethyl-6,7,8,9-tetrahydrobenzocycloheptene-5-ones 3a

A mixture of 2,3-dimethyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-5-one **1a** (10 mmol, 1.88 gm), 4-bromobenzaldelyde (10 mmol, 1.55 gm) in ethanolic potassium hydroxide was stirred at RT for 0.5 hr. During this time the product was formed. The reaction mixture was neutralized with acetic acid and diluted with water. The solid thus obtained was filtered and washed thoroughly with water and dried. Purification by recrystallization from methanol gave the product **3a** (3.2 gm, 92%) as colourless crystals m.p. 112-13^{o}C,. IR (KBr, cm^{-1}): 1660 (CO

chelated) and 1601 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00-2.20 (2H, m, 8-CH_2), 2.40 (6H, s, 2CH_3), 2.70 (2H, t, 7-CH_2), 2.85 (2H, t, 9-CH_2), 7.00-7.75 (8H, m, aromatic), 7.80 (1H, s, C=CH) ppm; Anal. Calcd for $C_{20}H_{19}BrO$: C, 67.60; H, 5.3. Found: C, 67.53; H, 5.21%.
Compound 3b. Yield 90%, colourless crystals, m.p. 124-25°C, IR (KBr, cm^{-1}): 1657 (CO), 1585 (C=C). Anal. Calcd for $C_{19}H_{17}BrO$: C, 66.86; H, 4.98. Found: C, 66.89; H, 4.96%.
Compound 3c. Yield 96%, colourless crystals, m.p. 124-26°C, IR (KBr, cm^{-1}): 1662 (CO), 1616 cm^{-1} (C=C). Anal. Calcd for $C_{20}H_{20}O$: C, 86.95; H, 7.24%. Found: C, 86.88; H, 7.15%.
Compound 3d. Yield 94%, colourless needle like crystals, m.p. 112-13°C, IR (KBr, cm^{-1}): 1661 (CO), 1601 cm^{-1} (C=C). Anal. Calcd for $C_{19}H_{18}O$: C, 87.02; H, 6.80. Found: C, 87.00; H, 6.80%.
Compound 3e. Yield 96%, colourless crystals, m.p. 82-83°C, IR (KBr, cm^{-1}): 1657 (CO), 1593 cm^{-1} (C=C). Anal. Calcd for $C_{21}H_{20}O$: C, 86.89; H, 7.58. Found: C, 86.88; H, 7.56%.
Compound 3f. Yield 95%, colourless crystals, m.p. 90-92°C, IR (KBr, cm^{-1}): 1657 (CO), 1593 cm^{-1} (C=C). Anal. Calcd for $C_{20}H_{20}O$: C, 86.95; H, 7.24. Found: C, 86.90; H, 7.20%.
Compound 3g. Yield 95%, colourless crystals, m.p. 86-88°C, IR (KBr, cm^{-1}): 1659 (CO), 1590 cm^{-1} (C=C). Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.35; H, 7.18. Found: C, 82.23; H, 7.05%.
Compound 3h. Yield 97%, colourless crystals, m.p. 110-12°C, IR (KBr, cm^{-1}): 1663 (CO), 1588 cm^{-1} (C=C). Anal. Calcd for $C_{20}H_{20}O_2$; C, 82.19; H, 6.84. Found: C, 82.00; H, 6.87%.
Compound 3i.Yield 80%, colourless crystals, m.p.192-94°C, IR (KBr, cm^{-1}): 1654 (CO), 1611 cm^{-1} (C=C). Anal. Calcd for $C_{18}H_{18}OS$: C, 76.59; H, 6.38. Found: C, 76.47; H, 6.24%.
Compound 3j.Yield 75%, colourless crystals, m.p. 135-37°C, IR (KBr cm^{-1},): 1653 (CO), 1580 cm^{-1} (C=C). Anal. Calcd for $C_{17}H_{16}OS$: C, 76.12; H, 5.97. Found: C, 76.52; H, 5.98%.
Compound 3k. Yield 76%, colourless crystals, m.p. 150-52°C, IR (KBr, cm^{-1}): 1660 (CO), 1614 cm^{-1} (C=C). Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.20; H, 6.76. Found: C, 81.13; H, 6.67%.
Compound 3l. Yield 73%, colourless crystals, m.p. 108-10°C, IR (KBr, cm^{-1}): 1657 (CO) 1593 cm^{-1} (C=C). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.95; H, 6.35. Found: C, 80.92; H, 6.37%.

General procedure for the synthesis of 4a-lSynthesis of 2-amino-4-(4-bromo-phenyl)-9, 10-dimethyl-6,7-dihydro-5*H*-benzo[6,7] cyclohepta[1,2-b]pyridine-3-carbonitrile 4a
A mixture of 6-arylidene-2,3-dimethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one 2a (10 mmol, 3.54 gm) and malanonitrile (10 mmol, 0.6 gm) and ammonium acetate (20 mmol, 1.54 gm) was heated under refluxed in ethanol (20 mL) for about 6 hr. The product was isolated and crystallized from ethanol **4a** (2.7 gm, Yield 68%), m.p.150-52°C, IR (KBr cm^{-1},): 1645 (C=N), 3325-3335 (NH); ^{1}H NMR (400 MHz $CDCl_3$): δ 1.60-1.80 (2H, m, 6-CH_2), 2.15 & 2.30 (6H, 2s, CH_3), 2.70-2.80 (2H, m, 7-CH_2), 2.85-2.95 (2H, t, 5-CH_2), 4.30-4.45 (2H, s, NH_2), 6.90-7.60 (6H, m, aromatic) ppm. MS: m/z 418 (M^+). Anal. Calcd for $C_{23}H_{20}BrN_3$: C, 66.04; H, 4.82; N, 10.03. Found: C, 65.90; H, 4.70; N, 10.00%.
Compound 4b. Yield 62% m.p. 136-148°C, IR (KBr, cm^{-1}): 1650 (C=N), 3325 (NH_2); ^{1}H NMR (400 MHz $CDCl_3$): δ 1.60-1.80 (1H, m, 6-CH_2), 2.40 (3H, s, CH_3), 2.65-2.75 (2H, t, 7-CH_2), 2.80-2.95 (2H, t, 5-CH_2), 4.30-4.50 (2H, s, NH_2), 6.90-7.60 (7H, m, aromatic) ppm; MS: *m/z* 405 (M+1), 406 (M+2). Anal. Calcd for $C_{22}H_{18}BrN_3$: C, 65.38; H, 4.49; N, 10.39. Found: C, 65.58; H, 4.30; N, 10.60%.
Compound 4c. Yield 70%, m.p. 165-167°C, IR (KBr, cm^{-1}):1649 (C=N),3315-3320 (NH); ^{1}H NMR (400, MHz $CDCl_3$): δ 1.45-1.60 (2H, m, 6-CH_2), 2.45 (6H, 2s, 2CH_3), 2.70-2.80 (2H, m, 7-CH_2), 2.85-2.95 (2H, t, 5-CH_2), 4.30 (2H, s, NH_2), 7.00-7.85 (7H, m, aromatic) ppm; MS: *m/z* 339 (M^+). Anal. Calcd for $C_{23}H_{21}N_3$: C, 81.40; H, 6.24; N, 12.36. Found: C, 81.38; H, 6.20; N, 12.32%.

Compound 4d. Yield 66%, m.p. 176-178°C, IR (KBr, cm^{-1}): 1648 (C=N) 3320-3330 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 1.5-1.80 (2H, m, 6-CH_2), 2.45 (3H, s-CH_3), 2.62-2.85 (2H, m, 7-CH_2), 2.90-3.00 (2H, t, 5-CH_2), 4.30-4.40 (2H, s, NH_2), 6.95-7.60 (8H, m, aromatic) ppm; MS: *m/z* 325 (M^+). Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.18; H, 5.87; N, 12.89.

Compound 4e. Yield 70%, m.p.145-147°C, IR (KBr, cm^{-1}): 1651 (C=N),3310-3318 (NH);; ^1H NMR (400 MHz, $CDCl_3$): δ 1.56-1.70 (2H, m, 6-CH_2), 2.26-2.30 (9H, 3s, 3X, C-CH_3), 2.72-2.74 (2H, m, 7-CH_2), 2.78-2.88 (2H, t, 5-CH_2), 4.31- 4.34 (2H, s, NH_2), 6.70-7.53 (6H, m, aromatic) ppm; MS: *m/z* 353 (M^+). Anal. Calcd for $C_{24}H_{23}N_3$: C, 81.55; H, 6.56; N, 11.89. Found: C, 81.50; H, 6.58; N, 11.85%.

Compound 4f. Yield 68%, m.p.198-200 °C, IR (KBr, cm^{-1}):1647 (C=N), 3305-3315 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 1.50-1.75 (2H, m, 6-CH_2), 2.20-2.45 (6H, 2s, 2X-CH_3), 2.65-2.75 (2H, m, 7-CH_2), 2.80-2.95 (2H, t, 5-CH_2), 4.35-4.46 (2H, s, NH_2), 6.90-7.75 (7H, m, aromatic) ppm; MS: *m/z* 339 (M^+). Anal. Calcd for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24; N, 12.38. Found: C, 81.36; H, 6.22; N, 12.36%.

Compound 4g. Yield 60%, m.p. 187-89°C, IR (KBr, cm^{-1}): 1656 (C=N), 3325-3330 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 1.60-1.80 (2H, m, 6-CH_2), 2.29 (6H, 2s, 2-CH_3), 2.88-2.95 (2H, m, 5-CH_2), 3.80 (3H, s, -OCH_3), 4.40-4.54 (2H, s, NH_2), 6.90-7.70 (6H, m, aromatic) ppm; MS: *m/z* 369 (M^+). Anal. Calcd for $C_{24}H_{23}N_3O$; C, 78.02; H, 6.27; N, 11.37. Found: C, 78.00: H, 6.25; N, 11.35%.

Compound 4h. Yield 58%, m.p. 177-79°C, IR (KBr, cm^{-1},): 1655 (C=N), 3300-3310 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 1.70-1.90 (2H, m, 6-CH_2), 2.40 (3H, s, -CH_3), 2.65-2.75 (2H, m, 7-CH_2), 2.80-2.95 (2H, t, 5-CH_2), 3.80(3H, s, -OCH_3), 4.55-4.60 (2H, s, NH_2), 6.90-7.70 (7H, m, aromatic) ppm; MS: *m/z* 355 (M^+). Anal. Calcd for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.96; N, 11.82. Found: C, 77.67; H, 5.94; N, 11.80%.

Compound 4i. Yield 60%, m.p. 165-67°C, IR (KBr, cm^{-1}): 1648 (C=N). 3295-3305 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 1.75-1.90 (2H, m, 6-CH_2), 2.30 (6H, s, 2-CH_3), 2.65-2.75 (2H, t, 7-CH_2), 2.80-2.95 (2H, t, 5-CH_2), 4.45-4.52 (2H, s, NH_2), 6.95-7.50 (5H, m, aromatic) ppm; MS: *m/z* 345 (M^+). Anal. Calcd for $C_{21}H_{19}N_3S$: C, 73.01; H, 5.54; N, 12.16. Found: C, 72.95; H, 5.52; N, 12.10%.

Compound 4j. Yield 72%, m.p. 176-78°C, IR (KBr, cm^{-1}), 1648 (C=N), 3326-3310 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 1.65-1.90 (2H, m, 6-CH_2), 2.35 (3H, s, -CH_3), 2.65-2.80 (2H, m, 7-CH_2), 2.80-2.90 (2H, t, 5-CH_2), 4.60 (2H, s, NH_2), 6.95-7.50 (6H, m, aromatic) ppm; MS: *m/z* 331 (M^+) Anal. Calcd for $C_{20}H_{17}N_3S$: C, 72.48; H, 5.17; N, 12.68. Found: C, 72.42; H, 5.13; N, 12.63%.

Compound 4k. Yield 65%, m.p. 155-57 °C, IR (KBr, cm^{-1}): 1648 (C=N), 3324-3310 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 1.30-1.75 (2H, m, 6-CH_2), 2.32 (3H, s, -CH_3), 2.60-2.70 (2H, m, 7-CH_2), 2.75-2.85 (2H, t, 5-CH_2), 4.35 (2H, s, NH_2), 6.90-7.50 (5H, m, aromatic) ppm; MS: *m/z* 329 (M^+). Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.52; H, 5.79; N, 12.73%.

Compound 4l. Yield 66% m.p. 167-69°C, IR (KBr, cm^{-1}): 1645 (C=N),3320-3330 (NH); ^1H NMR (400 MHz, $CDCl_3$): δ 1.50-1.75 (2H, m, 6-CH_2), 2.35 (3H, s, -CH_3), 2.60-2.80 (2H, m, 7-CH_2), 2.85-2.95 (2H, t, 5-CH_2), 4.70-4.79 (2H, s, NH_2), 6.90-7.50 (6H, m, aromatic) ppm; MS: *m/z* 315 (M^+). Anal. Calcd for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N, 13.32%. Found: C, 76.12: H, 5.40; N, 13.29%.

Acknowledgements

The authors wish to thank the UGC, New Delhi, for providing financial support to carry out this work.

Refere nces

1. C. Temple, G.A. Rener Jr, W.R.Raud, P.E.Noker, "Antimitotic agents structure-activity studies with some pyridine derivatives, *J. Med. Chem.*, **35**, 3686, (1992).
2. T. Murata,, M. Shimada, S. Sakakibara, T. Yoshino, H. Kadono, T.Masuda, M. Shimazaki, T. Shintani, K. Fuchikami , K. Sakai , H. Inbe, K. Takeshita, T. Niki, M. Umeda, K. B. Bacon, K.B. Ziegelbauer, T.B.Lowinger, "Discovery of novel and Selective IKK-β serine-threonine protein kinase inhibitors.Part1. *Bioorg. Med Chem. Lett.*, 13, 913 (2003).
3. (a) C.J.Shishoo, M.B.Devani,, V.S.Bhadti,, S. Ananthan, G.V. Ullas, "Electron transfer photooxygenation, 8.trapping of internal nucleophiles, *Tetrahedron Let.* 1983, *24*, 461. (b) K. Doe, K. Avasthi , R. Pratap, D.S.Bakuni, M.N.Joshi, *Indian*. *J. Chem, Sec B*, **29**, 459, (1990).
4. P. Satya , G. Rajiv, L. Andre, "Improved the synthesis of 2-amino-3-cyanopyridenes in solvent free conditions under microwave irradiation. *J Chem Research (S)*, 330- 331, (1998)
5. V. Peesapati,, V. Nageswara rao, "A novel synthesis of spiroisoxazoles via 1,3-dipolar Cycloaddition of nitrile oxide to 6-arylidene 6,7,8,9-tetrahydrobenzocylcohepten-5-one" *Indian J Chem*, ***46B***, 213-215, (2007).
6. S. Adel, I.S.Girgis Ahmad-Farag, "Synthesis of novel 2-alkoxy-5*H*-bezo[6,7]cyclohepten [1,2-*b*] pyridine 3-carbonitriles" *Z Naturforsch*, , **58b**, 698-703, (2003)
7. S. Feng, T. Shujiang, F. Fang,, L. Tuanjie, "One-pot synthesis of 2-amino-3-cyanopyridine derivatives under microwave irradiation without solvent" *ARKIVOC,* (**i**), 137-142, (2005)
8. Y. Inamori , "Synthesis of 2-Substituted Adenine-arabinosides and Related Compounds from 5-Amino-4-cyano-1-(β-D-ribofuranosyl)imidazole" *Chem Pharm Bull*, **39**, 1604 (1991).
9. K. Kyogoku, "Anti-ulcer Effect of Isoprenyl Flavonoids. II. Synthesis and Anti-ulcer activity of New Chalcones related to Sophoradin". *Chem Pharm Bull*, 27, 2943, 1979.
10. A. Sakurai, H. Midorikawa, "The Cyclization of Malononitrile and ketones by ammonium acetate", *Bull Chem Soc Japan*, **41**, 430, (1968)
11. A.G.Hammam, N.A.A.EI-Hafez, W.H.Midura, M.Mikolajczyk, *Z. Naturforch, B: Chem Sci*, **55b**, 417, (2000)
12. P. Koeckkrtiz, C. Ruhmann , D.Fieblinger, C.D.Schrodeder, B.V. Joksch, H.Heider, B. Weither, (Belin-Chemie A-G), 2-Aminopyridene 3-carbonitrile als selective hemmstoff des humanen cytomegalievirus. Ger Offen. De 4,117, 802 (Cl.C07D213/13). # Dec. 1992; *Chem Abstr*, 118, 191550, (1993).
13. J. Schubert , J. Wild, A.Harreus, T. Kuckenhoeher, H. Sauter, E. Ammermann, Lorenz (Basf A,-G) Ger Offen. DE 3,905,238 (Cl. C07D213/84) 23 Aug 1990, *Chem Abstr*. 114, 101740, (1991)
14. W. Kunz, K. Nebel, J. Wenger , (Novartis A,-G; Novartis-Erfindungen Verwaltungsgesell-schaft M.B.H., Switz.) PCT Int. Appl,. Novel herbicides, WO 9952,892 (Cl. C07D401/00). 21 Oct . 1999; *Chem Abstr*. 131, 286532, (1999).
15. J.E.Drumm , R.M.Lett, D.R.Rayner, M.P.Rorer, C.P.Tseng, (du Pont de Nemours, E.I. and Co) " Substituted pyridine herbicides" U.S. US 5,438,033 (Cl. 504130; A01 N 43/40) 1 Aug, 1995.
16. F.C.A. Gaeta, E.C. Stracker, (Geron Corporation. USA) Telomerase Inhibitors, US 5,770613 (Cl.514- \ 332; A61 K31/44). 23 Jun. 1998; *Chem Abstr*.,129,62962, (1998)

17. F. Monna, F.Chimenti, A.Balsco, B.Bizzari, W.Filippelli,, A.Fillippelli, L.Gagliardi, "Anti-inflammatory, analgesic and antipyretic 4,6-disubstituted-3-cyano-2-aminopyridines" *Eur J Med Chem*. **34**, 245, (1999)
18. R..M.Weier, L.F.Lee, R.A.Partis, F.J.Koszyk, (G D Searle & Co , USA) "2,3-substituted pyridines for the treatment of the inflammation" PCT Int WO 9624,584 (Cl. C017D213/61) 15 Aug. 1996, *Chem Abstr*. 125, 247624, (1996).
19. F.Manna, F.Chimenti, A. Bolasco, A.Filippelli, A. Palla, W.Filippelli, F. Lampa R.Mercantini, F.Manna, F.Chimenti, A.Bolasco, A.Filippelli, A.Palla, W.Filippelli, E.Lampa, R.Mercantini, "Anti-inflammatory, analgesic And antipyretic 4,6-disubstituted 3-cyanopyridens-2-ones and 3-cyno-2-Aminopyridenes". *Eur. J. Med. Chem*., **27(6),** 627-632, (1992)
20. *Gradwol's Clinical Laboratory methods and diagnosis* 1970, Vol II, 7th Edn; Mosby, C V Company, Germany, 1407.
21. *National Committee for Clinical Laboratory Standards*.1997, Reference method for broth dilution antifungal susceptibility testing of yeast. Approved standard NCCLS document M27– A. (ISBN 1 – 56238 – 328 – 0, ISSN 0273 – 3099). National Committee for Clinical Laboratory Standards, 940, West Valley Road, Suite 1400, Wayne, Pennsylvania, 19807.

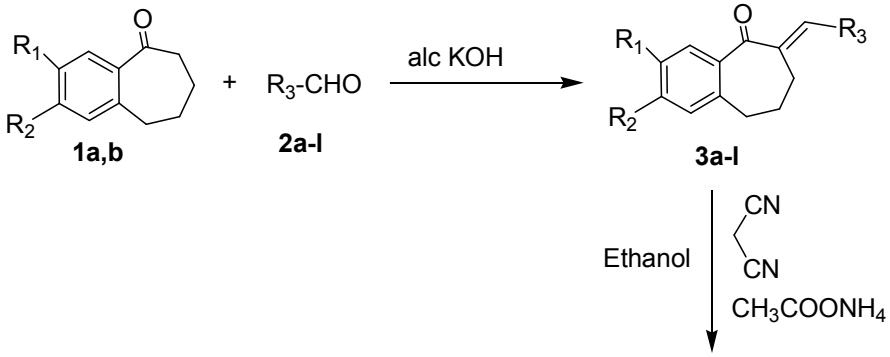
Scheme 1 Preparation of 2-amino- 3- cyanopyridine derivatives

Table 1: Antimicrobial activities of the compounds **4a – l**

Compound	Antibacterial activity					Antifungal activity			
	S.a	*E. c*	*S. a*	*S. f*	*P. a*	*B. s*	*A. n*	*C. a*	*C. v*
4a	++	++	++	++	+++	++	++	++	++
4b	++	++	++	++	++	+++	---	---	---
4c	+++	++++	+++	++	+	---	++	+	+
4d	+++	+++	++	+	++	+	++	++	---
4e	++++	++	+	+	+	++	++	++	---
4f	+++	++	++	++	++	++	++	++	++
4g	+++	++	+++	++	+++	++	++	++	++
4h	++	++	+	++	++	++	++	++	++
4i	++++	++	++	++	+++	++	++	++	++
4j	++	++	++	++	+++	++	++	++	++
4k	++	++	++	++	+++	++	++	++	++
4l	++	++	+++	++	+++	++	++	++	++

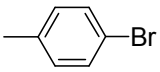
50 μgm/mL = ++++, 100 μgm/mL = +++, 150 μgm/mL = ++, 200 μgm/mL = +,
Not active upto 200 μgm/mL = – Ciprofloxacin, Cloxacillin & Gentamycin[21] is (++++) at ≤ 50 μgm/mL
S. a = Staphylococcus aureus, S. p = Salmonella paratyphi, E. c = Escherichia coli,
S. f = Shigella flexneri, P. a = Pseudomonas auregenosa, B. s = Bacillus subtilis,
C. v = Cerevesae vitae, C. a = Candida albicans, A. n = Aspergillus niger

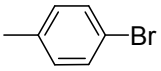
Scheme-

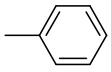


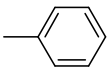
1a) R_1= CH_3, R_2= CH_3

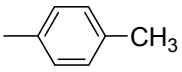
1b) R1= CH_3, R_2= H

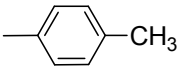
3&4a) R_1 & R_2= CH_3, R_3 = 

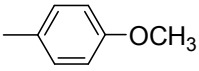
b) R_1= CH_3, R_2 = H, R_3 = 

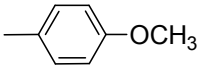
c) R_1 & R_2= CH_3, R_3= 

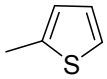
d) R_1= CH_3, R_2 = H R_3 = 

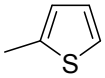
e) R_1 & R_2= CH_3, R_3 = 

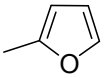
f) R_1= CH_3, R_2 = H,R_3 = 

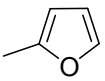
g) R_1 & R_2 = CH_3, R_3 = 

h) R_1= CH_3 ,R_2 = H, R_3 = 

i) R_1 & R_2 = CH_3, R_3 = 

j) R_1= CH_3, R_2 = H, R_3 = 

k) R_1 & R_2 = CH_3, R_3 = 

l) R_1= CH_3, R_2 = H, R_3 = 

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