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Synthesis Of Novel 1,8-Naphthyridine Derivatives As Potential Antimicrobial Agents

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ABSTRACT

Nine new 2-amino-4-substituted aryl-6-(2-methyl-1,8-naphthyridin-3-yl) nicotinonitriles **(3a-i)** have been synthesized from 3-acetyl-2-methyl-1,8-naphthyridine **(1)** by condensing it with a mixture of malononitrile and appropriate aromatic aldehydes in presence of ammonium acetate. Also, the compound **(1),** underwent smooth cyclocondensation when heated with a mixture of ethyl cyanoacetate and appropriate aromatic aldehydes in presence of ammonium acetate, to give nine new 4-substituted aryl-6-(2-methyl-1,8-naphthyridin-3-yl)-2-oxo–1,2-dihydropyridine-3-carbo-nitriles **(4a-i)**. The compounds **(3b)** and **(4c)** have been also prepared from 1-(2-methyl-1,8-naphthyridin-3-yl)-3-substituted phenyl-prop-2-en-1-one **(2)** by condensation with malononitrile and ethyl cyanoacetate respectively. The intermediate chalcone **(2)** was conveniently obtained by the treatment of methanolic 3-acetyl-2-methyl-1,8-naphthyridine with 4-chloro benzaldehyde in presence of mixture of triethylamine (TEA) and diethylamine (DEA**)**. The structures of compounds **(3a-i)** and **(4a-i)** were established on the basis of their elemental analysis and spectral (IR, ^{1}HNMR & MASS) data. All the new compounds were subjected to *in vitro* antibacterial testing against four pathogenic strains and antifungal screening against three fungi. Results indicate some of them exhibited promising activities and they deserve more consideration as potential antimicrobials.

KEYWORDS

2-methyl-3-acetyl-1,8-naththyridine;
Antibacterial & antifungal screening;
6-(2-methyl-1,8-naphthyridine-3-yl) pyridines;
Carbonitrile;
Nicotinonitrile.

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INTRODUCTION

1,8-Naphthyridine derivatives possess diverse types of biological properties such as antibacterial[1,2], antifungal[3], antitumour[4], diuretic[5], anti-inflammatory[6] molluscicidal[7], antihypertensive[8], antimalarial activities[9] and cutaneous anaphylaxis activity[10]. A thorough literature survey reveals that various pyridine derivatives have attracted considerable attention as they are also endowed with wide spectrum of pharmacological and antimicrobial activities[11,12]. Encouraged by the fact that, chemistry of bihetero cycles has emerged out as a frontier area of research in medicinal chemistry and in continuation of our interest in the chemistry of 1,8-naphthy ridines, it was planned to undertake the synthesis of title compounds **(3a-i)** and **(4a-i)** containing the above biodynamic heterocyclic systems aiming at investigation of new biheterocycles of enhanced pharmacological activities. The present study describes the synthesis of hither to unreported 6-(1,8-napthyridin-3-yl) pyridine derivatives **(3a-i and 4a-i)** and evaluation of their antibacterial and antifungal activities.

EXPERIMENTAL

Melting points were determined in open capillaries and uncorrected melting point apparatus: SERWELL Instruments INC, India.Purity of the compounds was checked by thin layer chromatography (TLC) on a silica coated aluminum sheet (silica gel $60F_{254}$) using chloroform and methanol (9:1, v/v). IR spectra (KBr pellets) were recorded (γ_{max} in max) on a PARAGON –1000 FTIR PERKIN ELMAR Spectrometer, and ^{1}H NMR spectra recorded on a Varian 300mHz NMR spectrometer using TMS as an internal standard. Chemical shifts are reported in ppm (δ) and signals are described as singlet (s), doublet (d), triplet (t), quartet (q), broad (br, s) and multiplet (m). Mass spectra were run on Vg–s-70-MICRO MASS, mass spectrometer operating at 70ev. Solvents and reagents were purchased from the commercial venders in the appropriate grade and were used without purification.

Chemistry

The reaction sequences employed for synthesis of title compounds is shown in figure 1. The key intermediate, 3-acetyl–2-methyl-1,8-naphthyridine (1) required for the preparation of the target compounds, was obtained by the condensation of 2-aminonicotinaldehyde with acetyl acetone in boiling methanol containing catalytic amount of piperidin[13]. The compound **(1)**, on reaction with 4-chlorobenza ldehyde in presence of TEA and DEA, under refluxing methanol afforded 1-(2-methyl-1,8-naphthy ridin-3-yl)-3-p-chlorophenylprop-2-en-1-one (2) smoothly. Treatment of (2) with malononitrile and ethyl cyanoacetate in refluxing methanolic ammonium acetate yielded the corresponding 4-chloro phenyl-6-(2-methyl-1,8-naphthyridine-3-yl) nicotinonitrile (3) and 4-chloro phenyl-6-(2-methyl-1,8-naphthyridin-3yl) 2-oxo-1,2-dihydropyridine-3-carbonitrile (4) respectively in good yields. Title compounds **(3a-i)** were also prepared directly in single step from (1) by treating it with a mixture of malono nitrile and appropriate aromatic aldehyde in refluxing methanolic ammonium acetate. Similarly title compounds **(4a-i)** were synthesized by following the same procedure using ethylcyanoacetate instead of malononitrile.

The structural elucidation of title compound, 2-Amino-4-phenyl-6-(2-methyl-1,8-naphthyridine-3-yl) nicotinonitrile **(3a)** was confirmed by its IR, ^{1}HNMR spectral MASS and elemental analyses. IR spectrum of it showed absorption band at 3290, 3160, 2215 and 1632 cm^{-1} due to NH_2, CH_3, CN, and -C=C- groups respectively, while ^{1}H-NMR showed sharp singlets at δ 2.35, 5.5 and 6.85 which corresponds to CH_3, NH_2 and pyridine C_5-H protons respectively. The multiplet at δ 7.5-7.54 shows the presence of five aromatic protons and multiplets at δ 7.6, 8.0, 8.2 and 9.16 indicating the presence of naphthyridine protons. Further, mass spectrum of it showed molecular ion peak at m/z 361 which is in agreement with the molecular formula $C_{21}H_{15}N_5$ + Sodium. The peaks at m/z 284, 215, 154,122, 94, and 67 were due to fragmentation of molecular ion.

The structural elucidation of title compound, 4-(4-Fluorophenyl)-6-(2-methyl-1,8-naphthyridine-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile **(4a)** was confirmed by its IR, ^{1}HNMR, mass spectral and el-

TABLE 1: Characterization data of compounds (3a-i) and (4a-i)

Compound	Ar	Mol. Formula	Mol Mass	MP (^{0}C)	Yield (%)	Elemental Analysis % found (cal)		
						C	H	N
3a	C_6H_5	$C_{21}H_{15}N_5$	337	>320	65	74.79 (74.77)	4.52 (4.45)	20.75 (20.77)
3b	4-Cl-C_6H_4	$C_{21}H_{14}ClN_5$	371.5	>320	63	67.86 (67.83)	3.74 (3.76)	18.90 (18.84)
3c	4-CH_3-C_6H_4	$C_{22}H_{17}N_5$	351	>320	60	75.22 (75.21)	4.87 (4.84)	19.99 (19.94)
3d	2-OCH_3-C_6H_4	$C_{22}H_{17}N_5O$	367	>320	64	71.88 (71.9)	4.68 (4.63)	19.13 (19.09)
3e	4-OH-C_6H_4	$C_{21}H_{15}N_5O$	353	>320	66	71.34 (71.38)	4.28 (4.24)	19.8 (19.83)
3f	2-Cl-C6H4	$C_{21}H_{14}ClN_5$	371.5	>320	67	67.88 (67.83)	3.72 (3.76)	18.91 (18.84)
3g	3,4-$(OCH_3)_2C_6H_3$	$C_{23}H_{19}N_5O_2$	397	>320	68	67.55 (67.51)	4.84 (4.82)	17.80 (17.6)
3h	4-OH-3-$OCH_3C_6H_3$	$C_{22}H_{17}N_5O_2$	383	>320	66	68.96 (68.92)	4.49 (4.47)	18.25 (18.27)
3i	4-F-C_6H_4	$C_{21}H_{14}FN_5$	355	>320	67	70.78 (70.98)	3.92 (3.94)	19.87 (19.71)
4a	4-F-C_6H_4	$C_{21}H_{13}FN_4O$	356	314	63	70.72 (70.78)	3.69 (3.68)	15.75 (15.73)
4b	3,4-$(OCH_3)_2$-C_6H_4	$C_{23}H_{18}N_4O_3$	398	>320	64	69.38 (69.34)	4.58 (4.55)	14.81 (14.06)
4c	4-Cl-C_6H_4	$C_{21}H_{13}ClN_4O$	372.5	296-298	66	67.63 (67.66)	3.54 (3.51)	15.04 (15.03)
4d	4-OH-C_6H_4	$C_{21}H_{14}N_4O_2$	354	>320	62	71.13 (71.18)	3.99 (3.98)	15.8 (15.81)
4e	4-CH_3-C_6H_4	$C_{22}H_{16}N_4O$	352	190-191	68	75.02 (74.98)	3.95 (3.97)	15.94 (15.90)
4f	2-Furyl	$C_{19}H_{12}N_4O$	328	>320	69	69.54 (69.51)	3.69 (3.68)	17.1 (17.06)
4g	4-OCH_3-C_6H_4	$C_{22}H_{16}N_4O_2$	368	>320	65	71.75 (71.73)	4.36 (4.38)	15.26 (15.21)
4h	4-OH-3-$OCH_3C_6H_3$	$C_{22}H_{16}N_4O_3$	384	>320	63	68.76 (68.75)	4.19 (4.2)	14.57 (14.58)
4i	C_6H_4	$C_{21}H_{14}N_4O$	338	197-198	65	74.58 (74.55)	4.18 (4.17)	16.50 (16.56)

emental analyses. IR spectrum of it showed absorption band at 3420, 3055, 2225, 1705, and 1655 cm^{-1} due to NH_2, CH_3, CN, C=O and C=C groups respectively, while ^{1}H-NMR showed sharp singlets at δ 2.64, 6.54 corresponds to CH_3, NH_2 and broad singlet at δ 7.1 corresponds to pyridine NH proton. The quartet at δ 7.6 and 7.7 indicates the presence of C_2 (C_3), C_5 (C_6) protons with fluorine coupling. The multiplets at δ 7.3, 7.86, 8.42 and 9.7 shows naphthy ridine C_6-H, C_4-H, C_5-H, and C_7-H proton respectively.Further, mass spectrum showed molecularion peak at m/z 356 which is in good agreement with the molecular formula $C_{21}H_{13}FN_4O$. The peaks at m/z 152, 135,115, 97, 83, 71 and 57 were due to fragmentation of molecularion.

The structural assignments to all the new compounds were based on their elemental analysis and spectral (IR, ^{1}HNMR and MASS) data. The characterization data of all the new compounds were summarized in TABLE 1

3-Acetyl-2-methyl- 1,8-naphthyridine(1)

The compound **(1)** was prepared according to the reported procedure[13].

General procedure for the preparation of 2-Amino-4-(substituted) phenyl-6-(2-methyl-1,8-

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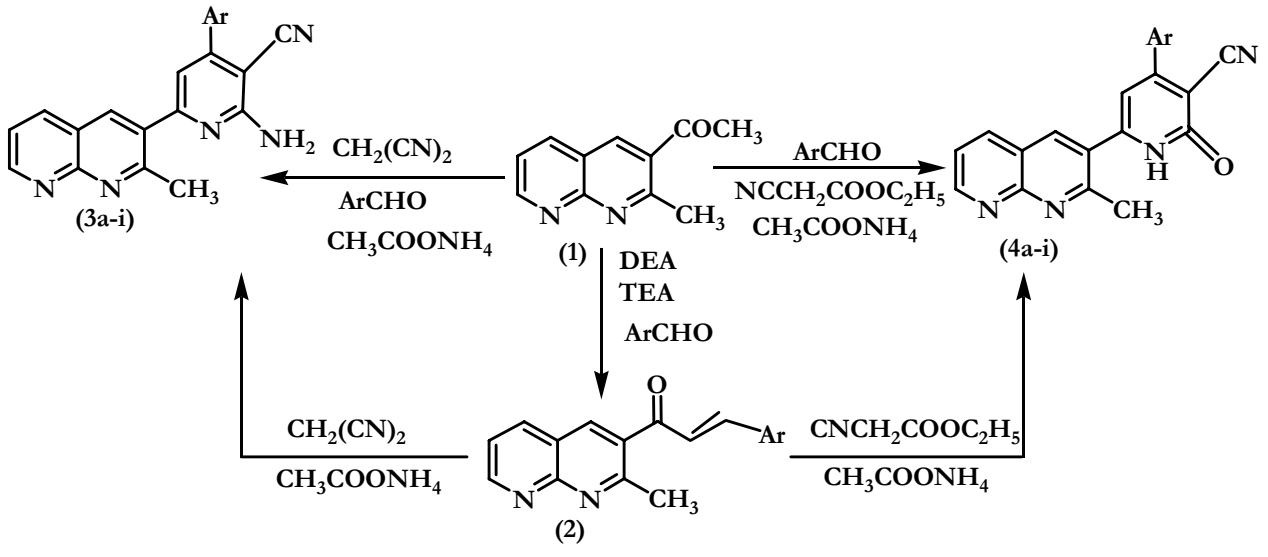

Figure-1

naphthyridine-3-yl) nicotinonitrile**(3a-i)**.

A mixture of 3-acetyl-2-methyl-1,8-naphthy ridine **(1)** (1mmol), malononitrile, (1mmol) appropriate aromatic aldehyde (1mmol) and ammonium acetate (10mmol) dissolved in ethanol (50ml) was heated under reflux for 4-6 h. The reaction mixture was left over night at room temperature and solid separated was collected by filtration, dried and crystallized from the proper solvent to offer compounds **(3a-i).** The characterization data were summarized in TABLE 1.

2-Amino-4-phenyl-6-(2-methyl-1,8-naphthy ridine-3-yl) nicotinonitrile(3a)

Crystallization solvent: Methanol and DMF; IR (KBr) γ cm^{-1}: 3290 (NH_2), 3160 (b, Ar-H), 2215 (s, CN), 1632 (C=C), 1557 (s, CN); ^{1}HNMR ($CDCl_3$): 2.35 (s, 3H, CH_3), 5.5 (s, 2H, NH_2), 6.85 (s, 1H, pyridine C_5-H), 7.5-7.54 (m, 5H J=6.7Hz, Aromatic $C_{2\text{-}6}$H), 7.6 (m, 1H J=8.3Hz, Naphthyridine C_6-H), 8.0 (s, 1H, Naphthyridine C_4-H), 8.2 (m, 1H, J=8.0 Hz Naphthyridine C_5-H), 9.16 (m, 1H, J=8.0, Naphthyridine C_7-H); Mass: (M/Z, %): 361 (M^++ Na), (66), 284 (16), 215 (26), 154 (32), 122 (100), 105 (22), 94 (84), 67 (46), 57 (44).

2-Amino-4-(4-chlorophenyml)-6-(2-methyl-1,8-Naphthyridin-3-yl) nicotinonitrile(3b)

Crystallization solvent: Chloroform and methanol; yield: IR (KBr) γcm^{-1}; 3360 (NH_2), 3150 (b, Ar –H), 2215 (s, CN), 1630 (C=C), 803 (C-Cl); ^{1}HNMR ($CDCl_3$): 2.8 (s, 3H, CH_3), 6.85 (s, 1H, pyridine C_5-H), 7.51 (m, 4H, Aromatic $C_{2\text{-}6}$H), 7.6 (s, 2H, NH_2), 8.1 (m, 1H, J=8.4Hz, Naphthyridine C_6-H), 8.66 (s, 1H, Naphthyridine C_4-H), 9.01(d, 1H, J=8.1Hz, Naphthyridine C_5-H), 9.3 (d, 1H, J = 6.62 Naphthyridine C_7-H); (M/Z,%) 395 (M^++ Na), (24), 284 (10), 256 (10), 249 (10), 194 (18), 183 (16), 161 (16), 139 (24), 118 (52), 105 (52), 91 (28), 60 (100), 57 (42).

2-Amino-4-(4-methyl phenyl)–6-(2-methyl-1,8-naphthyridin-3-yl) nicotinonitrile(3c)

Crystallization solvent: methanol; IR (KBr) γ cm^{-1}: 3260 (NH_2), 3090 (b, Ar –H), 2220 (s, CN), 1610 (C=C).

2-Amino-4-(4-methoxy phenyl)–6-(2-methyl-1,8-naphthyridin-3-yl) nicotinonitrile(3d)

Crystallization solvent: Chloroform and methanol; IR (KBr) γ cm^{-1}: 3260 (NH_2), 3090 (b, Ar –H), 2220 (s, CN), 1610 (C=C).

2-Amino-4-(4-Hydroxy phenyl)–6-(2-methyl-1,8-naphthyridin-3-yl) nicotinonitrile(3e)

Crystallization solvent: ethanol; IR (KBr) γ cm^{-1}: 3270 (NH_2), 3100 (b, Ar –H), 2225 (s, CN), 1600 (C=C).

2-Amino-4-(2-chloro phenyl)–6-(2-methyl-1,8-naphthyridin-3-yl) nicotinonitrile(3f)

Crystallization solvent: Ethanol; IR (KBr) γ cm^{-1}: 3400 (NH_2), 3150 (b, Ar –H), 2210 (s, CN), 1630 (C=C), 1578 (CN), 833 (C-Cl).

2-Amino-4-(3,4-dimethoxy phenyl)–6-(2-methyl-1,8-naphthyridin-3-yl) nicotinonitrile(3g)

Crystallization solvent: ethanol and chloroform; IR (KBr) γ cm^{-1}: 3300 (NH_2), 3130 (b, Ar –H), 2230 (s, CN), 1610 (C=C), 1570 (CN).

2-Amino-4-(3-Hydroxy, 4-methoxy phenyl)–6-(2-methyl-1,8-naphthyridin-3-yl) nicotinonitrile (3h)

Crystallization solvent: Ethanol and chloroform; IR (KBr) γ cm^{-1}: 3500 (b, OH), 3350 (NH_2), 3140 (b, Ar –H), 2220 (s, CN), 1630 (C=C), 1530 (CN).

2-Amino-4-(4-Fluro phenyl)–6-(2-methyl-1,8-naphthyridin-3-yl) nicotinonitrile(3i)

Crystallization solvent: Methanol and chloroform, IR (KBr) γcm^{-1}; 3340 (NH_2), 3214 (b, Ar –H) 2208 (s, CN), 1635 (C=C), 836 (C-F).

General procedure for the preparation of 4- substituted phenyl-6-(2-methyl-1,8-naphthyridine-3-yl) 1,2–dihydropyridine-3-carbonitrile(4a-i)

A mixture of 3-acetyl-2-methyl-1,8-naphthy ridine 1 (1mmol), ethylcyanoacetate (1mmol) , appropriate aromatic aldehyde (1mmol) and ammonium acetate (10mmol)dissolved in ethanol (50ml)was heated under reflux for 4-6 h. The reaction mixture was left over night at room temperature and solid separated was collected by filtration, dried and crystallized from the proper solvent to offer compounds **(4a-i)**. Their characterization data were summarized in TABLE 1.

4-(4-Fluorophenyl)-6-(2-methyl-1,8-naphthy ridine-3-yl)-2-oxo-1,2-dihydropyridine-3-carbo nitrile(4a)

Crystallization solvent: Chloroform–methanol, IR (KBr) γcm^{-1}: 3420 (NH), 3055 (Ar-H) 2225 (CN) ,1705 (C=O), 1655 (C=C), 1606 (C=C),1555 (CN) ^{1}HNMR ($DMSOd_6$+$CDCl_3$) 2.66 (s, 3H,CH_3), 6.54 (s,1H pyridine C_5-H), 7.1-(b,1H pyridine NH), 7.3 (m,1H J=7.8Hz,naphthyridin C_{6}-H), 7.6 (q,2H ,J=5.7 Hz aromatic $C_{2\text{-}3}$H and fluorine coupling),7.7 (q,2H J=5.3 aromatic $C_{5\text{-}6}$H and fluorine coupling), 7.86 (s, 1H Naphthyridine C_4-H), 8.42 (m,1H J=7.7 Naphthyridine C_5-H), 9.7 (m,1H J=8.5 Naphthyridine C_7-H); Mass:(M/Z,%), 356 (M^+,8) ,152(8), 135(8) , 115(8),97(30), 83(44) ,71(70),57(100).

4-(3,4-Dimethoxy)-6-(2-methyl-1,8-naphthy ridine-3-yl)-2-oxo-1,2-dihydropyridine-3-carbo nitrile(4b)

Crystallization solvent: Chloroform–methanol, IR (KBr) γcm^{-1}: 3420 (NH), 3065 (Ar-H) 2219 (s, CN) ,1651 (C=O), 1615 (C=C), 1587 (C=C), ^{1}HNMR ($CDCl_3$) 3.0 (s, 3H,CH_3), 3.96 (s, 3H, OCH_3), 4.0 (s, 3H, OCH_3), 6.97 (s, 1H pyridine C_5-H), 7.02 (d, 1H, J=8.0, Hz aromatic C_{6}-H) 7.29 (d,,1H J=8.2Hz aromatic C_{5}-H), 7.39 (m, 1H ,J = 7.78 Hz Naphthyridine C_{6}-H), 8.2 (s,1H pyridine NH), 8.8 (s, 1H, Naphthyridine C_4-H), 8.98 (s,1H aromatic C_2-H), 9.06 (m, 1H, J = 7.9 Naphthyridine C_5-H), 9.40 (d, 1H, J=8.1 Naphthyridine C_7-H); Mass: (M/Z,%), 398(M^+ 24), 261(28), 247(22), 185(18), 171(18), 143(28), 129(48), 129(52), 118(84), 91(100), 77(64).

4-(4-chlorophenyl)-6-(2-methyl-1,8-naphthy ridine-3-yl)-2-oxo-1,2-dihydropyridine-3-carbo nitrile(4c)

Crystallization solvent: Chloroform–ethanol, IR (KBr) γ cm^{-1}: 3426 (b, NH), 3165 (b, Ar-H), 2205 (s, CN), 1645 (C=O), 1615 (C=C).

4-(4-Hydroxyphenyl)-6-(2-methyl-1,8-naphthy ridine-3-yl)-2-oxo-1,2-dihydropyridine-3-carbo nitrile(4d)

Crystallization solvent: Ethanol, IR (KBr) γ cm^{-1}: 3550 (b, OH), 3406 (b, NH), 3150 (b, Ar-H) 2225 (s, CN), 1655 (C=O), 1610 (C=C).

4-(4-Methyphenyl)-6-(2-methyl-1,8-naphthy ridine-3-yl)-2-oxo-1,2-dihydropyridine-3-carbo nitrile(4e)

Crystallization solvent: Chloroform-ethanol, IR (KBr) γ cm^{-1}: 3426 (b, NH), 3105 (b, Ar-H), 2215 (s, CN), 1645 (C=O), 1600 (C=C).

4-(Furyl)-6-(2-methyl-1,8-naphthyridine-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile(4f)

Crystallization solvent: Chloroform-ethanol, IR (KBr) γ cm^{-1}: 3406 (b, NH), 3100 (b, Ar-H), 2230 (s, CN), 1655 (C=O), 1610 (C=C).

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4-(4-Methoxyphenyl)-6-(2-methyl-1,8-naphthyridine-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile(4g)

Crystallization solvent: Chloroform-ethanol; IR (KBr) γ cm^{-1}: 3433 (b, NH), 3014 (b, Ar-H), 2214 (s, CN), 1648 (C=O), 1616 (C=C).

4-(4-Hydroxy 3-methoxy phenyl)-6-(2-methyl-1,8-naphthyridine-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile(4h)

Crystallization solvent: Chloroform-ethanol, IR (KBr) γ cm^{-1}: 3500 (OH), 3400 (NH), 3010 (b, Ar-H), 2218 (s, CN), 1658 (C=O), 1606 (C=C).

4-(phenyl)-6-(2-methyl-1,8-naphthyridine-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile(4i)

Crystallization solvent: Chloroform- ethanol; IR (KBr) γ cm^{-1}: 3410 (NH), 3020 (b, Ar-H) , 2210 (CN), 1645 (C=O), 1605 (C=C).

1-(2-Methyl-1,8-naphthyridinm-3-yl)–3-(4-chlorophenyl)-prop-2-en-1-one(2)

The compound **(2)** was synthesized from 3-acetyl-2-methyl-naphthyridine by following procedure. A mixture of 3-acetyl-2-methyl-naphthyridine (1m mol) and appropriate aromatic aldehyde (1 mmol) triethyl amine (3ml, TEA) and diethyl amine (3ml, DEA) in absolute ethanol (50ml) was heated reflux for 4-6 h. The reaction mixture cooled and separated the solid was collected by filtration, dried and crystallized from ethyl acetate and n-hexane. Melting points of isolated compounds and analysis data matched with literature values.

The compound **(3b)** was prepared from **(2)** by the following method. A mixture of **(2)** (1m mol) malononitrile (1mmol) and ammonium acetate (10mmol) in absolute ethanol (50) ml was refluxed 10 h. The reaction mixture was left over night at room temperature and the solid formed was collected by filtration, washed with ethanol, dried and recrystallized from chloroform–methanol yield 70%. Its analysis data matched with that of **(3b).**

The compound **(4c)** was synthesized from 2 as described below.

A mixture of **(2)** (1m mol) ethyl cyanoacetate (1mmol) and ammonium acetate (10mmol) in absolute ethanol was refluxed for 8 h. The reaction mixture was left over night at room temperature and solid separated was collected by filtration, dried and recrystallized from chloroform-methanol. Yield was 68%. Its analysis matched with that of **(4c)**.

Biological Activity

Antibacterial screening

Compounds **(3a-i)** and **(4a-i)** were evaluated for their in vitro antibacterial activity against two gram positive bacteria viz., Bacillus sp, Staphylococcus aureus and two gram negative bacteria viz., Pseudomonas sp, E.coli using filter paper disc method[14] after dissolving them in N,N-dimethyl formamide (solvent) to obtain a 1mg/ml solution (1000 ppm). The inhibition zones of microbial growth surrounding the filter paper disc (5mm) were measured in millimeters at the end of an incubation period of three days at 37^0C for E-coli and at 28^0C for other bacteria. The solvent N, N-dimethylformamide alone showed no inhibition zone. The activity was compared with known standard drug, strepto-

TABLE 2: Antibacterial activity of the prepared compounds

Compound	Inhibition zone in mm			
	E. coli	*Bacillus sp*	*Pseudomonas sp*	*S. aureus*
3a	13	16	19	10
3b	16	15	18	15
3c	16	16	15	14
3d	15	14	16	13
3e	15	16	22	14
3f	9	10	10	12
3g	15	13	15	8
3h	14	16	16	10
3i	15	12	14	9
4a	14	9	11	14
4b	15	22	12	15
4c	16	13	15	19
4d	14	9	12	15
4e	13	10	14	12
4f	19	13	17	9
4g	15	9	14	13
4h	15	17	17	16
4i	12	13	10	9
Standard (Streptomycin)	20	24	24	21

TABLE 3: Antifungal activity of the prepared compounds

Compound	Inhibition zone in mm		
	A. niger	*A. flavus*	*Pencillium sp*
3a	18	14	16
3b	20	16	14
3c	19	14	15
3d	19	13	15
3e	24	12	16
3f	17	16	16
3g	16	16	19
3h	18	15	19
3i	18	16	17
4a	23	17	21
4b	15	16	21
4c	21	15	16
4d	18	23	18
4e	20	22	16
4f	18	14	17
4g	21	17	16
4h	18	13	17
4i	22	12	21
Standard (Flucanazole)	21	18	21

mycin, used at a concentration of 1000 ppm, for comparisons. The results are given in TABLE 2.

Antifungal screening

Compounds **(4a-i)** and **(3a-i)** were evaluated for their in vitro antifungal activity against A. Niger, A. Flavus and Pencillium sp using filter paper disc method[14] after dissolving them in N,N-dimethyl formamide to obtain a 1mg/ml solution (1000 ppm). The inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were measured in millimeters at the end of an incubation period of three days at 28^0C. The solvent N,N-dimethyl formamide alone showed no inhibition zone. The activity was compared with known standard drug Flucanazole, used at a concentration of 1000 ppm for comparisons. The results are given in TABLE 3.

RESULTS AND DISCUSSION

The investigation of antibacterial screening data revealed that all the compounds **(3a-i)** and **(4a-i)** inhibited 45-95% growth of the test organisms at 1000 ppm in dimethyl formamide. Of these, the most active compound **(4f)** exhibited the antibacterial activity almost equivalent to that of standard drug Streptomycin against E.Coli. In **(4f)** the presence of biologically active furyl group attached to pyridine nucleus has enhanced the activity. Compound **(4b)**, containing two methoxy groups in 2- and 4- positions, has showed 92% activity against Bacillus. Sp. Compound **(3e)** containing hydroxy group exhibited the highest activity against pseudomonas sp. Compound **(4c)** containing chlorine group in 4-position of phenyl group has caused good activity against S. aureus compared to standard. In conclusion, results of antibacterial testing revealed that presence of biologically active groups like methoxy, chloro and hydroxy in 4-position of phenyl ring and furyl group attached to position 4 of pyridine moiety caused good activity against most of the strains.

The results of the antifungal activity indicates that almost all the compounds **(3a-i)** and **(4a-i)** exhibited excellent activity in the range 76-130% some of the compounds like **(3e)**, **(4a)**, **(4i)** showed higher activity than that of standard Flucanazole, against A. Niger. Also compounds **(4d)** and **(4e)** are found to very good antifungal against A. Flavus. In general presence of groups like F, CH_3, Cl and OH at para position in phenyl moiety attached to 4-postion of pyridine moiety has brought about increased antifungal activity compared to standard.

CONCLUSION

The research study reports the successful synthesis and antimicrobial activity of new nicotinonitriles containing 1,8-naphthyridine moieties. The antimicrobial activity study revealed that all the compounds tested showed moderate to good antibacterial activity and moderate to excellent antifungal activity against pathogenic strains. Structure and biological activity relationship of title compounds showed that presence of F, OH, CH_3, OCH_3 groups in para position of phenyl moiety and furyl group attached to positon-4 of pyridine has enhanced the antimicrobial activity in newly synthesized title compounds.

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