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EFFICIENT SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 3-(3-ARYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-2-(TRIFLUOROMETHYL)-1,8-NAPHTHYRIDINES

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ABSTRACT

An efficient synthesis of 3-(3-Aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridines 5(a-h) was achieved by the cyclo condensation of 1-Aryl-3-(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)prop-2-en-1-ones(4a-h) with hydrazine hydrate. The compounds 4(a-h) were synthesized through a three-step procedure starting from ethyl 2-(trifluoromethyl)-1,8-naphthyridine-3-carboxylate (1). Antibacterial and antifungal activities of the final compounds 5(a-h) have been screened and compound 5h exhibited significant inhibition of bacterial and fungal growth. The structures of compounds 3-5 are assigned on the basis of their elemental analysis and spectral (IR, ^{1}H NMR, and MS) data.

Keywords: 1,8-Naphthyridiene, Ionic liquid, Dess–Martin periodinane, Pyrazole, Antibacterial Activity, and Antifungal activity

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INTRODUCTION

The nitrogen-containing heterocyclic systems are very interesting because of their physicochemical properties with relevance to the design of new drugs of pharmaceutical importance. In that respect, compounds containing the pyrazole ring system are known to possess a variety of biological and pharmacological properties.[1-8] 1,8-Naphthyridine derivatives have attracted considerable attention owing to their effective biological activity and extensive use.[9-12] Fluorine-containing organic compounds constitute an area of rapidly growing interested because of their unique physical and biological properties.[13] Alcohols undergo smooth oxidation with Dess–Martin-Periodinane (DMP) in ionic liquids at room temperature under mild conditions.[14-17] In recent years ionic liquids are attracting increasing interest as green recyclable alternatives to classical molecular solvents for synthetic organic chemistry.[18] Substituted 1,8-Naphthyridines are already well established as key cores in medicinal chemistry, along with that the pyrazoles have a lot of biological significance in connection with a present search on the design and synthesis of substituted 1,8-Naphthyridines linked to pyrazole in a single molecular framework. It was envisaged that these two active pharmacophores if linked together, would produce new molecular templates which are likely to display interesting biological properties.[19] The increasing incidence of bacterial and fungal resistance to a large number of antimicrobial agents has prompted studies on the development of novel potential antimicrobial compounds. Motivated by these observations, we have accomplished synthesis and antimicrobial activity of 3-(3-Aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridines 5.

Chemistry

The synthesis of target compounds was achieved by a synthetic sequence delineated in Scheme-I. To a solution of ethyl 2-(trifluoromethyl)-1,8-naphthyridine-3-carboxylate(1) in THF was added $LiAlH_4$ and stirred at room temperature to result (2-(trifluoromethyl)-1,8-naphthyridin-3-tyl)methanol(2). Compound 2 on oxidation with Dess–Martin periodinane in ionic liquid [bmim]BF_4 produced 2-(trifluoromethyl)-1,8-naphthyridine-3-carbaldehyde (3). Condensation of compound 3 with various acetophenones in the presence

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of NaOH produced 4(a-h). Finally, the reaction of 4(a-h) with hydrazine hydrate in EtOH presence of AcOH to furnish title compounds 5(a-h). The structures of compounds 3-5 were determined by their spectral (IR, ^{1}H NMR, and MS) analysis and analytical data.

Antibacterial Activity

Compounds 5(a-h) and the standard drug chloramphenicol were screened for their antibacterial activity against *E. coli ATCC 25922*, *B. subtilis ATCC 1633,* and *S. aureus ATCC 25923*. These compounds displayed varying degrees of antibacterial activity (Table-I). Only compound 5h revealed maximal inhibition with MIC 3.12-6.20µg/mL against bacterial strains used when compared to the standard drug. Compounds 5g and 5h exhibited prominent antibacterial activity. The rest of the compounds investigated in the present study have shown moderate activity.

Antifungal Activity

Antifungal activity of the compounds 5(a-h) along with reference drug fluconazole was carried out against *C. albicans ATCC 2091*, *A. niger ATCC 9029,* and *C. krusei ATCC 6258.* These compounds showed varying degrees of antifungal activity (Table-I). Compound 5h has displayed significant antifungal activity against the above strains with MIC 3.12, 12.55, and 1.59 µg/mL, respectively, as compared to fluconazole with MIC6.25, 12.5, and 3.125 µg/mL respectively. Compounds 5a, 5e, and 5f have been shown not to affect the growth of fungal strains. Compounds 5b, 5c, 5d, and 5g have shown mild to significant antifungal activity.

All the newly synthesized compounds 5(a-h) of the present study were evaluated *in vitro* to determine their antibacterial and antifungal activities against numerous pathogens. The results of the screening are given in Table-I. The effects of various substitutions on antibacterial and antifungal activities were examined and after reviewing the results for the compounds 5(a-h), a few conclusions could be drawn, such as It has been observed that compounds 5g and 5h bearing 4-nitrophenyl, 4-methoxyphenyl groups reflected most potent antibacterial and antifungal activities.

EXPERIMENTAL

Melting points were determined using a Cintex melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed by using Merck silica gel 60 F254 precoated plates (0.25 mm) and column chromatography was performed by using Silica gel (particle size 100-200 mesh). IR spectra (KBr) were recorded on a Perkin-Elmer BX series FTIR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer. Chemical shift values were given in ppm (δ) with TMS as an internal standard. Mass spectra were determined on Agilent LC-1100 (LC-MS) series instrument. Elemental analyses were performed on Carlo Erba 106 and Perkin Elmer model 240 analyzers. All the chemicals and reagents used in the present investigation were purchased from Sigma Aldrich Chemical Company.

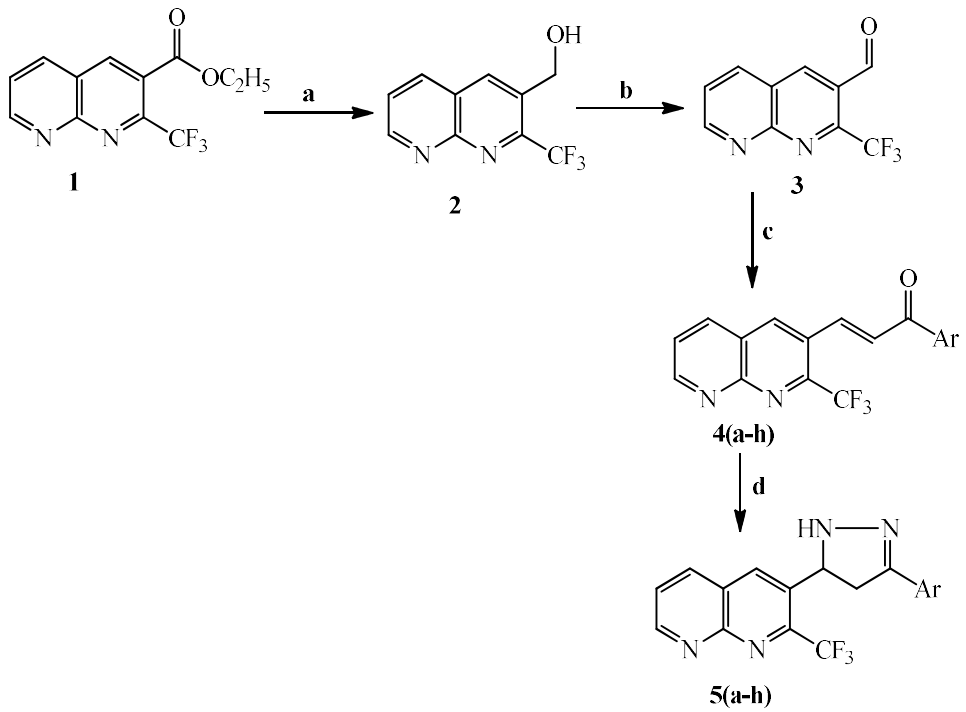
2-(Trifluoromethyl)-1,8-naphthyridine-3-carbaldehyde (3)

To a stirred solution of (2-(trifluoromethyl)-1,8-naphthyridin-3-yl)methanol (2) (6 g, 26.31 mmol) in Lewis acidic ionic liquid [bmim]BF_4 (50 mL) was added Dess–Martin periodinane (22.3g, 52.63 mmol) and this reaction mixture were stirred at room temperature for 2h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into ice-cold water.The obtained solid was filtered, washed with water, and purified by recrystallization from ethanol to obtain 2-(trifluoromethyl)-1,8-naphthyridine-3-carbaldehyde (**3**) as pale yellow solid, yield:87%, m.p.168–171°C. IR (KBr) ν_{max} (cm^{-1}): 3017, 2721, 1715, 1687, 1610, 1559, 1502, 1419, 97; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (m, 1H, C_6-H), 8.23 (s, 1H, C_4-H), 8.34 (m, 1H, C_5-H), 8.67 (m, 1H, C_7-H), 9.24(s, 1H, -CHO); LC-MS: *m/z* 227.2 $[M+H]^+$. Anal. Calcd for $C_{10}H_5F_3N_2O$: C 53.11%, H 2.23%, N 12.39%. Found: C 53.21%, H 2.27%, N 12.42%.

1-Aryl-3-(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)prop-2-en-1-ones4(a-h):

To a flask containing a stirred solution, 2-(trifluoromethyl)-1,8-naphthyridine-3-carbaldehyde (3) (5g, 22.11 mmol) in EtOH (50 mL) was added acetophenone (3 g, 25.53 mmol) and NaOH powder (1.02 g, 25.53 mmol) and the mixture was stirred at 90°C for 3h. The reaction was monitored by TLC in ethyl acetate. After completion of the reaction, the reaction mixture was poured into ice-cold water. The

purification was clinched using a short column of silica gel eluted with ethyl acetate to furnish 1-phenyl-3-(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)prop-2-en-1-one 4a as a yellow solid. The other derivatives 4(b-h) were also synthesized following the same procedure.



	Ar		Ar
a	C_6H_5	e	2-BrC_6H_4
b	2-Cl C_6H_4	f	3-Br C_6H_4
c	3-ClC_6H_4	g	4-$NO_2C_6H_4$
d	4-ClC_6H_4	h	4-$OCH_3C_6H_4$

Reagents and Conditions: a. LAH, THF, RT, 2h; b. [bmim]BF_4, Dess-Martin periodinane, RT, 2h; c. EtOH, NaOH, 90˚C, 3h; d. N_2H_4, EtOH, AcOH, 90˚C, 10h

Scheme-1: Synthetic routes to the 3-(3-Aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)- 1,8-naphthyridines 5

1-Phenyl-3-(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)prop-2-en-1-one(4a):
Yield 89%, m. p. 185-186ºC; IR (KBr) ν_{max} (cm^{-1}): 3028, 3010, 1729, 1625, 1605, 1555, 1507, 1419; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.40(d, 1H, J=7.95Hz olefinic C-H), 7.48-7.69 (m, 5H, Ar-H), 7.78 (m, 1H, C_6-H), 7.90(d, 1H, J=7.95Hz olefinic C-H), 8.18 (s, 1H, C_4-H), 8.42 (m, 1H, C_5-H), 8.67 (m, 1H, C_7-H); LC-MS: *m/z* 329.30 $[M+H]^+$. Anal. Calcd for $C_{18}H_{11}F_3N_2O$: C 65.85%, H 3.38%, N 8.53%. Found: C 65.97%, H 3.39%, N 8.57%.

(1-(2-Chlorophenyl)-3-(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)prop-2-en-1-one(4b):
Yield 92%, m. p. 174-176ºC; IR (KBr) ν_{max} (cm^{-1}): 3038, 2998, 1732, 1622, 1597, 1560, 1511, 1424; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45(d, 1H, J=8.02Hz olefinic C-H), 7.51-7.65 (m, 4H, Ar-H), 7.79 (m, 1H, C_6-H), 7.97(d, 1H, J=8.02Hz olefinic C-H), 8.27 (s, 1H, C_4-H), 8.36 (m, 1H, C_5-H), 8.74 (m, 1H, C_7-H); LC-MS: *m/z* 363.0 $[M+H]^+$. Anal. Calcd for $C_{18}H_{10}ClF_3N_2O$: C 59.60%, H 2.78%, N 7.72%. Found: C 59.73%, H 2.80%, N 7.74%.

((1-(3-Chlorophenyl)-3-(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)prop-2-en-1-one(4c):
Yield 90%, m. p. 210-212ºC; IR (KBr) ν_{max} (cm^{-1}): 3018, 3005, 1725, 1621, 1605, 1557, 1517 1410; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38(d, 1H, J=7.80Hz olefinic C-H), 7.42-7.69 (m, 4H, Ar-H), 7.71 (m, 1H, C_6-H), 8.02(d, 1H, J=7.80Hz olefinic C-H), 8.28 (s, 1H, C_4-H), 8.40 (m, 1H, C_5-H), 8.75 (m, 1H, C_7-

H); LC-MS: *m/z* 363.0 $[M+H]^+$. Anal. Calcd for $C_{18}H_{10}ClF_3N_2O$: C 59.60%, H 2.78%, N 7.72%. Found: C 59.73%, H 2.80%, N 7.74%.

(1-(4-Chlorophenyl)-3-(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)prop-2-en-1-one(4d):
Yield 94%, m. p. 192-194°C; IR (KBr) ν_{max} (cm^{-1}): 3025, 2997, 1722, 1634, 1625, 1567, 1514, 1447; ^1H NMR (400 MHz, DMSO-d_6): δ 7.40(d, 1H, J=7.92Hz olefinic C-H), 7.47-7.69 (m, 4H, Ar-H), 7.75 (m, 1H, C_6-H), 8.02(d, 1H, J=7.92Hz olefinic C-H), 8.23 (s, 1H, C_4-H), 8.34 (m, 1H, C_5-H), 8.67 (m, 1H, C_7-H); LC-MS: *m/z* 363.0 $[M+H]^+$. Anal. Calcd for $C_{18}H_{10}ClF_3N_2O$: C 59.60%, H 2.78%, N 7.72%. Found: C 59.73%, H 2.80%, N 7.74%.

(1-(2-Bromophenyl)-3-(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)prop-2-en-1-one(4e):
Yield 88%, m. p. 216-218°C; IR (KBr) ν_{max} (cm^{-1}): 3035, 3012, 1732, 1654, 1618, 1571, 1514, 1410; ^1H NMR (400 MHz, DMSO-d_6): δ 7.41(d, 1H, J=8.03Hz olefinic C-H), 7.41-7.55 (m, 4H, Ar-H), 7.78 (m, 1H, C_6-H), 8.07(d, 1H, J=8.03Hz olefinic C-H), 8.21 (s, 1H, C_4-H), 8.40 (m, 1H, C_5-H), 8.56 (m, 1H, C_7-H); LC-MS: *m/z* 406.2 $[M+H]^+$. Anal. Calcd for $C_{18}H_{10}BrF_3N_2O$: C 53.09%, H 2.48%, N 6.88%. Found: C 53.18%, H 2.50%, N 6.91%.

1-(3-Bromophenyl)-3-(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)prop-2-en-1-one(4f):
Yield 86%, m. p. 203-204°C; IR (KBr) ν_{max} (cm^{-1}): 3022, 3005, 1715, 1662, 1619, 1575, 1518, 1481; ^1H NMR (400 MHz, DMSO-d_6): δ 7.32(d, 1H, J=7.95Hz olefinic C-H), 7.52-7.61 (m, 4H, Ar-H), 7.74 (m, 1H, C_6-H), 8.05(d, 1H, J=7.95Hz olefinic C-H), 8.24 (s, 1H, C_4-H), 8.32 (m, 1H, C_5-H), 8.70 (m, 1H, C_7-H); LC-MS: *m/z* 406.2 $[M+H]^+$. Anal. Calcd for $C_{18}H_{10}BrF_3N_2O$: C 53.09%, H 2.48%, N 6.88%. Found: C 53.20%, H 2.51, N 6.90%.

1-(4-Nitrophenyl)-3-(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)prop-2-en-1-one(4g):
Yield 89%, m. p. 178-180°C; IR (KBr) ν_{max} (cm^{-1}): 3038, 2994, 1719, 1675, 1622, 1570, 1552, 1514, 1421; ^1H NMR (400 MHz, DMSO-d_6): δ 7.45(d, 1H, J=7.98Hz olefinic C-H), 7.58 (d, 2H, J=8.17Hz, Ar-H), 7.65-7.75 (m, 4H, Ar-H), 7.85 (m, 1H, C_6-H), 8.02(d, 1H, J=7.98Hz olefinic C-H), 8.23 (s, 1H, C_4-H), 8.37 (m, 1H, C_5-H), 8.65 (m, 1H, C_7-H); LC-MS: *m/z* 374.3 $[M+H]^+$. Anal. Calcd for $C_{18}H_{10}F_3N_3O_3$: C 57.92%, H 2.70%, N 11.26%. Found: C 57.38%, H 2.73, N 11.29%.

1-(4-Methoxyphenyl)-3-(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)prop-2-en-1-one (4h):
Yield 90%, m. p. 165-166°C; IR (KBr) ν_{max} (cm^{-1}): 3031, 3012, 2994, 1725, 1625, 1614, 1555, 1517, 1419; ^1H NMR (400 MHz, DMSO-d_6): δ 3.87 (s, 3H, OCH_3), 7.27(d, 1H, J=8.02Hz olefinic C-H), 7.48-7.62 (m, 4H, Ar-H), 7.75 (m, 1H, C_6-H), 8.02(d, 1H, J=7.87Hz olefinic C-H), 8.40 (s, 1H, C_4-H), 8.52(m, 1H, C_5-H), 8.73 (m, 1H, C_7-H); LC-MS: *m/z* 356.1 $[M+H]^+$. Anal. Calcd for $C_{19}H_{13}F_3N_2O_2$: C 63.69%, H 3.66%, N 7.82%. Found: C 63.78%, H 3.67%, N 7.84%.

3-(3-Aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridines 5(a-h):
To a stirred solution, 1-phenyl-3-(2-(trifluoromethyl)-1,8-naphthyridin-3-yl)prop-2-en-1-one(4a) (1.295 g, 3.95 mmol) in EtOH (10 mL) were added hydrazine hydrate (0.252 g, 7.90 mmol) and AcOH (0.474 g, 7.90 mmol). The resulting reaction mixture was stirred at 90°C for 10h. On completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature. The obtained product was filtered and purified by recrystallization from ethanol to obtain 3-(3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridine(5a) as pale-yellow solid, the other derivatives5(b-h) were also prepared following the same protocol.

3-(3-Phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridine (5a):
Yield 86%, m. p. 207-209°C; IR (KBr) ν_{max} (cm^{-1}): 3380, 3052, 2984, 2890, 1646, 1595, 1559, 1502, 1419; ^1H NMR (400 MHz, DMSO-d_6): δ 1.81 (m, 1H), 1.92 (m, 1H); 4.13 (m, 1H), 4.42 (brs, 1H, NH), 7.44-7.64 (m, 5H, Ar-H), 7.84 (m, 1H, C_6-H), 8.31 (s, 1H, C_4-H), 8.37 (m, 1H, C_5-H), 8.77 (m, 1H, C_7-H); LC-MS: m/z 343.1 $[M+H]^+$. Anal. Calcd for $C_{18}H_{13}ClF_3N_4$: C 63.16%, H 3.83%, N 16.37%. Found: C 63.29%, H 3.85, N 16.40%.

3-(3-(2-Chlorophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridine (5b): Yield 89%, m. p. 245-247°C; IR (KBr) ν_{max} (cm^{-1}): 3378, 3041, 2990, 2898, 1636, 1589, 1564, 1512, 1414; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.80 (m, 1H), 1.91 (m, 1H); 4.11 (m, 1H), 4.38 (brs, 1H, NH), 7.51-7.67 (m, 4H, Ar-H), 7.78 (m, 1H, C_6-H), 8.32 (s, 1H, C_4-H), 8.38 (m, 1H, C_5-H), 8.69 (m, 1H, C_7-H); LC-MS: m/z 377.3 $[M+H]^+$. Anal. Calcd for $C_{18}H_{12}ClF_3N_4$: C 57.38%, H 3.21%, N 14.87%. Found: C 57.47%, H 3.23, N 14.88%.

3-(3-(3-Chlorophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridine (5c): Yield 84%, m. p. 209-210°C; IR (KBr) ν_{max} (cm^{-1}): 3351, 3060, 2984, 2879, 1666, 1587, 1549, 1514, 1407; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.78 (m, 1H), 1.89 (m, 1H); 3.89 (m, 1H), 4.38 (brs, 1H, NH), 7.47-7.68 (m, 4H, Ar-H), 7.77 (m, 1H, C_6-H), 8.25 (s, 1H, C_4-H), 8.44 (m, 1H, C_5-H), 8.66 (m, 1H, C_7-H); LC-MS: m/z 377.3 $[M+H]^+$. Anal. Calcd for $C_{18}H_{12}ClF_3N_4$: C 57.38%, H 3.21%, N 14.87%. Found: C 57.47%, H 3.23, N 14.88%.

3-(3-(4-Chlorophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridine (5d): Yield 88%, m.p. 218-219°C; IR (KBr) ν_{max} (cm^{-1}): 3345, 3058, 2980, 2861, 1656, 1594, 1545, 1532, 1431; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79 (m, 1H), 1.88 (m, 1H); 4.04 (m, 1H), 4.35 (brs, 1H, NH), 7.44-7.67 (m, 4H, Ar-H), 7.65 (m, 1H, C_6-H), 8.33 (s, 1H, C_4-H), 8.43 (m, 1H, C_5-H), 8.68 (m, 1H, C_7-H); LC-MS: m/z 377.3 $[M+H]^+$. Anal. Calcd for $C_{18}H_{12}ClF_3N_4$: C 57.38%, H 3.21%, N 14.87%. Found: C 57.47%, H 3.23, N 14.88%.

3-(3-(2-Bromophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridine (5e): Yield 82%, m. p. 264-267°C; IR (KBr) ν_{max} (cm^{-1}): 3312, 3032, 2982, 2897, 1656, 1590, 1561, 1508, 1407; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81 (m, 1H), 1.92 (m, 1H); 4.12 (m, 1H), 4.38 (brs, 1H, NH), 7.58-7.71 (m, 4H, Ar-H), 7.79 (m, 1H, C_6-H), 8.33 (s, 1H, C_4-H), 8.54 (m, 1H, C_5-H), 8.78 (m, 1H, C_7-H); LC-MS: m/z 421.3 $[M+H]^+$. Anal. Calcd for $C_{18}H_{12}BrF_3N_4$: C 51.33%, H 2.87%, N 13.30%. Found: C 51.47%, H 2.88%, N 13.34%.

3-(3-(3-Bromophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridine (5f): Yield 80%, m. p. 251-252°C; IR (KBr) ν_{max} (cm^{-1}): 3336, 3058, 2984, 2912, 1646, 1594, 1559, 1514, 1428; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.80 (m, 1H), 1.93 (m, 1H); 4.11 (m, 1H), 4.36 (brs, 1H, NH), 7.48-7.66 (m, 4H, Ar-H), 7.80 (m, 1H, C_6-H), 8.30 (s, 1H, C_4-H), 8.44 (m, 1H, C_5-H), 8.71 (m, 1H, C_7-H); LC-MS: m/z 421.3 $[M+H]^+$. Anal. Calcd for $C_{18}H_{12}BrF_3N_4$: C 51.33%, H 2.87%, N 13.30%. Found: C 51.47%, H 2.88%, N 13.34%.

3-(3-(4-Nitrophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridine (5g): Yield 84%, m. p. 275-277°C; IR (KBr) ν_{max} (cm^{-1}): 3328, 3055, 2987, 2905, 1656, 1585, 1559, 1524, 1413; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81 (m, 1H), 1.80 (m, 1H); 4.13 (m, 1H), 4.48 (brs, 1H, NH), 7.52-7.69 (m, 4H, Ar-H),7.79 (m, 1H, C_6-H), 8.27 (s, 1H, C_4-H), 8.44 (m, 1H, C_5-H), 8.69 (m, 1H, C_7-H); LC-MS: m/z 388.2 $[M+H]^+$. Anal. Calcd for $C_{18}H_{12}F_3N_5O_2$: C 55.82%, H 3.12%, N 18.08%. Found: C 55.95%, H 3.13%, N 18.10%.

3-(3-(4-Methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridine (5h): Yield 87%, m. p. 250-252°C; IR (KBr) ν_{max} (cm^{-1}): 3347, 3042, 2984, 2887, 1674, 1587, 1565, 1514, 1432; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81 (m, 1H), 1.93 (m, 1H); 3.82 (s, 3H, OCH_3), 4.11 (m, 1H), 4.40 (brs, 1H, NH), 7.47-7.60 (m, 4H, Ar-H), 7.69 (m, 1H, C_6-H), 8.28 (s, 1H, C_4-H), 8.34 (m, 1H, C_5-H), 8.75 (m, 1H, C_7-H); LC-MS: m/z 372.2 $[M+H]^+$. Anal. Calcd for $C_{19}H_{15}F_3N_4O$: C 61.29%, H 4.06%, N 15.05%. Found: C 61.38%, H 4.07%, N 15.09%.

Antimicrobial Screening

All the compounds 5(a-h) prepared herein were screened for antibacterial and antifungal activities against different strains of bacteria and fungi.

Minimal Inhibitory Concentration (MIC)

The antimicrobial activity was assayed *in vitro* by two-fold broth dilution[20] against bacteria: *Escherichia coli ATCC 25922, Bacillus subtilis ATCC 1633,* and *Staphylococcus aureus ATCC 25923* and fungi: *Candida albicans ATCC 2091, Aspergillus niger ATCC 9029* and *Candida krusei ATCC 6258*. The minimal inhibitory concentrations (MIC in µg/mL)were defined as the lowest concentrations of a compound that completely inhibited the growth ofeach strain. All compounds dissolved in dimethyl sulfoxide (DMSO) were added to the culture media. Mueller-Hinton Broth for bacteria and Sabouraud Liquid Medium for fungi were used to obtain the finalconcentrations ranging from125 µg/mL to 1.592 µg/mL. The amount of DMSO never exceeded 1%v/v. Inocula consisted of 5.0 x 10^4 bacteria/mL and 1.0 x 10^3 fungi/mL. The MICs were noted after incubation at 37°C for 24 hr (bacteria) and at 30°C for 48 hr (fungi). Media with 1% v/v DMSO were employed as growth controls. Chloramphenicol and fluconazole were used as reference antibacterial and antifungal drugs, respectively.

Table-I: MIC Values of Compounds 5(a-h) Against Tested Bacterial and Fungal Strains

Compd	R	Antibacterial activity			Antifungal activity		
		E. coli ATCC 25922	B. substilis ATCC 1633	S. aureus ATCC 25923	C. albicans ATCC 2091	A.nigar ATCC 9029	A.krusei ATCC 6258
5a	C_6H_5	50	12.5	>125	__	__	__
5b	2-ClC_6H_4	25	20	40	30	25	25
5c	3-Cl C_6H_4	>125	50	>125	35	34	28
5d	4-ClC_6H_4	20.0	12.5	14.2	18	14	17
5e	2-BrC_6H_4	21.5	15.5	16.5	__	__	__
5f	3-Br C_6H_4	24	25	30	__	__	__
5g	4-$OCH_3C_6H_4$	12.0	6.25	11.5	8.25	10.5	7.5
5h	4-$NO_2C_6H_4$	6.25	3.12	6.20	3.12	12.55	1.59
[a] Control		0	0	0	0	0	0
Chloramphenicol		12.5	6.25	12.5			
Fluconazole					6.25	12.5	3.125

[a]DMSO served as control.
'-' Denotes no inhibition zone was observed.

CONCLUSION

In conclusion, we have synthesized a novel series of 3-(3-Aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(trifluoromethyl)-1,8-naphthyridines. All the synthesized compounds were characterized by IR, ^{1}H NMR, and mass spectrometry analysis. The advantages of this protocol include mild reaction conditions and high product yields with excellent purity. Most of the title compounds showed moderate to excellent activity toward the bacteria and fungi under investigation. Some of them, particularly 5g and 5h can be exploited for the formulation of bactericides and fungicides after detailed study.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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