RJC

RASĀYAN *J. Chem.*
Vol. 10 | No. 4 |1521-1528| October - December | 2017
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

# SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 2-((3/4-(1,8-NAPHTHYRIDIN-2-YL)PHENOXY)METHYL)-N-PHENYLBENZAMIDE DERIVATIVES

**Vijaya Bhasker G.[1], Laxminarayana E.[2], Latha A.[1] and Thirumala Chary M.[1,*]**

[1]Jawaharlal Nehru Technological University, Hyderabad, College of Engineering, Hyderabad -500 085, (Telangana) India.
[2]Sreenidhi Institute of Science and Technology, Yamnampet, Ghatkesar, Hyderabad-501 301, (Telangana) India.
*E-mail: mtcharya@yahoo.com

**ABSTRACT**

The synthesis of Quinoxalines with Naphthyridines has been intensively studied in the times of yore, particularly because of the unlike biological activities attributed to many representatives of these class of compounds. As a result, a large array of synthetic methods for the synthesis of title compounds has been reported in the literature. A series of novel 2-((4-(1,8-naphthyridin-2-yl)phenoxy)methyl)-N-phenylbenzamide derivatives (**10a-10h**) was synthesized. The compounds were characterized by $^{1}$H NMR, $^{13}$C NMR, Mass, and IR spectral analysis. Further these compounds were evaluated for their antibacterial activity.

**Keywords:** 2-aminonicotinaldehyde, anilines, hydroxy acetophenones, cyclization, antibacterial activity.



## INTRODUCTION

The synthesis of Quinoxalines has concerned important notice in the past decade.[1,2] They possess biological behavior like anti-viral,[3] antiseptic,[4] anti-inflammatory,[5] anti-protozoal,[6] anti-cancer.[7,8] 1,8-Naphthyridine derivatives have attracted considerable attention because the 1,8- naphthyridine skeleton is present in many compounds that have been isolated from natural substances, with various biological activities. In recent years, research on derivatives of 1,8-naphthyridine has been intensive because these compounds show a wide range of biological activities.[9-14]

In view of the importance of the Quinoxalines containing Naphthyridines, we report the synthesis of title compounds.

## EXPERIMENTAL

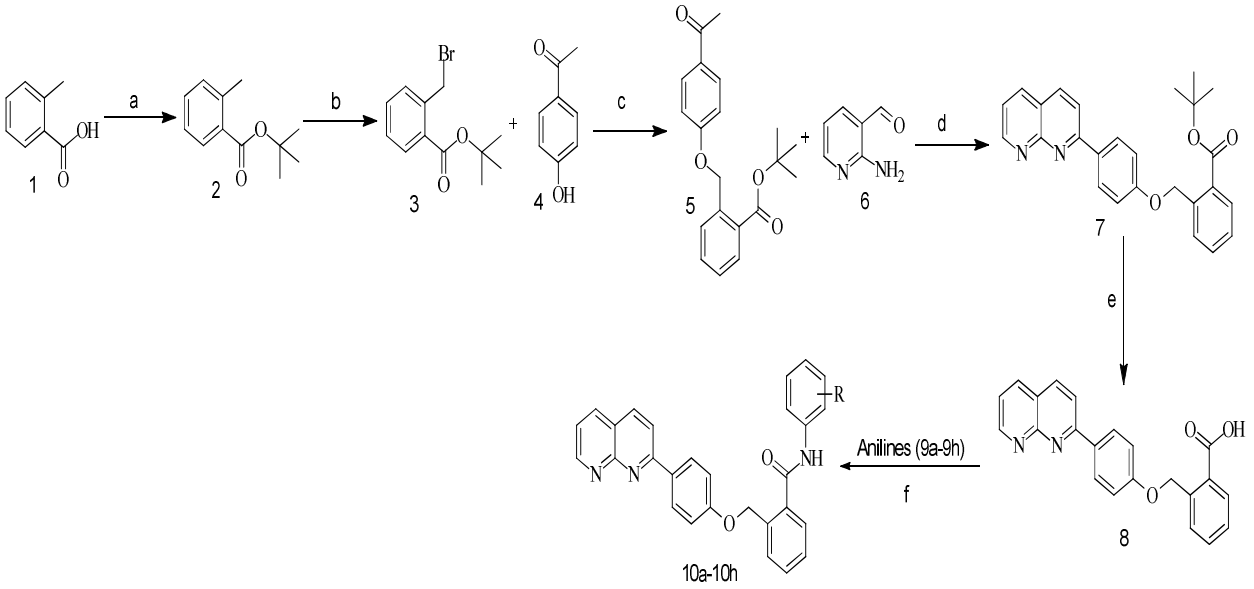
Chemicals used were acquired either from Fluka or Merck. Thin-layer chromatography (TLC) was performed on E.Merck AL silica gel 60 F254 plates and visualized under UV light. $^{1}$H NMR and $^{13}$C NMR spectra were recorded in DMSO- $d_6$ with a Varian Mercury plus 300/400/500 MHz and 75/125 MHz instruments respectively. Signals due to residual protonated solvent ($^{1}$H NMR) served as the internal standard. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The $^{1}$H NMR and $^{13}$C NMR chemical shifts and coupling constants were determined to assume first-order behavior. Mass spectra were recorded with a PE Sciex model API 3000 instrument. All the reactions were carried out under an inert atmosphere.

### Synthesis of *tert*-butyl 2-methylbenzoate (2)

To a stirred solution of 2-methyl benzoic acid **(1)** (4 g, 29.41 mmol) in dimethyl formamide (60 mL) were added *tert*-butanol (60 mL), di-tert-butyl dicarbonate (7.05 g, 32.35 mmol) followed by dimethyl amino pyridine (0.55 g, 4.54 mmol) at 0 °C and stirred at 60 °C for 6 h. After completion of the reaction (monitored by TLC), the crude was quenched with saturated aqueous sodium bicarbonate solution,

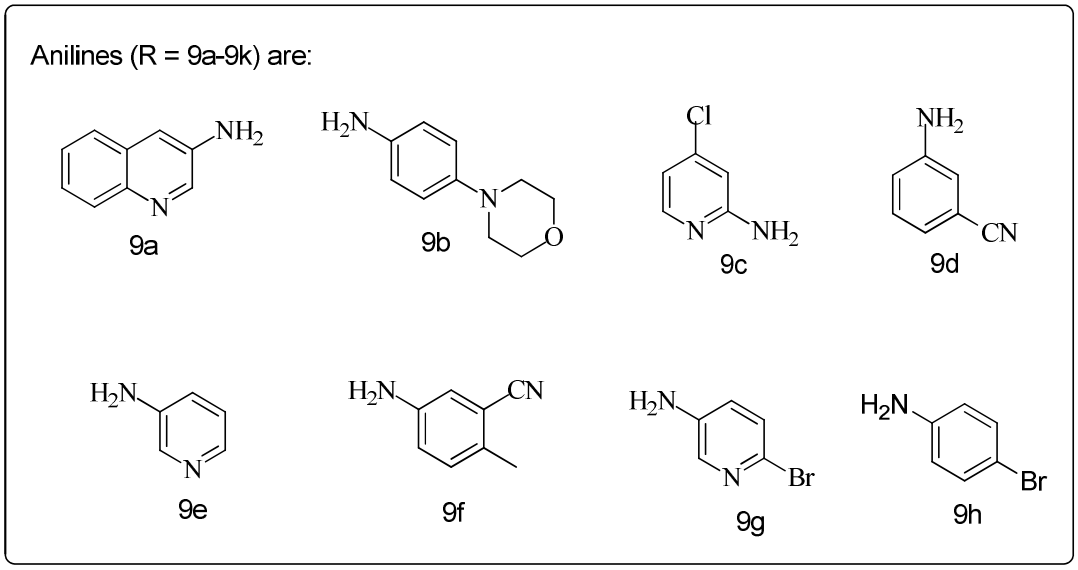

http://dx.doi.org/10.7324/RJC.2017.1041920

extracted from ethyl acetate. The combined organic layers were washed with brine solution, dried over sodium sulfate, filtered and concentrated, crude was purified by 100 – 200 mesh size silica gel column chromatography (10% ethyl acetate in pet ether mobile phase) to afford *tert*-butyl 2-methyl benzoate **(2)** as a colorless liquid. Yield: 2.3 g, 40%.




Scheme-1: Synthesis of 2-((4-(1,8-naphthyridin-2-yl)phenoxy)methyl)-N-phenylbenzamide derivatives 10a-10h. Reagents and conditions: (a) DMAP, $(Boc)_2O$, t-butanol, DMF, 60 °C, 6h; (b) NBS, AIBN, $CCl_4$, 70 °C, 16h, (c) $K_2CO_3$, acetone, 55 °C, 6h; (d) KOH, EtOH, Water, 70 °C 16h; (e) TFA, DCM, rt, 6h; (f) EDC.HCl, DMAP, THF, DMF, rt, 16h.

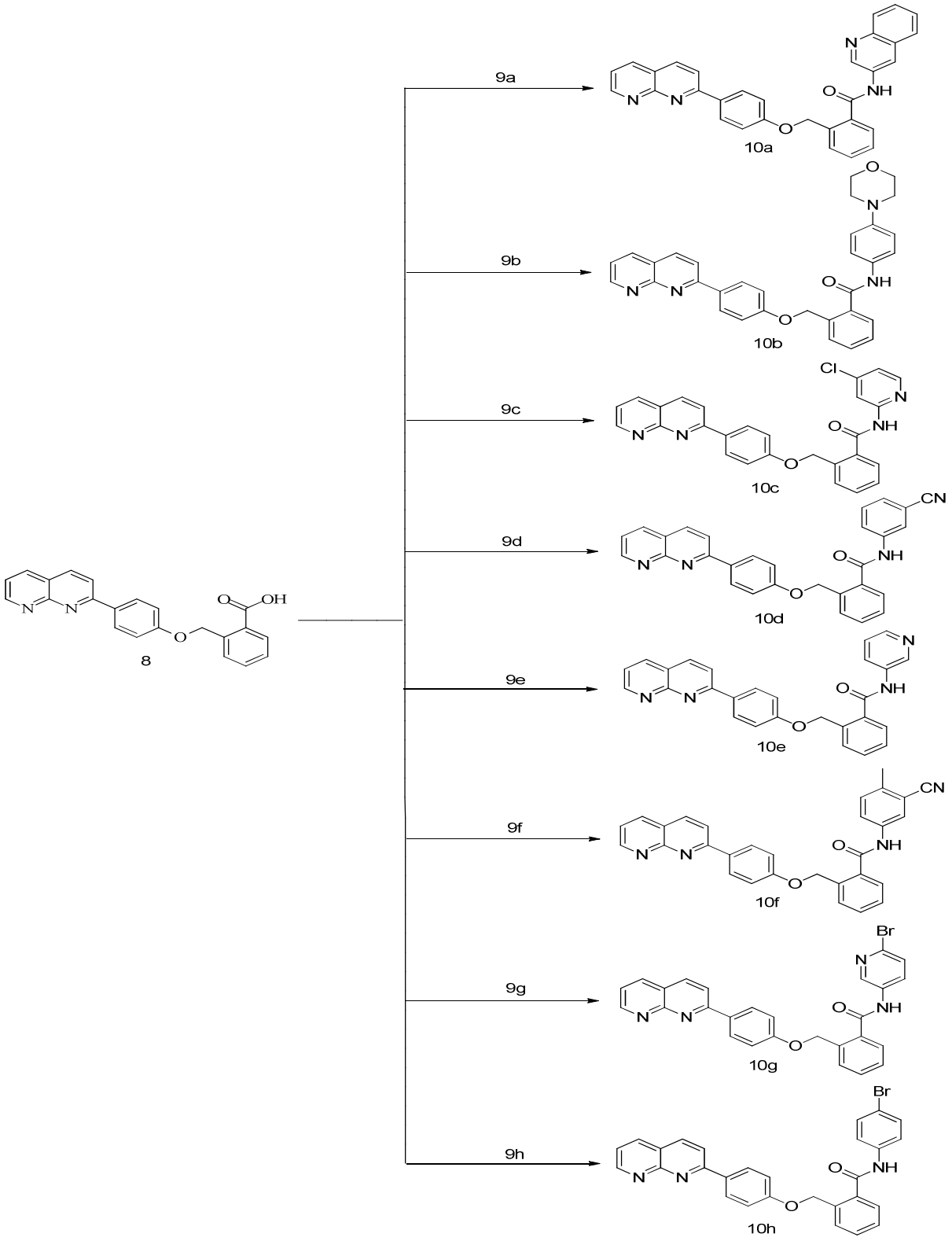
Where, 9a-9h are as:




**Synthesis of *Tert*-butyl 2-(bromomethyl)benzoate (3)**

To a stirred solution of *tert*-butyl 2-methyl benzoate **(2)** (2.3 g, 11.98 mmol) in carbon tetrachloride (25 mL) was added N-bromo succinimide (2.2 g, 12.58 mmol) followed by azo isobutyronitrile (0.19 g, 1.2 mmol) at room temperature and stirred at 70 °C for 16 h. After completion of the reaction (monitored by TLC), the crude was concentrated under reduced pressure and obtained crude was purified by 100 – 200

mesh size silica gel column chromatography (10% ethyl acetate in pet ether mobile phase) to afford *tert*-butyl 2-(bromomethyl)benzoate **(3)** as a colorless liquid. Yield: 1.5 g, 46%.




Scheme-2: The Synthesis of 2-((4-(1,8-naphthyridin-2-yl)phenoxy)methyl)-N-phenylbenzamide derivatives

**Synthesis of *Tert*-butyl 2-((3/4-acetylphenoxy)methyl)benzoate (5)**

To a stirred solution of 1-(3/4-hydroxyphenyl)ethanone **(4)** (1.5 g, 11.03 mmol) and *tert*-butyl 2-(bromomethyl)benzoate **(3)** (3.27 g, 12.13 mmol) in acetone (30 mL) was added potassium carbonate (3.8 g, 27.57 mmol) at 0 °C and stirred at 55 °C for 6 h. After completion of the reaction (monitored by TLC), crude was filtered through celite pad, filtrate was concentrated under reduced pressure and obtained crude was purified by 100 – 200 mesh size silica gel column chromatography eluted with 10% ethyl acetate in pet ether mobile phase to afford *tert*-butyl 2-((3/4-acetylphenoxy)methyl)benzoate **(5)** as an off-white solid. Yield: 1.9 g, 53%; m.p. 73-75 °C; IR (KBr): υmax 3404.42, 2978.22, 1711.14, 1258.35, 829.86 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.96 (dd, *J* = 1.0, 7.5 Hz, 1H), 7.95 (d, *J* = 2.0 Hz, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.51 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.37 (dt, *J* = 1.0, 8.0 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 5.53 (s, 2H), 2.55 (s, 3H), 1.58 (s, 9H); ESI-MS: *m/z*, 327 $(M+H)^+$.

**Synthesis of *Tert*-butyl 2-((3/4-(1,8-naphthyridin-2-yl)phenoxy)methyl)benzoate (7)**

To a stirred solution of 2-aminonicotinaldehyde **(6)** (1 g, 8.19 mmol) in ethylalcohol (20 mL) was added *tert*-butyl 2-((3/4-acetylphenoxy)methyl)benzoate **(5)** (2.93 g, 9.01 mmol) and potassium hydroxide (1.4 g, 24.59 mmol) at room temperature and refluxed for 16 h. After completion of the reaction (monitored by TLC), the mixture was concentrated under reduced pressure and obtained crude was diluted with water and precipitated solid was filtered, dried under vacuum to afford *tert*-butyl 2-((3/4-(1,8-naphthyridin-2-yl)phenoxy)methyl)benzoate **(7)** as an off-white solid; Yield: 1.8 g, 53%; m.p: 262-265 °C; IR (KBr): υmax 3435.55, 2975.43, 1698.17, 1599.50, 1253.16, 748.83 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.06 (dd, *J* = 2.0, 4.4 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.44 (dd, *J* = 2.0, 8.4 Hz, 1H), 8.32 (d, *J* = 1.6 Hz, 1H), 8.31 (d, *J* = 2.0 Hz, 1H), 8.22 (d, *J* = 8.8 Hz, 1H), 7.84 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.66 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.61 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.58 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.48 (td, *J* = 1.6, 7.6, 15.2 Hz, 1H), 7.18 (d, *J* = 1.6 Hz, 1H), 7.17 (d, *J* = 1.6 Hz, 1H), 5.46 (s, 2H), 1.50 (s, 9H); ESI-MS: *m/z*, 413 $(M+H)^+$.

**Synthesis of 2-((3/4-(1,8-Naphthyridin-2-yl)phenoxy)methyl)benzoic acid (8)**

To a stirred solution of *tert*-butyl 2-((3/4-(1,8-naphthyridin-2-yl)phenoxy)methyl)benzoate **(7)** (1.5 g, 3.64 mmol) in dichloromethane (30 mL) was added triflouro aceticacid (3 mL) at 0 °C and stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), the mixture was concentrated under reduced pressure and obtained crude was washed with 10% dichloromethane in diethyl ether to afford 2-((3/4-(1,8-naphthyridin-2-yl)phenoxy)methyl)benzoic acid **(8)** as an off-white solid; Yield: 1 g, 77%; m.p. 179–184 °C;

$^1H$ NMR (500 MHz, DMSO-$d_6$): δ 9.20 (dd, *J* = 2.0, 5.0 Hz, 1H), 8.84 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.69 (d, *J* = 8.5 Hz, 1H), 8.41 (d, *J* = 9.0 Hz, 1H), 8.36 (d, *J* = 2.0 Hz, 1H), 8.35 (d, *J* = 2.0 Hz, 1H), 7.96 (dd, *J* = 1.0, 7.5 Hz, 1H), 7.84 (dd, *J* = 5.0, 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.62 (dt, *J* = 1.0, 7.5 Hz, 1H), 7.47 (dt, *J* = 1.0, 7.5 Hz, 1H), 7.22 (d, *J* = 1.5 Hz, 1H), 7.20 (d, *J* = 1.5 Hz, 1H), 5.57 (s, 2H); $^{13}C$ NMR (125.77 MHz, DMSO-$d_6$): δ 168.0, 160.9, 160.4, 151.5, 151.2, 150.6, 150.4, 142.1, 139.0, 137.7, 132.1, 130.5, 129.7, 129.6, 129.5, 128.1, 127.8, 122.1, 122.0, 120.8, 115.3, 67.8; ESI-MS: *m/z*, 357 (M+1).

**General experimental procedure for the synthesis of novel 2-((3/4-(1,8-naphthyridin-2-yl)phenoxy)methyl)-N-phenylbenzamide derivatives (10a-10h)**

To a stirred solution of 2-((3/4-(1,8-naphthyridin-2-yl)phenoxy)methyl)benzoic acid **(8)** (100 mg, 0.28 mmol) in dimethyl formamide (2 mL), tetrahydrofuran (2 mL) were added corresponding aniline **(9a-9h)** (0.42 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (80 mg, 0.42 mmol) and dimethyl amino pyridine (3.4 mg, 0.028 mmol) at RT and stirred for 16 h. The reaction mixture was poured into ice cold water and extracted from AcOEt. The combined organic layers were washed with water followed by brine solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure; the crude material was washed with 50% of dichloromethane in pet ether to afford the pure compounds **(10a-10h)**. Yields of the products varied between 30 to 70%.

**2-((4-(1,8-Naphthyridin-2-yl)phenoxy)methyl)-N-(quinolin-3-yl)benzamide (10a)**
Yield: 70%; Off-white solid; m.p: 247-249 ºC; IR (KBr): $\upsilon_{max}$ 3432.71, 2929.49, 1598.23, 809.29 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.94 (s, 1H), 9.04 – 9.03 (m, 2H), 8.80 (d, *J* = 1.2 Hz, 1H), 8.46 (d, *J* = 8.7 Hz, 1H), 8.42 (dd, *J* = 1.8, 8.4 Hz, 1H), 8.23 (d, *J* = 1.2 Hz, 1H), 8.21 (d, *J* = 1.2 Hz, 1H), 8.15 (d, *J* = 8.7 Hz, 1H), 7.94 (t, *J* = 8.1 Hz, 2H), 7.76 – 7.52 (m, 7H), 7.14 (d, *J* = 1.8 Hz, 1H), 7.11 (d, *J* = 1.8 Hz, 1H), 5.46 (s, 2H); ESI-MS: *m/z*, 483 $(M+H)^{+\cdot}$

**2-((4-(1,8-Naphthyridin-2-yl)phenoxy)methyl)-N-(4-morpholinophenyl)benzamide (10b)**
Yield: 65%; Off-white solid; m.p: 218-220 ºC; IR (KBr): $\upsilon_{max}$ 3430.02, 2958.85, 1598.27, 1307.62, 1250.36, 1175.36, 811.22 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.29 (s, 1H), 9.05 (dd, *J* = 1.5, 4.2 Hz, 1H), 8.48 (d, *J* = 8.7 Hz, 1H), 8.43 (dd, *J* = 1.2, 8.1 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 2H), 8.26 (d, *J* = 8.4 Hz, 1H), 7.66 – 7.46 (m, 5H), 7.32 (s, 1H), 7.17 – 7.11 (m, 4H), 6.68 (t, *J* = 3.6 Hz, 1H), 5.39 (s, 2H), 3.67 (t, *J* = 3.9 Hz, 4H), 3.02 (t, *J* = 3.9 Hz, 4H); ESI-MS: *m/z*, 517 $(M+H)^{+\cdot}$

**2-((4-(1,8-Naphthyridin-2-yl)phenoxy)methyl)-N-(4-chloropyridin-2-yl)benzamide (10c)**
Yield: 35%; White solid; m.p: 216-221 ºC; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 10.74 (s, 1H), 9.06 (dd, *J* = 1.5, 4.0 Hz, 1H), 8.48 (d, *J* = 3.5 Hz, 1H), 8.45 (d, *J* = 4.0 Hz, 1H), 8.29 – 8.22 (m, 3H), 8.14 (s, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.59 – 7.51 (m, 3H), 7.24 – 7.19 (m, 3H), 7.03 (dd, *J* = 1.5, 5.5 Hz, 1H), 5.32 (s, 2H); ESI-MS: *m/z*, 467 $(M+H)^{+\cdot}$

**2-((4-(1,8-Naphthyridin-2-yl)phenoxy)methyl)-N-(3-cyanophenyl)benzamide (10d)**
Yield: 72%; Brown solid; m.p: 236–240 ºC; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.80 (s, 1H), 9.05 (dd, *J* = 1.8, 4.2 Hz, 1H), 8.48 (d, *J* = 8.7 Hz, 1H), 8.44 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.25 – 8.17 (m, 4H), 7.96 (dd, *J* = 2.4, 4.8 Hz, 1H), 7.67 (t, *J* = 6.3 Hz, 2H), 7.60 – 7.52 (m, 5H), 7.10 (d, *J* = 8.7 Hz, 2H), 5.41 (s, 2H); ESI-MS: *m/z*, 457 $(M+H)^{+\cdot}$

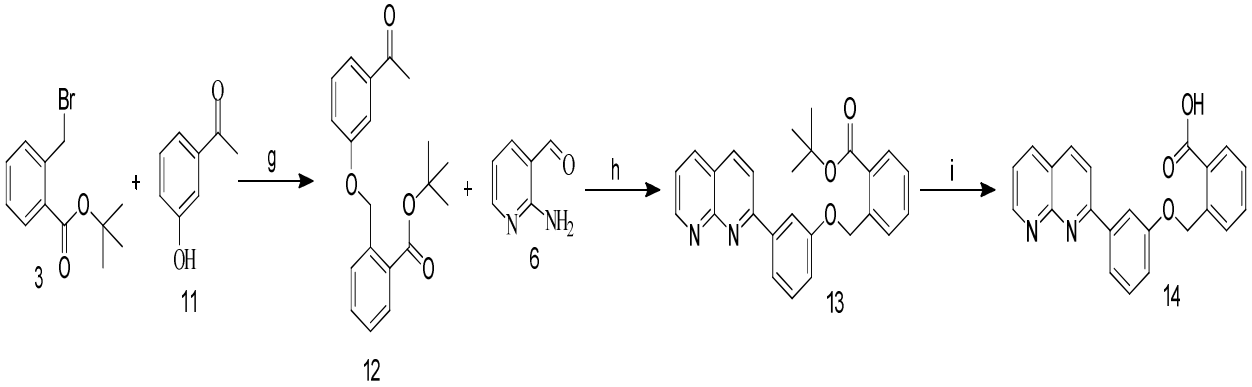
**2-((4-(1,8-Naphthyridin-2-yl)phenoxy)methyl)-N-(pyridin-3-yl)benzamide (10e)**
Yield: 66%; Off-white solid; m.p: 232-235 ºC; IR (KBr): $\upsilon_{max}$ 3431.05, 2974.61, 1599.28, 1309.71, 1245.76, 1173.70, 803.90 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.67 (s, 1H), 9.04 (dd, *J* = 1.8, 4.2 Hz, 1H), 8.85 (d, *J* = 2.1 Hz, 1H), 8.48 (d, *J* = 8.7 Hz, 1H), 8.43 (dd, *J* = 2.1, 8.1 Hz, 1H), 8.28 (dd, *J* = 0.9, 4.5 Hz, 1H), 8.25 (d, *J* = 1.2 Hz, 1H), 8.22 (d, *J* = 1.2 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 1.2 Hz, 1H), 7.68 (d, *J* = 1.2 Hz, 1H), 7.66 (d, *J* = 1.2 Hz, 1H), 7.59 (d, *J* = 4.2 Hz, 1H), 7.56 (d, *J* = 4.5 Hz, 1H), 7.52 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.36 (dd, *J* = 4.5, 8.1 Hz, 1H), 7.12 (d, *J* = 1.2 Hz, 1H), 7.09 (d, *J* = 1.2 Hz, 1H), 5.41 (s, 2H); ESI-MS: *m/z*, 433 $(M+H)^{+\cdot}$

**2-((4-(1,8-Naphthyridin-2-yl)phenoxy)methyl)-N-(3-cyano-4-methylphenyl)benzamide (10f)**
Yield: 70%; Off-white solid; m.p: 215-218 ºC; $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 10.70 (s, 1H), 9.05 (dd, *J* = 1.5, 3.9 Hz, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.43 (dd, *J* = 1.8, 8.1 Hz, 1H), 8.25 (d, *J* = 1.2 Hz, 1H), 8.22 (d, *J* = 1.2 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 1.8 Hz, 1H), 7.83 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.66 (td, *J* = 0.6, 7.8 Hz, 2H), 7.59 (d, *J* = 4.2 Hz, 1H), 7.56 (d, *J* = 4.8 Hz, 1H), 7.52 (dd, *J* = 0.9, 7.2 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.11 (d, *J* = 1.2 Hz, 1H), 7.09 (d, *J* = 1.2 Hz, 1H), 5.41 (s, 2H), 2.41 (s, 3H); ESI-MS: *m/z*, 471 $(M+H)^{+\cdot}$

**2-((4-(1,8-Naphthyridin-2-yl)phenoxy)methyl)-N-(6-bromopyridin-3-yl)benzamide (10g)**
Yield: 72%; Brown solid; m.p: 240-243 ºC; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.79 (s, 1H), 9.05 (dd, *J* = 2.0, 4.4 Hz, 1H), 8.70 (d, *J* = 2.8 Hz, 1H), 8.48 (d, *J* = 8.8 Hz, 1H), 8.43 (dd, *J* = 1.6, 8.0 Hz, 1H), 8.25 (d, *J* = 2.0 Hz, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 8.09 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.69 (t, *J* = 1.6 Hz, 1H), 7.67 (t, *J* = 1.6 Hz, 1H), 7.62 – 7.56 (m, 3H), 7.51 (dt, *J* = 0.8, 7.2 Hz, 1H), 7.10 (d, *J* = 1.6 Hz, 1H), 7.09 (d, *J* = 1.6 Hz, 1H), 5.41 (s, 2H);

$^{13}$C NMR (75.47 MHz, DMSO-$d_6$): δ 167.6, 163.4, 160.0, 158.6, 155.4, 153.7, 143.7, 141.6, 138.4, 137.2, 135.8, 135.1, 134.3, 133.4, 132.5, 130.9, 130.5, 130.2, 129.0, 128.1, 127.9, 127.8, 121.7, 121.2, 119.1, 115.0, 67.4; ESI-MS: *m/z*, 511 $(M+H)^{+.}$

**2-((4-(1,8-Naphthyridin-2-yl)phenoxy)methyl)-N-(4-bromophenyl)benzamide (10h)**
Yield: 76%; Off-white solid; m.p: 221-225 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 10.58 (s, 1H), 9.05 (dd, *J* = 2.0, 4.0 Hz, 1H), 8.48 (d, *J* = 8.8 Hz, 1H), 8.43 (dd, *J* = 2.0, 4.0 Hz, 1H), 8.25 (d, *J* = 2.0 Hz, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 1.6 Hz, 1H), 7.71 (d, *J* = 1.6 Hz, 1H), 7.67 – 7.54 (m, 4H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.50 (d, *J* = 3.2 Hz, 2H), 7.11 (d, *J* = 1.6 Hz, 1H), 7.10 (d, *J* = 1.6 Hz, 1H), 5.40 (s, 2H), $^{13}$C NMR (75.47 MHz, DMSO-$d_6$): δ 167.2, 164.4, 162.4, 160.0, 159.5, 158.6, 157.7, 155.4, 153.7, 148.4, 139.2, 138.5, 137.2, 136.8, 135.9, 131.4, 130.1, 129.0, 128.7, 128.1, 127.8, 123.4, 121.7, 121.2, 119.1, 115.2, 115.0, 67.3;
ESI-MS: *m/z*, 510 $(M+H)^{+.}$




Scheme-3: Reagents and conditions: (g) $K_2CO_3$, acetone, 55 °C, 6h; (h) KOH, EtOH, Water, 70 °C 16h; (i) TFA, DCM, rt, 6h.

**Synthesis of *Tert*-butyl 2-((3-acetylphenoxy)methyl)benzoate (12)**
Yield: 65%; Off-white solid; m.p: 71-75 °C; $^1$H NMR (500 MHz, $CDCl_3$): δ 7.96 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 2.0 Hz, 1H), 7.54 (dt, *J* = 1.0, 7.5 Hz, 1H), 7.51 (td, *J* = 1.5, 9.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.18 (dd, *J* = 2.5, 8.5 Hz, 1H), 5.49 (s, 2H), 2.58 (s, 3H), 1.59 (s, 9H); ESI-MS: *m/z*, 327 $(M+H)^{+.}$

**Synthesis of *Tert*-butyl 2-((3-(1,8-naphthyridin-2-yl)phenoxy)methyl)benzoate (13)**
Yield: 45%; Off-white solid; m.p: 168-171 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 9.29 (dd, *J* = 2.0, 5.0 Hz, 1H), 8.98 (dt, *J* = 1.5, 6.0 Hz, 1H), 8.81 (dd, *J* = 1.5, 8.5 Hz, 1H), 8.53 (d, *J* = 8.5 Hz, 1H), 8.01 (t, *J* = 1.5 Hz, 1H), 7.98 – 7.94 (m, 2H), 7.85 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.71 (t, *J* = 7.0 Hz, 1H), 7.61 (dd, *J* = 1.5, 5.0 Hz, 1H), 7.56 (dt, *J* = 3.0, 11.0 Hz, 1H), 7.48 (dt, *J* = 1.0, 8.5 Hz, 1H), 7.23 (dt, *J* = 2.0, 8.5 Hz, 1H), 5.49 (s, 2H), 1.49 (s, 9H); $^{13}$C NMR (125.77 MHz, DMSO-$d_6$): δ 168.1, 166.0, 160.8, 159.0, 150.4, 143.3, 139.4, 138.3, 137.8, 136.7, 132.1, 131.8, 131.1, 130.4, 129.0, 128.1, 122.5, 121.7, 120.6, 117.4, 113.8, 81.3, 68.0, 27.7; ESI-MS: *m/z*, 413 $(M+H)^{+.}$

**Synthesis of 2-((3-(1,8-Naphthyridin-2-yl)phenoxy)methyl)benzoic acid (14)**
Yield: 50%; Off-white solid; m.p: 169-173 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): δ 9.14 (dd, *J* = 1.5, 4.5 Hz, 1H), 8.61 (d, *J* = 8.5 Hz, 1H), 8.59 (dd, *J* = 1.5, 8.5 Hz, 1H), 8.33 (d, *J* = 8.5 Hz, 1H), 7.98 (t, *J* = 2.0 Hz, 1H), 7.95 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.70 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.62 (dt, *J* = 1.0, 8.5 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.18 (dd, *J* = 2.5, 8.0 Hz, 1H), 5.58 (s, 2H); $^{13}$C NMR (125.77 MHz, DMSO-$d_6$): δ 168.1, 159.1, 158.9, 153.2, 152.6, 139.4, 138.9, 138.6, 138.0, 132.1, 130.4, 130.2, 129.5, 128.1, 127.7, 122.2, 121.9, 120.1, 116.8, 113.5, 81.5, 67.7; ESI-MS: m/z, 357 $(M+H)^{+.}$

## RESULTS AND DISCUSSION

2-methyl benzoic acid **(1)** in DMF was treated with *tert*-butanol, di-tert-butyl dicarbonate and dimethyl amino pyridine to afford *tert*-butyl 2-methylbenzoate **(2)** which was reacted with N-bromo succinimide, azoisobutyronitrile to give *tert*-butyl 2-(bromomethyl)benzoate **(3)**, this product on treatment with 1-(3/4-hydroxyphenyl)ethanone **(4)** in acetone and potassium carbonate at 55 °C to afforded *tert*-butyl 2-((3/4-acetylphenoxy)methyl)benzoate **(5)**, Compound **5** was reacted with 2-aminonicotinaldehyde **(6)** in ethylalcohol with potassium hydroxide at 75 °C to afford *tert*-butyl 2-((3/4-(1,8-naphthyridin-2-yl)phenoxy)methyl)benzoate **(7)**, further treated with triflouro aceticacid in dichloromethane to get 2-((3/4-(1,8-naphthyridin-2-yl)phenoxy)methyl)benzoic acid **(8)**. The obtained acid product was reacted with corresponding anilines **(9a-9h)** in presence of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride and dimethyl amino pyridine in dimethyl formamide, tetrahydrofuran at room temperature to afford the corresponding 2-((4-(1,8-naphthyridin-2-yl)phenoxy)methyl)-N-phenylbenzamide derivatives **(10a-10h)**. It is observed that, the title compounds shown significant activity towards all bacteria compared to earlier reports.[10,12]

### Biological assay

The synthesized compounds were dissolved in dimethylsulphoxide at 20µg/10µL concentration (standard antibacterial drug, Ampicilline was used as the reference antibiotic) and tested against Gram negative strains of (1) *Escherichia coli*, (2) *Klebsiella pneumonia* and Gram positive strains of (3) *Staphylococcus aureus* and (4) *Bacillus subtilis* using agar well diffusion method. Activity was determined by zones showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control. All the samples were taken in triplicates.

### Antibacterial activity

These newly synthesized compounds were evaluated for their antibacterial activity against two Gram negative and two Gram positive bacterial strains viz., *Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus* and *Bacillus subtilis*. The outcomes of the results are summarized in Table-1 and ampicilline was used as positive control. The in vitro screening results revealed that some of the compounds possess considerable antibacterial activity.

It is observed that compounds **10d** and **10g** revealed excellent antibacterial activity with a zone of inhibition 2-6 mm against *Escherichia coli, Klebsiella pneumonia, Staphylococcus aureus* and *Bacillus subtilis*. The activity shown by synthesized compounds are presented in Table-1 and a comparative study was done on the chart (Fig.-1).

Table-1: Antimicrobial Activity of 2-((4-(1,8-naphthyridin-2-yl)phenoxy)methyl)-N-phenylbenzamide Derivatives

| S. No. | Compound Name | *E.coli* | *Staphylococcus aureus* | *Klebsiella pneumonia* | *Bacillus subtilis* |
|---|---|---|---|---|---|
| 1 | 10a(20µg/10µl) | 1 | 2 | 1 | 1 |
| 2 | 10b(20µg/10µl) | 2 | 5 | 1 | - |
| 3 | 10c(20µg/10µl) | 2 | 3 | 2 | 2 |
| 4 | 10d(20µg/10µl) | 5 | 4 | 4 | 5 |
| 5 | 10e(20µg/10µl) | 2 | 3 | 1 | 4 |
| 6 | 10f(20µg/10µl) | 1 | 1 | 3 | 1 |
| 7 | 10g(20µg/10µl) | 3 | 3 | 2 | 3 |
| 8 | 10h(20µg/10µl) | 2 | 3 | 4 | 2 |
| | Ampllicine (20µg/10µl) | 14 | 15 | 13 | 15 |

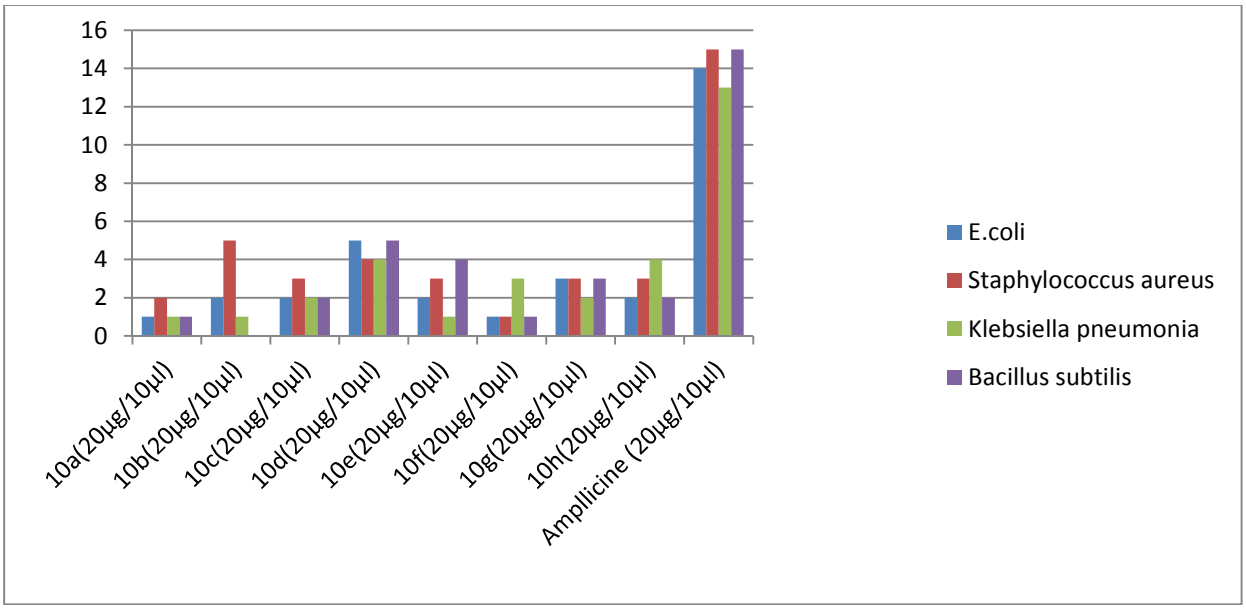



Fig.-1: Antimicrobial Activity of 2-((4-(1,8-naphthyridin-2-yl)phenoxy)methyl)-N-phenylbenzamide Derivatives

## REFERENCES

1. A. R.Katritzky, C.W.Rees, *Comprehensive Heterocyclic Chemistry*, Pergamon: Oxford, Part 2B, 3, 157, (1984).
2. D. Sherman, J. Kawakami, H. Y. He, F. Dhun, R. Rios, H. Liu, W. Pan, Y. J. Xu, S. P.Hong, M. Arbour, M. Labelle, M. A. J. Duncton, *Tetrahedron Lett.,***48**, 8943, (2007).
3. M. Loriga, S. Piras, P. Sanna, G. Paglietti, *Farmaco,* **52**, 157, (1997).
4. L. E. Seitz, W.J. Suling, R.C. Reynolds, *J. Med. Chem.*, **45**, 5604, (2002).
5. K. YB, K. YH, P. JY, K. SK, *Bioorg. Med. Chem. Lett.,* **14**, 541, (2004).
6. X. Hui, J. Desrivot, C. Bories, P.M. Loiseau, X. Franck, R. Hocquemiller, B. Figadere, *Bioorg. Med. Chem. Lett.,* **16**, 815, (2006).
7. C.W. Lindsley, Z. Zhao, W. H. Leister, R.G. Robinson, S.F. Barnett, D. Defeo-Jones, R.E. Jones, G. D. Hartman, J. R. Huff, H. E. Huber, M. E. Duggan, *Bioorg. Med. Chem. Lett*., **15**, 761, (2005).
8. D. V. Labarbera, E.B. Skibo, *Bioorg. Med. Chem.*, **13**, 387, (2005).
9. H. Egawa, A. Miyamido, Y. Nishimra, H. Okada, H. Uno, J. Matsumato, *J. Med. Chem.,* **27**, 1543, (1984).
10. J. Nezval, J. Halocka, *Experientia,* **23**, 1043, (1967).
11. E. M. Hawes, *J. Med. Chem.*, **20**, 124, (1977).
12. N. Suzuki, *Chem. Pharma. Bull.,* **28**, 761, (1980).
13. N. Suzuki, R. Dohmori, *Chem. Pharma*. Bull., **27**, 410, (1979).
14. G. B. Balin, W.L. Tan, *Aust. J. Chem.,* **37**, 1065, (1984).

[RJC-1920/2017]