



## Microwave Assisted Synthesis and Antimicrobial Activity of 1-(2-Chloropyridin-3-yl)-3-substituted Urea Derivatives

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A green one pot synthetic protocol method for 1-(2-chloropyridin-3-yl)-3-substituted urea derivatives from 2-chloropyridin-3-amine and *tert*-butyl substituted carbamates by using *bis*(trimethylaluminum)-1,4-diazabicyclo[2,2,2]octane (DABAL-Me<sub>3</sub>) under microwave irradiation is developed. The compound structures established by spectral data such as IR, <sup>1</sup>H NMR and mass spectroscopy. All the synthesized compounds were tested *in vitro* antimicrobial activity.

**Keywords:** 2-Chloropyridinyl urea derivatives, Microwave irradiation method, Antimicrobial activity.

### INTRODUCTION

The aryl urea derivatives exhibit a broad spectrum of biological activities such as antitumor [1], antimalarial [2], antidiabetic [3], anti-HIV [4], analgesic [5], antitubercular [6], antimicrobial [7], anti-inflammatory [8] and antiproliferative [9] activities. The urea derivatives are also having diverse applications in various fields including as pharmaceuticals, agrochemicals, petrochemical, organocatalysis [10,11] and also used as dyes for cellulose fiber and hair, in detergents, corrosion inhibitors and additives in fuels [12].

Furthermore, there are several diaryl urea derivatives are on clinical trial or have been used clinically such as sorafenib, regorafenib, linifanib, tivozanib and lenvatinib. Sorafenib is active against cancer activity [13], regorafenib is used for treatment for colorectal cancer and gastrointestinal stromal tumors [14]. Lenvatinib is a multireceptor tyrosine kinase inhibitor and to treat recurrent or metastatic, progressive, radioactive iodine refractory differentiated thyroid cancer [15]. Tivozanib is an inhibitor of vascular endothelial growth factor receptors and metastatic renal cell carcinoma [16]. Linifanib is active against advanced hepatocellular carcinoma [17]. Additionally, methods have reported for the synthesis of urea derivatives such as in general conversion of an amine to isocyanate or carbamate followed

by substitution amine [18], reaction of amine with phosgene derivative like triphosgene [19], oxidation of isonitrile and palladium catalyzed cross coupling of aryl chloride *via* isocyanate intermediate [20] and AlMe<sub>3</sub> [21]. The reported methods have inherent limitations such as narrow or limited substrate availability, use of corrosive chemicals and multistep reactions and trialkyl alanes have potential risks of pyrophoric character [22]. It suggests that the reaction of carbamates with an amine is more attractive.

In recent years, reports on the microwave assisted organic synthesis reaction condition is promising alternative to conventional methods as these reactions represent clean, effective, safe, economical and eco-friendly procedure and is believed to be a step towards green chemistry [23]. In view of the synthetic methods, biological activity of urea derivatives and importance of *bis*(trimethylaluminum)-1,4-diazabicyclo[2,2,2]octane (DABAL-Me<sub>3</sub>), we have developed a green one pot synthetic protocol for 1-(2-chloropyridin-3-yl)-3-substituted urea derivatives by using DABAL-Me<sub>3</sub> under conventional heating and microwave irradiation method.

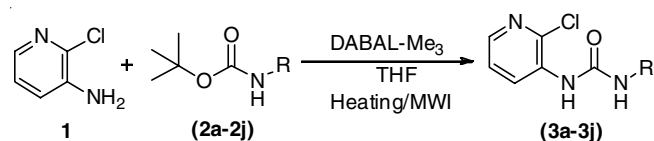
### EXPERIMENTAL

The melting points were determined in open capillary tube and are uncorrected. Purity of the compounds was checked

by TLC on silica gel 60 F<sub>254</sub> (Merck). Microwave reactions were carried out in a multiSYNTH series microwave system (Milestone). <sup>1</sup>H NMR spectra were recorded on Varian VNMRS-400 spectrometer using TMS as an internal standard (chemical shifts in δ ppm). IR spectra were recorded in KBr on a Perkin-Elmer 1800 spectrometer and mass spectra were recorded on a GCMS-QP 1000 mass spectrometer.

### General synthetic procedure of 1-(2-chloropyridin-3-yl)-3-substituted urea derivatives (3a-j):

**Conventional heating method:** A solution of 2-chloropyridin-3-amine (**1**, 1 mmol) and *tert*-butyl substituted carbamates (**2a-j**) (1 mmol) in THF (10 mL) and catalytic amount of *bis*(trimethylaluminum)-1,4-diazabicyclo[2,2,2]octane (DABAL-Me<sub>3</sub>) was taken into round bottom flask then stirred at 80 °C for 2 h. The reaction was monitored by TLC, after completion of reaction, it was quenched with 1 N HCl and neutralized with 10 % NaHCO<sub>3</sub> solution. The compound extracted with ethyl acetate twice (2 × 20 mL), then extracted solvent washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and purified by column chromatography to afford pure compounds (**3a-j**) (Scheme-I). The physical data of the synthesized compounds are given in Table-1.



Scheme-I: Synthesis of 1-(2-chloropyridin-3-yl)-3-substituted urea derivatives (**3a-j**)

**Microwave irradiation method:** A mixture of 2-chloropyridin-3-amine (**1**, 1 mmol) and *tert*-butyl substituted carbamates (**2a-j**) (1 mmol) in THF (2 mL) and catalytic amount of *bis*(trimethylaluminum)-1,4-diazabicyclo[2,2,2]octane (DABAL-Me<sub>3</sub>) was taken into quartz tube and subjected to microwave irradiation at 300 watts for 5-10 min with an every 30 s intervals. The reaction was monitored by TLC, after completion of reaction, it was quenched with 1 N HCl and neutralized with 10 % NaHCO<sub>3</sub> solution. The compound extracted with ethyl acetate (2 × 20 mL), then the extracted solvent washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and purified by column chromatography to afford pure compounds (**3a-j**).

**Antibacterial activity:** The compounds **3a-j** were tested *in vitro* antibacterial activity against four bacterial organisms such as *B. faecalis*, *S. aureus*, *K. pneumonia* and *E. coli*, ampicillin used as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm at the concentration 100 µg/mL in DMSO. The synthesized compounds **3g**, **3e** and **3i** showed good activity against the tested bacterial organisms and the remaining compounds showed low to moderate activity against the tested organisms with comparison with standard drug ampicillin (Table-2).

**Antifungal activity:** The compounds **3a-j** were tested *in vitro* antifungal activity against *Aspergillus niger* and *Candida metapsilosis* using grieseofulvin as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm at the concentration 500 µg/mL in DMSO. The synthesized compounds **3a**, **3e** and **3i**

TABLE-1  
PHYSICAL DATA OF 1-(2-CHLOROPYRIDIN-3-YL)-3-SUBSTITUTEDUREA DERIVATIVES (**3a-j**)

Compd. No.	R	m.p. (°C)	Conventional		MWI	
			Reaction time (h)	Yield (%)	Reaction time (h)	Yield (%)
<b>3a</b>	3-Methoxy phenyl	196-199	2	86	8	95
<b>3b</b>	6-Methylpyridin-3-yl	186-190	2	84	8	92
<b>3c</b>	2,3-Dimethylphenyl	198-200	2	81	10	93
<b>3d</b>	3-Fluorophenyl	183-186	2	84	6	92
<b>3e</b>	2-Fluoro-4-methoxyphenyl	195-198	2	80	8	90
<b>3f</b>	3-(Trifluoromethyl)phenyl	189-192	2	82	10	93
<b>3g</b>	2-(( <i>tert</i> -Butyldimethylsilyl)oxy)ethyl	187-190	2	86	10	95
<b>3h</b>	5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl	188-190	2	84	7	96
<b>3i</b>	Cyclopropyl	130-133	2	84	5	93
<b>3j</b>	Indoline-1-carboxylate	183-186	2	87	10	95

TABLE-2  
ANTIMICROBIAL ACTIVITY OF 1-(2-CHLOROPYRIDIN-3-YL)-3-SUBSTITUTEDUREA DERIVATIVES (**3a-j**)

Compd. No.	<i>B. faecalis</i>	<i>S. aureus</i>	<i>K. pneumoniae</i>	<i>E. coli</i>	<i>A. niger</i>	<i>F. oxysporum</i>
<b>3a</b>	11.5	16.2	18.8	15.5	8.6	11.0
<b>3b</b>	16.7	14.6	11.9	12.6	5.2	10.8
<b>3c</b>	10.8	13.6	22.1	11.6	6.1	9.6
<b>3d</b>	9.8	12.1	13.6	16.1	6.0	8.9
<b>3e</b>	20.4	14.8	12.9	14.7	8.8	10.2
<b>3f</b>	12.3	11.6	14.9	17.3	7.3	11.8
<b>3g</b>	18.7	16.3	12.8	11.9	6.9	13.6
<b>3h</b>	15.6	11.3	19.9	20.0	4.7	7.6
<b>3i</b>	22.4	13.1	24.3	24.3	9.0	12.3
<b>3j</b>	16.3	14.2	14.4	19.9	7.8	10.1
Ampicillin	33.4	20.2	35.8	33.5	–	–
Grieseofulvin	–	–	–	–	13.4	18.6

showed good activity against tested fungal organisms and the remaining synthesized compound showed low to moderate antifungal activity (Table-2).

### Spectral data

#### 1-(2-Chloropyridin-3-yl)-3-(3-methoxyphenyl)urea (3a):

Off-white solid. Elemental analysis of calcd. (found) % for  $C_{13}H_{12}N_3O_2Cl$ : C 56.22 (56.18); H 4.36 (4.30); N 15.13 (15.08). IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3309 (N-H), 1625 (C=O).  $^1H$  NMR  $\delta$  ppm: 3.75 (s, 3H), 6.65 (dd,  $J = 8.2$  Hz, 1H), 6.87 (dd,  $J = 8.2$  Hz, 1H), 7.05 (d,  $J = 7.5$  Hz, 1H), 7.19-7.22 (m, 1H), 7.64 (s, 1H), 8.01 (d,  $J = 8.0$  Hz, 1H), 8.08 (s, 1H), 8.60 (d,  $J = 6.5$  Hz, 1H); MS:  $m/z$ : 278 [M+1] $^+$ .

#### 1-(2-Chloropyridin-3-yl)-3-(6-methylpyridin-3-yl)urea (3b):

Off-white. Elemental analysis of calcd. (found) % for  $C_{12}H_{11}N_4OCl$ : C 54.87 (54.80); H 4.22 (4.25); N 21.33 (21.35). IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3322 (N-H), 1631 (C=O).  $^1H$  NMR  $\delta$  ppm: 2.40 (s, 3H), 7.19 (d,  $J = 8.4$  Hz, 1H), 7.40 (d,  $J = 8.2$  Hz, 1H), 7.81 (d,  $J = 8.36$  Hz, 1H), 8.05 (d,  $J = 2.8$  Hz, 1H), 8.47 (s,  $J = 2.5$  Hz, 1H), 8.51 (d,  $J = 8.16$  Hz, 1H), 9.29 (s, 1H, NH), 9.60 (s, 1H, NH); MS:  $m/z$ : 263 [M+1] $^+$ .

#### 1-(2-Chloropyridin-3-yl)-3-(2,3-dimethylphenyl)urea (3c):

Cream colour solid. Elemental analysis of calcd. (found) % for  $C_{14}H_{14}N_3OCl$ : C 60.98 (60.94); H 5.12 (5.10); N 15.24 (15.29). IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3316 (N-H), 1618 (C=O).  $^1H$  NMR  $\delta$  ppm: 2.14 (s, 3H), 2.24 (s, 3H), 6.86-7.06 (m, 2H), 7.35-7.51 (m, 2H), 8.01 (d,  $J = 4.6$  Hz, 1H), 8.51 (d,  $J = 8.1$  Hz, 1H), 8.69 (s, 1H, NH), 8.78 (s, 1H, NH); MS:  $m/z$ : 276 [M+1] $^+$ .

#### 1-(2-Chloropyridin-3-yl)-3-(3-fluorophenyl)urea (3d):

Pale cream solid. Elemental analysis of calcd. (found) % for  $C_{12}H_9N_3OClF$ : C 54.25 (54.22); H 3.41 (3.37); N 15.82 (15.80). IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3330 (N-H), 1620 (C=O).  $^1H$  NMR  $\delta$  ppm: 6.81 (m, 1H), 7.09-7.11 (m, 1H), 7.30-7.51 (m, 3H), 7.96 (d,  $J = 4.6$  Hz, 1H), 8.47-8.53 (m, 2H), 9.70 (s, 1H, NH); MS:  $m/z$ : 266 [M+1] $^+$ .

**1-(2-Chloropyridin-3-yl)-3-(2-fluoro-4-methoxyphenyl)urea (3e):** Off-white solid. Elemental analysis of calcd. (found) % for  $C_{13}H_{11}N_3O_2ClF$ : C 52.80 (52.87); H 3.75 (3.70); N 14.21 (14.18). IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3319 (N-H), 1622 (C=O).  $^1H$  NMR  $\delta$  ppm: 3.80 (s, 3H), 7.06-7.14 (m, 2H), 7.40 (d,  $J = 8.0$  Hz, 1H), 7.47 (d,  $J = 10.0$  Hz, 1H), 8.04 (d,  $J = 4.4$  Hz, 1H), 8.47 (s, 1H, NH), 8.53 (d,  $J = 8.4$  Hz, 1H), 9.57 (s, 1H, NH); MS:  $m/z$ : 296 [M+1] $^+$ .

**1-(2-Chloropyridin-3-yl)-3-(3-(trifluoromethyl)phenyl)urea (3f):** Off-white solid. Elemental analysis of calcd. (found) % for  $C_{13}H_9N_3OClF_3$ : C 49.46 (49.51); H 2.87 (2.90); N 13.31 (13.26). IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3312 (N-H), 1618 (C=O).  $^1H$  NMR  $\delta$  ppm: 7.34-7.42 (m, 2H), 7.55 (d,  $J = 5.2$  Hz, 2H), 8.03-8.07 (m, 2H), 8.51 (s, 1H, NH), 8.53 (t,  $J = 6.5$  Hz, 1H), 9.83 (s, 1H, NH); MS:  $m/z$ : 316 [M+1] $^+$ .

**1-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-3-(2-chloropyridin-3-yl)urea (3g):** Cream colour solid. Elemental analysis of calcd. (found) % for  $C_{14}H_{24}N_3O_2ClSi$ : C 50.97 (50.90); H 7.33 (7.38); N 12.74 (12.70). IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3308 (N-H), 1628 (C=O).  $^1H$  NMR  $\delta$  ppm: 0.04 (s, 6H), 0.86 (s, 9H), 3.20 (q, 2H), 3.16 (t,  $J = 5.6$  Hz, 2H), 7.13 (s, 1H, NH), 7.32 (d,  $J = 8.1$  Hz, 1H), 7.95 (d,  $J = 4.6$  Hz, 1H), 8.26 (s, 1H, NH), 8.48 (d,  $J = 8.2$  Hz, 1H); MS:  $m/z$ : 330 [M+1] $^+$ .

**1-(2-chloropyridin-3-yl)-3-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)urea (3h):** Pale cream solid. Elemental analysis of calcd. (found) % for  $C_{15}H_{12}N_5O_3Cl$ : C 52.11 (52.06); H 4.50 (3.44); N 20.26 (20.33). IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3311 (N-H), 1621 (C=O).  $^1H$  NMR  $\delta$  ppm: 3.84 (s, 3H), 7.14 (d,  $J = 7.8$  Hz, 2H), 7.47 (t,  $J = 7.6$  Hz, 1H), 7.84 (s,  $J = 8.0$  Hz, 2H), 8.15 (d,  $J = 7.6$  Hz, 1H), 8.58 (d,  $J = 7.7$  Hz, 1H), 10.0 (s, 1H, NH), 11.67 (s, 1H, NH); MS:  $m/z$ : 346 [M+1] $^+$ .

**1-(2-Chloropyridin-3-yl)-3-cyclopropylurea (3i):** Off-white. Elemental analysis of calcd. (found) % for  $C_9H_{10}N_3OCl$ : C 51.07 (51.02); H 4.76 (4.30); N 19.85 (19.89). IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3318 (N-H), 1615 (C=O).  $^1H$  NMR  $\delta$  ppm: 0.42 (m, 3H), 0.65 (m, 2H), 2.55 (s, 1H), 7.27 (s, 1H, NH), 7.33 (d,  $J = 8.2$  Hz, 1H), 7.95 (t,  $J = 6.3$  Hz, 1H), 8.00 (s, 1H, NH), 8.50 (d,  $J = 8.2$  Hz, 1H); MS:  $m/z$ : 212 [M+1] $^+$ .

**N-(2-Chloropyridin-3-yl)indoline-1-carboxamide (3j):** Off-white solid. Elemental analysis of calcd. (found) % for  $C_{14}H_{12}N_3OCl$ : C 61.43 (61.48); H 4.42 (4.40); N 15.35 (15.31). IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3320 (N-H), 1619 (C=O).  $^1H$  NMR  $\delta$  ppm: 3.21 (t,  $J = 8.8$  Hz, 2H), 4.16 (t,  $J = 8.8$  Hz, 2H), 6.93 (t,  $J = 7.6$  Hz, 1H), 7.13 (t,  $J = 8.0$  Hz, 1H), 7.23 (d,  $J = 7.6$  Hz, 1H), 7.44-7.48 (m, 1H), 7.84 (s,  $J = 8.0$  Hz, 1H), 8.09-8.11 (m, 1H), 8.23 (d,  $J = 2.8$  Hz, 1H), 8.36 (s, 1H, NH); MS:  $m/z$ : 274 [M+1] $^+$ .

## RESULTS AND DISCUSSION

The title compounds (**3a-3j**) were synthesized from 2-chloropyridin-3-amine (**1**) and *tert*-butyl substituted carbamates (**2a-2j**) by using DABAL-Me<sub>3</sub> under both conventional stirring and microwave irradiation methods, the microwave irradiation method proved to be a easy with shorter reaction time with higher yields (Table-1). The structure of compounds (**3a-3j**) was established on the basis of spectral data. In IR spectrum, the compounds showed characterizing stretching frequencies around 3320 and 1620  $cm^{-1}$  which are corresponds to N-H and C=O groups, respectively. In  $^1H$  NMR spectrum, the compounds shows characterizing two N-H protons showed at  $\delta$  8 ppm and above while in mass spectrometry the compounds showed their  $m/z$  proton peaks.

### Conclusion

We successfully synthesized 1-(2-chloropyridin-3-yl)-3-substitutedurea derivatives from 2-chloropyridin-3-amine and *tert*-butyl substituted carbamates by using DABAL-Me<sub>3</sub> under conventional heating and microwave irradiation method. The microwave method proved an easy, reduces reaction times with higher yields and all the synthesised compounds showed good antimicrobial activity against the organism.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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