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ANTIMICROBIAL ACTIVITY AND MICROWAVE ASSISTED SYNTHESIS OF 4-CHLOROPHENYL UREA DERIVATIVES BY USING DABAL-Me_3

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ABSTRACT:

A series of 4-Chlorophenyl urea derivatives have been synthesized from tert-butyl (4-chlorophenyl)carbamate with primary and secondary amines by using DABAL-Me_3 under conventional and microwave irradiation. All the synthesized compounds characterized by using spectral data such as IR, ^{1}H NMR, mass spectroscopy and evaluated there in vitro antimicrobial activity.

KEYWORDS: 4-Chlorophenyl urea, DABAL-Me_3, microwave irradiation, antimicrobial activity.

INTRODUCTION:

Urea and its derivatives are display a wide range of biological activities including as antioxidant[I], antiviral[II], anti-inflammatory[III], antimalarial[IV,V], anti-HIV[VI], pesticides[VII], herbicides[VIII] acativities and also used as inhibitors in the corrosion[IX], catalysts in various chemical reactions[X], HIV-1 protease inhibitors, endothelin antagonists, p38-MAP kinase inhibitors and antioxidants in gasoline[XI]. Peptide mimetic compounds containing urea functionality nowadays have drawn much attention due to urea bond is not vulnerable to proteolytic cleavage[XII,XIII]. Sorafenib, Regorafenib, Linifanib and Lenvatinib **(Figure-1)** are urea derivatives on clinical trial or have been used clinically. Moreover, in previous methods used to synthesize urea derivatives were associated with long reactions times, tedious work up procedures, low yields, and are non-eco-friendly in nature. Environment-friendly chemical process is the vital part of the current chemical research and development. The microwave assisted organic synthesis is promising alternative to conventional methods and the microwave method is believed to be a step towards green chemistry

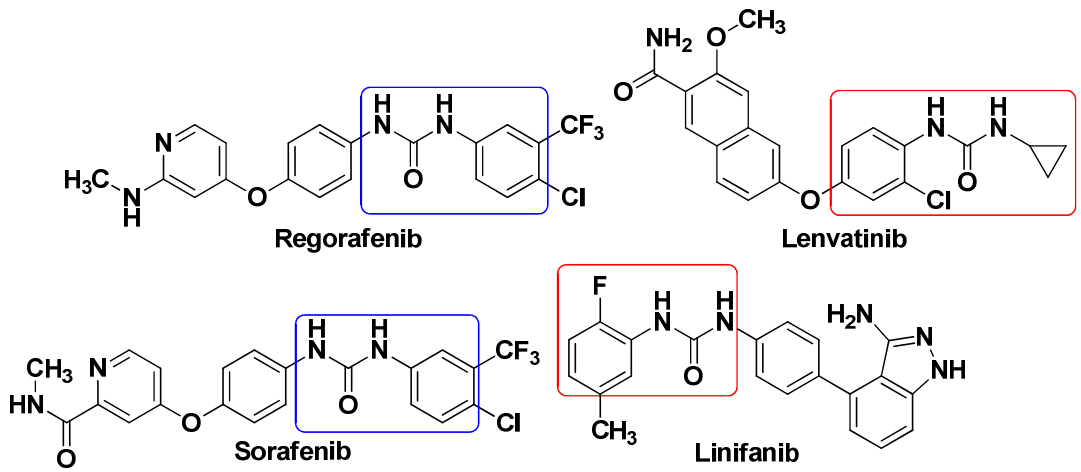


Figure-1: Some of the important urea derivative related to synthesized compounds.

In view of aryl urea derivatives synthetic methods and advantage of DABAL-Me_3 (being solid, non-pyrophoric, air stable, easy handled and keeps inert atmosphere or drying of solvents)[20] we have planned to synthesizes aryl urea derivatives under microwave irradiation method by using DABAL-Me_3 and compared the yields with conventional heating method **(Table-1)**. The microwave method proved that reaction carried out low reaction times with higher yields and more eco-friendly nature.

Scheme-1: Synthesis of 4-Chlorophenyl urea derivatives (3a-k).

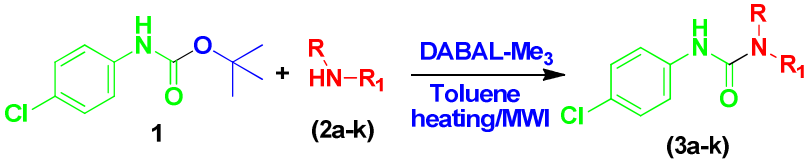
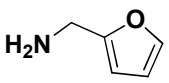
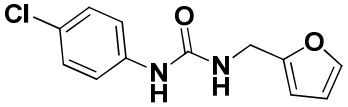
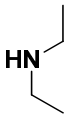
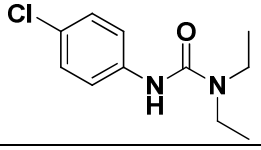
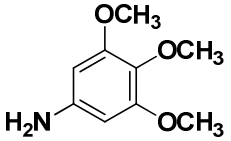
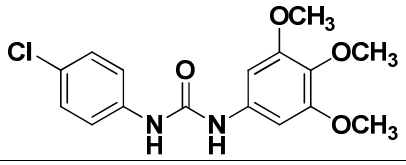
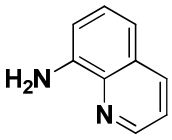
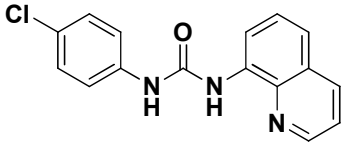
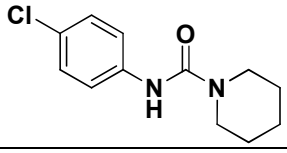
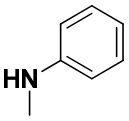
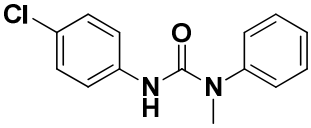
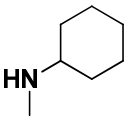
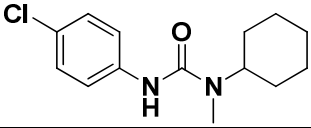
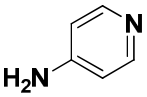
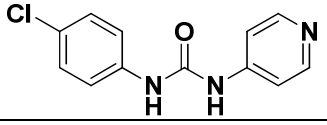
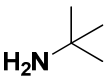
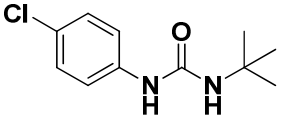
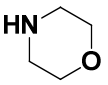
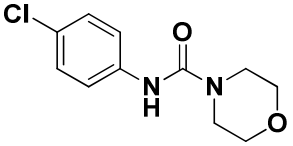
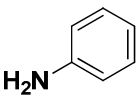
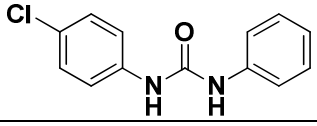


Table-1: Physical data of 4-Chlorophenyl urea derivatives

Entry	Compounds (2a-k)	Compounds (3a-k)	m.p. (°C)	% Yield	
				Conv. heating	MWI
3a			179-182	82	95
3b			122-124	85	98
3c			185-188	80	95
3d			180-183	83	96

3e			136-139	78	92
3f			182-185	81	95
3g			188-190	81	95
3h			225-228	85	98
3i			174-177	82	95
3j			183-186	81	96
3k			180-183	79	95

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC using precoated silica gel plates 60_{254}(Merck). Microwave reactions were carried out in milestone multi SYNTH microwave system. IR (KBr) spectra were recorded on a Shimadzu FT-IR-8400s spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer using tetra-methylsilane as an internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer.

ANTIMICROBIAL ACTIVITY

Antibacterial activity:

All the compounds were screened for their *in vitro* antibacterial activity against *Escherichia coli,* and *Staphylococcus aureus* using ampicillin as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm. The compounds were screened at the concentrations of 20 and 40 µg/ml in DMSO. The screening studies it is evident that the synthesized compounds **3i** and **3j** showed good antibacterial activity against both tested organisms.

Antifungal activity:

All the compounds were screened for their antifungal activity *in vitro* 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. The compounds were screened at the concentrations of 100 and 200 µg/ml in DMSO. The screening studies it is evident that the synthesized compounds **3h, 3i** and **3j** showed good antibacterial activity against both tested fungal organisms.

General Procedure for the Synthesis of Compounds (3a-k):

Conventional heating method:

To a stirred solution of *tert*-butyl(4-chlorophenyl)carbamate **1** (1 mmol), corresponding amine **(2a-k)** (1 mmol) and DABAL-Me_3 (1.5 mmol) in Toluene (10 ml) was heated to 100 ℃ and stirred for 3 hr at 100 °C. Monitor the reaction progress by TLC, after completion of the reaction, cooled to RT, quenched with 1N HCl and neutralized with 10% $NaHCO_3$ solution. Extract the compound with EtoAc (2 x 20 mL) followed by water washing, dried over Na_2SO_4 and concentrated under reduced pressure and purified by column chromatography to afford pure compounds (**3a-k).**

Microwave Irradiation method:

To a mixture of *tert*-butyl(4-chlorophenyl)carbamate **1** (1 mmol), corresponding amine **(2a-k)** (1 mmol) and DABAL-Me_3 (1.5 mmol) in Toluene (10 ml) was subjected to microwave irradiation at 160 W for 5-10 min. Monitor the reaction progress by TLC, after completion of the reaction, cooled to RT, quenched with 1N HCl and neutralized with 10% $NaHCO_3$ solution. Extract the compound with EtoAc (2 x 20 mL) followed by water washing, dried over Na_2SO_4 and concentrated under reduced pressure and purified by column chromatography to afford pure compounds (**3a-k).**

Spetral data:

1-(4-Chlorophenyl)-3-(furan-2-ylmethyl) urea (3a): Cream colour solid; IR (KBr, cm^{-1}): 3309 (N-H), 1625 (>C=O) and 1394 (-C-N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.67 (s, 1H, NH), 7.58 (t, J = 0.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.59 (bs, 1H, NH), 7.39 (d, J = 2.8 Hz, 1H), 6.26 (d, J = 3.2 Hz, 1H), 4.29 (d, J = 6.0 Hz, 2H); Mass (m/z): 251 (M+1).

3-(4-Chlorophenyl)-1, 1-diethylurea (3b): Off-white solid; IR (KBr, cm^{-1}): 3313 (N-H), 1655 (>C=O) and 1388 (-C-N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H, NH), 7.50 (d, J = 6.8 Hz, 2H), 7.25 (d, J = 6.8 Hz, 2H), 3.32 (q, 4H), 1.06 (t, J = 7.0 Hz, 6H); Mass (m/z): 227 (M+1).

1-(4-Chlorophenyl)-3-(3,4,5-trimethoxyphenyl) urea (3c): Off-white solid; IR (KBr, cm^{-1}): 3309 (N-H), 1625 (>C=O) and 1394 (-C-N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.84 (s, 1H, NH), 8.72 (s, 1H, NH), 7.47 (d, J = 6.8 Hz, 2H), 7.29 (d, J = 6.7 Hz, 2H), 6.78 (s, 2H), 3.73 (s, 6H), 3.59 (s, 3H); Mass (m/z): 337 (M+1).

1-(4-Chlorophenyl)-3-(quinoline-8-yl) urea (3d): Cream colour solid; IR (KBr, cm^{-1}): 3314 (N-H), 1633 (>C=O) and 1390 (-C-N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.99 (s, 1H, NH), 9.70 (s, 1H, NH), 8.66 (d, J = 4.2 Hz, 1H), 8.54 (t, J = 4.5 Hz, 1H), 8.39 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.2 Hz, 1H), 7.55 (m, 4H), 7.35 (d, J = 6.9 Hz, 1H); Mass (m/z): 298 (M+1).

N-(4-chlorophenyl) piperidine-1-carboxamide (3e): Off-white solid; IR (KBr, cm^{-1}): 3312 (N-H), 1635 (>C=O) and 1389 (-C-N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.54 (s, 1H, NH), 7.49-7.46 (m, 2H, Ar-H), 7.26-7.22 (m, 2H, Ar-H), 3.39 (m, 4H, N-CH_2), 3.39 (m, 4H, N-CH_2), 1.58-1.53 (m, 2H, CH_2), 1.49-1.44 (m, 4H, CH_2); Mass (m/z): 239 (M+1).

3-(4-Chlorophenyl)-1-methyl-1-phenylurea (3f): Off-white solid; IR (KBr, cm^{-1}): 3312 (N-H), 1635 (>C=O) and 1389 (-C-N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H, NH), 7.47-7.21 (m, 9H), 3.25 (s, 3H); Mass (m/z): 261 (M+1).

3-(4-Chlorophenyl)-1-cyclohexyl-1-methylurea (3g): White solid; IR (KBr, cm^{-1}): 3315 (N-H), 1631 (>C=O) and 1398 (-C-N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.29 (s, 1H,

NH), 7.49 (d, J = 6.8 Hz, 2H), 7.25 (d, J = 6.8 Hz, 2H), 3.98 (m, 1H), 2.78 (s, 3H), 1.76-1.05 (m, 10H);. Mass (m/z): 267 (M+1).

1-(4-Chlorophenyl)-3-(pyridine-4-yl) urea (3h): Cream colour solid; IR (KBr, cm^{-1}): 3318 (N-H), 1622 (>C=O) and 1398 (-C-N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.63 (s, 1H, NH), 9.85 (s, 1H, NH), 8.27 (d, J = 4.0 Hz, 1H), 7.83 (t, J = 7.1 Hz, 1H), 7.56-7.49 (m, 3H), 7.38 (d, J = 8.7 Hz, 2 H), 7.05 (d, J = 6.5 Hz, 1H);. Mass (m/z): 248 (M+1).

1-(tert-butyl)-3-(4-chlorophenyl) urea (3i): Off-white solid; IR (KBr, cm^{-1}): 3310 (N-H), 1622 (>C=O) and 1395 (-C-N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.73 (s, 1H, NH), 7.36 (d, J = 6.8 Hz, 1H), 7.20 (t, J = 6.8 Hz, 1H), 6.23 (s, 1H, NH), 1.25 (s, 9H); Mass (m/z): 227 (M+1).

N-(4-Chlorophenyl) morpholine-4-carboxamide (3j): Off-white solid; IR (KBr, cm^{-1}): 3312 (N-H), 1639 (>C=O) and 1391 (-C-N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.63 (s, 1H, NH), 7.48 (d, J = 6.8 Hz, 2H), 7.27 (d, J = 6.8 Hz, 2H), 3.59 (t, J = 5.0 Hz, 4H), 3.40 (t, J = 4.6 Hz, 4H); Mass (m/z): 241 (M+1).

1-(4-Chlorophenyl)-3-phenylurea (3k): Off-white solid; IR (KBr, cm^{-1}): 3321 (N-H), 1645 (>C=O) and 1390 (-C-N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.80 (s, 1H, NH), 8.69 (s, 1H, NH), 7.48-7.42 (m, 4H), 7.32-7.25 (m, 4H), 6.96 (t, J = 7.3 MHz, 1H); Mass (m/z): 247 (M+1).

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