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# Microwave assisted facile synthesis of amino pyrimidines bearing benzofuran and investigation of their antimicrobial activity

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2-acetylbenzofuran on treatment with substituted aldehydes under solvent free microwave irradiation affords the corresponding chalcones **2a-e**. The compounds **2a-e** on reaction with guanidine hydrochloride under microwave irradiation produce **3a-e**. The structures of the newly synthesized compounds have been established by elemental analysis and spectral data. The compounds **3a-e** have been evaluated for their antimicrobial activity.

**Keywords**: Benzofuran, chalcones, guanidine hydrochloride, amino pyrimidines, antimicrobial activity

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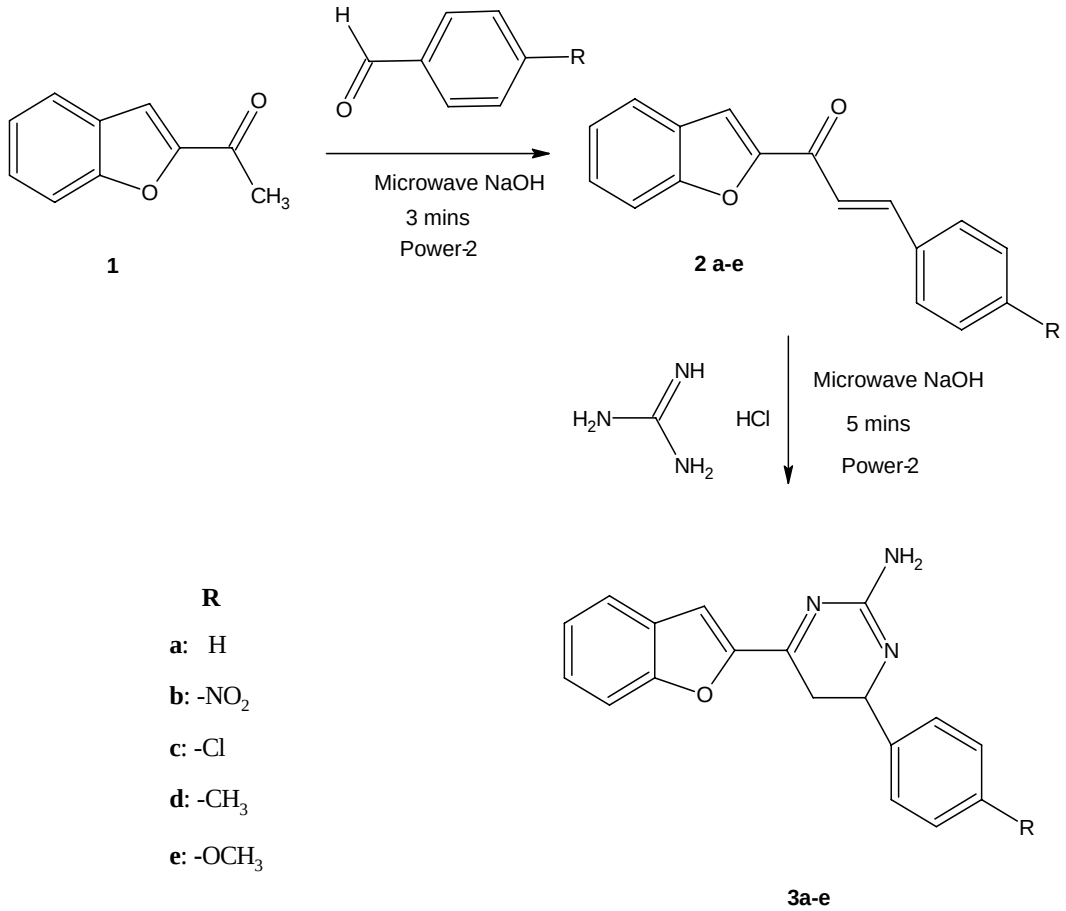
Nitrogen and oxygen containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activity. The pyrimidine derivatives have been reported to possess a variety of biological activity, notable among which are the analgesic[1], antihypertensive[2], antipyretic[3], antiviral[4] and anti-inflammatory activity[5]. These are also associated with nucleic acid, antibiotic, antimalarial and anticancer drugs[6]. Many of the pyrimidine derivatives are reported to possess potential CNS depressant properties[7]. Benzofuran derivatives, which are known to be present in many natural products[8], have physiological, pharmacological and toxic properties and find application as sedatives, hypnotics[9], agrochemicals[10], pharmaceuticals[11-16], cosmetics[17] and as the building blocks of optical brighteners[18]. Hence, there is continuing interest in their chemical synthesis. Cyclization reactions of various types have been used to produce substituted benzofurans[19-20]. The development of new synthetic approach is a challenge for the organic chemist. There are reports on the synthesis of pyrimidine derivatives by treating the chalcones with guanidine[21-22]. Hence, in the present paper is being reported a new and efficient method for the synthesis of substituted benzofuran derivatives containing pyrimidine ring at 2 position. This method is less time consuming and environmental friendly as compared to the existing conventional methods of synthesis.

The synthesis of key starting material 2-acetyl-benzofuran **1** from salicyl aldehyde with chloroacetone in presence of KOH in ethanol was reported earlier[23]. The benzofuro-3-arylprop-2-en-1-ones **2a-e** were prepared by irradiating **1** with microwave radiation in the presence of various aromatic aldehydes and NaOH under solvent free conditions (**Scheme I**). The IR spectrum of **2a** exhibited the absorption bands at 1650 (C=O), 1620 (C=C) and 1105-1115 $cm^{-1}$ (C-O-C). In the $^1H$ NMR spectrum ($CDCl_3$) doublets at δ 8.40 (1H, C=CH-Ar), δ 6.76-7.75 (10H, Ar-H) and at δ 6.45 (1H, -COCH=C) were observed. The mass spectrum showed molecular ion peak at m/z 248($M^+$) corresponding to its molecular weight. The IR, $^1H$ NMR and mass spectra of **2b-e** were in agreement with the structures. The irradiation of **2a** with




**Scheme I**

microwave radiation in presence of guanidine hydrochloride and base under solvent free conditions results in the formation of 6-(1-benzofuran-2-yl)-4-phenyl-4,5-dihydropyrimidin-2-amine **3a**. The IR spectrum of **3a** exhibited the absorption bands at 3350 ($-NH_2$) and 1550 $cm^{-1}$ (C=N). In its $^1H$ NMR, multiplets at δ 6.76-7.76 corresponding to 10 aromatic protons and a singlet at δ 5.36 due to $-NH_2$ group ($D_2O$ exchangeable) were observed. The new signals appeared as double doublets at δ 4.80-5.00 (1H, $CH_X$-Ar), δ 4.20-4.40 (1H, $CH_BH$) and δ 3.60-3.80 (1H, $CHH_A$) which indicated that the ring has not aromatized under base catalyzed microwave irradiation. The mass spectral data showed molecular ion peak at m/z 289 ($M^+$) corresponding to its molecular weight. The IR, $^1H$ NMR and mass spectra of **3b-e** were in agreement with the structures assigned to the molecules.

## Antimicrobial Activity

The *in vitro* antimicrobial activity study was carried out against 24 hr old cultures of two bacterial and two fungal species by cup-plate method[24-25]. The compounds **3a-e** have been tested for their anti-microbial activity against *Pseudomonas aerugenosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Curvularia*. Chloramphenicol and Flucanazole were used as standards for comparison of antimicrobial and antifungal activity respectively. The compounds were tested at a concentration of 0.001 mol/mL in DMF against all organisms. The zone of inhibition was compared with the standard drug after 24 hr of incubation at 25°C for antimicrobial activity and 48 hr at 30°C for antifungal activity. All compounds showed comparable antimicrobial activities. Results are reported in **Table I**.

## Experimental

Melting points were determined with open capillary and are uncorrected. IR spectra were recorded in KBr pellets by using JASCO FT-IR 300E spectrophotometer. $^1H$ NMR spectra were recorded in $CDCl_3$ on a Bruker Supercon FT-NMR instrument.

**Table I** – Antimicrobial activity

| Compd | Antimicrobial activity | | Antifungal activity | |
|---|---|---|---|---|
| | *P. aerugenosa* | *S. aureus* | *Aspergillus niger* | *Curvularia* |
| **3a** | 12 | 14 | 15 | 10 |
| **3b** | 10 | 11 | 12 | 13 |
| **3c** | 18 | 17 | 16 | 18 |
| **3d** | 17 | 16 | 18 | 16 |
| **3e** | 15 | 16 | 17 | 15 |
| Standard | 24 | 26 | 22 | 24 |
| DMF | +ve | +ve | +ve | +ve |

+ve indicates growth of microbes
Zone of inhibition expressed in mm.
Chloramphenicol, Flucanazole were used as standards for antimicrobial and antifungal activity respectively.
DMF used as control.

Chemical shifts are reported in δ relative to TMS as internal standard. Mass spectral data were obtained on a Jeol JMS-D 300 mass spectrometer operating at 70 eV. All the reactions were monitored by TLC. The reactions were carried out in a Whirlpool domestic microwave oven (operating between 80-800W, Model No. M-542). The reactions were carried out at power –2, which corresponds to 160W.

**Synthesis of 1-(1-benzofuran-2-yl)-3-phenyl-prop-2-en-1-one 2a**. A mixture of 2-acetylbenzofuran (0.01 mole, 1.60 g), benzaldehyde (0.01 mole, 1.1 mL) and NaOH (0.01 mole, 0.4 g) were taken in a mortar and made a homogenous paste using a pestle. The paste was exposed to microwave irradiation for 3 min at power -2 at intervals of 30s. After the completion of the reaction, the mixture was poured into ice cold water, extracted with chloroform, the organic layer dried over anhydrous sodium sulphate, concentrated under reduced pressure and the isolated solid purified by recrystallization from ethanol. The compounds **2b-e** were synthesized following a similar procedure.

**Synthesis of 6-(1-benzofuran-2-yl)-4-phenyl-4, 5-dihydropyrimidin-2-amine 3a**. A paste of **2a** (0.01 mole, 2.93 g), guanidine hydrochloride (0.01 mole, 0.96 g) and NaOH (0.01 mole, 0.40 g) was irradiated with microwave radiations for 5 min at intervals of 30s at power - 2, cooled and poured into ice cold water. The solid **3a**, which separated out was filtered off, washed with water, dried and purified by recrystallization from ethanol. Similarly, the compounds **3b-e** were synthesized from **2b-e**. The characterization data of the synthesized compounds are reported in **Table II**.

**1-(1-benzofuran-2-yl)-3-(4-nitrophenyl)prop-2-en-1-one 2b**: IR (KBr): 1648 (C=O), 1621 (C=C), 1080-1095 $cm^{-1}$ (C-O-C); $^1$H NMR ($CDCl_3$): δ 6.85 - 7.82 (m, 9H, Ar-H), 6.46 (d, 1H, -COCH=), 8.42 (d, 1H, =CH-Ar); MS: m/z 293($M^+$).

**1-(1-benzofuran-2-yl)-3-(4-chlorophenyl)prop-2-en-1-one 2c**: IR (KBr): 1652 (C=O), 1618 (C=C), 1085-1100 $cm^{-1}$ (C-O-C); $^1$H NMR ($CDCl_3$): δ 6.80 - 7.75 (m, 9H, Ar-H), 6.50 (d, 1H, -COCH=), 8.43 (d, 1H, =CH-Ar); MS: m/z 283($M^+$).

**1-(1-benzofuran-2-yl)-3-(4-methylphenyl)prop-2-en-1-one 2d**: IR (KBr): 1649 (C=O), 1622 (C=C), 1092-1107 (C-O-C), 745 $cm^{-1}$ (C-Cl); $^1$H NMR ($CDCl_3$): δ 6.85 - 7.72 (m, 9H, Ar-H), 6.45 (d, 1H, -COCH=), 8.35 (d, 1H, =CH-Ar), 0.95 (s, 3H, $CH_3$); MS: m/z 262 ($M^+$).

**1-(1-benzofuran-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one 2e**: IR (KBr): 1647 (C=O), 1619 (C=C), 1087-1103 $cm^{-1}$ (C-O-C); $^1$H NMR ($CDCl_3$): δ 6.70 - 7.80 (m, 9H, Ar-H), 6.51 (d, 1H, -COCH=), 8.21 (d, 1H, =CH-Ar), 3.88 (s, 3H, -$OCH_3$); MS: m/z 278 ($M^+$).

**6-(1-benzofuran-2-yl)-4-(4-nitrophenyl)-4,5-dihydropyrimidin-2-amine 3b**: IR (KBr): 3330 (-$NH_2$), 1595-1609 (C=N), 1110-1122 $cm^{-1}$ (C-O-C); $^1$H NMR ($CDCl_3$): δ 6.85 - 7.82 (m, 9H, Ar-H), 5.40 (s, 2H, -$NH_2$), 4.75 - 4.89 (dd, 1H, $CH_X$-Ar), 4.23 - 4.40 (dd, 1H, -$CH_BH$), 3.55 - 3.65 (dd, 1H, -$CHH_A$); MS: m/z 334 ($M^+$).

**6-(1-benzofuran-2-yl)-4-(4-chlorophenyl)-4,5-dihydropyrimidin-2-amine 3c**: IR (KBr): 3327 (-$NH_2$), 1595-1609 (C=N), 1110-1122 $cm^{-1}$ (C-O-C); $^1$H NMR ($CDCl_3$): δ 6.80 - 7.75 (m, 9H, Ar-H), 5.38 (s, 2H, -$NH_2$), 4.80 - 4.95 (dd, 1H, $CH_X$-Ar), 4.21 - 4.35 (dd, 1H, -$CH_BH$), 3.45 - 3.60 (dd, 1H, -$CHH_A$); MS: m/z 323 ($M^+$).

**6-(1-benzofuran-2-yl)-4-(4-methylphenyl)-4,5-dihydropyrimidin-2-amine 3d**: IR (KBr): 3335 (-

**Table II –** Characterization data of compounds **2a-e** and **3a-e**

| Compd | R | Mol. formula | Yield % | m.p. °C | Recryst. Solvent (Color of the crystals) | Found% (Calcd) C | H | N |
|---|---|---|---|---|---|---|---|---|
| **2a** | H | $C_{17}H_{12}O_2$ | 76 | 65 | EtOH | 82.24 | 4.87 | - |
| | | | | | (Light brown) | (82.56 | 4.90) | - |
| **2b** | $NO_2$ | $C_{17}H_{11}NO_4$ | 78 | 71 | $CHCl_3$ | 69.62 | 3.78 | 4.76 |
| | | | | | (Yellow) | (70.05 | 3.91 | 4.85) |
| **2c** | Cl | $C_{17}H_{11}ClO_2$ | 74 | 111 | EtOH | 72.22 | 3.92 | - |
| | | | | | (White) | (72.35 | 4.03) | - |
| **2d** | $CH_3$ | $C_{18}H_{14}O_2$ | 71 | 146 | EtOH | 82.42 | 5.38 | - |
| | | | | | (Light brown) | (82.56 | 5.40) | - |
| **2e** | $OCH_3$ | $C_{18}H_{14}O_3$ | 73 | 69 | $CHCl_3$ | 77.68 | 5.07 | - |
| | | | | | (Dark brown) | (78.07 | 5.15) | - |
| **3a** | H | $C_{18}H_{15}N_3O$ | 72 | 75 | EtOH | 74.72 | 5.23 | 14.52 |
| | | | | | (Dark brown) | (74.96 | 5.30 | 14.85) |
| **3b** | $NO_2$ | $C_{18}H_{14}N_4O_3$ | 75 | 118 | EtOH | 64.66 | 4.22 | 16.76 |
| | | | | | (Yellow) | (64.88 | 4.33 | 17.09) |
| **3c** | Cl | $C_{18}H_{14}ClN_3O$ | 69 | 152 | $CHCl_3$ | 66.77 | 4.36 | 12.98 |
| | | | | | (White) | (66.85 | 4.40 | 13.01) |
| **3d** | $CH_3$ | $C_{19}H_{17}N_3O$ | 70 | 116 | EtOH | 75.23 | 5.65 | 13.85 |
| | | | | | (Light brown) | (75.45 | 5.72 | 13.53) |
| **3e** | $OCH_3$ | $C_{19}H_{17}N_3O_2$ | 74 | 100 | $CHCl_3$ | 71.46 | 5.37 | 13.16 |
| | | | | | (Dark brown) | (71.50 | 5.40 | 13.40) |

$NH_2$), 1595-1609 (C=N), 1110-1122 (C-O-C), 747 $cm^{-1}$ (C-Cl); $^1$H NMR ($CDCl_3$): δ 6.85 - 7.72 (m, 9H, Ar-H), 5.42 (s, 2H, -$NH_2$), 4.72 - 4.95 (dd, 1H, $CH_X$-Ar), 4.25 - 4.40 (dd, 1H, -$CH_BH$), 3.56 - 3.72 (dd, 1H, -$CHH_A$); MS: m/z 303 ($M^+$).

**6-(1-benzofuran-2-yl)-4-(4-methoxyphenyl)-4,5-dihydropyrimidin-2-amine 3e**: IR (KBr): 3337 (-$NH_2$), 1595-1609 (C=N), 1110-1122 $cm^{-1}$ (C-O-C); $^1$H NMR ($CDCl_3$): δ 6.7 - 7.80 (m, 9H, Ar-H), 5.37 (s, 2H, -$NH_2$), 4.65 - 4.76 (dd, 1H, $CH_X$-Ar), 4.18 - 4.30 (dd, 1H, -$CH_BH$), 3.45 - 3.60 (dd, 1H, -$CHH_A$), 3.88 (s, 3H, -$OCH_3$); MS: m/z 319 ($M^+$).

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