ABSTRACT
Aminopyrimidines are important chemical motifs because of their close chemical association with biologically prevalent compounds such as thiamine diphosphate (ThDP, the vitamin B1 coenzyme) and the cytosine unit in nucleic acids. 2-Aminopyrimidine is also the key heterocyclic component in many commercial drugs and exhibit wide range of pharmacological properties. In the present investigation we synthesised aryl-1-furan-2ylprop-2en-1-ones irradiated (60-80 sec) in the domestic microwave oven with guanidine hydrochloride and alkali, 2-Amino-6-phenyl-4-(furan-2yl)pyrimidine,2-Amino-6-(4-chlorophenyl)-4-(furan-2yl)pyrimidine,2-Amino-6-(3-bromophenyl)-4-(furan-2yl)pyrimidine. Microwave assisted synthesis of 2-Aminopyrimidine has advantages due to reduced reaction time, solvent-free condition and high yield. The compounds were characterized by NMR and FT-IR.

Keywords Amino pyrimidine, microwave assisted synthesis, NMR, IR.

1. INTRODUCTION
Free radicals play an important role in the pathogenesis of many diseases, accounting for continuing interest in the identification and development of novel antioxidants that prevent radical-induced damage. The oxygen consumption inherent in cell growth leads to the generation of a series of oxygen free radicals. The interaction of these species with lipidic molecules produces new radicals: hydroxides and different peroxides. This group of radicals (super oxide, hydroxyl and lipoid peroxides) may interact with biological systems in a cytotoxic manner. Free radicals and their uncontrolled production. In fact, are responsible for several pathological processes, such as certain tumours (prostate and colon cancers) and coronary heart disease. The reducing properties of diaryl amines make them very important as antioxidants, especially as radical scavengers. Substituted aminopyrimidine structures are common in marketed drugs, such as anti atherosclerotic aronxil, anti-histaminic thonzylamine etc. it also exhibit wide range of biological properties and have been shown to be effective chemotherapy treatments for certain types of cancers. Recently we have reported the antibacterial activity of some new aminopyrimidine. In continuation of our research work we have here synthesis of some 2-amino-6-aryl-4-(furan-2yl)pyrimidines.

ANTIOXIDANT
Free radical formation is associated with the normal natural metabolism of aerobic cells. The oxygen consumption inherent in cell growth leads to the generation of a series of oxygen free radicals. The interaction of these species with lipidic molecules produces new radicals: hydroperoxides and different peroxides. This group of radicals (superoxide, hydroxyl, and lipoid peroxides) may interact with biological systems in a cytotoxic manner. Free radicals and their uncontrolled productions, in fact, are responsible for several pathological processes, such as certain tumours (prostate and colon cancers).
and coronary disease. Dietary antioxidants, including polyphenolic compounds, vitamin E and C, and carotenoids, are believed to be the effective nutrients in the prevention of these oxidative stress related diseases. Reactive oxygen species are cytotoxic due to the intermediate formed from univalent reduction of molecular oxygen, including the superoxide radical (\(O_2^-\)), hydrogen peroxide (\(H_2O_2\)), and the hydroxyl radical (\(OH\)). These oxygen intermediates differ significantly in their interactions and can cause extensive cellular damage such as nucleic acid strand scission (Adelman et al., 1988), modification of polypeptides, lipid peroxidation, etc. (Pryor and Porter, 1990). The screening of the compounds, which scavenge the reactive oxygen species, could lead to promising radioprotectors. Most of the antioxidants used in therapy are derived from natural sources. About 28% of the drugs approved by the FDA between 1981 and 2002 are either natural products or chemicals derived from them (Weiss and Landauer, 2003; Clardy and Walsh, 2004). Therefore, exploration of chemicals as radioprotectors is a promising drug development strategy.

This study is devoted to the synthesis and comparative investigation of the antioxidant activity of a series of new 2-amino-6-aryl-4-furan-2ylpyrimidines. These compounds have lipophilic aryl ends and can be easily converted into water soluble by halides.

### 2. RESULT AND DISCUSSION

#### SYNTHESIS

Some 2-amino-6-aryl-4-(furan-2yl)pyrimidines were obtained in two steps using microwave technique. First step involves Claisen-Schmidt condensation of 1-(2-firanyl)ethanone 1 with a suitably substituted benzaldehyde 2 in presence of sodium hydroxide to yield 3-Aryl-1-(2-furanly)prop-2-en-1-one (scheme 1). As show in scheme 2, 2-amino-6-aryl-4-(furan-2yl)pyrimidines 3-5 were obtained by treatment of 3-5 with guanidine hydrochloride in presence of sodium hydroxide. These compounds were characterized using IR and NMR.

![Scheme 1](image)

**Where,**
\[
\begin{align*}
X = H & \quad (3) \\
X = 4-\text{Cl} & \quad (4) \\
X = 3-\text{Br} & \quad (5)
\end{align*}
\]
Scheme 2

MW, 320, 60-80 sec, solvent free 70-80%

Where,
X=H (9)
X=4-Cl (10)
X=3-Br (11)

In IR spectra of the compound 4 displayed characterized absorption bands (cm⁻¹) in the regions 3150-3500 NH stretching and symmetric stretching vibration of the primary amino group. The absorption frequency at 3100-2900 is assigned to aromatic C-H stretching vibrations. The band at 1654-1600 indicates N-H in plane bending vibrations of the primary amino group. The absorption band at 1240-1220 is consistent with C-N stretching vibration. The absorption at 820-810 is due to the C-H out-of-plane bending in 2-substituted furan.

The ¹H NMR shows characteristic peaks at δ(ppm) 5.0-5.3(NH₂), around 7.3(H-5) and 7.2-8.2(Ar-H).¹³C NMR displays characteristic peaks at δ(ppm) 156.5(C-6), 101.9(C-5), 166(C-4), 163.5(C-2), 137.3 and 152.1(ipso carbons).

ANTIOXIDANT RADICAL-SCAVENGING ACTIVITY
DPPH radical scavenging assay:
The radical scavenging activity of compounds against DPPH was determined by spectrophotometrically by the method of Brand Williams et al., 1995. DPPH is a stable free radical and accepts an electron, or hydrogen radical to become a stable diamagnetic molecule. DPPH reacts with an antioxidant compound that can donate hydrogen and gets reduced. The change in color (from deep violet to light yellow) was measured. The intensity of the yellow colour depends on the amount and nature of radical scavenger present.

The reaction mixture in a total volume of 3mL contained 1mL of DPPH, various concentrations of compounds (1, 2, 3, 4, 5, 6,7,8,9 & 10µg) and made up to 3mL with water. The tubes were incubated for 10 min at 37°C. a blue colour chromophore was formed, the absorbance of which was measured at 517nm. Ascorbic acid was used as standards for comparison.

Note: DDPH, 2, 2-Diphenyl-1-picryl hydrazyl

ABTS radical cation decolorization assay:
The generation of the ABTS radical cation forms the basis of one of the spectrophotometric methods that has been applied for the measurement of the total antioxidant activity of solutions of pure substances (Welfendened & Willson 1982). The improved technique for the generation of ABTS described here involves the direct production of the green ABTS chromophore through the reaction between ABTS and potassium persulphate. Addition of compounds and other antioxidants compete with ABTS diminishes the color formation.

ABTS was dissolved in water at a concentration of 7mM. The stock solution was mixed with 2.45mM potassium persulphate (final concentration). The mixture was allowed to stand in the dark at room
temperature for 12-16hrs before use for incomplete oxidation of ABTS. The radical was stable in this form for more than two days when stored in the dark at room temperature. The incubation mixture in a total volume of 5mL contained 0.54mL of ABTS, 0.5 mL of phosphate buffer and varying concentrations of compounds (1, 2, 3,4,5,6,7,8,9 & 10µg), the blank contained water in place of sunphenon. The absorbance was read in spectrophotometer at 734nm and compared with standards ascorbic acid at same concentrations.

Note: ABTS 2, 2’ - Azinobis - ( 3 - ethylbenzothiazoline -6- sulfoinic acid)

Superoxide anion scavenging assay:
Superoxide anion scavenging activity of sunphenon was determined by the method of Nishimiki et al (1972) with modifications. The assay was based on the oxidation of NADH by phenazine methosulphate (PMS) to liberate PMSred. PMSred converted oxidized nitroblue tetrazolium (NBTred) to the reduced form NBTred which formed a violet colour complex. The colour formation indicated the generation of superoxide anion, which was measured spectrophotometrically at 560nm. A decrease in the formation of colour after addition of the antioxidant was a measured of its superoxide radical scavenging activity.

To 1mL of NBT, 1mL of NADH solution and carrying volumes of compounds (1, 2, 3, 4, 5, 6,7,8,9 & 10µg) were added and mixed well. The reaction was started by the addition of 100µL of PMS. The reaction mixture was incubated at 30°C for 15 min. the absorbance was measured at 560nm. Incubation with water in plate of compounds was used as blank. Ascorbic acid was used as standards for comparison.

Hydroxyl radical scavenging assay:
The hydroxyl radical scavenging activity of sunphenon was determined by the method of Halliwell et al (1987). In this assay, hydroxyl radicals are produced by the reduction of H₂O₂ by the transition metal (iron) in the presence of ascorbic acid. The generation of hydroxyl radical is detected by its ability to degrade deoxyribose to form products, which on heating with TBA forms a pink colour chromogen. Addition of sunphenon competes with deoxyribose for hydroxyl radicals and diminishes the colour formation.

The incubation mixture in a total volume of 1mL contained 0.1mL of buffer, varying volumes of compounds (1, 2, 3, 4, 5, 6,7,8,9 & 10µg), 0.2mL of ferric chloride, 0.1mL of ascorbic acid, 0.1mL of EDTA, 0.1mL of hydrogen peroxide and 0.2mL of 2-deoxyribose. The contents were mixed thoroughly and incubated at room temperature for 60 min. then added, 1mL of TBA and 1mL of TCA. All the tubes were kept in a boiling water bath for 30 min. the absorbance of the supernatant was read in a spectrophotometer at 535 nm with reagent blank containing water in place of extract. The efficiency of compounds was compared with various concentrations (1, 2, 3, 4, 5, 6,7,8,9 & 10µg) of standards ascorbic acid.

Nitric oxide radical inhibition assay:
The nitric oxide radical inhibition activity of sunphenon was measured by the method of Garrat, 1964. Sodium nitroprusside in aqueous solution at physiological pH spontaneously produces nitric oxide which interacts with oxygen to produce nitrite ions. This can by estimated using Griess reagent.

The reaction mixture (3mL) containing sodium nitroprusside (2mL), PBS (0.5mL) and compounds or standard solution (0.5mL) was incubated at 25° C for 15 min. after incubation, 0.5mL of the reaction mixture containing nitrite was pipetted and mixed with 1 mL of sulfuric acid reagent and allowed to stand for 5 min for completing diazotization. Then 1mL of naphthalene diamine hydrochloride was added, mixed and allowed to stand for 30 min at 25° C. a pink colour chromophore was formed, the absorbance of which was measured at 540nm.

3. EXPERIMENTAL

All melting points were taken in open capillaries tubes and are uncorrected. Purity of the compounds was checked by TLC. IR spectra were recorded in a NICOLET AVATAR 330 FT-IR instrument. NMR spectra were recorded on BRUCKER 100 MHz spectrometer using CDCL3 solvent for ¹H NMR and ¹³C NMR. Mass spectra were recorded on a Q-Tof microhybrid quadrupole time of flight mass spectrometer by Atmospheric Pressure chemical Ionization (APCI).

3.1 GENERAL PROCEDURE FOR PREPARATION OF 3-ARYL-1-FURAN-2YLPROP-2-EN-1-ONE’S (3-5)
A mixture of appropriate benzaldehyde (0.01 mole), 2-furyl methyl ketone (0.01mole) and sodium hydroxide pellets (0.05 mole) was finely powdered in a pestle and mortar. The mixture was transferred into a 100 ml beaker and irradiated in the domestic microwave oven (LG Grill, MG 395WA). The mixture was irradiated at 320W for 30–40 seconds. Then, distilled water was added, the separated solid was collected in a Buckner – Funnel filtered and dried. The compound was recrystal with suitable
solvent. Yields were in the range of 69.3-80.2%. The formed products were confirmed through FT-IR spectra.

3.2 General Methods for Preparation of 2-Amino-6-aryl-4-(2-furanyl)pyrimidines (9-11)
A mixture of 3-aryl-1-furan-2ylprop-2-en-1-one (0.01 mole), guanidine hydrochloride (0.01 mole) and sodium hydroxide pellets (0.05 mole) was finely powered in a pestle and mortar. The mixture was transferred into a beaker and irradiated in the domestic microwave oven (LG Grill, MG395 WA). The mixture was irradiated at 320 W for 60-80 seconds. Then, distilled water was added to remove the excess of alkali and then filtered and dried. The product was separated from the reaction mixture by column chromatography using benzene and ethyl acetate mixture as eluting solvent.

3.3 2-Amino-6-phenyl-4-(furan-2yl)pyrimidine (9)
$^1$H NMR (CDCl$_3$), δ, ppm: 5.37 (NH$_2$); 8.06 (H-5); 6.5-7.7 (aromatic protons); $^{13}$C NMR (CDCl$_3$), δ, ppm: 101.9 (C-5); 163.3 (C-2); 156.9 and 166.0 (C-6 and C-4); 137.3, 152.1 (ipso carbons); IR (KBr), cm$^{-1}$: 3325 and 3201 γ(N-H); 2923 γ(C-H); 1645 γ(N-H in-plane bending); 1239 γ(C-N); 822 γ(O-H out-of-plane bending in 2-substituted furan); m.p.157-159°C.
3.42-Amino-6-(4-chlorophenyl)-4-(furan-2yl)pyrimidine (10)

$^1$H NMR (CDCl$_3$), δ, ppm: 5.21 (NH$_2$); 7.59 (H-5); 6.5-8.0 (aromatic protons); $^{13}$C NMR (CDCl$_3$), δ, ppm: 101.7 (C-5); 163.3 (C-2); 157.2 and 164.8 (C-6 and C-4); 135.8, 152.0 (ipso carbons); IR (KBr), cm$^{-1}$: 3338 and 3188 γ(N-H); 2956 γ(C-H); 1654 γ(N-H in-plane bending); 1239 γ(C-N); 815 γ(O-H out-of-plane bending in 2-substituted furan); m.p.188-190°C.

($^1$H NMR)  

($^{13}$C NMR)
IR
3.52-Amino-6-(3-bromophenyl)-4-(furanyl-2yl)pyrimidine (11)

$^1$H NMR (CDCl$_3$), δ, ppm: 5.27 (NH$_2$); 8.20 (H-5); 6.5-7.9 (aromatic protons); $^{13}$C NMR (CDCl$_3$), δ, ppm: 101.8 (C-5); 163.2 (C-2); 157.1 and 164.4 (C-6 and C-4);

139.3, 151.9 (ipso carbons); IR (KBr), cm$^{-1}$: 3456 and 3314 γ(N-H); 3194-3065 γ(C-H); 1630 γ(N-H in-plane bending); 1239 η(C-N); 815 γ(O-H out-of-plane bending in 2-substituted furan); m.p.130-131°C.

($^1$H NMR)  ($^{13}$C NMR)
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IC\textsubscript{50} values for the different antioxidant activity assay:

Table 1

<table>
<thead>
<tr>
<th>Radicals</th>
<th>Ascorbate µg/mL</th>
<th>9 µg/mL</th>
<th>10 µg/mL</th>
<th>11 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPPH</td>
<td>4.94</td>
<td>5.39</td>
<td>3.24</td>
<td>3.32</td>
</tr>
<tr>
<td>ABTS</td>
<td>5.32</td>
<td>5.87</td>
<td>3.48</td>
<td>3.74</td>
</tr>
<tr>
<td>Superoxide</td>
<td>5.35</td>
<td>5.41</td>
<td>3.10</td>
<td>3.39</td>
</tr>
<tr>
<td>Hydroxyl</td>
<td>4.23</td>
<td>5.22</td>
<td>2.94</td>
<td>3.24</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>4.50</td>
<td>5.37</td>
<td>3.16</td>
<td>3.44</td>
</tr>
</tbody>
</table>

All the compounds are found to be an efficient scavengers of free radicals such as DPPH free radical, ABTS\textsuperscript{+}, OH, O\textsubscript{2}\textsuperscript{−}, and nitric oxide in dose dependence manner. The various antioxidant activities of the compound were compared to the standard ascorbic acid. Compounds 23-29 showed more antioxidant properties whereas compound 24 exhibited low antioxidant property, when compared to standard ascorbic acid. The scavenging potential was in the order of 9>10>11>ascorbic acid.

The IC\textsubscript{50} values for compounds are represented in Table-1

CONCLUSION

Microwave assisted synthesis of 2-Aminopyrimidine has advantages due to reduced reaction time, solvent-free condition and high yield. The compounds (9-11) were characterized by \textsuperscript{1}H NMR, and \textsuperscript{13}C NMR. H-NMR spectrum shows a signal in the range of 5.1-5.3 ppm and IR spectrum show bands in the range 3456-3182 cm\textsuperscript{-1} due to the free amino group of compounds (9-11). All the compounds are found to be an efficient scavengers of free radicals such as DPPH free radical, ABTS\textsuperscript{+}, OH, O\textsubscript{2}\textsuperscript{−}, and nitric oxide in dose dependence manner. The various antioxidant activities of the compound were compared to the standard ascorbic acid. The scavenging potential was in the order of 9>10>11>ascorbic acid.

REFERENCES