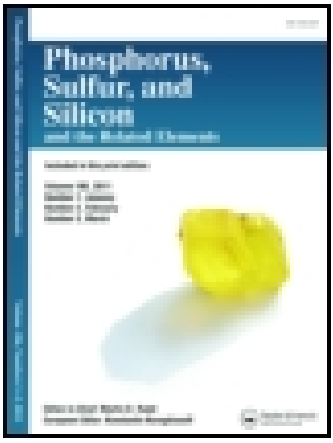

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Synthesis and Biological Activity of Some Novel N-Aryl-N′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]ureas

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Synthesis and Biological Activity of Some Novel *N*-Aryl-*N*′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]ureas

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*With the aim of searching for biologically active urea compounds, a series of new N-aryl-N′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]ureas have been designed and synthesized. Their structures were confirmed by IR, ^{1}H NMR, and elemental analysis. The crystal structure of **3f** was further determined by single crystal X-ray diffraction to obtain the structural information on this class of compounds. The preliminary bioassay showed that the title compounds exhibit promising cytokinin activity.*

Keywords 1,3,4-Thiadiazole; crystal structure; cytokinin activity; urea

INTRODUCTION

1,3,4-Thiadiazole derivatives have been attracting widespread attention due to their significant biological activities, such as fungicidal,[1] insecticidal,[2] plant-growth regulating,[3] and pharmacological properties.[4–7] In general, pyridine can serve as effective bioisostere of benzene in drug design and considerable interest has been

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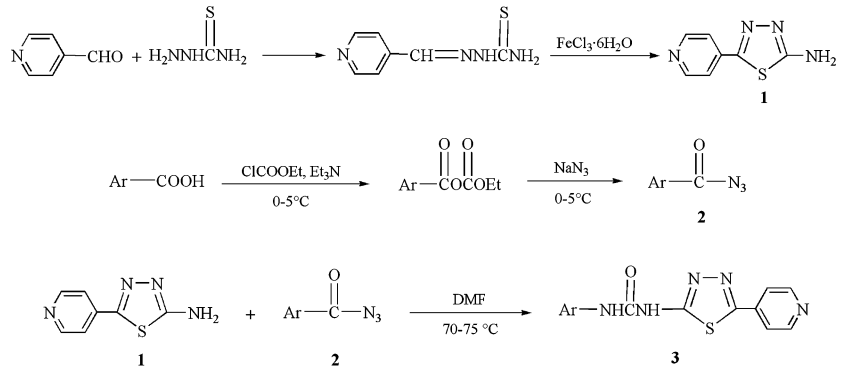
shown in pyridine derivatives in the field of modern agrochemistry and medicinal chemistry because substitution of benzene by pyridine may result in the good biological activity and low toxicity of molecules.[8,9] Not only N^6-substituted adenine derivatives, like benzyladenine or furfuryladenine (kinetin), but also substituted urea derivatives, like *N*-phenyl-*N*′-(1,2,3-thiadiazol-5-yl)urea (thidiazuron, TDZ), show cyokinin activity,[10,11] which seems to be a property of the two classes of compounds. Moreover, it is generally believed that the active site of purine and urea cytokinins are common,[12] so that no special molecular shape other than flatness is required for activity.[13] In our continuing search for new urea cytokinins, we would like to synthesize the urea molecules characterized by plane structure and incorporating both 1,3,4-thiadiazole and pyridine rings for evaluating their cytokinin activity. The synthetic route of the title compounds **3** is depicted in Scheme 1.



Ar = C_6H_5 (a), 3-FC_6H_4 (b), 4-FC_6H_4 (c), 2-ClC_6H_4 (d), 3-ClC_6H_4 (e), 4-ClC_6H_4 (f), 3-$CH_3C_6H_4$ (g), 4-$CH_3C_6H_4$ (h)

SCHEME 1

RESULTS AND DISCUSSION

The required 2-amino-5-(pyrid-4-yl)-1,3,4-thiadiazole **1** was obtained *via* the oxidative cyclization of thiosemicarbazone in the presence of ferric chloride hexahydrate according to the literature method.[14] Acyl azides were efficiently prepared directly from carboxylic acids, ethyl chloroformate and sodium azide by one-pot procedure, undergoing facile Curtius rearrangement at elevated temperature to isocyanates, then react with 2-amino-5-(pyrid-4-yl)-1,3,4-thiadiazole resulting in the formation of the corresponding ureas. This general method involves readily

available starting material, mild reaction conditions, simple handling procedure, and avoids the unstable and toxic isocyanates being directly employed.

The structures of compounds **3** were verified spectroscopically. For example, the IR spectra contained absorption bands due to stretching vibrations of the two NH groups (two broadened bands in the regions 3360–3390 and 3180–3210 cm^{-1}), and carbonyl group (1700–1735 cm^{-1}) in the urea bridge. In the ^1H NMR spectra (DMSO-d_6) compounds **3a–3h** displayed the pyridyl signals from protons as a pair of doublets (AA′BB′ system), each appearing near 7.90 and 8.70 ppm and $J = 5.2$ Hz, while the aromatic signals appeared between δ 6.88–8.14ppm as multiplets. Each NH groups showed a broadened singlet at δ 8.90–9.30 and 11.20–11.45 ppm. Thus it can be seen that the data of ^1H NMR, IR and elemental analysis for the products are in good agreement with the structures of the title compounds.

The structure of product **3f** was unambiguously proved by the X-ray diffraction data, for the purpose of obtaining the structural feature of this class of compounds. The molecular structure is shown in Figure 1. The X-ray diffraction reveals that the title molecule **3f** which consists of three rings is essentially planar, the dihedral angles formed by the thiadiazole ring with the pyridine and benzene planes being only 6.82(14)° and 3.64(12)°, respectively. It is obvious that the flatness of the molecule can be attributed to the presence of the extended π conjugated system throughout the whole molecule.

The cytokinin activity of all the title compounds **3** was investigated by the method of *cucumber cotyledon expansion*.[15] Their promotive percentages tested at the concentration of 10 ppm were 45.1%, 34.2%, 38.0%, 23.6%, 32.7%, 41.6%, 19.5% and 21.8% respectively. The results of preliminary bioassay indicated that these new urea derivatives exhibit moderate-to-good cytokinin activity, especially the promotive

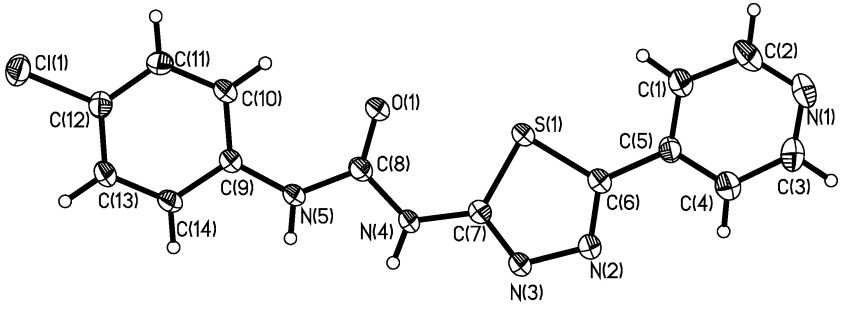


FIGURE 1 Molecular structure of compound **3f** with the atomic labeling.

percentage reached above 40% as for compounds **3e** and **3g**, which deserve further research. We would conclude therefore that such good biological effects could be ascribed to the flatness of the molecule together with introduction of the 1,3,4-thiadiazole heterocycle and the pyridyl group into the urea molecule.

EXPERIMENTAL

All chemicals and solvents used for the preparation the compounds were of analytical grade. The ^{1}H NMR spectra were obtained on a Varian Mercury Plus-400 MHz Spectrometer with TMS as internal standard and DMSO-d_6 as the solvent. The IR spectra were recorded in the range 4000–400 cm^{-1} on a Nicolet NEXUS 470 FT-IR spectrophotometer, using KBr pellets. Elemental analysis was performed by a Vario EL III analyzer. Melting points were determined by an X-4 microscopic melting apparatus and uncorrected.

General Method for the Synthesis of Compounds 3

To the solution of substituted benzoic acid (11 mmoles) in 10 mL of acetone was successively added triethylamine (1.21 g, 12 mmoles) and the solution of ethyl chloroformate (1.52 g, 14 mmoles) in 4 mL of acetone below 5°C. After the mixture was stirred for 30 min, the solution of sodium azide (0.98 g, 15 mmoles) in 5 mL of water was added dropwise below 5°C. The reaction mixture was stirred at 0–5°C for a further 1.5 h and then filtrated. The clear filtrate was extracted with toluene (2 × 4 mL), and the combined organic layer were washed with brine and dried over $MgSO_4$. The solution of acyl azide **2** obtained was added dropwise to the solution of intermediate **1** (1.78 g, 10 mmoles) in 5 mL of freshly dried dimethylformide (DMF), which had been preheated to 70–75°C. The resulting reaction mixture was stirred at this temperature for another 3.5–4 h. The mixture was then cooled, and the solid was filtrated and recrystallized from ethanol/DMF to give the desired products **3a–3h** as yellowish crystal. m.p. >300°C.

N-Phenyl-N′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]urea (3a)

Yield: 71.8%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (bs, 1H, NH), 9.12 (bs, 1H, NH), 8.73 (d, 2H, $J = 5.2$ Hz, pyridyl 2,6-H), 7.89 (d, 2H, $J = 5.2$ Hz, pyridyl 3,5-H), 7.06–7.53 (m, 5H, Ar-H); IR (KBr, ν in cm^{-1}): 3379, 3198 (N—H), 1725 (C=O); Anal. Calcd for $C_{14}H_{11}N_5OS$: C 56.55; H 3.73; N 23.55. Found: C 56.72; H 3.55; N 23.63.

N-(3-Fluorophenyl)-N′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]urea (3b)

Yield: 66.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.53 (bs, 1H, NH), 9.38 (bs, 1H, NH), 8.72 (d, 2H, $J = 5.2$ Hz, pyridyl 2,6-H), 7.88 (d, 2H, $J = 5.2$ Hz, pyridyl 3,5-H), 6.88–7.53 (m, 4H, Ar-H); IR (KBr, ν in cm^{-1}): 3382, 3208 (N–H), 1725 (C=O); Anal. Calcd for $C_{14}H_{10}FN_5OS$: C 53.33; H 3.20; N 22.21. Found: C 53.45; H 2.97; N 22.39.

N-(4-Fluorophenyl)-N′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]urea (3c)

Yield: 67.1%; ^{1}H NMR (400MHz, DMSO-d_6): δ 11.36 (bs, 1H, NH), 9.17 (bs, 1H, NH), 8.72 (d, 2H, $J = 5.2$ Hz, pyridyl 2,6-H), 7.88 (d, 2H, $J = 5.2$ Hz, pyridyl 3,5-H), 7.15–7.55 (m, 4H, Ar-H); IR (KBr, ν in cm^{-1}): 3378, 3201 (N–H), 1728 (C=O); Anal. Calcd for $C_{14}H_{10}FN_5OS$: C 53.33; H 3.20; N 22.21. Found: C 53.12; H 3.06; N 22.43.

N-(2-Chlorophenyl)-N′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]urea (3d)

Yield: 64.2%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.92 (s, 1H, NH), 8.81 (s, 1H, NH), 8.74 (d, 2H, $J = 5.2$ Hz, pyridyl 2,6-H), 7.90 (d, 2H, $J = 5.2$ Hz, pyridyl 3,5-H), 7.15–8.14 (m, 4H, Ar-H); IR (KBr, ν in cm^{-1}): 3356, 3180 (N–H), 1711 (C=O); Anal. Calcd for $C_{14}H_{10}ClN_5OS$: C 50.68; H 3.04; N 21.11. Found: C 50.59; H 2.87; N 20.92.

N-(3-Chlorophenyl)-N′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]urea (3e)

Yield: 66.0%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.43 (bs, 1H, NH), 9.35 (bs, 1H, NH), 8.74 (d, 2H, $J = 5.2$ Hz, pyridyl 2,6-H), 7.90 (d, 2H, $J = 5.2$ Hz, pyridyl 3,5-H), 6.89–7.55 (m, 4H, Ar-H); IR (KBr, ν in cm^{-1}): 3381, 3190 (N–H), 1709 (C=O); Anal. Calcd for $C_{14}H_{10}ClN_5OS$: C 50.68; H 3.04; N 21.11. Found: C 50.80; H 2.91; N 21.29.

N-(4-Chlorophenyl)-N′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]urea (3f)

Yield: 67.5%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.36 (bs, 1H, NH), 9.27 (bs, 1H, NH), 8.73 (d, 2H, $J = 5.2$ Hz, pyridyl 2,6-H), 7.89 (d, 2H, $J = 5.2$ Hz, pyridyl 3,5-H), 7.38–7.57 (m, 4H, Ar-H); IR (KBr, ν in cm^{-1}): 3375, 3206 (N–H), 1731 (C=O); Anal. Calcd for $C_{14}H_{10}ClN_5OS$: C 50.68; H 3.04; N 21.11. Found: C 50.73; H 2.95; N 20.96.

N-(3-Methylphenyl)-N′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]urea (3g)

Yield: 60.3%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.30 (bs, 1H, NH), 9.04 (bs, 1H, NH), 8.73 (d, 2H, $J = 5.2$ Hz, pyridyl 2,6-H), 7.89 (d, 2H, $J = 5.2$ Hz, pyridyl 3,5-H), 6.89–7.36 (m, 4H, Ar-H), 2.31(s, 3H, CH_3); IR (KBr, ν in cm^{-1}): 3388, 3207 (N–H), 1729 (C=O); Anal. Calcd for $C_{15}H_{13}N_5OS$: C 57.86; H 4.21; N 22.49. Found: C 58.01; H 3.98; N 22.38.

N-(4-Methylphenyl)-N′-[5-(pyrid-4-yl)-1,3,4-thiadiazol-2-yl]urea (3h)

Yield: 62.7%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.23 (bs, 1H, NH), 9.03 (bs, 1H, NH), 8.73 (d, 2H, $J = 5.2$ Hz, pyridyl 2,6-H), 7.89 (d, 2H, $J = 5.2$ Hz, pyridyl 3,5-H), 7.14–7.41 (m, 4H, Ar-H), 2.27 (s, 3H, CH_3); IR (KBr, ν in cm^{-1}): 3381, 3202 (N–H), 1709 (C=O); Anal. Calcd for $C_{15}H_{13}N_5OS$: C 57.86; H 4.21; N 22.49. Found: C 57.75; H 4.14; N 22.62.

X-Ray Crystallography of Compound 3f

A single crystal of compound **3f** with dimensions of $0.30 \times 0.20 \times 0.04$ mm^3 was mounted on a BRUKER SMART APEX-CCD diffractometer equipped with a graphite-monochromated Mo Kα ($\lambda = 0.71073$ Å) radiation at 292(2) K. A total of 5529 reflections were collected in the range of $1.28 \leq \theta \leq 26.00^\circ$ by using a ψ-ω scan mode with 2742 independent ones (R_{int} 0.0247), of which 2001 with $I > 2\sigma(I)$ were considered as observed and used in the succeeding refinements. Triclinic crystals with the following unit cell parameters: $a = 5.8550(8)$, $b = 7.5668(10)$, $c = 16.416(2)$ Å; $\alpha = 78.364(2)^\circ$, $\beta = 81.204(2)^\circ$, $\gamma = 84.749(2)^\circ$; $V = 702.58(16)$ Å^3; $M = 331.79$; $Z = 2$; $D_{calc} = 1.568$ g/cm^3; $\mu = 4.29$ cm^{-1}; $F(000) = 340$; space group $P\bar{1}$. The structure was solved by direct Fourier methods. The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were added according to theoretical models. Full-matrix least-squares refinement was based on F^2 using SHELXL-97 program.[16] The final refinement gave $R_1 = 0.0442$ and $wR_2 = 0.1092$ ($w = 1/[\sigma^2(F_o^2) + (0.0705P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$). The maximum and minimum residual peaks on the final difference Fourier maps amounted to 0.275 and -0.254 e/Å^3, respectively.

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